Published in final edited form as:

Ultrasound Med Biol. 2013 November ; 39(11): 2176–2184. doi:10.1016/j.ultrasmedbio.2013.05.018.

COMBINED PHOTO-ACOUSTIC AND ACOUSTIC IMAGING OF HUMAN BREAST SPECIMENS IN THE MAMMOGRAPHIC GEOMETRY

Zhixing Xie, Fong Ming Hooi, J Brian Fowlkes, Renee W. Pinsky, Xueding Wang, and Paul L. Carson

Department of Radiology, University of Michigan School of Medicine, Ann Arbor, MI, USA

Abstract

A photo-acoustic volume imaging (PAVI) system was designed to study breast cancer detection and diagnosis in the mammographic geometry in combination with automated 3-D ultrasound (AUS). The goal of the work described here was to validate the design and evaluate its performance in human breast tissues for non-invasive imaging of deeply positioned structures covering such geometry. The good penetration of nearinfrared light and high receiving sensitivity of a broad-bandwidth, 572-element, 2-D poly(vinyl difluoride) array at a low center frequency of 1 MHz were used with 20 channel simultaneous acquisition. Pseudo-lesions filled with dilute blood were imaged in three human breast specimens at various depths up to 49 mm. With near-infrared light illumination and 256-sample averaging, the extrapolated maximum depth in imaging a 2.4-mm blood-rich lesion with a 3-dB contrast-to-noise ratio in a compressed breast was 54 mm. Three-dimensional photo-acoustic volume image stacks of the breasts were co-registered with 3-D ultrasound image stacks, suggesting for the first time that PAVI, based on the intrinsic tissue contrast, can visualize tissue interfaces other than those with blood, including the inner skin surface and connective tissue sheets. With the designed system, PAVI revealed satisfactory imaging depth and sensitivity for coverage of the entire breast when imaged from both sides in the mammographic geometry with mild compression.

Keywords

Photo-acoustic imaging; Breast cancer; Ultrasound imaging; Mammography

INTRODUCTION

Modern ultrasound, in combination with mammography, has increased substantially the cancer detection rate compared with X-ray mammography alone, particularly in dense breasts (Berg et al. 2008; Kolb et al. 2002). Contrast magnetic resonance imaging (MRI) has provided even better detection, principally by revealing vascular anomalies, and is now recommended for screening high-risk women, particularly those with dense breasts (Lee et al. 2010). MRI and ultrasound have each increased call-back rates from screening compared with mammography alone (e.g., Berg et al. 2008; Kolb et al. 2002; Lee et al. 2010). We expect, however, that having the area of any questionable mass in one modality easily

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Address correspondence to: Xueding Wang and Paul L. Carson, Department of Radiology, University of Michigan School of Medicine, 3226 B Med Sci 1, 1301 Catherine Street, Ann Arbor, MI 48109. xdwang@umich.edu or pcarson@umich.edu.

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Wang, 2009; Zhixing et al., 2009.

identified in the images of the other modality or modalities will allow reduction of call backs for further diagnostic workup (Padilla et al. 2013), with the attendant reduction of financial and emotional costs. This clear spatial alignment of information in two image volume sets can be accomplished by imaging the breast with two or more modalities while the breast is stabilized, as in mammographic compression or a slight reduction thereof. Robust alignment of breast image volumes by imagebased registration of ultrasound and X-ray tomosynthesis is made difficult not only by the heterogeneous stiffness of the breast, but also by the substantial attenuation and other artifacts in ultrasound images at the nominal 8- to 17-MHz frequency usually employed in breast cancer diagnosis. Thus, registration of ultrasound and X-ray tomosynthesis is probably best performed in a combined system or, at the least, systems that image the breast in the same geometry. Our previous work with such a combined system has shown promise, although the ultrasound image coverage of the breast in the initial system was unnecessarily limited (Sinha et al. 2007a, 2007b).

