Quantification of breast arterial calcification using full field digital mammography

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Breast arterial calcification is commonly detected on some mammograms. Previous studies indicate that breast arterial calcification is evidence of general atherosclerotic vascular disease and it may be a useful marker of coronary artery disease. It can potentially be a useful tool for assessment of coronary artery disease in women since mammography is widely used as a screening tool for early detection of breast cancer. However, there are currently no available techniques for quantification of calcium mass using mammography. The purpose of this study was to determine whether it is possible to quantify breast arterial calcium mass using standard digital mammography. An anthropomorphic breast phantom along with a vessel calcification phantom was imaged using a full field digital mammography system. Densitometry was used to quantify calcium mass. A calcium calibration measurement was performed at each phantom thickness and beam energy. The known (K) and measured (M) calcium mass on 5 and 9 cm thickness phantoms were related by $M=0.964K-0.288$ mg ($r=0.997$ and $SEE=0.878$ mg) and $M=1.004K+0.324$ mg ($r=0.994$ and $SEE=1.32$ mg), respectively. The results indicate that accurate calcium mass measurements can be made without correction for scatter glare as long as careful calcium calibration is made for each breast thickness. The results also indicate that composition variations and differences of approximately 1 cm between calibration phantom and breast thickness introduce only minimal error in calcium measurement. The uncertainty in magnification is expected to cause up to 5% and 15% error in calcium mass for 5 and 9 cm breast thicknesses, respectively. In conclusion, a densitometry technique for quantification of breast arterial calcium mass was validated using standard full field digital mammography. The results demonstrated the feasibility and potential utility of the densitometry technique for accurate quantification of breast arterial calcium mass using standard digital mammography. © 2008 American Association of Physicists in Medicine. [DOI: [10.1118/1.2868756](https://doi.org/10.1118/1.2868756)]

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I. INTRODUCTION

Cardiovascular disease is a major cause of death and disability in women. Coronary artery disease is very common in women and it is often not detected before leading to myocardial infarction or sudden death. Mammograms acquired as part of breast cancer screening may help identify women at risk for coronary artery disease. There is increasing evidence that breast arterial calcification, observed on mammograms, can potentially serve as a marker for general vascular disease.¹⁻³ It can potentially be a useful tool for assessment of coronary artery disease in women since mammography is currently in widespread use as a screening tool for early detection of breast cancer. Several studies suggest that breast arterial calcification is associated with cardiovascular disease, diabetes, or hypertension and may be used as a marker for coronary artery disease.^{1,3,4} On the other hand, other large scale studies have reported minimal or no association between breast arterial calcification and cardiovascular risk factors.^{5,6} The association between breast arterial calcification and risk for coronary artery disease is the subject of

current research interest. However, there are no currently available techniques for quantification of calcium mass for breast arterial calcification.

Coronary artery calcification has been quantified using electron beam computed tomography and more recently multidetector computed tomography.⁷ There are also current efforts to develop cone-beam computer tomography (CT) techniques for breast imaging, which could potentially be used to detect and quantify breast arterial calcification.⁸ However, these techniques are not currently available for routine clinical application.

Another technique for quantification of arterial calcium is dual energy imaging. We have previously used dual energy subtraction for quantification of coronary artery calcium mass.⁹⁻¹¹ There have also been previous reports of dual energy mammography for improved detection of breast calcification.^{12,13} Dual energy mammography could also be used for quantification of breast arterial calcium mass. However, dual energy mammography is not currently available for clinical application.

Previous studies on breast arterial calcification have reported only the presence or absence of calcification in a mammogram. The purpose of this study is to determine whether it is possible to quantify breast arterial calcium mass using standard digital mammography. An anthropomorphic breast phantom along with a vessel calcification phantom was imaged using a full field digital mammography system. Densitometry was used to quantify calcium mass. The effects of scatter correction, breast thickness, breast density, anatomic background, and magnification error on calcium mass quantification were investigated.

II. METHODS

II.A. Calcium quantification

The transmission of a monoenergetic x-ray beam through an attenuating object containing soft tissue (T) and calcium (Ca) is given by expression

$$I_p = I_o e^{-(\mu/\rho)_T \delta_T - (\mu/\rho)_{Ca} \delta_{Ca}}, \quad (1)$$

where μ/ρ and δ are the mass attenuation coefficient and the areal density, respectively. In the background area surrounding the calcium, the x-ray intensity is

$$I_p^{BG} = I_o e^{-(\mu/\rho)_T \delta_T}. \quad (2)$$

In absence of scatter, after log transformation and subtraction of the background tissue signal, the log subtracted signal intensity (SI) can be written as

$$SI = \ln \left[\frac{e^{-(\mu/\rho)_T \delta_T}}{e^{-(\mu/\rho)_T \delta_T - (\mu/\rho)_{Ca} \delta_{Ca}}} \right] = [(\mu/\rho)_{Ca}] \delta_{Ca}, \quad (3)$$

which for each pixel is proportional to the amount of calcium mass present. The total signal is found by summing over all pixels in a region and mass is calculated (mg calcium) by multiplication with a conversion factor made from previous measurements of known amounts of calcium mass.

The effects of scatter and glare (SG) on the detected intensity (I_d) can be taken into account by including additional terms

$$I_d = I_p + I_{SG},$$

$$I_d^{BG} = I_p^{BG} + I_{SG}. \quad (4)$$

The SG can be expressed as

$$I_{SG} = R_{SG} I_p^{BG}, \quad (5)$$

where R_{SG} is the spatially varying SG-to-primary ratio. In order to simplify and the fact that the calcium signal is small, I_{SG} is determined from the background primary signal intensity close to the calcification (I_p^{BG}). By combining Eqs. (4) and (5), the total detected intensity at the location of calcium and background can be expressed as

$$I_d = I_p + R_{SG} I_p^{BG},$$

$$I_d^{BG} = (1 + R_{SG}) I_p^{BG}, \quad (6)$$

where it is assumed that SG is unchanged in the presence of calcium since the calcium signal is small. By combining Eqs.

