REVIEW

Urological applications of near infrared spectroscopy

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Objective: *Near infrared spectroscopy (NIRS) uses light to monitor changes in the concentration of oxyhemoglobin and deoxyhemoglobin in living tissue non-invasively and in real time. Applications of NIRS in urology research and the strengths and limitations of this technology are reviewed.*
Material and methods: *A Medline and Pub-Med search using "spectroscopy" with heading terms: near infrared (NIR), near infrared spectroscopy (NIRS), urology, kidney, renal, urinary tract, bladder, prostate, testis and penis.*
Results: *Research incorporating NIRS has investigated a range of urologic conditions where a hemodynamic or vascular etiology is thought to be the underlying pathophysiology: as an aid to diagnosis in cryptorchidism, testicular torsion and vasculogenic erectile dysfunction; to evaluate renal metabolism and bladder dysfunction, and to study skeletal muscle metabolism in end stage renal disease. Strengths and limitations of NIRS relate primarily to the basic physics of how light in the NIR spectrum penetrates tissue and is scattered and absorbed.*
Conclusions: *NIRS is a non-invasive, portable, real time measure of changes in tissue perfusion and oxygenation. In urology NIRS appears particularly applicable in ischemic conditions, and the evaluation of disorders associated with alterations in regional tissue hemodynamics (due to local changes in pressure, muscle contraction and urinary tract obstruction). Because the bladder detrusor can be interrogated transcutaneously NIRS may also provide a non-invasive means of evaluating patients with voiding dysfunction. Studies to date warrant further research and specific refinement of instrumentation and algorithm software for urologic applications, as NIRS could provide urologists with new methods of non-invasive physiologic diagnostic evaluation.*

Key Words: near infrared spectroscopy, urology, urinary tract, renal, bladder, testis, penis, prostate, kidney, urinary incontinence

Introduction

Near infrared spectroscopy (NIRS) is a non-invasive technology which uses energy from light in the near infrared (NIR) spectrum to monitor changes in local blood flow and hemodynamics and detect differences in tissue oxygen delivery, consumption and utilization.[1,2] This monitoring technique, which shares many technical principles with pulse oximetry, has been widely applied as a research, diagnostic and clinical monitoring tool,[3,4] and there are comprehensive reviews of the applicable science, instrumentation, methods of measurement, limitations and principal applications in the literature.[1-8] Recent studies using NIRS to investigate urological conditions offer the prospect of this technology being used to provide additional diagnostic and evaluation techniques for urologists.

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The science of NIRS

NIRS employs many of the physics principles relating to the transmission of light through tissues. At most wavelengths of the light spectrum, light is absorbed by skin and tissue, but photons of light generated in the near infrared spectrum 700-1300 nanometers (nm) scatter in tissue and pass through skin, soft tissue and bone.[5] However, naturally occurring compounds called chromophores absorb these photons in varying amounts determined by the chemical structure and color of each chromophore and the wavelength of the light transmitted, and their concentration in tissue. It is the unique relation between the transparency of tissue to near infrared light and the specific absorption spectra of individual chromophores that forms the basis of clinical near infrared spectroscopy.[6]

The principal chromophore of interest in studies using NIRS is hemoglobin which has a different extinction coefficient (absorption characteristic) across the NIR spectrum when oxygenated (O_2Hb) and deoxygenated (HHb). Figure 1 shows the varying absorption of O_2Hb and HHb at different near infrared wavelengths and the extinction coefficients of adult Hb. Cytochrome-c-oxidase (CCO), the terminal enzyme of the mitochondrial respiratory chain, also absorbs light differently across the NIR spectrum depending on its redox status[9] although the contribution of CCO to overall absorption is considerably less (approximately one tenth) than that of hemoglobin.[1]

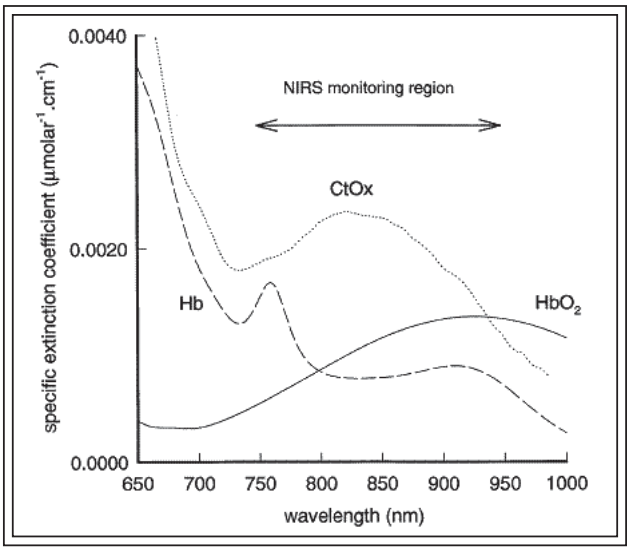

Figure 1. The extinction coefficients of adult Hb and the varying absorption of O_2Hb (HbO_2) and HHb (Hb) and CytOx (CCO) across the NIR spectrum. (Reprinted with permission of The Royal Society from Delpy D and Cope M. Quantification in tissue near-infrared spectroscopy. *Phil Trans R Soc Lond B* 1997;352:649-659).