Photo-acoustic imaging (PAI) is an emerging hybrid imaging technique featuring both optical contrast and ultrasonic resolution. There is evidence that optical imaging can detect many vascular anomalies in the breast and help characterize them with its ability to distinguish hypoxic blood pools (Tromberg et al. 2008). Perhaps, in detecting many of the vascular anomalies currently detected by MRI, with gadolinium contrast agent injection and high cost and inconvenience, PAI could contribute substantially to dynamic or static contrasts, looking for vascular abnormalities and breast cancer screening. The adaptation of PAI to breast cancer imaging has been reported by several groups. Oraevsky's group developed a laser-based PAI system using an arc-shaped transducer array, first with 32 elements and later with 128 elements, to visualize a 2-D slice of the breast (Andreev et al. 2000; Ermilov et al. 2009a). Based on the same thermo-acoustic effect, Kruger et al. (2000) used microwaves at 434-MHz frequency instead of a laser to achieve imaging of the breast. This microwave-induced thermo-acoustic imaging was sensitive to the concentration of ionic water in the breast tissues. Most recently, that group reported impressively detailed breast angiography on one subject with PAVI at the relatively high frequency of 5 MHz using the high focal gain of small ultrasound (US) elements on a spherical surface (Kruger et al. 2010). Manohar et al. (2005) built a photo-acoustic mammoscope named the Twente system by using a planar 2-D array with 590 elements read out by a single processing channel for 3-D breast imaging. Wang et al. (1997) fabricated a system that can conduct both thermo-acoustic and photo-acoustic imaging of a breast specimen. The two modalities were achieved using a microwave and a laser, respectively, while sharing the same signal acquisition realized through the scan of a single-element transducer (Pramanik et al. 2008). Oraevsky and his colleagues also explored the feasibility of photo-acoustic imaging of the breast by using a commercial US scanner. With PAI and US sharing the same acquisition system, including a handheld linear ultrasonic probe, images presenting ultrasonic and optical contrast were co-registered on a 2-D B-scan plane (Ermilov et al. 2009b).

The potential of PAI led us to explore its inclusion in a new combined system with full-coverage, automated 3-D ultrasound imaging in the mammographic geometry. This was the first system designed for compatibility with conventional mammography and tomosynthesis systems in the seated geometry. Our flat acoustic array, chosen for use in the mammographic geometry, allowed simultaneous synthetic focusing throughout a large (8 cm in diameter by 5 cm deep) approximately cylindrical volume through the breast; we referred to the technique as photo-acoustic volume imaging (PAVI). The goal of the work described in this article was initially to validate the performance with depth of this newly developed PAVI system in whole breast specimens. Inserted blood-containing structures were imaged, and photoacoustic signals from other tissue boundaries were identified by comparison with ultrasound image stacks obtained in the same positioning. It should be possible to spatially align the resulting PAVI and ultrasound image volumes with those from the previously

developed combined 3-D X-ray tomosynthesis and ultrasound system (Sinha et al. 2007a, 2007b). That alignment will be accomplished by image-based registration of the ultrasound image volumes from the two systems, allowing evaluation of the need for and potential of a system combining the three modalities.

