Chapter 54
A Clinical Tissue Oximeter Using NIR Time-Resolved Spectroscopy

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Abstract The tNIRS-1, a new clinical tissue oximeter using NIR time-resolved spectroscopy (TRS), has been developed. The tNIRS-1 measures oxygenated, deoxygenated and total hemoglobin and oxygen saturation in living tissues. Two-channel TRS measurements are obtained using pulsed laser diodes (LD) at three wavelengths, multi-pixel photon counters (MPPC) for light detection, and time-to-digital converters (TDC) for time-of-flight photon measurements. Incorporating advanced semiconductor devices helped to make the design of this small-size, low-cost and low-power TRS instrument possible. In order to evaluate the correctness and reproducibility of measurement data obtained with the tNIRS-1, a study using blood phantoms and healthy volunteers was conducted to compare data obtained from a conventional SRS device and data from an earlier TRS system designed for research purposes. The results of the study confirmed the correctness and reproducibility of measurement data obtained with the tNIRS-1. Clinical evaluations conducted in several hospitals demonstrated a high level of usability in clinical situations and confirmed the efficacy of measurement data obtained with the tNIRS-1.

Keywords Time-resolved spectroscopy • NIRS • Tissue oximeter • Multi-pixel photon counter • Medical device

1 Introduction

In the nearly 40 years since tissue near infrared spectroscopy (NIRS) was first described, demonstrated and developed by F. Jobsis [1], it has become an established tool to monitor the oxygenation of brain tissue and other tissues. During these years, several types of NIRS machines based on such methods as modified-Beer Lambert (MBL) [2], spatially-resolved spectroscopy (SRS) [3], and time-

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resolved spectroscopy (TRS) [4], were developed. Since devices based upon the MBL and SRS methods employ continuous wave (CW) light and have advantages of cost and practicability, such devices have long been used in clinical settings as approved medical devices [5, 6]. On the other hand, the TRS method is well-known for its superiority over the SRS and MBL methods with respect to correctness and reproducibility of the measured data [7]. However, until now, devices used for TRS measurements have been bulky and expensive, and they required sophisticated technologies to handle the picosecond-speed signals. Therefore, although a TRS device has long been sought for clinical bedside measurements, the use of TRS oximeters has been limited to research fields. Our purpose was to develop a small-size, low-cost and easily-operated TRS tissue oximeter suitable for use in clinical environments. This paper describes the technical features of the instrument, the results of measurements from blood phantoms and healthy volunteers, and clinical data obtained during cardiac surgery to replace a descending aorta.

2 Theory of Measurement

Propagation of photons in highly scattering media can be described by the diffusion approximation [8]. For a semi-infinite half-space geometry, the solution of the photon diffusion equation for the impulse (δ-function) input is expressed by Eq. (54.1) [8].

$$R\left(\rho, t, \mu_a, \mu_s^{'}\right) = (4\pi Dc)^{-\frac{3}{2}} \frac{1}{\mu_s^{'}} t^{-\frac{5}{2}} \exp(-\mu_a ct) \exp\left(-\frac{\rho^2 + \mu_s^{'-2}}{4Dct}\right) \tag{54.1}$$

where R is the intensity of reflected light, ρ and t are the distance and time from the impulse input, respectively, μ_a and μ_s' are the absorption and reduced scattering coefficients, respectively, $D = 1/3(\mu_a + \mu_s')$ is the diffusion coefficient and c is the velocity of light in the medium.

In TRS measurements, the instrument response function, IRF(t), which represents the response waveform of the instrument itself, is measured in advance with a proper optical filter and is stored in the instrument. The time response waveform including the measured tissue, M(ρ, t), is theoretically expressed by the convolution of IRF and R as shown in Eq. (54.2).

$$M(\rho, t) = IRF(t) * R\left(\rho, t, \mu_a, \mu_s^{'}\right) \tag{54.2}$$

Therefore, with the conventional iteration method, the μa and μs′ which give the least square error between M(ρ,t) and IRF(t)*R(ρ, t, μ_a, μ_s') are determined as those of the measured tissue. With the tNIRS-1, the absorption coefficients at three wavelengths, $\mu_a(\lambda_1)$, $\mu_a(\lambda_2)$ and $\mu_a(\lambda_3)$, are measured, and the concentration of oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) are

calculated by the conventional method [7]. The tissue total hemoglobin (tHb) and oxygen saturation (StO_2) are derived from the equations, $tHb = O_2Hb + HHb$ and $StO_2 = (O_2Hb/tHb) \times 100$, respectively.

