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LETTER

Oxygenation dynamics of sepsis patients undergoing far-infrared intervention based on near-infrared spectroscopy

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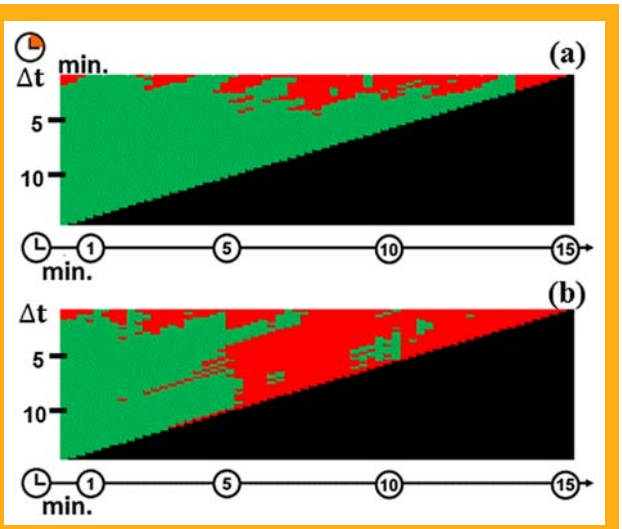
Near-infrared spectroscopy (NIRS; continuous wave type) is a noninvasive tool for detecting the relative change of oxyhemoglobin and deoxyhemoglobin. To make this change, intervention methods must be applied. This study determined the hemodynamics of 44 healthy participants and 35 patients with sepsis during exposure to FIR as a novel physical intervention approach. Local microcirculation of their brachioradialis was monitored during exposure and recovery through NIRS. The variations in blood flow and microvascular reaction were determined by conducting paired and unpaired *t* tests. The oxyhemoglobin levels of the healthy participants increased continuously, even during recovery. In contrast to expextations, the oxyhemoglobin levels of the patients plateaued after only 5 min of FIR illumination. The proposed method has potential applications for ensuring efficient treatment and facilitating doctors in diagnosing the functions of vessels in intensive care units.



Mapping diagrams of HbO_2 in healthy males and males with sepsis illustrated unique scenarios during the process.

1. Introduction

Sepsis is a systemic inflammatory response syndrome during infection. Articles have increasingly demonstrated that the disease is related to the microcirculation of patients, such as blood perfusion, tissue oxygenation, and even cellular or organ dysfunction [1–4]. Depending on these parameters, physiological situations can be exposed. Near-infrared spectroscopy (NIRS) has been proposed as a real-time and noninvasive system for monitoring regional circulation [5].

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NIRS technology is based on different absorption and scattering coefficients of more than two wavelengths in the near-infrared spectrum (700–1000 nm), and it measures chromophores like hemoglobin in biological tissues. Recently, this technology has sparked increasing interest in the assessment of microcirculation of regional tissues because of its noninvasive properties and easy applicability to critically ill patients [6]. However, commercial devices are always continuous wave type (CW-type), with lower prices and techniques in hardware and software; additionally, they measure only the change values of oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb), in addition to requiring physical intervention to trigger the changes.

Well-known methods are exercise and vascular occlusion, which have been applied in previous studies of sepsis [7, 8]. Nevertheless, the drawbacks of these methods, such as the pain from skin contact and high pressure with tier as well as hurt because of microcirculation block, indicate that these options are not always viable. Additionally, exercise cannot be executed in intensive care units (ICUs). Therefore, we propose far-infrared (FIR) illumination as a novel intervention method to determine alterations in hemodynamics.

Currently, FIR are used to treat disorders of microcirculation, although the associated mechanism remains obscure. According to previous studies, FIR transfers energy by resonating with water and proteins in the human body [4, 9, 10]. Energy released in the form of the heat in the skin increases blood flow in both the skin and the tissues underneath. Additionally, the non-thermal effects of FIR, namely nitric oxide released from endothelial cells and the genes of nitric oxide synthase, accelerate translation. Nitric oxide can induce the relaxation of vessel muscles and improve blood flow. HbO_2 ultimately increases and the change can be detected by NIRS.

