Blood Flow Reduction in Breast Tissue due to Mammographic Compression

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Rationale and objectives: This study measures hemodynamic properties such as blood flow and hemoglobin concentration and oxygenation in the healthy human breast under a wide range of compressive loads. Because many breast-imaging technologies derive contrast from the deformed breast, these load-dependent vascular responses affect contrast agent–enhanced and hemoglobin-based breast imaging.

Methods: Diffuse optical and diffuse correlation spectroscopies were used to measure the concentrations of oxygenated and deoxygenated hemoglobin, lipid, water, and microvascular blood flow during axial breast compression in the parallel-plate transmission geometry.

Results: Significant reductions ($P < .01$) in total hemoglobin concentration (~30%), blood oxygenation (~20%), and blood flow (~87%) were observed under applied pressures (forces) of up to 30 kPa (120 N) in 15 subjects. Lipid and water concentrations changed <10%.

Conclusions: Imaging protocols based on injected contrast agents should account for variation in tissue blood flow due to mammographic compression. Similarly, imaging techniques that depend on endogenous blood contrasts will be affected by breast compression during imaging.

Key Words: Mammographic compression; breast cancer; blood flow; breast imaging; diffuse optics.

Exogenous contrast agents are playing an increasingly important role in breast cancer screening and diagnosis, because they improve image signal-to-noise and offer novel targeting potential as tissue biomarkers. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) uses intravenous injection of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), for example, and is currently recommended as a screening tool for high-risk women (1). Similarly, contrast-enhanced digital x-ray tomosynthesis often uses injection of iodine-based agents into the compressed breast (2,3). Both of these techniques rely on adequate blood flow to control the delivery, uptake, and spatial distribution of the contrast agent. Deformation of breast tissue during compression, however, can lead to modifications of regional blood flow that alter tissue oxygenation and metabolism as well as contrast agent delivery. Furthermore, the mechanical properties of tumors are generally different from those of the surrounding tissues (4–12), and these differences can lead to uncontrolled and heterogeneous vascular responses of the breast to compression. Thus, compression can significantly reduce cancer contrast.

In addition to the standard clinical techniques mentioned previously, scientists continue to explore new technologies to enhance breast cancer specificity and sensitivity. Diffuse optical spectroscopy (DOS) and tomography (DOT), for example, are novel methodologies that utilize photons in the near-infrared (NIR, 650–950 nm) tissue transmission window to measure properties of normal and diseased breast tissues noninvasively and *in vivo* (13–39). In breast cancer, these physiological parameters typically include the concentration of oxygenated and deoxygenated hemoglobin (HbO_2 and Hb, respectively), from which total tissue hemoglobin concentration ($Hb_t = HbO_2 + Hb \propto$ blood volume) and blood oxygen saturation ($StO_2 = HbO_2/Hb_t$) are readily calculated. These hemodynamic parameters, including other tissue properties such as water and lipid concentration and reduced tissue scattering (μ_s'), all provide significant endogenous tumor contrast for the optical method. In

Acad Radiol 2014; 21:151–161

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http://dx.doi.org/10.1016/j.acra.2013.10.009

practice, clinical DOS/DOT measurements typically involve placing breast tissue under some type of mild compression, however, and the effects of this compression on breast tissue vasculature are not generally considered in the analysis of DOT results, despite observations suggesting that compression effects are present (24,30,40–48).

In light of these issues concerning hemodynamics and contrast agent delivery, the primary focus of the present article is to characterize the blood flow responses of healthy breast tissue to compression. We use a compression similar to that performed in clinical mammograms and in contrast-enhanced x-ray tomosynthesis—that is, a parallel-plate geometry with applied loads up to 120 N. Importantly, the data derived provide the first direct measurements of microvascular blood flow changes during compression and provide insight about healthy breast tissue hemodynamic responses to compression. Ultimately, these results should provide guidance for use of contrast agents to enhance tumor visibility in the compressed breast and for optimal implementation of DOT and DOS.

