Development of a near-infrared spectroscopy instrument for applications in urology

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Introduction: *Near infrared spectroscopy (NIRS) is an established technology using photons of light in the near infrared spectrum to monitor changes in tissue of naturally occurring chromophores, including oxygenated and deoxygenated hemoglobin. Technology and methodology have been validated for measurement of a range of physiologic parameters. NIRS has been applied successfully in urology research; however current instruments are designed principally for brain and muscle study.*
Objective: *To describe development of a NIRS instrument specifically designed for monitoring changes in chromophore concentration in the bladder detrusor in real time, to facilitate research to establish the role of this non-invasive technology in the evaluation of patients with voiding dysfunction*
Method: *The portable continuous wave NIRS instrument has a 3 laser diode light source (785, 808 and 830 nanometers), fiber optic cables for light transmission, a self adhesive patient interface patch with an emitter and sensor, and software to detect the difference between the light transmitted and received by the instrument. Software incorporated auto-attenuates the optical signals and converts raw optical data into chromophore concentrations displayed graphically.*
Results: *The prototype was designed, tested, and iteratively developed to achieve optimal suprapubic transcutaneous monitoring of the detrusor in human subjects during bladder filling and emptying. Evaluation with simultaneous invasive urodynamic measurement in men and women indicates good specificity and sensitivity of NIRS chromophore concentration changes by receiver operator curve analysis, and correlation between NIRS data and urodynamic pressures.*
Conclusion: *Urological monitoring with this NIRS instrument is feasible and generates data of potential diagnostic value.*

Key Words: chromophores, urodynamics, detrusor, oxyhemoglobin, deoxyhemoglobin

Introduction

In 1995, Colier et al used near infrared spectroscopy (NIRS) to assess the blood flow and viability of the testes in an animal model of cryptorchidism.[1] Since that time a series of studies have used NIRS to evaluate a variety of tissue and organs in the genitourinary tract.[2] These studies have used instruments designed for monitoring brain or muscle tissue.

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NIRS is a noninvasive method for measuring the presence of oxygen in tissue and evaluating hemodynamics in vivo in real time, based on monitoring changes in the concentration of oxygenated and deoxygenated hemoglobin.[3,4] NIRS shares many of the principles of physics that are used to make pulse oximetry (PO) possible, although NIRS differs significantly from PO in several important respects. Unlike PO NIRS does not require pulsatile flow, it has greater depth penetration, and the wavelengths used are all in the near infrared (NIR) region and more in number.[5] NIRS provides a unique method for monitoring tissue oxygenation and blood supply. Initially, NIRS was utilized experimentally and clinically to investigate cerebral oxygenation. Now it is widely used to study oxygen dynamics, oxidative metabolism, and hemodynamics in a variety of tissue including muscle.[6,7]

Several types of NIRS instruments are commercially available, most are designed for research use,[7-9] some have been designed for applications in a clinical

context. These instruments are able to measure a wide range of parameters directly or indirectly.[7] However, most are designed to monitor brain or muscle tissue and to date NIRS research in urology has had to rely on these instruments.[2] We now describe the development of an NIRS unit specifically designed for interrogation of the bladder detrusor, to enable research to be done to establish the role of this technology in the evaluation of patients with voiding dysfunction. Research to date suggests that NIRS monitoring is able to add physiologic information of relevance and diagnostic scope to invasive urodynamics (UDS).[10-16] Further research will establish whether NIRS data combined with UDS and uroflow parameters can be used by urologists to classify patients with specific pathologies and contribute to research evaluating the physiologic basis of voiding dysfunction.