Our previous study from 2012 showed a linear correlation of oxygenation dynamic signals between FIR illumination and an arterial-occlusion test, implying that FIR illumination can be applied in clinical diagnoses [11]. Subsequently, we determined that FIR hemodynamics vary between sexes, with females experiencing smaller increases in HbO_2 than males do. We argue that the primary factor is estrogen, which generally increases nitric oxide production to relax the smooth muscle of blood vessels in the daily life of a female [12].

In the present study, FIR illumination intervened in blood oxygenation, and NIRS monitored the change noninvasively. However, the method still lack for clinical usage. In this letter, we present the variations of HbO_2 and Hb in healthy participants and patients with sepsis, during and after exposure to FIR, as determined by statistical analysis. We offer additional parameters to help doctors in diagnosing the physiological situation of patients. Overall, the temporary effect of FIR was clearly revealed for both the healthy participants and patients with sepsis. In our opinions, the innovative method has potential to improve the clinical NIRS measurement process in the future.

2. Methods

2.1 Participants

Prior to participant recruitment, approval was obtained from the Institutional Review Board of Chung Shan Medical University Hospital. Similar to our previous study, four groups comprising healthy males (17), healthy females (27), males with sepsis (17), and females with sepsis (18) were recruited. For healthy participants, the inclusion criterion was aged older than 50 years; the exclusion criteria were 1) no plan to engage in exercise, and 2) no use of drugs within 2 weeks, including medicine for chronic disease. Exercise and drinking beverages with caffeine were not allowed on the day of the study. Conversely, for patients with sepsis, the inclusion criteria were 1) aged older than 50 years, 2) infection with inflammation, and 3) ICU admission; the exclusion criteria were 1) >1+ in edema of the arms, 2) incomplete skin on the arms, and 3) restlessness.

2.2 Instruments

An FIR therapy unit (TY-101N, WS Far Infrared Medical Technology Co. Ltd., Taipei, Taiwan) was placed beside each participant's bed, with the emitter 20 cm directly above the arms. Three intensity settings were applied, namely low, medium, and high, and the power density received by the irradiated region was 20 mW/cm^2 at high intensity. The wavelength of the light generated from electrified ceramic plates ranged between 3 μm and 25 μm, with a peak of 5 μm.

Hemodynamic measurements were conducted by a CW-type NIRS probe (PortaLite, Artinis, Medical System, Zetten, the Netherlands). The probe has three pairs of light sources and a photodetector, with the distance between the sources and the detector measuring 25 mm, 30 mm, and 35 mm. Each source pair contains two LEDs (wavelength = 760 nm and 850 nm; power = below 5 mW; sampling rate = 50 Hz). The probe was connected to a computer through Bluetooth, and measurement data were processed using Oxysoft (PortaLite, Artinis Medical Systems BV, Netherlands).

A modified Beer–Lambert law was used to solve the relative concentration of hemoglobin.

$$\mathrm{OD}_\lambda = \log \frac{I_0}{I} = \varepsilon_\lambda \cdot c \cdot L \cdot B_\lambda + \mathrm{OD}_{R,\lambda} \quad (1)$$

In (1), OD_λ is the optical density of the medium; I_0 is the incident radiation; I is the transmitted radiation; ε_λ ($\mathrm{mM^{-1}/cm^{-1}}$) is the extinction coefficient of the chromophore; c ($\mathrm{mM^{-1}}$) is the concentration of the chromophore; L (cm) is the distance between the light entry and exit points; λ (nm) is the wavelength; B_λ is the differential pathlength correction factor; and $\mathrm{OD}_{R,\lambda}$ is the oxygen-independent light loss attributed to scattering in the tissue. Under the assumption that $\mathrm{OD}_{R,\lambda}$ remains constant during our process, the concentration of HbO_2 and Hb could be determined. Equation (2) was written as the final equation. Two wavelengths (760 nm and 850 nm) were used to solve $\Delta[HbO_2]$ and $\Delta[Hb]$ in (2), where $\varepsilon_{760,\mathrm{HbO_2}} = 0.586\ \mathrm{mM^{-1} \cdot cm^{-1}}$, $\varepsilon_{760,\mathrm{Hb}} = 1.548\ \mathrm{mM^{-1} \cdot cm^{-1}}$, $\varepsilon_{850,\mathrm{HbO_2}} = 1.058\ \mathrm{mM^{-1} \cdot cm^{-1}}$, $\varepsilon_{850,\mathrm{Hb}} = 0.691\ \mathrm{mM^{-1} \cdot cm^{-1}}$, L = 3.5 cm, and both B760 and B850 = 4.

