Effect of Source-Detector Distance on the Measurement of Hemoglobin Using Near-Infrared Spectroscopy in Breast Cancer

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Abstract

We measured total hemoglobin concentrations in breast tumors by near-infrared time-resolved spectroscopy. Muscles interfere with measurement when the probe is close to the chest wall. Since the target area of measurement depends on the distance between the light source and probe detector, we inferred that this issue could be solved by reducing the source-detector distance. The purpose of this study was to examine the effects of the source-detector distance on the measurement of total hemoglobin concentration in the breast. We examined 26 patients with breast tumors. Total hemoglobin concentration was measured in tumors and the contralateral normal breasts at source-detector distances of 20 and 30 mm. The difference in total hemoglobin concentration between each tumor and the contralateral breast was calculated. The normal breast total hemoglobin concentration was significantly smaller for the source-detector distance of 20 mm than for the source-detector distance of 30 mm. Differences in source-detector distance did not significantly affect tumor total hemoglobin. The difference in total hemoglobin concentration between the tumor and the contralateral breast obtained at the source-detector distance of 20 mm was significantly higher than that obtained at the source-detector distance of 30 mm. From these results, we considered that measurement with a source-detector distance of 20 mm is less affected by the chest wall than with a source-detector distance of 30 mm and that the difference in total hemoglobin concentration between the tumor and the contralateral breast at a source-detector distance of 20 mm can better reflect the net total hemoglobin concentrations of the breast tumors. In conclusion, using a probe with a source-detector distance of 20 mm can more accurately evaluate the total hemoglobin concentration in breast tumors.

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Introduction

Optical imaging and spectroscopy using near-infrared light have great potential in the assessment of tumor vasculature. It was reported that tumors have higher concentrations of total hemoglobin (tHb) than normal breast tissue.[1-3]

Since 2008, we have measured the optical characteristics of breast tumors with a near-infrared time-resolved spectroscopy system. This system can measure hemoglobin concentrations and oxygen saturation at the capillary level. The system is based on reflection geometry. Equipment that measures by reflection is smaller than equipment that measures by transmission or a ring, and it is advantageous in that it can measure conveniently at the bedside. However, measurements by reflection geometry can be influenced by the chest wall muscles, which contain high levels of hemoglobin and myoglobin. There are some papers to address chest wall effects using coregistered ultrasound as guidance.[4,5]

A simple method to address this issue is to reduce the distance between the light source and the detector of the probe (SDD),[4,6] because the target area of the measurement depends on the SDD. The effect of the SDD on measurements in actual breasts has not been sufficiently studied. In the present study, we examined the relationship between the SDD and measured tHb values in breast tumors and normal breast tissue.

Patients and Methods

We examined 31 patients with breast tumors between May 2014 and November 2016. As chemotherapy affects optical parameters,[7-10] 5 patients after chemotherapy were excluded. Ultimately, 26 patients were included in the study.

All patients were female and their median age was 58.5 years, with a range from 33 to 78 years. Six patients were premenopausal and 20 patients were postmenopausal. Seventeen tumors were shown to be invasive ductal cancer, 5 tumors were ductal carcinoma *in situ*, 2 tumors were invasive lobular carcinoma, and 1 tumor each was malignant phyllodes tumor and medullary carcinoma, all confirmed histopathologically. The mean tumor thickness was 10 mm, with a range from 5 to 26 mm.

The study protocol was approved by the Ethical Review Committee of Hamamatsu University School of Medicine. All patients provided written informed consent.

Measurements were taken in the supine position. The skin-to-chest wall distance, thickness of the tumor, and distance from skin to the anterior border of the tumor were measured by an ultrasonography (US) system (EUB-7500; Hitachi Medical Corporation, Tokyo, Japan). A linear probe with a frequency of 6 to 14 MHz was used (EUP-L65; Hitachi Medical Corporation).