METHODS

The performance of our newly fabricated PAVI system was reported previously (Zhixing et al. 2011). A low-frequency 2-D array from the GE Lunar Achilles bone densitometry system (GE Healthcare, Milwaukee, WI, USA), as used for PAI by Manohar et al. (2005), was modified to a -6 dB bandwidth of 0.6–1.7 MHz, with 20-channel instead of 1-channel readout. These modifications, plus removal of a segment of the array from one side to allow closer approach of more elements to the chest wall, were performed by HG Systems (Edgerton, WI, USA). We referred to the resulting 572-element array as the Pyrrah array. Figure 1a is a schematic of the array. The 86-mm-diameter transducer array consisted of a 110- μ m-thick poly(vinyl difluoride) (PVDF) film with 572 active elements of 2×2 mm with 3.175-mm pitch. The front cover of the transducer was an 18-mm-thick layer of high-density polyethylene, with acoustic properties similar to those of soft tissues, enabling good acoustic coupling between the PVDF film and the sample. Figure 1b is a schematic of the combined 3-D ultrasound and PAVI system for breast imaging. A Q-switched Nd-YAG pumped dye laser (ND6000, Continuum, Santa Clara, CA, USA), at that time, provided a pulse duration of 5 ns and repetition rate of 10 Hz, with pulse energy up to 2 J at 1064 nm. The laser beam was directed by a series of mirrors or prisms and expanded by a negative lens before hitting the surface of the imaged object. The Q-switched, synchronizing signal of the laser was transmitted to a digital delay/pulse generator (DG535, Stanford Research Systems, Sunnyvale, CA, USA) to set the time window for photo-acoustic signal acquisition. A 12-bit full-waveform data acquisition unit (DAU) (AcquiREC 32–24, Acquittek, Massy, France) in a PC chassis acquired the signal in 20 parallel channels, each sampling at up to 10 MHz. The acquired raw data were stored in the PC and reconstructed offline to rebuild the 3-D image of the sample. The image reconstruction was performed on the basis of a modified synthetic aperture algorithm (Zhixing et al. 2011). The photo-acoustic (PA) signal traced from each element was weighed by the apodization function and directivity function and then was summed with a two-layer model of time delay. This model differentiated the polyethylene layer of the front cover of the Pyrrah array from the sample. The displayed images were compensated exponentially along the depth direction for the light fluence decay according to the Monte Carlo simulation for light propagation in scattering tissues (Wang et al. 1997; Zhixing et al. 2011). A black rubber sphere of radius 0.2 mm embedded in the gel made of 8% gelatin and 92% water was set on the Pyrrah array to measure the point-spread function of the PAVI system. From analyses of the point-spread function at different distances from the surface of the array, it was concluded that the lateral resolution of the system after reconstruction ranged from 2.9 to 4.2 mm, and the axial resolution, from 1.9 to 3.7 mm, within a distance of 60 mm from the array (Zhixing et al. 2011).

Three-dimensional ultrasound imaging was achieved with a GE LOGIQ 9 B-scanner (GE Healthcare) with the linear probe driven by a two-axis motorized positioning system. The GE 10 L array transducer with a center frequency of 7.5 MHz was operated at the 10-MHz setting. The motion of the two-axis positioning system was controlled by computer to move the probe close to the region of interest and then translate it from left to right in a horizontal (XY) plane normal to the array imaging plane at a speed of 2 mm/s. The B-scanner triggering rate was set at 10 Hz to ensure acquisition of a parallel stack of 2-D US images at 0.2-mm intervals. The 3-D US image was then reconstructed and interpolated to have the same pixel size as that in the PAVI image. More details for the automatic 3-D ultrasound

imaging of the breast can be found in our previous work (Booi et al. 2007; Goodsitt et al. 2008; Sinha et al. 2007a, 2007b; Wodnicki et al. 2011).

The breast specimens were positioned in the mammographic geometry between a compression paddle above and the Pyrrah array below. In our *in vivo* breast ultrasound studies, this relatively mild compression reduced patient motion induced by patient discomfort and still controlled respiratory and most other motion, hence benefitting the co-registration between image data acquired in that compression with different modalities. Moreover, the compression also lowered the imaging depth requirements for covering the entire breast from one or two sides, improving the optical coverage and allowable ultrasound frequencies and, thus, contrast and resolution. Breast compression could be controlled so that it did not eliminate most of the blood or its flow from the breast. In fact, given the varying degrees of abnormal pooling of arterial or venous blood and low impedance shunts in many breast cancers, changing the degree of compression could lead to further diagnostic information similar to that obtained from dynamic contrast imaging (LeCarpentier et al. 2006). For good optical and acoustic penetration, a compression paddle was made from fish line, as pictured in Figure 1c (Blane et al. 2010). We now favor more closely spaced fiber meshes. Both coarse and fine meshes help stabilize the breast better and at lower compressions than solid paddles when the slick acoustic coupling gel is applied to the skin. The porous meshes also facilitate application of coupling agent. For this study, the ultrasound imaging probe acquired the ultrasound image from the top through the compression paddle. In the PAVI mode, the ultrasound probe was removed for the laser beam to illuminate the top surface of the breast through the compression paddle. The expanded laser beam covered an area of 81 cm² with an incident energy density of 18 mJ/cm², less than the American National Standards Institute (ANSI) safety limit at 1064 nm. The photo-acoustic signals were detected in the transmission mode by the Pyrrah array serving only as a receiver lying beneath the breast. The benefit of this design was avoidance of the severe impacts on weak PA signals from deeper tissues of the huge PA waves from the laser-illuminated surface and their acoustic reverberations from air boundaries. Each photo-acoustic image was acquired in 12 min with 256 times averaging. Because the relative positions of the B-scan probe and the Pyrrah array were known, co-registration of the 3-D ultrasound image and the 3-D PAVI image could be accomplished accurately.

