Published in final edited form as:

Appl Opt. 2009 April 1; 48(10): D130–D136.

Measurement of pressure-displacement kinetics of hemoglobin in normal breast tissue with near-infrared spectral imaging

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Abstract

Applying localized external displacement to the breast surface can change the interstitial fluid pressure such that regional transient microvascular changes occur in oxygenation and vascular volume. Imaging these dynamic responses over time, while different pressures are applied, could provide selective temporal contrast for cancer relative to the surrounding normal breast. In order to investigate this possibility in normal breast tissue, a near-infrared spectral tomography system was developed that can simultaneously acquire data at three wavelengths with a 15 s time resolution per scan. The system was tested first with heterogeneous blood phantoms. Changes in regional blood concentrations were found to be linearly related to recovered mean hemoglobin concentration (Hb_T) values ($R^2 = 0.9$). In a series of volunteer breast imaging exams, data from 17 asymptomatic subjects were acquired under increasing and decreasing breast compression. Calculations show that a 10 mm displacement applied to the breast results in surface pressures in the range of 0–55 kPa depending on breast density. The recovered human data indicate that Hb_T was reduced under compression and the normalized change was significantly correlated to the applied pressure with a p value of 0.005. The maximum Hb_T decreases in breast tissue were associated with body mass index (BMI), which is a surrogate indicator of breast density. No statistically valid correlations were found between the applied pressure and the changes in tissue oxygen saturation (S_tO_2) or water percentage (H_2O) across the range of BMI values studied.

1. Introduction

Interstitial fluid pressure (IFP) is the hydrostatic pressure of liquid within a matrix of cells, proteins, and microvessels [1]. IFP is significantly higher in tumors than in surrounding normal tissues [1–3]. The addition of external pressure can apparently increase this localized IFP contrast even further as a result of the increased stiffness of the tumor [4]. Adding localized external pressure to tissue causes changes in IFP that depend on its elastic properties, geometry, blood pressure, and blood vessel microanatomy [5] and has the potential to cause transient microvascular alterations that reduce the vascular volume and deoxygenate the transiently localized blood. Recent work has shown that the imaging contrast and resolution of cancer may be enhanced [6] by capturing the dynamic response of tissue to different applied pressures.

Some research has begun to investigate these pressure-enhanced microvascular changes in breast tissue with the goal of achieving higher sensitivity in cancer detection based on the biophysical characteristics of the tumor that can be determined with near-infrared (NIR) imaging [6–9]. Localized physiological properties such as total hemoglobin concentration

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OCIS codes: 110.0110, 170.0170, 120.0120.

(Hb_T), tissue oxygen saturation (S_tO₂), and water percentage (H₂O) can be quantified diagnostically in breast with NIR imaging systems [10–14]. In order to exploit the potential of imaging dynamic contrast, near-infrared spectral (NIRS) tomography must be performed with acquisition rates of the order of seconds, rather than minutes, and multiwavelength data must be acquired to allow spectral recovery and separation of the effects of Hb_T, S_tO₂, and scatter. Full spectral tomography with more than two wavelengths at a frame rate of several seconds has not been previously demonstrated, even though it is technologically feasible, because the clinical benefits of imaging these changes are not yet apparent.

The complicating factor in understanding the pressure dependency of image contrast arises from the heterogeneity in breast tissue composition between subjects, which dramatically modulates the response to externally applied pressure or tissue displacement at the surface of the breast. Prior calculations have indicated that low density adipose tissue can sustain large surface movement or displacement with very little pressure elevation because the lateral deformation that is possible alleviates the buildup of IFP [5]. Dense breast tissue, on the other hand, has higher intrinsic stiffness such that small surface displacements from externally applied pressure directly translate into elevated IFP. Most breasts are composed of a mixture of fibroglandular and adipose components in the interior surrounded by a layer of fat with variable thickness nearest the skin. In this compositional pattern, the relationship between applied displacement and internal pressure is more unpredictable. Direct modeling and prediction of the relationship is feasible only with volumetric imaging of tissue stiffness with a technique like MR elastography [15,16]. However, interpreting pressure effects in the breast may also be possible with the aid of surrogate measures of breast composition, such as radiographic density or body mass index (BMI).

