QUANTIFICATION OF MRI SENSITIVITY FOR MONODISPERSE MICROBUBBLE-BASED CONTRAST AGENT TO MEASURE FLUID PRESSURE CHANGES.

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Mono-disperse microbubbles are known to be used as contrast agents, particularly within ultrasound imaging[1]. The in-vivo direct measurement of fluid pressure is not possible with MRI unless contrast agents are used. There are no such contrast agents presently commercially available. Those demonstrated in the past do not provide high enough MR sensitivity to allow *in-vivo* measurement of pressure changes.

In this study we present the first quantitative study of the MR sensitivity to the presence of monodisperse microbubble populations with varying mean radius. To achieve this, monodisperse microbubbles were prepared[2] with a mean radius of 1.2 ± 0.8 µm. Contrast agents with increasing volume fraction of bubbles were made and the contribution the bubbles bring to the relaxation rate was quantitated as a function of echo time (see figure 1). This was further benchmarked against the prediction of an improved numerical simulation[2].

We found that bubble relaxation rate, R_2^{bub} increases with T_E (see figure 1), and is remarkably well described by a phenomenological equation in the form of bi-exponential recovery,

$$R_2^{bub}(TE) = {}^1R_2^{max}\left(1-\exp\left(-\frac{TE}{TE_1^{eff}}\right)\right) + {}^2R_2^{max}\left(1-\exp\left(-\frac{TE}{TE_2^{eff}}\right)\right).$$

The exponential recovery curves are characterised by the value of the asymptotic relaxation achieved through extremely long echo times, and the value of the time constant of echo time that dictates the curvature of the data. Our numerical simulations (see figure 2A) show good qualitative agreement with our results, and demonstrates higher bubbles radius for lower effective curvature (see figure 2B).

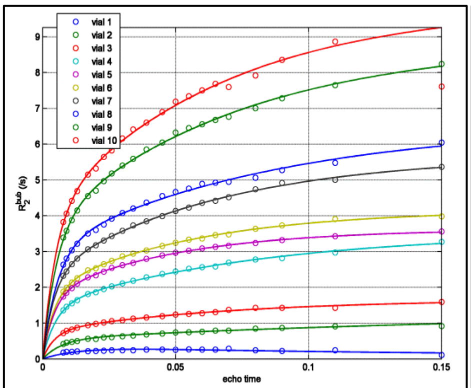

Fig.1 Microbubbles relaxation rate (R_2) as a function of echo time, measured on a Bruker BIOSPEC 2.35 T, for increasing values of bubble density from vial 1 (0.4 % gas volume fraction) to vial 10 (4% gas volume fraction).

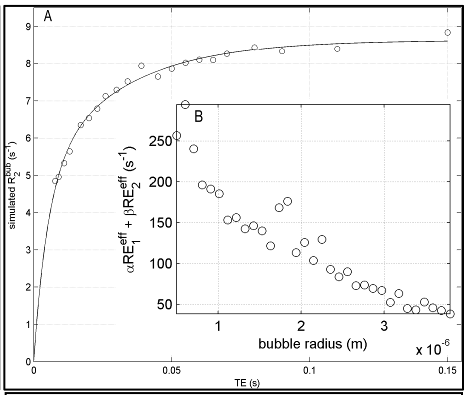

Fig.2 (A) Bubble contribution to the relaxation rate as a function of echo time, from numerical simulation. (B) (Insert) effective curvature of the data shown in (A) as a function of bubble radius.

In a separate experiment, a periodic pressure change was continuously applied to the microbubbles contrast agent, until the change in MR signal was only due to bubble radius change. An excellent MR sensitivity of 23 % bar^{-1} has been found for pressure changes (see figure 3).

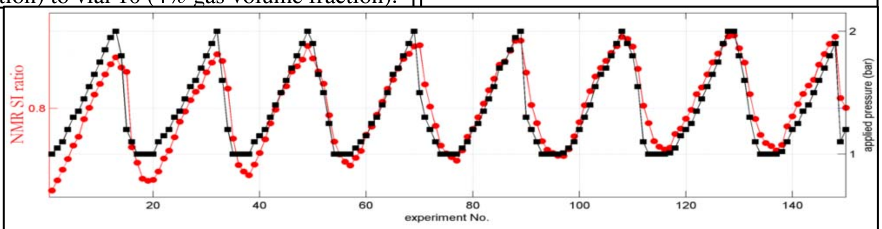

Fig.3 Time course of the measured pressure (black) and MR signal intensity ratio in the contrast agent and in the control (bubble-free) gel (red) over 150 experiments (18 minutes).

We hope the development and the use of mono-disperse bubbles based contrast agents will prove to be a useful technique in the future for medical diagnostic procedures.

References.

[1] A.L.Klibanov,"Microbubble contrast agents - targeted ultrasound imaging and ultrasound-assisted drug delivery applications", Investigative Radiology, vol. 41, no. 3, pp. 354–362, 2006.

[2] Martin Bencsik, et al., Quantitation of MRI sensitivity to quasi-monodisperse microbubble contrast agents for spatially resolved manometry, submitted to Magnetic Resonance in Medicine, accepted, Nov. 2012.