

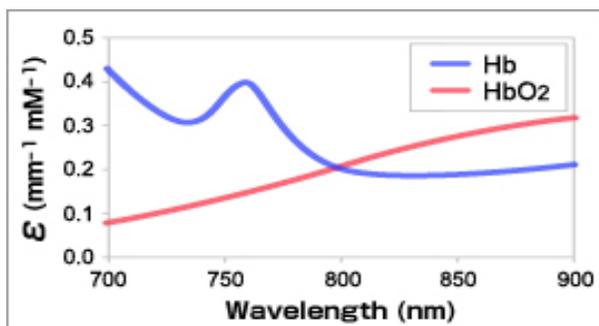
# Placenta Imaging with the Vevo LAZR Photoacoustic Imaging System



## Introduction:

An important research focus in the field of obstetrics and gynecology is on the placenta. The placenta is the main organ that mediates transfer of nutrients from the mother to the fetus and waste from the fetus to the mother. Suboptimal placental development has been linked to maternal and fetal conditions such as preeclampsia and intrauterine growth restriction<sup>1</sup>. Therefore imaging the placenta and assessing placental function is essential in detection of suboptimal placental development.

Photoacoustics is an imaging modality which combines the sensitivity of optical imaging with the low acoustic scattering and resolution of micro-ultrasound. Photoacoustic imaging takes advantage of the “photoacoustic” effect, which states that when an object is illuminated by pulsed electromagnetic radiation, acoustic waves are generated, and subsequently are detected by the ultrasound transducer. Recent advancement in photoacoustic imaging led to the development of the Vevo<sup>®</sup> LAZR platform, which integrates both the photoacoustics and micro-ultrasound components. The photoacoustic component is led by a tunable laser that outputs near-infrared light at wavelength from 680 to 970 nm. The ultrasound component is equipped with ultra high-resolution linear array transducers.



**Fig 1** - Absorption spectra for oxygenated (HbO<sub>2</sub>) and deoxygenated (Hb) blood. The wavelength in nanometers is on the x-axis and the absorbance coefficient is on the y-axis.

Two major advantages of photoacoustic imaging are the abilities to assess oxygen saturation and to detect and quantify nano-sized contrast agents. Oxygen saturation in tissue is assessed based on the differential absorption characteristics of

oxygenated vs. deoxygenated hemoglobin in blood (Figure 1). The Oxy-Hemo Mode on the Vevo LAZR system utilized laser wavelength of 750 and 850 nm to estimate oxygen saturation. At 850 nm, there is a preferential absorption in oxygenated hemoglobin, whereas at 750 nm, there is high absorption in all hemoglobin. Based on data obtained in these two wavelengths, a mathematical model is applied to quantify oxygen saturation in blood<sup>2</sup>. Photoacoustic imaging can also detect nano-sized contrast agents due to the high sensitivity of optical imaging. Nanoparticles are unique due to the fact that they are not limited to the intravascular space. They can cross vessel walls and enter the extracellular as well as intracellular space. This phenomenon can be exploited in countless ways<sup>3</sup>, such as increasing tumor drug efficacy, intracellular targeting of molecular markers, and enhanced molecular target detection in tissue.

In this study, we investigate photoacoustic imaging in the placenta. More specifically, we assess oxygen saturation in the placenta as well as determine whether gold nanorods can cross the fetomaternal placental barrier.

## Materials and Methods:

### Animal Model and Preparation

Pregnant CD1 mice (day 15.5-17.5 gestation) were used for all imaging. The animal was anaesthetized using isoflurane (1.5-2.0%) and secured to a heated animal handling platform which allows for monitoring of the ECG, respiration and temperature of the animal. The fur was removed from the abdominal area using a depilatory cream. Ultrasound gel was used to provide a coupling interface between the ultrasound probe and the animal. Placentae were imaged transabdominally through the maternal skin and with a small surgical incision to expose uterine horn.

### Photoacoustic Imaging

The Vevo LAZR photoacoustic imaging system equipped with a LZ250 probe (VisualSonics Inc, Toronto, Canada) was used to acquire all images.



The ultrasound components of the LZ250 operates at a center frequency of 21 MHz and the optical component transmit tuneable laser wavelengths from 680-970nm with energy output of approximately 18 mJ/cm<sup>2</sup>. Oxy-Hemo Mode was used to quantify oxygen saturation during 100% and 5% oxygen inhalation and single wavelength mode tuned to 808 nm for was used for gold nanorods imaging.

