STUDY OF PRESSURE DEPENDENCE OF SIGNALS FROM ULTRASOUND CONTRAST AGENTS

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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) are particularly well suited for pressure measurements because pressure changes affect the reflectivity of the microbubbles after their injection. 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 that of the sub-harmonic, may be a suitable parameter for estimation of the 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.**

Keywords **- Noninvasive, Hydrostatic pressure, Ultrasound, Contrast agent**

I. INTRODUCTION

The problem of noninvasive pressure estimation using ultrasound contrast agents (UCA) is studied here. The blood pressure measurement in heart cavities, in internal organs or in the peripheral vascular system is very important because these are the locations where the pressure needs to be known. It also allows calculation of the flow through valves, stenosed arteries, etc., and it provides essential information about the blood perfusion of the given organ. Currently such pressure measurements are invasive. The possibility of exploiting particular properties of UCA as a tool for noninvasive pressure estimation seems to be promising [1], [2]. Current investigations in this field use the assumption that changes of the ambient pressure alter significantly the bubble dimensions; consequently their resonant frequency is changed, resulting in changes in the characteristics of backscattered signal. Using harmonic and sub-harmonic frequencies instead of resonant original frequency, allows to exclude artifacts from the surrounding media and to improve signal-to-noise ratio [3]. The current paper conducts comparative analysis of the pressure sensitivity of some UCA, using computer simulation. It also evaluates the parameter best correlated to the ambient pressure, using both computer simulation and 'in-vitro' experiments. The particular problem discussed here is how to avoid the UCA backscatter time dependence, so that hydrostatic pressure can be estimated.

II. METHODS

The aim of the current work was to assess the sensitivity of different UCA to ambient pressure changes and determine the particular properties that may make the UCA perform as 'pressure sensors'.

1) *Simulation studies*

4 kinds of UCA micro-bubbles (air, Albunex, octafluoropropane, Optison) were compared for their pressure sensitivity, by studying the following features: frequency shift, first harmonic amplitude, second harmonic amplitude, the sub-harmonic amplitude and its threshold, "sub-harmonic to the first harmonic" and "sub-harmonic to second harmonic" ratios. Different ultrasound frequencies and pressures were tested.

The study was performed by using a modified Rayleigh-Plesset equation, derived for the case of a single spherical gas bubble whose surface is occupied by molecules which behave collectively as a continuous, damped, elastic solid [4]. The results obtained were corrected according to the size distribution of the micro-bubbles. The Rayleigh-Plesset model was chosen, based on a study [5] that found that the Rayleigh-Plesset model gives satisfactory results for the bubbles within the radius range $R_{\max} / R_0 \le 2$ (Mechanical Index $MI \approx 0.3$).

2) *Experimental design and conditions*

The aim of the experiments was to find the most sensitive parameters for estimating the pressure changes, taking into account the fact that the essential properties of the UCA are strongly depended on time since injection.

A. The experimental setup

The pressure tank used was made from Perspex, and its size was 17cm high x 13cm long x 13cm wide. The tank was filled with 1.5L Saline solution, which was utilized as the carrying and propagation medium. All measurements were conducted at room temperature around 25C. An inlet and an outlet of the tank were constructed for injecting microbubble suspensions and for applying external 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. FDA has approved Optison^R for use

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Abstract

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in clinical echocardiography in the United States. Optison^R consists of a sterile suspension of human serum-albumin-coated microspheres filled with Octafluoropropane (C_3F_8) in concentration of 5.0-8.0 x 10^8 bubbles/ml. The microbubbles have mean diameters in the range of 2.0-4.5 micron with 93% being smaller than 10 micron. Optison^R was injected into the Saline solution using 20G syringe, at a maximum injection rate of less than 1.0 ml/s. To limit excessive acoustic attenuation and multiple scattering, a diluted solution of Optison^R in Saline with a concentration of 0.1µl/ml was used. After the introduction of the UCA, the suspension was agitated by means of a slow rotating magnetic stirrer.

