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Breast tumor hemodynamic response during a breath-hold as a biomarker to predict chemotherapeutic efficacy: preclinical study

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Abstract. Continuous wave diffuse optical tomographic/spectroscopic system does not provide absolute concentrations of chromophores in tissue and monitor only the changes of chromophore concentration. Therefore, it requires a perturbation of physiological signals, such as blood flow and oxygenation. In that sense, a few groups reported that monitoring a relative hemodynamic change during a breast tissue compression or a breath-hold to a patient can provide good contrast between tumor and nontumor. However, no longitudinal study reports the utilization of a breath-hold to predict tumor response during chemotherapy. A continuous wave near-infrared spectroscopy was employed to monitor hemodynamics in rat breast tumor during a hyperoxic to normoxic inhalational gas intervention to mimic a breath-hold during tumor growth and chemotherapy. The reduced oxyhemoglobin concentration during inhalational gas intervention correlated well with tumor growth, and it responded one day earlier than the change of tumor volume after chemotherapy. In conclusion, monitoring tumor hemodynamics during a breath-hold may serve as a biomarker to predict chemotherapeutic efficacy of tumor. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JBO.23.4.048001](https://doi.org/10.1117/1.JBO.23.4.048001)]

Keywords: inhalational oxygen gas modulation; breast cancer; tumor vascular response; therapeutic efficacy.

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1 Introduction

Breast cancer is one of the highest occurrence rates of cancer among females and is still on the rise.¹ By far, surgery remains the most viable option for breast cancer treatment. However, to increase the success rate of surgery, multiple cycles of neoadjuvant chemotherapy (3 to 6 months) are performed before the surgery to reduce the tumor size,² and the tumor response from adjuvant chemotherapy could be confirmed by observing tumor volume change using mammography,³ ultrasound,⁴ and magnetic resonance imaging (MRI).⁵ However, it takes a few months to find if the adjuvant chemotherapy works on the tumor or not. Therefore, it is very important to develop a way to predict tumor response much earlier so that patients suffer less from the side effects of chemotherapy and thus enhance the quality of life. Compared with traditional imaging methods, diffuse optical technologies provide hemodynamics information such as blood volume, oxygenation, and flow from relatively deep tissue (~cm).⁶ The system is low cost and safe with no radiation, and therefore, it is safe for daily monitoring tumor response to treatment.

Recently, there have been various approaches to monitor tumor response during chemotherapy by utilizing diffuse optical imaging or tomography (DOI or DOT)⁷⁻⁹ and by combining two different optical techniques such as a combination of diffuse optical spectroscopy (DOS) with diffuse correlation spectroscopy (DCS).¹⁰ Diffuse optical spectroscopy/imaging (DOS/I) or DOT studies showed that there were significant differences

of posttreatment oxy- (OHb), deoxy- (RHb), total (THb) hemoglobin, lipid, and water between responder and nonresponder compared with pretreatment.^{7,8} In the DOS with DCS study, chemotherapy caused significant changes in tumor versus normal blood flow contrast and concentrations of OHb, RHb, and lipid contrast compared with pretreatment.¹⁰ Others also have tried to detect or to monitor tumor response during chemotherapy by combination of diffuse optical tomography with other medical imaging modalities such as mammography,¹¹ MRI,¹² and ultrasound.¹³

There have also been interesting trials that applying a pressure on the breast,¹⁴ or vasoactive inhalational gases to the patient¹⁵ to detect tumors by causing a significant difference of hemodynamic contrast between normal (healthy) and tumor breast. In addition, there are reports of using the hemodynamic change during a breath-hold as a biomarker to predict tumor response to chemotherapy. Gunther et al.¹⁶ reported that THb and RHb concentration changes at two weeks after the first treatment are significantly different among pathologic complete response, pathologic partial response, and no response groups. They recently showed that kinetic parameters of deoxyhemoglobin change during a breath-hold show statistically significant differences between patients with pathologic complete response and without pathologic complete response as determined 5 months after treatment initiation.¹⁷ However, it does not show longitudinal changes of hemodynamic parameters caused by a breath-hold during tumor growth and chemotherapy. Moreover, the breath-hold approach may not be suitable for patients,

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who have a lung disease, such as asthma.¹⁸ Connecting a ventilator to animals through tracheotomy will allow simulating a breath-hold in an animal study, but it prohibits a longitudinal study. Therefore, an inhalational gas intervention from hyperoxic to normoxic gas under anesthesia was applied to mimic the hemodynamic change caused by a breath-hold. In this study, a hyperoxic to normoxic gas intervention was applied to animals bearing breast tumor, and the hemodynamic changes during the mimicked breath-hold were compared with the change of tumor volume during tumor growth and chemotherapy.