The majority of NIRS instruments used clinically are continuous wave units with lasers that transmit pulses of multiple wavelengths of light into the tissues, and sensors to detect the photons returning that are not absorbed. The changes in absorption at discrete wavelengths generate raw optical data that can be converted by software algorithms into concentration changes for each chromophore using a modification of the Lambert-Beer law.[7] The related algorithms and software necessary for NIRS data to be used clinically also accommodate for a number of limitations posed by the nature of human tissue, including the pathlength of NIR light and loss of photons undetected because of scattering beyond the field of view.[6]

It is important to recognize that as the full extent of the field through which light scatters is always unknown in vivo, the initial concentration of each chromophore is unknown. Hence, clinical NIRS can only measure absolute changes in concentration relative to the initial baseline concentration, and NIRS cannot distinguish between arterial and venous hemoglobin. However, with real time sampling and graphic conversion of data, patterns of change in chromophore concentration and magnitudes of change are derived which can be used to infer physiological change occurring within the tissue interrogated. Such changes include: an increase or decrease in O_2Hb (an indirect measure of oxygen content); an increase or decrease in the total hemoglobin (change in blood volume); an abrupt decrease in O_2Hb with simultaneous increase in HHb (ischemia); and a gradual decrease in O_2Hb and increase in HHb (hypoxia).

As cytochrome-c-oxidase drives > 95% of O_2 consumption and the synthesis of adenosine triphosphate (ATP) within mitochondria, changes in CCO redox status provide information relating to electron transport and oxidative phosphorylation at a cellular level. This aspect of NIRS monitoring has been investigated principally in the brain and spinal cord in animal models and human studies,[10,11] and literature relating cytochrome redox status to urological conditions is lacking. However, interpretation of NIRS data that includes changes in O_2Hb, HHb and CCO signals can offer important insights into oxygen utilization, energy dynamics and cellular well being.

Instrumentation

Continuous wave NIRS instruments typically incorporate the following: a) at least one pulsed laser diode for each chromophore being sampled.

Typically the lasers emit light in 1, 2 or 4 wavelengths in the 729 nm to 920 nm near infrared wavelength range with a 5 nm spectral width and pulse duration of 100 nanoseconds at 2 kHz cycle frequency; b) fiber optic bundles that transmit light from the source to a tissue interface (probe or patch) and back to the instrument; c) optodes in the tissue interface that emit light into the tissue and receive the photons returning; d) photon counting hardware (photomultiplier or photodiode); d) computer with software containing algorithms for converting raw optical data into chromophore concentrations, storing and displaying data; e) a visual display where NIRS data are typically displayed graphically against time. Some instruments provide a choice from multiple wavelengths, and the option to use more than one data channel to allow comparison of different sites is available;[8] a few incorporate additional spatial resolution that allows measurement of the ratio of oxygenated to total tissue hemoglobin which can be displayed as a measure of tissue oxygenation; and monitoring in the form of a regional map using arrays of emitters and receivers is now possible.[12] Figure 2 illustrates a NIRS instrumentation system configured for transcutaneous monitoring, and the 'banana' shaped field of view generated by the penetration of NIRS photons into human tissue.[13]

Care must be taken when conducting research or interpreting published studies that the characteristics and limitations of the hardware, algorithms and software of the NIRS equipment employed

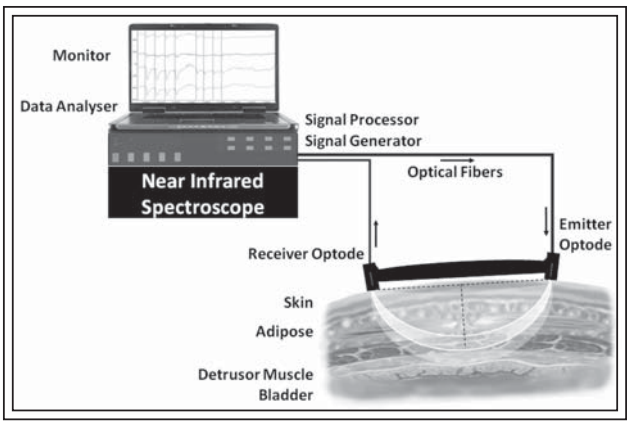

Figure 2. The configuration of a NIRS system for transcutaneous interrogation of the bladder detrusor; illustrating the 'banana" shape of the photon path through tissue between the emitter and receiver of the optode, and the effective depth of penetration for NIRS - approximately half the distance chosen to separate the emitter and receiver on the skin surface.

