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Fetal transabdominal pulse oximeter studies using a hypoxic sheep model

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Abstract

Objective. This study investigates the validity of transabdominal pulse oximetry using a sheep fetal hypoxia model with fetal arterial hemoglobin saturation.

Methods. Four pregnant ewes were anaesthetized and cannulated through the brachial artery to measure direct arterial blood saturation, SaO_2. Next, the transabdominal pulse oximeter was used to measure indirect measurement of the arterial saturation of the fetus, SpO_2, from the maternal abdomen. Hypoxia was induced by a balloon placed in the maternal aorta.

Results. There is a linear relationship between SaO_2, arterial blood saturation values of the fetus, and SpO_2, the values measured by the transabdominal pulse oximetry with a slope of 0.75 ($r^2 = 0.76$).

Conclusion. This information can be used to calibrate the transabdominal pulse oximeter as a measurement of fetal arterial saturation. With these results, we can advance the accurate, no-risk, noninvasive transabdominal fetal pulse oximeter for human use. This research may contribute to the more accurate diagnosis of the diseases of the fetus including Hypoxic Ischemic Encephalopathy.

Keywords: *Transabdominal, pulse oximeter, sheep, fetus, hypoxia*

Introduction

Pulse oximetry (arterial oxygen saturation monitoring), developed in the last 20 years, is one of the most reliable sources of information to monitor patients' circulation [1]. It is used in most medical fields including newborn intensive care units [2,3]. In Obstetrics, fetal heart rate (FHR) monitoring, an indirect measure of fetal oxygenation, continues to be the gold standard for antepartum and intrapartum assessment of fetal well-being [4]. Intrapartum fetal oxygen saturation monitoring, a relatively new technique [5–12], provides objective and reliable information regarding fetal arterial oxygen status and has resulted in a 50% reduction in Cesarean section cases when FHR monitoring reveals non-reassuring FHR patterns [13]. Although the transvaginal technique has been available for a number of years, it has not been accepted into care patterns.

Since current intrapartum oxygen saturation monitoring requires a cervical dilation of at least 2 cm and ruptured membranes, and noninvasive transabdominal fetal pulse oximetry can be used without these constraints, it is an ideal tool for evaluating fetal oxygenation during all stages of pregnancy.

The noninvasive transabdominal fetal pulse oximeter we are investigating is based on technology that uses conventional continuous wave near infrared spectroscopy (NIRS) since many human studies have approached deeper brain tissues with these technologies [14,15]. Fetus head models through the transabdominal approach have been tested and have shown the possibility and feasibility of obtaining fetus information from the maternal abdomen [16–19]. For transabdominal fetal pulse oximetry, continuous-wave (CW) near infrared (NIR) technology is ideal since large amounts of photons penetrate the maternal tissue and reach the fetus. The spectrometer uses more light intensity and greater distance between light source and detectors [18,19]. Recently, we successfully showed that transabdominal saturation values in an animal fetus model [20] and in a human fetus, SpO_2 was between 50 and 75% [21].

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In this investigation, our objective is to determine the accuracy of the fetal saturation measurements (SpO_2) using the transabdominal NIRS signal by comparing them with direct fetal arterial saturation during fetal hyperoxia to hypoxia in four ewes. This study will give a wide range of arterial saturations in this model. Comparing the two results will verify the transabdominal fetal arterial saturation measurement. In addition, using the relationships of the transabdominal SpO_2, and direct fetal arterial saturation, SaO_2, we can develop the correct algorithms to establish the accuracy of the transabdominal fetal oximetry. The results showed a promising relationship and can be used to develop more accurate fetal SpO_2 measurements.

Methods

The animal study follows the Institutional Animal Care and Use Committee guidelines promulgated by the National Institute of Health. We used four healthy pregnant ewes with gestational ages between 130 and 150 days. The animals received Halothane anesthesia with 50% N_2O [22], and were catheterized with a regular venous line and with a Fogarty catheter in the aorta, which can be used for occlusion of the uterus artery. The fetus was exposed through a mid-line maternal abdominal incision. Following a hysterotomy, both fetal brachial arteries were cannulated for fetal blood sampling and fetal blood pressure monitoring. Then, the fetus was returned to the uterus and the maternal abdominal incision was closed.

We used a continuous wave NIRS transabdominal oximeter (Optical Device Inc., PA) with a light Emitting Diode (LED) as a light source and a Photomultiplier (PMT, Hamamatsu TO8) as a detector. The LED consisted of 12 multi elements with wavelengths of 730, 805 and 850 nm confined in an 8-mm transistor socket. The lights were pulsed with 84 Hz. The PMT detected three lights with time-share which were amplified through several gain control systems and digitalized through an ADC card (NI, DAQ1200) and saved on a PC.