(1), (2), and (6), the log subtracted signal intensity (SI_{SG}) can be written as

$$SI_{SG} = \ln \left[\frac{(1 + R_{SG}) e^{-(\mu/\rho)_T \delta_T}}{e^{-(\mu/\rho)_T \delta_T - (\mu/\rho)_{Ca} \delta_{Ca}} + R_{SG} e^{-(\mu/\rho)_T \delta_T}} \right]. \quad (7)$$

Using the fact that the calcium thickness δ_{Ca} is small, Eq. (7) can be approximated using power series and keeping up to second order terms

$$SI_{SG} \approx \frac{(\mu/\rho)_{Ca} \delta_{Ca}}{1 + R_{SG}} - \frac{R_{SG} (\mu/\rho)_{Ca}^2 \delta_{Ca}^2}{2 \cdot (1 + R_{SG})^2}. \quad (8)$$

It can be seen that the existence of SG introduces nonlinearity to the signal. When the calcium amount δ_{Ca} is small and R_{SG} is low, SI_{SG} is approximately linear with the calcium amount. However, the slope of the linear relation is reduced by a factor of $1/(1+R_{SG})$. This indicates that the calcium measurement can still be accurate without scatter correction, as long as the calibration is done at the same scatter condition.

The use of polychromatic x-ray spectrum introduces energy dependence in μ . Since the amount of calcium is small, Eq. (8) is still valid. However, the polychromatic x-ray spectrum will require the use of effective μ . Due to the dependence of effective μ on breast thickness and composition; it is desirable to perform the calibration with the same breast thickness and density. However, it is not practical to use a phantom that simulates the exact thickness and density for each patient. Therefore, calibration will be done using slabs of standard breast tissue equivalent material. The systematic error introduced by the mismatched thickness and density will be studied in the following sections.

II.B. Image acquisition and processing

All images in this study were acquired using a full-field digital mammography system (Senographe 2000D, GE Medical Systems, Milwaukee, WI), which uses an $aSi:H$ flat panel detector coupled with a CsI(Tl) converter layer with an antiscatter grid. The antiscatter grid consists of 5:1 grid ratio and 31 lines/cm. The images were acquired using the automatic exposure control (AEC) in standard (STD) mode. Depending on the phantom thickness, both Mo/Mo and Rh/Rh x-ray tube target and filter combinations were used. Images were acquired at the Department of Radiology, Kaiser Permanente San Francisco Medical Center and transferred to a workstation for image analysis at University of California, Irvine.

II.C. Calcium phantom development

The fully developed breast arterial calcification has a classic linear or curvilinear, “train track” like appearance that can be easily recognized on a mammogram (see Fig. 1). However, there is no available data on the range and composition of breast arterial calcification. A calcium phantom was constructed using a plastic resin as the base material and calcium hydroxyapatite to simulate arterial calcification.^{14–16} 1.50 g of calcium hydroxyapatite ($CaHA$) ($Ca_5HO_{13}P_3$)

FIG. 1. A lateral mammogram with an arrow showing a linear tubular calcification clearly associated with a blood vessel.

(Sigma-Aldrich, Inc., St. Louis, MO) powder was added into 4.50 g of the plastic resin. The two components were well mixed. Then, 0.54 g of curing agent was added and mixed. The mixture was then placed under low vacuum for approximately 15 min to eliminate air bubbles introduced by mixing. Finally, the mixture was injected into silicon tubing with different internal diameters (0.6–1.89 mm) using a syringe. The silicone tubing was carefully peeled off after 48 h of curing. This process produced plastic rods of different diameters with a known CaHA weight fraction. The dimension and calcium content of the rods were chosen to approximately simulate the observed breast arterial calcification in mammograms.

The weight of the plastic rods were then precisely measured and that weight and the known mass and percent CaHA were used to calculate the exact CaHA content of each rod. Finally, the rods were sealed into plastic resin blocks of 3.00 mm thickness. Two calcification phantoms were fabricated using the above method, one is called “calcium calibration phantom” and the other is called “vessel calcification phantom.” The latter has a larger range of rod diameter and mass (see Table I). The rod lengths for the two phantoms are different, which changes the total CaHA mass for the same diameter rod in the two phantoms. This was done to simulate

the fact that a calibration phantom may not be able to cover the entire range of calcification size and mass in the clinical application.

II.D. Calcium measurement on uniform phantom

Calcium measurements were made on uniform breast tissue equivalent material (BR12, GAMMEX RMI, Middleton, WI). BR12 is a homogenous material that mimics the attenuation properties of average density breast with 50% glandular/50% adipose breast tissue over the range of energies used in mammography.¹⁷ The measurements were made to determine the consistency between the calcium calibration and vessel calcification phantoms in addition to determining the accuracy of the technique to quantify calcium mass in a uniform background. The system was initially calibrated using the calcium calibration phantom imaged on a uniform BR12 phantom. The vessel calcification phantom was then imaged on the same thickness BR12 phantom and its calcium masses were measured. The measurements were repeated on 3 and 4 cm uniform BR12 phantoms. Images in this study were calibrated with the BR12 phantom at the same thickness and corrections for the calibration and calcification images were the same.

