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Clinical NIRS of the urinary bladder – A demonstration case report

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Abstract. Urinary incontinence is a common affliction among people of all ages throughout the world. There are many causes of incontinence, treatment options are determined by the cause, and current diagnostic methods require urodynamic assessment, which involves urethral and rectal catheterization, which are uncomfortable and distasteful for patients. Since clinical near infrared spectrophotometry (NIRS) is a non-invasive, rapid means of measuring tissue oxygenation status at the bedside, we examined whether NIRS could be useful as a diagnostic tool for bladder dysfunction. An adult patient attending an incontinence clinic for routine urodynamic testing also had NIRS data collection during the standard bladder filling regimen. NIRS optodes were placed on the skin of the intact abdomen over the supra pubic region. Changes in oxy and de-oxy hemoglobin concentration and changes in cytochrome c oxidase net redox status via NIRS were collected at 6 Hz. The magnitudes of change that occurred during NIRS data collection are on the order of 0.5 μmol/l and the moments of change correspond to the subject's reported sensations of bladder filling and emptying, and with conventional urodynamics. These observations suggest that NIRS may be a disruptive technology with a role to play in non-invasive evaluation of bladder dysfunction in humans.

1. Introduction

Modern clinical NIRS emerged in 1977 when Norris described the application of NIRS to the study of *in situ* human tissues, and Jobsis described the application of NIRS to the study of cerebral metabolism as related to the mitochondrial respiratory enzyme cytochrome c oxidase (Cyt), also known as cytochrome a,a_3 [16,24]. Today, there are more than a dozen commercial versions of clinical NIRS devices available for non-invasive transcutaneous sampling of oxygenated hemoglobin (HbO_2), de-oxygenated hemoglobin (Hb) and Cyt redox status [4]. Clinical NIRS has been used to sample cohorts of all ages; and although intended as a cerebral monitor, it has been used to sample limb muscle, liver, breast, spine, tumours, lung, testis, spinal cord, kidney, heart, bowel and the splanchnic bed [5,6,8–10,15,18–21,23, 25,27,29,32,33].

Traditional urodynamic monitoring, the current technology for assessment of bladder dysfunction, measures the pressure exerted on the bladder by the accumulating urine during filling and measures the urine voiding rate and voided volume during emptying [34]. This technique requires invasive catheterization of both rectum and urethra [31]. Unfortunately, 40% of those with symptoms refuse testing because of embarrassment and fear of catheterization [30,35]. There is no NIRS counterpart for any of

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the traditional urodynamics urine measurements, and conversely there are no traditional urodynamics counterparts for any of the NIRS measurements [3].

As people age, their bladder capacity tends to decrease, leading to increased frequency of voiding (micturition), especially at night [17]. If the bladder neck and urethral sphincters are injured then they are not as effective at retaining the urine in the bladder (incontinence) [14]. The detrusor muscle itself may be unstable or overactive as a result of nerve damage or ischemia from either child-birth or previous incontinence surgery [12]. Anything that interferes with the parts of the brain involved in bladder monitoring can affect bladder function [28]. Anything pressing on the bladder can cause problems [26]. Cancer tumours can occur in the bladder wall and interfere with detrusor contraction [2]. Particulates in the urine can crystallize into stones within the bladder that then obstruct the urethra to hinder micturition [13,22]. In males, the prostate surrounds the urethra beneath the bladder, and if swollen can cause a constriction that hinders micturition [11]. In 1998, the World Health Organization (WHO) conservatively estimated that world-wide direct and indirect costs of urinary incontinence exceed US$16 billion annually within the major pharmaceutical markets (USA, Top 5 European nations, and Japan). At that time, WHO estimated that bladder control problems affected more than 200 million people world wide.

In the urological setting, NIRS primarily interrogates the bladder wall, which consists of three layers: an outer layer (serosal) of connective tissue, a muscularis layer of smooth muscle (detrusor), and an inner mucous membrane comprised of transitional epithelial cells (urothelium) supported by a boundary of fibroblasts and sparse smooth muscle cells (lamina propria) [1,7].

This is the first report of successful interrogation of the bladder using NIRS non-invasively in a urology clinic.

2. Method

An adult human suffering from urinary incontinence was enrolled in a study approved by the university's Human Ethics Review Committee. The subject underwent urethral catheterization to facilitate routine urodynamic evaluation, including emptying and filling of the bladder via the catheter.

In this trial, NIRS was used in reflectance mode with the NIRS emitter and detector of a Hamamatsu NIRO-300 (Hamamatsu Photonics KK, Hamamatsu City, Japan), placed bilaterally on the intact skin surface above the midline of the *in situ* bladder. Data was collected at 6 Hz with 40 mm inter-optode spacing.

