Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans

Takafumi Hamaoka
National Institute of Fitness and Sports
Department of Exercise Science
Shiromizu 1
Kanoya, 891-2393 Japan
E-mail: kyp02504@nifty.com

Kevin K. McCully
University of Georgia
115 Ramsey Center
330 River Road
Athens, Georgia

Valentina Quaresima
University of L'Aquila
Department of Sciences
and Biomedical Technologies
L'Aquila, 67100 Italy

Katsuyuki Yamamoto
Hokkaido University
Biomedical Systems Engineering Division
of Bioengineering and Bioinformatics
Graduate School of Information Science
and Technology
North 14 West 9
Sapporo 060-0814, Japan

Britton Chance
University of Pennsylvania
Department of Biochemistry and Biophysics
Philadelphia, Pennsylvania 19104-6059

Abstract. Near-infrared spectroscopy (NIRS) was initiated in 1977 by Jobsis as a simple, noninvasive method for measuring the presence of oxygen in muscle and other tissues *in vivo*. This review honoring Jobsis highlights the progress that has been made in developing and adapting NIRS and NIR imaging (NIRI) technologies for evaluating skeletal muscle O_2 dynamics and oxidative energy metabolism. Development of NIRS/NIRI technologies has included novel approaches to quantification of the signal, as well as the addition of multiple source detector pairs for imaging. Adaptation of NIRS technology has focused on the validity and reliability of NIRS measurements. NIRS measurements have been extended to resting, ischemic, localized exercise, and whole body exercise conditions. In addition, NIRS technology has been applied to the study of a number of chronic health conditions, including patients with chronic heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, varying muscle diseases, spinal cord injury, and renal failure. As NIRS technology continues to evolve, the study of skeletal muscle function with NIRS first illuminated by Jobsis continues to be bright. [DOI: 10.1117/1.2805437]

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1 Introduction

The purpose of this review article is to highlight the most recent noninvasive near-infrared spectroscopy (NIRS) and NIR imaging (NIRI) studies aimed at evaluating skeletal muscle O_2 dynamics and oxidative energy metabolism, in light of historical studies that initiated this important and still developing technology. A brief background on the methodologies and approaches are presented, along with examples of how these methodologies and approaches have been used to better understand muscle function in both health and disease. A number of detailed review articles have previously described some aspects of the use of NIRS in muscle exercise pathophysiology.[1–6] A number of recent detailed review articles describing the principles, limitations, and applications of NIRS have appeared in the literature.[7–13]

Address all correspondence to Takafumi Hamaoka, National Institute of Fitness and Sports Kanoya, Kagashima, Japan shiromizu 1-kanoya, kagoshima 891-2393 Japan; Tel: 81 994 46 4935; Fax: 81 994 46 4935; E-mail: kyp02504@nifty.com

The primary reason NIRS technology is so valuable for the study of skeletal muscle is the strong dependence of skeletal muscle on oxidative metabolism. During exercise, skeletal muscle O_2 consumption (VO_2) can rise 50 fold with subsequent increases in O_2 delivery (DO_2) of up to 10 fold. Because of this, pathological impairments of either VO_2 or DO_2 will severely limit exercise and thus functional capacity. The net oxidative energy pathway in muscles can be described by the following equation:

$$3ADP + 3Pi + NADH + H^+ + 1/2O_2 = 3ATP + NAD^+ + H_2O,$$

where ADP is the adenosine diphosphate, Pi is the inorganic phosphate, NADH is the reduced nicotinamide adenine dinucleotide, ATP is the adenosine triphosphate, and NAD^+ is the nicotinamide adenine dinucleotide.

Early developments of dual wavelength spectrophotometers set the stage for the development of NIRS *in vivo*.

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In-vitro studies by Chance[14] and Chance and Connelly[14,15] showed that the newly discovered mitochondrial signal of NADH responded to electrical muscle stimulation in a fraction of a second, even at less than 10 °C, coupling muscle contraction to mitochondrial function. Jobsis,[16] together with Ramirez, Weber, and others, followed up with *in-vitro* optical studies of the bioenergetics of organs, heart, liver, brain, and adrenal and salt glands. Jobsis focused especially on skeletal muscle and greatly improved the technique when he moved to Duke University, where he performed a series of outstanding muscle physiology studies. These studies bridged the gap between bioenergetics and physiology and exploiting the relationship of the previous equation, that DO_2 in combination with the provision of other chemical substances, are the major key players for mitochondrial VO_2 or muscle oxidative metabolism.

Prior to the development of NIRS, skeletal muscle oxygenation (a balance between DO_2 and VO_2) and metabolism were evaluated in humans by conventional analytical biochemistry invasive methods after obtaining biopsy specimens. The strength of the biopsy approach is that a wide array of metabolites can be measured for studying specific metabolic pathways. The disadvantage of the biopsy technique is that biopsies cannot be easily performed during muscle contractions and have limited repeatability, thus limiting the ability to obtain time course data. To overcome these disadvantages, magnetic resonance spectroscopy (MRS)[17] was developed to measure *in-vivo* free (active) forms of phosphate compounds and intracellular pH, as well as intramyocelluar myoglobin (Mb) levels. MRS remains a valuable technology for the measurement of *in-vivo* energy status, oxygen saturations, and blood flow, but its high cost, large size, and limited availability reduce the usefulness of this method.

The continuing development of NIRS technology eventually leads to the study of intact organisms. The extension of the optical technology to wider spectral and time regions was epitomized by the elegant instrument of Lubbers and Thiefs (rapid spectroscopy) and by the work of Kramer and others who explored the NIR region, noting that the NIR light penetrated the hand, setting the stage for Jobsis' brilliant discovery[18] that the skull is not a barrier to NIR light, as recounted in his own words as follows.[19] Very briefly, on 28 December 1976 his family enjoyed a grilled chuck roast with a part of the shoulder blade of the steer—a flat piece of bone 3 or 4 mm thick. When his son Paul held the object up against the light, Jobsis noticed that the shadow of a finger could easily be seen in the diffused red light coming through the bone. Then he speculated that NIR light at longer wavelengths would penetrate the human skull and provide access to the tissue. His extraordinary scientific exploration started at a table with his family over a dinner with a very American cut of beef (he used this expression himself). In fact, the properties of the skull to enhance the NIR signals was later quantified in studies of the cat brain, where the removal of the skull shortened the NIR photon migration pathlength. Thus Jobsis' discovery opened the very active field of NIR studies of brain and stimulated the studies of skeletal muscle in human subjects, a tradition carried on elegantly by his son, Paul Jobsis.

In the intervening years, numerous studies have developed and refined the NIRS approach of studying skeletal muscle *in vivo*. They have experimented with the wavelengths and arrangement of light sources and detectors, as well as the portability of the devices.[20–26] Equally variable have been the experimental approaches and subject populations used to take advantage of NIRS technologies.

