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ABSTRACT

Recent findings in animal models and human tissue suggest that deficient menstrual endometrial hypoxia results in heavy menstrual bleeding (HMB)[1]. There is no current method available to directly measure endometrial oxygen concentrations during hysteroscopy investigation of the underlying cause of HMB. We propose that an optical fibre-based probe delivered through the working channel of a hysteroscope can accurately assess uterine oxygenation. This probe will be designed to transmit and collect broadband white / NIR (~550 nm – 1050 nm) light using multiple fibre optics co-packaged and modified for side emission / collection of light passing through different depths of tissue. Observed spectral variations reveal haemoglobin oxygen saturation, while the controlled depth measurement allows comparison of the endometrium layer to the deeper myometrium muscular outer layer to observe the expected (or defective) relative hypoxia in the menstrual endometrium. An initial co-packaged fibre probe has been prototyped, optimising diffuse emission and collection of light into surrounding tissue. An initial investigation shows real time spectral changes, observing the variation in haemoglobin oxygenation due to pulse and breathing. Fibre probes were placed onto tissue and the separation of the fibre probes was varied, allowing the spectral properties of different tissue types at varying depths to be observed. Introducing more fibres into the probe offers better resolving of obscured tissue layers, a customised multi-fibre spectroscopy measurement instrument is in development to enable this.

Thus, our probe could provide a clinical diagnostic tool to quantify tissue hypoxia in the endometrium and facilitate personalised diagnosis and management of the common, debilitating symptom of HMB.

Keywords: Heavy menstrual bleeding (HMB), Uterine, Oxygenation, Fibre optic sensors, diffuse reflectance spectroscopy

1. INTRODUCTION

One in four women will experience heavy menstrual bleeding (HMB) at some point in their reproductive lives [2]. This can cause anaemia, that may require blood transfusion, has a significant negative impact on quality of life and results in a huge socio-economic burden [3]. Medical treatments such as hormonal therapies are available, however due to efficacy and side effects, up to 60% of women resort to risky, fertility-ending surgical procedures[3]. There is a clear unmet need for effective monitoring and diagnostic tools that would lead to fertility-preserving, personalised medical treatments for HMB[3].

Recent findings in animal models and human tissue suggest that menstrual endometrial hypoxia occurs transiently at menstruation and drives the repair process necessary to stop menstrual bleeding. Mice and humans with evidence of defective menstrual endometrial hypoxia displayed prolonged and/or HMB[1].

The National Institute of Health Care and Excellence recommend hysteroscopy for patients with HMB with suspected endometrial pathology [4]. However, there are no currently available methods to detect endometrial hypoxia at hysteroscopy. Minimally invasive solutions to aid research into this hypothesis are urgently needed to improve patient care[5]. We propose an optical fibre-based probe delivered through the working channel of a hysteroscope that can accurately assess uterine

oxygenation levels through absorption. To access information about menstrual hypoxia requires comparison of oxygenation level between the endometrium and the deeper myometrium muscular outer layer.

In general, blood oxygen saturation is a tightly controlled physiological parameter and monitoring a person's oxygen saturation through non-invasive pulse oximetry methods is often the first act to access the patient's condition[6]. The most common approach is transmissive pulse oximetry where the sensor is placed usually on the patient's fingertip or ear lobe. As hypoxia occurs locally in the endometrial tissue at menstruation a more local measurement of oxygen is required. The developed fibre-based probe focuses on reflectance pulse oximetry through multiple point side-emitting optical fibres, allowing for future adaptation for the uterine cavity.

There are many different types of processes that occur in light-tissue interactions when a source is incident on a biological sample. There is reflection off the tissue, autofluorescence of the tissue as well as the scattering and absorption of the light by the tissue itself. This work will focus on the absorption in human tissue (hand / finger) and how measurement throughout different depths of the tissue can result in blood oxygen characteristics. By using the Beer-Lambert Law[7], it is possible to calculate the absorbance (A) of a light source that propagates through tissue allowing properties of the tissue to be revealed.

$$A = log_{10}\frac{I_0}{I_t} = -log_{10}T \tag{1}$$

Where I_0 is the initial intensity of the light prior to propagation through tissue, I_t is the intensity after and T is transmission of light. P. Upputuri et. al.,[8] and others detail wavelength dependent variations of the absorption coefficient of light in tissue. For wavelengths in the visible (less than 600 nm), the absorption coefficient is greatly affected by blood, reducing the measurement depth in tissue. By using a broadband light source, it is possible to identify the absorption coefficients of oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (Hb) using the visible part of the spectra. Operating in the NIR-1 band (~700 nm – 1000 nm), light is less affected by blood and is affected more by skin and water content in biological tissues. By developing a fibre bundle that operates with a broadband source, both shorter and longer wavelength absorption can be observed.

