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Abstract. Deep vein thrombosis (DVT) has become a severe disease with a rising incidence rate. The conventional diagnosis relies on complicated imaging modalities that may also involve invasive contrast agent injection and ionizing procedures (e.g., venography). Noninvasive near-infrared spectroscopy (NIRS) methods have been explored which required the DVT patients to follow some exercise protocols. Here, we attempt to use portable NIRS under patients' natural state for DVT diagnosis. Nine DVT patients and seven healthy subjects participated in NIRS measurements of concentration of oxy- and deoxy-hemoglobins ($\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$) relative to data on a tissue mimicking phantom at six particular sites of calves. It was found that $\Delta[\text{HbO}_2]$ is significantly lower in DVT patients than healthy ones, whereas $\Delta[\text{Hb}]$ is distinctly higher. Moreover, after thrombolytic therapy, both $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ in DVT calves assume a gradual convergence to the curves of healthy ones. This reveals the potential of NIRS for the noninvasive, continuous, and straightforward monitoring/therapeutic effect evaluation of DVT in clinics with appropriate bedside monitoring capability. © 2015 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JBO.20.1.010502]

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Deep vein thrombosis (DVT), a significant complication resulting in serious morbidity and mortality, often happens in inpatients and especially with the postoperative population.¹ Without prophylaxis, the incidence of hospital-acquired DVT is approximately 10% to 40% among general surgical or medical patients and 40% to 60% among those enduring large-scale orthopedic surgery.² Most patients with episodes of DVT are

at risk of developing post thrombotic syndrome, which may lead to long-term morbidity and cause diseases such as ulceration, skin changes, chronic swelling, and other clinical manifestations.³

Currently, some techniques have been developed to diagnose DVT. The criterion is contrast venography;^{4,5} however, a contrast agent is required to be injected in a vein below the clot and then x-ray imaging is employed to show where and how the DVT blocks.⁶ Magnetic resonance imaging can detect DVT; but contrast agents' injection is also suggested.⁴ Both the technologies involve an ionizing detection procedure. Recently, venous ultrasonography has also been developed for the initial diagnostic test.⁵ However, all the approaches above are complicated, discontinuous, and incapable of being used for bedside monitoring.

The near-infrared spectroscopy (NIRS) measurements, e.g., the concentration of oxy- and deoxy-hemoglobins ($\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$), are known to primarily reflect the hemodynamics in capillaries, small arterioles, and venules.⁷ Researchers have gained insights by using NIRS in DVT diagnosis. Hemelt et al.⁶ have initially tested the potential of NIRS in DVT diagnosis with a phantom study.⁶ Scott et al.⁸ have reported about using NIRS combined with a six-stage calf raising exercise protocol to differentiate DVT and normal legs in terms of $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$.⁸ Using a similar exercise-protocol-combined NIRS methodology, Hosoi's and Yamaki's groups have displayed successful DVT diagnosis by the $\Delta[\text{Hb}]$ -based venous retention index.^{3,9} However, due to the requirement for exercise protocol, the measurement process is time consuming and inconvenient. It is also uncomfortable and quite a burden for most DVT patients to repeat the exercise protocol.

Here, we attempt to merely utilize NIRS under the DVT patient's natural state and to evaluate the feasibilities of $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ for monitoring, diagnosis, and evaluation of therapeutic effect on DVT.

The NIRS developed for thrombosis monitoring¹⁰ [Fig. 1(a)] is a continuous-wave device employing 735- and 850-nm wavelength. The separation between light source and detector is 2.8 cm. Of note, DVT could make the tissue hard and painful if being secured with elastic bandages or medical proof fabrics. Thus, we got rid of this widely used NIRS probe design. The customized probe resembled that of ultrasonography and can be secured easily with a hand [Fig. 1(b)]. The radian of the probe is fixed and matches well with most people's calves, which ensures full and comfortable touch between the probe and the measured DVT tissue. The complete device was tested by the India-ink experiment [Fig. 1(c)] and the human cuff protocol [Fig. 1(d)] to be reliable, sensitive, and low noise. The modified Beer-Lambert law was utilized to translate optical densities into $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ data.^{11,12}

