The Application of Wireless Near Infrared Spectroscopy on Detecting Peripheral Circulation in Patients With Diabetes Foot Ulcer When Doing Buerger’s Exercise

Min-Ling Chen, MD,1 Bor-Shyh Lin, PhD,2 Cheng-Wei Su, BS,2 Yen-Bin Lin, MD,1 Mei-Yen Chen, RN, PhD,3 Jen-Hsiang Shen, MD,4 and Chang-Cheng Chang, MD1,2,5

1Department of Plastic Surgery, Chiayi Chang Gung Memorial Hospital, Wound Care Center, Chiayi County 613, Taiwan
2Institute of Imaging and Biomedical Photonics, College of Photonics, National Chiao Tung University, Tainan, Taiwan
3Department of Nursing, Chang Gung University of Science and Technology, No. 261, Wen-Hua 1st Rd., Kwei-Shan, Taoyuan 333, Taiwan
4Department of Ophthalmology, Chang Gung Memorial Hospital, Taoyuan 333, Taiwan
5School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

Background and Objectives: The majority of patients with diabetes foot ulcer have peripheral arterial disease. The technique of near infrared spectroscopy (NIRS) used to monitor the dorsal foot blood circulation condition is by measuring the absorption differences between oxy-hemoglobin and deoxy-hemoglobin.

Study Designs/Materials and Methods: Patients with diabetic foot ulcer (DFU) treated in our wound care center were divided into two sub-groups based on the Duplex ultrasound or angiography. Patients with peripheral arterial disease (PAD) and non-peripheral arterial disease were divided into group A1 and A2, respectively. We applied wireless NIRS on patients’ dorsal foot to assess the peripheral circulation by continuously detect the signal penetrating the tissue while patients were asked to do Buerger's exercise. The same procedure was also repeated on 15 healthy participants as control group B.

Results: From January to August 2015, 30 patients with DFU (Group A) were enrolled in the study, 9 patients in Group A1 and 21 patients in Group A2. Tissue concentration of oxygenated hemoglobin (HbO2) in each group varied in a similar trend among five stages of Buerger’s exercise. HbO2 concentration increases at post-exercise stages in all groups (P = 0.006 in Group A1, P = 0.223 in Group A2, P = 0.03 in Group B), however, there were significant difference in both pre- and post-exercise stages (P = 0.001 and P = 0.01, respectively) between Group A and B. Moreover, significant differences (P = 0.0009) of HbO2 were also found between Group A1 and A2 in pre-exercise status, but no significant difference (P = 0.294) was found in post-exercise status. Similar results were also found in total hemoglobin (Hb) concentration analyses.

Conclusions: Buerger’s exercise could increase peripheral HbO2 and total Hb circulation in patients with diabetes foot ulcer. The NIRS could continuously and quantitatively monitor real-time peripheral circulation in postural changes and is novel to rehabilitation program. A larger scale study to prove the accuracy of NIRS system in detecting peripheral circulation could be worthwhile. Lasers Surg. Med. 49:652–657, 2017. © 2017 Wiley Periodicals, Inc.

Key words: near infrared spectroscopy; diabetes foot ulcer; Buerger’s exercise

INTRODUCTION

Up to 25% of patients with diabetes suffered from foot problems in their lifetime [1,2], and about 39% of diabetic patients might have comorbid peripheral arterial occlusive disease [3]. Lower extremity ischemia are both precipitating and exaggerating factors to diabetic foot ulcer (DFU) [4]. Once DFU is infected, it could progress into gangrene and major amputation, and eventually leads to life disability or even death [5]. Therefore, the surveillance of lower extremity circulation is crucial in both prevention and further care for patients with diabetic foot.

Near infrared spectroscopy (NIRS) is a noninvasive technique applied to oxygenated hemoglobin (HbO2) proportion evaluation within tissues. The system not only delivers near infrared light relative transparent to other part of tissue components, but also is mainly absorbed by hemoglobin (Hb) [6–8]. HbO2 and deoxygenated hemoglobin (deoxygen-Hb) absorb light equally

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Contract grant sponsor: Chia-Yi Chang Gung memorial Hospital; Contract grant numbers: CORPG6D0291, CORPG6D0292.