In this study, a three-wavelength NIRS tomography approach was developed to allow measurement of the dynamics of breast tissue response to externally applied pressures, with 15 s temporal resolution. Results obtained from heterogeneous blood phantoms were used to validate system performance. A series of clinical breast exams delivered to 17 women with normal mammography (BIRADS I) were analyzed to investigate how pressure changes affect the NIRS imaging response of normal breast tissue across a range of breast densities and BMI values.

2. Methods

A. Imaging System and Reconstruction

The basic system schematic and a photograph of the breast interface for pressure-enhanced NIRS imaging are shown in Fig. 1. NIR light from three laser diodes is used simultaneously to illuminate the tissue through one fiber at a time with a total power of less than 80 mW. Three driving current subsystems are composed of both DC and RF components with the RF modulated by a function generator with frequencies of 100.0005, 100.0009, and 100.0013 MHz, respectively. The diffusely transmitted light is detected simultaneously by 15 fiber bundles coupled to individual photomultiplier tubes, operating in parallel. The electrical outputs from each of the photomultiplier tubes are heterodyned with a 100.0000 MHz signal to generate offset frequencies of 500, 900, and 1300 Hz. Using a digital lock-in detection technique, the total mixed signal containing each of the three frequencies is sampled, and the individual signals are extracted in software to yield their respective amplitudes and phases. The process is repeated at each of the 16 source positions for all 15 detectors, such that 240 data points of amplitude and phase are acquired at each frequency from the array of source–detector positions. One complete acquisition at all source locations occurs in approximately 15 s.

The three wavelengths used in the system are 658, 785, and 826 nm. The output light from each diode laser is combined and delivered to the breast interface by a custom-manufactured fiber combiner. Three DC suppliers provide current for each of the laser diodes. A custom-designed signal generator (HS4A, Holzworth Instrumentation, Boulder, Colorado) produces AC current, which modulates the three diode lasers at their individual wavelengths and provides the reference signal to the mixer to heterodyne the signal for detection. Frequency and power levels for each output channel on the signal generator are controlled to within 1 Hz and 1 dBm by a computer running LabVIEW software. All the output channels are phase locked with Direct Digital Synthesis technology. The power level used to modulate each laser diode was 13 dBm, and the power of the local wave mixer was 7 dBm.

Figure 1(b) is a photograph of the circular interface of optical fiber bundles. Three motorized planes of optical fiber bundles are used to apply pressure to the imaging volume and record data along 3 cm of breast from the chest wall toward the nipple. Amplitude and phase measurements from 240 source–detector pairs for each wavelength were collected for each plane. The pressure applied to the breast surface was measured by two transducers (Omega, LCFD-1 kG). The electrical signal from each transducer was amplified (Omega, DMD-465) and recorded in real time through a USB data acquisition module. The accuracy of the pressure data obtained with these transducers was approximately 0.1 kPa. Since the primary focus of this study was assessment of the pressure changes resulting from different displacements of the fiber array, the pressure measured by the transducer on the lower (caudal) side of the breast (Transducer 1) was used as an estimate of the average pressure applied to the whole breast. Similar pressure values were measured by the transducer located on the upper (cranial) side of the breast (Transducer 2), which ensured that the breast was positioned approximately in the center of the fiber array.

A spectrally constrained chromophore and scattering reconstruction method was used to recover chromophore images [17]. In this method, chromophore constraints are incorporated into the reconstruction algorithm to estimate oxyhemoglobin, deoxyhemoglobin, and water, while an empirical approximation to Mie scattering theory is used to constrain scattering amplitude (SA) and scattering power (SP). Instead of assuming a fixed homogeneous H₂O concentration throughout the whole breast [7], localized H₂O values were estimated from the data acquired with the new system, which was enabled by the fast temporal measurement of three wavelengths of amplitude and phase recordings.