2. METHODOLOGY

The fibre-based probe is based around 400 µm core multimode optical fibres (FT400EMT, Thorlabs), which allow the transmission and collection of broadband white/NIR (~550 nm – 1050 nm) down the working channel of an hysteroscope. Side-emission of the broadband light and collection of the back scattered light was achieved by cutting the distal ends of each fibre at 45 degrees to allow total internal reflection to take place. To improve side emission, a silver coating was added to the distal ends to prevent any stray light propagating straight out the end of the fibres.

To characterise their performance, the intensity of the side emitted light was measured by rotating a detector 360 degrees around the bevelled fibre end, which was suspended inside a ping pong / table tennis ball. It was found that without the additional silver coating, the emission angle was not well defined and light propagation straight out of the distal fibre end still occurred. This was presumably due to multimode guidance within the 400 µm fibre. The application of the silver coating increased side emission, producing a tight (~50°) cone of light as well as preventing light propagation straight through the end of the fibre.

The initial prototype fibre-based oxygen sensor consists of two angled fibres positioned as such to allow for diffuse emission and collection of light into tissue, a schematic can be seen in Figure 1. By connecting a broadband white light source (SLS201L, Thorlabs) to the emission fibre, and a spectrometer (QEPro, OceanOptics) to the collection fibre, scattered light through tissue can be captured and measured. In initial prototypes the spacing between fibre tips can be varied.

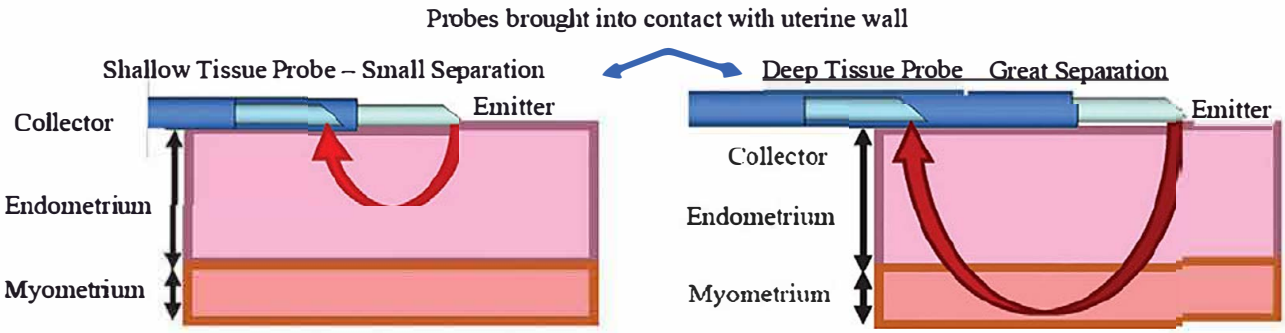

Figure 1 Once deployed down the working channel of an endoscope, both emitter and collector fibres will be brought into contact with the endometrium layer inside the uterus. By varying the separation of the emitter and the collector fibre, the penetration depth can be varied. With a large separation, the broadband light can propagate into the myometrium (muscle layer) of the uterine wall and provide a reference measurement. Shortening the separation, the endometrium layer can be measured and compared to the reference measurement to observe relative hypoxia at that particular site.

By controlling the separation of these fibre probes, the penetration depth of the white light used can be controlled, approximating a distorted semi-circular path through the tissue[9]. This control allows the probes to measure tissue at a lesser or greater depth, such as the myometrium layer and compare it to the endometrium layer, enabling a self-referencing probe.

Initial measurements were made by placing the probes onto the soft tissue of the palm. A separation of 5 mm was used to measure at a shallow penetration depth. Here, light was expected to propagate in the skin layer of the hand. Figure 2(a) (spectrum in black) shows a shallow hump at ~750 nm, as expected from the literature for a measurement of skin [10]. Increasing the distance between the collection fibre and the emission fibre, measurements at 15 mm separation and 25 mm separation were recorded. Data were aligned for all three absorbance curves at 800 nm (a natural crossing point of Hb and HbO_2)[8] and at 970 nm (dominated by water/fat content) to enable a more direct comparison of spectral features. At the larger separation of 25 mm (spectrum shown in blue) the light is expected to propagate deeper into the tissue of the hand, into the muscular layer which is indicated by the larger hump at ~750 nm as expected from the literature for a measurement of muscle [10]. By first collecting a deep tissue measurement in the uterus, by propagating the light into the myometrium layer, a shallow tissue measurement can be acquired at the same spatial position, by propagating light into the endometrium layer, allowing a comparison to be made.