2 Methodological Issues Related to the Noninvasive Evaluation of Muscle Oxygenation and Metabolism Using Near-Infrared Spectroscopy

The first issue related to the use of optics to study skeletal muscle *in vivo* is the choice of wavelengths. Wavelengths ranging from 700 to 3000 nm show much less scattering and thus better penetration into biological tissue than visible light. However, light absorption by water limits the tissue penetration above 900-nm wavelength, leaving the 650- to 900-nm range. The major absorbing compounds of this wavelength region are intravascular hemoglobin (Hb), intramuscular Mb, skin melanin, and mitochondrial cytochrome c oxidase.[18] NIRS measurements rely on O_2 dependent absorption changes that occur in the theme, and copper containing compounds.

The most common, commercially available NIRS devices use single-distance continuous-wave light (NIR_{SDCWS}). To calculate the changes in oxy-Hb/Mb, deoxy-Hb/Mb, or total-Hb/Mb, the equation of a two- or multiple-wavelength method can be applied according to the following Beer-Lambert law.

$$\Delta OD = -\log_c(I/I_0) = \varepsilon PL\Delta[C], \tag{1}$$

$$\Delta[C] = \Delta OD/\varepsilon PL, \tag{2}$$

where ε is the extinction coefficient ($OD/\mathrm{cm}/\mathrm{mM}$) (=constant), PL is the pathlength, $[C]$ is the concentration of absorber (mM), I is the detected light intensity, I_0 is the incident light intensity, and OD is the optical density.

The major advantage of NIR_{SDCWS} devices is in their simple design. The invention of laser diodes and LED light sources in the NIR region, and of Si diode integrated chip detectors, has made possible inexpensive and wearable NIR detectors of muscle function.[23,27] A major limitation to the NIR_{SDCWS} devices is that they currently provide only the relative values of tissue oxygenation. The main reason for a lack of quantification by NIR_{SDCWS} is the unknown path of NIR light through biological tissues. The pathlength of light will vary due to variations in tissue composition (adipose tissue versus muscle, discussed later), blood volume (can increase or decrease heme concentrations over time), and muscle shape (altered during muscle contractions).

The pathlength of NIR light can be measured using other optical approaches, including time-resolved spectroscopy (NIR_{TRS})[20,24,28] and phase modulation spectroscopy (NIR_{PMS}).[29–31] NIR_{TRS} uses expensive single photon detectors to measure the time the light spends in the tissue, while NIR_{PMS} uses the change in phase of coherent light to determine the time the light spends in the tissue. These approaches provide absolute values of oxygenated and deoxygenated Hb/Mb and Hb/Mb O_2 saturation (SO_2) in the skeletal muscle. Spatially resolved NIR_{SRCWS} (NIR_{SRCWS})[32,33] provides relative changes in Hb/Mb and absolute values of SO_2. NIR_{SRCWS} using multiple light sources coupled to one detec-

tor solves multiple equations for pathlength. These approaches have been used in the study for skeletal muscle oxygenation and metabolism, and technological improvements will make these approaches more practical in the future.

What is known about the pattern of the light path from the light source to the detector is that it follows a banana-shaped curve, in which the penetration depth into the tissue is approximately equal to half the distance between the light source and the detector.[23] If light source-detector separation was set to be 3 cm, penetration depth would be 1 to 2 cm and the measured volume would be approximately 4 cm^3.[20] Usually, light source-detector distance ranges from 12 to 50 mm.[34–37] Subcutaneous adipose tissue thickness greatly influences the light pathlength and makes it difficult to quantify tissue oxygenation, especially in the measurements of muscle oxygenation from the skin surface.[11,32,38–40] The influence of adipose tissue thickness on the NIR spectra of human muscle was studied by Monte Carlo simulations of a two-layer structure and with phantom experiments.[41] The study suggested that subject-to-subject variation in the fat optical coefficients and thickness can be ignored if the fat thickness is less than 5 mm when the source-detector separation is 40 mm. Other studies indicated that for a fat thickness of 5 mm, the signal intensity reduces approximately by 0.2 (80% signal of zero fat thickness) with a light source-detector separation being 30 to 40 mm, and further reduces by 0.3 to 0.6 with a separation of 15 to 20 mm, respectively.[39,42] The correction curve is presented for the influence of an adipose tissue thickness ranging from 0 to 15 mm with a source-detector separation being 15 to 40 mm.[39,42,43] The curve was obtained from the results of both Monte Carlo simulation and *in-vivo* experiments.[39,42]

$$S = \exp[-(h/A_1)^2] - A_2 G(\alpha,\beta), \tag{3}$$

where S is normalized measurement sensitivity, h is adipose tissue thickness, $G(\alpha,\beta)$ is a gamma distribution, and the constants A_1, A_2, α, and β at a light source-detector separation of 15 mm are 6.9, 1.15, 7.86, and 0.80, respectively. Considering that the value of S is determined in practice only by h, then the corrected values are obtained by dividing the measured values by S. A qualitative description of reduced NIRS signal intensity by a larger adipose tissue thickness was illustrated in a previous review.[11]

In NIR_{SDCWS} measurements, there is the assumption that pathlength does not show any significant change during exercise, recovery, and other intervention periods, otherwise the values obtained are either underestimated or overestimated, as is shown in Eqs. (1) and (2). During and after the end of arterial occlusion, the changes in pathlength of the forearm muscle ranged from −8.3 to −2.1% at 780 nm, and from −2.2 to 0.74% at 830 nm.[28] Changes in pathlength were less than 10% during arterial occlusion with maximum voluntary contraction (MVC).[24] Differential pathlength factor (DPF) in the thigh muscle decreased slightly, but significantly from baseline (DPF at 690 nm=5.22; DPF at 830 nm=4.49 on average) to peak cycle exercise (DPF at 690 nm=4.88; DPF at 830 nm=4.27 on average) (−6.5% at 690 nm and −4.9% at 830 nm).[44] For an accurate evaluation of muscle oxygenation during arterial occlusion, exercise, and recovery, changes in pathlength should be extensively examined in a wide range of exercise mode/intensity and among varying subjects.

A technological limitation to the use of NIRS is the similar absorption spectra for Hb and Mb. This makes it difficult to distinguish between the two by the optical properties alone. A number of studies have taken advantage of ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) measurements of Mb[45–47] to estimate the relative contributions of Hb and Mb to the total NIR signal. Combined ^{1}H-MRS and NIRS studies of canine muscle during exercise in normoxic and hypoxic conditions concluded that the NIR signal came 65% from Hb and 35% from Mb.[48] As canine muscle contains more Mb than human muscle, this suggests more than 65% of the signal from human muscle comes from Hb during normoxic conditions. During ischemia, MbO_2 levels appear to decline only after 4 min,[49] while NIRS measured oxygen signals decline almost immediately and reach near maximal levels at 4 min.[50,51] From this, Ferrari, Mottola, and Quaresima suggested that NIRS-measured SO_2 values would reflect predominantly (at least 80%) HbO_2 saturation during exercise in humans.[2] A simulation experiment based on combined measurements of ^{1}H-MRS and NIRS concluded that the overall NIR signal would be greater than ~50% Hb.[52] In contrast, Tran et al. reported a greater contribution of Mb signal than Hb to the overall NIR signals in a study using ^{1}H-MRS.[53] The differing conclusions from these studies highlight the need for additional studies to clarify not only the issue of the contribution of Mb to the NIR signal, but also the kinetics and the amount of Mb desaturation during exercises under different conditions.[54] To acknowledge this concern, many studies present NIRS-measured oxygen saturation as HbO_2/MbO_2. For simplicity, this work presents oxygenated Hb/Mb expressed as O_2Hb, deoxygenated Hb/Mb as HHb, and total Hb/Mb as tHb.