While direct fiber contact, especially under increasing pressure, is known to deform the breast surface and can be compensated for accurately during NIR image reconstruction [18], we did not have access to detailed surface topography during these breast imaging exams, and therefore, did not account for the geometric distortion introduced by incrementing the fiber array, which is a limitation of the imaging results reported here.

B. Phantom Study

To validate the values of Hb_T, S_tO₂, and H₂O recovered by the system, a series of phantoms with well characterized properties were used. The phantom background consisted of a 90 mm diameter gelatin cylinder with 1.00% of pig blood and titanium dioxide (TiO₂) as a scattering agent to stimulate tissue. The weight of TiO₂ was adjusted to fix the reduced scattering coefficient, μ_s' , at 0.9 mm⁻¹ for 785 nm illumination. A 20 mm hole was created close to the edge of the phantom exterior. An Intralipid solution with blood concentrations ranging from 1% up to 1.75% filled the hole to mimic an inclusion of tissue with increasing blood volume fraction. The concentration of Intralipid inside the hole was adjusted to match μ_s' in the background gelatin [19,20].

C. Preliminary Normal Subject Study

This study was carried out under a protocol, which was approved by Dartmouth's Institutional Review Board (IRB). In total, 23 subjects were recruited to participate and gave informed consent. All had previous mammograms with normal (BIRADS I) findings. The age and BMI of these women were in the range of 37–49 years old and 19.9–40.6, respectively. The mammographic breast density of the participants covered all four radiologic categories of fatty, scattered, heterogeneously dense, and extremely dense. In each category, the number of the subjects varied between 2 and 7. Due to the limited number of enrollments in each radiographic density group, BMI was used as one of the variables in the study because of its association with breast composition [21]. One subject that was using hormone replacement therapy has been excluded from the study. During the NIRS breast exam for each subject, a fixed 10 mm displacement of the diameter of the circle formed by the fiber bundles was imparted. This displacement induced pressure changes over a range from 0 to 55 kPa. Figure 2 shows a diagram of the time course of the pressure change procedures. After 1 min, zero-pressure data (the fibers just touching the breast) were acquired, and then the breast was compressed by closing the fiber array diameter in five separate increments of 2 mm each. The data were acquired in the 15 s immediately after each compression step. Two extra data sets were recorded (for 40 s) when the breast was held at the maximum displacement of 10 mm. Then, the displacement was reduced in a series of five steps of 2 mm each, returning to the initial zero-pressure position. Adding 5 s between each image to allow for pressure measurement and the return of the source fiber from position 16 (the last location of the prior image acquisition) to position 1 (the starting position for the next image recording), the total time for each compression or release increment was 20 s. The entire compression–release cycle was completed in approximately 6 min, and 17 image data sets were acquired during that time.

A total of 17 of the 23 subjects were imaged successfully. The remaining, unsuccessful exams (6) resulted from either high signal attenuation (2 cases) or insufficient pressure increase (4 cases) when the displacement reached its maximum 10 mm extent because the breast was too small or its elastic properties were too low to result in a measurable increase in pressure.

3. Results

Images of the heterogeneous phantom are shown in Fig. 3(a). The blood concentration inside the hole and the background gelatin were 1.75% and 1%, respectively. Images were reconstructed for chromophore and scattering values within the entire domain. The contrast between the inclusion and the background gelatin was readily evident in the Hb_T image. Figure 3(b) shows results from the image reconstructions presented as a graph of estimated Hb_T , S_tO_2 , and H_2O versus blood concentration. The filled and nonfilled circles show the average Hb_T , S_tO_2 , and H_2O values inside and outside the inclusion, respectively. The error bars represent the standard deviation of all point estimates averaged over their respective regions. The solid lines are the linear fit to the estimated Hb_T values, inside and outside the hole, versus blood concentration. From the graph, there is a clear linear correlation between the estimated Hb_T in the inclusion and blood concentration ($R^2 = 0.9$). The average Hb_T values outside the hole were constant with a variation of less than 1.7%. As expected, S_tO_2 and H_2O values inside and outside the hole were constant with a variation of less than 1%.