Correspondence to: Chang-Cheng Chang, MD, School of Medicine, College of Medicine, China Medical University, No. 91, Hsueh-Shih Road, Taichung 40402, Taiwan.

E-mail: changcc1975@gmail.com

Accepted 9 March 2017
Published online 5 June 2017 in Wiley Online Library (wileyonlinelibrary.com).

DOI 10.1002/lsm.22667

© 2017 Wiley Periodicals, Inc.
Exercise) stage, followed by legs elevation at 45–60°. Subjects began with a supine position at the first (pre-exercise) stage, by a well-trained research assistant. Participants were also enrolled as control group B. Fifteen general health patients into group A1 with PAD and group A2 without PAD. We further divided the patients into group A1 with PAD and group A2 without PAD based on the Duplex findings. Fifteen general health participants were also enrolled as control group B.

In 2013, Kawasaki et al. demonstrated the relationship between peripheral circulation and positional change [14]. Based on this concept, we applied NIRS system to patients with DFU in order to investigate reliability and effectiveness of NIRS on continuous peripheral circulation changes detection while asking the patients to do Buerger’s exercise. Buerger’s exercise consists of five stages of lower limb postural changes, which were believed to be able to improve lower limbs circulation in patients with DM foot [15,16].

METHODS

Designs and Samples

Patients with DFU treated in a wound care center of tertiary hospital between January 2015 and August 2015 were included in this study. Exclusion criteria are those unable to coordinate, who had smoked within 24 hours prior the examination, participants who had previous amputations, by-pass surgeries, and venous ulcers. All participants signed their informed consents after the procedures were fully explained. The study design was reviewed and approved by Chang Gung Medical Foundation Institutional Review Board (IRB number: 103-3263B).

After obtaining the medical histories from participants involved in this study, we used duplex ultrasound (Viasonix FALCON/Pro, ISRAEL) to detect the existence of peripheral arterial disease (PAD). We further divided the patients into group A1 with PAD and group A2 without PAD based on the Duplex findings. Fifteen general health participants were also enrolled as control group B.

Afterwards, all participants were taught to do the Buerger–Allen exercise by a well-trained research assistant. Subjects began with a supine position at the first (pre-exercise) stage, followed by legs elevation at 45–60° using a pillow support for 3 minutes at the second stage. In the third stage, participants sat on the edge of a bed with feet down, and then performed an alternating dorsi- and plantar-flexion along with inward and outward movements for 3 minutes at the fourth stage. Ultimately, patients lay supine with a blanket covering both feet for 3 minutes as the fifth stage (post-exercise stage).

Equipment

A wireless NIRS system was applied on participants’ dorsal feet to continuously detect the signal penetrating tissues, while doing Buerger’s exercise in order to examine the reliability and efficacy of NIRS system on detecting tissue HbO2 concentration changes between different exercise stages among all groups. The absorption of red or near-infrared wavelength in most of human tissues is far less than that in tissue Hb. Therefore, the absorptions of HbO2 and deoxy-Hb should be considered as primary indexes in such model. The principle of NIRS is based on the differences between HbO2 and deoxy-Hb absorptions using a red or near infrared light penetrating through the tissue, and then the relative concentrations of HbO2 and deoxy-Hb can be obtained from the changes in two or more—wavelength light intensities according to modified Beer–Lambert law [17]. Beer–Lambert law is an empirical equation used to describe optical attenuation in a medium. The concentrations of the medium can be calculated using a penetrated light. Moreover, HbO2, deoxy-Hb, and water are the main absorber in human tissue under near infrared light, and the use of NIRS technique can be applied to measure relative HbO2 and deoxy-Hb concentrations [18]. The basic scheme of the proposed wireless NIRS was shown in Figure 1. It mainly consists of a wearable optical device and a host system. The wearable optical device contains an optical probe, wireless signal acquisition module, and a wearable mechanical design. In this study, the optical probe can provide a tri-wavelength light source (640/700/910 nm) and receive the light penetrating through the tissue. The wearable mechanical design is aimed to fix the wearable optical device on the ankle of the user. When the red or near infrared light penetrates through the tissue, the light signal received from the optical probe will then be amplified and filtered, and transmitted to the host system wirelessly via Bluetooth.