We used a single-channel near-infrared time-resolved spectroscopy system (TRS-20SH; Hamamatsu Photonics K.K., Hamamatsu, Japan) with a handheld probe. The system consisted of pulsed lasers and a detector unit. The pulsed lasers

(PLP; Hamamatsu Photonics K.K.) emitted light pulses with an average power of 200 μW and a pulse rate of 5 MHz at 3 wavelengths (758, 795, and 833 nm), each with a pulse width of approximately 100 ps. The pulsed lasers were guided to a single optical fiber via a fiber coupler (NTT Advanced Technology Corp, Kawasaki, Japan). Each source fiber (GC200/250L; Fujikura Ltd, Tokyo, Japan) had a core diameter of 200 μm and a numerical aperture (NA) of 0.25. The detector unit consisted of a photomultiplier tube (H7422-50MOD; Hamamatsu Photonics K.K.), constant fraction discriminators, time-to-amplitude converters, A/D converters, and histogram memories, and it collected diffuse reflectance from the tissue with a detector fiber to generate temporal profiles using a time-correlated single-photon counting method. The detector fiber (Schott Moritex Corp, Asaka, Japan) had an NA of 0.26 and a bundle diameter of 3 mm. The instrumental response function (IRF) had a pulse width of approximately 320 ps and time resolution of 10 ps.

On the handheld probe, 1 detector fiber and 2 source fibers were arranged in a line to create SDDs of 20 mm and 30 mm. The optical switch selected one of the source fibers via customized software. The software enabled us to perform measurements at each SDD within 3 seconds.

A nonlinear least-squares method was applied to fit the solution of the time-domain photon diffusion equation[11,12] to temporal profiles with a semi-infinite homogeneous model to obtain the absorption coefficient and reduced scattering coefficient at each wavelength. The zero boundary condition of the reflectance mode was employed. The time range for the data fitting was from −560 to 5440 ps, in which 0 ps was set as the time of the maximum value of IRF. We confirmed that our fitting process was successfully implemented when the reduced χ^2 value was within the range of 0.8 to 1.2.[13]

The concentrations of oxygenated hemoglobin and deoxygenated hemoglobin were calculated from the absorption coefficients after subtracting the values for water and lipid absorption in breast tissue. We assumed that the water content was 18.7% and the lipid content 66.1%.[14] Total hemoglobin was the sum of the concentrations of oxygenated hemoglobin and deoxygenated hemoglobin.

Each breast tumor and the corresponding area of the contralateral normal breast were marked on the skin using US as a guide. The spectroscopic probe was positioned on the mark, and optical parameters were measured at SDDs of 20 and 30 mm. Total hemoglobin (t - n) was calculated by subtracting the tHb concentration of the contralateral normal breast from that of the tumor.

Statistical examinations were performed using Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington) and StatFlex version 6.0 (Artech Co, Ltd, Osaka, Japan).

The differences in the distance from skin to chest wall of the tumor side breast and the normal breast were tested using the nonparametric Wilcoxon signed rank test. The differences between SDDs of 20 mm and 30 mm in measured tHb concentration of normal breast and the
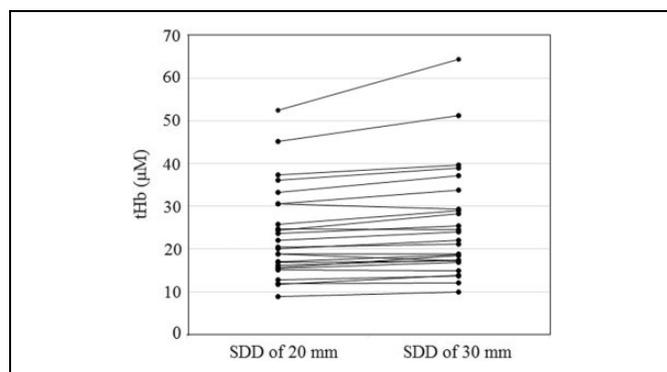
Figure 1. The normal breast tHb concentrations were significantly higher with the SDD of 30 mm than with the SDD of 20 mm (n = 26; $P = .0002$). SDD indicates source-detector distance; tHb, total hemoglobin.

difference between SDDs of 20 mm and 30 mm on tHb (t - n) calculation were tested using the nonparametric Wilcoxon signed rank test.

Results

The mean distance from skin to tumor was 7 mm (range: 3-16 mm). In normal breast measurements, the mean distance from skin to chest wall was 19.5 mm (range: 8-35 mm). In the tumor-side breast, the mean distance from skin to chest wall was 22 mm (range: 9-36 mm). The distance from skin to chest wall in the tumor side breast was significantly larger than the distance from skin to chest wall in the normal breast ($P < .01$). The normal breast tHb concentrations were significantly higher with the SDD of 30 mm than with the SDD of 20 mm ($P = .0002$; Figure 1).