2 Material and Methods

2.1 Experimental Setup

Our continuous-wave near-infrared spectroscopy (CWNIRS) system consists of two broadband light sources (tungsten halogen, HL-2000-HP, Ocean Optics) and two NIR spectrometers (600 to 1100 nm, USB 4000, Ocean Optics) as detectors. Two laptops were used to acquire and process the NIRS data. Each source and detector probe was fabricated to have bundled multimode optical fibers with 2-mm diameter and was placed on the top of breast tissue. The probe was carefully fixed on the breast with light pressure to minimize motion artifacts during the experiment. The nipple was centered between the source and detector fibers so that data can be taken from the same position on tumors as close as possible through experiments. Source and detector fibers were placed 5-mm apart. The inhalational gas intervention was performed using a gas mixer with an isoflurane

vaporizer. We maintained 1.5% to 2% isoflurane to keep the anesthesia state of the animal and used a warm water pad to keep the animal body temperature and to prevent hypothermia under anesthesia state.

2.2 Animal Model

One million of 13762 MAT B-III (CRL-1666, ATCC, Manassas, Virginia) rat breast cancer cells were inoculated onto a mammary fat pad of Fisher 344 female rats (180 to 200 g).¹⁹ Animals were divided into three groups (control, chemo, and early chemo group) with six animals per each group. To see the tumor volume dependence of tumor response to chemotherapy, chemo group (tumor volume $\sim 370 \text{ mm}^3$) received chemotherapy at day 7 post cell inoculation while early chemo group (tumor volume $\sim 35 \text{ mm}^3$) had chemotherapy at day 5 post cell inoculation. The detailed description of preparing animal breast tumor model can be found in our previous report. The size of the tumor was measured using a caliper daily, and its volume was calculated by ellipsoid volume formula. About 13,762 MAT B-III cancer cell line is known to highly respond to alkylating agents, such as cyclophosphamide. A single high dose of cyclophosphamide (100 mg/kg body weight) was administered via intraperitoneal (i.p.) injection to both chemo- and early chemo groups, whereas the control group received the same amount of saline. The procedures in this study were approved by the Institutional Animal Care and

