MRI manometry using gas filled microbubbles exhibiting high membrane to gas synergy: towards clinical relevance

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Introduction: It has been shown that compressible microbubbles containing a gas and coated with a lipid membrane can be used to measure pressure using MRI[1]. Whilst the inclusion of paramagnetic agents in the membrane of the microbubble promises enhanced sensitivity of the technique in the future[2], the fragile nature of the membrane and the propensity of the gas to dissolve in the surrounding medium renders this technique unsuitable for *in vivo* clinical measurements of blood pressure. Recent developments have shown promise in the use of perfluorocarbon (PFC) gas bubbles coated with a perfluoroalkylated (PFA) lipid membrane as a more stable agent[3]. Preparations using PFC gas and standard phospholipid membranes are already available as agents for ultrasound imaging and are currently undergoing clinical trials for treatment of vascular thrombosis[4]. In this study, microbubbles produced with a single phospholipid membrane[5] and a single PFA membrane[3] are tested and compared.

Background: Owing to the fact that the microbubbles are gas filled and therefore present a different magnetic susceptibility to the surrounding medium, a system of micro-gradients is established surrounding each microbubble. As the protons in the surrounding medium undergo self diffusion, they sample various field strengths dependent on their location relative to the microbubble. The extent to which these field perturbations radiate from the surface of the microbubble is dependent on its size: Smaller microbubbles yield perturbations which do not extend as far as those for larger microbubbles. A change in the pressure of the system will result in a change in the size of the microbubble and therefore the extent of the perturbations. As the protons sample different fields, dephasing occurs more rapidly thus yielding T_2^* image contrast.

Materials: Two preparations are tested to demonstrate the improvement facilitated by the PFC gas and lipid components: air filled capsules with a monolayer of distearoyl phosphatidylcholine (DSPC); and PFC filled capsules with a monolayer of perfluoroalkylated glycerophosphatidylcholine. Both preparations are immobilised in a viscous gel[6] to allow for evaluation of their performance without the need to compensate for artefacts caused by bubble migration. For both samples a microbubble size distribution centred on 3µm is used. In order to prevent microbubble migration, it is desirable to increase the viscosity of the liquid phase. In order for the susceptibility contrast mechanism of the microbubbles to remain effective, the diffusion coefficient must remain near that of bulk water whilst the viscosity is increased. We showed[6] that using a concentration of 2% w/v of Gellan gum with distilled water, a vast increase in viscosity is produced whilst maintaining a proton diffusion coefficient within 90% of that of bulk water[6].

Experimental conditions: To be clinically relevant, the microbubbles must be able to withstand an environment similar to that found within the body. For the purposes of this study, the microbubble must remain stable at pressures up to 960mmHg at a temperature of 37°C representing typical maximum values found in the human body. To monitor the stability of our preparations under these conditions, the external pressure is varied (from 760mmHg to 960mmHg and back to 760mmHg) three times in succession whilst the NMR signal intensity is recorded. This is performed in a bulk fluid cell whilst imaging is performed using a Bruker Biospec 2.35T scanner with a standard multi slice RARE sequence[7]. The image area over the sample is averaged and compared to the pressure measured using piezoelectric pressure sensors for the three cycles to and from 960mmHg, shown in Fig 1.d.

Preliminary results and conclusions:

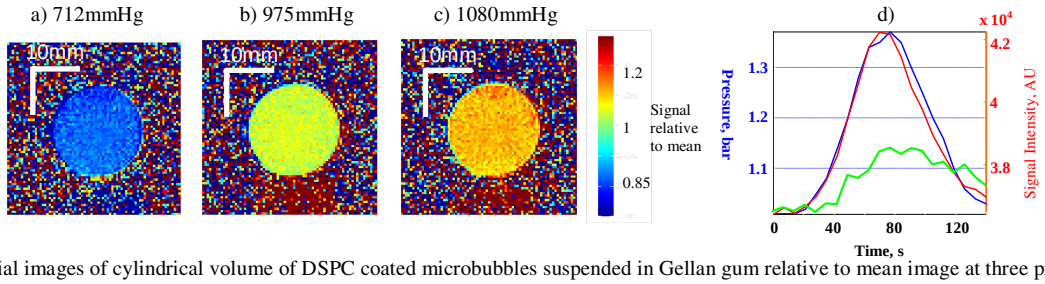

Fig.1 a), b), c) Axial images of cylindrical volume of DSPC coated microbubbles suspended in Gellan gum relative to mean image at three pressures and d) correlation between pressure and signal intensity for microbubbles before and after pressure induced damage (red and green respectively)

The images demonstrate the change in signal intensity due to a change in external pressure and an excellent correlation between signal intensity and applied external pressure with no measurable microbubble migration for at least one hour, whilst maintaining a high sensitivity (~20% SI change per bar). The current method of using DSPC coated microbubbles will not allow imaging of the pressure *in vivo* as they suffer a strong hysteresis above 850mmHg (see Fig. 1d), and it now remains to be seen whether the PFC microbubbles will allow such a contrast agent to remain stable in the blood stream for a sufficient time to make *in vivo* pressure measurements.

References: [1] Alexander A.L. et al., (1996), Mag. Res. Med., **35** 801-806. [2] Dharmakumar R, (2005), Phys. Med. Biol. **50:** 4745-4762; [3] Gerber F. et al, (2006), New J. Chem., **30**: 524-527; [4] Unger, E.C. et al, (2004), Adv Drug Deliv Rev **56**: 1291-1314 [5] Morris R.H. et al, (2007), Mag Res Im, **25** (4):509-512; [6] Morris R.H. et al, (2007) J. Mag. Res. In preparation. [7] Hennig, J. et al., (1986), Mag. Res. Med. **3**(6) 823-833