In order to optimize the placement of the NIR probe on the maternal abdomen, before the surgeon closed the Ewe's abdominal wall, we observed the location of the head and body of the fetus. We observed the location of the fetal head with reference to the maternal abdominal skin location, where the NIR probe was later placed. Next, we palpated the head location again and placed the detector in the middle of the head. The NIR probe has a source (LED) and a detector (optodes) site (Figure 1). The distance between the source and the detector in the NIR probe was adjusted by the signal to noise ratio taken from the transabdominal pulse oximeter measurements. The fetal signal is recognized by the same frequency as the FHR shown in Figure 2.

The protocol of the hypoxia started by taking the baselines with a maternal inspired oxygen level of 50%, which caused a hyperoxic fetal saturation. The measurements of NIR pulse oximeter and the fetal arterial blood sampling were performed several times before the hypoxia. The balloon located in the aortic catheter was inflated to attenuate uterine arterial blood flow and induce fetal hypoxia. The balloon was inflated with small amounts of warm saline to produce graded ischemia in a graded fashion with every 0.05–0.1 ml fluid until the severe ischemia occurred with the fetal blood pressure dropping rapidly. The balloon was deflated and the fetus was allowed to recover. Blood samples were drawn from the fetus during each graded hypoxia stage. We sampled the maternal arterial blood and periodically checked the maternal arterial saturation levels to ensure accuracy for our data analysis. Maternal and fetal arterial blood oxygen saturation from blood samples were measured with an OSM3 Hemoximeter (Radiometer Medical, Copenhagen). In addition, the maternal arterial saturation from the skin of the inguino-abdominal area which reflects lower aortic flow was monitored with a Nonin 8600 pulse oximeter (Nonin Medical Inc., Plymouth, MN).

Data analysis

In the four ewes, we made a hypoxia cycle with an approximate total of 5–6 graded stages with a 10–15 min duration. Five total hypoxic cycles were analyzed including one ewe with two hypoxic cycles. In each stage of a hypoxia cycle, after a few minutes

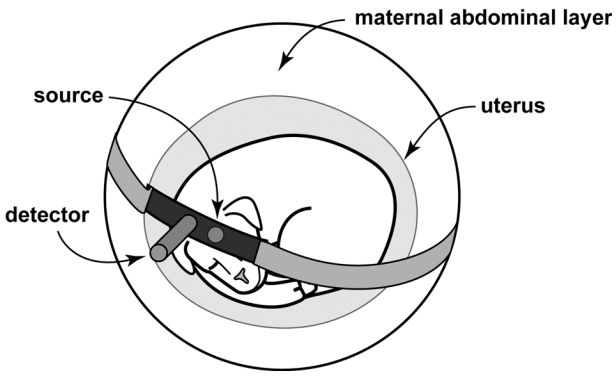

Figure 1. The CWS pulse oxymeter probe (a light source and a detector) is located on the maternal abdomen. The detector was directly above the fetus' body.