Background

Near infrared spectroscopy is a basic science technique that uses photons of light in the near infrared spectrum to interrogate tissue non-invasively. The physics principles underlying NIRS include: 1) the relative transparency of tissue to light in the NIR spectrum which allows photons to penetrate through the skin and into tissue, and 2) the different absorption spectra of hemoglobin at specific wavelengths in the NIR spectrum depending on whether or not the hemoglobin molecule is carrying oxygen.[8,17] NIRS instruments generate light using multiple lasers or photodiodes that emit photons of different wavelengths between 700 nm-1000 nm.[18] These photons are transmitted transcutaneously, scatter in tissue and are variably absorbed by chromophores which are naturally occurring chemicals in tissue that absorb light. The principal chromophores of interest in human tissue are oxygenated hemoglobin (O_2Hb) and reduced hemoglobin (HHb). Given that the absorption spectra of O_2Hb and HHb are different, a set of linear equations can be solved simultaneously using the difference between the light emitted and received by the instrument to derive the changes occurring in the concentration of these chromophores in the tissue monitored. Changes in the concentration of a third chromophore cytochrome c-oxidase (CCO), which is the terminal enzyme of the mitochondrial respiratory chain, can also be determined via changes in the redox status of CCO detected from known differences in NIR light absorption.[17,19] In addition information regarding an increase or decrease in blood volume can be inferred from the trend of the total tissue hemoglobin concentration (tHb) derived from the sum of O_2Hb and HHb,[20] and in situations where hypoxia or ischemia develop characteristic and reproducible patterns of chromophore change occur. Thus NIRS data enable changes in oxygen delivery, oxidative metabolism and hemodynamic change to be monitored in a variety of tissue via real time changes in the concentration of these chromophores.[6]

There are also techniques to quantify blood volume and blood flow non-invasively in brain and muscle.[7] Muscle function is strongly dependent on oxidative metabolism as during contraction O_2 consumption (VO_2) rises many fold associated with an increase in O_2 delivery (DO_2). Consequently, pathology that impairs VO_2 or DO_2 via either a hemodynamic or metabolic mechanism can adversely affect the functional capacity of muscle or a muscular organ.[6]

The full range of measurement parameters possible using NIRS is shown in Table 1,[17,21-53] and NIRS measurements have been reported in healthy subjects, and in patients with various organ diseases and muscle-specific disorders.[6] However in the context of urology many of the measurement parameters possible with NIRS require methodologies that at present cannot be applied to the bladder or other organs in the urinary tract.

The initial studies demonstrating the feasibility of NIRS to monitor the bladder detrusor in animals and humans[10,12-15] used either Hamamatsu NIRO 500 or 300 continuous wave spectrophotometers. Both instruments use multiple lasers of different wavelength to generate the required photons, and either a photomultiplier tube (NIRO 500) or a photodiode (NIRO 300) to measure the photons returning unabsorbed or unscattered from the tissue. These and subsequent studies indicated that changes in chromophore concentration could be obtained from the detrusor during filling and emptying the bladder, and that NIRS data could be obtained simultaneously during conventional urodynamic monitoring. Because urodynamics measures pressure, and NIRS measures changes in chromophore concentration related to oxygenation and hemodynamic change, NIRS provides additional data not readily obtained by other means. Such data are of potential value as a means of evaluating the etiology of voiding dysfunction, particularly where the underlying pathology relates to a disorder of oxidative metabolism or hemodynamics involving the bladder and or urinary sphincter.

Several factors support the hypothesis that the magnitude and patterns of change in chromophore

TABLE 1. **Parameters measured directly and indirectly by near-infrared spectroscopy and imaging instrumentation**