II.E. Calcium measurement on breast phantom

Calcium measurements were made on an anthropomorphic breast phantom (“Rachel” Anthropomorphic Breast Phantom, Gammex-RMI, Middleton, WI) to determine the accuracy of the technique to quantify calcium mass in a clinically relevant anatomical background.¹⁸ The anthropomorphic breast phantom is made of BR12 molded into variable thickness to simulate the anatomic background of a breast. A mercury intensified film layer is also included to simulate fine detail structures observed on a mammogram. In order to make the calcium calibration clinically relevant, the calibration phantom cannot be placed directly on the breast. Therefore, calcium calibration can be performed using uniform BR12 of appropriate thickness after mammography. All image acquisition parameters (thickness, kVp, and anode-filter combination) used for the calibration have to be the same as those for the mammography. In this phantom study, the calibration images on BR12 with 5–9 cm thicknesses were acquired using the system automatic exposure control. The x-ray parameters (kVp, anode-filter combination, and mA s) were recorded. The anthropomorphic breast phantom images were then acquired at predetermined x-ray parameters with the automatic exposure control off. The breast phantom was assumed to be equivalent to 5 cm of BR12. Additional uniform thickness BR12 was added to the breast phantom in order to simulate 6–9 cm breast thicknesses that are 50% adipose/50% glandular in composition. To assess the affect of anatomical background on calcium measurement, images were acquired with the vessel calcification phantom placed at seven different positions over the breast phantom by shifting the calcification phantom over the breast phantom by approximately 0.5 cm between each image. All the image acquisition parameters were kept fixed. The above

TABLE I. Diameters and CaHA masses are shown for vessel calcification and calcium calibration phantoms.

Diameter (mm)	CaHA (mg)— Vessel calcification phantom	CaHA (mg)— Calcium calibration phantom
0.6	1.7	
0.76	6.7	3.8
0.89	7.7	4.8
1.02	10.5	8.2
1.2	14.7	10.2
1.57	25.2	18.9
1.89	37.8	28.3

FIG. 2. Images of calcium calibration phantom over BR12 along with the ROI (left) and breast calcification phantom over anthropomorphic breast phantom (right) are shown after logarithmic transformation.

method was used to assess the effect of anatomical background on calcium measurement. However, for clinical implementation, the mammography image can be acquired with the automatic exposure control and the calibration images can be acquired using the same x-ray parameters with the automatic exposure control off. Therefore, the following procedure can be used for the clinical implementation purposes:

- (1) Mammogram is acquired with STD automatic exposure control.
- (2) Calcium calibration image is acquired on uniform BR12 of the same thickness using the same x-ray parameters (automatic exposure control off).
- (3) Breast thickness can be determined using the compression paddle separation.
- (4) Calibration phantom thickness can be within 1 cm of the breast thickness.
- (5) The entire image analyses for the mammograms and the calibration phantom images will be the same.

The original raw images were initially logarithmically transformed. The next step was to relate pixel gray level with calcium mass [see Eq. (8)]. Figure 2 shows calibration and breast phantom images after log transformation. A region-of-interest (ROI) was then drawn around each individual calcium mass element. The surrounding local background was estimated and subtracted using the following linear interpolation algorithm. Each pixel inside the ROI is assigned a shortest line that passes through the pixel and connects to pixels bordering the ROI. Bordering pixels that yield the shortest line are found by searching eight radial directions surrounding the pixel in 45 deg increments. The gray value for pixels inside the ROI is linearly interpolated from the two closest pixel values found during the search. When more than one shortest path length exists, the average of the interpolated gray values from each path length is used. This background estimate was subtracted from the original region of interest in order to yield an image estimate of the calcium element alone [see Eq. (3)]. This process is shown in Fig. 3. The remaining pixel values within each ROI after image subtraction were summed and recorded for further analysis. As shown in Fig. 3, background estimation produces visible lin-

FIG. 3. Steps required for image densitometry are shown. An example using the calcium calibration phantom imaged over 4 cm of BR12 (top) and the vessel calcification phantom imaged over the anthropomorphic breast phantom (bottom) is shown. First, a region of interest is selected around a particular signal (left). Next, the local background is estimated from surrounding pixel values just outside the ROI (center). Third, the two images are subtracted, which removes the background and leaves only an estimate of the contrast object (right).

ear streak artifacts in the local background and the final subtracted calcification image. These artifacts arise because pixels along a line share common nearest pixels adjacent to the ROI. The interpolation of these pixels gives rise to the observed linear artifacts.¹⁹

Image densitometry values from the calibration set were averaged over phantom positions and plotted against known mass for each thickness as demonstrated in Fig. 4. A line was fit to each plot and the resulting calibration slopes were recorded and subsequently used in reverse order to estimate mass from image densitometry values for the breast data. A similar calibration measurement was performed for each phantom thickness.

The calcification phantom, consisting of seven different calcium rods, was imaged at seven different locations for each breast phantom thickness. As shown in Fig. 3, the same background estimation and subtraction procedures were used

FIG. 4. A calibration curve for the 5 cm BR12 where the densitometry values (D) and the known CaHA mass (K) and were related by $D=63.5K-31.1$ ($r=0.999$ and $SEE=18.6$).

TABLE II. Chemical components and density of breast tissues and phantom materials. The information was obtained from a published database by National Institute of Standards and Technology (Ref. 27).

Material	Density (g/cm ³)	Chemical components				
		H	C	N	O	Others
Glandular	1.02	0.106	0.332	0.03	0.527	0.005
Adipose	0.95	0.114	0.598	0.007	0.278	0.003
PMMA	1.19	0.0805	0.6	0	0.32	

for both calibration and breast phantom images. Seven calcium rods imaged at seven different locations results in 49 mass measurements. The root-mean-square (RMS) error (or RMS accuracy) from the true calcium mass was calculated using

$$\text{Error}_{\text{RMS}} = \sqrt{\frac{\sum_{i=1}^N (M_i - K_i)^2}{N}}, \quad (9)$$

where M is the measured calcium mass and K is the known calcium mass of each calcium rod of the vessel calcification phantom. The measured masses were plotted against the true values. A linear regression was then performed for each breast thickness. The standard error of estimate (SEE) of all the data points from the linear-regression line represents the RMS precision. The RMS precision reflects the overall effect of variation of anatomic background, which includes the uncertainty and accuracy of background estimation and subtraction. It also includes the fluctuation of x-ray signal, which is mainly due to quantum noise. The RMS precision excludes the systematic error due to nonunit slope, which is caused by possible differences in scatter condition and effective attenuation coefficients between calibration and calcium measurements.