Recent advances in NIRS technology have included the addition of multiple-source detector pairs to "image" skeletal muscle. This has been done to take advantage of classical studies that have shown regional differences in skeletal muscle oxygenation and metabolism in different locations within a muscle.[55] Several multiple-channel NIR imaging systems have been developed to detect regional differences in muscle oxygenation.[43,56–62] By simultaneously collecting data from multiple muscle regions, these devices avoid the variability caused by position dependent differences in muscle oxygenation that plague all single location measurements. Imaging devices also allow the study of regional differences in how skeletal muscle responds to exercise. The challenge of NIR imaging systems is how to evaluate the much greater amounts of information that are collected. The application of NIR imaging technology to the study of exercising muscles is illustrated in Fig. 1.

3 Types of Measurements Made on Skeletal Muscle Using Near-Infrared Spectroscopy

3.1 *Muscle Oxygenation*

The most common measurement made with NIRS is muscle oxygenation, or the fraction of Hb that is bound to oxygen. Relative changes in O_2Hb, HHb, and tHb are also reported. Because of the difficulty in quantifying NIR_{SDCWS}, muscle

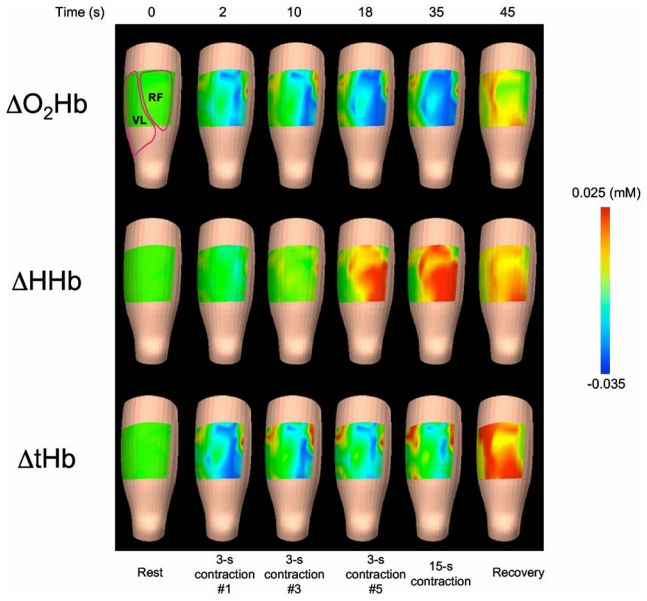

Fig. 1 Near-infrared (NIR) images from the quadriceps muscles before, during, and after intermittent isometric knee-extension exercise (IKEx). The NIR imaging system had 200 channels that covered a 45 cm × 15 cm^2 area. The top left image indicates the approximate location of specific muscles. Contractions 1, 3, and 5 indicate images obtained during a series of 3-s duration contractions at 50% of maximum voluntary contraction (MVC), with one second rest in between. The 15-s contraction shows data at the end of a continuous 15-s MVC. The recovery image was obtained 10 s after the last contraction. These images demonstrate the spatial differences seen within muscles during exercise and recovery. The detailed description of the system and the source-detector arrangement are described in a previous paper.[42] O_2Hb is oxygenated hemoglobin and myoglobin; HHb is deoxygenated hemoglobin and myoglobin; and tHb is total hemoglobin and myoglobin.

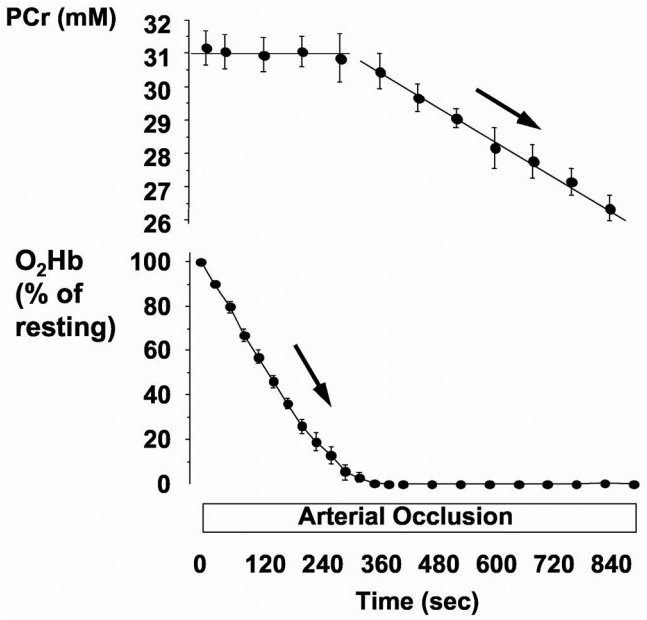

Fig. 2 An example of how to quantitatively calibrate the NIRS signal. Changes in phosphocreatine (PCr) and oxygenated hemoglobin and myoglobin (O_2Hb) in the forearm muscle were measured during 15 min of arterial occlusion by magnetic resonance spectroscopy and near-infrared spectroscopy. The detailed description of the methods is described in a previous paper.[50] Copyright (c) The American Physiological Society. Reproduced by permission of the publisher.

oxygenation is usually expressed in arbitrary units [optical density (OD)], $\mu M \times cm$ or μM (using DPF × source-detector spacing) for O_2Hb, HHb, and tHb. A wide variety of skeletal muscles have been evaluated using this approach, including the back extensor muscles,[63–66] gluteus maximus,[67,68] vastus lateralis,[44,69–72] vastus medialis,[70] rectus femoris,[70,71] biceps femoris,[68] calf,[72–76] dorsiflexors,[77,78] respiratory muscles,[79] trapezius,[34,80,81] deltoid,[82] triceps,[83,84] biceps brachii,[85,86] extensor carpi radialis brevis,[87] forearm flexors,[88] thenar muscles,[89] brachioradialis,[90] and masseter muscle.[91] Some researchers have used NIRS at multiple sites, such as vastus lateralis versus serratus anterior[92] and vastus lateralis versus rectus femoris,[73,93] to obtain a clearer understanding of physiological changes in the various tissues during exercise. Most studies have evaluated muscle oxygenation changes during aerobic types of exercise, but several studies have also examined high intensity[94,95] or resistance types of exercise.[96,97] While most of the information obtained pertains to muscle oxygenation, there are several studies that have documented the changes in tHb during exercise.[98,99] While most studies have evaluated muscle oxygenation changes of the exercising limb some researchers have studied inactive limb muscle oxygenation during dynamic exercise of the other limb.[83,100]

