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● *Original Contribution*

MEASURING ABSOLUTE BLOOD PRESSURE USING MICROBUBBLES

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Abstract—Gas microbubbles are highly compressible, which makes them very efficient sound scatterers. As another consequence of their high compressibility, the radii of the microbubbles are affected by the pressure of the fluid around them, which changes their resonance frequency. Although the pressures present within the human body cause only minor variations in the radii of uncoated microbubbles (∼0.2% per 10 mmHg) and, therefore, very small variations in the resonance frequency (∼1 kHz per 10 mmHg), it was found in the work described here, through both simulations and *in vitro* measurements, that large changes in resonance frequency can occur in phospholipid-coated microbubbles for small blood pressure variations because of the exotic buckling dynamics of phospholipid monolayers (up to 240 kHz per 10 mmHg). This method should allow non-invasive measurement of the gauge blood pressure in deep blood vessels as long as the microbubble physical properties are well controlled. **(E-mail: charles.tremblay.darveau@gmail.com)**

Key Words: **Microbubble imaging, Blood pressure, Acoustic spectroscopy.**

INTRODUCTION

Intravascular contrast agents are well established as a means of improving conventional medical imaging techniques. For example, paramagnetic particles (*e.g.,* iron oxide, gadolinium) can be used in magnetic resonance imaging because of their high magnetic susceptibility. In ultrasound, micron-size gas spheres of high compressibility coated by a thin shell, commonly referred to as microbubbles, are used. Microbubbles (1–10 μm in diameter) are similar in size to red blood cells (6–8 μm) and, therefore, do not diffuse through the walls of blood vessels, making them true intravascular agents. When microbubbles are injected, blood echoes become brighter on a B-mode image as a result of the coupling of the radial motion of the microbubble wall with the surrounding liquid, considerably increasing the backscattered signal. Microbubbles behave as non-linear scatterers, even when driven at low acoustic pressures, and emit signals at integer (harmonic) and fractional (sub-harmonic, ultra-harmonic) multiples of the insonation frequency. Another consequence of their high compressibility has been suggested by Fairbank and Scully (1977), who noted that the scattering properties of unshelled microbubbles are also affected by static fluid pressure and, therefore, could provide a direct way to measure local blood pressure deep within the body using ultrasound. Fairbank and Scully (1977) reported that increasing the static pressure effectively compresses the microbubble, which shifts the resonance frequency of microbubbles upward. Notably, a small shift in the resonance frequency of unshelled microbubbles was observed for 30- to 40-μm diameter microbubbles and hydrostatic pressure changes of about 0.2 atm. Ishihara et al. (1988) validated this later in a similar experiment.

Non-invasive measurement of the gauge pressure within the body would have many clinical applications. It would be especially groundbreaking in the case of early diagnosis of portal vein hypertension. Portal vein hypertension is a common complication of liver cirrhosis, in which the vascular resistance of the portal-hepatic bed is drastically increased because of fibrosis. This causes an increase in pressure within the portal vein from 5–10 mmHg in healthy individuals to >12 mmHg. The pressure in the portal vein cannot be measured with usual sphygmomanometry techniques. Although it is possible in theory to catheterize through the jugular vein and inferior vena cava and then puncture through the liver to

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access the portal circulation to measure local blood pressure with a manometer, such a procedure is extremely invasive and places the patient at high risk. A non-invasive way to measure blood pressure (*i.e.,* gauge pressure) with a pressure resolution of ~10 mmHg within non-limb vessels would have important value in the diagnosis of portal vein hypertension. Unfortunately, the resonance frequency shift of unshelled microbubbles for 10 mmHg is on the order of 1 kHz, which is too small for clinical application to portal vein hypertension diagnosis, even considering the resolution improvement achieved with a dual-frequency system (Leighton et al. 1997; Newhouse and Shankar 1984; Shankar et al. 1986).