To accomplish this goal, DOS is used for the measurement of average tissue chromophore concentrations, and a relatively new technique, diffuse correlation spectroscopy (DCS), is used for direct measurement of microvascular breast tissue blood flow (14,49–60). Briefly, DCS measures fluctuations in light intensity collected after transmission through the breast. These temporal fluctuations depend on the flow of red blood cells. Larger flows yield faster fluctuations of the detected light field and a more rapid decay of the field temporal autocorrelation function. DCS blood flow indices (BF) are derived from the measured temporal decay rate of the autocorrelation function; the flow indices have been validated previously (61–74). Notably, the study described here also represents the first DCS-flow measurements detected in *transmission* through human breast, and because full tomographic diffuse optical reconstruction of breast generally requires *transmission* measurements, the study takes an important first step toward optical blood flow *tomography* of human breast.

METHODS

Recruitment

A total of 30 healthy volunteers over the age of 18 years were recruited. Because of mechanical limitations of our tissue interface, we initially restricted recruitment to women who wore B-cup or larger bras; after gaining experience with measurements, we limited further recruitment to women with C-cup or larger bras (patient demographics are described in Table 1). Five subjects were not included in analysis because of motion artifacts or tissue contact issues; eight subjects were excluded because of low DCS signal; and two subjects were excluded because of instrumental mechanical failure. Partial datasets, however (e.g., the left breast of a woman who moved during right breast measurements), were included in the analysis. Thus, the data reported are derived from 15 healthy volunteers.

TABLE 1. Demographic Information for Healthy Subjects Studied in the Compression Investigation

Parameters	Subjects (*N* = 15)
Age, yr	35 ± 16 (19, 67)
BMI, kg/m^2	26 ± 7.8 (19.6, 49.3)
Menopausal status	
Premenopausal	12 (75%)
Postmenopausal	3 (25%)
Bra cup size	
B	1 (7%)
C	8 (53%)
D	5 (33%)
E	1 (7%)
Race/ethnicity	
Caucasian	11 (73%)
African American	3 (20%)
Asian	1 (7%)
Hispanic	0 (0%)

Race/ethnicity and bra cup size are self-reported. Body mass index (BMI) and age are reported as mean ± standard deviation (minimum, maximum).

Measurement Protocol

After the instrument height was properly adjusted for each subject (Fig 1a), baseline measurements of force (load), pressure, and optical properties were collected. Optical measurements utilized a time-domain DOS (TD-DOS) system. The TD-DOS instrument consisted of 690, 750, 785, 800, 830, and 838 nm pulsed diode lasers (Picoquant, Berlin Germany), photon-counting photomultiplier tubes (H7422-50P, Hamamatsu, Hamamatsu City, Japan), and time-correlated single photon-counting electronics (SPC-134, Becker and Hickl, Berlin, Germany), all described in Busch (75). The blood flow measurements were carried out with the DCS technique using a light source at 785 nm and detectors described in Durduran et al. (62). We used a single source and detector position for the optical measurements, colocating and averaging eight DCS detectors to improve the signal-to-noise ratio (SNR). Optical measurements were performed serially; TD-DOS measurements at all six wavelengths were followed by DCS measurements at a single wavelength. Integration times for each technique were adjusted to provide acceptable SNR for each technique; the TD-DOS wavelength was integrated for ~1–2 seconds at the baseline plate separation and ~0.5–1 seconds during compression; DCS signal was integrated for ~3–5 seconds throughout the experiment. The integration times were chosen generously to improve SNR; in the future, various technical alterations should permit faster data acquisition.

Skin pressure was measured using an array of 26 sensors (Tactilus Free Form, Sensor Products, Madison, NJ) distributed on the upper and lower compression plates (Fig 1b,c). The pressure readings across the breast were highly heterogeneous due to edge effects; therefore, we used three sensors immediately adjacent to the fiberoptics, that is, close to the location where the breast was centered, for further analysis.