The pressure measured when the breast was compressed with a 10 mm displacement is plotted in Fig. 4 as a function of subject BMI. The data from the 17 subjects who were successfully imaged are reported in this figure. The diamonds represent the pressure values from each subject. A range of pressures (measured from 0 to 55 kPa) was recorded. No statistically significant correlation was found between pressure and BMI.

An example of the dynamic breast tissue response to the applied pressure is shown in Fig. 5. The radiographic density category of this 53 year old subject was extremely dense. The pressure values are recorded immediately after each fiber array displacement increment. The circles and error bars in each graph show the average values and the standard deviations in Hb_T , S_tO_2 , H_2O , SA, and SP, estimated over the whole breast. Hb_T reduces when pressure is increased and then increases proportionately as the pressure is released. The reduction in Hb_T at higher pressure can be interpreted as a reduction in the average blood volume in this part of the breast resulting from compression. Although it can be seen that S_tO_2 , H_2O , SA, and SP are perturbed by the different displacements, no substantial pressure response was observed in these parameters.

Similar trends were found in the dynamic changes in Hb_T , S_tO_2 , and H_2O from the 13 subjects with a total pressure change in the range of 1–30 kPa. Figure 6 shows the percent change in Hb_T , S_tO_2 , and H_2O between the values recovered at different pressures (P_i), relative to the zero-pressure (P_0) base-line, plotted as a function of the applied pressure in 13 subjects. The data from 4 subjects were excluded from Fig. 6 because either the pressure changes between each 2 mm displacement were too low to be measured accurately (3 subjects) or the pressure was much higher than all the other subjects (1 subject). Here $\Delta p_i - p_0$ represents the difference in values (of Hb_T or S_tO_2 or H_2O) at P_i and those at zero pressure, P_0 . Vp_0 is the value (of Hb_T or S_tO_2 or H_2O) at P_0 . The maximum pressure was measured at 10 mm displacement in each subject. The R^2 value between change in Hb_T and pressure was 0.44, and statistical regression showed that the two are significantly correlated with a p value of 0.005. No statistically significant correlations were found between the applied pressure and changes in S_tO_2 and H_2O (p values of 0.4 and 0.7, respectively) in this cohort of subjects and NIRS breast exams.

Figure 7 shows a summary of the maximum change in Hb_T , S_tO_2 , and H_2O as a function of BMI when the breast was compressed 10 mm in diameter. BMI was used as the independent ordinate because it is a surrogate measure of the ratio of fatty to fibroglandular composition in the breast. The maximum change was defined as the difference between values at zero displacement and those at the maximum pressure and displacement. Maximum Hb_T changes increased with larger BMI in a linear regression with $R^2 = 0.35$ and a slope that was significantly different from zero (p value = 0.02). No statistically significant changes were observed in the graphs of S_tO_2 and H_2O versus BMI (p values of 0.1 and 0.07, respectively).

4. Discussion

The experimental study presented here applied the same displacements to all breasts examined. An alternative, and perhaps better, way to conduct the study would have applied the same pressure to the surface of the breast during all exams. However, as is indicated in the mammography literature [22] and shown in Fig. 4, there is a large variation in BMI between women, which corresponds to large compositional changes in the breast resulting in variable stiffness properties. In fact, the range of stiffness varies so significantly that it is likely not possible to complete a study designed to apply a fixed pressure to the breast because some of the fattiest breasts simply cannot sustain sufficiently high pressure values no matter how much compression is imposed. Perhaps most important is the need to record pressure as well as displacement at the surface in order to account for the effects of breast tissue stiffness.