Fig. 1. The NIRS system consists of a wearable optical device (containing an optical probe, wireless signal acquisition module, and a wearable mechanical design) and a host system. The optical probe provides a tri-wavelength light source (640/700/910 nm) and receives the light penetrating through the tissue. NIRS: near infrared spectroscopy.

Beer–lambert law [17]. Beer–Lambert law is an empirical equation used to describe optical attenuation in a medium. The concentrations of the medium can be calculated using a penetrated light. Moreover, HbO2, deoxy-Hb, and water are the main absorber in human tissue under near infrared light, and the use of NIRS technique can be applied to measure relative HbO2 and deoxy-Hb concentrations [18]. The basic scheme of the proposed wireless NIRS was shown in Figure 1. It mainly consists of a wearable optical device and a host system. The wearable optical device contains an optical probe, wireless signal acquisition module, and a wearable mechanical design. In this study, the optical probe can provide a tri-wavelength light source (640/700/910 nm) and receive the light penetrating through the tissue. The wearable mechanical design is aimed to fix the wearable optical device on the ankle of the user. When the red or near infrared light penetrates through the tissue, the light signal received from the optical probe will then be amplified and filtered, and transmitted to the host system wirelessly via Bluetooth.

Fig. 1. The NIRS system consists of a wearable optical device (containing an optical probe, wireless signal acquisition module, and a wearable mechanical design) and a host system. The optical probe provides a tri-wavelength light source (640/700/910 nm) and receives the light penetrating through the tissue. NIRS: near infrared spectroscopy.
Finally, the host system will estimate the information of HbO2 and deoxy-Hb concentration from the received light signal based on the difference of absorption ability between each other.

**Statistical Analysis**

Continuous data were expressed as mean ± standard deviation (SD). A pair t test was used to compare the significance of pre/post-exercise HbT and HbO2 concentration in each group. A two-sample t test was used to compare the significance of HbT/HbO2 concentration between group A/control group and group A1/group A2 in different stages of Buerger’s exercise. All statistical assessment were single-tailed and considered significantly different if \( P < 0.05 \). Statistical analysis was performed using Excel 2016 (Microsoft, Washington D.C).

**RESULTS**

From January to August 2015, 30 patients with DFU were enrolled in the study. They were further divided into PAD and non-PAD group in accordance to Doppler ultrasound report. The PAD group (group A1) involved 21 patients (with average age 70.62 years), while the non-PAD group (group A2) involved 9 patients (with average age 57.78 years). Control group B contained 15 generally healthy populations (with average age 20.67 years). The age-comparable group (Gr A2) was defined as PAD group (Gr A1) while 9 patients (average age 57.78 years) as non-PAD group (Gr A2). Fifteen generally healthy participants (average age = 20.67 years) were also involved as control group (Gr B). The HbO2 and HbT concentrations were increased in post-exercise stages in all groups. Data were expressed as mean ± SD. PAD, Peripheral arterial occlusion disease; HbO2, Oxygenated hemoglobin concentration in tissues; HbT, Total hemoglobin concentration in tissues; NA, Not applicable.

