Near-infrared spectroscopy: validation of bladder-outlet obstruction assessment using non-invasive parameters

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Introduction: *Near infrared spectroscopy (NIRS) is a non-invasive optical technique able to monitor changes in the concentration of oxygenated and deoxygenated hemoglobin in the bladder detrusor during bladder filling and emptying.*
Objective: *To evaluate the ability of a new NIRS instrument and algorithm to classify male patients with LUTS as obstructed or unobstructed based on comparison with classification via conventional invasive urodynamics (UDS).*
Method: *Male patients with LUTS were recruited and underwent uroflow and urodynamic pressure flow studies with simultaneous transcutaneous NIRS monitoring following measurement of post residual volume (PVR) via ultrasound. Data analysis first classified each subject as obstructed or unobstructed using the standard pressure flow data and nomogram, then compared these results with a classification derived via a customized algorithm which analyzed the pattern of change of the NIRS data plus measurements of PVR and Qmax.*
Results: *Seventy subjects enrolled: 57 data sets had all required parameters [13 incomplete sets due to: communication error between NIRS and urodynamics instruments (9); data saving error (1); damaged fiber optic cables (3)]. Two complete data sets were excluded [subjects with hematuria (2)]. Thus data from 55 subjects was analyzed.*
The NIRS algorithm correctly identified those diagnosed as obstructed by conventional urodynamic classification in 24 of 28 subjects (sensitivity = 85.71%) and, and those diagnosed as unobstructed in 24 of 27 subjects (specificity = 88.89%).
Conclusion: *Scores derived from NIRS data plus PVR and Qmax are able to correctly identify > 85% of subjects classified as obstructed using UDS.*

Key Words: near infrared spectroscopy, pressure flow studies, lower urinary tract obstruction, urodynamics

Introduction

Near infrared spectroscopy (NIRS) is an established technology that uses light to monitor changes in the concentration of oxyhemoglobin and deoxyhemoglobin in living tissue non-invasively and in real time.[1-6] Recently NIRS has been used in urological research applications to evaluate oxygenation and hemodynamic parameters and investigate cryptorchidism, testicular torsion and vasculogenic erectile dysfunction, evaluate renal metabolism, prostatic tissue and bladder dysfunction, and study skeletal muscle metabolism in end stage renal disease.[7] Initial studies involved animal models, but recent research has demonstrated the feasibility of using NIRS to monitor changes in oxygenated and deoxygenated hemoglobin concentration in the bladder detrusor non-invasively and in real time.[7,8] This research extends the scope of urological applications of NIRS to the evaluation of physiologic changes of clinical relevance in vivo, and builds on similar progress with NIRS in a range of organs and tissues.

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Because the brain and voluntary muscle have been the principle tissues of interest[2,4,6,9] most NIRS instruments are designed principally to evaluate brain and striated muscle. A new NIRS instrument has been developed for urological applications and for interrogation of the bladder detrusor specifically.[10] This instrument uses three lasers to generate light in the near infrared (NIR) spectrum at wavelengths of 785, 805, and 830 nanometers (nm). These wavelengths cover the optimum range for the absorption spectra of the chromophores oxygenated and deoxygenated hemoglobin.[11] The physics principles underlying NIRS include the relative transparency of tissue to light at these wavelengths, and that changes occurring in the concentration of oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) can be detected within tissue because of their different absorption spectra across NIR wavelengths.[3,6,11] NIRS derived changes in the concentration of these chromophores (O_2Hb and HHb) provide a measure of changes in oxygenation, and in addition total hemoglobin (tHb), which is the sum of the O_2Hb and HHb signals, provides hemodynamic data reflecting changes in blood volume.[1,2,4,9]

Prior to development of the instrument used in this trial, the work in animals and humans demonstrating the feasibility of monitoring the bladder detrusor was done with either Hamamatsu NIRO 500 or 300 continuous wave spectrophotometers.[12-15] Both instruments were designed to study brain and muscle and use algorithms developed for that purpose. In this study, the NIRS instrument incorporates a customized algorithm and software optimized to monitor changes in chromophore concentration in the bladder detrusor.[10] A specific algorithm analyzes the NIRS data and measurement of peak uroflow rate (Qmax) and post-voiding residual volume (PVR), and uses these data to classify patients as obstructed or unobstructed. We report a prospective study evaluating this NIRS instrument via simultaneous collection of NIRS data during conventional uroflow and invasive urodynamic testing (UDS) in males with lower urinary tract symptoms.