It should be pointed out that the anthropomorphic breast phantom used here is made from BR12 material, which does not simulate the variation of density within the breast. It provides variation of detector signals only from changing of thickness. Thus, it does not simulate the exact scatter and beam quality of a real breast. However, it is sufficient for study of the effect of anatomic background variation. The effect of scatter and breast density was studied separately in the following sections.

II.F. Effect of scatter correction on calcium measurement

X-ray scatter intensity was estimated with a technique utilizing an array of 8×8 apertures in a 2 mm lead sheet to sample primary x-ray intensity.²⁰ The apertures were 2.4 mm in diameter and 10.2 mm apart. The aperture matrix was placed on the collimator, 33 cm above the imaging detector, in order to sample primary x-ray intensity. The measurements were made with a phantom on the breast support plate.

The open area fraction in the lead sheet was calculated to be 4.38%. Therefore, the x-ray exposure-area product for an aperture matrix image is approximately 4.38% relative to that for an open field image.

The scatter intensity in these locations was calculated by subtracting the sampled primary intensity from an open field image, which contains both primary and scatter. The open field image was then convolved with a Gaussian-shaped convolution kernel corresponding to a full width at half maximum of 2 cm.^{21,22} The convolved gray level and the scatter intensity based on the sampled primary intensity were correlated using a second degree polynomial. The generated correlation was then used to estimate scatter for the entire image. The estimated scatter image was then subtracted from the original image to produce a scatter free image. We have previously reported the details of the scatter estimation technique.²⁰

To determine the effect of scatter correction on calcium quantification, calcium measurements were made before and after correcting the images for scatter in the 5 and 9 cm breasts. Calcium measurements for 5 and 9 cm breasts were repeated after scatter correction. This was done by initially performing the calcium calibration on uniform BR12 and then calcium measurement on the breast phantom using the images corrected for scatter.

II.G. Effect of breast density on calcium measurement

The effect of breast density on calcium measurement needs to be assessed since breast density is not known and the calcium calibration will only be done on BR12, which is 50% adipose/50% glandular in composition. Two extreme breast densities were tested on 5 and 8 cm breasts: 100% adipose tissue and 100% glandular tissue. Chemical components and attenuation coefficients of adipose tissue, glandular tissue and poly(methylmethacrylate) (PMMA) were studied (Tables II and III). Although PMMA has lower mass attenuation coefficient than glandular tissue, their linear attenuation coefficients are very close in the range of x-ray energy used in the current study. Thus, 5 and 8 cm of PMMA were used to simulate 5 and 8 cm of dense breast, respectively. On the other hand, PMMA has almost the same mass attenuation coefficient as that of adipose tissue, due to their similar chemical components (Table II). However, PMMA's density (1.19 g/cm³) is higher than that of adipose tissue (0.95 g/cm³). To account for this density difference, 4 and 6.39 cm PMMA were used to simulate 5 and 8 cm fatty breast, respectively. Spectrum simulations were performed based on a previously reported technique to generate a molybdenum anode mammography spectrum.²³ Figure 5(a) compares the spectrum after filtration of 8 cm adipose tissue

TABLE III. Attenuation coefficients of breast tissues and phantom materials. The information was obtained from a published database by National Institute of Standards and Technology (Ref. 28)

Energy (keV)	Mass attenuation coefficients (g/cm ²)			Linear attenuation coefficients (1/cm)		
	Glandular	Adipose	PMMA	Glandular	Adipose	PMMA
15	1.38	1.08	1.10	1.41	1.03	1.31
18	0.88	0.71	0.71	0.89	0.67	0.85
20	0.69	0.57	0.57	0.70	0.54	0.68
22	0.57	0.48	0.48	0.58	0.45	0.57
25	0.45	0.39	0.39	0.46	0.37	0.46
30	0.34	0.31	0.30	0.35	0.29	0.36

and 6.39 cm PMMA for 32 kVp Rh–Rh beam. The two spectra are almost identical. Figure 5(b) shows the spectrum comparison between 8 cm glandular tissue and 8 cm PMMA. Although the PMMA filtered beam is slightly softer than that by glandular, the two spectra are close. Calcium calibration was performed using the same thickness (5 and 8 cm) of BR12 and x-ray parameters.

For each breast thickness (5 or 8 cm), the vessel calcification phantom was imaged on the top of the simulated 100% adipose breast and 100% glandular breast, using the AEC in STD mode. Two sets of x-ray parameters, corresponding to the two breast densities, were recorded. These parameters were then used to acquire two calibration images on the BR12 stacks of the same thickness.

II.H. Effect of magnification error on calcium measurement

The error from a known difference in magnification can be easily corrected.²⁴ However, as the true location of any calcification is unknown, the error can only be predicted for any given location. In clinical implementation, the calcified vessel will be assumed to be in the middle of the compressed breast. This will necessarily introduce errors if the assumed

position is different from the true position. The error relative to the mass of calcium measured from the image is given by

$$\text{Relative error} = \frac{|M_t - M_m|}{M_m}. \quad (10)$$

The true mass (M_t) is related to the measured mass (M_m) by multiplying the measured mass by the square of the ratio of the two image magnifications (MAG),

$$M_t = M_m \times \left(\frac{\text{MAG}_m}{\text{MAG}_t} \right)^2. \quad (11)$$

This ratio is squared because of the two-dimensional aerial nature of image densitometry and is given explicitly by

$$\left(\frac{\text{MAG}_m}{\text{MAG}_t} \right)^2 = \left(1 + \frac{\delta}{\text{SOD}} \right)^2 = 1 + \frac{2\delta}{\text{SOD}} + \frac{\delta^2}{\text{SOD}^2}, \quad (12)$$

where SOD is source-to-object distance and is the distance from the x-ray source to the calcium calibration phantom. δ is the distance from the calcium calibration phantom to the true location of the calcium mass in the breast.

The distance to the true location of the calcification (δ) can also be expressed as

$$\delta = \text{SOD}_t - \text{SOD}_m. \quad (13)$$

FIG. 5. Spectra of 32 kVp Rh–Rh x-ray beam filtered by 8 cm adipose tissue and 6.39 cm PMMA (a) and 8 cm glandular tissue and 8 cm PMMA (b).