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demographics</th>
<th>Control group</th>
<th>Non-PAD</th>
<th>PAOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.67 ± 1.89</td>
<td>57.78 ± 5.85</td>
<td>70.62 ± 11.16</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>NA</td>
<td>11.44 ± 6.27</td>
<td>14.95 ± 11.42</td>
</tr>
<tr>
<td>HbO2 (µmol/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-exercise</td>
<td>110.03 ± 4.32</td>
<td>108.18 ± 4.50</td>
<td>103.27 ± 2.90</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>111.41 ± 4.93</td>
<td>109.12 ± 4.00</td>
<td>105.97 ± 5.01</td>
</tr>
<tr>
<td>P value</td>
<td>0.030</td>
<td>0.2</td>
<td>0.004</td>
</tr>
<tr>
<td>HbT (µmol/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-exercise</td>
<td>127.52 ± 5.49</td>
<td>125.83 ± 4.09</td>
<td>121.03 ± 3.66</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>129.08 ± 6.04</td>
<td>126.36 ± 4.58</td>
<td>123.67 ± 5.61</td>
</tr>
<tr>
<td>P value</td>
<td>0.042</td>
<td>0.367</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Twenty-one participants (average age = 70.62 years) were classified as PAD group (Gr A1) while 9 patients (average age = 57.78 years) as non-PAD group (Gr A2). Fifteen generally healthy participants (average age = 20.67 years) were also involved as control group (Gr B). The HbO2 and HbT concentrations were increased in post-exercise stages in all groups. Data were expressed as mean ± SD. PAD, Peripheral arterial occlusion disease; HbO2, Oxygenated hemoglobin concentration in tissues; HbT, Total hemoglobin concentration in tissues; NA, Not applicable.

The analysis of HbT concentration was also compatible as above findings (Table 1).

**DISCUSSION**

An ideal monitoring technique should be noninvasive, continuous, reliable, accurate, timely, easy to use, and inexpensive. In the diagnosis of PAD, invasive procedure such as angiography is beneficial due to its direct observation over the severity of vessel stenosis with the highest accuracy. However, the procedure demands the injection of contrast medium, which could be harmful in subjects with impaired renal function. Moreover, it also has drawbacks such as high cost, inconvenience, and it was unable to present the change in circulation timely. The most important fact is that angiography could only visualize the flow of main artery and its branches but the microvascular blood flow that directly affects peripheral tissue perfusion [19].

Noninvasive methods for peripheral blood flow evaluation includes ankle-brachial index (ABI), transcutaneous oxygen pressure (TcPO2), and skin perfusion pressure (SPP). However, for diabetic patients, the efficiency of ABI found (\( P = 0.294 \)) between Group A1 (105.97 ± 5.01 µmol/ml, \( n = 21 \)) and Group A2 (109.12 ± 4.00 µmol/ml, \( n = 9 \)) at post-exercise stage (Table 2). In the contrary, HbO2 concentrations were significantly different between Group A and B no matter in pre- or post-exercise status (\( P = 0.001 \) and \( P = 0.01 \), respectively). The hypothesis of this inconsistent result is described in Discussion.

The analysis of HbT concentration was also compatible as above findings (Table 1).
seems to be limited due to higher false negative rate caused by vessel calcification [20]. The evaluation of TcPO2 requires local skin heating before examination, which is also an indirect estimation of partial pressure of oxygen in arterial blood (PaO2); hence, it is unable to demonstrate real value of skin tissue oxygenation [21]. Besides, the accuracy of TcPO2 measurement was easily affected by motion, so it cannot be applied to blood flow evaluation during exercise. SPP was thought to be an effective noninvasive method assessing the severity of PAD or predicting wound healing than the previously discussed two methods [22], but the measuring of SPP required a special machine and was too expensive to be applied broadly, not to mention it required plenty of time to measure. Therefore, SPP cannot be used to detect the continuous variance of blood flow. Based on above reasons, an effective noninvasive tool monitoring peripheral circulation of diabetes foot is still to be developed.

In 2013, Kagaya et al. proposed the possibility of applying NIRS system on tissue perfusion assessment in patients with critical limb ischemia [19]. The authors concluded that tissue perfusion estimation using the concept of traditional angiosome measurement by angiography might be inappropriate because total occlusion of a feeding artery is not equal to total ischemia of its feeding area [19]. They thereby proposed a new concept of “real angiosome,” which was evaluated by using a near-infrared tissue oximeter monitor, which was more accurate to reflect the real distribution of peripheral tissue perfusion [19]. However, we believed that the true angiosome model might be more complicated because of its collateral vessels and choke vessels, that is, the application of NIRS system on detecting the severity of DM vasculopathy and individual discriminations is still to be proved in another way. By contrast, our methods allowed us obtaining real-time and direct quantitative HbO2 concentrations within a specific area of tissue. That is, blood hemoglobin concentration would not be changed in such a short period while detecting the signal, and the vasculature in a given area of tissue was supposed to be the same. The amount of HbT (The sum of HbO2 and deoxy-Hb) in a given area of tissue could indirectly represent the blood flow of the peripheral tissue in our unique apparatus.