Parameter	Units	Modality	Author (Reference)
ΔO_2Hb,ΔHHb, ΔtHb			Delpy 1997[17]
ΔoxCCO	a.u., µM x cm, µM	D	Tisdall 2007[21]
OI			Grassi 1999[22]
		D (by SRS)	Matcher 1995,[23] De Blasi 1993,[24] 1994,[25] Quaresima 2002,[26] Cuccia 2005[27]
Tissue O_2 saturation	%	D (by PMS)	Fantini 1995[28]
		D (by TRS)	Oda 1996[29]
		D (by callibration)	Benni 2005[30]
		Second differential	Matcher 1994,[31] Cooper 1996[32]
Muscle SvO_2	%	I (by VOM)	Yoxall 1997[33]
		D	Franceschini 2002[34]
Muscle tHb	µM	D (by PMS)	Franceschini 1997[35]
	a.u.	D (by DWS)	Durduran 2003[36]
Muscle BF	ml/100 ml/min	I (by VOM)	De Blasi 1994[25]
		I (by ICG)	Boushel 2000[37]
Muscle Hb flow	µM / min	I (by VOM)	Wolf 2003[38]
Muscle VO_2	Ml/ 100 g/min	I (by VOM)	De Blasi 1993,[24] 1994[25]
		I (by AOM)	
Muscle recovery time	s	D	Chance 1992[39]
Muscle compliance	ml/l/mmHg	I	Binzoni 2000[40]
Cerebral SvO_2	%	I (by VOM)	Yoxall 1995[41]
		D	Wolf 1997[42]
Cerebral tHb	µM	D (by PMS)	Choi 2004[43]
		I (by O_2 swing)	Wolf 2002[44]
		I (by O_2 swing)	Wyatt 1990,[45] Wolf 2002[44]
Cerebral BV	ml/100 ml	SRS and second differential	Leung 2006[46]
		I (by ICG)	Hopton 1999[49]
	a.u.	D (by DWS)	Durduran 2004,[48] Li 2005[49]
Cerebral BF	ml/100 ml/min	I (by O_2 swing)	Edwards 1998[50]
		I (by ICG)	Roberts 1993,[51] Keller 2000[52]
Cerebral VO_2	ml/100 g/min	Combination cerebral SvO_2 and BF	Elwell 2005[53]

Δ = Relative chances from arbitrary baseline, AOM = arterial occlusion Method, a.u. = arbitrary units, BF = blood flow, BV = blood volume, DWS = diffusing-wave spectroscopy, D = directly, I= indirectly, ICG = indocyanine green, OI = oxygenation index (ΔO_2Hb-ΔHHb), oxCCO = cytochrome c oxidase redox state, PMS = phase modulation spectroscopy, SRS = spatially resolved spectroscopy, SvO_2 = venous O_2 saturation, tHb = O_2Hb+HHb, TRS = time resolved spectroscopy, VO_2 = oxygen consumption, VOM = venous occlusion method.

(Reproduced with permission from: Wolf M, Ferrari M, Quaresima V. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *J Biomed Optics* 2007;12(6):062104).

concentration observed in the detrusor during transcutaneous suprapubic monitoring are physiologic in origin.[2] NIRS changes during voiding only occur in temporal relationship to permission to void and uroflow, and such changes are only detected from a suprapubic NIRS sensor and are not seen in a control monitoring channel placed elsewhere on the abdomen (right sub-costal region over the liver). The logic of using NIRS in urology is supported by data from NIRS applications to study other organs and tissue, and data obtained using NIRS simultaneously with other technologies.[1,6-9] The unique 'coiled' nature of the bladder vasculature,[54] the high mitochondrial content of the detrusor,[55] and the changes in blood flow associated with voiding,[56] all support the potential value of having NIRS equipment designed to measure detrusor oxygenation and hemodynamics, in order to add physiologic data to the evaluation of patients with voiding dysfunction.

Materials and methods

Design goals

To explore this concept further we collaborated in the development of an NIRS monitor specifically designed for evaluation of the bladder. Key design goals are shown in Table 2.

Hardware

The instrument was designed with 3 class 4 laser diodes with wavelengths of 785, 808 and 830 nanometers (nm). These NIR wavelengths cover the optimum range for the absorption spectra of the chromophores of interest shown in Figure 1.[17]