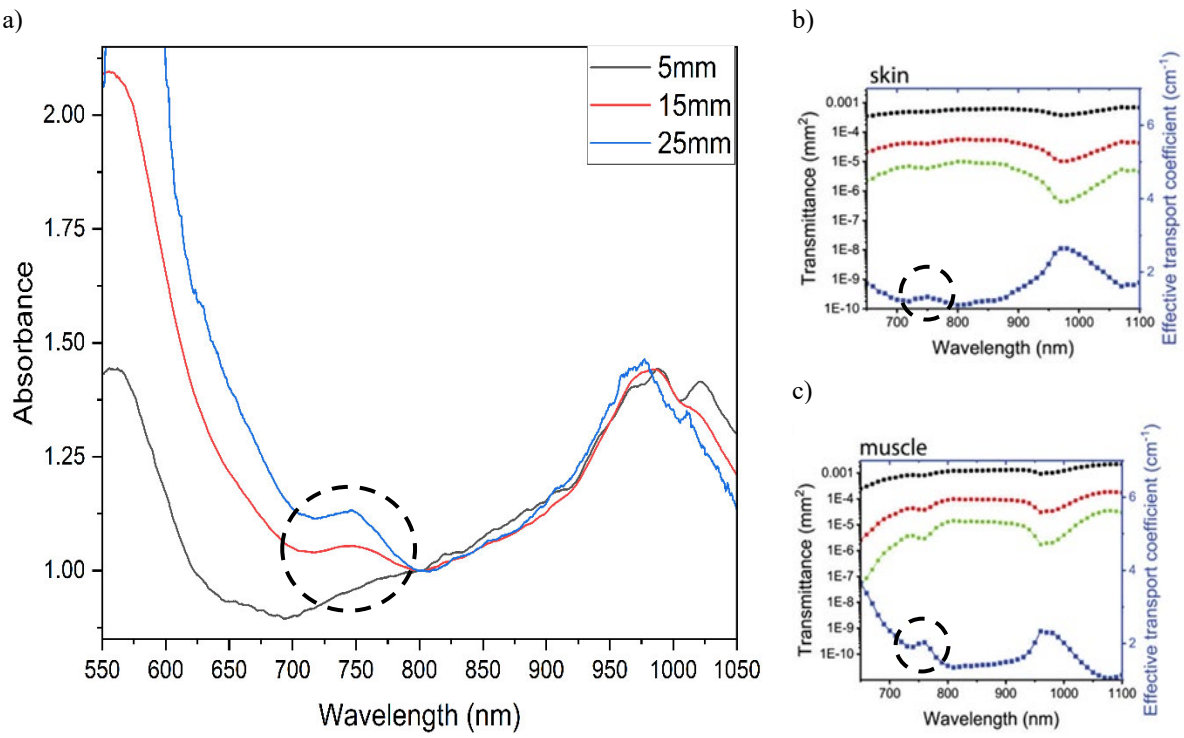

Figure 2 Spectra obtained with the probe taken on the hand (a) compared to spectra from literature (b, c). Figures (b, c) are reproduced from Mosca et al [10] with licence CC BY 4.0. The probes were placed onto the palm of the hand with an initial 5 mm separation. Using the broadband white light source and the QEPro spectrometer, an absorption spectrum from the hand was produced (in black) showing an expected response of skin tissue with a small hump at ~750 nm by comparing (a) with (b). After separating the probes, two more measurements were taken, with 15 mm and 25 mm separation shown in red and blue. As the probe separation is increased, the penetration depth of the light increased into the tissue, resulting in an absorption spectrum with an increased similarity to that expected from the lower muscular layer by comparison to (c) [10]. Data in (a) have been offset and scaled to match at 800 nm and 970 nm to enable comparison of spectral shape.

Maintaining contact with the palm and a 25 mm separation between the emission and collection fibres, the QEPro spectrometer was set to record data for 337 seconds. During the length of this experiment, shown in Figure 3, the spectral response was recorded for the Red and NIR bands of absorbed light. Throughout this experiment there were three phases in which breathing was changed to affect the blood oxygen levels in the body: hyperventilating, a breath hold, and then returning to normal breathing. As a control, denoted by the red line in Figure 3, a commercial pulse digit oximeter was placed on the index finger of the same hand as the probes. By hyperventilating, as seen in Figure 3(a) the blood oxygen levels in the hand were near 100% SpO_2 creating a steady baseline. After hyperventilating for ~120 seconds, a breath hold was conducted for a further ~100 seconds to reduce the blood oxygen levels, seen in Figure 3(b), before returning to normal breathing, Figure 3(c). Our probe qualitatively matched the response from a commercial pulse digit oximeter showing clear changes in blood oxygen levels. Additionally, by operating at a high data acquisition rate, it was possible to detect more subtle changes as well as a quicker response to change.