Extensive clinical and preclinical research has indicated that neo-angiogenesis, playing a crucial role in cancer generation and progression, is a prognostic marker and a potential target for tumor therapy. For imaging tumor angiogenesis or, more generally, tumor vascularization with PAVI, deoxygenated hemoglobin and oxyhemoglobin are two of the dominant chromophores for near-infrared (NIR) light. The difference in their absorption spectra allows discrimination of these two states of hemoglobin, offering another possibility for discrimination of breast cancer. Minimally pigmented tissues of high saline or lipid content constitute the imaging background. Although breast tissues have the best optical penetration in the “optical window” between 700 and 900 nm and the best contrast of blood is at 725 nm, imaging at 1064 nm should favor detection of additional interfaces in the breast based on contrast other than blood. This is due to the stronger and differing optical absorption at 1064 nm of the main breast constituents, water and lipids. The average water content of tumors is about 26%, compared with 16% in normal breast tissue (Lihong 2009), providing tumors with an absorption contrast 1.6-fold to that of normal breast tissue at 1064 nm. The hemoglobin concentration in tumors is also greater than the concentration in normal tissue (Lihong 2009). Because of the higher concentrations of hemoglobin and water, breast tumors possess a well-detectable optical absorption contrast up to 2.9-fold to that of normal breast tissue at 1064 nm (Cerussi et al. 2006). In addition, at the time of this study, the highest laser power output was available only at 1064 nm from Nd:YAG lasers.

Fresh un-embalmed breast specimens were obtained from the University of Michigan Medical School Necropsy Laboratory. The cadavers were provided to the Anatomical Donations Program with consent for educational and research use. To maintain the shape of the breast, the whole breast was harvested from the cadaver together with all or part of the connected chest wall. The first specimen was from a 58-y-old woman and was predominantly fatty as judged from the sonograms. In the first study with no artificial lesion embedded, we tried to image the tissue features in a breast based on the intrinsic tissue optical contrast. For comparison with photo-acoustic findings in addition to pulse echo ultrasound, anatomic photographs of the specimen were taken after the imaging experiment. Before anatomic examination, in the necropsy laboratory, the breast was first frozen and then sliced, using a bandsaw, along the YZ orientation of our imaging system, approximately a para-coronal body plane.

In the second study on the fatty specimen from a 58-y-old woman, we explored the maximum depth of this system in imaging blood-rich vessels or lesions in the mammographic geometry. Artificial vessels of soft, optically transparent Tygon tubes (inside diameter: 2.4 mm outside diameter: 4.0 mm) were embedded at different depths (25, 37, 40 and 49 mm) from the compressed sample surface to be illuminated with light. They were then filled with 10% blood diluted with saline and used to simulate the blood volume, because the specimen was not perfused with blood as *in vivo*, and implantation of or search for the same blood vessels at different depths in the breast *in vivo* to provide a statistical comparison is not allowed. In an MRI study of 51 (54) breasts with (without) malignant lesions, the mean maximum vessel diameter per breast was 3.6 mm in patients with a malignancy and 2.6 mm in controls (Grubstein et al. 2010). The 10% blood solution simulated a small tumor of 10% fractional blood volume, homogeneously distributed. The tube simulated a tumor that, for convenience, is very long.