Following instillation of the catheter, the subject voluntarily voided and any residual urine volume was removed from the bladder by syringe withdrawal. NIRS was then initialized and data collection commenced. After a two minute stable resting baseline, bladder filling commenced via infusion pump at a rate of 1 ml/min. The subject reported the first sensation of filling, the sense of urgency to void, and the sensation of being filled to capacity. The subject was then asked to attempt to prevent the bladder from leaking urine and shortly thereafter data collection was terminated to allow the subject to void.

3. Results

A typical NIRS adult human abdominal bladder Hb and HbO_2 data collection is given in Fig. 1.

A typical NIRS adult human abdominal bladder Cyt data collection is given in Fig. 2. Our Fig. 2, is a companion to Fig. 1; its cytochrome data was collected simultaneously with the hemoglobin data using the same NIRS device.

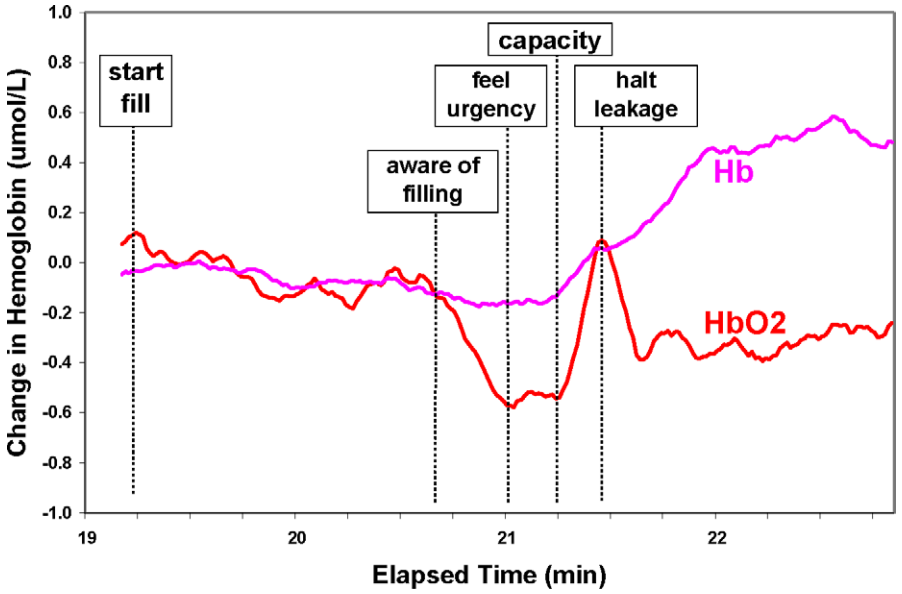

Fig. 1. Typical hemoglobin changes during controlled filling and emptying of the urinary bladder in a clinical urodynamics examination.

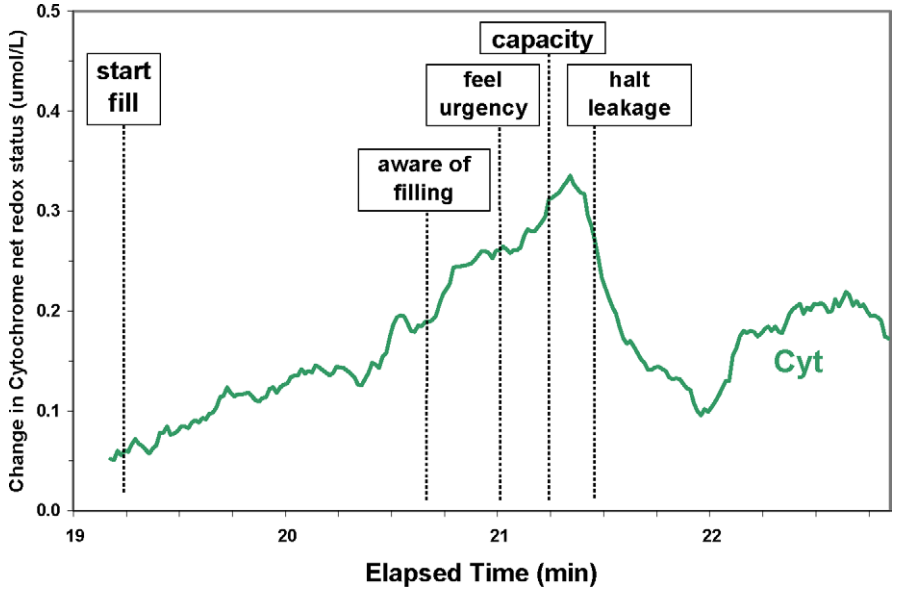

Fig. 2. Typical net oxidized minus reduced cytochrome c oxidase redox status changes during the same controlled filling and emptying of the urinary bladder as shown in Fig. 1.