The tHb concentrations of the tumor and the normal breast at each SDD are shown in Figure 2. The normal breast tHb concentration tended to increase as the skin-to-chest wall distance decreased. The tHb concentrations of the tumors were higher than those of normal breast in 23 cases at the SDD of 20 mm and in 21 cases at the SDD of 30 mm.

The tHb concentrations of the tumor at each SDD are shown in Figure 3. Differences in the SDD did not significantly affect tumor tHb ($P = .9797$).

The difference in the tHb concentration measurements between tumor and normal breast at each SDD are shown in Figure 4. Total hemoglobin (t - n) obtained at the SDD of 20 mm was significantly higher than that obtained at 30=mm ($P = .0005$).

Discussion

For tHb measurement in breast tumors, the influence of the chest wall is a challenging problem. High levels of myoglobin and hemoglobin in the chest wall cannot be distinguished from blood hemoglobin by the spectroscopy system.

The tHb concentration tends to increase for a smaller skin-to-chest wall distance. This is consistent with a previous study.[15]

Probes with a longer SDD detect reflections from more deeply located tissues.[16] Measurement by a probe with a longer SDD would likely include higher amounts of hemoglobin and myoglobin from chest wall muscles.

When the distance from skin to chest wall is about 20 mm or less, the tHb measured for the SDD of 30 mm had the effects of the chest wall.[15] In order to remove the influence of the chest wall and measure the tHb of the tumor breast more accurately, we compared the result for the SDD of 30 mm, which we have been using for our experiments, with that of the shorter SDD which should be less affected by the chest wall. Empirically, it is considered that the light diffusion equation holds for the SDD of 15 mm or more, so we employed the SDD of 20 mm to compare with the SDD of 30 mm.

The normal breast tHb concentrations were smaller for the SDD of 20 mm than the SDD of 30 mm. It seems likely that measurement with the SDD of 20 mm did not include as much of the chest wall as that with the SDD of 30 mm.

In the tumor breast, it is presumed that the tHb concentration increases for shorter SDD as the proportion of the light passing through a tumor increases in the optical path length, and it decreases as the contribution from the chest wall decreases. On the contrary, the opposite trend occurs for longer SDD. The estimated tHb concentration did not show significant differences with the change of SDD in the tumor breast.

The near-infrared spectroscopy imaging has been used for the assessment of neoadjuvant chemotherapy.[7-10] Although the difference in the SDD was small, 20 versus 30 mm, measurement with an SDD of 20 mm would be appropriate for the assessment of treatment response. Another technique to reduce interference of the chest wall on the measurement is the subtraction method. Total hemoglobin (t - n) would be an indicator allowing the chest wall effect to be canceled out. The SDD of 20 mm measurements of tHb (t - n) being larger than those at 30 mm suggests again that 20 mm is less susceptible to the chest wall.

Short SDDs may be disadvantageous for measurements of deeply located tumors. Tumor tHb measured at the SDD of 20 mm was not low compared with the SDD of 30 mm for tumors in this study. However, the patients were exclusively Japanese with small breasts. Further studies using more deeply located tumors are needed.

There is a limitation in the evaluation of tHb (t - n). As in the previous study,[15] this study found that the distance from skin to chest wall was significantly larger in the tumor side breast than in the contralateral normal breast due to the presence of the tumor. For this reason, the influence of the chest wall on the tumor side was smaller than on the contralateral normal breast, making it impossible to accurately evaluate tHb (t - n) in some cases. We speculated that this is the reason why tHb (t − n) was below 0 in 5 cases in this study.