Compared to the compression of 4.5–13.6 kg placed on the breast by parallel plates in mammography, the compression force on the breast at each of the 48 fiber bundles is less than 0.23 kg. As shown in Fig 6, Hb_T decreased when pressure increased, and the normalized relative change was significantly correlated with the measured pressure at the

breast surface. However, no significant correlations were found between S_tO_2 and H_2O change and the applied pressure. This can be understood in terms of the way in which pressure was induced (with a circular breast interface), which functioned effectively as a blood pressure cuff around the breast circumference that reduced its blood supply.

The *in vivo* results can also be interpreted relative to phantom studies and linear elastic finite element analyses, which showed that the relationship between displacement and induced pressure in fibroglandular breast tissue is more direct than that in its adipose counterpart [5]. The major complication in interpreting the data presented in Fig. 7 is the presumption that the change in Hb_T is most likely caused by a change in the perfused vascular space that results from volume changes caused by shifts in the balance of extravascular tissue pressure relative to intravascular blood pressure. As the extravascular tissue pressure exceeds the intravascular blood pressure, blood flow is constricted and vessel volume is reduced. Interestingly, the maximum Hb_T changes occurred in subjects with a larger BMI (Fig. 7), which might result from the pressure in these fatty breast tissues that causes a larger volume change since the breast tissue is subject to unseen lateral motion. Volumetric imaging data would help to resolve the physiological reasons for this change. In future studies, we will combine this NIR pressure test with MRI so we can understand in more detail the deformation that occurs in the breast and its relationship to the complex dynamics of the tissue response to the applied pressure.

In principle, increasing the number of wavelengths used in the reconstruction process should improve the accuracy in estimating chromophore concentrations. In this study, data acquired at three wavelengths simultaneously was used to recover Hb_T , S_tO_2 , and H_2O concentrations inside breast simulating phantoms as well as normal breast tissue. While more wavelengths would be desirable, the technical implementation and cost considerations are not easily solved for tissue tomography at depth. The system studied here used three wavelengths, which is sufficient to allow separation of Hb_T , S_tO_2 , and H_2O within medium-sized tissue regions.

Increasing the number of pressure transducers would provide more detailed information about pressure and improve the accuracy of the results. An array of pressure sensors is likely to be more important in cases where there is a large change in breast shape or where the heterogeneity in breast composition is high. Two transducers were used here to provide a global estimate of pressure changes induced through different displacements of the fiber array. While more pressure data are desirable, the symmetry of most breast tissue was considered to be sufficient to allow useful data to be acquired with only two transducers.

5. Conclusion

A NIRS tomography system that can simultaneously acquire data at three wavelengths has been developed to measure changes in physiological properties with 15 s time resolution to evaluate the potential of pressure-enhanced breast imaging. Results from heterogeneous blood phantom studies indicated that the R^2 value between average estimated Hb_T values and blood concentration is 0.9. In normal-subject clinical exams, 17 women were successfully studied through a series of image acquisitions during which external pressure was incrementally applied and released. The pressure applied to the breast surface resulting from a 10 mm displacement was recorded for each subject and ranged from zero (not measurable) up to 55 kPa. The recovered NIRS image data showed that Hb_T decreased in volume fraction when the pressure increased and the relative change in Hb_T was directly correlated to the measured pressure across all subjects. The maximum Hb_T reduction in each subject, from displacement of the breast by 10 mm, was correlated with BMI. No statistically significant correlation between S_tO_2 or H_2O change was observed with either

pressure or BMI. Future studies of NIRS measurements within a MRI scanner are planned and should lead to data that will indicate how the adipose-to-fibroglandular tissue volumes are changing in the NIRS imaging field of view during compression.

Acknowledgments

This work has been sponsored by the National Institutes of Health (NIH) through grants K25CA106863 and PO1CA80139.

