Enhancement of Hemodynamic Contrast in the Cancerous Breast by Carbogen Inspiration

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INTRODUCTION

Hallmarks of the tumor phenotype include 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 normally achieves a tight coupling between the vascular supply and prevailing metabolic demand, but that the fidelity of vascular autoregulation may be attenuated in tumor tissue as a consequence of alterations in the vascular endothelium and surrounding vascular smooth muscle [2]. One consequence of this is that many tumor types operate on the brink of hypoxia, 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 interstitial scaffolding [1]. We hypothesized that manipulations of the oxygen supply-demand balance may produce responses that differ markedly between the tumor and surrounding healthy tissue. One approach that has recently been explored is the inspiration of carbogen [4]. While the carbogen response is tissue-specific, the most commonly seen response is vasodilation as a consequence of the effects of elevated CO2 [4]. Here we use a recently developed an NIRs-based breast imaging system [5] to explore the response of the healthy and tumor-bearing breast to a carbogen mixture consisting of 98% O2 and 2% CO2, as a basis for producing additional modulation of the oxygen supply-demand balance.

EXPERIMENTAL PROTOCOL

Following a five-minute baseline scan, while breathing room air, a non-rebreathing face mask was applied and subjects breathed a modified carbogen mixture consisting of 98% O2 and 2% CO2 for an additional five minutes. 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) [6].

STUDY POPULATION

Table 1. Subjects’ clinical information. Within the group of women who had active breast cancer at the time of the examination, there were 10 with invasive ductal carcinoma, 2 with invasive mammary carcinoma, 1 with intraductal carcinoma, the one with invasive lobular carcinoma in situ (DCIS), and 1 with invasive mucinous carcinoma in addition to extensive DCIS. Tumor dimensions ranged from 0.5 cm to 5 cm.

<table>
<thead>
<tr>
<th>Category</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
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<tbody>
<tr>
<td>Active cancer (n = 16)</td>
<td>50.8 ± 9.3</td>
<td>33.1 ± 7.8</td>
</tr>
<tr>
<td>Benign pathologies (n = 18)</td>
<td>48.2 ± 9.5</td>
<td>33.3 ± 6</td>
</tr>
<tr>
<td>Healthy (n = 14)</td>
<td>53.5 ± 11.5</td>
<td>32.6 ± 3.4</td>
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MHALANOBIS DISTANCE-BASED RESULTS

Fig. 8: Computation of the inter-breast Mahalanobis distance (MD) [6]. (a) Scatterplot (each dot represents one image point) of two Hb-signal components (HbSat and HbT) in these examples reveal that they tend to co-vary. Thus we seek to incorporate both of them into a single index. (b) In this related and revised representation of the scatterplot, the MD for each data point is the distance from the point to the origin. Empirically, we find that approximately 1% of data points have MD > 3.0 (black circles in b), for both healthy and affected breasts. But for cancer subjects, the inter-breast contrast is substantially increased when we modify the MD computation by referencing the data for one breast to the mean, and covariance estimates for the contralateral breast, as indicated in the following formula:

$\text{MD} = \sqrt{\sum (x_i - \bar{x})^2 / (\Sigma (x_i - \bar{x})^2)}$

where $x_i$ is the value of the $i$th variable, $\bar{x}$ is the mean value of the $i$th variable, and $\Sigma$ is the sum of the squared differences. The result is a distance measure that is independent of the scale of the variables and is therefore appropriate for comparing different data sets.

CONCLUSION

The results presented here indicate that the implementation of carbogen inspiration protocol can improve image contrast between breast tumors and both the surrounding healthy tissue and the contralateral breast. The markedly different responses between tumor and non-tumor tissues presumably is a reflection of differences in oxygen supply-demand balance.


Acknowledgments
This research was supported by the National Institutes of Health (NIH grant R21CA160102, the U.S. Army grant DAMD17-01-1-0018, the Susan G. Komen Foundation, the New York State Department of Health, Center for Clinical Research Investigator Program), and by the New York State Foundation for Science, Technology and Innovation—Technology Transfer Initiative Program (NYSTAR—TP2) grant C020041.