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Using Microbubble as Contrast Agent for High-Energy X-ray In-line Phase Contrast Imaging: Demonstration and Comparison Study

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Abstract

The ability of microbubbles to benefit the imaging quality of high-energy in-line phase contrast as compared with conventional low-energy contact mode radiography was investigated. The study was conducted by comparing in-line phase contrast imaging with conventional contact-mode projection imaging under the same dose delivered to a phantom. A custom designed phantom was employed to simulate a segment of human blood vessel injected with microbubble suspensions. The microbubbles were suspended in deionized water to obtain different volume concentrations. The area contrast-to-noise ratio (CNR) values corresponding to both imaging methods were measured for different microbubble volume concentrations. The phase contrast images were processed by phase-attenuation duality phase retrieval to preserve the imaging quality. Comparison of the resultant CNR values indicates that the microbubble suspension images deliver a higher CNR than the water-only image, with monotonically increasing trends between the CNR values

and microbubble concentrations. Compared to low-energy conventional images of the microbubble suspensions, high-energy in-line phase contrast CNRs are lower at high concentrations and are comparable, even better than, at low concentrations. This result suggests that 1) the performance of copolymer-shell microbubble employed in this study as x-ray contrast agent is constrained by the detective quantum efficiency (DQE) of the system and the attenuation properties of the shell materials, 2) the PAD phase retrieval method has the potential to preserve image quality for areas with low concentration of microbubbles, and 3) the selection of microbubble products as a phase contrast agent may follow criteria of minimizing the impact of absorption attenuation properties of the shells and maximizing the difference factor of electron densities.

Index Terms

High-energy in-line phase contrast; microbubble; radiation dose; contrast agent

I. Introduction

Breast cancer is one of the most common cancers diagnosed in adults. According to estimates by the American Cancer Society for the year 2017, 255,180 new breast cancer cases will be diagnosed, and 41,070 deaths will result from breast cancer. [1] Early diagnosis and treatment of breast cancer is essential for improving the survival of patients.

X-ray mammography, a 2-D projection imaging technique, has been widely-used as a method for breast cancer screening, but the imaging contrast of the current mammography technique relies on the small attenuation differences between normal tissues and tumors. Efforts to improve contrast between breast parenchyma and cancers in x-ray mammography and digital breast tomosynthesis include techniques such as contrast enhanced mammography (e.g. employing iodinated contrast agents) and dual energy mammography.

When x-rays pass through an object, they also undergo phase shifts. The changes of the x-ray wave field can be expressed by the complex x-ray transmittance:

$$T(x, y) = A(x, y)e^{-i\phi(x, y)} \quad (1)$$

where $A(x, y) = e^{-\int \frac{\mu(x, y, z)}{2} dz}$ and $\phi(x, y) = -\frac{2\pi}{\lambda} \int \delta(x, y, z) dz$, in which $A(x, y)$ is amplitude, $\phi(x, y)$ is phase shift, μ denotes the attenuation coefficient and δ denotes refractive index decrement. [2] Several x-ray imaging techniques based on phase contrast have been investigated. [3–5] In-line phase contrast x-ray imaging is one of these methods. The clinical feasibility of 2-D phase contrast mammography based on the in-line principle has been widely reported, and its potential to improve signal-to-noise ratio (SNR) and reduce exposure time as well as radiation dose have been demonstrated in phantom studies. [6]

In order to further improve the imaging quality and maximize the benefits of the phase contrast mechanism, concepts of tissue engineering were proposed to introduce the application of microbubbles into phase contrast related imaging techniques. Microbubbles

have been widely used as an ultrasonic contrast agent. Based on the morphology of microbubbles, they can be also considered as a population of lens scattering x-ray photons providing a sequence of multi-refraction. Considering the interaction between high-energy x-ray photons and matter, Compton scattering dominates when the microbubbles are made of materials with low atomic numbers, $Z < 10$. The phase shifts due to the Compton scatterings among different types of scattering sources/structures are characterized by the refractive index decrement, δ , which can be described by:

$$\delta = \frac{\lambda^2 r_e}{2\pi} \cdot N_A \cdot \rho \cdot \sum_i \frac{w_i \cdot Z_i}{A_i}, \quad (2)$$

where λ is wavelength, $r_e = 2.8179402894 \times 10^{-15}$ m is the classical electron radius, N_A is Avogadro's number ($\approx 6.022 \times 10^{23} \text{ mol}^{-1}$), ρ is mass density, w_i is the weight fraction of the i -th element, Z_i denotes its atomic number, A_i is the atomic mass ([g/mole]), and $N_A \cdot \rho \cdot \sum_i \frac{w_i \cdot Z_i}{A_i}$ denotes the number of electrons per unit volume for compounds and

mixtures. [7, 8] Therefore, based on the unique mass density and atomic mass provided by the components of microbubbles, distributions of microbubbles have the potential to modify the local interaction between x-ray photons and the sample and, thus, introduce additional phase shifts by changing the regional average electron density within a finite space. The resulting phase contrast information can be combined with the intrinsic attenuation contrast information to improve image quality by employing phase retrieval techniques.

Microbubbles as an x-ray phase contrast imaging contrast agent have been reported in the literature using analyzer-based [9] and propagation-based synchrotron x-ray phase contrast methods [10–12] and the Talbot-Lau interferometry phase contrast method. [13, 14] 3D computed tomography imaging of microbubbles was also demonstrated by Tang *et al.* in 2013 with a differential phase contrast system accompanied by object rotation. [15] A recent study done by Millard, *et al.* indicated that microbubble contrast agents provide the potential to perform dynamic imaging with analyzer-based synchrotron x-ray phase contrast. [16] However, in those previous studies, the radiation dose delivered to tissues/samples was not controlled., Thus, the significance of microbubbles as phase contrast imaging agents and the impact of the microbubble shell materials on image contrast, were not comprehensively evaluated

In this study, we demonstrate experimentally the use of microbubbles as an x-ray scattering agent for an in-line phase contrast imaging system operated at high tube voltage, 120 kVp, and controlled low-dose conditions. High-energy in-line phase contrast planer imaging technique with phase-attenuation duality (PAD) phase retrieval has been demonstrated to be a powerful, low dose x-ray imaging method. [6] Considering the clinical conditions where the microbubbles may be distributed around the tumor via blood supply and self-targeting mechanisms, the tumor areas with microbubble distributions may have improved image contrast relative to non-microbubble distributed regions due to the differences in attenuation contrast and phase contrast information. Thus, the changes in image contrast can be

estimated by calculating the contrast-to-noise ratio (CNR) when considering the water-only images as the pure backgrounds, e.g. the non-microbubble distributed area. The object used in this study is a microbubble-infilled cylinder cavity with a single dimension of $\Phi 4$ mm internal diameter to simulate the diameter of a blood vessel with comparable dimension of an adult human coronary artery. [16]

II. Methods and materials

A. Experimental Configurations

In this study, a micro focus x-ray source (Model L8121-03, Hamamatsu Photonics) able to generate x-ray photons ranging from 40 kVp to 150 kVp with an adjustable tube current was employed. Nominal focal spot sizes of 7 μm , 20 μm , and 50 μm can be selected and/or determined by the desired output power. High-energy in-line phase contrast images were acquired with 120 kVp tube voltage, 500 μA tube current. The low-energy contact-mode imaging prototype was operated with 40 kVp tube voltage and 500 μA tube current. A prime beam filter made of 2.5 mm Al was utilized to harden the prime beam for both the phase contrast mode and contact mode configurations. [17] Images were acquired with a CCD detector coupled with a CsI:Tl scintillator (66 mm $\times$ 66 mm, ImageStar 9000, Photonic Science Ltd.), providing 21.6 μm of sampling pixel pitch.