References

1. Heldin CH, Rubin K, Pietras K, Östman A. High interstitial fluid pressure—an obstacle in cancer therapy. *Nat Rev Cancer*. 2004; 4:806–813. [PubMed: 15510161]
2. Boucher Y, Jain RK. Microvascular pressure is the principal driving force for interstitial hypertension in solid tumors: Implications for vascular collapse. *Cancer Res*. 1992; 52:5110–5114. [PubMed: 1516068]
3. Saminathan GRD, Nathan S, Casas-Ganem JE, Hoang BH, Sowers Rebecca, Yang Rui, Huvos AG, Gorlick R, Healey JH. Elevated physiologic tumor pressure promotes proliferation and chemosensitivity in human osteosarcoma. *Clin Cancer Res*. 2005; 11:2389–2397. [PubMed: 15788690]
4. Stuhr LEB, Lepsøe S, Myklebust R, Wiig H, Reed RK. Fluid pressure in human dermal fibroblast aggregates measured with micropipettes. *Am J Physiol: Cell Physiol*. 2003; 285:C1101–C1108. [PubMed: 12878487]
5. Darling AL, Yalavarthy PK, Doyley MM, Dehghani H, Pogue BW. Interstitial fluid pressure in soft tissue as a result of an externally applied contact pressure. *Phys Med Biol*. 2007; 52:4121–4136. [PubMed: 17664598]
6. Brenner JR, Parisky Y. Alternative breast-imaging approaches. *Radiol Clin North Am*. 2007; 45:907–923. [PubMed: 17888777]
7. Jiang S, Pogue BW, Paulsen KD, Kogel C, Poplack SP. In vivo near-infrared spectral detection of pressure-induced changes in breast tissue. *Opt Lett*. 2003; 28:1212–1214. [PubMed: 12885024]
8. Carp SA, Kauffman T, Fang Q, Rafferty E, Moore R, Kopans D, Boas D. Compression-induced changes in the physiological state of the breast as observed through frequency domain photon migration measurements. *J Biomed Opt*. 2006; 11:064016. [PubMed: 17212539]
9. Wang B, Povoski SP, Cao X, Sun D, Xu RX. Dynamic schema for near infrared detection of pressure-induced changes in solid tumors. *Appl Opt*. 2008; 47:3053–3063. [PubMed: 18516127]
10. Fantini S, Heffer EL, Pera VE, Sassaroli A, Liu N. Spatial and spectral information in optical mammography. *Technol Cancer Res Treat*. 2005; 4:471–482. [PubMed: 16173819]
11. Chance B, Nioka S, Zhang J, Conant EF, Hwang E, Briest S, Orel SG, Schnall MD, Czerniecki BJ. Breast cancer detection based on incremental biochemical and physiological properties of breast cancers: a six-year, two-site study. *Acad Radiol*. 2005; 12:925–933. [PubMed: 16023383]
12. Cerussi A, Shah N, Hsiang D, Durkin A, Butler J, Tromberg BJ. In vivo absorption, scattering, and physiologic properties of 58 malignant breast tumors determined by broadband diffuse optical spectroscopy. *J Biomed Opt*. 2006; 11:044005. [PubMed: 16965162]
13. Poplack SP, Paulsen KD, Hartov A, Meaney PM, Pogue BW, Tosteson TD, Soho SK, Wells WA. Electromagnetic breast imaging—pilot results in women with abnormal mammography. *Radiology (Oak Brook, Ill)*. 2007; 243:350–359.
14. Carpenter CM, Pogue BW, Jiang S, Dehghani H, Wang X, Paulsen KD, Wells WA, Forero J, Kogel C, Weaver JB, Poplack SP, Kaufman PA. Image-guided optical spectroscopy provides molecular-specific information in vivo: MRI-guided spectroscopy of breast cancer hemoglobin, water, and scatterer size. *Opt Lett*. 2007; 32:933–935. [PubMed: 17375158]
15. Van Houten EE, Weaver JB, Miga MI, Kennedy FE, Paulsen KD. Elasticity reconstruction from experimental MR displacement data: initial experience with an overlapping subzone finite element inversion process. *Med Phys*. 2000; 27:101–107. [PubMed: 10659743]