$$\Delta\mathrm{OD}_\lambda = (\varepsilon_{\lambda,\mathrm{HbO_2}} \cdot \Delta[\mathrm{HbO_2}] + \varepsilon_{\lambda,\mathrm{Hb}} \cdot \Delta[\mathrm{Hb}]) \cdot L \cdot B_\lambda \quad (2)$$

2.3 Measurement protocol

All participants stayed in a quiet room with a temperature of 27 °C for 1 h before measurement. The NIRS probe was set on the skin of the brachioradialis with medical tape to monitor hemodynamic changes. The participants laid on beds during the process, and the FIR emitter was turned on for preheat for 5 min. The NIRS signals were recorded for 20 min in the following three steps: 1) stabilization for 5 min, 2) FIR illumination on the skin of the brachioradialis for 10 min, and 3) removal of the FIR and recovery for 5 min. HbO_2, Hb, and total hemoglobin (tHb) were recorded by NIRS during the entire procedure. The measured signal from the first step was used as the baseline of hemoglobin concentration, and the signals in the second and third steps were used as indicators of microcirculation.

2.4 Statistics and analysis

Three sets of signals were obtained from each participant, and they were averaged for statistical analysis. The original data from the first step were reset as the baseline because the change was not engendered by FIR; it was instead attributed to thinking, feeling, movement, or other external factors. Every

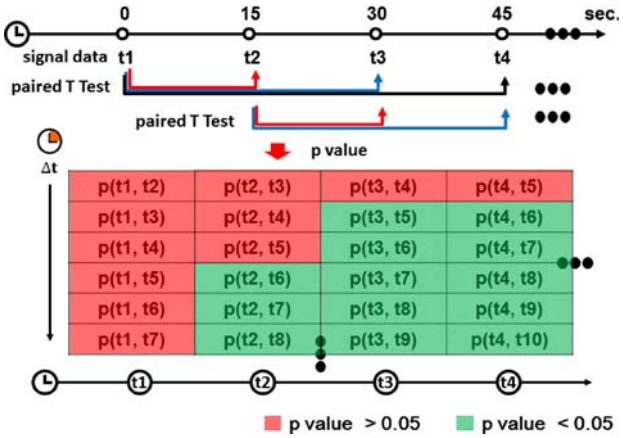

Figure 1 Rules of the mapping diagram in Figures 3 and 4. Paired *t* tests were applied to two of the signal data, and the *p* values were presented in a table and marked with red or green.

15 s, the variance among the times was succinctly presented. All results and statistics include mean, standard deviation, paired *t* test, and unpaired *t* test. Because of a variation in hemodynamics between different sexes under FIR illumination, these groups were analyzed separately.

In this study, we presented the results of the paired t test differently (Figure 1): For example, t1 was set as the data acquired between 0 s and 15 s and t2 as the data acquired between 15 s and 30 s. We attempted to match all data from different time in the paired *t* test. The *p* value, for example, from *t*1 and *t*2 was written in the form of *p* (*t*1, *t*2). Subsequently, the *p* values whose time intervals were 15 s were placed in the first row of a table: *p* (*t*1, *t*2), *p* (*t*2, *t*3), *p* (*t*3, *t*4) and so on. *P* values with 30 s intervals were placed in the second row: *p* (*t*1, *t*3), *p* (*t*2, *t*4), and *p* (*t*3, *t*5). Only one *p* value (*p* (*t*1, *t*60)) was presented in the last row. The grid was depicted in green for significant results (*p* value <0.05) and red for non-significant results (*p* value >0.05). According to the preceding rules, the derived data were visualized by this mapping style (Figures 3 and 4). The healthy participants and patients were also compared through the unpaired *t* test (Figure 5).