A simple and common method of calibrating NIR_{SDCWS} signals is to use the range of muscle oxygenation caused by arterial occlusion followed by reactive hyperemia.[23] The arterial occlusion method is based on the assumptions that 5 to 6 min of ischemia will result in the complete disappearance of O_2Hb, and that the reactive hyperemia after occlusion will almost completely eliminate HHb. So while O_2Hb and HHb in arbitrary units may vary between measurement sites and individuals, the occlusion calibration will account for these changes. Quantitative calibration of NIR_{SDCWS} signal is possible in a combination with MRS measurement by applying a 15-min ischemia to the muscles (Fig. 2).[50] The rate of decline of muscle O_2Hb during ischemia can be compared with that of muscle PCr in mM per second or a conversion to mMO_2 per second. As a result, this method provides quantitative values of both muscle oxygen store and muscle VO_2 (mVO_2).

Several studies reported the validity of NIRS-measured O_2Hb and HHb signals in animals and humans under steady-state conditions. Wilson et al. demonstrated a linear relationship between NIRS measurements and venous SO_2 (SvO_2) using an *in-situ* canine muscle preparation.[101] Shiga et al. found a strong linear relationship ($r=0.934$; $P=0.01$) between the change in the HHb signal and arterial SO_2 (SaO_2) in a hypoxic-dog model.[27] Mancini et al. found muscle oxygenation and SvO_2 of human forearm muscles to be closely related during exercise.[102] They also demonstrated that muscle oxygenation level decreased with an intravascular norepinephrine administration, and increased with a vasodilator (nitroprusside) administration. Muscle deoxygenation was quantified during resting arterial occlusion in human skeletal

muscles using NIR_{TRS}. In a study using NIR_{TRS}, muscle deoxygenation (SO_2-TRS) during arterial occlusion was compared to SvO_2 and interstitial partial pressure ($PintO_2$).[28] At the end of occlusion, SO_2-TRS ($24.1 \pm 5.6\%$) agreed with SvO_2 (26.2 ± 6.4); and $PintO_2$ (14.7 ± 1.0 Torr) agreed with PvO_2 (17.3 ± 2.2 Torr). Thus, there are several studies that have validated NIRS measurements relative to established invasive methods.

However, there have been a number of studies that have failed to validate NIRS measurements. Both Costes et al. and MacDonald et al. reported discrepancies between the NIR signal of the vastus lateralis and the femoral SvO_2 during a cycling exercise under normoxic conditions, while a correlation between the two parameters was reported under hypoxic conditions.[103,104] A possible explanation for the discrepancies is that the NIRS signal contains information of arterioles, capillaries, venules, and intracellular Mb, and that the O_2 gradient from an arteriole to venule is large in normoxic conditions, such that variations in blood volume from arteriole to venule could alter the NIRS signal without change in venous oxygen signals.[11] The lower oxygen levels during hypoxic conditions would reduce this effect. However, further research is needed to clarify NIRS signal contribution from arterioles, capillaries, venules, and Mb under varying oxygenation status and in varying measurement protocols.

Recently, good association was found between regional quadriceps oxygenation at three different measurement sites and SvO_2 during one-legged dynamic knee extension exercise, even under normoxic conditions.[93] It may be that by using multiple measuring locations, the NIRS signal shows better agreement with the entire extremities SvO_2. A good relationship was also found between vastus lateralis oxygenation and femoral arterio-venous O_2 difference ($a\text{-}vO_2D$) during one-legged dynamic knee extension exercise under normoxic as well as hypoxic and hyperoxic conditions.[7] Thus, it is broadly accepted that the NIRS-oxygenation/deoxygenation signal has considerable agreement with the changes in SvO_2 and/or $a\text{-}vO_2D$ under varying oxygenation status of the human muscles.

In nonsteady-state conditions, such as at the onset of exercise and in recovery after exercise, changes in muscle oxygenation determined by NIRS provide relevant information on muscle oxidative function. The rate of deoxygenation at the onset of exercise,[105] recovery time of muscle reoxygenation after submaximal to maximal exercise,[23,106–110] and the rate of reoxygenation after brief high intensity MVC exercise[111] are among indicators for evaluating muscle oxidative capacity. These studies have reported good agreement between faster PCr recovery kinetics and faster oxygenation kinetics measured with NIRS. A different outcome was obtained after maximal short-duration isometric exercise, where higher oxidative capacity muscle (faster PCr kinetics) was inversely related to the rate of muscle reoxygenation after the exercise.[111] The result of this study was attributed to the hypothesis that muscle reoxygenation rate after this type of short high intensity exercise may be influenced more by VO_2 than by DO_2, when O_2 demand is still high and O_2 supply is not fully activated.

3.2 *Muscle Oxygen Consumption and Muscle Blood Flow*

3.2.1 *Transient arterial occlusion method*

Evaluation of muscle energy metabolism using NIRS is difficult, because the measured oxygenation levels do not specifically reflect mVO_2; rather, they reflect the balance between muscle DO_2 in relation to mVO_2. To dissociate mVO_2 from DO_2 using NIRS, two approaches have been used; the transient arterial occlusion method and the venous occlusion method. The transient arterial occlusion uses 10 to 30 s of arterial occlusion provided by a pneumatic tourniquet to interrupt DO_2 to the monitored muscle.[26,50,112–116] Measurements of resting mVO_2 using this approach in the forearm muscles of young health males was found to have a small amount of variability ($23.0 \pm 1.2\%/\text{min}$),[50] and to be consistent between studies by different investigators.[51] NIR_{TRS} has also been used to measure resting mVO_2, providing results in absolute units ($0.82\ \mu M\ s^{-1}$).[28] The transient arterial occlusion method has also been used to measure forearm muscle metabolism during exercise.[50] Varying moderate intensities were used to provide a range of mVO_2 levels, and resulting mVO_2 values were compared to simultaneous MRS measurements of phosphorus metabolities. A significant correlation was found between NIRS measured mVO_2 and MRS measured PCr ($r^2=0.99$, $p<0.01$), and ADP ($r^2=0.98$, $p<0.01$) concentrations. The linear relationships between exercise intensity and the NIRS and MRS measured indicators of mVO_2 supports both the thermodynamic[117,118] and kinetic[119] regulation models of mitochondrial respiration in skeletal muscle.