**Nanoparticle Imaging**

Gold nanorods (Nanopartz, California, USA) were used to assess whether they can cross the feto-maternal placental barrier. These have axial and long diameter of 25 nm and 103 nm respectively (aspect ratio of 4.1) and has a peak absorption wavelength of 808 nm. 150 µL of the gold nanorod solution (concentration 3.146x10<sup>13</sup> nanoparticles/mL) was injected into the maternal circulation through the tail vein and the maternal kidney and fetal heart were imaged to detect presence of gold nanorods.

**Results**

**Oxygen Saturation**

Changes in oxygen saturations were monitored in the placenta, as well as the maternal kidney and fetus during 100%, followed by 90 seconds of 5%, and a return back to 100% oxygen inhalation. When 5% oxygen was introduced, all tissues (kidney, placenta and embryo) showed a marked decrease in oxygen saturation. When 100% was

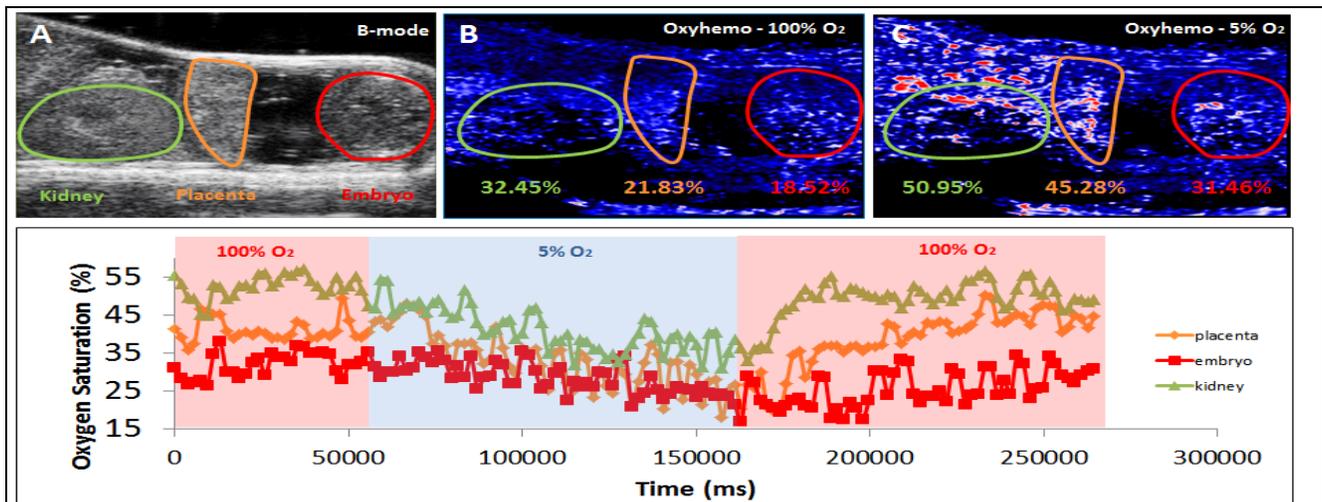
reintroduced, oxygenation in all tissue returned to initial levels (Figure 2 & Table 1).

**Table 1.** Oxygen saturation values (arbitrary units) during 100% and 5% oxygen inhalation.

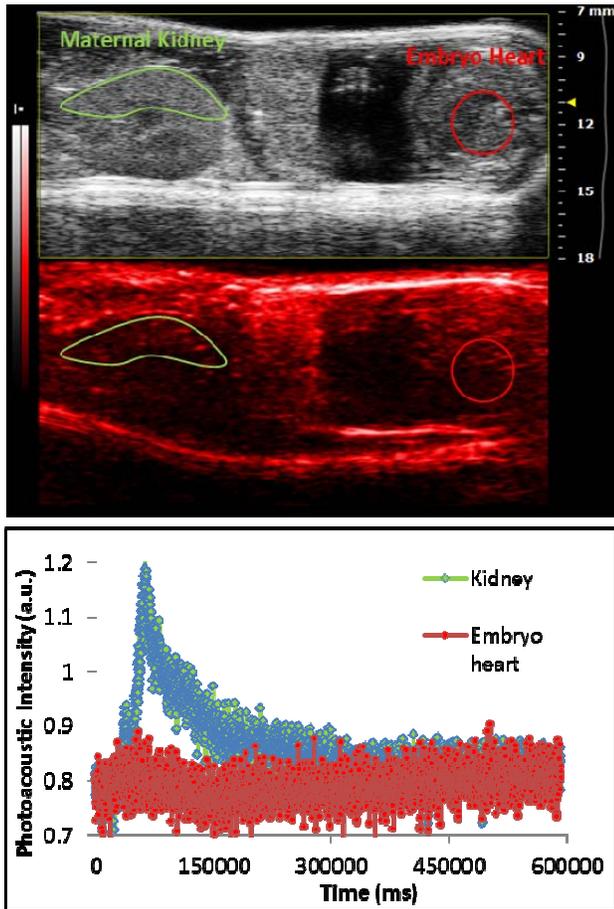
	Placenta	Embryo	Kidney
100% Oxygen	41.21	31.93	52.74
5% Oxygen	27.70	24.46	38.04
100% Oxygen (recovery)	44.21	27.64	51.15