A pulse-echo measurement system was constructed, which consist of:

- The RITEC advanced measurement system, which includes a high power gated RF amplifier, an internal pulse generator and a broadband receiver;
- 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 inserted into the water through the tank's wall

B. The experimental procedure

All measurements were carried out during 11 minutes after Optison^R injection. During 1 minute after injection the tank was sealed and hydrostatic pressure established. During the following 10 minutes, the acoustic measurements have been made.

A sine wave burst of 8 cycles was generated by the RITEC pulse generator and then was supplied to the acoustic transducer. The transmitted frequency was selected to be 2.0 MHz, which corresponds to the (approximate) resonance frequency of Optison^R [7]. The amplitude of the ultrasound pulse was adjusted in two ways: by the internal amplifier gain = 50% and by means of the high power attenuator RITEC RA-30, to the value of -18dB. The measurements of the acoustic pressure in the region of interest (ROI), within 3cm to 8cm from the transducer's surface, were carried out by a hydrophone, model: PVDF-GL-0400IA (Specialty Engineering Associates, Soquel, CA). The value of the acoustic pressure was estimated – 0.5 – 0.4 MPa, which corresponds to the Mechanical Index = 0.3 for the given transmittance frequency. Ultrasound signals were transmitted at repetition frequency of 5Hz.

The scattered signals were measured by the same transducer and amplified by the RITEC internal receiver, with receiver gain of – 30 dB. The amplified signals were than acquired using a digital oscilloscope Tektronix TDS 460, digitized at a sampling frequency of 50MHz, then transferred to a PC over a HPIB bus.

In order to enable good comparison, normalization of the transducer sensitivity was performed, for the acquisition of second harmonic and the sub-harmonic. Fig.1 shows the calculated power spectral sensitivity distribution of a transducer for the acquisition of the first, second, and sub harmonic frequencies, as a function of the emission frequency. For example: for emission frequency of 2MHz, the difference in sensitivity between the first and second harmonics – 9.8dB; between the first and sub-harmonic – 4.2dB.

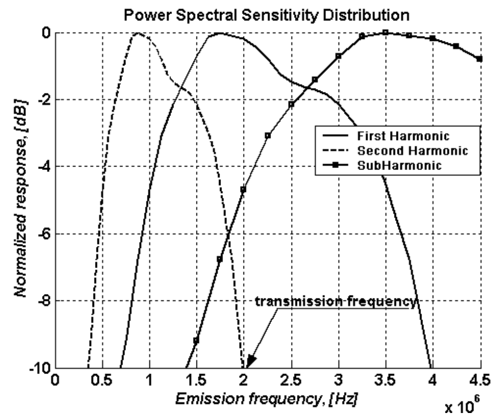


Fig.1 The power spectral sensitivity of the transducer, for different harmonic frequencies, as a function of the emission frequency for a 2.17 MHz transducer with 94.93% bandwidth.

III. Results

1) *Simulation results*

Optimal results were found when using ultrasound frequencies similar to the UCA resonance, and $MI \approx 0.3 - 0.4$. Free air and Octafluoropropane microbubbles demonstrated the larger frequency shift and the 1-st, 2-nd harmonic amplitude changes. On the other hand, encapsulated bubbles showed better correlation between the sub-harmonic amplitude changes and the ambient pressure, than the main harmonic amplitude. The sub-harmonic threshold for encapsulated microbubbles is lower by ~30% than for non-encapsulated microbubbles (consistent with experimental results [6]). Also, the increase of the ambient pressure produces a decrease of about 40% of the sub-harmonic threshold.

