Interventional photoacoustic imaging of the human placenta with ultrasonic tracking for minimally invasive fetal surgeries

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Abstract. Image guidance plays a central role in minimally invasive fetal surgery, such as photocoagulation of inter-twin placental anastomosing vessels to treat twin-to-twin transfusion syndrome (TTTS). Fetoscopic guidance provides insufficient sensitivity for imaging the vasculature that lies beneath the fetal placental surface due to strong light scattering in biological tissues. Incomplete photocoagulation of anastamoses is associated with postoperative complications and higher perinatal mortality. In this study, we investigated the use of multi-spectral photoacoustic (PA) imaging for better visualization of the placental vasculature. Excitation light was delivered with an optical fiber with dimensions that are compatible with the working channel of a fetoscope. Imaging was performed on an *ex vivo* normal term human placenta collected at Caesarean section birth. The photoacoustically-generated ultrasound signals were received by an external clinical linear array ultrasound imaging probe. A vein under illumination on the fetal placenta surface was visualized with PA, and good correspondence was obtained between the measured PA spectrum and the optical absorption spectrum of deoxygenated blood. The delivery fiber had an attached fiber optic ultrasound sensor positioned directly adjacent to it, so that its spatial position could be tracked by receiving transmissions from the ultrasound imaging probe. This study provides strong indications that PA imaging in combination with ultrasonic tracking could be useful for detecting the human placental vasculature during minimally invasive fetal surgery.

1 Introduction

Image guidance is a central component of minimally invasive fetal surgery for treatment of twin-to-twin transfusion syndrome (TTTS). The gold standard for

treatment involves laser photocoagulation of anastamosing vessels on the fetal side of the placenta [1]. In current practice, anastomosing vessels are identified with vessels along the equator using a fetoscope. Due to the limitations of this modality, there is a risk that sub-surface vessels that are small and those that are at the periphery of the placenta are missed, so that treatment is incomplete. Ultrasound (US) imaging with a probe positioned at the external surface of the mother provides inadequate visualization for small placental vessels. Visualization with US can be particularly poor when the placenta is on the posterior of the uterus, at a large distance from the imaging probe so that low US frequencies are required. Power Doppler (PD) was also proposed by several groups to visualize the placenta vasculature [2, 3]. One challenge with PD is that successful vessel identification is strongly dependent on the skill of the operator and the vessel orientation; additionally, this technique lacks sensitivity for small vessels due to low US contrast for soft tissues.

Photoacoustic (PA) imaging has strong potential to provide guidance information during TTTS that is complementary to fetoscopy and external US imaging. With PA imaging, pulsed or temporally modulated excitation light is absorbed in tissue, which causes temperature rises and subsequent generation of US waves [4]. These US waves can be received with an imaging probe at the surface of a patient and reconstructed to form 2D or 3D images with contrast for tissue chromophores. Multispectral PA images, which are acquired by varying the wavelength of excitation light, can be used to provide quantitative information about chromophore concentrations [5].

Conventional implementations of PA imaging, in which excitation light is delivered at the surface of the patient, may be suboptimal in the context of TTTS. As placental vessels typically lie more than five centimeters below the surface, the PA signals may be very low or undetectable due to the prominence of scattering and absorption of excitation light [6]. In this study, light is delivered directly to the placental surface using an optical fiber that is sufficiently small to be inserted into the instrument channel of a fetoscope. The generated PA signals were detected by a commercial linear array US imaging probe.

The PA imaging system in this study was extended to allow for real-time in-plane ultrasonic tracking of the optical fiber that delivers excitation light. Ultrasonic tracking was implemented with a fiber-optic hydrophone that was positioned alongside the delivery fiber. Multispectral PA imaging and ultrasonic tracking were performed on a human placenta *ex vivo*, and the measured photoacoustic spectrum from a vein was compared with the optical spectra of oxy- and deoxy-hemoglobin.