3. Results and discussion

As presented in Table 1, heart rate, blood pressure, respiratory rate, mean arterial pressure (MAP), and other parameters from the medical monitor and medical record system of Chung Shan Medical University Hospital were also recorded. Although patients with sepsis may have higher disease severity, such as septic shock or severe sepsis, this was not a

Table 1 Physiological parameters.

	healthy volunteers		patients with sepsis	
	Males	females	males	females
Number (n)	17	27	17	18
Age (years)	68 ± 8.2	63.7 ± 10.3	62.6 ± 16.7	71.2 ± 13.7
BMI (kg/m^2)	24.7 ± 2.2	23.0 ± 3.0	22.0 ± 4.7	22.2 ± 5.4
Heart rate (bpm)	–	–	94.0 ± 18.7	97.7 ± 20.4
MAP (mm Hg)	–	–	75.6 ± 14.5	79.7 ± 20.4
SpO_2 (%)	–	–	97.8 ± 2.1	97.6 ± 2.8
GCS	–	–	9.9 ± 3.8	9.8 ± 3.4
APACHE II	–	–	17.9 ± 7.5	20.1 ± 7.8
Respiratory rate (breath/min)	–	–	19.5 ± 5.1	20.5 ± 7.2
Mechanical ventilation use(n)	–	–	14	12
Vasopressors (n)	–	–	5	4
volume of intravenous fluids (ml)	–	–	905 ± 356	841 ± 268

BMI: body mass index, MAP: mean arterial pressure, GCS: Glasgow Coma Scale, APACHE II: acute physiology and chronic health evaluation score.

criterion for participation and was not analyzed in detail because of the number of such patients may be insufficient. Before recruitment, the disease was diagnosis and the type of infection was found. Disease: Pneumonia ($n = 25$), urinary tract infection ($n = 4$), deep neck infection ($n = 1$), septic arthritis ($n = 1$), lung abscess ($n = 1$), epidural abcess ($n = 1$), intra-abdominal infection ($n = 1$), infectious colitis ($n = 1$); type of infection: gram positive ($n = 19$), gram negative ($n = 20$), fungal infection ($n = 14$) There is no patients with surgery.

Figure 2 shows the average change and standard deviation in HbO_2 (red line), Hb (blue line), and tHb (green line) during the analysis. The temporal tracings can be divided into two parts: FIR illumination (0–10 min) and recovery time (10–15 min). Figure 2(a) and (b) illustrate the signals of the healthy males and males with sepsis, respectively. Among all four groups, HbO_2 markedly rose during FIR exposure; however, HbO_2 was nearly 1 a.u. higher in the healthy males (approximately 3.6 a.u.) than in the healthy females after illumination, and continued to

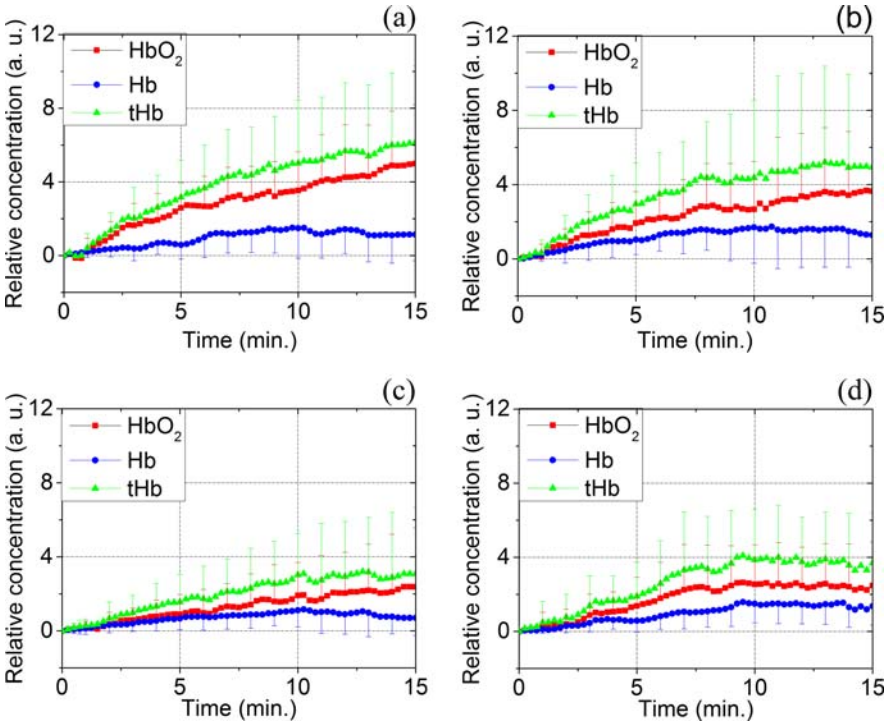

Figure 2 Mean of three channels in four different groups. (**a**) Healthy males, (**b**) males with sepsis, (**c**) healthy females, and (**d**) females with sepsis. The red lines indicate HbO_2, blue lines indicate Hb, and green lines indicate tHb.