The study hypothesis was that the NIRS instrument and algorithm would accurately classify/specify 80% or more subjects using non-invasive NIRS derived changes in chromophore concentration during voiding in conjunction with measurements of PVR and Qmax, as compared with standard diagnostic classification using invasive urodynamics.[16]

Methods

All patients completed an informed consent which was approved by the University of British Columbia ethics committee HO6-70108.

Male subjects, age 19 year of age or greater, with lower urinary tract symptoms (LUTS) were included. Subjects were consecutive referrals for evaluation of possible lower urinary tract obstruction by their urologist for standard pressure flow studies. All subjects completed an International Prostate Symptom score upon arrival. Height and weight were recorded for calculation of body mass index along with patient ethnicity (re relative degree of skin pigmentation). Subjects naturally filled their bladder and were instructed to report to the UBC Bladder Care Centre with a full bladder to allow for measurement of a non-invasive uroflow. An ultrasound was performed to delineate the bladder size and to calculate urine volume. The NIRS sensor patch was attached with the emitter and sensor optodes positioned horizontally across the midline 2 cm above the pubis. Simultaneous data collection of NIRS and urodynamic data was begun. After a stable NIRS baseline was obtained the subject spontaneously voided into the uroflow meter. The event marker was used to indicate completion of micturition. Following voiding a post uroflow resting baseline (1 minute) was obtained and then the data collection was paused.

Standard double lumen urethral and rectal urodynamics catheters were placed with the subject in the supine position. Data collection was then reinitiated and a resting baseline was obtained. Following this the bladder was filled with sterile water at a rate of 1 ml per second. The event mark was used to indicate 175 ml of filled volume. At this point a second partial fill data baseline was recorded. The infusion was then restarted to fill to 350 ml volume. The infusion was then paused and a baseline at this fill volume was obtained. Data collection was then halted and the subject changed position to allow for voiding. The data collection was restarted and the subject voided into the flow meter following pre voiding baseline data. The event marks included peak uroflow rate (Qmax). The voided volume was recorded and post-uroflow data collected. The data collection was then halted and the NIRS sensor patch and catheters removed. Post void residual volume (PVR) was then measured by ultrasound.

Sample size was set at a significance level of $\alpha = 0.05$ and the precision measure of $d = 0.15$, $\pi = 0.8571$ and result $N = 21$ for the obstructed group, i.e. the minimum number of subjects in this category was 21. (The number of subjects included in this group was 28). At the same level of significance and precision $\pi = 0.8889$ result was $N = 17$ for the unobstructed group i.e. the minimum number of subjects in this category was 17. (The number of subjects included in this group was 27). Precision measures were done to relate NIRS parameters to the known categories of obstruction versus nonobstruction based on the patient's pressure flow nomograms.

Precision measure for the obstructed group

The estimated proportion was 0.8571 over 28 samples. Using the equation to construct the intervals $p_i \pm \Phi^{-1}(1-\alpha_i/2)\sqrt{\frac{p_i(1-p_i)}{N}}$ (where p_i was the proportion of the N trials that had outcome i; N was the number of trials (the sample size); α_i was significance level for this interval; and Φ was the cumulative distribution function [CDF] for the standard normal distribution; Φ^{-1} was the inverse of the standard normal CDF), the half width of the confidence interval was 0.13. So at the 0.05 significance level, the precision of the estimated proportion was +/- 13 percentage points.

Precision measure of the unobstructed group

The estimated proportion was 0.8889 over 27 samples. Using the same equation, the half width of the confidence interval was 0.12, so at the 0.5 significance level the precision of the estimate proportion was +/- 12 percentage points.