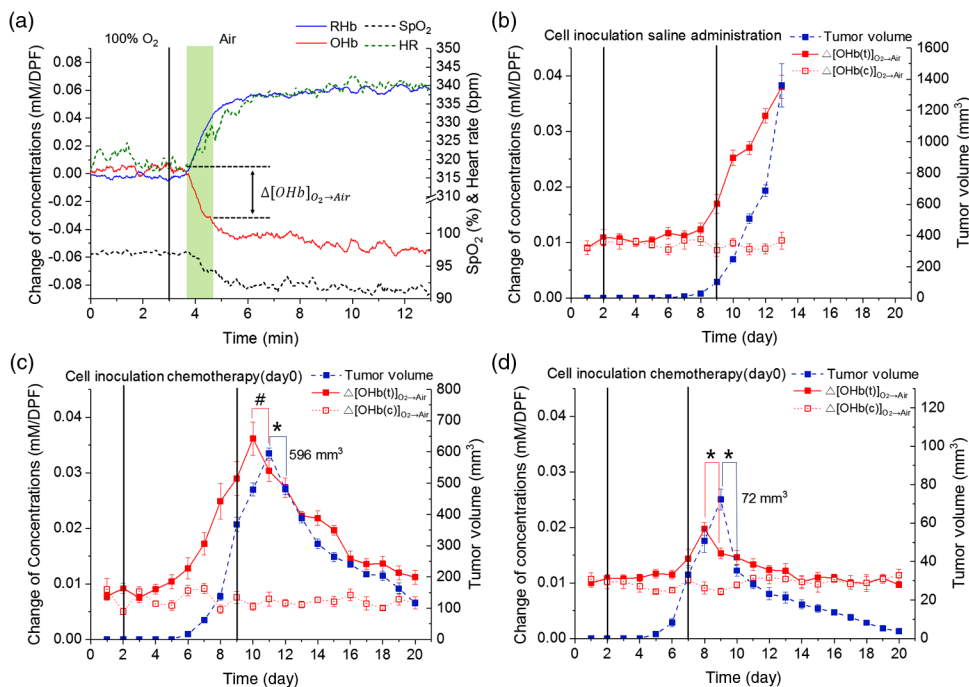


Fig. 1 (a) The representative changes of OHb, RHB, SpO₂, and HR in a tumor breast during inhalational oxygen gas intervention. The averaged change of OHb concentration decreases and tumor volume change for (b) the control group ($n = 6$), (c) chemo group ($n = 6$), and (d) early chemo group ($n = 6$) in the contralateral breast and tumor breast. Thick straight lines with filled markers represent $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ (red) in the tumor breast. The dashed line with hollow symbol represents $\Delta[\text{OHb}(c)]_{\text{O}_2 \rightarrow \text{Air}}$ (red) in the contralateral breast. Thick dashed line with filled markers represents tumor volume. $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ was compared between day 0 and day 1 postchemotherapy and between day 1 and day 2 day after chemotherapy. [Asterisks (*) represent significance level of p -value < 0.05 , and a crosshatch (#) denotes p -value = 0.06]

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2.3 Experimental Procedure

Inhalational oxygen gas modulation was performed automatically by a gas mixer system through a mask along with a continuous supply of isoflurane (1.5% to 2%). Baseline values were recorded for 3 min with 100% oxygen, and then the gas was switched to air for 10 min. Hemodynamic changes were monitored using CWNIRS for the entire 13 min of the protocol.⁵ The pulmonary oxygen saturation (SpO_2) values and heart rate (HR) were measured by a pulse oximeter (Mouse Ox, Starr Inc.) from a hind foot during the experiment.

2.4 Data Analysis

For this study, we obtained reflectance intensities at five wavelengths (730, 750, 800, 830, and 850 nm) and applied the modified Beer-Lambert's law to obtain concentration changes of oxy- (OHb), deoxy- (RHb), and total (THb) hemoglobin. The detailed description can be found in our previous report.¹⁹ Once the changes of OHb, RHb, and THb were acquired during a respiratory challenge, $\Delta[OHb]_{O_2 \rightarrow Air}$ was measured starting from the time it starts falling for another minute when 100% oxygen was switched to air [Fig. 1(a)].

2.5 Statistical Analysis

A two-tailed, paired sample *t*-test was applied to examine whether $\Delta[OHb]_{O_2 \rightarrow Air}$ and tumor volume decrease after reaching their maximum are significant from the maximum values. For instances, $\Delta[OHb]_{O_2 \rightarrow Air}$ at day 2 postchemotherapy (day 11 in chemo group and day 9 in early chemo group) and the value at day 1 postchemotherapy were compared (day 10 in chemo group and day 8 in early chemo group). Tumor volume at day 3 postchemotherapy was also compared with the value at day 2 postchemotherapy. A *p*-value of <0.05 was considered as a statistically significant difference.

3 Results

A representative change of OHb and RHb concentration from 100% oxygen to 21% oxygen inhalation is shown in Fig. 1. As the inhalation gas was switched to normoxic gas, SpO_2 value decreased from 97% to 91%, and heart rate increased from 320/min to 345/min at the end of air inhalation. The low SpO_2 value of air inhalation is due to the suppression of pulmonary function from isoflurane anesthesia effect.²⁰ Therefore, 100% oxygen inhalation under anesthesia can represent the oxygen supply during air breathing in a patient, and 21% oxygen gas breathing can mimic the low oxygen delivery during a breath-hold in a patient.