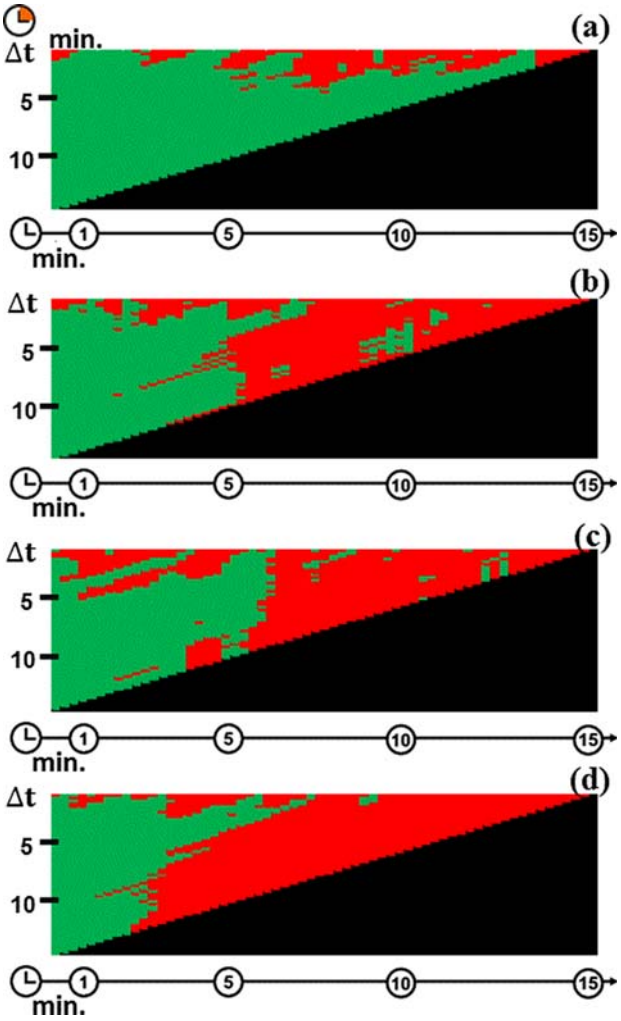

Figure 3 Mapping diagram of the males, as derived from the paired *t* test. The red regions indicate a non-significant difference and the green regions indicate a significant difference. (**a**) HbO_2 of the healthy males, (**b**) HbO_2 of the males with sepsis, (**c**) Hb of the healthy males, and (**d**) Hb of the males with sepsis.