2 Materials and methods

2.1 PA imaging and ultrasonic tracking system

The system that was used for PA imaging and tracking was based on a clinical ultrasound imaging system with a 128-element, 10 MHz linear-array ultrasound

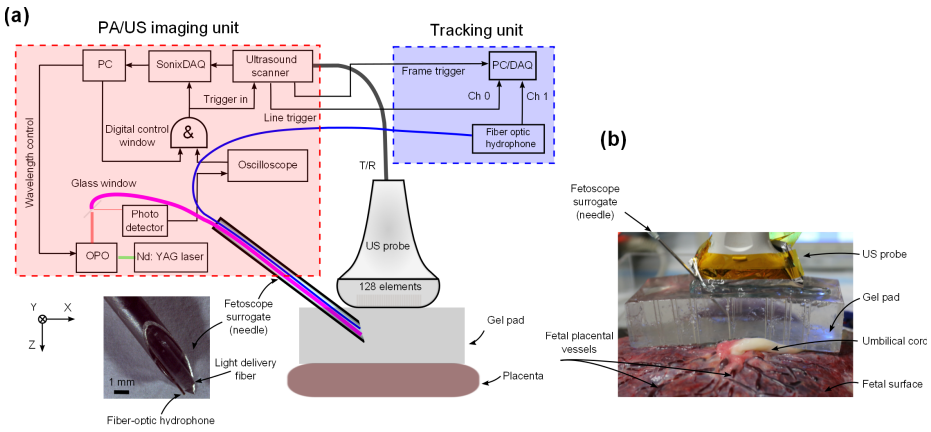

Fig. 1. (a) Schematic illustration of the photoacoustic imaging and ultrasonic tracking system. (b) Photograph of the fetal surface of a human placenta under the imaging probe.

probe (SonixMDP, Analogic Ultrasound, Richmond, BC, Canada) as shown in Figure 1a. It was operated in research mode which provides the access to low-level libraries for acquisition of B-mode images, transmission of ultrasound pulses for tracking and collection of pre-beamformed RF data through a 128 channel DAQ system (SonixDAQ, Analogic Ultrasound, Richmond, BC, Canada) for PA imaging.

PA imaging Pulsed light with multiple wavelengths was provided by an optical parametric oscillator (OPO) system (VersaScan L-532, GWU-Lasertechnik, Erftstadt, Germany) pumped by a Nd:YAG laser (pulse width 6 ns, repetition rate 10 Hz, Quanta-Ray, INDI-40-10, Spectra-Physics, Santa Clara, CA). The signal and the idler from the OPO provided two wavelength ranges: 700-900 nm and 1100-2200 nm respectively. In this study only the signal ouput was used (Figure 1a). The OPO output was coupled into an optical fiber with a 910 μm core diameter (FG910LEC, Thorlabs, Newton, NJ). A small portion of this output (4%) was deflected to a photodetector (DET10A, Thorlabs, Newton, NJ) to compensate for pulse-to-pulse energy fluctuations and to provide optical triggering. A maximum pulse energy of 6 mJ was used in this study was delivered from the distal end of the fiber (flat-cleaved at normal incidence). Control of PA image acquisition was realized using a logic AND gate with two inputs: the optical trigger and a digital control window provided by a LabView control program via a digital I/O card (NI-USB-6501, National Instruments, Berkshire, UK). PA image reconstruction was performed in real-time using a custom delay-and-sum beam-forming algorithm; offline, a more accurate Fourier-domain reconstruction algorithm [7].

Ultrasonic tracking A fiber-optic hydrophone (125 μm cladding, Precision Acoustics, Dorchester, UK) [8] was used to receive US transmissions from the linear array probe (Figure 1a). Each element of the linear array was excited by a bipolar electrical pulse (Figure 2a). The fiber-optic hydrophone (FOH) data collection were synchronized with the US tracking transmissions using two output triggers: a frame trigger corresponding to the start of each image frame, and a line trigger corresponding to the start of each transmission. Using the frame trigger, the line trigger signal and the FOH data was digitized using a DAQ card (USB-5132, National Instrument, Austin, Texas) as illustrated in Figure 1a. The line triggers were used to parse the FOH data according to the start of each US tracking transmission. With knowledge of the sound speed in the medium, the time-of-flights of the ultrasound pulses determine the distance between the hydrophone tip and the centers of the transmitting elements (Figure 2a). The peaks of the time-gated signals form a parabolic shape (Figure 2b). A received transmission from transducer element number 30 is shown in Figure 2c. An image of the hydrophone tip was reconstructed by applying a Fourier-domain reconstruction algorithm which was developed initially for PA imaging [7] (Figure 2d). An important advantage of the ultrasonic tracking is that the conventional B-mode ultrasound image, photoacoustic image and the tracking image are inherently co-registered.