Shown in Fig. 1, the test object was placed on a stage with a 68.58 cm source-to-object distance (SOD) for both imaging prototypes. For high-energy in-line phase contrast imaging, Fig. 1(a), a source-to-image distance (SID) value of 168.91 cm was selected to deliver optimal phase shift effects according to the principles of in-line phase contrast imaging, as well as to reduce the loss of x-ray photons during propagation through the air gap. [2, 18–20] The low-energy contact-mode imaging experiments were conducted with 76.20 cm SID as shown in Fig. 1(b). No anti-scattering grid was used for either configuration based on the following technical tradeoffs: (1) for low-energy contact mode imaging, small objects generate only a small amount of scattering; (2) introducing an anti-scattering grid may minimally enhance image contrast and resolution, at the expense of a greater radiation dose to the object; [21] (3) scattering signals from the surrounding structure of the phantom can be minimized using flat fielding image processing; (4) although the back-and-forth movements of the grid can reduce the blocking effects, the error resulting from the flat fielding operations still cannot be avoided; and, (5) the relatively long air gap between the object and the detector provides scatter rejection for high-energy in-line phase contrast mode imaging. [20–24] All measurements were conducted with 2.590 mGy average glandular dose calculated based on a 50/50 breast tissue composition. This dose level was also used to determine the exposure time for each imaging mode. The resultant high-energy in-line phase contrast images were processed by the PAD retrieval method. [2, 6, 18–20]

Since the two imaging methods in this study utilized different x-ray tube voltages, the energy compositions of x-ray photons and detective quantum efficiencies (DQE) were quantitatively measured using the methods detailed in Ref. [17] and shown in Fig. 2. The measured $DQE(0)$ of the low-energy conventional projection method and the high-energy in-line phase contrast are 0.743 and 0.340, respectively.

B. Phantom Design

In this study, the phantom was constructed with a $\Phi 4.0$ mm diameter hole drilled along the central line of an acrylic rod to mimic the vessel structure where the microbubble suspensions with different concentrations were injected (Fig. 3). [16, 25]

The microbubbles employed in this study were copolymer-shell microspheres (Expancel 461 DU 20 by AkzoNobel, Sweden) infilled with isobutene (C_4H_{10}) gas. The copolymer shell was made of $(C_5H_8O_2 \cdot C_3H_3N \cdot C_2H_2Cl_2)_n$ (poly acrylonitrile-co-vinylidene chloride-co-methyl, CAS No.: 25214-39-5). The diameter of the microbubbles ranges from 6 μm to 9 μm . Before administration, 5 cm^3 Expancel microspheres were suspended into 20 mL water at room temperature to obtain an original suspension with 20% volume concentration. Then, the 20% suspension was further dissolved by adding water to acquire different relative concentrations. The volume concentrations administrated in this research were 5.0%, 2.0%, 1.0%, 0.5 %, 0.2 %, 0.1 % and 0 %.

During the image acquisitions the phantom was rotated continuously to maintain an even distribution of microbubbles in the cavity and to prevent precipitation. Thus, the whole area of the microbubble-infilled cavity can be considered a uniform object.

C. Determination of Exposure Time

In this study, because the average glandular dose was a fixed value for both high-energy in-line phase contrast imaging mode and low-energy contact mode, the object entrance exposure, X_{ESE} , is determined as follows:

$$X_{ESE} = \frac{D_g}{D_{gN}} \quad (3)$$

where the average glandular dose, D_g was selected as 2.590 mGy and the normalized average glandular dose coefficient, D_{gN} , was determined by experimentally measuring the x-ray output spectrum and applying computer simulation methods. [6, 26–29] The normalized x-ray output spectra for both imaging modes are shown in Fig. 4. The exposure time, T , of each mode was determined from the object entrance exposure and the entrance exposure rate, R_X ,

$$T = \frac{X_{ESE}}{R_X} \quad (4)$$

The resultant exposure time for each mode is shown in Table I, corresponding to exposures of 40 kVp and 120 kVp tube voltages, respectively.