Nine DVT patients in the intensive care unit of Xinhua Hospital provided their written informed consent to take part in the study. Six of them were double-leg DVT, and the other three were single-leg DVT. Seven healthy doctor volunteers were also recruited to get the control measurements. The DVT usually occurred in the legs,^{1,3} and the calf was most recommended region within leg for DVT diagnosis studies.^{1,8,9} All patients and healthy subjects were measured with the optical probe placed at three conjunctive sites on each calf and covering the middle head of the gastrocnemius muscle^{1,8,9}

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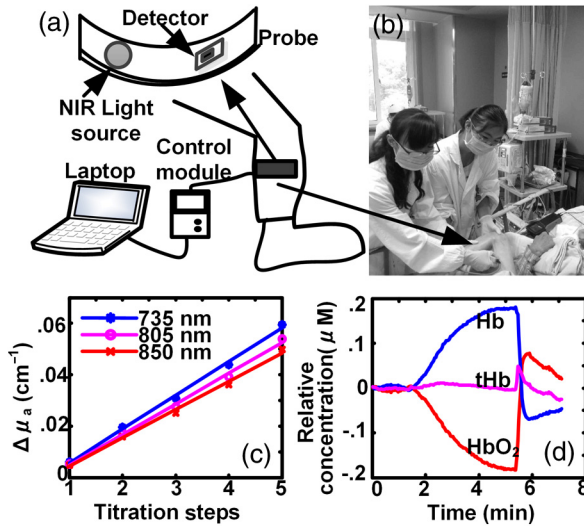


Fig. 1 Customized near-infrared spectroscopy (NIRS) device for thrombosis monitoring: (a) instrumentation; (b) the use of the NIRS device in thrombosis clinics; (c) titration, and (d) human cuff tests of the device.

[Figs. 1(a) and 1(b)]. $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ were simultaneously acquired at 10 Hz for 3 min at each measurement site after the stability of the hemodynamic response was confirmed. Prior to the measurements on each subject, we also measured the data on a solid tissue phantom and used the data as the reference. This tissue phantom was made with a reduced scattering coefficient (μ'_s) of 7 cm^{-1} and absorption coefficient (μ_a) of 0.1 cm^{-1} , which were the medians of reported human limbs (μ'_s : 3.88 to 8.48 cm^{-1} ; μ_a : 0.08 to 0.21 cm^{-1})¹² and accordingly minimized the calibration error resulting from the mismatch of optical properties between the phantom and human subjects. Hence, the simple CW NIRS device was able to provide a relative measure of the oxygenation levels on calf muscles to the same standard phantom, which can roughly be used for comparison among subjects. The mean values of the data sequences were obtained for statistical analysis. The double-leg DVT patients (64.2 ± 5.6 years old) were compared with the age-matched healthy volunteers (63.6 ± 5.3 years old) to identify the diagnosis/monitoring potential of NIRS for DVT and the effectiveness of $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ as indicators. The remaining single-leg DVT patients were involved in the evaluation of the efficacy of thrombolytic therapy. Similar measurements were taken along with thrombolytic therapy every 12 h (8 a.m. and 8 p.m. every day) until the patients recovered (six times in total). The presented protocol was approved by Xinhua Hospital and University of Electronic Science and Technology of China in Ethics Review Boards.

All the data were analyzed using MATLAB (2010b, Mathworks). The mean and standard deviation among populations were calculated and shown by bar plots. Student *t*-tests were also carried out to test the difference in significance degree between double-leg DVTs and healthy ones for each measured site. For single-leg DVT patients, the variation tendencies of $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ with time in both DVT and healthy calves were analyzed to verify the potential of these indicators for thrombosis therapeutic effect evaluation.

Figure 2 shows the comparison between double-leg DVT patients and healthy volunteers in $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ for each measured site. No matter which measured site is used,