Diagnostic algorithm

The algorithm was written to classify patients based on interpretation of a combination of three non-invasive data components:

1) The pattern of slope of chromophore concentration (NIRS) during voiding; 2) The maximum uroflow rate (Qmax) in ml per minute; 3) The post voiding residual volume (PVR) in ml. Each component was identified within the algorithm as indicative of the subject being either obstructed or unobstructed.

The sequential execution of the diagnostic algorithm is shown in Figure 1. Data sets were first identified as

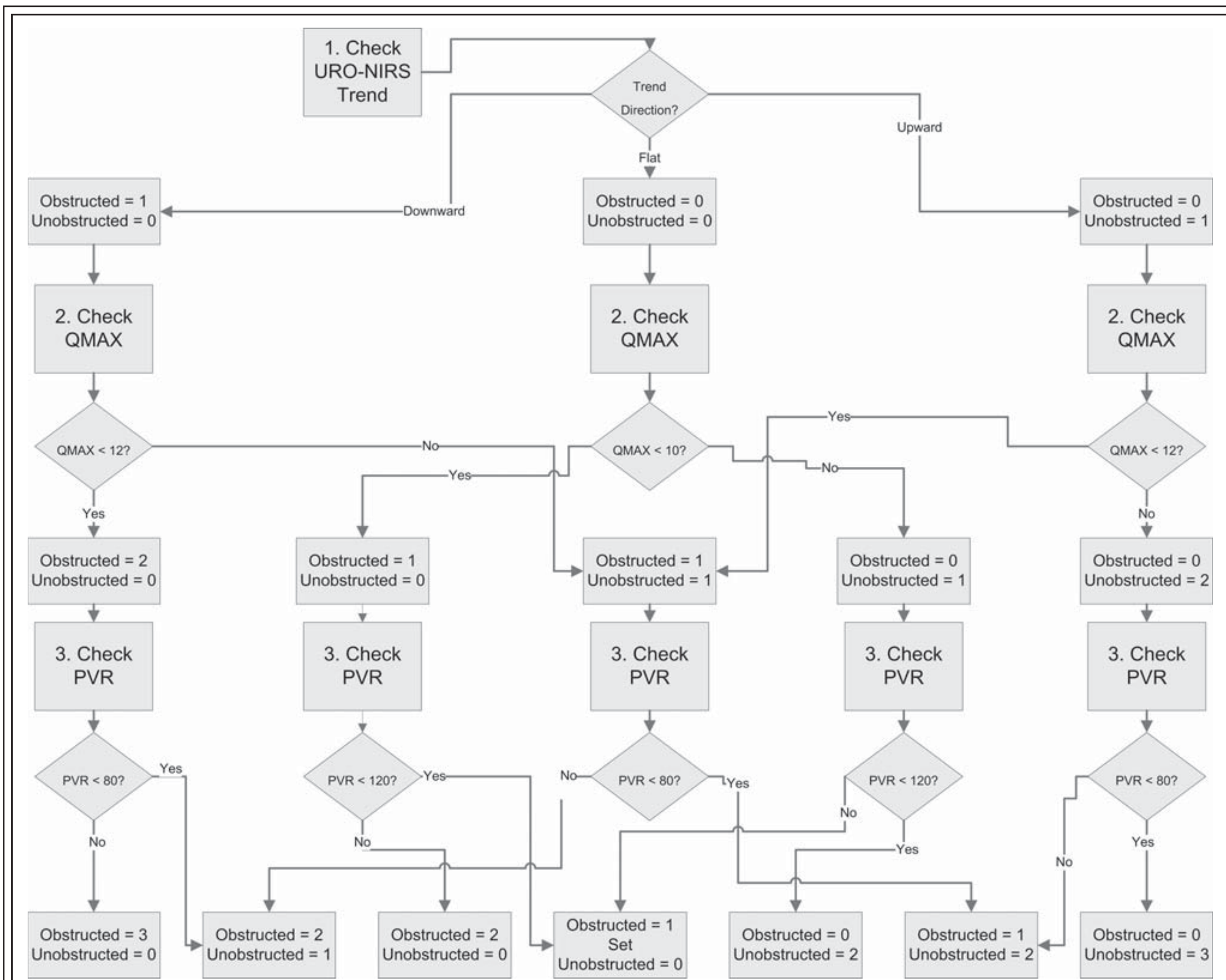

Figure 1. Flow diagram of the sequential decisions and classification analysis of the diagnostic algorithm URO-NIRS patterns=NIRS changes in chromophore concentration; Qmax=peak uroflow rate; PVR=postvoiding residual volume.

valid or not valid for classification by the algorithm based on voided volume. To be deemed valid data required the subject to void a volume of > 150 ml.