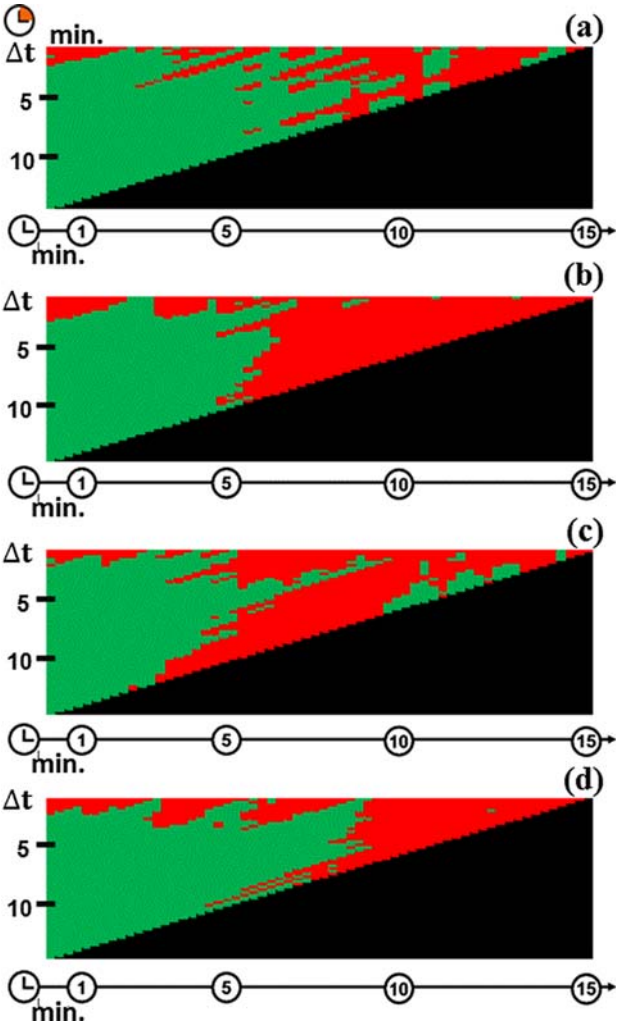

Figure 4 Mapping diagram of the females, as derived from the paired *t* test. The red regions indicate a non-significant difference and the green regions indicate a significant difference. (**a**) HbO_2 of the healthy females, (**b**) HbO_2 of the females with sepsis, (**c**) Hb of the healthy females, and (**d**) Hb of the females with sepsis.

rise during recovery. The measured blood volume also increased because of HbO_2. Conversely, the HbO_2 level in the males with sepsis stopped rising once the emitter was turned off. These phenomena, as derived from the paired *t* test, are presented more clearly in Figure 3. The changes in Hb were smaller and more similar in both male groups. Figure 2(c) and (d) show the signals of the healthy females and females with sepsis, respectively. Their increases in HbO_2 were similar (approximately 2.2 a.u.); however, the females with sepsis seemed to exhibit reduced HbO_2 production during recovery; meanwhile, changes in Hb were not obvious. These findings also are consistent with those of our previous study indicating that males have a larger change in HbO_2 than females do [12].

To determine the difference in hemodynamics over time, the paired *t* test was conducted on the same groups. Figures 3 and 4 present mapping diagrams with the corresponding *p* values, as derived from the paired *t* test. The *p* values in the same column are from a signal with fixed time and other signals with various times, with the fixed time shown on the horizontal axis. By contrast, the *p* values in the same row are from the same interval between two signals, with the time interval shown on the vertical axis. The red blocks indicate a non-significant difference, green blocks indicate a significant difference, and black blocks are blank. Additionally, the upper rims of the figures indicate whether they are significantly different in a short interval, whereas the lower rims indicate whether they are significantly

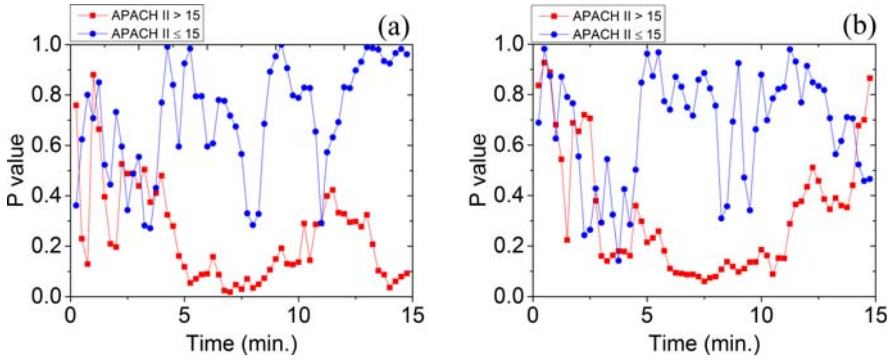

Figure 5 Diagrams of the *p* values derived from the unpaired *t* test between the healthy participants and the patients: (**a**) males and (**b**) females. The blue lines indicate the patients with slight illness and the red lines indicate the patients with severe illness.

different in a long interval. Figure 3(a) depicts the mapping diagram of HbO_2 in the healthy males. As indicated by the red triangle in the upper left corner, HbO_2 was not affected by FIR until nearly 1 min. Moreover, the upper rim of Figure 3(a) is green, suggesting large increases in HbO_2 in a short time. After 5 min, the upper rim has red blocks again; this signifies that the increase in HbO_2 developed slowly, and only signals with longer intervals showed a significant difference until the end of the process. Figure 3(b) shows the mapping diagram of HbO_2 in the males with sepsis. Initially, significant differences were observed when the time interval was more than 5 min. Red blocks then occupied most of the upper rim and the density sustained growth with time. Finally, all columns became red with minimal green areas, indicating that the increase in HbO_2 had nearly stopped after 5 min of FIR illumination. With this mapping diagram, we can estimate the limits of vasodilation in patients, which plateaus 5 min later. Figure 3(c) and (d) demonstrate the Hb parts of the healthy males and males with sepsis, respectively. Hb increases indicate the oxygen consumption during process. More oxygen was consumed at the beginning, although the overall average had limited changes. The observed Hb between the healthy males and males with sepsis reached a plateau at 3 min and 5 min, respectively, indicating that the healthy males have longer oxygen consumption times. Figure 4(a) and (b) present the mapping diagrams of HbO_2 of the healthy females and females with sepsis, respectively. Similar to the male groups, HbO_2 rose slowly in the healthy females but stopped in the females with sepsis after 5 min. Overall, females had less HbO_2 change than did males, with red areas appearing after only 5 min. Figure 4(c) and (d) show the observed Hb of the healthy females and females with sepsis, respectively. In contrast to expectations, the females with sepsis had noticeable oxygen consumption, a phenomenon that requires more study to determine the cause.