3 Design of the Instrument

The design of the instrument is shown schematically in Fig. 54.1. Temperature controlled pulsed LDs (typical wavelengths: 755, 816 and 850 nm, repetition rate: 9 MHz), which are chosen from the products available, are sequentially irradiated to the skin through the emission fibers. Light transmitted through the tissue is collected by the detection fibers and detected by the MPPCs through the variable neutral density filters (NDFs), which enables a dynamic range of the TRS measurement up to 3 orders of magnitude. The pulse width of the IRF of the tNIRS-1 is approximately 1.5 ns. In the time period between LD trigger and the photon detection by MPPCs, TDC measures the time of flight (TOF) of the transmitted light with an accuracy of 27 ps. The time response waveforms are created as a histogram of TOF every 5 s.

Figure 54.2 shows the external appearance of the instrument. The size is 292 mm (W) × 207 mm (D) × 291 mm (H) and the weight is 7.5 kg. The user operates the system using a touch screen. The system has sufficient battery back-up power to operate the system for 30 min. The probe consists of fiber bundle cables that are placed in a pad containing optical prisms that is secured in a rubber holder and attached to the patient. The patient pad is disposable and may be easily attached or detached from the patient, enabling it to be left in place on the patient between measurements. In this way, intermittent measurements with high reproducibility are

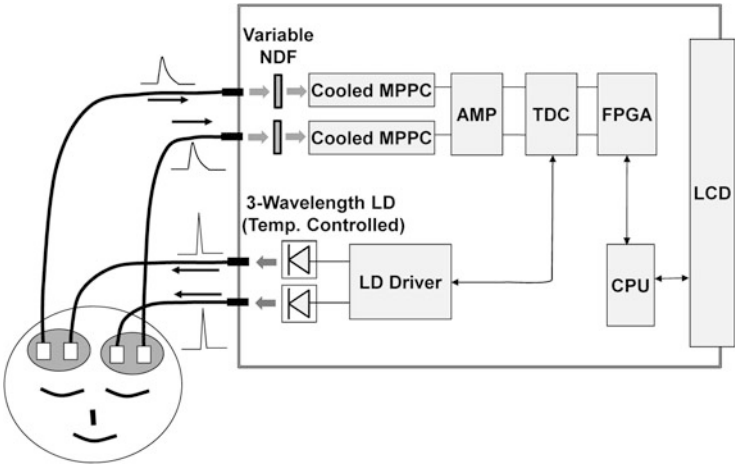

Fig. 54.1 Block diagram of the tNIRS-1

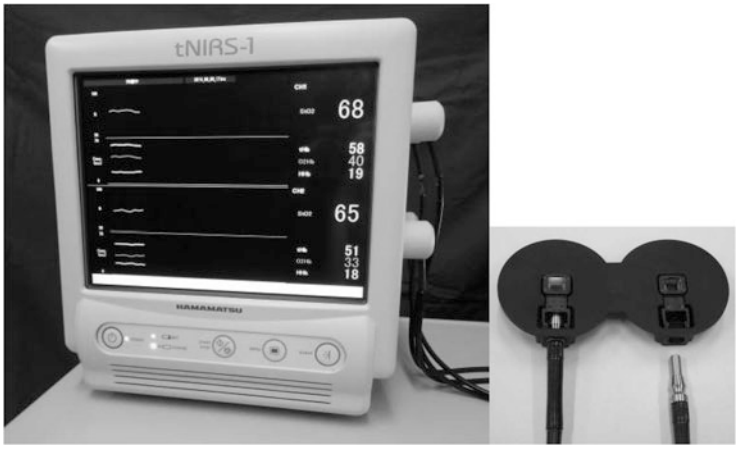

Fig. 54.2 The tNIRS-1 device and the probe

possible without restricting patient movement when measurements are not being made.

4 Measurements made for Instrument Evaluation

The correctness of tHb measured with the tNIRS-1 was evaluated using blood phantoms [5]. While adding human blood with known hemoglobin content measured by Stat Profile pHOx (Nova Biomedical Co., USA) into intralipid solutions (0.6 and 1.0 %) using a particular step, the tHb was recorded, and the hemoglobin concentrations in the phantoms and tHb were compared. As shown in Fig. 54.3a, the tHb values correlate well with the hemoglobin concentration in both of the intralipid solutions.

We performed a comparative study with the tNIRS-1 and another TRS system designed for research purposes (TRS-20, Hamamatsu Photonics [7]). Oxygen saturation measured with the TRS-20 (SO_2) and the tNIRS-1 was compared using a blood phantom (hematocrit; 1.1 %, intralipid; 0.7 %). As shown in Fig. 54.3b, good correlation between oxygen saturation measured with TRS-20 and tNIRS-1 was obtained.

Regarding the y-intercepts of −3.5 in Fig. 54.3a and −6.6 in Fig. 54.3b, we did not find any factors of systemic offset and think it comes from a limitation of the experiment accuracy.