Analysis of the NIRS data pattern

An averaging filter was applied to smooth the raw NIRS data. A start point was identified (permission to void) on the NIRS total hemoglobin (O_2Hb plus HHb) or O_2Hb data stream (whichever was greater). A trend point was then identified where a first local minimum or maximum data point was found by applying a first derivative calculation with respect to time. As a secondary measure, this trend point was defined as the Qmax point, if no trend point was identified between permission to void and Qmax. The pattern of slope in the NIRS data between the start point and trend point was then identified. The classification based on the NIRS data was assigned a numerical value. If the slope was positive and cleared the threshold for upward pattern a score of 1 was added to the unobstructed score. If the slope was negative and cleared the threshold for downward pattern a score of 1 was added to the obstructed score. Finally, if the slope did not clear either threshold (a flat pattern) no score was assigned and 0 added.

Figure 2 shows a sample graph for defining start point, trend point and slope of NIRS data.

Analysis of Qmax and PVR

Where an *upward or downward pattern* was present in the NIRS data, Qmax was scored as follows:

a) Where Qmax was > 12 ml/sec. 1 was added to the obstructed score
b) Where Qmax was < 12 ml/sec. 1 was added to the unobstructed score
c) Where PVR was > 80 ml. 1 was added to the obstructed score
d) Where PVR was < 80 ml. 1 was added to the unobstructed score

