Carbogen Inspiration Enhances Hemodynamic Contrast in the Cancerous Breast

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Abstract: We have explored the vascular response of the breast to inspiration of Carbogen. Results show greater changes in vasoconstriction and HbSat in the tumor-bearing breast compared to the healthy contralateral breast of the same patient.
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1. Introduction

Key hallmarks of the tumor phenotype are increased stiffness [1], enhanced angiogenesis with sluggish perfusion [2], increased vascular leakiness leading to increased interstitial pressures [3], and increased metabolic demand [2]. Separately, it is known that the vascular autoregulation mechanism achieves a tight coupling between the vascular supply and prevailing metabolic demand. Additionally, it is appreciated that the fidelity of vascular autoregulation may be attenuated in tumor tissue as a consequence to alterations in the peripheral effector complex comprising the vascular endothelium and surrounding vascular smooth muscle [2]. One consequence of this is the finding that many tumor types operate on the brink of hypoxemia, suggesting that the otherwise enhanced supply actually is limited, perhaps as a consequence of disturbances in hydrostatic pressures caused by vascular leakiness and changes to the interstitium scaffolding [1].

A simple consideration that embraces all of these elements is the expectation that manipulations of the oxygen supply-demand balance could well produce responses that differ markedly between the tumor and surrounding healthy tissue. One approach that has recently been considered is the inspiration of carbogen [4]. The response to carbogen is tissue-specific, likely reflecting the differential sensitivity of chemoreceptors and differences in reserve autoregulatory capacity, among other factors. While the typical carbogen response is vasodilation, as a consequence of the effects of elevated CO_2, elevated oxygen levels *per se* typically cause vasoconstriction [4].

In this report we have explored the response of the healthy and tumor-bearing breast to a reduced carbogen mixture (98% O_2, 2% CO_2), at rest and in response to controlled articulation maneuvers, as a basis for producing additional modulation on the oxygen supply-demand balance.

2. Methods

Simultaneous bilateral breast imaging was performed using the optomechnical imaging system recently described by Al abdi *et al*. [5]. The system provides for high-density dynamic optical tomographic imaging and simultaneous measures of the viscoelastic response to precise articulation. After obtaining informed consent and a brief medical history from the research participants, they were seated and the sensing heads were adjusted to make good contact with both breasts. Following a five-minute baseline scan while breathing room air, a facemask was applied and subjects breathed a modified carbogen mixture consisting of 98% O_2 and 2% CO_2 for an additional five minutes. In other cases, a series of articulation maneuvers were applied following each respective baseline period.

Optical data were analyzed offline, using the Normalized Difference Method to reconstruct tissue oxygen saturation (HbSat) and blood volume (HbT) images [6]. Prior to reconstruction, data were filtered using a low-pass filter with a 0.2-Hz cutoff frequency.

3. Results

Figure 1 shows volume-averaged HbSat and HbT time series, derived from data collected from a healthy subject. Carbogen inspiration was started at about 5 minutes, as indicated in the graph by the red dot. It is seen in Fig. 1(a) that, following a delay of less than 20 seconds after initiation of carbogen breathing, HbSat levels begin to increase. Interestingly, we observed a marked time delay in the expected vasoconstriction in the tumor bearing breast. It is observed in Fig. 1(b) that HbT levels decrease, indicating a vasoconstrictive response. Both trends in Fig. 1 are physiologically reasonable, given the large increase in the oxygen content of the inspired gas.

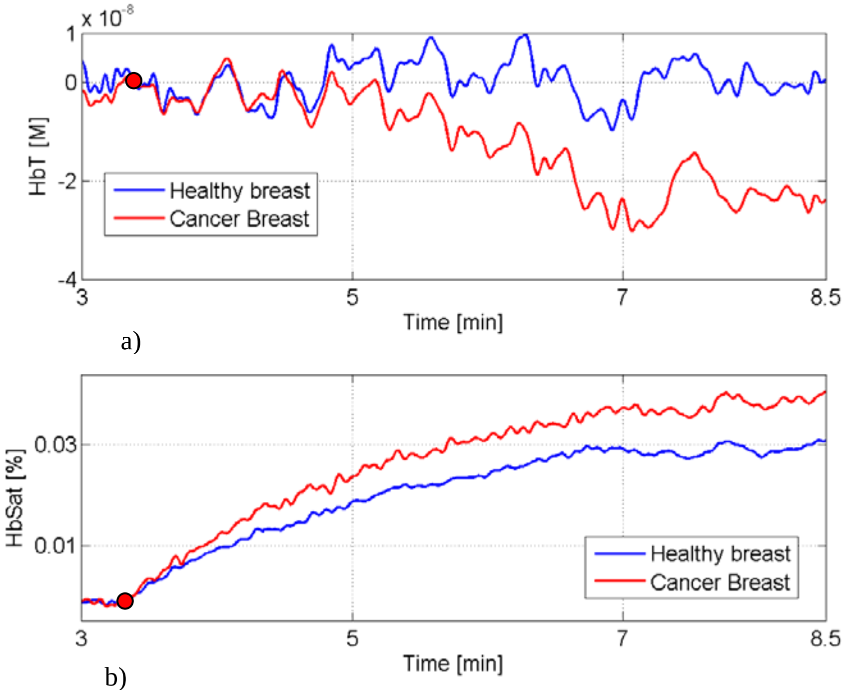

Figure 1. Spatial mean time series of hemodynamic response to carbogen inspiration. a) HbSat, b) HbT. Subject was 75 years old, with a BMI of 24 and size C breasts, and she had a 1-cm IDC tumor. Results are calculated from a first-order perturbation equation, which tends to underestimate the magnitudes of hemodynamic variables [7].