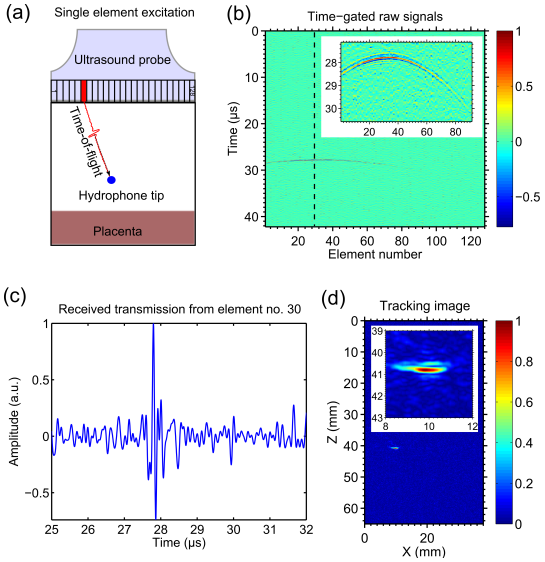

Fig. 2. (a) Schematic illustration of the single-element excitation of the linear array imaging probe. (b) Time-gated 128 transmissions received by the hydrophone. (c) The received transmission from transducer element number 30. (d) The reconstructed tracking image.

The fiber-optic hydrophone and the excitation light delivery fiber were inserted into the cannula of a 14 gauge spinal needle (Terumo, Surrey, UK), which served as a surrogate for the fetoscope. The distal ends of the fibers were flush with the bevel surface of the needle (Figure 1a).

2.2 Imaging and tracking with a human placenta

A term human placenta was collected after a caesarean section delivery at the University College London Hospital (UCLH). The study was approved by a Joint Committees of UCL and UCLH on the Ethics of Human Research and the placenta was collected after written informed consent from the mother. Following delivery, the umbilical cord was clamped immediately to preserve the maximum amount of blood inside the placental fetal vasculature.

PA imaging of the placenta was performed with a block of gel positioned between the US probe and the fetal surface of the placenta. This gel, which was optically and acoustically transparent, served to simulate the amniotic fluid within the gestation sac (Figure 1b). During PA imaging, it was chosen in place of saline or similar aqueous solutions to limit diffusion of blood out of the placenta. With ultrasonic tracking, gel was not used as its acoustic coupling with the hydrophone was poor; the placenta was immersed in a saline and the fetoscope surrogate was inserted to the placenta surface at an angle of 62 degrees (measured relative to the US probe surface).

3 Results and discussion

With PA imaging, a portion of the placental surface that was illuminated with excitation light was visualized (Figure 3a-c). A circular region with high signal amplitudes, which corresponded to a major vein on the placental surface, featured prominently in the PA images. A decrease in the average PA signal amplitude across the wavelength range of 760 nm to 840 nm (Figure 3d) was also apparent in the images (Figure 3a-c). Across the wavelength range of 750 to 900 nm, good correspondence between the average PA signal and the optical absorption spectrum of deoxygenated blood was observed (Figure 4d). Absorbing structures at a depth in tissue of approximately 5 mm were apparent, which were attributed to small blood vessels. The appearance of the fetoscope surrogate (needle), which is consistent with previous studies [9, 10], can be attributed to photoacoustic excitation from back-scattered excitation light. The PA signal from the fiber could be used to provide an indication of the fiber location relative to B-mode ultrasound images; however, severe artifacts resulting from ultrasound reflections within the fetoscope surrogate are likely to limit the accuracy of this method.

With ultrasonic tracking, the hydrophone tip was clearly visualized (Figure 4). At two depths (25 mm and 41 mm), the ultrasound (Figure 4a,d) and tracking (Figure 4b,e) images of the tip of the fetoscope surrogate had excellent spatial agreement. High SNRs were achieved for the tracking images (490

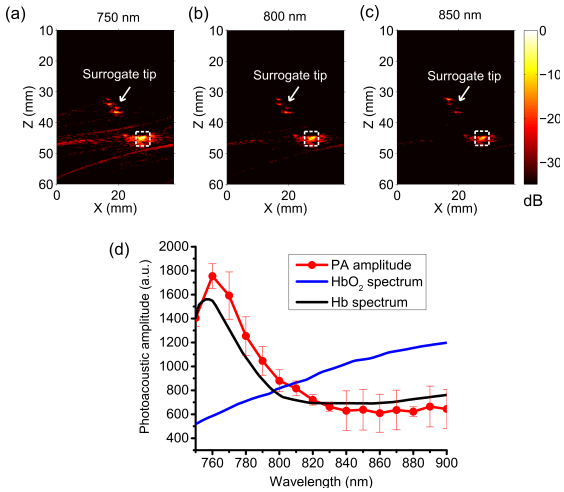

Fig. 3. Photoacoustic images of the placenta at wavelengths of (a) 750 nm, (b) 800 nm and (c) 850 nm. The averaged photoacoustic amplitude over the region of interest (white box) as a function of excitation light wavelengths are shown in (d), with the optical absorption spectrum of oxygenated and deoxygenated blood provided for comparison.

and 480, respectively). The full width at half maximum values of the axial and lateral profiles, which can be taken as measures of the tracking accuracy, were consistently in a sub-millimeter level (Figure 4c,f).