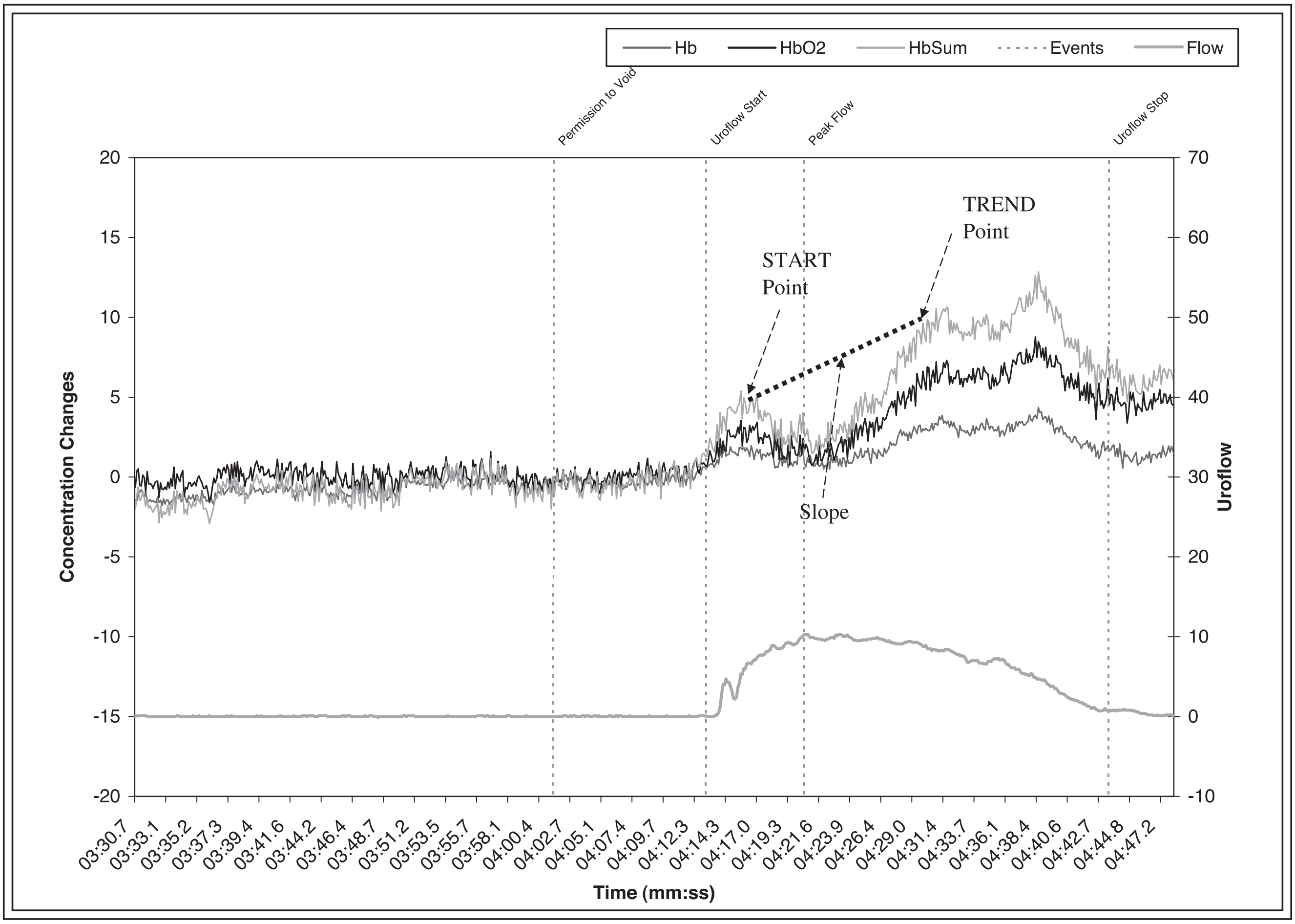

Figure 2. A sample graph of the concentration changes in oxygenated (O_2Hb), reduced (HHb), and total (tHb) hemoglobin prior to and during uroflow showing the defined START and TREND points used to define the SLOPE of the pattern of change in chromophore concentration.

Where a *flat pattern* was identified the NIRS algorithm determines obstruction based on uroflow parameters. [The obstructed flow curve was asymmetric with Qmax reached early in voiding. If Qmax was < 10 ml/sec where voided volume was > 150 ml, the accuracy of predicting bladder outlet obstruction was 90%[17]].

Thus, with a flat NIRS pattern the cutoff values for scores derived from Qmax and PVR were modified as follows:

a) Where Qmax was > 10 ml/sec. 1 was added to the unobstructed score
b) Where Qmax was < 10 ml/sec. 1 was added to obstructed score
c) If PVR was < 120 ml 1 was added to unobstructed score
d) If PVR was > 120 ml 1 was added to obstructed score

Where *a flat NIRS data pattern* occurred there was the potential for the algorithm to derive an equal score (i.e. 1 for both an obstructed and an unobstructed diagnosis) from the Qmax and PVR measurements. In this event the algorithm was written to categorize the patient as obstructed, and a final clinical decision re classification was then required from a physician, based on the available medical history, clinical information and medication record in addition to Qmax, PVR and uroflow data.

Results

Data from 55 subjects were used in the mathematical calculations. Initially, 70 subjects were recruited. Complete data sets with all required elements (NIRS, urodynamics, uroflow and ultrasound) were obtained

TABLE 1. **Characteristics of subjects based on urodynamic pressure flow study diagnosis. IPSS (International Prostate Symptom Score)**