D. Contrast-to-noise Ratio Calculation

Regions of interest (ROIs), as defined in Fig. 5, were 581×111 and 1481×281 pixels for low-energy contact mode and high-energy in-line phase contrast mode, respectively. The relative

contrast-to-noise ratios (CNR) of the microbubble-injected area were calculated from the signal intensities and the background, employing the following formula: [13]

$$\text{CNR} = \frac{|I - I_B|}{\sigma_B}, \quad (5)$$

where I represents the intensity, averaged pixel values, of the area filled with microbubble suspensions, I_B represents the intensity, average pixel value, of the pure water image, and σ_B is defined as the noise, the standard deviation of the pure background. [13] Statistically, according to the definition of ROIs, the standard errors for the measurements of imaging intensities were estimated using $\frac{\sigma}{\sqrt{N}}$, where N represents the number of pixels included in the ROIs. In addition, since the CNRs of the microbubble-infilled area were similarly determined by the differences between the imaging intensities of the microbubble-infilled area and the intensity of the water-only background, the percentage uncertainties of CNRs were estimated using the following:

$$\text{Uncertainty}(\%) = \frac{\sqrt{\frac{\sigma_S^2 + \sigma_B^2}{2}}}{I - I_B} \cdot 100\%, \quad (6)$$

where σ_S is the standard deviation of the area filled with microbubble suspensions.

III. Results

The images of the microbubble suspension injected areas plus water-only areas acquired by low-energy conventional projections and PAD retrieved high-energy in-line phase contrast projections are shown in Fig. 6. The measured area intensities, noise levels, and calculated CNRs corresponding to each microbubble concentration for each imaging method are listed in Table II and Table III.

The images acquired using both imaging methods demonstrated observable gradual intensity changes from low microbubble concentration to high concentration. The PAD retrieved high-energy in-line phase contrast images provided in Fig. 6(b) displayed visible contrast between the water-only (0.0%) image and the microbubble suspension images.

By calculating the signal intensities for the images and considering the water-only images as the backgrounds for each imaging method, the contrast-to-noise ratios of the microbubble images were determined and plotted as a function of microbubble volume concentration in Fig. 7. The curves illustrate that the microbubble distribution provides the ability to improve the area CNR. In addition, the overall CNRs of microbubble concentrations imaged by the low-energy conventional projections are better than those acquired by PAD retrieved high-energy in-line phase contrast. However, at low microbubble concentrations of 0.1%, 0.2% and 0.5%, the CNR curves of both imaging methods are very close to each other. Finally, the

CNR values of both imaging methods exhibit an increasing trend as the microbubble suspensions become denser.

IV. Discussion

The resultant curves (Fig. 7) indicate that the CNRs of the images acquired in conventional low-energy mode are up to 1.34 times that of the high-energy in-line phase contrast images. This may be mainly due to the system properties. As detailed in Section II, the $DQE(0)$ for low-energy contact mode was 2.2 times higher than that of high-energy in-line phase contrast mode. Thus, for approximately the same entrance exposure level, the difference between the signal intensity and the background was higher for the conventional contact mode than the phase contrast mode by a factor of 2.2.

In addition, the mass densities of the copolymer material, gas infill material and water are 1.6 g/cm^3 , $2.51 \times 10^{-3} \text{ g/cm}^3$ and 1.00 g/cm^3 , respectively. When estimating the absorption attenuation coefficients (μ) by multiplying mass densities (ρ) with mass attenuation coefficients (μ/ρ), the absorption attenuation coefficient curves as functions of x-ray energy are presented in Fig. 8. Considering the copolymer shell and the gas infill together, the volume ratio of these two components was 4:1, thus, the overall absorption attenuation of the microbubble would be dominated by the copolymer shell and significantly greater than water when x-ray photon energy ranges from 5 keV to 120 keV. This means the regional absorption attenuation coefficients of microbubble suspensions would increase as the population of microbubble per volume increases until becoming saturated. For low-energy, (5 to 40 keV), the difference between attenuation coefficients of water and microbubble concentrations was more significant than at high-energy (40 to 120 keV). Thus, based on the same radiation dose delivery and similar entrance exposure level, the high-energy photons employed in high-energy in-line mode provided less contribution to the imaging contrast than in low-energy contact mode. Therefore, combining the effects of absorption attenuation coefficients impacts with system DQEs on the signal intensities of microbubble suspensions, the behavior of CNR-concentration curves can be explained. The imaging contrasts of high-concentration microbubble suspensions ($>0.5\%$) were dominated by the attenuation contrast and constrained by the intrinsic characteristics of the corresponding systems.