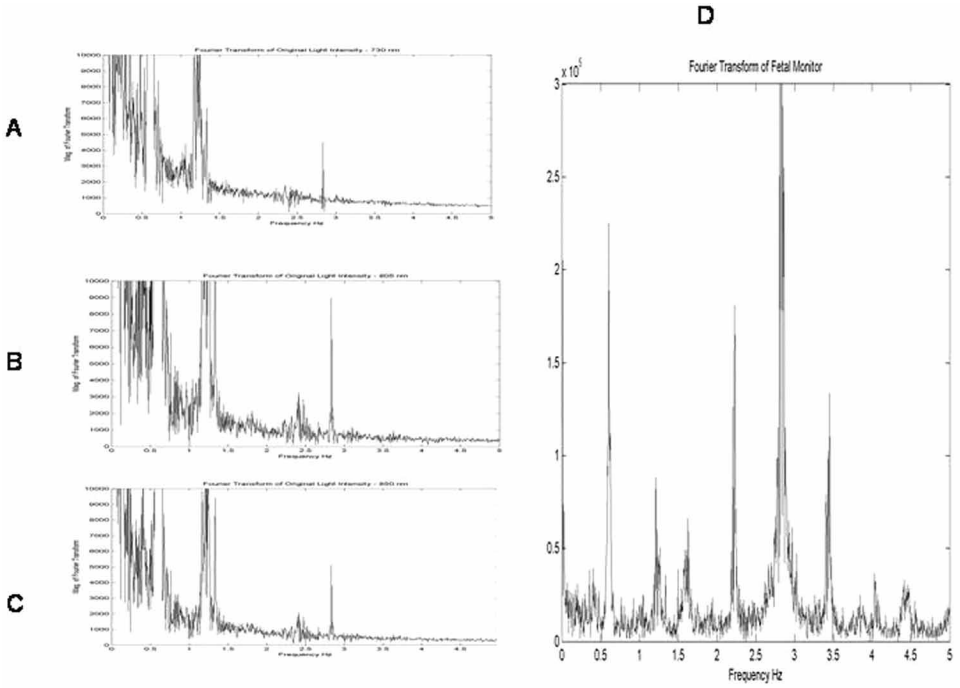

Figure 2. Fourier Transformed spectra of transabdominal NIR signals with three wavelengths (A, 735, B, 805 and C, 850 nm) and fetal heart rate monitor (FHR, D). The NIRS signals show the fetal pulse at the same rate as FHR (2.75 Hz, or 165 /min) and maternal HR 1.2 Hz, or 72/min, with high S/N ratio of more than 10. Detector – LED separation was 8 cm.

of the stage initiation, a few NIR data were acquired, each with 3 min and one or two arterial blood gas samples. The SaO_2 and the SpO_2 from the NIRS in each stage were both averaged and served as a pair for comparison.

With regard to the calculation of SpO_2, raw light intensity data from the NIRS were used to calculate oxy-hemoglobin (HbO_2) and deoxy-hemoglobin (Hb) changes associated with heart beats using a modified Beer-Lambert law [23]. The law states that the injected light from the LED migrates into maternal and fetal tissues where absorption and scattering events mainly occur by the most abundant cholorophors, oxy-Hemoglobin (HbO_2), and deoxy-Hemoglobin (Hb). Then, the migrated light ends up at the detector with the lost amount linearly correlated to the concentration changes of HbO_2 and Hb. The blood volume increases (ΔHb, ΔHbO_2) due to the heart beat are explained as arterial volumes, and presented in Fourier transformed power spectra at the maternal and fetal heart rate frequencies (Figure 2). The saturation by the pulse oximeter is expressed as $SpO_2\ \% = 100\ * \Delta HbO_2/\ (\Delta Hb + \Delta HbO_2)$.

Original HbO_2 and blood volume (BV, or HbO_2 + Hb) data contain the mother and fetus' heart rate and the respiration embedded in the steady background noises. First, in order to capture the SpO_2 of the fetus, the respiration and noise effects are eliminated from the data by two band-pass linear phase finite impulse response (FIR) filters [24]. Secondly, the amount of noise in the filtered fetal SpO_2 was assessed using the maternal NIR signals at the maternal HR frequency after processing the filtered Hb, HbO_2 data. We used the prior knowledge of the maternal SpO_2, measured separately with the Nonin pulse oximeter placed on the maternal inguino-abdominal region, to be the gold standard; true value of the maternal SpO_2 in the NIRS. The difference of the maternal NIRS data from the gold standard was considered to be a background noise. We assume that the same quantity of the noise exists in most of the frequencies; therefore, we are able to subtract this systematic noise from the data at the fetal HR frequency to yield the fetal SpO_2.

The data are displayed as means and standard deviations. The relationship between SpO_2 and SaO_2 are shown by the linear fit curve and the correlation coefficient (r^2).

Results

The typical fetal SpO_2 values from the transabdominal pulse oximeter are shown with the SaO_2 from the fetal arterial blood sample, the maternal skin SpO_2, and the maternal and fetal HR in the time

course of the hypoxia (Figure 3). There is a slight time lag between the arterial sampling time and when the transabdominal SpO_2 was measured. The arterial saturation values from the fetal blood samples (SaO_2) and NIRS oximeter data (SpO_2) are generally in agreement.

During the hypoxia, the fetus responded with high blood pressure and tachycardia. Using the paired information, the relationship between SaO_2 and SpO_2 is plotted as shown in Figure 4. The correlation shows a significant slope of 0.75 with a correlation coefficient (r^2) of 0.76. This relationship demonstrated that the transabdominal SpO_2 under-estimated the higher saturation values, resulting in the slope of 0.75.

When we plot SpO_2 and SaO_2 in hyperoxia and hypoxia, the tendency to under-estimate the SpO_2 in hyperoxia can be clearly seen in Figure 5. The mean difference of saturation between SpO_2 and SaO_2 is about 21% in hyperoxia (78% vs. 57%), however in hypoxia, there was no difference of saturation between them (18% vs. 18% for SpO_2 and SaO_2).