	Obstructed (STD)	**Unobstructed (STD)**	**p (t-test)**
Age	67.3 (10.5) 50-91	56.8 (13.02) 40-77	0.07 (0)
Height (inch)	67.8 (4.2) 60-76	68.8 (2.8) 65-73	0.60 (0)
Weight (kg)	72.6 (18.3) 50-114	83.8 (10.4) 67-99	0.14 (0)
BMI	24.3 (4.6) 18-32	27.4 (2.9) 23-32	0.10 (0)
IPSS-1	3.1 (1.8) 0-5	2.7 (2.2) 0-5	0.65 (0)
IPSS-2	3.5 (1.4) 1-5	3.6 (1.2) 1-5	0.89 (0)
IPSS-3	2.9 (1.7) 0-5	2.4 (2.4) 0-5	0.59 (0)
IPSS-4	2.8 (1.7) 0-5	3.7 (1.7) 0-5	0.35 (0)
IPSS-5	3.4 (1.4) 0-5	2.5 (2.0) 0-5	0.29 (0)
IPSS-6	2.0 (2.0) 0-4	2.0 (1.7) 0-4	1.0 (0)
IPSS-7	2.0 (2.0) 0-5	3.2 (1.8) 0-5	0.08 (0)
IPSS-Total	19.6 (6.4) 8-27	20.2 (9.1) 2-30	0.86 (0)
IPSS-Q	1.2 (4.3) 3-6	4.7 (1.3) 3-6	0.42 (0)

TABLE 2. **Results: composite comparison of subject classification as either obstructed or unobstructed using UDS based and NIRS based diagnosis respectively**

	UDS-based diagnosis	NIRS-based diagnosis	
Obstructed	28	Obstructed 24	(Unobstructed 4)
Unobstructed	27	Unobstructed 23	(Obstructed 4)
Total	55	47	(8)

in 57 of these 70. The 13 incomplete sets were due to: an initial communication error between NIRS device and the urodynamic system (9), a data saving error (1), and damage to fiber optic cables limiting light transmission (3). Two complete data sets were also excluded due to 2 subjects having hematuria (a potential confounder for NIR light attenuation (2). Thus 55 subjects were included in the data analysis.

The age and physical characteristics of these subjects based on their urodynamic pressure flow study classification are shown in Table 1. The ethnicity of the subjects was Caucasian with the exception of 15 Asian, 2 East Indian, and 1 subject of Latin origin.

The invasive urodynamics and uroflow data from these subjects were first reviewed by a urologist and categorized using the standard pressure flow data nomograms.[16] Where this resulted in an equivocal classification the urologist assigned the patient to either the obstructed or unobstructed categories based on all elements of the patient's history, physical examination and non-NIRS study data available. This led to classification of the 55 subjects as obstructed [n = 28] and unobstructed [n = 27].

The NIRS data combined with PVR and Qmax measurements was then analyzed using the customized software and algorithm and the subjects classified as either obstructed or unobstructed. The composite data comparing the UDS based diagnostic classification and the NIRS based diagnostic classification are shown in Table 2. Without the NIRS data Qmax and PVR alone were not predictive.

The NIRS derived classification of subjects as obstructed correctly matched paired classifications from the UDS 'gold standard' nomogram in 24 of 28 subjects (sensitivity = 85.71%), and correctly matched paired classifications of subjects as unobstructed with the gold standard in 24 of 27 subjects (specificity = 88.89%).

Discussion

This study demonstrates that non-invasive NIRS data combined with measurements of Qmax and PVR can provide via a proprietary diagnostic algorithm a diagnosis of obstructed versus unobstructed in more than 80% of the subjects studied. The data used to separate patients into these diagnostic categories was collected during simultaneous invasive urodynamics and uroflow studies. First, the 'gold standard' pressure flow data and nomograms were used to classify the patients on the basis of their urodynamics study. Then this classification was compared with the classification derived using the NIRS methodology and data analysis algorithm. This is the first reported study of the use near infrared spectroscopy in a human population to investigate voiding dysfunction, and categorize male patients presenting with LUTS as either obstructed or unobstructed. Consequently, following this proof of principle study we suggest further investigation of an additional cohort to validate our findings.

The principles of NIRS have been widely used to study many tissues and organs in order to derive a range of quantitative measurements reflecting physiologic variables in health and disease.[1-6,9] Many such measurements rely on an event which changes oxygenation or blood flow in the tissue studied. Examples of such events include arterial occlusion to generate ischemia, jugular vein compression to increase cerebral blood volume, and alterations in oxygen saturation to induce hypoxia or send a bolus of oxygenated blood through the tissue of interest.[1-4,18] In studies of muscle, additional use is made of physiologic events such as isometric exercise,[4,5,9] and specific physical movements. Visual, olfactory, auditory or painful stimuli are used in fNIRS mapping of brain function to generate changes in blood flow.[19-21] Consequently, monitoring the changes in chromophore concentration that occur in the bladder detrusor during the physiologic effects of filling and emptying the bladder is a logical application of NIRS methodology.