For the low-concentration zone, 0.1 to 0.5%, the effects of microbubble concentration changes on attenuation coefficient changes are not significant, since the population per volume of the microbubble is very low. Thus, the impact of the high attenuation result from the copolymer becomes less significant than in high concentration distributions. Considering the microbubble was made of copolymer shell ($\sum_i \frac{w_i \cdot Z_i}{A_i} = 0.29 \text{ mol/g}$ and $\rho = 1.6 \text{ g/cm}^3$) and isobutene gas infill ($\sum_i \frac{w_i \cdot Z_i}{A_i} = 0.65 \text{ mol/g}$ and $\rho = 2.51 \times 10^{-3} \text{ g/cm}^3$), the estimated average electron density of the microbubble can be different from water ($\sum_i \frac{w_i \cdot Z_i}{A_i} = 0.56 \text{ mol/g}$ and $\rho = 1.0 \text{ g/cm}^3$). This factor of difference in electron densities may induce more phase shift for microbubble distributed areas than for the water-only area. As mentioned in Section I,

$\phi(x, y) = -\frac{2\pi}{\lambda} \int \delta(x, y, z) dz$, this rapid change of phase between microbubble distributed and water-only areas may further induce more phase image intensity changes based on the relationship of $I(x, z) = 1 - \frac{\lambda z}{2\pi} \Delta \phi(x)$, [2, 18, 19, 22] where $I(x, z)$ represents the pure phase image intensity and Δ is the Laplacian operator. Thus, by retrieving the phase shifts resulting from the electron density discrepancies, the image quality of the microbubble images acquired by high-energy in-line phase contrast can be preserved even when the microbubble concentration goes as low as 0.1 %, but is still constrained by the quantum efficiency of the imaging system.

As detailed in Ref. 20, the application of the PAD phase retrieval method may also suffer from imperfections due to the composition of the x-ray photon energies. Since the perfect PAD application conditions are achieved experimentally by using heavy filtration to remove x-ray photons with energy under 60 keV, [17, 30] the 2.5 mm Al prime beam filtration used in this study removed most of the x-ray photons under 30 keV and introduced the experimental trade-off condition to approximately satisfy the application condition of the PAD retrieval method.

The results of this study (1) compared the performance of high energy in-line phase and low energy conventional systems for copolymer-shell microbubble contrast imaging at the same radiation dose, (2) demonstrated the feasibility of copolymer-shell microbubble images using a high-energy in-line phase contrast system, (3) indicated that the conventional contact-mode imaging improves the CNR for higher concentration of copolymer-shell microbubbles, while the high-energy in-line phase contrast imaging improves the performance for low-concentration ones, and (4) elucidated why the imaging capability of the high-energy in-line phase contrast system was not as powerful as was expected based on the results shown in previous studies [6, 17]. However, our study is limited because only a single $\phi 4$ mm internal diameter object was used in this phantom study. This limitation may weaken the spatial resolution or spatial dimension imaging results. Therefore, for a future preclinical study testing should be conducted using simulated vessels of smaller diameter or actual vasculature in a biological specimen.

5. Conclusion

In this study, area CNRs were measured from images of a single-dimension blood vessel-simulating phantom using different concentrations of microbubble suspensions for a comparison of high-energy in-line phase contrast with low-energy conventional imaging at the same radiation dose of 2.59 mGy. CNR results indicate the feasibility of using microbubbles as phase contrast imaging agent in high-energy in-line phase contrast imaging techniques to improve image quality.

The comparison of CNR-concentration curves for both imaging methods suggests that the overall CNRs of low-energy conventional mode are higher than that of high-energy in-line phase contrast mode, with the exception of the low microbubble concentration zone where the CNR values of both imaging methods are comparable. As detailed in the discussion section, although the difference factor of electron densities existing between water and

microbubbles is still within the same scale of magnitude, the PAD phase retrieval preserved the imaging contrast of high-energy in-line phase contrast mode, especially at low microbubble concentration. Therefore, when considering microbubbles as a potential clinical x-ray phase contrast agent, optimization of candidate agents should include minimizing the impact of microbubble shell materials and gas infill on absorption attenuation coefficient, and maximizing the difference factor of electron densities among microbubbles, blood and on; however, the absorption attenuation of the copolymer shells also plays an important role in generating image contrast among tissues.