We performed comparison studies on the reproducibility of measured data with a conventional SRS device (NIRO-200NX, Hamamatsu Photonics). With 8 healthy subjects (A–H), reproducibility of the data was evaluated by (i) repeating the attachment and detachment of the probe 8 times at the same position on the forehead and (ii) repeating the measurements at the 6 different positions on the

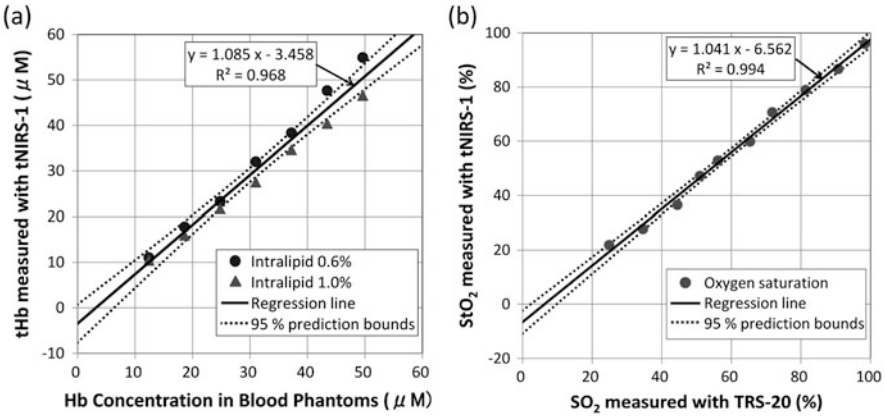

Fig. 54.3 (**a**) Hb concentration in blood phantoms and tHb measured with tNIRS-1, (**b**) Oxygen saturation measured with TRS-20 and tNIRS-1

Table 54.1 Average of standard deviations of measured oxygen saturation among eight subjects

Measurements \ Results	Average of SDs of measured oxygen saturation among 8 subjects	
	NIRO-200NX	tNIRS-1
(i) 8 times at the same position	2.0 %	1.0 %
(ii) 6 different positions	5.1 %	2.1 %

forehead. Each measurement was carried out for 1 min, and the mean values over this time were recorded. The results of (i) and (ii) are shown in Table 54.1. In measurement (i), standard deviations of TOI (NIRO-200NX) and StO_2 (tNIRS-1) were 2.0 and 1.0 %, respectively, and in the measurement (ii), these were 5.1 and 2.1 %.

The results show that reproducibility of the measured data with the tNIRS-1 is higher than that with the NIRO-200NX, particularly in cases of measurements at different positions. Since the SRS method tends to be susceptible to the geometry or curvature of measured parts, the reproducibility of data was much improved with the TRS method.

Figure 54.4 shows an example of clinical data during cardiac surgery (descending aorta replacement with the circulating blood temperature of 18 °C). The probes were set on the forehead of the patient. In each stage of the surgery, expected data changes such as the decrease in StO_2 and tHb during circulatory arrest were observed.

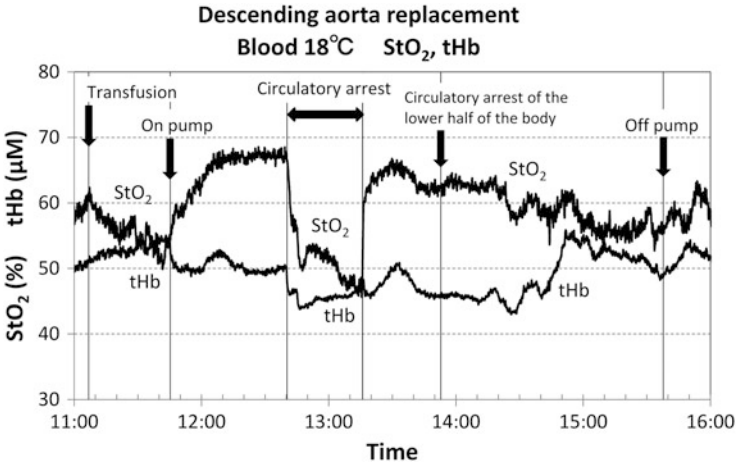

Fig. 54.4 An example of clinical data (By courtesy of Dr. Kenji Yoshitani, Department of Anesthesiology, National Cerebral and Cardiovascular Center, Japan)

In all the clinical evaluations performed thus far, the tNIRS-1 has demonstrated a high degree of usability, and the efficacy of the measured data in terms of correctness and reproducibility has been confirmed.

5 Conclusions

The tNIRS-1, a new clinical tissue oximeter using the TRS method, has been developed. A small size and low power design has been realized by employing advanced semiconductor devices such as MPPC and TDC. Expected performances were confirmed by evaluating measurements with blood phantoms, healthy volunteers and clinical measurements. The tNIRS-1 has been approved for use as a medical device in Japan. The applications to the US and EU countries are also intended.

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