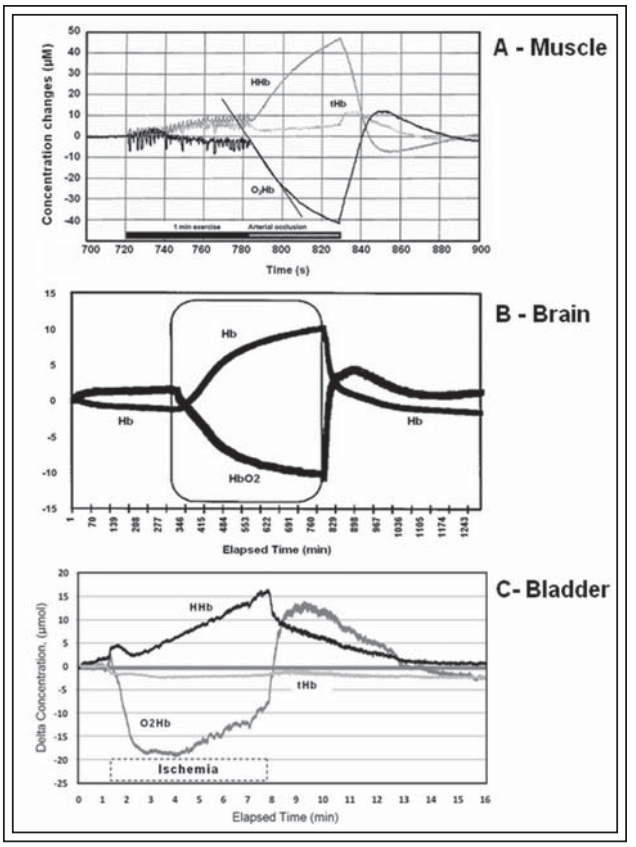

Figure 3 A-C. Three graphs showing the pattern of change in chromophore concentration in response to ischemia in different tissues. NIRS values for (oxygenated hemoglobin [O_2Hb], deoxygenated hemoglobin [HHb]) are plotted against time and illustrate the consistency of the pattern of change seen.

Figure 3A. Ischemia in muscle (human forearm during arterial occlusion - following rhythmic isometric exercise) – Artinis NIRS prototype – transcutaneous mode.
Reprinted with the permission of Blackwell Pub. Ltd. from: van Beekvelt M et al. *Clin Physiol & Fun Im* 2002;22(3):1-8. [stable total hemoglobin [tHb] indicates no change in blood volume].

Figure 3B. Ischemia in brain (human - during circulatory arrest on cardiac bypass) – Hamamatsu NIRO 300 – transcutaneous mode.
Reprinted with the permission of IOS Press from: Macnab A et al. *Spectroscopy* 2003;17:483-490. [the equal and opposite change in cerebral O_2Hb and HHb indicates no change in total blood volume].

Figure 3C. Ischemia in bladder (rabbit - in response to aortic occlusion – Hamamatsu NIRO 300 with emitter and receiver directly opposed across the surgically exposed bladder [the rise in HHb is unequal to the fall in O_2Hb due to volume loss via the unobstructed venous outflow in this model].

are recognized. NIRS hardware and software are continuously evolving.[2,4] However, there is consistency and reproducibility in the patterns of change in O_2Hb and HHb concentration observed using conventional NIRS in different tissues, in studies conducted by different investigators, and when using NIRS equipment from different manufacturers. This applies particularly to the patterns of chromophore change that occur in response to ischemia, hypoxia or changes in blood volume. Figure 3 illustrates such patterns in response to ischemia generated in forearm muscle and the brain in human subjects measured via transcutaneous NIRS and the bladder detrusor in the rabbit model measured via direct application of NIRS sensors to the exposed bladder. Similar comparability in the patterns of change observed occurs in these three tissues in response to the onset of hypoxia, and also during a change in blood volume.