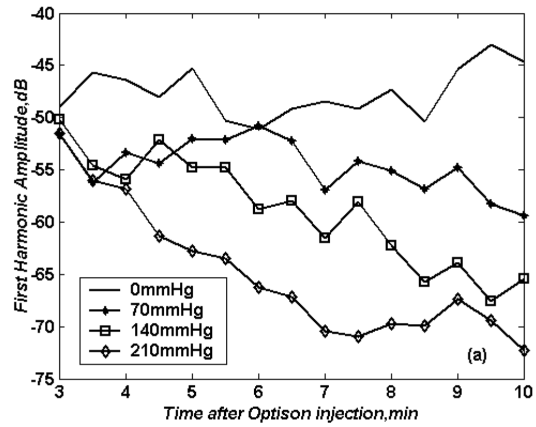
2) *Experimental results*

A. Pressure dependence on harmonics response

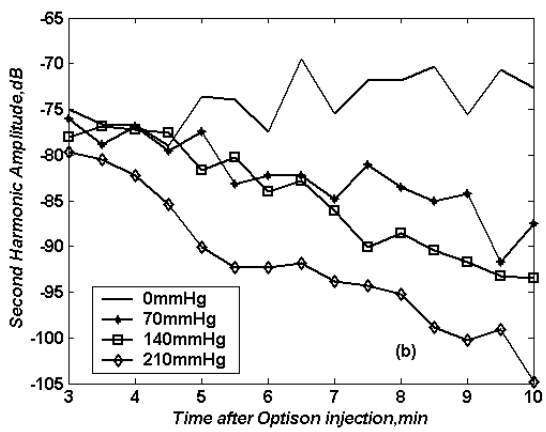
The changes of amplitudes, as a function of time, of the first, second harmonic and sub-harmonic components of scattered signals, were measured during 7 minutes, for 4 values of excessive hydrostatic pressure: 0; 70; 140; 210mmHg. The measurements started only 3 minutes after Optison injection, since it was reported that it takes a time, for microbubbles injected into Saline, to reach the equilibrium and the maximum response [7].

The first and second harmonic and sub-harmonic amplitudes vs. time for different values of ambient pressure are plotted in Fig. 2a, b and c respectively.

(a)



(b)



(c)

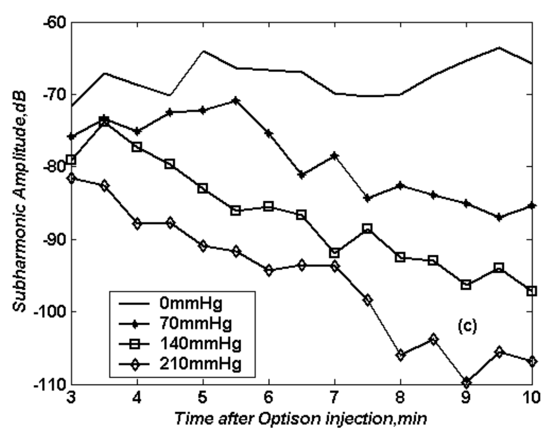


Fig.2 The first and second harmonic and the sub-harmonic amplitudes are displayed as a function of time (after UCA injection), for 4 values of excessive ambient pressure: 0; 70; 140; 210 mmHg. (a) the first harmonic amplitude; (b) the second harmonic amplitude; (c) the sub-harmonic amplitude.

The results of single experiment are depicted in this figure. 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. For a pressure change of 210 mmHg, the change in sub-harmonic amplitude reaches almost 10dB. The experimental results imply that the time dependence of the UCA response can be properly correlated with the ambient pressure. The values of the decays are estimated for first and second harmonic and sub-harmonic amplitudes and presented in Table1:

Table1. The slope rates for 4 values of ambient pressure

Ambient pressure, [mmHg]	1st harm. , [dB/min]	2nd harm., [dB/min]	Subharm., [dB/min]
0	0.5	0.74	0.42
70	-1.74	-1.66	-1.76
140	-2.32	-2.66	-2.89
210	-3.22	-3.53	-3.91

The results displayed in Table 1 demonstrate a good correlation between the decay rate of all 3 harmonics and the hydrostatic pressure. The first and second harmonics and the sub-harmonic reveal very similar behavior in time. Consequently the harmonic ratios should be studied as a possible indicator of the ambient pressure changes.