In the third study, an all-silicone balloon catheter (8 Fr, 3 cc, C. R. Bard, Covington, GA, USA) filled with whole blood was embedded in the moderately dense breast of a 60-y-old woman, centered at a depth of 31 mm, for both photo-acoustic and ultrasound imaging. By imaging the same breast sample sequentially with 3-D PAVI and 3-D US without relocating the specimen, we could compare the features in the two modalities. The breast specimen had a total thickness of 52.7 mm after mild compression. The balloon and catheter tube allowed good optical and acoustic penetration. Moreover, by controlling the volume of blood injected into the balloon, we could precisely control the size of the artificial lesion. We first used one syringe at one end of a four-way stopcock to evacuate the balloon and then used another syringe at another end of the stopcock to fill the balloon with blood slowly to ensure that no air was left in the balloon to affect imaging. The balloon of up to 3 cc was well within the range of sizes of vascular breast cancers. Images of the uniform blood or diluted blood in the balloon would be edge enhanced because of the limited bandwidth of the ultrasound array, and boundaries normal to the transducer would be seen most strongly as in pulse echo ultrasound. It was expected that most malignant breast tumors would have enough vascular heterogeneity to produce photo-acoustic signals throughout much of the tumor, as observed in the few previous breast cases (Ermilov et al. 2009a; Jose et al. 2009) and in MRI enhancement (Karahaliou et al. 2010).

RESULTS

In Figure 2 are the imaging results for a breast specimen with no artificial lesion embedded. In the anatomic photograph (Fig. 2a), a subsurface streak of blood, probably extravasation from a vessel, can be seen. This lesion was at a depth of 41.3 mm from the sample surface illuminated with laser light. The reconstructed PAVI data are presented as maximum amplitude projection (MAP) images in the XY, XZ and YZ planes, in Figures 2(b–d),

respectively). Based on the high sensitivity of PAVI to blood, the lesion in the breast could be recognized clearly in each PAVI image (see red arrows). The average contrast-to-noise ratio (CNR) was 7.8 dB. In Figure 2(c and d), the interface between the Pyrrah array and sample is indicated by the *yellow arrow*.

In Figure 3 are the imaging results for a compressed breast specimen containing artificial lesions/vessels. The coordinate of minimum depth $Z = 0$ refers to the position where the light entered the breast, the plane furthest from the ultrasound detecting elements of the Pyrrah array in PAVI space. Figure 3a is a sample photograph of two artificial lesions made from blood-filled tubes and embedded at different depths. In the MAP images (Fig. 3c–e), two lesions 25 and 37 mm from the sample surface illuminated by laser light could be recognized clearly. In another test in which the depths of the two lesions were 40 and 49, mm respectively, we could still recognize the two lesions in each image, as observed in Figure 3(f–h), although the CNRs were degraded. In Figure 3(i) the plot of CNR versus depth is linear. CNR was calculated on the basis of the voxels in the middle region in PAVI space. It was mainly because fewer detecting elements could be used for the reconstruction with the receiving angles covering the voxel in the edge region than in the common middle region. Because of the strong light attenuation in the breast tissue and the large illuminated surface, light fluence decayed essentially exponentially with depth. Therefore, in imaging of embedded lesions, CNR (in dB) exhibited a nearly linear relationship with depth. The relationship was consistent with the exponential decay of the fluence distribution predicted by Monte Carlo simulation (Wang et al. 1997; Zhixing et al. 2011). The compensating scaling along the depth for rendering the PAVI images would not affect the CNR, because both contrast and noise were scaled up at the same ratio. The CNR did not exhibit a reciprocal relationship with distance from the ultrasound detecting elements, because at the low frequency of 1 MHz, attenuation of the ultrasound wave was much smaller than the attenuation of the light propagation in breast tissue; the latter dominated the CNR-depth curve. Figure 3(i) indicates that with 256-sample averaging and 1064-nm wavelength, the extrapolated maximum depth in imaging a 2.4-mm blood-rich lesion with a 3-dB CNR in a compressed breast is 54 mm.

