

Preliminary Study on Microscale Tissue Characterization with *in situ* Inducible Microbubbles

局所生成気泡によるマイクロ組織性状イメージングに関する基礎検討

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1. Introduction

Ultrasound scanners can visualize a variety of human-body functionalities by means of dopplar imaging and tissue-strain imaging, for example. The emergence of contrast agents has even broadened their application possibilities to molecular imaging and early-stage tumor detection.

While conventional methods provide excellent macro-scale information such as the presence of a tumor, they are yet to provide details such as the malignance of a tumor. Our aim is to characterize tumors in further detail by using in-situ ultrasound inducible microbubbles generated from a novel contrast agent called “phase-change nano droplets” (PCNDs). A PCND is a submicron-sized perfluorocarbon liquid droplet whose liquid phase can be instantly changed into a gaseous phase upon application of an ultrasound pulse [1]. This unique contrast agent possesses tumor-tissue accessibility via the enhanced permeation and retention (EPR) effect [2] because of its small (200 to 400 nm) particle size. Once it reaches the targeted site and the ultrasound pulse is applied, it exhibits excellent ecogenisity comparable to that of conventional microbubble contrast agent. Previous studies demonstrate the effectiveness of PCNDs in targeted therapeutic and imaging applications in vivo [3] [4]. Combining tissue accessibility and good acoustic scattering, PCNDs are an excellent candidate for imaging micro-scale tissue characteristics.

Figure 1 is a schematic image of functional imaging using PCNDs. As the PCNDs distribute through blood circulation, they permeate into tumor tissues through porous neovasculature and gradually accumulate in the tumor tissue (step 1). Upon application of an ultrasound pulse, those accumulated PCNDs instantly turn into microbubbles (step 2). This rapid expansion results in an impulsive volumetric change in the localized tissue region (i.e., focal volume), which responds in accordance with tissue characteristics

such as visco-elastic properties (step 3). The resulting pulse echo signal therefore contains information on the surrounding tissue (step 4), which can then be superimposed onto a conventional B-mode image. When realized, this process is applicable to deeply seated tumors such as liver cancers as well as superficial sites such as breast and prostate cancer.

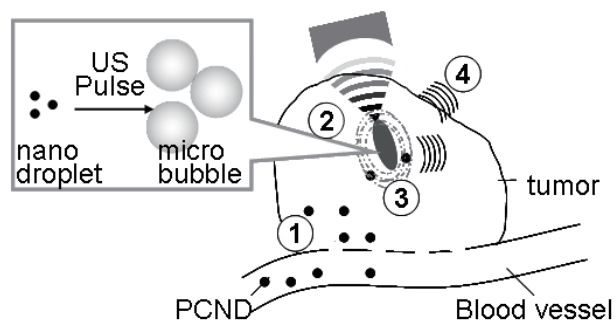


Fig. 1: Schematic image of functional imaging using PCND

In this study, the capability of imaging micro-scale tissue characteristics by using PCND suspended in various concentrations of polyacrylamide(pAA) gel phantom is presented. In addition, difference in phase change behavior is closely observed in accordance with pAA concentration of gels.

2. Methods

A PCND dispersion was prepared with perfluorocarbon (PFC) mixture and emulsifier at various PFC-to-emulsifier ratio, and it was emulsified at 20 MPa. A laser-diffraction particle size analyzer is used for particle characterization. The PCND dispersion was suspended in pAA gel phantom at pAA concentration from 5 to 20%, which was placed in a water bath at 37°C for ultrasound application at frequency of 3.3 MHz, pulse average intensity of 1.2 kW/cm², and a total of 10 cycles. Bubble generation was monitored using a conventional linear probe on a B-mode image at 9 MHz. Focused hydrophone was used to gather acoustic response, which was then analyzed offline.

3. Results and Discussion

Change in pAA concentration results in phantom gels with different properties such as porosity and elasticity. Figure 2 shows a typical acoustic response obtained from phase change. The gray solid line represents the response from 15%-pAA gel to which a low pass filter was applied for further analysis. The resulting waveform is shown as a black solid line. The ultrasound pulse applied is shown at the timing of application to focus. The dashed gray line represents response from 5%-pAA gel. Acoustic responses in the 5%-pAA-gel and 20%-pAA-gel cases differ significantly.