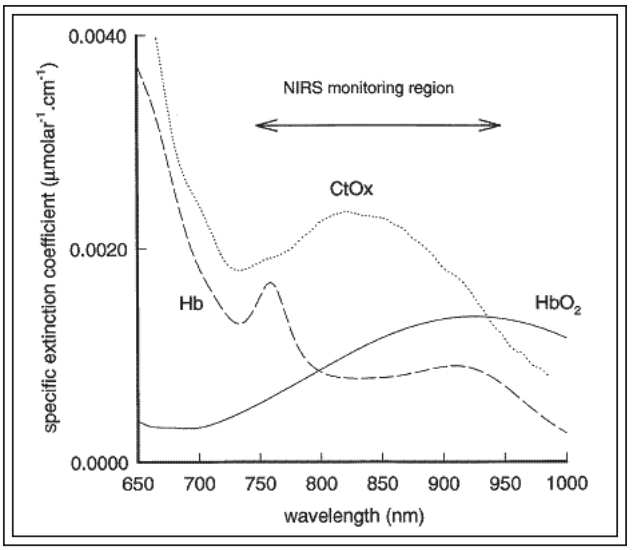

Figure 1. The extinction coefficients of adult Hb and the varying absorption of O_2Hb (HbO_2) and HHb (Hb) and CytOx (CCO) across the NIR spectrum. (Reprinted with permission of The Royal Society from Delpy D and Cope M. Quantification in tissue near-infrared spectroscopy. *Phil Trans R Soc Lond B* 1997;352:649-659).

The optical peak power of each laser diode is 2.3 mW with a pulse duration of 4us which makes the instrument a class I medical device. The beam characteristic is divergent and laser operating temperature is 0-40°C. A laser safety interlock system in the device monitors the receiver signal and will shut down the laser emitters if the event that an improper signal is detected. The laser output is also auto-

TABLE 2. **Goals for degisn of a NIRS instrument for urological applications**

	Goal
1	Selection of lasers with wavelengths specific to absorption spectra for oxygenated and deoxygenated hemoglobin and cytochrome c-oxidase (CCO).
2	Optimal design for the conduct of NIRS monitoring simultaneously during invasive urodynamic assessment of voiding function.
3	Algorithms designed to convert NIRS data from the detrusor into real-time changes in chromophore concentration.
4	Software to enable simultaneous on-screen display of the NIRS and urodynamics data in real time.
5	A patch incorporating the fibreoptic light emitter and light receiving photo diode with appropriate shielding to exclude extraneous light.
6	An interoptode distance appropriate to the depth of penetration required to interrogate the detrusor.
7	An auto attenuation system to enable patients with a range of body mass index (BMI) values to be monitored.

attenuated across a range of output to ensure sufficient light transmission for the required number of photons to return for counting by the photodiode in patients within the normal range for BMI values. In obese subjects the depth between the skin and the detrusor may be too great for adequate photon penetration. In addition adipose tissue has absorption properties that impact the NIRS signal.[57] Calibration of laser output can be obtained by use of a specified phantom or neutral density filter which enables checks of absolute optical density to be made.

The instrument is portable [250 mm (length) x 250 mm (width) x 100 mm (height)], and weighs 2 kg. Light transmission from the lasers in the instrument to the patient is achieved using an optical cable containing multifilament optical glass fiber bundles comprised of 40 µm glass fibers with a numerical aperture of 1.05 mm. The diameter of the optical cable is 4.5 mm. The sensor cable has 3 fiber optic connectors that plug into the 3 laser emitters in the instrument. The cable transmits the light to an emitter in the optical sensor. A photodiode in the sensor detects the light returning from the tissue that is unabsorbed and has not been lost to scattering, and converts these photons into an electrical signal that is transmitted back to the instrument via a detector port. The length of the cables can be either 3 m or 4.5 m to allow for the necessary separation between the patient and the monitoring module. The cables are jacketed with latex free silicone rubber for protection, but the nature of the glass fibers they contain makes them vulnerable to damage if kinked or compressed.

The optical sensor incorporating the emitter and photodiode is made of a latex free thermoplastic polyurethane elastomer. The silicon photodiodes of the type used in the sensor are highly sensitive and exhibit excellent linearity with respect to incident light in the NIR range. The optical sensor interface is incorporated into a disposable sensor patch which couples the sensor to the patient. The optical sensor fits into apertures in the patch which are shaped differently so as to accommodate the emitter and receiver in a consistent orientation. The distance between the emitter and the photodiode known as the interoptode distance (IOD) is 4 cm. This IOD was determined to be optimal based on early trials in volunteers where a series of different IODs were used with a suprapubic patch application, and evaluated for signal quality during transcutaneous monitoring of the bladder detrusor. An IOD of 4 cm equates with a mean depth of light penetration of approximately 2 cm.[58]

The disposable sensor patch measures 13 cm x 7 cm^2, has a medical grade pressure sensitive peel-and–stick acrylic (latex free) adhesive backing for skin attachment, and incorporates a shield to protect the sensor from ambient light. This instrument does not incorporate a daylight filter of the type used in some research instruments,[18] hence the need for screening in the patch. Additional screening of ambient light may be required in circumstances where levels of ambient light are high such as in the operating room.