Recent literature suggests that some microbubble coatings can strongly affect the response to blood pressure. Shi et al. (1999), Forsberg et al. (2005), Andersen and Jensen (2010a, 2010b) and Li et al. (2012) recently observed that sub-harmonic emissions (*i.e.,* the echo scattered at half of the insonification frequency) of phospholipid microbubbles are dependent on blood pressure. In particular, Frinking et al. (2009, 2010) found experimentally that phospholipid microbubbles increase their sub-harmonic power considerably when the ambient over-pressure forces the bubble to enter a surface tension-free state (*e.g.,* buckling). On the basis of these results, it has been suggested that the amplitude of the sub-harmonic mode might be a useful indicator of the local relative blood pressure. Yet the gauge pressure, and not the relative pressure, is needed to diagnose portal vein hypertension. It has been reported by Marmottant et al. (2005) that buckling dynamics also strongly affect the compressibility of phospholipid microbubbles, making the resonance frequencies of these bubbles more sensitive than those of microbubbles with simple shell models, such as a viscoelastic shell.

In this study, we found that the resolution of the Fairbank and Scully (1977) method for measuring gauge blood pressure, in the light of an understanding of the effects of buckling phospholipid shells, can considerably be improved such that the required 10 mmHg resolution for portal vein hypertension diagnosis can be reached. Two different models were compared to illustrate the effect of shell elasticity on bubble sensitivity to ambient pressure: a viscoelastic surface tension model (de Jong et al. 1994) and a buckling surface tension model (Marmottant et al. 2005), which apply to a protein shell and a phospholipid shell, respectively. A summary of uncoated and shelled microbubbles, the linearized properties of microbubbles and the full numerical solutions of the Marmottant equation for the parameters of interest is presented. These simulations predict a significant improvement in the sensitivity of phospholipid microbubbles to blood pressure, which is investigated *in vitro* for Optison (a commercial protein-shelled microbubble) and for generic phospholipid microbubbles. We also found that inhomogeneity of physical properties (size, elasticity, surface tension at rest) can affect the reproducibility of blood pressure measurements by introducing a systematic bias in estimation of the resonance frequency. The extent of homogeneity in the microbubble radius distribution required to minimize statistical variability was investigated through simulations. Relevant technologies for the production of microbubbles that satisfy these requirements are discussed.

THEORY

Rayleigh-Plesset equation and shell models

The phenomenon of stable cavitation of a vapor-filled bubble was initially explained by Rayleigh (1917) and Plesset (1949), as the result of the application of Newton's third law to a spherical interface. This initial form of the Rayleigh-Plesset equation neglected the effects of viscosity and the compressibility of the surrounding medium, which were later introduced by Keller and Miksis (1980). Whereas the Rayleigh-Plesset equation explains the response of free gas bubbles (Plesset 1949; Rayleigh 1917), many models compete to describe the behavior of shelled microbubbles. Notably, the models of de Jong et al. (1994), Church (1995), Hoff et al. (2000), Khismatullin and Nadim (2002), Chatterjee and Sarkar (2003), Allen and Rashid (2004), Sarkar et al. (2005), Marmottant et al. (2005), Doinikov and Dayton (2007), Stride (2008) and Tsiglifis and Pelekasis (2008) use different assumptions and different levels of complexity to represent the effect of the shell on microbubble oscillations. De Jong et al. (1994) proposed the addition of two *ad hoc* terms to the Rayleigh-Plesset equation to compensate for shell friction, κ_s, and elasticity, χ_0, such that the equation becomes

$$\rho_l\left(R\ddot{R}+\tfrac{3}{2}\dot{R}^2\right)=\left(p_o+\tfrac{2\sigma(R_o)}{R}\right)\left(\tfrac{R_o}{R}\right)^{3\kappa}\left(1-\tfrac{3\kappa}{c}\dot{R}\right) -\tfrac{2\sigma(R_o)}{R}+2\chi_o\left(\tfrac{1}{R_o}-\tfrac{1}{R}\right) -\tfrac{4\mu_l\dot{R}}{R}-\tfrac{4\kappa_s\dot{R}}{R^2}-P_o-P(t) \quad (1)$$

where $R(t)$ is the instantaneous microbubble radius, R_0 is the equilibrium radius, κ is the polytropic constant, ρ_l is the liquid density, μ_l is the liquid viscosity, P_0 is the static fluid pressure, $\sigma(R)$ is the bubble-liquid interface surface tension and $P(t)$ is any other applied pressure field (*e.g.,* ultrasound). This model describes many fundamental properties of shelled microbubbles, such as an increase in resonance frequency and damping, and it is accurate for simpler shells such as protein. However, because the shell properties used are analogues of Hooke's law and Newton's viscous law (Doinikov and Bouakaz 2011), it