While in some situations NIRS data generate readily recognizable patters of change (e.g. in ischemia and hypoxia), other patterns of change require software analysis in order for them to be classified and quantified. And this is the case in the application of NIRS described in our study. This is also the case with the more familiar application of many of the physics principles employed in NIRS that are relied on in order to make oximetry the functional and widely applicable technology that it is.[22] The raw data derived by oximeters requires conversion by proprietary software into the displayed percentages relied on routinely by clinicians.

Hence, with the prior demonstration of the feasibility of monitoring changes in chromophore concentration in the detrusor,[8,12-15,23-26] the data from this study warrant extension of urological research using this NIRS instrument combined with the necessary software to establish NIRS parameters in normal subjects and investigate patients with other specific pathologies. However, we recognize there are limitations in our research. This is a proof of principle study using an algorithm developed iteratively; hence algorithm refinement should be considered. Such refinement might include weighting of the parameters, modification of start and end points, and/or sensitivity analysis around appropriate cut off values for Qmax and PVR. Although the objective was 80% agreement with standard pressure-flow studies and our data indicate an 85% agreement with a confidence interval of 13%, we recognize that this means that there is a potential in a general population for only 72% agreement on occasion. However, we would suggest that because the methodology we describe is non-invasive as it combines NIRS parameters with Qmax and PVR, this approach would still be clinically useful as a preliminary investigative measure even if this lower threshold should occur. In the context of the algorithm, the principles employed in algorithm development are to use measureable endpoints which are readily obtained and have physiologic relevance in the first instance. And the weight and relative merit of each endpoint are not a major consideration until the relative efficacy of the algorithm has been established. Following this, the next step is to weight parameters, and consider alterations to the chosen criteria or the addition of new ones. Similarly algorithm refinement is accompanied by increasing specificity with regards to the characteristics or diagnoses of the patient groups studied. Importantly, in the research reported we were not conducting a case control study, but seeking to establish the presence or absence of proof of our concept that NIRS parameters combined with other non-invasive measures have discriminant ability. We also recognize that a simple algorithm based on the presence or absence of obstruction risks oversimplifying the process of patient classification, and may undermine the true potential utility of incorporating NIRS technology in patient evaluation. However, our approach is in keeping with the first iteration and development of other algorithms which have subsequently become more refined and discriminant.

Because urodynamics measures pressure, and NIRS measures changes in chromophore concentration that reflect tissue oxygenation and hemodynamics, the observation that these parameters have concordant patterns indicating a good statistical correlation is also important,[26] and adds to the probability that data from simultaneous NIRS and UDS studies will add previously unavailable physiologic information to the diagnostic evaluation of patients with voiding dysfunction.

The data reported warrant further studies to validate the diagnostic algorithm described, and further explore the ability of NIRS to contribute to urological diagnostic evaluation. Importantly, NIRS is a non-invasive technology where the equipment is portable, allowing bedside collection of data in conjunction with other technologies. It is probable that the unique combination of NIRS and UDS data will contribute information of use to urologists in their evaluation of patients with bladder dysfunction, particularly those where a vascular etiology or hemodynamic factors may contribute to the underlying pathology. Certainly unique insights have been gained when NIRS has been used in combination with other technologies in the study of other organs. From the patients' standpoint there is a high level of acceptance as the NIRS energy source is cold light and non-toxic, and the only interface required is a self-adhesive patch applied to the skin of the lower abdomen.

Conclusion

Analysis via algorithm of non-invasive NIRS data combined with PVR and Qmax measurements enables male patients with LUTS to be classified as obstructed or unobstructed. These data warrant further studies with simultaneous NIRS and UDS measurements, and add evidence supporting the relevance of application of NIRS technology to the diagnostic evaluation of patients with voiding dysfunction. □

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