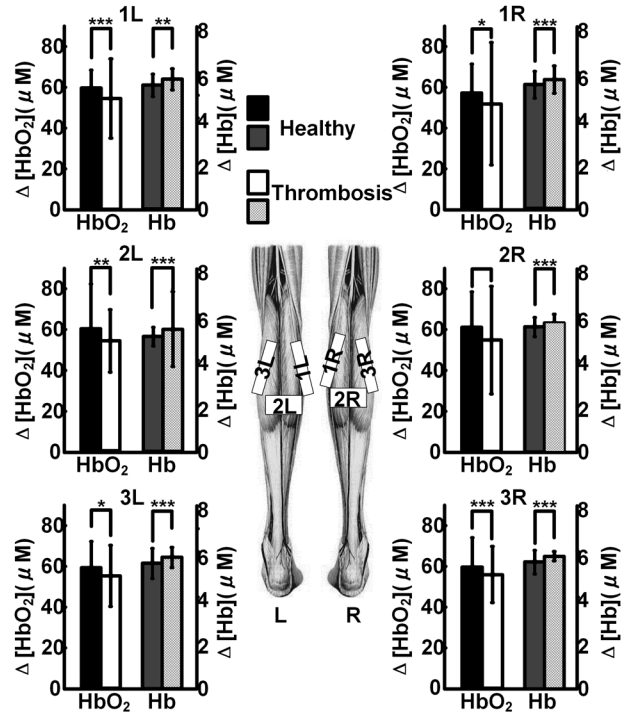


Fig. 2 Comparison between deep vein thrombosis (DVT) and healthy groups in NIRS measurements. Statistical significance was assigned for *P* value <0.05 as *. ** denoted that *P* value <0.01, whereas *** denoted that *P* value <0.001.

the $\Delta[\text{Hb}]$ data in DVT patients are distinctly higher than those in healthy volunteers ($P < 0.001$). Conversely, the data of $\Delta[\text{HbO}_2]$ at five measured sites are significantly lower in patients than those in healthy volunteers ($P < 0.044$). The insignificant difference in $\Delta[\text{HbO}_2]$ between the groups is showed in only one measured site “2R,” which may be due to the limited sample size. However, measurement at this site still presents lower mean values in DVT patients. In addition, $\Delta[\text{HbO}_2]/\Delta[\text{Hb}]$ shows a greater distinction between DVT patients and healthy ones at all measured sites (see Fig. 3). The results also indicate that the measurement site is highly critical for use for differentiating the two groups.

Figure 4 shows the typical variation tendencies of $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ in both DVT and healthy calves of a single-leg DVT patient. The error bar denotes the standard error among all measured sites. Other patients presented similar curves as shown in

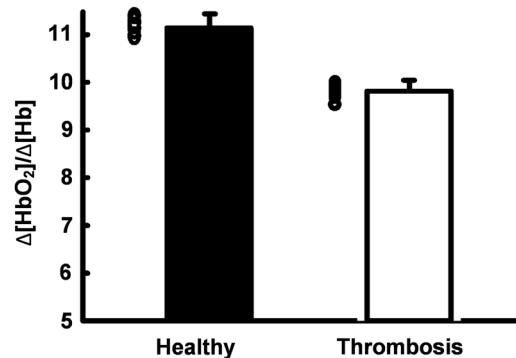


Fig. 3 Comparison between DVT and healthy groups in combined indicator $\Delta[\text{HbO}_2]/\Delta[\text{Hb}]$ at all measured sites with values denoted by dots.

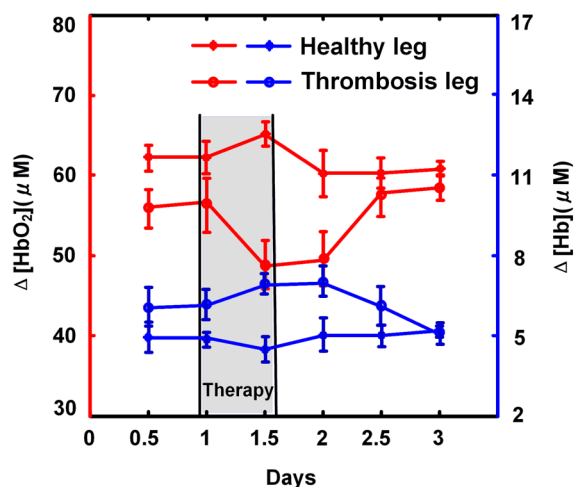


Fig. 4 Hemodynamic variation in DVT and healthy calves along with treatment procedure.