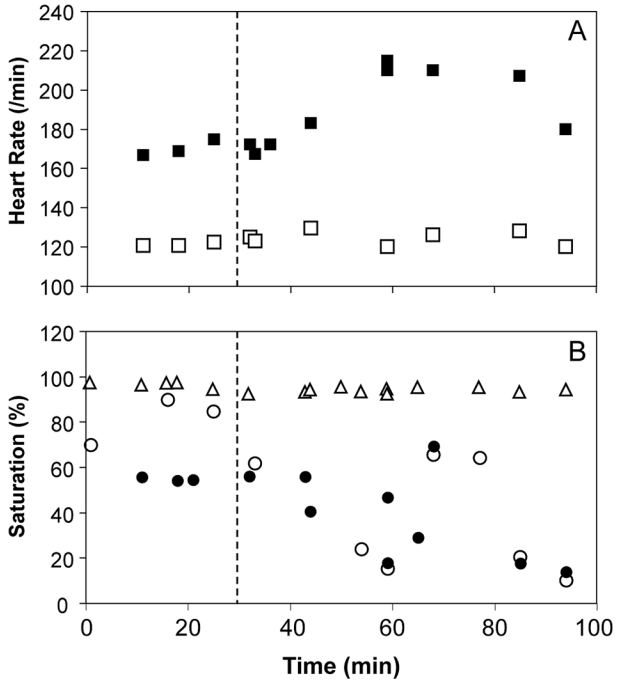

Figure 3. 3-A indicates time course of maternal (opened rectangle) and fetal (closed rectangle) HR and 3-B includes time course of SaO_2 (opened circle) and SpO_2 (closed circle), maternal SpO2 (triangle), obtained during the hypoxic experiment in a sheep. The vertical line indicates a hypoxic cycle started after a 30-min hyperoxic baseline.

Discussion

In this investigation, we compared the SpO_2 from the newly developed transabdominal fetal pulse oximeter with the SaO_2 from the fetal arterial blood samples in a sheep model. The results showed that the transabdominal SpO_2 correlated with SaO_2 linearly through the range of hyperoxia to hypoxia, with a slope of 0.75.

The SpO_2 was under-estimated with higher SaO_2, especially when the ewes were given higher FiO_2 than normal. The SpO_2 was not responding to the hyperoxia with FiO_2 50%, and it remained around 60%, while the fetal SaO_2 was observed higher than normal (up to 89%, mean 78% $\pm$ 7.4). Previous studies showed no significant compensatory mechanisms in maternal uterine blood flow against acute variations in oxygenation in sheep models [25,26] (maternal arterial PO_2, from 40 to 300 mmHg), and no significant changes in the umbilical or uterine blood flows or oxygen uptake in primate fetuses with maternal hyperoxia to 257 mmHg [27]. These non-compensatory mechanisms of the maternal uterus imply that O_2 concentration in maternal arterial blood indicates O_2 delivery to the uterus. The PO_2 in the fetal

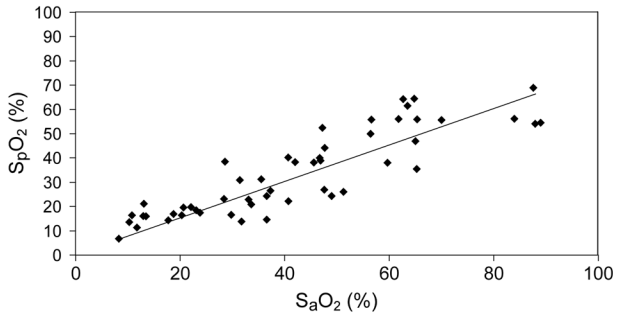

Figure 4. The relationship between fetal SaO_2 from the blood sample and fetal transabdominal pulse oximeter SpO_2 is shown in the four sheep. Line indicates a linear fit with a slope of 0.75 (r^2 = 0.76).

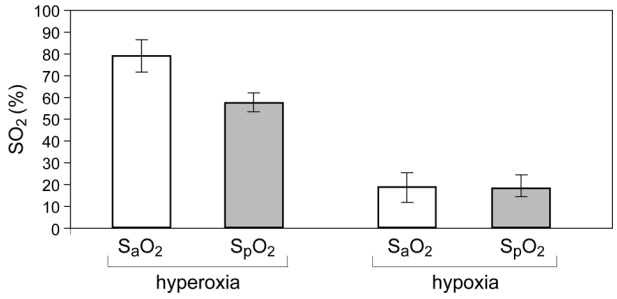

Figure 5. Comparison of fetal saturation values, SaO_2 (white) and SpO_2 (gray) during hyperoxia and hypoxia. Error bars present standard deviations.