Figures 1(b)–1(d) show the absolute values of averaged dropped OHb concentration with tumor volume change from both the contralateral breast, $\Delta[OHb(c)]_{O_2 \rightarrow Air}$, and tumor breast, $\Delta[OHb(t)]_{O_2 \rightarrow Air}$, in control [Fig. 1(b)], chemo [Fig. 1(c)], and early chemo group [Fig. 1(d)]. As shown in Figs. 1(b)–1(d), the changes of $\Delta[OHb(c)]_{O_2 \rightarrow Air}$ in the contralateral breast for all groups kept almost same value during the whole experiment. In contrast, the changes of $\Delta[OHb(t)]_{O_2 \rightarrow Air}$ show different trends compared with the changes of $\Delta[OHb(c)]_{O_2 \rightarrow Air}$ as the tumor grows and during chemotherapy.

As can be seen in Fig. 1(b), $\Delta[OHb(t)]_{O_2 \rightarrow Air}$ in tumor breast increased as tumors grow until the end of the experiment. The measurement was ceased at day 13 due to large tumor volume ($\sim 1360 \text{ mm}^3$), which had to be sacrificed. For the chemo group, cyclophosphamide was administrated at 7 days after cell inoculation when tumor size grew to $\sim 8 \text{ mm}$ in diameter. $\Delta[OHb(t)]_{O_2 \rightarrow Air}$ corresponded well with the change of tumor volume during tumor growth and chemotherapy. However, it should be emphasized that $\Delta[OHb(t)]_{O_2 \rightarrow Air}$ started to decrease 1 day earlier than tumor volume changes after chemotherapy (*p*-value = 0.06 between day 1 and day 2 posttreatment).

Figure 1(d) shows the result of early chemo group. As tumor response to chemotherapy can be different depending on tumor size at the time of chemotherapy start, chemotherapy was performed 2 days earlier than chemo group (~ 5 to $\sim 8 \text{ mm}$ of tumor diameter). The tumor showed a very rapid decrease in the volume after chemotherapy compared with chemo group, whereas the trend of $\Delta[OHb(t)]_{O_2 \rightarrow Air}$ change was similar, but much smaller in magnitude compared with chemo group due to small

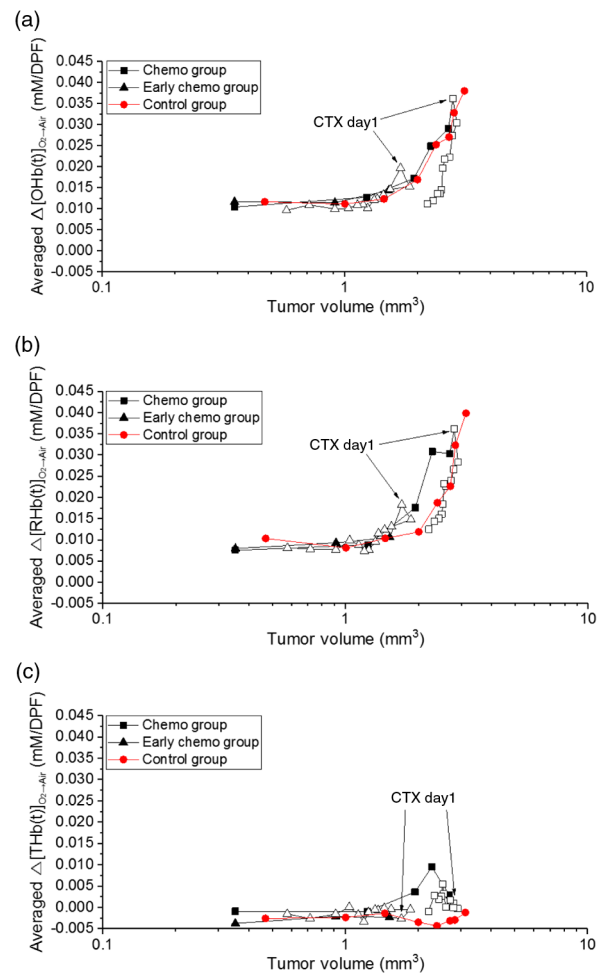


Fig. 2 The averaged changes of (a) $\Delta[OHb(t)]_{O_2 \rightarrow Air}$, (b) $\Delta[RHb(t)]_{O_2 \rightarrow Air}$, and (c) $\Delta[THb(t)]_{O_2 \rightarrow Air}$ along with tumor volume change (log scale) from breast tumors. Solid lines with rectangular and triangle markers (black) represent the result of chemo- and early chemo group, respectively. Filled symbols represent tumor volume during its growth, and open symbols represent tumor volume after chemotherapy. A solid line with filled circles (red) represents the tumor volume change in control group.

tumor size at the time of cyclophosphamide administration. $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ at day 2 postchemotherapy (day 9) became significantly small compared with the value at day 1 postchemotherapy (day 8). This result again showed that $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ started to decrease 1 day earlier than tumor volume changes after chemotherapy.