**Nanoparticles Imaging**

Gold nanorods were injected into the maternal circulation to observe whether they can cross the feto-maternal placental barrier. Photoacoustic intensities in the maternal kidney and fetal heart were assessed to quantify relative levels of gold nanorods in the maternal and fetal circulation respectively. Following the gold nanorod injection, there was a sharp rise in intensity in the kidney, followed an initial rapid decline, and a latter gradual decrease over time (Figure 3). During the period of gradual decrease in the kidney, there is a gradual increase over time in the fetal heart. This suggests gold nanorods do cross the placental barrier. 10 minutes following the nanorods injection, the intensities in the kidney and embryo heart had reached similar levels, suggesting the maternal and fetal gold nanorods had reach near equilibrium.



**Figure 2.** Oxygen saturation in the placenta, maternal kidney and embryo during a) 100%, b) 5%, and c) 100% oxygen recovery.



**Figure 3.** Photoacoustic intensities of the maternal kidney and embryonic heart during a bolus injection of gold nanorods into the maternal circulation.

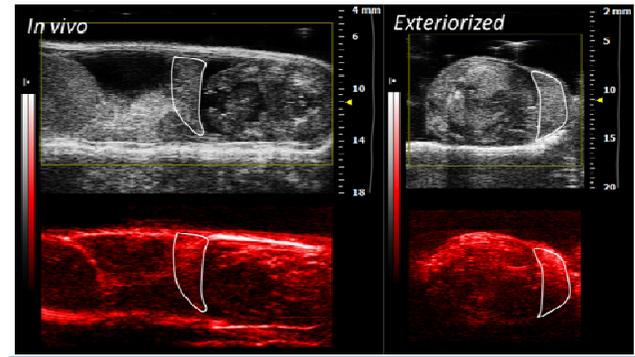
***In Vivo vs. Exteriorized Imaging***

Imaging was also done with the uterus exteriorized to examine the extent of photoacoustic attenuation caused by the maternal skin (Figure 4). There appear to be no drastic improvement in terms of depth of penetration and photoacoustic intensity in the *in vivo* relative to the exposed placenta images.

**Conclusions:**

These findings indicate that photoacoustic imaging was able to detect changes in oxygenation when the inhaled gas was varied from 100% to 5% and vice versa. Detecting changes in oxygen saturation levels can be instrumental in obstetric and

gynecological research. Changes in placental oxygen saturation has been linked to maternal and fetal conditions. For example, maternal conditions such as placental abnormalities (infarction, deformed placenta, lobed placenta), severe preeclampsia and chorangiosis have higher placental oxygen saturations, while fetal conditions such as umbilical cord abnormalities (e.g. velamentous cord insertion and hypercoiled cord) have lower placental oxygen saturations<sup>4,5</sup>.



**Figure 4.** Left- *in vivo* Right- exteriorized placenta

When gold nanorods were injected into the maternal circulation, gradual increase in photoacoustic intensity in the embryo was observed, suggesting gold nanorods to cross the placental barrier. This is consistent with previous findings that suggest nanoparticles less than 200 nm can cross the placental barrier<sup>6</sup>. This provides potential means to deliver agents such as drug or gene therapeutic compounds which can be carried by nanocarriers and delivered into the fetus through the maternal circulation.

We have also shown that the maternal skin did not significantly attenuate photoacoustic signal in the placenta. Due to the limited depth of penetration in photoacoustic imaging, the most effective approach in obtaining good signal in the placenta is to position the placenta as superficial as possible.

This study has demonstrated that photoacoustic imaging is a practical tool for placental research. Assessing oxygen saturation and exploiting use of nanoparticles will undoubtedly provide a substantial boost to obstetrics and gynecology research.



## References:

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- <sup>2</sup> Li, C., Wang, L.V. Photoacoustic tomography and sensing in biomedicine. *Physics in Medicine and Biology*. 2009; **54**(19); R59-97.
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## Recommended VisualSonics Protocols:

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VisualSonics Vevo LAZR Imaging System, Operators Manual

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