In Figure 4 are the co-registered PAVI (a) and ultrasound (b) images of the same 2-D YZ plane in a human breast. The imaged cross section contained a catheter balloon filled with 0.3 mL of blood. Working with the high-frequency linear array transducer, the B scan indicated clearly the internal structure of the breast specimen, including a variety of interfaces between glandular, adipose and skin tissues. Some of these structures could also be seen in the co-registered PAVI image, as a result of variations in optical absorbance contrast. It was the first time, to the best of our knowledge, that PAVI, based on the intrinsic tissue optical contrast at 1064 nm, could differentiate different tissues in a human breast. The catheter, marked with a *solid red arrow*, and the bottom interface of the breast specimen with the Pyrrah array, marked with a *dashed red arrow*, could be recognized clearly in both images as a reference. The position of the balloon in the B-mode image volume is enclosed by a *dashed red circle*, as confirmed before the PAVI acquisition by observing in real time the balloon's inflation and deflation. The balloon appeared as a hypoechoic area in the B-scan, whereas the PAVI image provided a clear rendering of the balloon's front surface. Various tissue interfaces were marked with yellow arrows from top to bottom in both images and matched well.

DISCUSSION

A PAVI system employing a 2-D multi-channel PVDF array was developed for breast imaging in combination with full-coverage, automated 3-D ultrasound and X-ray breast tomosynthesis. This was the first system designed for compatibility with conventional

mammography and tomosynthesis systems in the seated geometry. The array covered the cylindrical imaging space of 86-mm diameter. The lateral resolution of the system after imaging reconstruction ranged from 2.9 to 4.2 mm, and the axial resolution, from 1.9 to 3.7 mm, within 60 mm from the array. The performance of this system in imaging breast tissue features and blood-rich lesions deep in *ex vivo* whole breasts harvested from fresh cadavers was explored. Taking advantage of the good penetration of NIR light and the high receiving sensitivity of the broadband 2-D PVDF array, imaging of artificial lesions made from Tygon tubes filled with 10% diluted blood was achieved non-invasively to a depth up to 49 mm in the breast. The imaging depth could be extrapolated to 54 mm at a 3-dB CNR. Although the blood volume in the excised breasts was probably considerably lower than it was *in vivo*, these results provided the best available indication of the potential for breast imaging with our system. Most breasts do not have a large fractional blood volume, as indicated by 3-D Doppler ultrasound (Le Carpentier et al. 2001). With this imaging depth, increased by the more powerful lasers now available and greater blood volume in many breasts *in vivo*, PAVI should have little problem covering the breasts of most patients with one to several placements or view angles from each side in the mammographic geometry. The PAVI system has received institutional review board approval for further *in vivo* human studies at the University of Michigan Medical School.

Other than artificial lesions, PAVI, based on the intrinsic tissue optical contrast, has also been used successfully to image some breast tissue features, including the interfaces on both sides of the skin, the connective tissue sheet in subcutaneous fat and the lobar capsule, as illustrated in Figure 4, as well as endogenous blood, as indicated in Figure 2. Knowledge of the shape and density of pools of blood or blood vessels and their oxygenation concentrations is thought to be helpful in detecting and diagnosing breast cancer, and PAVI renders this information much better than ultrasound imaging. As proven in Figure 4, the position of the blood-filled balloon in the B-mode image volume was blurred and appeared as a hypoechoic area, whereas the PAVI image provided a clear rendering of the balloon's front surface. We know of no existing literature reporting the absorption coefficient at 1064 nm of the major components of fresh breast specimens. When measured in thawed frozen sections, at 900 nm, the absorption coefficients of the glandular, adipose and fibrocystic tissues of the breast are 0.6, 0.8 and 0.3 cm^{-1} , respectively (Cheong et al. 1990). The absorption coefficient of lipid at 1064 nm is 0.053 cm^{-1} (Van Veen et al. 2005). The absorption coefficients of water and blood at 1064 nm are about 0.128 cm^{-1} (Irvine and Pollack 1968) and 5.5 cm^{-1} (Cheong et al. 1990), respectively. The tube phantom filled with 10% diluted blood has an estimated absorption coefficient of 0.67 cm^{-1} . As a reference, the absorption coefficient of breast fibroadenoma at 900 nm is 0.7 cm^{-1} as measured in thawed frozen sections (Cheong et al. 1990). Because the photo-acoustic effect responds to the differential of the optical absorption at the targeted location, some of the interface images obtained with PAVI, as evidenced by pulse echo US in Figure 4, reveal that such tissues as skin, connective tissue sheets in fat and lobar capsule, have detectably different optical absorption properties at 1064 nm in fresh breast specimens. Though US imaging provides better contrast than current PAVI for these interfaces, this new knowledge should be helpful in further extending the capabilities of PAVI.