![Fig. 2. The tissue HbO2 and HbT concentrations among three sub groups varied similarly in each stage of Buerger’s exercise.](image-url)
In 2013, Kawasaki et al. demonstrated the relationship between positional change and peripheral circulation by measuring different SPP levels in four positions (supine, lower limbs elevation, sitting, and reclining bed of 20° elevation) [14]. They found that SPP was increased significantly in sitting position in both critical limb ischemia and healthy control groups [14]. In Figure 2, we discovered that HbO2 and HbT concentrations were changed in a similar trend between three groups at each stage of Buerger’s exercises. The result suggested that NIRS system could distinguish different peripheral circulation status and was able to detect subtle changes in peripheral concentrations of HbO2 and HbT while continuously doing Buerger’s exercises. Based on Kawasaki’s report and our result, we believe that NIRS system used in this study is able to continuously monitor peripheral circulation during a standardized exercise to reflect the changes timely without the interferences of movement in both DFU with/without PAD groups or in general healthy group. Hence, NIRS system benefited by its noninvasive, continuous, accurate, and easy to use properties as well as the potential of being used as a remote monitor for lower limb circulation. The application of wireless NIRS to remotely monitor lower limbs circulation among patients with PAD and as a feedback system for patients require rehabilitation or exercise programs is very promising.

As we predicted, there are significant differences of HbO2 concentrations between DM foot group and health control group both in pre-exercise and post-exercise stages. This result demonstrated that NIRS not only was able to detect the differences of tissue oxygenation among healthy subjects and those with DM feet, but also to prove the increase of tissue oxygenation immediately after Buerger’s exercises. Interestingly, the differences of tissue oxygenation at post-exercise stages between non-PAD and PAD group were not significant, when those were significant at pre-exercise stages. The result implied that the improvement of tissue perfusion after Buerger’s exercise might be better in PAD group than in non-PAD group (Fig. 3). Abundant compensative angiogenesis of microvasculature which ensure better improvement of peripheral circulation during Buerger’s exercise in PAD patients might be attributable to such phenomenon. In addition, the findings may indirectly suggest that Buerger’s exercise increases peripheral tissues circulation by augmenting flows of microvasculatures rather than those of three main vessels in lower limbs, even though the long-term effects of Buerger’s exercise on lower extremities remain unclear.

Furthermore, in addition to the immediate beneficial results in patients with PAD, a practical therapeutic regimen (including exercise protocols) based on the severity of PAD is still to be determined. A further randomized cohort study comparing the long-term effects of Buerger’s exercises on perfusion improvement between patients with or without PAD is required, so the most optimal Buerger’s exercise could be established to maximize the benefits to peripheral circulation.

**CONCLUSIONS**

Wireless NIRS is a useful apparatus for DFU patients effectively inspecting their peripheral circulation improvement during rehabilitation program. Due to its
noninvasive, continuous, accurate, easy to use, and remote monitoring properties for lower limbs circulation, it is believed to be an apparatus to be promoted. This equipment could be applied to all populations and is able to discriminate DM foot with or without PAD as well as health ones. Furthermore, we also proved that Buerger’s exercise immediately increased peripheral tissues oxygenation in lower limbs. However, long-term benefit of Buerger’s exercise for peripheral circulation improvement is still needed to be determined using other cohort study designs. In addition, a larger scale study to prove the accuracy of NIRS system in detecting peripheral circulation, for example, comparing with toe pressures or doppler studies, could also be worthwhile.

ACKNOWLEDGMENTS

The research was sponsored by Chia-Yi Chang Gung memorial Hospital (grant number CORPG6D0291, CORPG6D0292) and had been orally reported at the 36th ASLMS annual conference in the basic science session held in Boston in 2016 with an honor of travel grants award. We appreciate PTSGI Incorporated and Joe Chi-Cheng Fang, MBBS Candidate of University of Queensland, for English editing.

REFERENCES
