Title: Enhancement of Hemodynamic Contrast in the Cancerous Breast by a Controlled Articulation

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Details of blood delivery to tissue and bulk fluid redistribution among the various tissue compartments frequently are impacted by disease or trauma. For example, derangements in hemodynamic states, accompanied by increased tissue stiffness and local edema, is a common breast cancer phenotype [1]. Accordingly, we have hypothesized that externally applied mechanical forces can produce distinct dynamic responses between diseased and healthy tissue fractions, thereby enhancing diagnostic image contrast. Additional evidence for this sort of contrast-enhancing effect comes from recently reported correspondences that we have observed, between fNIRS-based hemodynamic image data and results of computed estimates of internal mechanical stress and pressure distributions, as a function of various applied articulation maneuvers [2]. The reported concurrences suggest that spatial distributions of hemodynamic variables in the fNIRS images represent redistributions of blood in response to changes in the internal stress.

To evaluate the hypothesis that image contrast between breast tumors and surrounding healthy tissue may be enhanced via controlled articulation maneuvers, we have conducted a pre-clinical study using a recently developed an fNIRS-based breast imaging system [3]. A principal technological element of the imager is concurrent bilateral measurements of the viscoelastic and hemodynamic properties of the breast, in response to a wide range of controlled articulation maneuvers. After giving informed consent and providing a brief medical history, research participants were seated and the sensing heads were adjusted to make good contact with both breasts. Following a five-minute baseline scan, the skin-optode contact pressure was rapidly (~2 s) increased to a level of either 4.4 N or 7.1 N, and data collection continued during the subsequent period of stress relaxation (60-120 s). Optical data were analyzed offline: application of a low-pass filter with a 0.2-Hz cutoff frequency was followed by use of the Normalized Difference Method to reconstruct images of oxygenated and deoxygenated hemoglobin (HbO, HbD), tissue oxygen saturation (HbSat), and blood volume (HbT) [4].

Imaging results obtained from 61 subjects (17 breast cancer, 21 benign pathology, 23 healthy control) are consistent with the hypothesis that the articulation maneuvers enhance the contrast between tumor and healthy tissue. Also noteworthy is the finding that image contrast is further improved by transforming pairs of co-varying image-values [i.e., (HbD,HbSat), (HbD,HbT), or (HbSat,HbT)] to measures of the statistical extremeness (i.e., the Mahalanobis distance [5]) for each pixel. The magnitude of the preceding effect is maximized by referencing the image-pixel data of one breast to the distribution of image values for the contralateral breast. In the final analysis, the paired difference between the numbers of image pixels identified as abnormal is greater for subjects with breast cancer than for either of the other sub-groups, by a statistically highly significant amount ($p \leq 0.007$, unequal variance t-test). In addition, diagnostic accuracies for breast cancer of 80-90% (ROC analysis [6]) are achieved. This is a concrete demonstration of the utility of the simultaneous dual-breast measurement approach; of the fNIRS-based breast imagers reported to date, to our knowledge this strategy has been implemented only in the instrument described in Ref. 3. Thus we have demonstrated that controlled manipulation of the internal force distribution of breast tissue can enhance the detectability of cancer, by exploiting a known tumor phenotype.

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