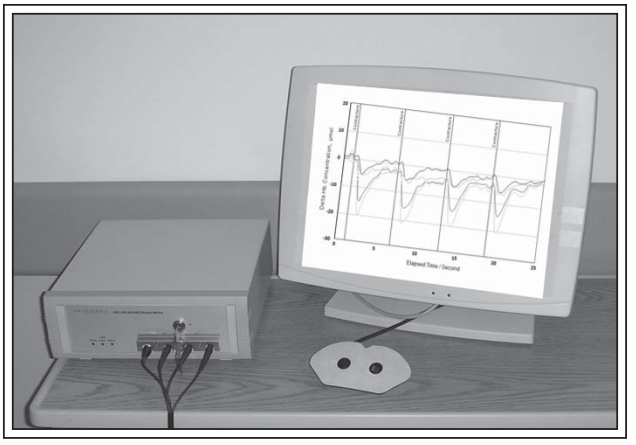

Figure 2. The continuous wave near infra-red spectrometer designed for applications in urology. Showing the instrument containing the lasers, control computer and photon counting hardware, the fiber optic cables linking the instrument to the patient, and the self-adhesive sensor patch incorporating the emitter and receiver optodes.

The system is controlled by a touch screen personal computer. The system allows for data to be displayed graphically in real time for each of the chromophores (O_2Hb, HHb and CCO), and for total hemoglobin (tHb), with the addition of event markers added to the data stream in real time via the computer, Figure 2.

Software and algorithms

Incorporated software converts the raw optical density data to chromophore concentration. This is done using a modification of the standard form of NIRS algorithm which uses a modified Beer-Lambert law,[17] and requires the addition of a value representing the path of light through the tissue between the emitter and detector, known as the differential pathlength factor (DPF). Because of photon scattering the DPF is longer than the distance between the emitter and the sensor, and is also a tissue specific value. The DPF values of certain tissues such as brain and muscle have been determined *in vitro* studies.[59] However, because the optical pathlength for detrusor tissue is a parameter which has not yet been determined, a constant factor is incorporated in the algorithm used to generate the

relative changes in chromophore concentration. This follows the convention used for NIRS instrument software whenever tissue without a known DPF is studied.[60]

Development and trials

An iterative process was used in the design of all aspects of the NIRS monitoring instrument, hardware and software. In the case of the optode patch serial design improvements ensured optimal adhesion and light screening, accommodated the defined interoptode distance of 4 cm, and kept the footprint of the patch as small as possible. Patch modifications during clinical trials included an improved adhesive interface, optimal sizing and the incorporation of a grounding element to prevent electromagnetic interference (EMI). EMI is a common cause of interference between electronic devices particularly in a hospital setting.[61] Consequently this is an important design factor to address. Some EMI occurred in early trials. Confirmation that it was EMI that was disrupting the signal, and that the source was the infusion pump used for the urodynamic studies, was first achieved by isolation of the pump, and then via a simple grounding strap attached to the patient's wrist.

Fibers in early versions of the fiber optic bundles proved prone to periodic failure. This resulted in a loss of signal in two instances, and was remedied with a design feature that allowed for greater flexibility of the fibers and enhanced protection from a thicker light insulating jacket on the outside of the bundle. A cable holder where the cables can be coiled and stored when not in use has also been incorporated on the side of the instrument and provides significant additional protection.

The early software required modification to optimize the signal, reduce noise and make display and data recording more 'user friendly'.