FIG. 6. Calcium (CaHA) mass measurements on 3 (a) and 4 cm (b) BR12 along with the best fit line. The known (K) and measured (M) calcium mass on the 3 and 4 cm thickness phantoms were related by $M=1.049K-0.215$ mg ($r=0.999$ and $SEE=0.467$ mg) and $M=1.047K-0.322$ mg ($r=0.999$ and $SEE=0.516$ mg), respectively.

When Eqs. (11) and (12) are substituted into the Eq. (10), the relative error becomes

$$\text{Relative error} = \left| \frac{2\delta}{\text{SOD}} + \frac{\delta^2}{\text{SOD}^2} \right|. \quad (14)$$

If the calibration phantom and calcium mass are at the same position, then δ and the relative error are both zero. The calibration can be calculated for the center layer of the breast, which reduces the relative error.

II.I. Repeatability of calcium measurement

In order to assess whether the calcium measurements can be repeated by different operators, the calcium measurement in the 5 cm breast phantom was repeated by two different operators. The ROI for each calcium element was drawn by two different operators, which can be the only source of potential interobserver variability in calcium measurement for a clearly delineated calcification. The remaining steps for calcium quantification are automated.

II.J. Effect of calibration thickness on calcium measurement

It is not clinically practical to perfectly match the compressed breast thickness and BR12 thickness for calcium calibration. Therefore, it is expected that the calibration may be done with slightly mismatched BR12 thickness. However, it is required that the same x-ray parameters (kVp and anode-filter combinations) are used for both calibration and calcium measurement images. The potential error introduced by any mismatch in thicknesses was tested by performing calcium measurement at 4 cm and calibration at 3 cm of BR12. It is expected that calcium calibration can be done with a phantom and breast thickness variation of approximately 1 cm.

III. RESULTS

III.A. Calcium measurement on uniform phantom

The results of calcium measurements using a vessel calcification phantom on uniform BR12 phantoms are shown in Fig. 6. The known (K) and measured (M) calcium mass on the 3 and 4 cm thickness phantoms were related by $M=1.049K-0.215$ mg ($r=0.999$ and $SEE=0.467$ mg) and $M=1.047K-0.322$ mg ($r=0.999$ and $SEE=0.516$ mg), respectively. The calcium measurements using densitometry show that the vessel calcification and calcium calibration phantoms are consistent and the technique is accurate in the case of uniform background.

III.B. Calcium measurement on breast phantom

Calcium measurements using vessel calcification phantom on the 5 and 9 cm breast phantoms are shown in Fig. 7. As shown in Fig. 7, at each known calcium mass, there are seven data points corresponding to the measurements at seven different locations on the breast phantom. Linear regression results, RMS accuracy, and RMS precision are presented in Table IV. The RMS accuracy is approximately 1.5 mg and there is not much change with the breast thickness. The RMS precision isolates the effect of anatomic background variation and signal fluctuation from the systematic error. It can be seen that variation of anatomic background is the major contributor to the overall RMS accuracy. The reproducibility of the results when the images were acquired under identical conditions, i.e., the same location and x-ray parameters, has not been evaluated. However, the error from measurements under identical conditions is already convolved into the RMS accuracy of repeated measurement at different locations and is expected to be relatively small. Figure 8(a) shows a plot of standard deviation of CaHA mass measurements due to variation of anatomic background with respect to the known CaHA mass for different breast thick-

FIG. 7. Calcium (CaHA) mass measurements at seven different locations of the 5 (a) and 9 cm (b) anthropomorphic breast phantoms along with the best fit line. The known (K) and measured (M) calcium mass on the 5 and 9 cm thickness phantoms were related by $M=0.964K-0.288$ mg ($r=0.997$ and $SEE=0.878$ mg) and $M=1.004K+0.324$ mg ($r=0.994$ and $SEE=1.322$ mg), respectively.

nesses. The measurement fluctuation averaged among breast thicknesses ranges from 0.56 mg for 1.7 mg calcium to 1.7 mg for 37.8 mg of calcium. The fluctuation in mass increases with the increasing calcium mass. However, the relative fluctuation, which is calculated from the percentage of standard deviation with respect to the total measured calcium mass, reduces from an average of 33% for 1.7 mg calcium mass to 4.4% for 37.8 mg calcium mass [Fig. 8(b)].

III.C. Effect of scatter correction on calcium measurement

The results of calcium measurement for 5 and 9 cm breast phantoms after correcting the images for scatter are shown in Fig. 9. The known (K) and measured (M) calcium mass on the 5 and 9 cm thickness phantoms were related by $M=1.088K-0.303$ mg ($r=0.996$ and $SEE=1.182$ mg) and $M=1.056K+0.369$ mg ($r=0.994$ and $SEE=1.429$ mg), respectively. For the 5 cm thickness RMS errors are 1.26 and 1.85 mg before and after scatter correction, respectively. For the 9 cm thickness RMS errors are 1.35 and 2.30 mg before and after scatter correction, respectively. The RMS errors and results from Figs. 7 and 9 indicate that scatter correction does not improve the calcium measurement. As shown in

Table V, the scatter fraction in the 5 and 9 cm breast phantoms was measured to be 0.18 ± 0.03 and 0.22 ± 0.04 , respectively. The scatter fraction in the 5 and 9 cm uniform phantoms was measured to be 0.18 ± 0.01 and 0.25 ± 0.01 , respectively. A previous report using a slightly different kVp and grid has reported scatter fractions of 0.19 and 0.26 for 4 and 6 cm phantoms, respectively.²⁵ Our scatter measurements are in reasonable agreement with the previously reported results.²⁵ Scatter correction is expected to allow for the differences in scatter fractions between the breast and uniform phantoms. However, the differences in scatter fraction are relatively small. Therefore, the fact that scatter correction did not change the accuracy of calcium measurement can be expected.