Figure 2 shows the averaged changes of $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$, $\Delta[\text{RHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$, and $\Delta[\text{THb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ along with the tumor growth and regression from chemo, early chemo, and control group. In chemo- and early chemo groups, both $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ [Fig. 2(a)] and $\Delta[\text{RHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ [Fig. 2(b)] continued to increase during tumor growth, and then returned to baseline after chemotherapy. The $\Delta[\text{THb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ were obtained by subtracting the $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ from $\Delta[\text{RHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$. Compared with $\Delta[\text{THb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ and $\Delta[\text{RHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$, $\Delta[\text{THb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ values were relatively constant in all groups. It means the amount of $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ and $\Delta[\text{RHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ are similar to each other during inhalational oxygen gas intervention.

4 Discussion

In this study, we monitored the change of OHb concentration during the inhalation of hyperoxic (100% oxygen) to normoxic (21% oxygen + 79% nitrogen) gas during tumor growth and after chemotherapy. The purpose of this protocol is to mimic a breath-hold, which has been applied in a clinical study to differentiate tumor from the nontumor. The voluntary breath-hold test has an advantage that it does not need an additional device or a machine to modulate inhalational oxygen concentration, but it may not be comfortable to patients, who are elderly or have respiratory diseases, such as asthma.¹⁸ Moreover, the breath-hold time may vary depending on subjects, and thus it can be hard to analyze the data and to conclude the results from many patients.

The goal of this study was to apply a breath-hold to monitor tumor response to chemotherapy in an anesthetized animal model. Even though connecting a ventilator to animals through tracheotomy will allow us to simulate a breath-hold, it prohibits a longitudinal study such as collecting hemodynamic signals throughout tumor growth and chemotherapy. Therefore, respiratory challenges were designed to mimic the condition of breath-hold in human subjects as follows.

In a normal condition, SpO_2 is close to 100% with an air inhalation, but it is much lower in an anesthetized animal (91% to 92%) during air inhalation due to a suppression of pulmonary function as can be seen in Fig. 1(a). Therefore, we applied 100% oxygen gas to make SpO_2 to around 98%, which mimics air breathing in a normal condition. Strohl et al.²¹ in 1984 showed that SpO_2 is falling with a rate of 0.16%/s during a breath-hold when initial SpO_2 was 97%. Thus, 30 s of breath-hold in Flexman et al.'s report will cause SpO_2 close to 92%, and therefore, SpO_2 drop in anesthetized animals from 100% oxygen gas to air inhalation can simulate a breath-hold condition in a patient.

It became a question that what will be the minimum oxygen percentage in inhalational gas to make a safe condition in clinical trials. To answer this question, the literature was surveyed to find the degree of oxygen saturation and oxygen percentage in the air that does not cause health problems in humans. According to the *Wilderness Medicine* book,²² oxygen saturation is above 95% at an altitude below 2000 m, which has

16.3% as an effective oxygen. In the case of Denver (Colorado), which located at a high altitude (~1600 m), the effective oxygen is about 17.3%, and Aspen at Colorado has ~15.4% of effective oxygen and 92% oxygen saturation due to a higher altitude (~2400 m) than Denver. Even with this low oxygen level, however, these cities are attractive places where many citizens and tourists can stay without having health problems. Therefore, a respiratory challenge from air to hypoxic (16% oxygen + 84% nitrogen) gas instead of a breath-hold may be suitable in clinical tests to provide a contrast between tumor and nontumor without having problems that a breath-hold test may cause.

The reason why a respiratory challenge from 100% oxygen to air was not considered for clinical setting instead of air to hypoxic gas is that SpO_2 during air inspiration is already close to 100%, and thus 100% oxygen breathing does not improve SpO_2 much. Therefore, a switch from 100% oxygen to air-breathing cannot cause a significant change in tissue oxygenation. Compared with this, switching inhalational gas from air to 16% oxygen will make SpO_2 changing from 98% to <95%, which may cause a sufficient change in tumor oxygenation while normal tissue maintains its oxygenation by autoregulatory vascular reactivity.