umbilical vein increased significantly [27], therefore we expected to observe higher arterial saturation values when maternal FiO_2 is as high as 50%. Maternal hyperoxia (FiO_2 100%) resulted in higher brain tissue PO_2 (from 12 to 24 mmHg) in the fetal cortex [28], and higher carotid arterial PO_2 from 29 torr (75% SaO_2) to 34 torr (83% SaO_2) [29]. However Guilbeau noted there was quite large variability among subjects [28], and we have observed such variability among subjects as well as over time within subjects (standard deviation of baseline SaO_2 averaged 7.58% for within subjects).

However, this unknown mechanism of variability during hyperoxia cannot fully explain the discrepancy between SaO_2 and lower SpO_2. The lower SpO_2 was not due to a contamination of maternal information because, if there was a contamination of a signal in the SpO_2 from maternal arterial blood, then the SpO_2 signal would have been greater than fetal SaO_2, since maternal SaO_2 was near 100% at that time. On the other hand, if the NIRS measured blood signals including the lower body, then the SpO_2 may have shown a lower saturation [30], while the fetal arterial saturation reflected more saturated blood, supplied to the upper body. Although we placed the NIRS detector under the fetal head, which we viewed before placement, 8 cm distance to the light source allows the measurement to include some of the non-brain tissues.

The fetal hypoxic effect with restricting maternal uterine blood flow has been studied previously [31]. The fetal hypoxia increased amount of cerebral blood flow by 24% [32] to 50% [33], depending on the severity of the hypoxia and gestations [34]. In our sheep model, we also have seen increases in blood pressure and heart rates. The compensatory increases in the blood pressures were seen previously [32,33,35]. Together with reduction of vascular resistance [36], BP increases CBF, but these studies showed the initial increases followed by the decreases in the HR in the hypoxic hypoxia, different from our results, showing higher HR. This mechanism of lowering HR was considered to be due to chemoreceptor vagal reflex and hypoxic myocardial depression [31].

With regard to the cerebral arterial saturation in the hypoxia in the carotid artery, the PO_2 and SaO_2 decreased from 28 torr (73% SaO_2) at air breathing to 21 torr (51% SaO_2) at 15% FiO_2, and to 11 torr (16% SaO_2) at 10% breathing [29]. These results are analogous to our findings.

The CW NIR technology has been used to make the existing finger oximeter as well as the transabdominal pulse oximeter. The difference between the existing adult pulse oximeter technology and the fetal oximeter is that the adult devices only measure surface tissue with the light only penetrating less than 1 cm [37,38] with their probe alignment. In this case, transmittance measurement is available at the fingertips and with an ear probe at wavelengths of 660–690 and 880–900 nm range. On the other hand, the fetal transvaginal pulse oximetry probe uses fetal cheek tissue necessitating a deeper tissue penetration. Therefore, the wavelength is changed from 660 nm to the 720–750 nm range since the 600 nm range absorbs too much hemoglobin and does not penetrate enough light [39]. Likewise, using similar ranges of wavelengths, a previous study obtained the fetal signal from the maternal surface with sufficient accuracy [20,21].

The noninvasive transabdominal fetal pulse oximeter that is used in this study has three wavelength LEDs (735, 805 and 850 nm) as light sources and a photomultiplier tube as a detector. The separation between these optodes is from 6 to 12 cm, two to three times the distance between fetal head and the maternal abdominal skin surface. Therefore, we could successfully measure the fetus signal as hemoglobin saturation. The instrument has multiple processes to reduce noise with differential amplifiers incorporating dark current subtraction, analog high and low pass filters, and sample-and-hold system. These processes enable us to detect a signal as low as 125 dB. The LEDs can yield 5–50 mW/cm^2. We successfully used this CWS technology to yield a signal to noise ratio as high as 10 in the fetal signal from the maternal abdomen, typically shown in Figure 2.

These results provide data on the healthy physiological SpO_2, which can be used to diagnose abnormality of oxygenation, i.e., hypoxic-ischemic encephalopathy (HIE). Diagnosis and treatment may be improved by the use of the transabdominal fetal pulse oximeter, a SpO_2 monitor during gestation, since it will lead to earlier intervention in disease prevention and treatment. Furthermore, it will reduce health care costs by reducing diseases associated with HIE, cerebral palsy and epilepsy. In addition, the number of unnecessary Cesarean sections (resulting in false positives) will be reduced since the transabdominal fetal pulse oximeter will provide more accurate information on fetal health status.

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