III.D. Effect of breast density on calcium measurement

The effect of breast density on calcium measurement for 5 and 8 cm effective thicknesses are shown in Table VI. Calcium measurements in the case of 100% adipose and 100% glandular tissue are shown. Different calibrations were done for different breast density with BR12 of the same thickness. The results indicate that breast density variation can introduce 5%–9% systematic error if the calibration is done with

TABLE IV. Regression results, RMS accuracy, and RMS precision due to variation of anatomic background of calcium mass measurements.

Breast thickness (cm)	Slope	Intercept (mg)	r	RMS accuracy (mg)	RMS precision (mg)
5	0.964 ± 0.011	-0.288 ± 0.204	0.997	1.3	0.85
6	1.048 ± 0.015	-0.181 ± 0.288	0.995	1.4	1.2
7	1.052 ± 0.018	-0.189 ± 0.334	0.993	1.6	1.4
8	1.050 ± 0.017	-0.281 ± 0.313	0.994	1.5	1.3
9	1.004 ± 0.016	0.324 ± 0.307	0.994	1.4	1.3

FIG. 8. Plots of (a) standard deviation of CaHA mass measurements at seven different anatomic backgrounds and (b) relative fluctuation (standard deviation divided by the total mass) with respect to the known CaHA mass for different breast thicknesses.

an average breast density, i.e., using BR12 phantom. Table VI also shows that the calcium mass was overestimated for a fatty breast and underestimated for dense breast.

III.E. Effect of magnification error on calcium measurement

The effect of magnification error on calcium measurement is shown in Fig. 10. The results indicate that the error increases with increasing breast thickness. For a 9 cm breast thickness, the maximum distance of calcification to the assumed position (middle layer) is $\delta=4.5$ cm, which results in

a relative error of approximately 15%. A relative error of approximately 5% is expected for a 5 cm breast thickness.

III.F. Repeatability of calcium measurement

The result of calcium measurement for different operators to analyze the images is shown in Fig. 11. The first (M_f) and second (M_s) measured calcium masses were related by $M_s = 1.003M_f + 0.186$ mg ($r=1.000$) and a SEE of 0.21 mg. This indicates that there is not a large variability in calcium measurements when images are analyzed by different operators.

FIG. 9. Calcium (CaHA) mass measurements after scatter correction on 5 (a) and 9 cm (b) anthropomorphic breast phantoms along with the best fit line. The known (K) and measured (M) calcium mass on the 5 and 9 cm thickness phantoms were related by $M=1.088K-0.303$ mg ($r=0.996$ and SEE=1.182 mg) and $M=1.056K+0.369$ mg ($r=0.994$ and SEE=1.429 mg), respectively.

TABLE V. Measured scatter fraction for uniform and breast phantoms of different thickness.

Thickness (cm)	kVp	Uniform BR12 scatter fraction	Breast phantom + BR12 scatter fraction
5	28	0.18 ± 0.01	0.18 ± 0.03
6	31	0.20 ± 0.01	0.16 ± 0.03
7	32	0.22 ± 0.01	0.18 ± 0.04
8	32	0.23 ± 0.01	0.22 ± 0.05
9	32	0.25 ± 0.01	0.22 ± 0.04

III.G. Effect of calibration thickness on calcium measurement

The effect of calibration thickness on calcium measurement is shown in Fig. 12. In the case where calcium measurement was imaged at 4 cm and calibration was made at 3 cm of BR12, the known (K) and measured (M) calcium mass were related by $M=0.950K-0.286$ mg ($r=0.999$ and $SEE=0.468$ mg). For example for a 10 mg calcification, the results for the 4 cm phantom with the 3 cm calibration yields a mass of 9.21 mg, whereas that for 4 cm phantom with 4 cm calibration yields a mass of 10.15 mg (see Fig. 6). Corresponding values for a 20 mg calcification are 18.71 and 20.62 mg. The results indicate that there is not a large error in calcium measurement for a 1 cm difference between calibration thickness and breast thickness.

IV. DISCUSSIONS

Experimental results using both uniform and anthropomorphic breast phantoms show that it is possible to quantify calcium mass using standard full field digital mammography images. Calcium calibration was performed for each mammogram on a uniform phantom of the same thickness as the breast phantom. The x-ray beam parameters were also kept the same as those used for breast phantom image acquisition. This indicates that a specific calibration image at a particular phantom thickness will be necessary after each mammogram. Alternatively, it may also be possible to perform a detailed calibration at different phantom thicknesses and x-ray techniques in advance. Depending on the reproducibility of the system, the calibration process can be repeated at certain time intervals. It is also possible to include a calcium calibration phantom within each mammogram. This can be accomplished by placing the phantom on a balloon filled

TABLE VI. Regression results for 5 and 8 cm effective breast thicknesses showing the effect of breast composition on estimation of calcium mass.

Effective breast thickness (cm)	Breast composition	Slope	Intercept (mg)	r
5	100% adipose	1.057	0.065	1.000
	100% glandular	0.972	0.081	1.000
8	100% adipose	1.087	0.132	0.999
	100% glandular	0.956	0.093	0.999

FIG. 10. Relative error in calcium measurement due to the uncertainty in the true location of calcification within the breast.

with a mixture of water and oil. The balloon can be placed in the image field next to the breast. This calibration method does not require acquisition of an additional image for calibration. However, it slightly modifies the standard image acquisition for clinical mammography, which might hamper its clinical implementation. This technique has previously been used for x-ray beam equalization purposes.²⁶ However, it has not been implemented in general clinical mammography.

The calcium quantification technique was performed by drawing a region of interest around the calcium signal in the mammogram. The surrounding local anatomical background was estimated and subtracted using a linear interpolation algorithm. Due to the limited accuracy of background estimation, the variation of anatomical background will result in uncertainty of calcium mass measurement.¹⁹ This effect was

FIG. 11. Calcium (CaHA) mass measurements obtained from repeated analysis by two different operators along with the best fit line. The first (M_f) and second (M_s) measured calcium masses were related by $M_s=1.003M_f+0.186$ mg ($r=1.000$) and a SEE of 0.21 mg.