Validation of NIRS measurements of mVO_2 have been performed using MRS measurements of PCr kinetics, as well as measurements of whole body VO_2 performed by measuring expired gas concentrations. NIRS measured mVO_2 using the transient arterial occlusion method was significantly related to the rate of PCr recovery, a biochemical process of ATP resynthesis via oxidative phosphorylation after muscle contractions ($r=0.965$).[115] Repeated transient arterial occlusions after exercise can provide successive mVO_2 values, information that is basically similar to that determined from PCr recovery kinetics,[117,120–123] an indicator for muscle oxidative capacity. Thus, the time constant for mVO_2 recovery is an indicator for evaluating muscle oxidative capacity (Fig. 3).[124]

NIRS measured muscle oxygenation was also compared to pulmonary O_2 consumption (pVO_2) in 16 healthy males during an exercise tolerance test on a cycle ergometer.[125] A significant positive correlation was observed between HHb and pVO_2 ($r=0.893$ to 0.986), and a negative correlation between pVO_2 and O_2Hb ($r=0.726$ to 0.978). There are several reports indicating that: 1. oxygenation of forearm flexor muscles closely reflected the exercise intensity and the metabolic rate determined by MRS during exercise[112,126,127] and during recovery,[112,126] and 2. that muscle oxygenation level (percent of arterial occlusion) showed a linear relationship with mVO_2, though in a limited range ($3.2 < mVO_2 < 13.3$ fold of resting), during exercise (Fig. 4)[128] and recovery. These studies suggest that the initial rate of muscle deoxygenation during transient arterial occlusion is a direct measure of mVO_2, and that muscle oxygenation level itself is a reflection of mVO_2.

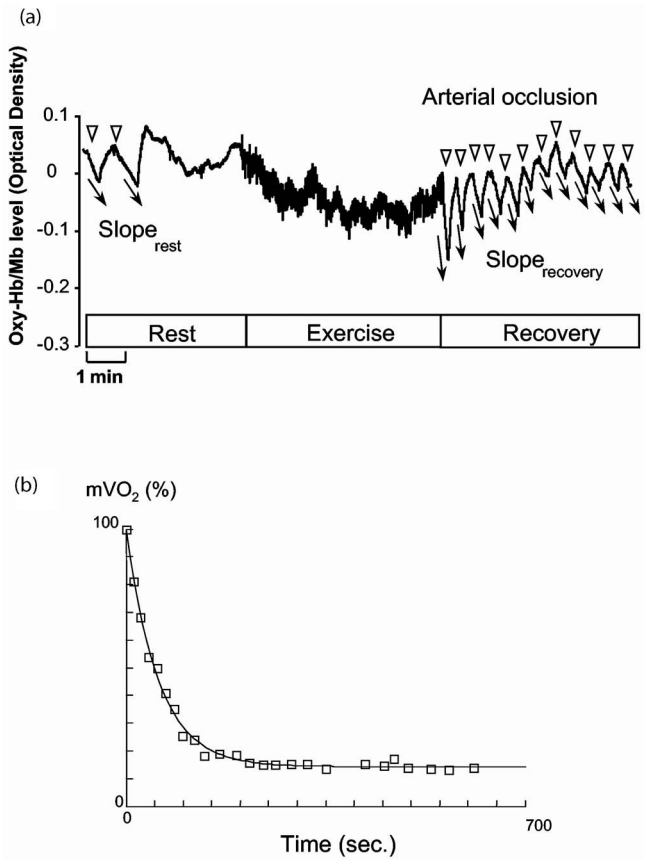

Fig. 3 An example of the repeated transient arterial occlusion method of measuring muscle oxygen consumption (mVO_2). (a) Transient arterial occlusion was applied at rest and then at various times after exercise. As highlighted by the arrows, the slope of desaturation of the O_2Hb signal was less rapid during rest than after exercise, consistent with the higher rates of mVO_2 after exercise. (b) Calculated mVO_2 values after exercise show an exponential decline consistent with changes in phosphocreatine levels from magnetic resonance spectroscopy.

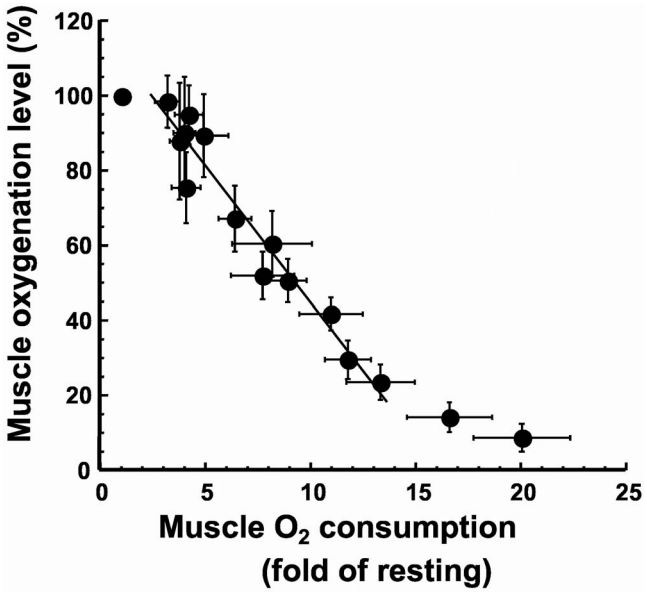

Fig. 4 Relationship between muscle oxygenation level and muscle oxygen consumption (mVO_2) in the calf muscle during incremental intermittent isometric plantar flexion exercise (IPFx). Changes in muscle oxygenation level and mVO_2 in the calf muscle were measured during IPFx (6-s contraction/4-s relaxation). The subjects performed IPFx, starting at 10% of maximum contraction (MVC) until exhaustion. The value of mVO_2 was measured by transient arterial occlusion method. Muscle oxygenation level was normalized to the overall changes during ischemia. The fall in oxygenation level reflected increases in exercise intensity, and the NIRS measurements demonstrate the increased muscle oxygen consumption results from increased exercise intensity. There is a linear relationship between muscle oxygenation level and mVO_2 in a certain range ($3.2 < mVO_2 < 13.3$, determined by the best fit by a piece-wise linear regression model) during this type of exercise.

3.2.2 *Venous occlusion method*

The venous occlusion method can be used to determine mVO_2 and muscle blood flow (mBF) by applying the same technique used in conventional venous plethysmography.[114,129] Briefly, transiently applied low cuff pressures (typically 60 mm Hg) occlude venous outflow while minimally obstructing arterial inflow. The increase in deoxygenated blood is then used to calculate mVO_2 and mBF. NIRS-determined measures of mBF and mVO_2 by the venous occlusion method have been shown to agree with traditional measurements using plethysmography[114,129] and the Fick method.[114,116,129] The advantage of NIRS is that it is capable of providing information about mVO_2 and mBF in a local area of a muscle. One of the difficulties in validating NIRS studies are that conventional methods such as plethysmograpy, Doppler sonography, and the Fick method cannot provide localized measurements. The disadvantage of using the venous occlusion method as well as the transient arterial occlusion method is that exercise must be interrupted to make the measurements. The assumption is that both mVO_2 and the mBF measured immediately after the end of the exercise reflect the mVO_2 and mBF values during exercise.