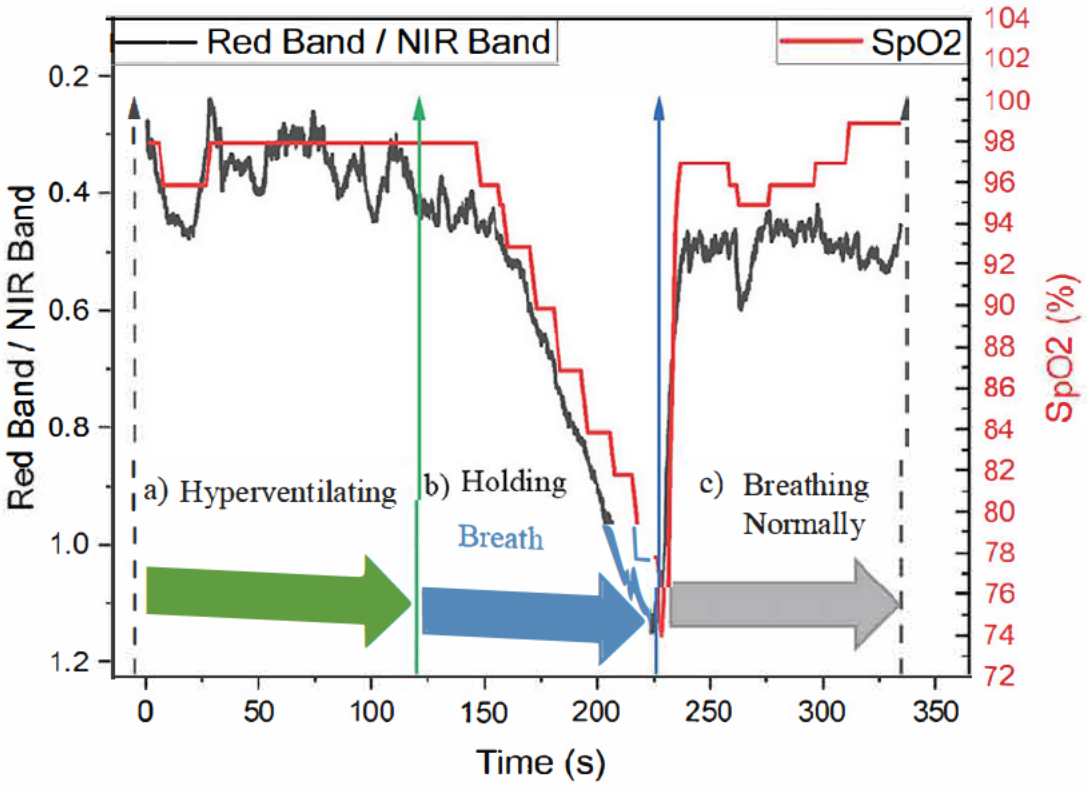

Figure 3 Taking measurements every 100 ms, the QEPro spectrometer was set to record for 337 s. By taking the ratio of the Red band (650 nm – 750 nm) and the NIR band (850 nm – 950 nm) of light collected by the collection fibre from the palm of the hand illuminated by a broadband light source, a blood oxygen response can be monitored (shown in black). Simultaneously a pulse digit oximeter was placed on the middle finger of the same hand to get a comparison (shown in red). (a) hyperventilation was conducted to increase blood oxygen until saturation before a breath hold was instigated at (b). (c) breathing was then returned to normal and blood oxygen levels recovered.

3. SUMMARY

We demonstrate a straightforward fibre-based oxygen probe with a potential for minimal invasive application via the working channel of a hysteroscope to access endometrial menstrual hypoxia in the future.

With the use of only a broadband light source and spectrometer, the fibre probe presented here is able to collect diffuse scattered and reflected light through tissue and reveal physiological parameters such as the oxygenation saturation in different tissue layers utilising spectral variation in their absorption spectrum. Furthermore, we demonstrate that the flexible fibre probe (suitable for deployment down the working arm of a hysteroscope for use in the uterus) is able to monitor and return changes in blood oxygen levels. With the ability to monitor different tissue spectral variations at various depths we aim to reveal haemoglobin oxygen saturation. The controlled depth measurement aims to enable comparison of the endometrium layer to the deeper myometrium muscular outer layer to observe the expected (or defective) relative hypoxia in the endometrium. Thus, our probe aims to diagnose a lack of hypoxia in the endometrium at menstruation during hysteroscopy, enabling research into this condition, potentially aiding the correction of this defect.

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