FIG. 12. Effect of differences between breast thickness and phantom calibration thickness on calcium mass measurements is shown. In the case where calcium measurement was imaged at 4 cm and calibration was made at 3 cm of BR12, the known (K) and measured (M) calcium mass were related by $M = 0.950K - 0.286$ mg ($r = 0.999$ and $SEE = 0.468$ mg).

determined by repeating the calcium measurements in different locations over the breast phantom. The average fluctuation of the measurement ranged from 33% for very small calcium mass (1.7 mg) to only 4.4% for large calcium mass (37.8 mg) (see Fig. 8). The relative fluctuation of the measurement is determined by the quantum and anatomical background noise in addition to the size of the calcium rod. The background estimation and subtraction procedure does not introduce uncertainty by itself since the same ROI on the same image will result in exactly the same subtraction. However, the background estimation does depend on the ROI, which is user dependent. The repeatability of calcium mass measurement was evaluated using repeated measurements by two different operators (see Fig. 11). The interobserver SEE was 0.21 mg, which is relatively small as compared to other potential errors in calcium mass measurements.

Our comparison of calcium mass measurements before and after scatter correction shows that scatter correction does not improve the quantification of calcium mass (see Figs. 7 and 9). This is due to the fact that scatter fractions for the breast phantom images and the calibration images are comparable (see Table V). The results show that the RMS error in calcium measurement was slightly increased after scatter correction. This is expected to be due to the error in scatter correction for the uniform and breast phantom images, which might be higher than the mean difference in scatter fraction between the original images. Therefore, in order to simplify the eventual clinical implementation of this technique, the scatter correction was not used in this study. Equation (8) indicates that when calcium amount is small and scatter level is low, scatter correction will not be necessary as long as the calibration images are acquired at the same thickness as the compressed breast. However, in the case where a calcified vessel is located toward the edge of the breast, the thickness

may be different from that at the center of the breast. This can potentially introduce some error in calcium mass measurement.

Variation in breast density can potentially introduce some error in calcium calibration measurement. Calcium calibration is performed on a BR12 phantom of uniform thickness. BR12 mimics the attenuation properties of average density breast with 50% glandular/50% adipose breast tissue over the range of energies used in mammography. Therefore, the expected errors can be due to the deviations of the breast density from the average density breast, which in turn changes the effective attenuation coefficient of calcium. Using spectrum simulation,²³ the effective μ of 0.2 mm thick CaHA on top of 8 cm adipose tissue and 8 cm BR12 (32 kVp Rh–Rh) are 9.9 and 9.16 cm^{-1} , respectively. The 8% deviation is consistent with the result shown in Table VI. The results of calcium measurement for 5 and 8 cm effective breast thicknesses with two extreme densities (100% adipose and 100% glandular composition) indicate that breast density variation can introduce 5%–9% systematic error if the calibration is done with an average breast density, i.e., using BR12 phantom. In addition to the errors introduced through calcium calibration, variation in breast density can potentially introduce additional uncertainty in calcium measurement by limiting the detectability of arterial calcification. This will particularly affect the calcifications near the threshold of detectability. This effect was not investigated in this study.

The uncertainty in magnification of calcification within the breast will introduce error in calcium mass measurement. Breast calcification can be assumed to be at the center layer of the compressed breast. The maximum error due to the uncertainty in magnification can be 5%–15% for 5 and 9 cm breast thickness, respectively. This could be the largest source of potential error in the case of large breast thicknesses. This error can possibly be minimized by more accurate estimation of the location of calcification within the compressed breast. The two images acquired during conventional mammography can possibly be used to estimate the location of calcified artery within the breast.

Another potential source of error in calcium mass measurement is the thickness variation between the breast and calibration phantom. This difference, which is similar to the effect of variation of breast density, causes a change in the effective μ for calcium. Spectrum simulation shows that the effective μ for 0.2 mm thick CaHA is 16.6 cm^{-1} with 4 cm BR12 and 26 kVp Mo–Mo beam. If the calibration is done on 3 cm BR12, the effective μ will be 17.6 cm^{-1} . This mismatch of calibration thickness will cause the calcium mass on 4 cm breast to be underestimated by approximately 5%, which is in reasonable agreement with the result shown in Fig. 12. This error can be significantly reduced if the calibration can be done at finer thickness steps. For example, the error can be approximately halved by using 0.5 cm BR12 slabs.

This technique can quantify the total calcium mass in each breast. It might be of interest to quantify the distribution of calcium mass within the breast. Determination of calcium

distribution within the breast is complicated by the uncertainty in the out of plane angle of the calcified artery. The out of plane angle can possibly be calculated using mammography images acquired at two different projections.²⁴ However, it is not clear yet whether the knowledge of calcium distribution within the breast is of any clinical utility.

The proposed technique is intended for calcifications detected by standard digital mammography. Detectability and quantification of arterial calcification is hampered by the background anatomical structure. This introduces a large relative error in calcium mass measurement for low contrast vessels (see Fig. 8). Dual energy mammography can potentially improve the detectability and quantification of breast arterial calcification. The cone-beam CT techniques that are currently under development for breast imaging are expected to further improve the detectability and quantification of breast arterial calcification.⁸ However, additional studies are necessary to determine the clinical importance of quantifying small breast arterial calcifications that are not currently detectable by standard digital mammography.

The advantage of quantification of arterial calcification using standard mammography is that it does not require any extra x-ray exposure to the patient. With the commonly accepted and widely implemented breast cancer screening program, the ability to provide an additional diagnosis for arterial diseases can be of potentially great benefit to the public.

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¹ J. M. Kemmeren, D. Beijerinck, P. A. van Noord, J. D. Banga, J. J. Deurenberg, F. A. Pameijer, and Y. van der Graaf, "Breast arterial calcifications: Association with diabetes mellitus and cardiovascular mortality. Work in progress," *Radiology* **201**, 75–78 (1996).