B. Dependence of harmonics amplitude differences on pressure

It was found that during first 10 minutes after the UCA injection, the differences between harmonics stay constant. When performing the measurements after 10 minutes (or more), it was discovered that, for excessive hydrostatic pressures, the difference between first and second harmonics and difference between first harmonic and the sub-harmonic are diminish to zero, because the amplitudes of the first, second harmonic and sub-harmonic approach the noise level -120dB. In the case of no excessive hydrostatic pressure, the decrease of the differences between harmonics' amplitudes may be noticed even after 20-25 min after Optison injection (*MI = 0.3*), since their destruction is slow.

The differences between first and second harmonic amplitudes and between first harmonic and sub-harmonic amplitudes vs. the excessive hydrostatic pressure are plotted in Fig. 3. The results of single experiment are exhibited.

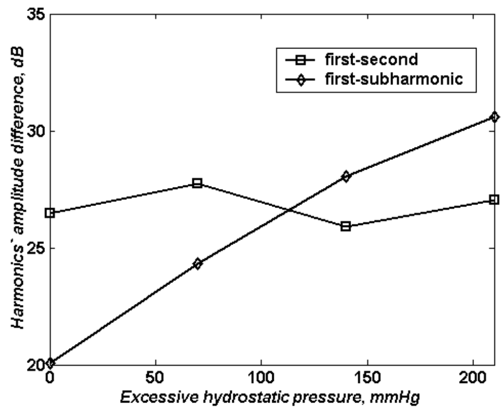


Fig.3 The differences between the first and second harmonic amplitudes and between the first harmonic and sub-harmonic amplitudes are depicted as a function of the excessive hydrostatic pressure. The mean values of the amplitude's difference are calculated for every 7 minutes of data's acquisition (starting 3 minutes after the UCA injection).

The behavior of the difference between the first harmonic and the sub-harmonic amplitudes reveals a good correlation with the changes of the hydrostatic pressure. At the same time the first-to-second harmonic difference does not depict a correlation with the pressure changes.

IV. DISCUSSION

The simulation studies, which were based on a modified Rayleigh-Plesset model, indicated that it is possible to use the encapsulated UCA for the purposes of estimation of the ambient pressure, since the sub-harmonic amplitude or ratio between the main and sub-harmonic amplitudes provide a possible indication of the hydrostatic pressure.

The dependence of the nonlinear response of UCA on hydrostatic pressure has been investigated by in-vitro experiments. The optimal set of parameters (acoustic pressure, transmission frequency) for the evaluation of the pressure dependence was chosen.

Over the pressure range of 0-210 mmHg, the sub-harmonic amplitude demonstrates the best pressure sensitivity (-10dB) measured immediately after injection and pressure change. Taking into account the influence of time on the UCA behavior (Fig.2), a high correlation was demonstrated between the decreasing rates of the harmonic amplitudes (first, second and sub-harmonic).

Moreover, the slopes given in Table1 are almost identical for all amplitudes of the harmonics, for a given hydrostatic pressure. This fact indicates a nearly fixed behavior of the differences between the amplitudes of the first and second harmonics and between the amplitudes of the first harmonic and that of the sub-harmonic, thus reducing the dependence of the time factor in the evaluation of the pressure dependence. The results have been obtained for data measured during 7 minutes, starting 3 minutes after the UCA injection. Data acquisition for more than 10 minutes reveals that the differences between harmonics amplitudes approach zero, since the amplitude each of the harmonics approaches the noise level.

Fig.3 demonstrates the excellent correlation between the difference of amplitude of the first harmonic and that of the sub-harmonic, and the hydrostatic pressure. It should be emphasized that within the particular time window (in current experiment – 7min), this parameter is stable and is not depended on time.

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