In the context of minimally invasive fetal surgery, there are several potential benefits of ultrasonic tracking. First, knowledge of the position of the fiber that delivers excitation light relative to the ultrasound imaging probe could be used to model the light and ultrasound propagation, and further to facilitate the accurate recovery of optical absorption spectra of chromophores. Ultrasonic tracking of the fetoscope tip, which would be possible if the hydrophone were integrated directly to the fetoscope, could facilitate fusion of fetoscopic and ultrasound images, as well as mosaicking of fetoscopic images. Further the orientation of the fetoscope relative to the ultrasound probe could be tracked using multiple hydrophone sensors distributed along it.

In the context of medical device tracking, an optical hydrophone as an US sensor has several advantages relative to a conventional piezoelectric US transducer [8, 11]. First, it is narrow and flexible, which facilitates integration into devices. Second, it provides sufficient sensitivity for tracking as demonstrated with a high SNR shown in Figure 4. Finally, it possesses nearly omnidirectional sensitivity below 25 MHz, which allows the tracking with steep insertion angles.

The experimental paradigm in this study has several limitations. First, while the gel block phantom was designed to represent typical experiences encountered in clinical practice, it did not allow for very large distances between the US imaging probe and the placenta such as those that may be encountered with obese patients. Second, it would have been useful to have co-registration with other

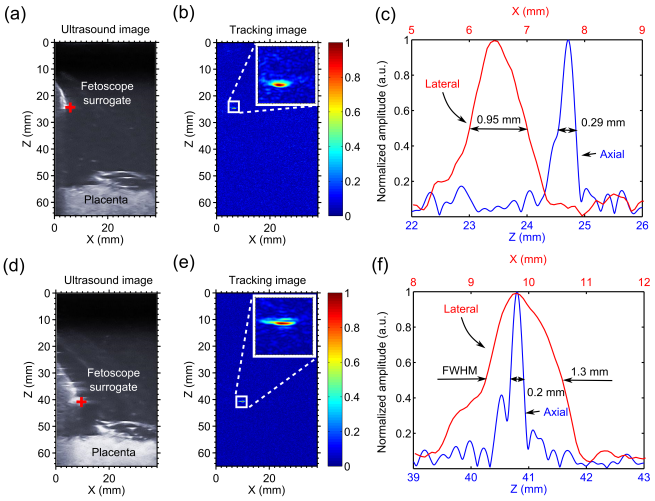

Fig. 4. The hydrophone tip tracked at two locations within the ultrasound image plane. Two ultrasound images are shown in (a) and (d) with corresponding tracking images shown in (b) (e) respectively. The axial and lateral profiles for the hydrophone tip image at two locations are shown in (c) and (f) with the full width at half maximum values indicating the accuracy of the tracking method.

modalities such as MRI and CT, but the accuracy would be limited by placental deformations. Third, follow-on studies are required to thoroughly compare the tracking method used in this paper with others. An alternative tracking method to consider is the use of an ultrasound reflector on the fetoscope.

Interventional photoacoustic imaging has attracted great attention in recent years [10, 12–15]. However, to the authors knowledge, this proof-of-concept study is the first to provide multispectral photoacoustic imaging of the human placenta, and also the first to provide ultrasonic tracking in a fetoscopic context. It sets the stage for comprehensive PA imaging across the surface of the placenta in both normal and pathological cases in concert with histology. In future studies, perfusion models that incorporate mechanisms for modifying the blood oxygenation could be used to assess the sensitivity of PA images to blood flow [16], and oxygen saturation [5]. Further multispectral PA imaging could be used to discriminate coagulated and non-coagulated blood during TTTS, based on their absorption spectra [17]. Photoacoustic imaging has strong potential to improve visualization of placental vasculature during minimally invasive treatment of TTTS, and thereby to improve procedural outcomes.

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