4. Discussion

Figure 1 shows an adult human detrusor data collection with filling controlled by saline infusion pump. Interpretation of Fig. 1 indicates an immediate loss of blood volume in the bladder wall that is evident with the start of bladder filling, and that progresses until capacity is reached. The notations

on the graph ("aware of filling", "feeling urgency", and "capacity") are the patient's comments. These markers suggest that NIRS might be able to serve as a biofeedback monitor. The graph notation "halt leakage" is when the subject began voluntary bladder sphincter contraction to attempt to retain urine. As this contraction continues, equal and opposite changes in concentration between oxy and de-oxy haemoglobin occur, probably as a result of the energy expenditure by the muscle consuming the oxygen. Although leakage is slowed initially, after 30 seconds the rate of leakage rises and there is an increase in detrusor blood volume as bladder volume decreases and wall thickness is restored.

Figure 2 illustrates concentration changes in the net oxidized minus reduced redox states of the intracellular respiratory chain enzyme, cytochrome c oxidase or cytochrome a,a_3 (Cyt). Interpretation of Fig. 2 suggests that the diminished availability of oxygen (see HbO_2 in Fig. 1) secondary to filling leads to an increase in the number of Cyt molecules retaining electrons. At the same stage, proton pumping in conjunction with the electron transfer is likely diminished thereby hindering adenosine triphosphate (ATP) synthesis, and by corollary, depleting energy stores. Oxygen availability and electron transfer are restored when leakage begins to occur after retention capacity is reached and vestibular pressure is reduced thereby permitting recovery of oxygenated blood volume in the resting bladder wall.

Importantly, there are portions of this human data collection (Figs 1 and 2) where NIRS data provides physiologic insight that the traditional urodynamics does not. One example that is noticeable is the 'halt leakage' graph point in Fig. 2 where there is a sharp drop in cyt absorbance detected. This observation could be due to the intensity of muscle work required in the voluntary attempt to halt leakage. Also, there are events detected via change in the cytochrome signal that are not evident in the haemoglobin pattern and vice versa. Hemoglobin resides in the blood, cytochrome resides in mitochondria. Hemoglobin provides a partial glimpse into cellular physiology by indicating whether oxygen has been delivered or depleted. In contrast, changes in the oxidation state of cytochrome c oxidase reflect more intricate physiology, indicating whether there was oxygen uptake, whether cells had switched from oxidative phosphorylation to substrate level phosphorylation, whether glucose stores are depleted, and whether ATP synthesis has become impaired. For this reason, a direct correspondence between changes in hemoglobin and changes in cytochrome is not expected.

Changes in cytochrome differ in quality from those in hemoglobin. Whereas hemoglobin reacts rapidly to changes in its environment so that a change can be quickly offset by some manipulation by a clinician, cytochrome balance is slower to respond, and thus is susceptible to over-correction. As a result, it is possible that if a change in the NIRS haemoglobin signal indicates an event that is having an adverse physiological effect and a corrective change is made that restores normality to the haemoglobin signal, the cytochrome pattern of change may still indicate that, in spite of improvement in the oxygen delivery (haemoglobin), cellular function is still being affected at the mitochondrial level.

In the single subject monitoring reported here, the increased reduction of cytochrome is likely due to voluntary muscle contraction depleting the ATP stores required to maintain effective muscle contraction. As a result of this demand for more ATP, higher rates of proton pumping within the cytochrome complex are required in synchronization with oxygen transit through the cytochrome complex. Thus, while cytochrome responds adequately to this ATP demand initially, cytochrome becomes reduced as HbO_2 becomes depleted when the bladder volume increases and blood volume in the bladder wall decreases. Thus, the oxygen available as filling commences is progressively depleted and cytochrome becomes progressively reduced because there are fewer oxygen molecules to which to transfer its electrons. This is because the HbO_2 available as the bladder filling commences becomes depleted as the bladder filling pressure rises, the volume of blood present in the bladder muscle decreases as the wall thing. Without

restoration of the HbO_2 concentration, a reduction in ATP production occurs with the result physiologically that the subject is no longer able to maintain the voluntary contraction and involuntary urination then follows.

5. Conclusion

Non-invasive NIRS monitoring can provide data from which physiologic aspects of bladder function, including mitochondrial metabolism in the detrusor muscle, can be inferred. This will provide advances in our ability to evaluate bladder function.

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