Shown in Figure 2 are axial, sagittal, and coronal views of HbSat and HbT changes upon application of carbogen in two subjects: one was healthy and the second one had a 1-cm IDC tumor in the right breast at 4 o'clock, middle depth. The HbT and HbSat contrast maps were determined by computing the difference between the mean of HbSat/HbT values after the subjects had breathed carbogen for four minutes and the HbSat/HbT seen during the baseline period, while the subject was breathing room air. Inspection reveals that the region undergoing the largest increase in HbSat and largest decrease in HbT coincides closely with the known tumor location [see Fig. 2(a) and 2(c)], while images of the healthy subject reveal more homogeneous responses in both breasts, for both HbSat and HbT.

4. Summary

Results we obtained are consistent with the motivating hypothesis that carbogen and room air would have differential impacts on healthy and tumor tissues' microvasculature, comparable to a previously reported effect seen when comparing pure oxygen and carbogen [4]. In particular, we have found that tumor tissue shows a larger drop in HbT and concomitant rise in HbSat in comparison to healthy tissue. One plausible explanation for the enhanced response of cancerous tissue is the relative absence of the compensatory mechanisms in the tumor microvasculature, which in healthy tissue seek to maintain HbSat within a physiologically optimal range.

While the results shown in Fig. 2 are a representative response for two individuals, the results of more than 30 subjects concur with the results shown. Thus we have demonstrated that controlled manipulation of the tissue oxygen supply-demand balance can enhance the detectability of breast cancer by exploiting known physiological abnormalities of tumor tissue. While in this instance the manipulation consisted of modifying the composition of the inspired gas, other, equally straightforward, approaches can be adopted.

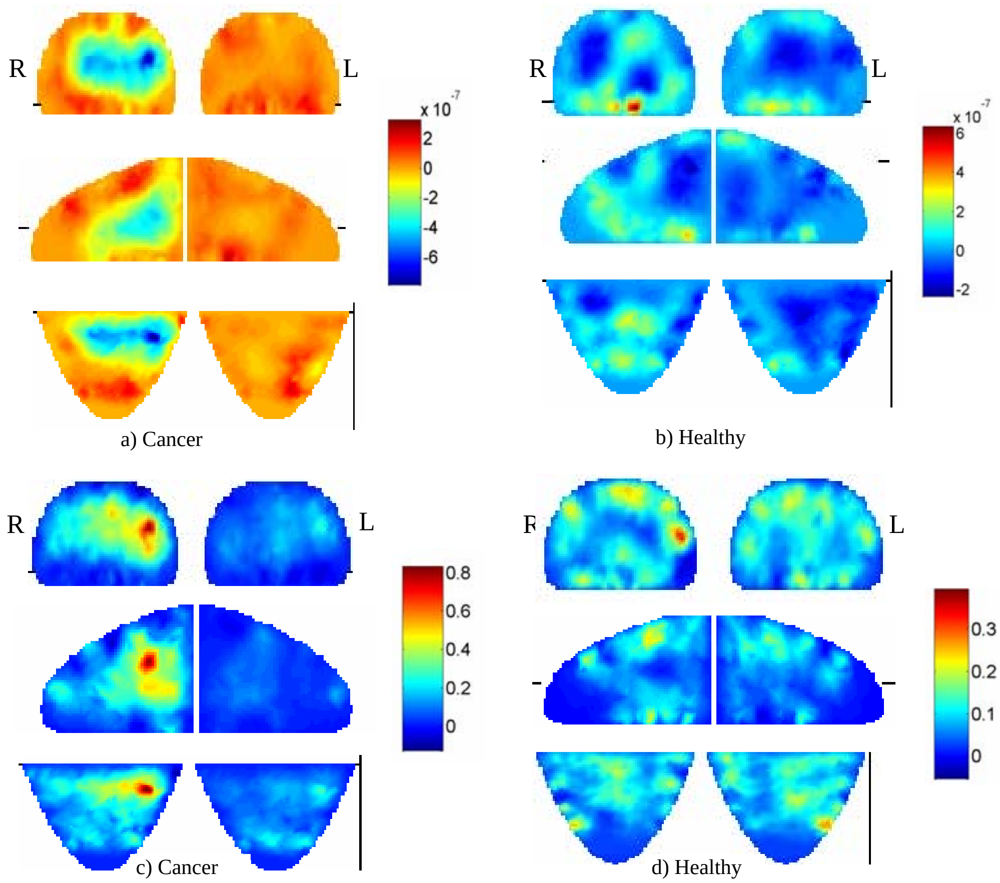

Figure 2: Spatial maps of difference between hemodynamic response before and after carbogen inspiration, for a healthy and a cancer patient. (a) and (b) the HbT difference for cancer and healthy patient, respectively, (c) and (d) the HbSat difference for the cancer and healthy subject, respectively. The cancer patient was a 34 year-old woman, DD breast size, BMI of 29, and a 1-cm IDC tumor in the right breast. The healthy subject was 39 years old, with D breast size and BMI of 32.

5. Acknowledgments

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