The Hielscher group applied a voluntary breath-hold as a physiological intervention to cause a hemodynamic change in breast tissue, which was monitored by diffuse optical tomography imaging system. They found that the percentage change of RHb ($\Delta[\text{RHb}]\%$) during a breath-hold shows a higher contrast than the percentage change of OHb ($\Delta[\text{OHb}]\%$) in tumor region.¹⁸ However, our results show that both $\Delta[\text{OHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ and $\Delta[\text{RHb}(t)]_{\text{O}_2 \rightarrow \text{Air}}$ correlated well with tumor growth from all groups (Fig. 2).

Recently, they reported the results of utilizing breath-hold-induced hemodynamic parameters to predict the response to neoadjuvant chemotherapy.¹⁷ They found that the kinetic parameters rather than the magnitude of $\Delta[\text{RHb}]\%$ can better predict patients with the pathologic complete response and also nonresponders to neoadjuvant chemotherapy. In our study, kinetic parameters were not analyzed due to the lack of 100% O_2 inhalation after air breathing, but $\Delta[\text{OHb}]_{\text{O}_2 \rightarrow \text{Air}}$ itself showed potential as a biomarker to predict the response to chemotherapy by showing a response one day earlier than tumor volume change (Fig. 1).

However, there are some limitations and issues to be addressed in this study. First, this study does not include the data from “nonresponding” group, and therefore it is hard to know if the trend of $\Delta[\text{OHb}]_{\text{O}_2 \rightarrow \text{Air}}$ is different in tumors not responding to cyclophosphamide. Even though this study does not have data from the nonresponding group, previous clinical studies showed that there exists a significant difference between pathologically complete response versus incomplete response group in terms of percentage change of total hemoglobin during the first cycle of adjuvant chemotherapy.²³ Another study also showed that the trends of both blood flow and total hemoglobin concentration are different depending on the level of response to chemotherapy.¹⁰ Therefore, it is reasonable to believe that $\Delta[\text{OHb}]_{\text{O}_2 \rightarrow \text{Air}}$ during a respiratory challenge will also be different between responding and nonresponding tumor, but it should be confirmed by further study.

Second, the duration time and the concentration of oxygen during a hypoxic gas inhalation need to be optimized to ensure the safety of patients when the inhalational protocol is applied to clinic test. According to our results, HR and SpO_2 levels fell

quickly and then maintained their level during 10 min of air inhalation (hypoxic gas in the clinical test). As the cardiopulmonary function and metabolism between a rat and human are different, clinical trials are required to optimize the inhalation protocol to ensure the safety and also the maximum contrast between tumor and normal breast.

Third, a hemoglobin concentration change during the respiratory challenge was acquired with the assumption that scattering property of tumor does not change during the respiratory challenge. However, there is a high chance that scattering property will change as the respiratory challenge causes both blood volume and oxygenation changes, which will affect the scattering property. How much of this scattering property change will affect the results of this study can be answered by employing a quantitative NIRS system such as time-domain and frequency-domain systems. Despite these limitations, our results showed a high potential tumor response that could be monitored by observing tumor hemodynamics during a respiratory challenge, and it may show an earlier response than the tumor volume change.

5 Conclusions

A respiratory challenge of switching from 100% oxygen to 21% oxygen gas was applied to anesthetized animals during tumor growth and chemotherapy to mimic the breath-hold in a clinical test. The results showed that $\Delta[\text{OHb}]_{\text{O}_2 \rightarrow \text{Air}}$ in tumor breast during the first minute of respiratory challenge correlated well with tumor growth, whereas the contralateral nontumor breast showed a similar level of OHb drops regardless of tumor size. It has also been found that the $\Delta[\text{OHb}]_{\text{O}_2 \rightarrow \text{Air}}$ during the respiratory challenge responded one day earlier than the tumor volume changes after chemotherapy. These results support that hemodynamic changes during a breath-hold or an inhalational oxygen gas intervention can be a biomarker to monitor an earlier response to chemotherapy than monitoring tumor volume change.

Disclosures

We declare that there are no relevant financial interests and no other potential conflicts of interest in this article.

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