² J. Cox, W. Simpson, and D. Walshaw, "An interesting byproduct of screening: Assessing the effect of HRT on arterial calcification in the female breast," *J. Med. Screen.* **9**, 38–39 (2002).

³ C. Iribarren, A. S. Go, I. Tolstykh, S. Sidney, S. C. Johnston, and D. B. Spring, "Breast vascular calcification and risk of coronary heart disease, stroke, and heart failure," *J. Womens Health* **13**, 381–389; discussion 390–382 (2004).

⁴ A. C. Moshedy, A. H. Puthawala, R. J. Kurland, and D. H. O'Leary, "Breast arterial calcification: Association with coronary artery disease. Work in progress," *Radiology* **194**, 181–183 (1995).

⁵ M. Kataoka, R. Warren, R. Luben, J. Camus, E. Denton, E. Sala, N. Day, and K. T. Khaw, "How predictive is breast arterial calcification of cardiovascular disease and risk factors when found at screening mammogra-

phy?" *AJR Am. J. Roentgenol.* **187**, 73–80 (2006).

⁶ A. H. E. M. Maas, Y. T. van der Schouw, D. Beijerinck, J. J. M. Deurenberg, W. P. T. M. Mali, and Y. van der Graaf, "Arterial calcifications seen on mammograms: Cardiovascular risk factors, pregnancy, and lactation," *Radiology* **240**, 33–38 (2006).

⁷ L. Wexler, B. Brundage, J. Crouse, R. Detrano, V. Fuster, J. Maddahi, J. Rumberger, W. Stanford, R. White, and K. Taubert, "Coronary artery calcification: Pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group," *Circulation* **94**, 1175–1192 (1996).

⁸ J. M. Boone, A. L. Kwan, K. Yang, G. W. Burkett, K. K. Lindfors, and T. R. Nelson, "Computed tomography for imaging the breast," *J. Mammary Gland Biol. Neoplasia* **11**, 103–111 (2006).

⁹ S. Molloi, R. Detrano, A. Ersahin, W. Roeck, and C. Morcos, "Quantification of coronary arterial calcium by dual energy digital subtraction fluoroscopy," *Med. Phys.* **18**, 295–298 (1991).

¹⁰ J. L. Ducote, T. Xu, and S. Molloi, "Optimization of a flat-panel based real time dual-energy system for cardiac imaging," *Med. Phys.* **33**(6), 1562–1568 (2006).

¹¹ T. Xu, J. L. Ducote, J. T. Wong, and S. Molloi, "Feasibility of real time dual-energy imaging based on a flat panel detector for coronary artery calcium quantification," *Med. Phys.* **33**, 1612–1622 (2006).

¹² S. C. Kappadath and C. C. Shaw, "Quantitative evaluation of dual-energy digital mammography for calcification imaging," *Phys. Med. Biol.* **49**, 2563–2576 (2004).

¹³ S. C. Kappadath and C. C. Shaw, "Dual-energy digital mammography for calcification imaging: Scatter and nonuniformity corrections," *Med. Phys.* **32**, 3395–3408 (2005).

¹⁴ R. Detrano and S. Molloi, "Radiographically detectable calcium and atherosclerosis: The connection and its exploitation," *Int. J. Card. Imaging* **8**, 209–215 (1992).

¹⁵ R. Detrano, X. P. Kang, P. Mahaisavariya, W. Y. Tang, A. Colombo, S. Molloi, D. Garner, and S. Nickerson, "Accuracy of quantifying coronary hydroxyapatite with electron beam tomography," *Invest. Radiol.* **29**, 733–738 (1994).

¹⁶ A. Trion and A. van der Laarse, "Vascular smooth muscle cells and calcification in atherosclerosis," *Am. Heart J.* **147**, 808–814 (2004).

¹⁷ D. R. White, "The formulation of tissue substitute materials using basic interaction data," *Phys. Med. Biol.* **22**, 889–899 (1977).

¹⁸ C. B. Caldwell and M. J. Yaffe, "Development of an anthropomorphic breast phantom," *Med. Phys.* **17**, 273–280 (1990).

¹⁹ J. T. Wong, F. Kamyar, and S. Molloi, "Quantitative coronary angiography using image recovery techniques for background estimation in un-subtracted images," *Med. Phys.* **34**, 4003–4015 (2007).

²⁰ Y. Zhou, T. Mathur, and S. Molloi, "Scatter and veiling glare estimation based on sampled primary intensity," *Med. Phys.* **26**, 2301–2310 (1999).

²¹ J. M. Boone, K. K. Lindfors, V. N. Cooper III, and J. A. Seibert, "Scatter/primary in mammography: Comprehensive results," *Med. Phys.* **27**, 2408–2416 (2000).

²² V. N. Cooper III, J. M. Boone, J. A. Seibert, and C. J. Pellot-Barakat, "An edge spread technique for measurement of the scatter-to-primary ratio in mammography," *Med. Phys.* **27**, 845–853 (2000).

²³ J. M. Boone, T. R. Fewell, and R. J. Jennings, "Molybdenum, rhodium, and tungsten anode spectral models using interpolating polynomials with application to mammography," *Med. Phys.* **24**, 1863–1874 (1997).

²⁴ S. Molloi, Q. Dang, and J. Breault, "Effect of vessel orientation on videodensitometry quantitative coronary arteriography," *Med. Phys.* **30**, 2862–2868 (2003).

²⁵ G. T. Barnes, "Contrast and scatter in x-ray imaging," *Radiographics* **11**, 307–323 (1991).

²⁶ K. L. Lam and H. P. Chan, "Effects of x-ray beam equalization on mammographic imaging," *Med. Phys.* **17**, 242–249 (1990).

²⁷ <http://physics.nist.gov/PhysRefData/XrayMassCoef/cover.html>.

²⁸ <http://physics.nist.gov/PhysRefData/Xcom/Text/XCOM.html>.