The evolution of NIRS

In 1876 the German physiologist Karl von Vierordt published a report describing the use of spectroscopy to identify the conversion of oxyhemoglobin to deoxyhemoglobin in the human hand following occlusion of arm blood flow.[14] In 1977, Norris described the application of NIRS to the study of in situ human tissues, and Jobsis reported the first in vivo NIRS study of cerebral metabolism in the cat, demonstrating that biological tissues have relatively good transparency for light in the near-infrared region.[5,15] Over the following two decades, many studies focused on the assessment of O_2Hb, HHb and CCO within the brain, especially in neonates,[16-18] and on muscle blood flow and oxygen consumption.[19-21]

During the last decade the application of NIRS and related spectroscopic techniques in health science research has grown steadily.[3,4,9,12,22-26] In particular NIRS has been used as a means of monitoring brain hemodynamics and oxygenation, measuring skeletal muscle oxygenation and detecting muscle ischemia during conditions of hypoxia. Other applications include: continuous monitoring of tissue hemodynamics during surgical operations and at the bedside; evaluation of neurological conditions such as hydrocephalus and acute cerebral infarction; and evaluation and monitoring of tissue status in skin flaps, burns and compartment syndrome. At the cellular level, NIRS studies have advanced the understanding of metabolic and mitochondrial myopathies.

Limitations of NIRS

Although near infrared light penetrates into tissue the depth of effective monitoring during NIRS studies is limited which restricts the transcutaneous application of NIRS to the interrogation of superficial tissues and organs. However, many studies have incorporated a NIRS emitter and sensor into a probe which is introduced invasively to a location where tissue apposition allows sufficient penetration of photons for the organ of interest to be studied, and use of NIRS during surgical procedures is possible.[27-29]

Other limitations that need to be considered in NIRS studies include: the presence of myoglobin (Mb) when muscle tissue is within the NIRS field as a small proportion of light absorption will then occur because Mb is also a chromophore; reduced photon penetration in patients with dark skin pigmentation; altered optical path length in situations such as acute hemodilution; potential interference from ambient light; alteration in the distance between the emitter and the sensor (inter-optode distance) as any change in this distance during monitoring adversely affects NIRS data collection; and electromagnetic interference as this generates noise that obscures the NIRS signal.[2,4,7,13,22]

The impact of specific limitations of NIRS to applications in urology is addressed in the discussion.

Urological conditions studied using NIRS

Urological conditions studied with NIRS include testicular ischemic conditions,[30,31] erectile dysfunction,[32] bladder dysfunction[33] and renal dysfunction.[34] In addition, NIRS has been used to study the skeletal muscle metabolism in patients with end stage renal disease,[35-37] normal voiding[38] and the toxic effects of contrast media,[39] Table 1.

Cryptorchidism

The first application of NIRS in urology was reported by Colier et al in 1995.[30] Recognizing the difficulty in assessing both the blood flow and viability of an affected testis they used NIRS in combination with pulse oximetry to measure the blood supply to intra abdominal testes in an animal model of cryptorchidism. They hypothesized that NIRS combined with pulse oximetry would achieve deeper penetration; provide measurement of blood flow to the testis as a whole; and allow calculation of the active testicular blood volume before and after temporary occlusion of the spermatic vessels. The technique was performed in 10 boars with normal and intra abdominal testis. They demonstrated that in the case of an intra abdominal testis, because

TABLE 1. **Urological applications of near infrared spectroscopy**

Authors	Study subject	NIRS application
Colier et al [1995]	10 boars	Measurement of blood supply to the abdominal testis
Capraro et al [2007]	6 sheep	Diagnosis of testicular torsion
Burnett et al [2000]	38 patients with ED	Diagnosis of vasculogenic erectile dysfunction
Krause et al [2002]	36 rats	Evaluation of the effects of contrast media on renal tolerance
Macnab et al [2005]	1 patient with UI	Evaluation of bladder dysfunction
Petrova et al [2006]	10 preterm infants	Monitoring of renal cortex oxygenation during hypoxic events
Vaux et al [2003]	13 patients with ESRD	Evaluation of the effects of carnitine supplementation on muscle metabolism
Kemp et al [2004]	23 patients on HD	Evaluation of muscle oxygen metabolism
Matsumoto et al [2006]	10 uremic children	Evaluation of muscle oxygen metabolism
Stothers and Macnab et al [2006-2008]	4 prospective trials with urodynamics (UDS)	NIRS urology instrument; discriminant ability of NIRS in BOO, and CART algorithm analysis; female UDS NIRS and pelvic ultrasound; fNIRS of dynamic change in detrusor O_2HB and HHb during voiding

ED = erectile dysfunction; HD = hemodialysed; ESRD = end stage renal disease; UI = urinary incontinence

of subsequent atrophy, there is no significant active testicular blood volume after temporary ligation of the spermatic vessels. They suggested that NIRS combined with pulse oximetry could quantify the active testicular blood volume, which could in turn be used to examine the viability of an abdominal testis. Because of the ability of NIRS to detect changes of blood volume in real time this application of NIRS to an important clinical issue in urology warrants further study.