16. Van Houten EEW, Doyley MM, Kennedy FE, Paulsen KD, Weaver JB. A three-parameter mechanical property reconstruction method for MR-based elastic property imaging. *IEEE Trans Med Imaging*. 2005; 24:311–324. [PubMed: 15754982]
17. Srinivasan S, Pogue BW, Jiang S, Dehghani H, Paulsen KD. Spectrally constrained chromophore and scattering near-infrared tomography provides quantitative and robust reconstruction. *Appl Opt*. 2005; 44:1858–1869. [PubMed: 15813523]
18. Dehghani H, Doyley M, pogue BW, Jiang S, Geng J, Paulsen KD. Breast deformation modeling for image reconstruction in near-infrared tomography. *Phys Med Biol*. 2004; 49:1131–1145. [PubMed: 15128194]
19. Brooksby B, Srinivasan S, Jiang S, Dehghani H, Pogue BW, Paulsen KD, Weaver J, Kogel C, Poplack SP. Spectral-prior information improves Near-Infrared diffuse tomography more than spatial-prior. *Opt Lett*. 2005; 30:1968–1970. [PubMed: 16092235]
20. Brooksby B, Jiang S, Dehghani H, Pogue BW, Paulsen KD, Weaver J, Kogel C, Poplack SP. Combining near-infrared tomography and magnetic resonance imaging to study in vivo breast tissue: implementation of a Laplacian-type regularization to incorporate magnetic resonance structure. *J Biomed Opt*. 2005; 10:051504. [PubMed: 16292948]
21. Srinivasan S, Pogue BW, Jiang S, Dehghani H, Kogel C, Soho S, Chambers JG, Tosteson TD, Poplack SP, Paulsen KD. Interpreting hemoglobin and water concentration, oxygen saturation, and scattering measured by near-infrared tomography of normal breast in vivo. *Proc Nat Acad Sci, USA*. 2003; 100(21):12349–12354. [PubMed: 14514888]
22. Poulos A, McLean D. The application of breast compression in mammography: a new perspective. *Radiography*. 2004; 10:131–137.

Fig. 1.
(a) System schematic and (b) patient interface.

Fig. 2.
Timeline for adding and releasing pressure.

Fig. 3. (Color online) Heterogeneous blood phantom experiments. (a) Reconstructed images of a phantom. The blood concentrations inside and outside the inclusion are 1.75% and 1%, respectively. (b) Estimated average Hb_T , S_tO_2 , and H_2O values inside (filled circles) and outside (nonfilled circles) the phantom inclusion.

Fig. 4.
Pressures measured when the breast was compressed 10 mm in diameter as a function of subject BMI.

Fig. 5. Dynamic pressure response of a normal subject. Average Hb_T is reduced when pressure is applied to the breast surface. Error bars represent the standard deviation in the imaged property over the whole breast.

Fig. 6.

Percent change in Hb_T, StO₂, and H₂O between the values at different pressures (P_i), relative to zero pressure (P_0), plotted as a function of the pressure applied to 13 subjects, where the total pressure change ranges from 1 to 20 kPa. Here, $\Delta p_i - p_0$ is the difference in the values (of Hb_T or StO₂ or H₂O) at P_i and that at zero pressure, P_0 . V_{p0} is the value (of Hb_T or StO₂ or H₂O) at P_0 .

Fig. 7.

(Color online) Maximum Hb_T , StO_2 , and H_2O change when the breast was compressed 10 mm in diameter versus BMI. Total hemoglobin change was correlated with BMI with statistical significance ($p = 0.02$).