In clinical trials the NIRS instrument was used simultaneously with a urodynamics unit (Laborie Medical Technologies Inc, Mississauga, Ontario, Canada). Initially the tracings from the two instruments were time-sequenced manually. Now, with incorporation of the necessary software, simultaneous signal display of the NIRS chromophore concentrations and urodynamics data on a single screen has been achieved. Simultaneous display improves functionality, the accuracy of data analysis, and the ability of the operator to relate NIRS data and their relevance to urodynamic pressure data and to uroflow in real time. This improvement is of relevance in both clinical and research applications of simultaneous NIRS and UDS monitoring.

Subsequent prospective studies with the NIRS prototype reported separately add correlation with other urodynamic parameters. Two studies recorded simultaneous NIRS and UDS data in men with LUTS and probable bladder outlet obstruction. The first showed good specificity and sensitivity of the chromophore concentration changes in the detrusor during pressure flow studies by receiver operator curve (ROC) analysis.[11] In the second a custom written algorithm for the URO-NIRS data correctly classified > 80% of the patients diagnosed as obstructed using the UDS pressure flow study measurements and the standard Abrahams Griffiths nomogram.[62] The algorithm analyzes the patterns of chromophore concentration change in the detrusor during voiding and measurements of post voiding residual volume (PVR) and peak uroflow rate (Qmax). Data from simultaneous monitoring in women with LUTS shows synchrony between NIRS chromophore concentrations and urodynamic pressures (Pdet) using mathematical modeling of detrusor hemoglobin concentration.[63] The concordant patterns observed during voiding indicate good statistical correlation between NIRS parameters and urodynamic pressures.

Discussion

Our hypothesis that the data generated by this NIRS instrument reflects physiologic change within the detrusor is supported by NIRS applications using other instruments in other organs and tissue[7] where the same physics principles relating to NIR photon transmission, scattering, and absorption by chromophores apply. Prior basic and human research studies have established the ability of NIRS to monitor changes in tissue oxygenation and hemodynamics.[4,6,8,9] The initial urological applications of NIRS,[2] and our use of instruments designed to study brain and muscle to monitor the detrusor invasively in animal studies[2] and via transcutaneous monitoring in human subjects[10-16,62,63] provide further evidence.

A NIRS instrument designed for urological applications has now been developed, iteratively modified, and evaluated. In initial prospective clinical trials this instrument has proved able to provide real time monitoring of changes in chromophore concentration within the bladder detrusor during filling and emptying of the bladder for conventional urodynamic study. Data obtained in men and women with LUTS indicate significant correlation between changes in oxygenated, deoxygenated and total hemoglobin concentration with urodynamic parameters, and the ability of NIRS data to contribute to diagnostic classification.

Prospective clinical trials are now required using this NIRS instrument and the dedicated software that provides real time display and recording of both NIRS and urodynamics data. Initial studies should analyze

NIRS data collected simultaneously during invasive urodynamic monitoring, to address the validity of our findings and evaluate the potential for a NIRS instrument designed for urological applications to contribute to the assessment of patients with lower urinary tract symptoms.

Because NIRS data reflects changes in oxygenation and hemodynamics the data from such studies could add significantly to the understanding of voiding dysfunction caused by vascular or hemodynamic pathology. Prospective clinical trials with sufficient power would determine to what extent NIRS monitoring of the pattern and magnitude of changes in the concentration of hemoglobin (O_2Hb, HHb and tHb) in the detrusor can contribute clinically for urologists. In parallel, software and mathematical models can be developed to aid in the analysis of NIRS data and algorithms constructed that can contribute to patient classification. Basic science research using NIRS could also expand our understanding of the pathophysiology of bladder function.

Conclusion

A near infrared spectroscopy (NIRS) instrument specifically designed for urological applications has been developed and evaluated. This instrument allows non-invasive monitoring of changes in concentration of oxygenated, deoxygenated and total hemoglobin in the detrusor during bladder filling and emptying. Simultaneous NIRS monitoring during invasive urodynamics is feasible and generates data of potential diagnostic value in patients with lower urinary tract symptoms. □

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