Fig. 4. For each of these patients, the thrombolytic therapy started on the DVT calf just before acquiring the second data point and ended just after acquiring the fourth data point (see Fig. 4). Before the therapy, the values of $\Delta[\text{HbO}_2]$ in the DVT leg were significantly higher than that in the healthy leg; while the $\Delta[\text{Hb}]$ presented the opposite result, which confirmed the findings shown in Fig. 2. As the therapy started, the $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ in the DVT leg started to decrease and increase, respectively, while these data in the healthy leg showed the opposite trend. Then, after the therapy, these indicators shifted into the opposite trends to those under therapy. What is more, the variation amplitude in the DVT leg was greater than in the healthy leg. Interestingly, after the therapy, the $\Delta[\text{Hb}]$ in the DVT calf became closer and closer to that in healthy calf as did $\Delta[\text{HbO}_2]$. When the patient felt better and was allowed to leave the hospital, the values of $\Delta[\text{Hb}]$ in DVT calf even agreed well with that of healthy calf.

Previous researchers attempted to diagnose DVT by using NIRS combined with exercise protocol that induced specified blood volume capacity and directional blood flow, which might be helpful for magnifying the DVT symptoms and accordingly promote the distinction between DVT and healthy populations. In this study, without the aid of patients' exercise, NIRS measurements of both the direct indicators $\Delta[\text{HbO}_2]$ and $\Delta[\text{Hb}]$ under the patients' natural state have already differed significantly between the DVT and normal groups (Figs. 2 and 3) and can continuously follow a patient's DVT recovery status during the therapy process (Fig. 4). Particularly, due to the opposite trends of these two indicators between DVT and normal ones, the difference can be made visibly obvious by combining the two (Fig. 3). This suggests that a more sensitive NIRS indicator (e.g., $\Delta[\text{HbO}_2]/\Delta[\text{Hb}]$) could be composited to distinguish DVT patients from normal ones, and better identification of

DVT severity or type could also be possible. Our methodology, merely NIRS without any protocol, was validated in DVT monitoring, diagnosis, and therapeutic effect evaluation and could be advantageous over previous NIRS studies in DVT clinics^{3,9} with continuous and straightforward measurements, convenient implementation, and fast diagnosis. This study reveals the potential of NIRS measurement at a patient's natural state as an appealing method for point of care setting in DVT clinics.

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References

1. J. S. Mino et al., "Line-associated thrombosis as the major cause of hospital-acquired deep vein thromboses: an analysis from National Surgical Quality Improvement Program data and a call to reassess prophylaxis strategies," *Am. J. Surg.* **208**(1), 45–49 (2014).
2. W. H. Geerts et al., "Prevention of venous thromboembolism," *Chest* **133**(6), 381s–453s (2008).
3. Y. Hosoi et al., "Influence of popliteal vein thrombosis on subsequent ambulatory venous function measured by near infrared spectroscopy," *Am. J. Surg.* **177**(2), 111–116 (1999).
4. S. M. Bates et al., "Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines," *Chest* **141**(2 Suppl), e351S–e418S (2012).
5. T. Jang et al., "Resident-performed compression ultrasonography for the detection of proximal deep vein thrombosis: fast and accurate," *Acad. Emerg. Med.* **11**(3), 319–322 (2004).
6. M. W. Hemelt et al., "Application of near-IR time-resolved spectroscopy and frequency response analysis for deep vein thrombosis detection," *Biotechnol. Prog.* **13**(5), 640–648 (1997).
7. T. Hamaoka et al., "The use of muscle near-infrared spectroscopy in sport, health and medical sciences: recent developments," *Philos. Trans. R. Soc., A* **369**(1955), 4591–4604 (2011).
8. F. D. Scott, Jr., K. A. Kang, and G. M. Williams, "Diagnosis of deep vein thrombosis with NIR spectroscopy," in *Proc. First Joint BMES/EMBS Serving Humanity, Advancing Technology*, Atlanta, Georgia Vol. 2, p. 1101, IEEE (1999).
9. T. Yamaki et al., "Deep vein thrombosis after total knee or hip arthroplasty is associated with increased preoperative calf muscle deoxygenation as measured by near-infrared spectroscopy," *J. Vasc. Surg.* **54**, 39s–47s (2011).
10. T. Li et al., "Innovative monitoring device for thrombosis," China, Patent of Invention 201410636048.1 (2014).
11. G. Strangman, M. A. Franceschini, and D. A. Boas, "Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters," *Neuroimage* **18**(4), 865–879 (2003).
12. T. Li et al., "Simultaneous measurement of deep tissue blood flow and oxygenation using noncontact diffuse correlation spectroscopy flow-oximeter," *Sci. Rep.* **3**, 1358 (2013).