Testicular torsion

Capraro et al[31] also used NIRS to monitor testicular blood flow and assessed the feasibility of detecting acute testicular hypoxia in a sheep model of testicular torsion. Recognizing that the blood flow in a symptomatic testis is decreased or absent, the importance of early and accurate diagnosis and the limited applicability of technology such as Doppler flow studies, Capraro hypothesized that NIRS would offer an effective means of evaluating testicular blood circulation. The study showed sensitive detection via NIRS of testicular hypoxia following testicular torsion and also reperfusion of the hypoxic testis after torsion was reduced. Although valuable data and a logical use of NIRS because of the proven ability of the technology to detect ischemia in real time further animal studies and randomized clinical trials are required for this animal research to be translated into clinical practice.

Erectile dysfunction

Increasing awareness of the hemodynamics in vasculogenic erectile dysfunction has led to the development of a wide range of diagnostic tests, but there is still no single "gold standard" test for diagnosing this condition.[40] Burnett et al[32] used NIRS to study the physiology and vascular properties of the penis that pertain to erection. In an in vivo study they performed penile spectroscopy on 38 patients with erectile dysfunction and 18 volunteer subjects using a customized NIRS probe with wavelength selectivity of 805 nm for the hemoglobin absorption spectra simultaneously with color duplex ultrasonography of the penis. Strain gauge penile circumference monitoring, penile tonometry and clinical assessments were also completed. Penile blood volume changes and their time course were studied following intracavernous stimulation. These researchers reported that NIRS technology can evaluate hemodynamic phenomena in the penis and NIRS suitably discerns erectile end-organ failure. They suggested NIRS as a method of producing diagnostic ranges that identify non-vasculogenic to severe vasculogenic causes of erectile dysfunction, with the aim of helping urologists to predict which patients would most likely benefit from first line pharmacological treatments. While penile NIRS is a promising method for non-invasive evaluation of vasculogenic erectile dysfunction the role of NIRS as a diagnostic entity remains unclear,

and further research to address the limitations of NIRS methodology applied to erectile dysfunction is needed prior to wider use of this modality.

Bladder dynamics

Our group's work has examined the feasibility of NIRS in evaluating bladder dysfunction. Macnab et al described simultaneous transabdominal NIRS of the bladder during urodynamic evaluation of an adult patient with urinary incontinence.[33] An optode patch was applied suprapubically and transcutaneous NIRS monitoring demonstrated a temporal change between O_2Hb and HHb concentration during voiding. This finding suggested that NIRS might be a useful tool in evaluation of bladder function. Subsequent studies[41-45] have explored the potential of non-invasive transcutaneous NIRS to study bladder filling and emptying in normal subjects, and distinguish between specific urinary pathologies using the patterns of chromophore change generated by NIRS monitoring during simultaneous urodynamic studies. Most recently it has been demonstrated that in men requiring evaluation for lower urinary tract symptoms NIRS data combined with measurements of post residual volume (PVR) and peak uroflow (Qmax) can be used to distinguish between those with and without obstruction;[46] it is feasible to use a transvaginal NIRS probe to interrogate the urethral sphincter,[47] and Stothers et al have reported the use of a 4 cm X 4 cm two channel four point NIRS array to transcutaneously map dynamic change of detrusor hemodynamics during voiding.[38] The array uses the established principles of functional near infrared spectroscopy developed for brain mapping (fNIRS). It appears that NIRS monitoring is able to provide data that reflect physiological change occurring in the detrusor during bladder filling and emptying. With further studies and validation of diagnostic algorithms based on chromophore patterns of change NIRS may provide a new diagnostic approach to bladder dysfunction.

Cerebral and renal oxygenation

Petrova and Mehta[34] performed a study on 20 preterm neonates to evaluate the effect of hypoxic episodes on cerebral and renal tissue oxygenation. Studies using simultaneous NIRS and pulse oximetry have shown a direct correlation between arterial oxygen saturation and cerebral tissue oxygenation,[48,49] and as isolated hypoxic episodes occur frequently in preterm neonates the effects of such episodes on the brain and kidney are relevant.[50] Arterial oxygen saturation by pulse oximeter and cerebral and renal venous oxygen saturation via NIRS were monitored simultaneously with NIRS transmitter/receiver patches placed on the forehead and on the skin over the thoracolumbar region over the right kidney. In mechanically ventilated preterm neonates episodes of compromise of cerebral oxygen utilization in the majority of infants, but there were increases in oxygen extraction in renal tissue. Obvious advantages of using NIRS in this study were its non-invasive nature, the ability to study infants at the bedside without the need to move them from the nursery, the safety of light as an energy source, and continuous data collection over time.