In future studies, the use of microbubbles as a contrast agent for in-line phase contrast imaging will be further investigated by utilizing optimized microbubble products and objects with various dimensions and by imaging with 3D techniques (such as tomosynthesis) to improve imaging quality at a regulated or reduced radiation dose delivery.

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Fig. 1. Configurations of (a) the high-energy in-line phase contrast and (b) the low-energy contact-mode imaging prototypes.

Fig. 2.
DQE curves measured for low-energy conventional projection method and high-energy in-line phase contrast.

Fig. 3.
The schematic of the acrylic phantom with a $\phi 4$ mm diameter and 50 mm long opening inside to simulate a segment of human blood vessel.

Fig. 4. Normalized x-ray source output spectrum obtained under (a) 40 kVp and (b) 120 kVp. A 2.5 mm Al prime beam filter was applied for both tube voltage settings.

Fig. 5.

The region of interest defined to estimate the area signal intensity for each concentration mode of microbubble suspension. The sizes of the ROIs were 581×111 and 1481×281 pixels for low-energy contact mode and high-energy in-line phase contrast mode, respectively.

Fig. 6.

(a) Low-energy conventional projection images and (b) high-energy in-line phase contrast images of the regions infilled with different concentration microbubble suspensions. The dash-line rectangles denote the examples of ROIs selections for calculating the microbubble signal intensities.

Fig. 7. Comparison of CNR to volume concentration curves between low-energy conventional contact-mode method and high-energy in-line phase contrast at the same radiation dose.

Fig. 8.

Attenuation coefficient of water, copolymer and C_4H_{10} gas inflill calculated by multiplying the densities (1000 mg/cm^3 for water, 1600 mg/cm^3 for the copolymer, and 2.51 mg/cm^3 for C_4H_{10} gas) with mass attenuation coefficient data for each compound acquired from NIST database.

TABLE I

ExperimentAL Parameters for Different Tube Voltages

Tube Voltage (μA)	Tube Current (μA)	Focal Spot Size (μm)	Prime Beam Filtration	D _g (mGy)	D _{gS} (mrad/R)	X _{ESE} (mR)	R _X (mR/s)	Exposure Time(s)
40	500	50	2.5 mm Al	2.590	5.88	440.48	2.13	206.80
120		50			5.79	447.32	24.80	18.04

TABLE II

values of the low-energy conventional contact-mode images

Concentration (V/V)	Intensity (<i>I</i>)	σ	Standard Error	CNR	Uncertainty of CNR (%)
5.0%	2529.30	5.45	0.021	8.91	9.79
2.0%	2514.90	5.80	0.023	6.33	14.34
1.0%	2504.33	5.84	0.023	4.44	20.54
0.5%	2493.87	5.63	0.022	2.57	34.67
0.2%	2489.63	5.54	0.022	1.81	48.71
0.1%	2483.20	5.80	0.023	0.66	137.82
0.0%	2479.52 (I_b)	5.59 *	0.022	(0)	-

* Noise level of the water-only image is considered as overall noise.

TABLE III

and CNR values of the high-energy in-line phase contrast images

Concentration (V/V)	Intensity (<i>I</i>)	σ	Standard Error	CNR	Uncertainty of CNR (%)
5.0%	1886.56	4.23	0.0066	6.66	15.02
2.0%	1881.09	4.16	0.0065	5.37	18.50
1.0%	1876.16	4.15	0.0064	4.20	23.62
0.5%	1871.95	4.11	0.0064	3.20	30.83
0.2%	1868.79	4.22	0.0065	2.45	40.77
0.1%	1864.62	4.26	0.0066	1.46	68.61
0.0%	1858.44 (I_b)	4.22 [*]	0.0065	(0)	-

^{*} Noise level of the water-only image is considered as overall noise.