In this study, PAVI of the breast was performed together with 3-D automated US in a combined breast imaging system. With the breast compressed between the Pyrrah array and a mesh compression paddle, the high-frequency linear array was scanned along the top for pulse echo US images. With the linear array out of the way, the low-frequency Pyrrah array on the bottom detected the PA signals from laser illumination on the top. Through this design, the system facilitated 3-D imaging of an entire breast with both optical and ultrasonic contrast mechanisms. Because the dual-modality imaging was conducted without the need to relocate the specimen, PAVI and ultrasound image stacks could be co-registered

accurately. The resolution of this PAVI system with its flat, low-frequency ultrasound transducer array was not as high as that of the sharply focused, higher-frequency array of Kruger et al. (2010). However, a very large volume of the breast was covered in a single view with our system, and the lower frequency offered the potential to remove edge effects from larger areas of highblood-content capillary beds. Although further development and optimization are needed before this system can be adapted to clinical trials on patients, the success in this preliminary study suggests that PAVI, when combined with other modalities such as 3-D ultrasound and/or digital tomosynthesis, might well contribute to breast cancer detection, diagnosis and prognosis.

Acknowledgments

This work was supported by NIH Grants R01 CA91713 and CA91713-S1. Partial support from the Samsung GRO 2012 Program is acknowledged. We acknowledge Kai Thomenius at GE Global Research, Niskayuna, New York, USA, for suggesting and helping to arrange the development of the Pyrrah array, and Mr. Richard F. Morris, HGsystems, LLC, for his development and continuing support of the Pyrrah array. Dean A Mueller, MOL, of the Anatomical Donations Program at the University of Michigan is acknowledged for preparing and providing the specimens and helping with the anatomic photographs.

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Fig. 1.

(a) Schematic of the Pyrrah array. (b) Schematic of the multimodal system for 3-D photoacoustic volume imaging (PAVI) and ultrasound imaging of breast in the mammographic geometry. (c) Photograph showing the mesh paddle compressing the breast and the motorized positioning system driving the probe for 3-D automatic ultrasound imaging.

Fig. 2.

(a) Anatomic photograph of a slice in the breast in the YZ plane containing an endogenous blood collection, or “lesion.” Z was the direction of incident light and ultrasound. (b–d) Maximum amplitude projection images of photoacoustic volume images of the breast on the XY, XZ and YZ planes, respectively. The lesion at the depth of 41.3 mm is indicated by the *red arrows*. The interface between the Pyrrah surface and the sample is indicated by the *yellow arrows*.

Fig. 3.

(a) Sample photograph. (b) Diagram of tube orientations in the XY plane. (c–e) Maximum amplitude projection images on the XY, XZ and YZ planes of the imaging space, where the depths of the two tubes are 25 and 37 mm. (f–h) Maximum amplitude projection images on the XY, XZ and YZ planes of the imaging space, where the depths of the two tubes are 40 and 49 mm. The positions of tubes in each image are indicated by the *red arrows*. (i) Contrast-to-noise ratios in images of the artificial lesions in the breast as a function of depth. The extrapolated maximum imaging depth at a 3-dB CNR is 54 mm.

Fig. 4.

Co-registered photo-acoustic (a) and ultrasound (b) images of a cross section of a compressed breast containing a catheter balloon filled with blood (*dashed red circle*). The balloon's catheter is indicated by the *solid red arrow*. The interface between the breast specimen and the Pyrrah surface is indicated by the *dashed red arrow*. The balloon appeared as a hypoechoic area in the B-scan, whereas photo-acoustic volume imaging provided a clear rendering of the balloon's front surface. Some possible tissue features lying approximately parallel to the receiver array surface in these still edge-enhanced images are (indicated by the *yellow arrows*), from top to bottom, the external and interior interfaces with the skin, connective tissue sheets in subcutaneous fat and a capsule of a lobe.