We also conducted a comparison between control and experimental groups. The signals of patients and healthy participants were analyzed with an unpaired *t* test to reveal the HbO_2 differences. Initially, they showed non-significant differences (not shown); therefore, we set more severe conditions (APACH II > 15) for the patients. We divided our patients into two groups with APACH II > 15 and APACH II ≤ 15. APACH II is an indicator of disease severity, with a score of 15 representing the clinical boundary. APACH II > 15 applies to patients with more severe sepsis. Figures 5(a) and (b) show the APACH II results for males and females, respectively. The red line depicts the patients (APACH II > 15) and healthy participants, whereas the blue line depicts the patients (APACH II < 15) and healthy participants. For both sexes, a significant difference was observed after 5 min of FIR illumination, and this is the same conclusion as those illustrated in Figures 3–5. During recovery, the *p* values demonstrated varying trends between the sexes. Although there was no evidence, we hypothesize that the vasodilation of females with FIR seems to easily reach the limitation of the vessels; this may account for the higher *p* values toward the end. In addition to blood vascular reaction, APACH II consists of many physiological parameters; however, the trends may appear rough because of our broad classification.

We can divide the temporary effects of FIR into thermal and non-thermal effect [8–10]. The thermal effect is associated with the heat from radiant energy that increases skin microcirculation, whereas the non-thermal effect is engendered by endothelial cells that release nitric oxide to enlarge vessels. Overall, patients with sepsis show dysfunctional endothelial cells and have a weak non-thermal effect [1, 2]. In our results, the rise of HbO_2 stagnated after 5 min of illumination, and even decreased slightly without FIR; the lack of the non-thermal effect is clear. The increase in Hb seemed to be stagnant for oxygen consumption and metabolism from the heat. The Hb patterns of the females with sepsis were particularly contrary to our expectations, and they warrant further study.

Lower muscle oxygen consumption and vascular reactivity, as determined by a vascular occlusion test, was demonstrated in patients with sepsis [7]. Our

findings also indicate a lower response from vessels with a softer and more direct method. FIR illumination offers a positive user experience and a touchless intervention procedure, in addition to improving microcirculation. Overall, it has a more precise signal because it is associated with no pain [7]. However, measurement over the long term, and of smaller changes in hemodynamics, should also be considered.

The proposed method has the potential to be a physician reference index about vessels in ICU treatment; however, the study still has challenges. Several factors were not considered, and incorporating factors such as disease severity, medical treatments, time spent in the ICU, and vasopressors can enhance the clarity of our results. Moreover, the presented results pertain solely to sepsis, although the peripheral microcirculation could be affected by other diseases and conditions such as heart failure and lung disease. For example, a weak heart does not pump enough blood into arterial vessels, and gas exchange is influenced by lung disease, consequently causing hemoglobin to carry less oxygen. Edema also changes the signal because of the thickness of edema fluid. Therefore, the number of patients must be increased to expand the application of the proposed method and clarify the signals among different diseases.

4. Conclusion

We demonstrate various hemodynamic patterns in healthy participants and patients with sepsis through NIRS, with FIR serving as a physical intervention. The results imply that the HbO_2 patterns of the patients reached a plateau after only 5 min of FIR illumination, which releases the dysfunction of the vessels. We also determined that increased oxygen consumption may result from heat and metabolism. Finally, the patients with severe sepsis were clearly distinguishable. This study demonstrates the potential clinical application of FIR illumination and NIRS in the near future.

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