Human muscle metabolism in renal dysfunction

Vaux et al[35] studied the effect of L-carnitine supplementation on muscle bioenergetics and function in patients with chronic renal failure (CRF) on hemodialysis. Hemodialysis (HD) patients have skeletal muscle wasting and impaired exercise tolerance due to reduced oxidative capacity,[51] and also become carnitine deficient.[52] MRI and NIRS studies were done of calf muscle in 13 patients with CRF on maintenance hemodialysis 2-3 weeks before and 16 weeks after administration of L-carnitine. NIRS was used to monitor oxygenated hemoglobin, deoxygenated hemoglobin and myoglobin concentration before and after an exercise protocol. The measures used were the half time for recovery of the NIRS signal as an indicator of tissue oxygenation and return of perfusion to resting level after exercise. No significant effects of L-carnitine on objective measures of muscle metabolism, function and bioenergetics in vivo or any improvement in clinical status was found. In a study on similar patients Kemp et al[36] evaluated the contributions of reduced muscle section area (CSA), intrinsic mitochondrial dysfunction, abnormal contractile efficiency and reduced muscle oxygen supply to skeletal muscle dysfunction in patients with CRF on HD. They performed NIRS on calf muscle in 23 HD patients and 15 control subjects at rest, during and after an exercise protocol to monitor muscle oxygenation and blood perfusion and compared the results between groups. They demonstrated an effect of muscle mass on dialysis efficiency rather than a direct effect of muscle CSA or metabolism, and concluded that development of muscle dysfunction in HD patients is related to a mitochondrial defect. Matsumoto and Osada[37] measured skeletal muscle oxidative metabolism in children with end stage renal disease (ESRD). They performed NIRS on the forearm in 10 patients before and after renal transplantation, and monitored alternations in Hb/Mb (myoglobin) deoxygenation during arterial occlusion as an indicator of the rate of oxygen consumption in mitochondria, and recovery time as an indicator of muscle aerobic capacity following a hand-grip exercise. Oxidative metabolism in skeletal muscle during exercise was impaired and improved remarkably after renal

transplantation. They recommended NIRS as a useful method to monitor muscle metabolism in children with ERSD. NIRS has been used extensively to study human muscle metabolism and these studies are based on validated principles.

Renal tolerance to contrast media

Krause et al[39] used NIRS in an animal model to assess renal tolerance to contrast agents with differing osmolality and study the effects of addition of a prostacyclin analogue. A small NIRS probe was placed on the renal cortex of rats to measure alteration of tissue oxygen saturation after injection of iodinated contrast media and after addition of iloprost. They demonstrated a significant decrease in total hemoglobin, oxygenated hemoglobin and tissue oxygen saturation in the rat kidney after injection of contrast media. In addition, they showed that iloprost attenuated the decrease in oxygen saturation of renal tissue. Development of less toxic contrast media has long been a subject of research in uroradiology.[53] Contrast agents have a direct effect on glomerular filtration[54] and medullary blood flow,[55] and addition of a prostacyclin analog can prevent the negative effects of contrast on the microcirculation.[56] The measurement of renal tissue oxygenation by NIRS may be a useful adjunct to such research, although the depth of penetration of near infrared light limits non-invasive application in human subjects.

Other spectroscopic techniques applied to urology

Spectroscopic techniques other than continuous wave NIRS are used to evaluate the genitourinary system. These techniques vary from NIRS in how they apply the physical principles of absorption, emission and scattering of light in different wavelengths. NIRS (absorption spectroscopy) measures light absorbed.[57] Fluorescence (reflection) spectroscopy (FS) measures the amount of light reflected from a substance to detect differences in the fluorescent properties of pathological tissues.[58] This technique relies on differences in fluorescent emission of photons by different molecules when they are exposed to a monochromatic light source such as a laser. Raman (scattering) spectroscopy, measures the wavelengths that a substance or tissue reflects upon excitation by laser light and generates unique Raman spectra in vitro that can be used to determine the composition of the tested sample.[59] Time resolved (TR) spectroscopy measures the time of flight in addition to light intensity and is used experimentally to determine the optical properties of tissues, three-dimensional imaging and tomography.[1]