3.2.3 *Other methods for measuring muscle oxygen consumption and blood flow with near-infrared spectroscopy*

A variation of the transient arterial occlusion method is to take advantage of the ischemia produced during high intensity isometric muscle contractions. Contraction-induced compression and crimping of blood vessels produces ischemia without the need for externally applied arterial occlusion. Using the ischemic exercise method, the rate of deoxygenation measured at the onset of intermittent (5-s contraction/5-s relaxation) isometric exercise at 50% MVC followed an exponential time course with a time constant of 42.0±12.5 s (mean ±SD).[126] The NIRS measurements were in good agreement with the time constant of the decrease in PCr measured simultaneously (48.2±10.2 s). Muscle blood flow can be quantitatively, though invasively, measured using NIRS with an indocyanine green (ICG) dye infusion.[130] More recently, NIR diffuse correlation spectroscopy (NIR_{DCS}) and diffuse reflectance spectroscopy (NIR_{DRS}) have been developed for measuring changes in muscle oxygenation and mBF, and are able to compute mVO_2.[131] NIR_{DRS} methodology uses the unique approach of monitoring mBF by measuring the optical phase

shift caused by moving blood cells. NIR_{DCS} methodology is able to monitor tissue optical properties, such as the absorption coefficient (μa) and reduced scattering coefficient ($\mu s'$), without applying arterial occlusion or venous occlusion to a limb. The ability to measure mVO_2 and the mBF without occlusion is a strong potential advantage, although an extensive validation study in humans is needed before broadly applying this technique to practical and clinical use.

3.3 *Other Indicators*

NIRS is able to provide other indicators than those mentioned. SvO_2 is estimated by measuring changes in O_2Hb over tHb during venous occlusion,[132] and by the method based on the respiration-induced oscillations of the NIR absorption in tissues, named spiroximetry.[30] A method for measuring the compliance of the microvascular superficial venous system of the limb using NIRS has been developed.[133] More indicators have been proposed and used specifically in clinical science, which is addressed in the following section.

4 Near-Infrared Spectroscopy in Combination with Other Methodologies

NIRS has been used in combination with a large variety of other invasive and noninvasive methodologies to evaluate physiological and pathological changes in peripheral muscle and/or whole body metabolism. The noninvasive methods that have been used in combination with NIRS in recent studies (2000 to 2006), include: MRS,[88,128,134,135] magnetic resonance imaging (MRI),[78,135–138] electromyography (EMG),[68,71,136,139–143] ultrasound sonography and Doppler,[35,144–147] plethysmography,[76,148] respiratory gas analysis,[98,149–159] transcutaneous oxygen pressure measurement,[160–162] laser Doppler skin blood flow and skin oxygenation measurements,[163–167] pulse oximetry,[152,168] mechanomyography,[66,169,170] muscle force and power measurements,[78,94,171–173] muscle fatigue index measurements,[77] ankle-brachial (blood pressure) index measurements,[74,75] and sweat response measurements.[174] The invasive methods that have been used in combination with NIRS in recent studies include: blood gas measurement,[93,175,176] muscle sympathetic activity measurement,[145] blood biochemical measurements (including lactate),[34,69,98,177] muscle biopsy,[34,150,178] intramuscular pressure measurements,[169,179] and positron emission tomography.[180,181] Among them, substantial numbers of studies have been conducted to examine the relationship between respiratory gas indicators and NIRS indicators.[151–155,157] Recently, there have been several studies to evaluate oxygen uptake kinetics during exercise using NIRS indicators such as HHb delay, HHb mean response time, and HHb time constant at the onset of exercise.[35,149,150,156]

5 Examples of the Use of Near-Infrared Spectroscopy in the Assessment of Human Skeletal Muscle Function

5.1 *Healthy Subjects*

A number of different studies have evaluated the influence of increased activity as well as decreased activity on muscle function using NIRS. Costes et al. examined whether exercise-training-induced adaptations in muscles can be determined by NIRS.[182] Training did not change the pattern of muscle oxygenation, though a significant relationship was found between blood lactate and muscle oxygenation at the end of exercise. Ichimura et al. examined the interaction of age and habitual physical activity on recovery time of muscle oxygenation following maximal cycling exercise.[107] They found that NIRS measured recovery time was prolonged with aging, regardless of habitual physical activity levels. However, habitual physical activity may prevent the age-related prolongation in the recovery time of muscle oxygenation after maximal cycling exercise. Changes in skeletal muscle oxidative function were measured by NIRS in immobilized forearm muscles, evaluating the preventive effect of the endurance training protocol on deterioration of skeletal muscle.[124] Muscle oxidative function was determined by the time constant for the recovery of mVO_2, applying repeated transient arterial occlusions after exercise. This study suggested that NIRS can be used clinically for noninvasive monitoring of deconditioning and reconditioning of skeletal muscle oxidative functions.

NIRS has also been used for evaluating acute and chronic (training) effects of exercise on muscle oxygenation for athletes such as endurance cyclists,[13,149,152,183–186] sprinters,[187] endurance runners,[152,187] swimmers,[188] triathletes,[25,152,183] soccer players,[189] resistance-trained athletes,[190] skaters,[191] and cross-country skiers.[192] What has emerged from these studies is that several NIRS derived indicators can be useful for evaluating the effect of exercise training on muscle metabolism. These include the recovery time for muscle reoxygenation and the time constant for mVO_2 recovery after exercise in healthy subjects. However, most of the studies on the influence of training have been performed using cross-sectional study design, and there is a need for more longitudinal studies on exercise training that use NIRS measurements. Further, if NIRS is to be used in examining the alteration of intervention for longitudinal studies, it is imperative that the reliability of the technique be demonstrated. Currently there is limited research[193,194] that has documented the reliability of NIRS during exercise.

5.2 *Patients*

5.2.1 *Peripheral vascular disease*

A number of studies have used NIRS to evaluate patients with peripheral vessel disease (PVDs). Peripheral arterial disease (PAD) involves partial occlusion of arterial flow, usually to the legs, that impairs function. The impaired function can be quite severe, and is termed intermittent claudication. PAD has been shown to produce impaired oxidative metabolism,[195] despite observations of increased mitochondrial enzyme content.[196] The increase in mitochondrial volume indicates an adaptive response to the low DO_2.