At t_0 , droplets in the focal volume turns into microbubbles, resulting in impulsive volumetric change (ΔV) in the focal volume (illustrated in Fig. 2). This expansion creates instant “push” to the gel (P_{ex}) and results in a peak in positive pressure in the waveform. After the push, a pressure depression follows as ΔV creates a local pressure depression, which then propagates through the gel. The time that the gel experiences the negative pressure as a response to the impulse is represented by t_{res} . Next, the difference between t_{res} values and that between amplitudes of peaks 1 and 2 were evaluated.

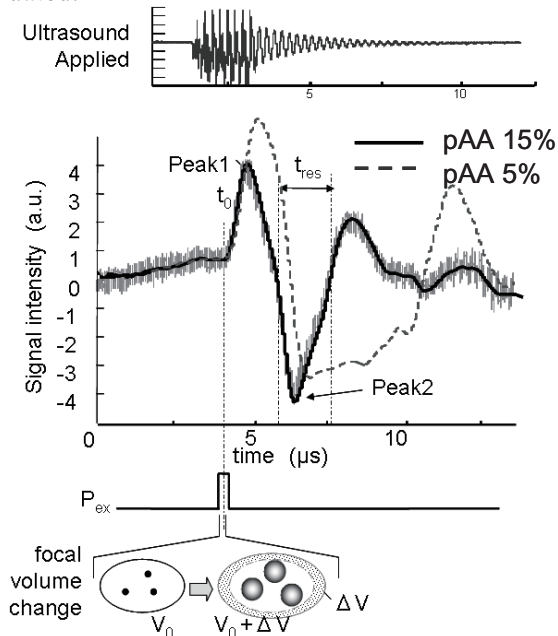


Fig. 2 Typical acoustic signal obtained

To compare each gel’s response to the impulse, frequency of responding motion to impulse (f_{res}) was derived from t_{res} and is plotted against their Young’s moduli in Fig. 3. Error bars represent standard deviation of four measurements. Overall positive correlation is observed in a range between Young’s modulus of 10 to 50 kPa. This is an

indication that f_{res} can be a variable indication of tissue characteristics. Under the assumption that the gel’s motion is predominantly determined by its elasticity, the correlation from Fig. 3 suggest that f_{res} is a valid indication of elasticity. Meanwhile, a weak correlation between f_{res} and Young’s modulus is observed below 10 kPa.

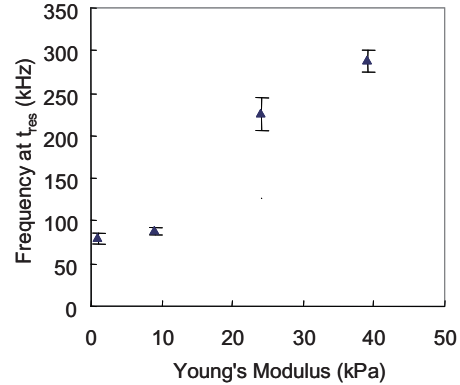


Fig.3 f_{res} of different gel phantoms (plotted against each gel’s estimated Young’s modulus)

The excellent correlation of f_{res} with Young’s modulus in the range of 10 to 39 kPa implies the possibility for PCND-mediated elasticity imaging. While impulse amplitude of peak 1 correlates well with gel’s Young’s modulus, it is important to note that change in pAA concentration could affect more than gels’ elasticity, especially change in viscosity. The impact of viscosity to impulse amplitude cannot be neglected as viscosity plays an important role in phase-change induction. Since f_{res} is independent of viscosity, given free oscillation at t_{res} , f_{res} is a valid measure of elasticity.

The limitation of PCND method is the weak correlation of Young’s modulus below 10 kPa. Moreover, the difference in impulse amplitude suggests that change in pAA concentration affects the magnitude of phase-change induction. To verify that f_{res} is solely dependent on elasticity, phase-change magnitude must be normalized.

Acknowledgement

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Reference

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