FS has been used to explore differentiation of normal from neoplastic epithelium, including differentiating normal urothelium from transitional cell carcinoma of the bladder.[60-62] Although several reports have confirmed the high sensitivity of this technique the specificity is low.[63] RS provides detailed cellular analysis and an objective method for diagnosis of pathology such as cancer[64] and infection,[65] and in urology shows promise for in vitro diagnosis and grading of bladder and prostate cancers.[66,70] RS can also be used to identify the composition of urinary stones[71,72] and their effect on renal medullary collecting ducts through analysis of biopsies from renal papillae.[73] New developments in RS will likely provide in vivo urological applications for guiding endoscopic procedures and assessing tumor resection margins.[74] Other extensions of spectroscopic technology such as TR are being explored experimentally to examine the optical properties of prostatic tissue in vivo in the context of developing photodynamic therapy as a modality for the treatment of prostate cancer.[75]

Discussion

The principles of NIRS and the physiological parameters that can be monitored are applicable to the field of urology, and many urological problems that currently present a challenge for evaluation and diagnosis are ones that NIRS could be used to address. However research using NIRS in a urological context has been limited to date, even though multiple applications have been employed in other health sciences research where a range of methods exist for quantitative measurement.[4,76]

The urological research done with NIRS indicates that since NIRS is an extremely sensitive monitor of tissue perfusion and oxygenation, this technology can be applied effectively to investigate ischemic urological conditions. In addition, it may be a useful tool for evaluation of clinical conditions where pathology alters regional tissue hemodynamics, such as local changes in pressure, muscle contracture or urinary tract obstruction.

Benefits of NIRS

The benefits of NIRS technology include its non-invasive nature, non-toxic energy source, and ability to monitor a range of physiological change continuously, in real time, at the bedside. NIRS can be used simultaneously with other technology such as ultrasound, and during urodynamic pressure flow studies. It is also not an expensive technology.

Limitations of NIRS

Limitations relevant to urological applications of NIRS include restrictions posed by the basic science principles underlying NIRS and constraints imposed by current hardware and software. NIRS only provides measurement of change in chromophore concentration from baseline rather than an absolute quantitative measurement, as the exact concentration of hemoglobin within the tissue being studied is not known. Consequently NIRS data are most informative where a temporary change in the physiological state of the tissue is anticipated e.g. hypoxia or ischemia, or can be induced e.g. via a change in oxygen saturation or blood volume; and where physiological changes occur as a result of organ function e.g. detrusor muscle and pelvic floor contraction and urinary sphincter activity.[76,77]

When transmitting light via NIRS through tissue some light is lost because of scattering and some is absorbed by compounds other than the chromophores of interest. The principal compound in this context is myoglobin when muscle tissue is within the NIRS field. The absorption spectra for hemoglobin and myoglobin do overlap but the contribution by myoglobin in the NIRS signal is regarded as small unless muscle tissue predominates. In urological studies absorption by myoglobin is essentially constant as the concentration of this compound remains unchanged within the NIRS field of view during the period of study. However, because of scattering many photons are also 'lost'. Consequently only a small proportion of the photons transmitted are detected returning from the tissue. For reasons such as these NIRS relies on software algorithms to enable the basic principles of NIRS physics to be applied in a clinical context and to facilitate data interpretation. In this regard NIRS is no different to other technologies already in the medical mainstream such as oximetry, the most widely used application of photonics technology, and CT and MRI imaging. Similarly, it is important to recognize when comparing a novel technology such as NIRS to a current gold standard that virtually all extant technologies also make similar 'concessions' through their software algorithms to a range of basic science principles in order for them to have clinical applicability.

While the anatomical location of many organs of interest to the urologist is too deep for transcutaneous NIRS study, the use of prototype catheters and probes incorporating NIRS sensors enables transurethral, intravesical, vaginal and rectal study of related organs.[77] Advances in the technique of functional near infrared spectroscopy (fNIRS) also make it possible to study a larger area on the surface of an organ than is currently interrogated using a single channel with one emitter and sensor e.g. the human detrusor.

If noise caused by electromagnetic interference disrupts the NIRS tracing this effect can be resolved by grounding the patient via a wrist strap or contact incorporated within the NIRS patch.[76] Similarly in the event of ambient light interference studies can be conducted in a dark room, or with the sensor patch covered with an opaque material. Alternatively a daylight filter can be incorporated within the receiver cable.[8]

Confidence in NIRS measurements

In any application of NIRS to urology, and with our group's use of NIRS to study the detrusor in particular, a number of theoretical confounders and practical and theoretical issues need to be considered. The principal ones are how do we know we are detecting changes in chromophore concentration that reflect physiologic change? Is the organ of interest within the field interrogated by the NIRS photons (i.e. is the organ anatomically orientated to the NIRS sensors and at a depth penetrated by the photons)? And; what effect does organ movement have during NIRS monitoring?