A consistent finding with NIRS measurements in PAD patients is slower rates of calf reoxygenation after exercise.[74,75,197–199] The magnitude of the impairment could be very large, with recovery rates being up to five times slower than healthy control subjects.[109] Good correlation was found between measurements of Doppler pressure waveforms and ankle arm systolic pressures (AAI) and the NIRS recovery time constant.[109] An important aspect of this study was that

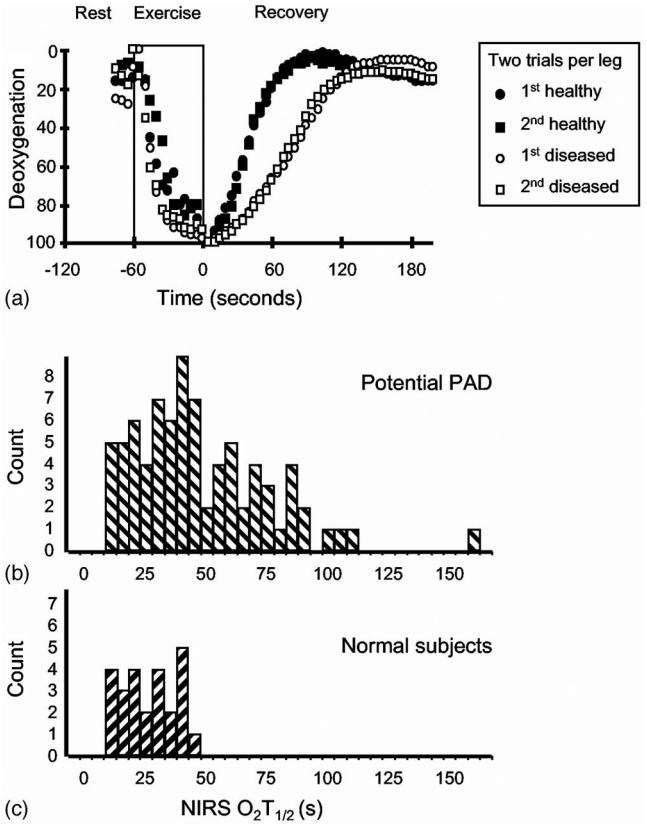

Fig. 5 An example of NIRS measurements of the rate of reoxygenation after exercise in patients with peripheral arterial disease (PAD). (a) Four measurements from one elderly male subject with PAD in only one leg. Note that multiple trials on one leg produce very similar results, while the diseased leg shows a much slower rate of recovery. (b) The distribution of reoxygenation rates in a population of older subjects with suspected PAD by self report. Note the wide and continuous range of responses. Subjects with faster recovery rates were shown to be normal on clinical examination, while those with slower recovery rates had PAD. (c) Recovery rates for healthy subjects for comparison. Copyright (c) The Gerontological Society of America. Reproduced by permission of the publisher.

the degree of impairment appeared to be continuous, demonstrating that clear separation of healthy and diseased people is difficult (Fig. 5). Komiyama et al. successfully classified patients with a varied severity of PVD by using patterns of calf oxygenation kinetics during treadmill exercise and recovery.[198] Impaired muscle O_2 usage at the exercise onset was also observed in PAD patients.[200] Interestingly, Mohler et al. reported an interaction between PAD and the presence or absence of diabetes mellitus (DM) using changes in muscle capillary blood expansion and reoxygenation recovery.[75] Capillary blood expansion was reduced in patients with DM, regardless of the existence of PAD; therefore, this parameter might be a good indicator for evaluating vascular impairment in DM patients. Taking into account that not all studies have shown positive results, NIRS appears to be able to identify and quantify the severity of patients with PAD.

Several studies have evaluated peripheral venous occlusive diseases using NIRS.[201–203] A calf venous blood filling index was tested on standing patients, and the calf venous retention index was monitored after exercise testing in patients with acute deep vein thrombosis from 1 to 12 months after treatment. These indicators were able to distinguish between successfully treated patients and those remaining with deep vein thrombosis after a period of 12 months.

5.2.2 *Heart diseases*

A number of studies have used NIRS to evaluate skeletal muscle in patients with heart disease. In addition to functional deficits associated with impaired cardiac function, heart disease has also been shown to be associated with impaired muscle metabolism.[204] This decrease in muscle metabolism has been linked to reduced exercise tolerance and decreased pVO_2, and increased risk of cardiovascular disease.[205,206]

NIRS measured muscle oxygenation kinetics have been studied in patients with congestive heart failure (CHF).[101,106,207–209] Wilson et al. concluded that CHF patients exhibited greater deoxygenation compared with the controls, due partly to the pump failure of the heart and the consequent skeletal muscle hypoperfusion. A correlation between changes in tHb and leg vessel conductance was found in patients with and without cardiac dysfunction during submaximal dynamic exercise, but there was some discrepancy between the NIRS and leg vessel conductance measurements at near maximal exercise levels.[148] Recently, skeletal muscle oxygenation was evaluated in heart transplant recipients (HTR).[151] The changes in HHb during submaximal exercise were steeper in HTR than in the control subjects, while the peak value of HHb was lower in HTR. The authors suggested that NIRS allows the detection of an impairment of both DO_2 and O_2 extraction in the HTR skeletal muscle.

To elucidate with heart failure, NIRS has been used to assess respiratory muscle deoxygenation in patients with CHF or HTR during leg cycling exercise.[159,210,211] The rationale for these studies is that exercise-induced dyspnea is common in patients with heart disease. The NIRS measurements were consistent with respiratory muscle hypoperfusion combined with the greater work of breathing in patients with CHF.

5.2.3 *Chronic obstructive pulmonary disease*

Patients with chronic obstructive pulmonary disease (COPD) frequently develop skeletal muscle and vascular abnormalities as complications of their disease, similar to patients with heart disease.[212,213] These observations suggest that deteriorated oxidative metabolism is related to lowered muscle oxidative capacity, elicited both by chronic inactivity and abnormal metabolic regulation, as well as reduced DO_2 to muscles. Evidence for a peripheral mechanism for exercise intolerance is supported by studies that have shown that exercise capacity was improved with endurance exercise training in patients with COPD.[213]

NIRS measured recovery of oxygen saturation after exercise has been shown to correlate with expired air pVO_2 off kinetics in COPD patients.[214] In a study measuring oxygen saturation in skeletal muscle with NIRS during incremental cycling exercise in 16 COPD patients and 10 age-matched healthy subjects, the slope of SO_2 was significantly steeper in COPD patients than in healthy subjects. The rate of the decrease in SO_2 with increasing exercise intensity in COPD patients significantly correlated with body mass index (BMI), suggesting that BMI contributes independently to the change

of muscle SO_2 with exercise.[215] NIRS was used to obtain the time constant of the deoxygenation recovery signal (HHb-Tc) during three constant work exercise tests, one below and two above the lactic acidosis threshold.[110] This study found significant correlations between changes in oxidative enzyme activity and changes in HHb-Tc and endurance time. It was concluded that leg training accelerates the speed of reoxygenation of the vastus lateralis muscle after exercise. This improvement is correlated to changes in the oxidative enzymes.[110]

5.2.4 *Muscle diseases*

NIRS measurements have been used to study patients with neuromuscular disorders. Exercise intolerance and fatigue are common complaints in patients with neuromuscular disorders.[216,217] Although neuromuscular disorders encompass a variety of pathologies, physical deconditioning often contributes to the limited exercise capacity in these chronic disorders. Previous studies using MRS have shown the utility of measuring muscle energetics in patients with cytochrome b deficiency.[218–220]