Other limitations of this study were as follows: Light measurement and recording of the US image were not performed at the same time. The distance to the tumor and the distance to the
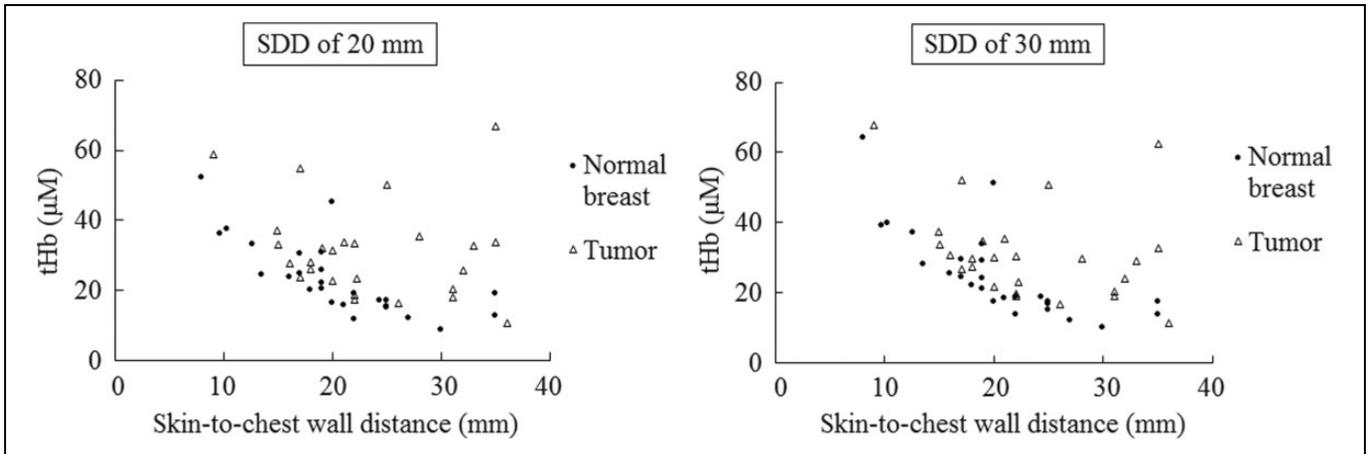
Figure 2. The tHb concentrations of the tumor and the normal breast at each SDD. The normal breast tHb concentration tended to increase as the skin-to-chest wall distance decreased (n = 26). SDD indicates source-detector distance; tHb, total hemoglobin.
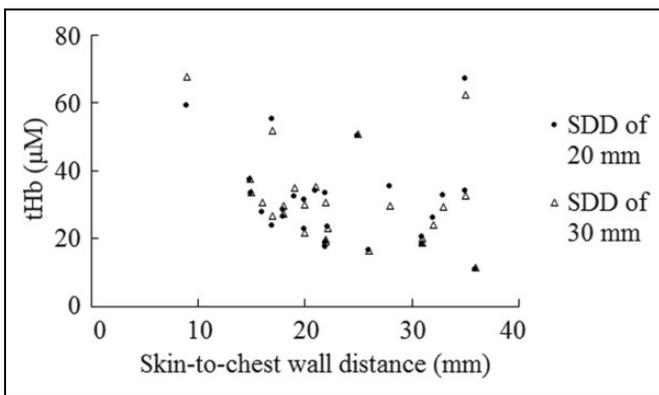
Figure 3. The tHb concentrations of the tumor at each SDD. Differences in the SDD did not significantly affect tumor tHb (n = 26; P = .9797). SDD indicates source-detector distance; tHb, total hemoglobin.
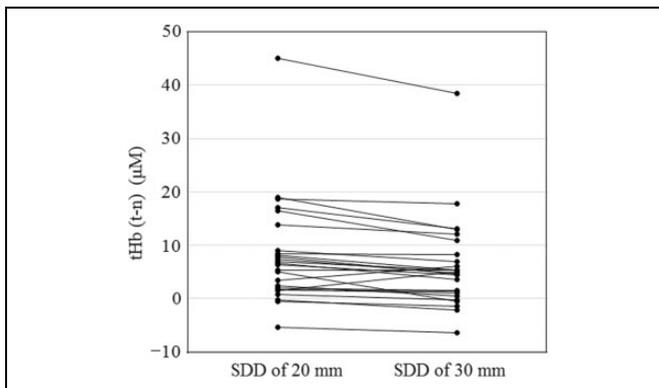
Figure 4. The tHb (t - n) at each SDD (n = 26). The tHb (t - n) obtained at the SDD of 20 mm was significantly higher than that obtained at 30 mm (P = .0005). SDD indicates source-detector distance; tHb, total hemoglobin.

chest wall from the skin can change depending on the compression by the ultrasound probe. Also, especially in small tumors, it is difficult to position the optical probe exactly above the tumor. We currently use a probe that can simultaneously perform optical measurement and recording of ultrasonographic images. This probe allows more accurate evaluation.

In conclusion, the probe with the SDD of 20 mm was less affected by chest wall muscles and could more accurately evaluate the tHb concentration in breast tumors.

Declaration of Conflicting Interests

Funding

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