Confidence that NIRS signals represent physiological change in an organ of interest rather than happenstance, interference from subcutaneous tissue, or an effect of movement is based on a variety of scientific data. Characteristic patterns of change in the concentration of chromophores O_2Hb and HHB occur with specific physiological events or interventions, notably acute ischemia, hypoxia, changes in blood volume and muscle contraction. Moreover there is marked consistency in these patterns across multiple studies involving animals and humans, and different organs and tissues. In the context of urology the same characteristic patterns of change occur when NIRS sensors are placed directly on the surface of the exposed bladder in a rabbit model as are seen with transcutaneous measurement over forearm muscle and the brain in humans. This applies during ischemia, see Figure 3, in response to the onset of hypoxia, and also with a change in blood volume.

In NIRS studies of the detrusor consistent changes of significant magnitude and duration in chromophore concentration only occur in temporal association with the filling and voiding cycle, and events such as spontaneous movement, cough and Valsalva generate different and distinct patterns of change. In addition, simultaneous transcutaneous recording of NIRS parameters suprapubically over the bladder and at a remote abdominal site yield patterns that are random over the abdomen and specific to the voiding cycle over the bladder.

Ensuring that the organ of interest is within the field of view and that a significant amount of tissue is being interrogated also depends on the important issue of how near infrared light penetrates the tissues. While it is important to remember that light is scattered widely once below the skin surface, the field interrogated via NIRS is conventionally regarded as being a 'banana' shaped area between the emitter and sensor, see Figure 2, that extends as photons penetrate into tissue.[13] The depth of penetration of NIR light for effective tissue interrogation is approximated as half the distance between the emitter and the sensor, which provides penetration in the order of 30 mm-40 mm, with 60 mm the approximate limit for O_2 monitoring in the microcirculation.[23] In transcutaneous NIRS studies evaluation of the detrusor by ultrasound can be used to confirm that the bladder remains within the field of view during monitoring,[78] and measure its depth below the skin and wall thickness. Further evidence suggesting that the detrusor is interrogated in normal subjects comes from the observation that in patients with a high body mass index (BMI) the more obese the subject is the less likely it becomes that reproducible NIRS data will be obtained. While some increased photon absorption does occur in thicker adipose tissue,[25] the inability to interrogate the detrusor in obese patients hypothetically indicates that in this subject group it is situated deeper than the effective depth of penetration for transcutaneous NIRS.

Movement of the bladder as it changes in size during filling and emptying is an important potential theoretical confounder. However, the suprapubic monitoring site used[46,76] probably locates the sensors where least movement of the bladder wall occurs based on pelvic ultrasound data during NIRS monitoring,[78] and changes in chromophore concentration consistent with physiological change are evident between permission to void and uroflow start when bladder volume is constant and following cessation of uroflow when change in bladder size has ended.[43,45,46]

Patient movement is obvious in the data stream as soon as it occurs, usually as a major deviation of all parameters from baseline at magnitudes that far exceed the limits of physiological change. Many instruments have a control to reset the baseline. A brief period of immobility in order to record a stable baseline prior to monitoring an event simplifies data analysis. Because any change in the interoptode distance influences photon transmission through the tissue and alters pathlength it is essential that the patch or holder maintains the precise position of the NIRS emitter and sensor during monitoring.

Potential future role of NIRS in urological research and practice

Because NIRS has proved to be useful in a variety of research and clinical settings, and there is now literature demonstrating the feasibility and relevance of applying NIRS in urology future studies appear warranted. NIRS is "on the verge of entering (some) everyday clinical applications"[4] and could provide a rapid, continuous, non-invasive, safe and reliable diagnostic and monitoring technique for a range of urological conditions. Because NIRS is a sensitive means of monitoring tissue perfusion and oxygenation, NIRS may be useful for evaluating urological conditions that change regional tissue hemodynamics and oxygen delivery and consumption via mechanisms such as local pressure, muscle contracture or the effects of urinary tract obstruction. More extensive research confirming the relevance and reproducibility of NIRS monitoring should expand its usefulness, and by addressing actual and theoretical limitations posed by use in urology could lead to improved diagnostic and clinical monitoring applications. Novel future applications of NIRS to urology include: Non invasive screening for specific bladder pathologies using diagnostic algorithms; monitoring the effect of vasoactive drugs on the bladder; the ability to use functional NIRS (fNIRS) to map changes in chromophore concentration dynamically and over a larger area of the detrusor than is possible with a single emitter/receiver channel; trans vaginal monitoring of simultaneous detrusor and urethral sphincter activity; other forms of invasive optode placement; and intraoperative monitoring. □

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