Using NIRS, an increase in muscle oxygenation at the onset of treadmill exercise has been detected in patients with cytochrome c oxidase deficiency,[221] in patients with mitochondrial myopathy caused by mitochondrial DNA mutations,[222] and in patients with Friedreich's ataxia.[223] This paradoxical oxygenation is due to the combination of impaired mVO_2 along with normal physiological increase of DO_2 (vasodilatation), stimulated by muscle pump and/or myogenic activity. Muscle hyperoxygenation measured with NIRS has been used as a diagnostic in many cases of suspected mitochondrial disease. Quite recently, patients with mitochondrial myopathies (MM) or myophosphorylase deficiency (McArdle's disease, McA) were tested for changes in the capacity for O_2 extraction, maximal aerobic power, and exercise tolerance during cycle exercise using NIRS.[69] HHb peak (percent of arterial occlusion), an index of O_2 extraction, was lower in MM ($25.3 \pm 12.0\%$) and McA ($18.7 \pm 7.3\%$) than in control subjects ($62.4 \pm 3.9\%$). These results suggest that NIRS is a promising tool for monitoring noninvasively the metabolic impairment in the settings of follow-up and in the assessment of therapies and interventions.

5.2.5 *Spinal cord injury*

NIRS has also been used to evaluate the extensive changes that occur to paralyzed muscles in the lower leg with spinal cord injury (SCI). Bhambhani et al. found a lower degree of muscle deoxygenation during maximal exercise and faster changes in muscle deoxygenation with respect to the pVO_2 during functional electrical stimulation cycle exercise in SCI patients when compared to healthy subjects.[86] Olive et al. found normal rates of reoxygenation after muscle stimulation exercise and ischemia in SCI subjects, although the SCI subjects had to have their legs warmed prior to testing to control for temperature.[224] NIRS has been used to evaluate potential therapies for SCI. Six motor-complete SCI subjects and four neurologically normal controls were placed on a gait-training apparatus that enabled the SCI subjects to stand and move their legs passively.[142] The O_2Hb level gradually increased, whereas the HHb decreased in the patients. This response differed from normal controls. Six SCI patients underwent electrical stimulation training (45 min daily for 3 days per week for 10 weeks) with different loads on muscle oxygenation of the paralyzed lower limbs using NIRS.[178] NIRS detected attenuated muscle deoxygenation after static training compared with prevalue.

5.2.6 *Renal failure*

NIRS has been used to evaluate the potential for vascular and metabolic dysfunction in patients with renal failure. Forearm vasodilator responses to 3-min arterial occlusion were measured by NIRS in patients receiving hemodialysis.[171] Vasodilator responses estimated by the ratio of the maximum value of O_2Hb after release of arterial occlusion to its minimum value before the release were significantly smaller in the renal failure patients compared with those in the controls (132 ± 20 versus $161 \pm 27\%$, $p < 0.05$). No improvement in the vasodilator responses was observed after exercise training. Muscle oxygenation and metabolism were examined by using NIRS in ten children with end-stage renal disease (ESRD) before and after renal transplantation (ages 12.4 ± 3.1 years) and in ten controls (ages 12.8 ± 2.6 years) during submaximal hand grip.[81] The rate of initial decrease in oxygenation during transient arterial occlusion after exercise relative to the value at rest (S2/S1) and recovery time (TR) after exercise was used as an indicator of O_2 delivery to the muscle and aerobic capacity. S2/S1 and TR after exercise improved significantly after renal transplantation ($P < 0.01$ and $P < 0.05$, respectively) and were not significantly different from those of controls. These studies show that NIRS is able to detect muscle hypoperfusion in patients with renal failure as well as the functional alterations of muscle oxidative metabolism that occur after renal transplantation. The noninvasive nature of the NIRS measurements is an advantage in the study of children with renal failure as well as children with other diseases.[81,208,225]

5.2.7 *Diabetes mellitus*

NIRS has been used to evaluate the potential for vascular and metabolic disorders in skeletal muscle of patients with either type-1[138,225] or type-2 diabetes mellitus (DM).[138,225–227] After exercise, NIRS measured muscle reoxygenation rates as well as MRS measured PCr recovery rates were slower in patients with type-2 DM. Exercise duration correlated negatively with deoxygenation rates and HbAlc levels, while reoxygenation times correlated positively with HbAlc levels.[227] In patients with type-1 DM, the NIRS measured muscle reoxygenation rate correlated with percentage body fatness, visceral and abdominal subcutaneous fat volume, and dietary fat intake, but not with the duration of diabetes nor HbAlc.[138]

5.2.8 *Other diseases*

A number of other diseases and syndromes have been studied with NIRS. Muscle metabolism in chronic fatigue syndrome (CFS) was measured using NIRS and MRS.[228,229] These studies suggested that CFS may have altered control of blood flow, but this is unlikely to influence muscle metabolism. Patients with chronic compartment syndrome showed greater maximum relative deoxygenation during exercise and slower reoxygenation during recovery than the control patients.[230] Patients with traumatic acute compartment syndrome had

lower SO_2 values relative to the control patients, which was usually normalized after fasciotomy. NIRS evaluation may offer a rapid, noninvasive method of assessing extremities at risk for compartment syndrome.[231] Muscle perfusion and oxygen consumption have been measured in septic-shock patients[232,233] and in digit replantation patients.[234]

6 Conclusion

There is an increasing need to develop noninvasive and real-time methods for evaluating skeletal muscle metabolism in humans. NIRS has been developed to fill this need, and this work reviews some of the studies that have evaluated skeletal muscle oxidative metabolism and blood flow. Special reference is taken to examine the validity of the indicators determined by NIRS, and the application of these indicators for monitoring training-induced changes in oxidative metabolism in healthy and diseased muscles. For the most part, NIRS indicators are shown to be useful for the detection of changes in muscle metabolism and oxygen delivery in healthy subjects, as well as in patients with various organ diseases as well as muscle-specific disorders. The advantage of using NIRS over invasive techniques and MRS measurement is that the equipment itself is more portable and the procedure can be done more simply. The use of NIRS is therefore suitable for practical and clinical use. However, the variety of NIRS equipment that is available as well as the addition of new developed equipment will require continued validation studies. It can be argued that there are too many NIRS derived indices, and that standardization of testing approaches is needed to allow for greater ease of comparison between research studies. In addition, along with applied clinical studies, basic research is still needed, such as the origin of the NIR signal (which fractions from arterioles, capillary, and venules, as well as from Hb and Mb), the NIR penetration depth or measurement area in tissue with varying source-detector arrangement (orientation) in the multilayer model, including the effect of nonmuscular tissue, and changes in optical properties during a wide range of tissue oxygenation status, varying subjects, and exercise modality. Thus, NIRS technology remains a promising and continually development methodology. We are grateful for Jobsis' discovery of the NIR window into biological tissues, and we are proud to be among those who strive to continue his legacy by advancing the research of human skeletal muscle function with NIRS.

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