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Placental Pulsatility: A quantitative assessment of placental bed vasculature by 2D Doppler cine imaging

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Abstract

Objectives—Vascular resistance is known to be one of the determinants of pulsatile flow. This study aims to investigate whether quantitative 2D Doppler ultrasound can capture and evaluate the pulsatility within the placental bed vasculature.

Methods—The placental bed vasculature was imaged using directional power Doppler ultrasound. 10-second cines were recorded using standardized machine settings. A region of interest with prominent Doppler signal in the utero-placental interface was analyzed for percent vascularity to generate a time-vascularity waveform. A vascular pulsatility index (VPI) representing variation over cardiac cycle was calculated by the ratio of the systolic-diastolic difference in vascularity to mean vascularity. The acquisitions were repeated with six different pulse repetition frequencies (PRF) and three wall motion filter (WMF) settings to evaluate their impact on the Doppler measurements.

Results—Ten sets of cine clips were analyzed for this study. The pulsatile nature of the vascularity was readily apparent in each cine. The measured time-vascularity waveforms showed uniform cyclic variation in vascularity over cardiac cycle, with systolic vascularity significantly higher than diastolic vascularity at each combination of PRF and WMF. A gradual increase in VPI was observed with increasing the PRF or WMF. Normalization of systolic to diastolic measurement provided a stable vascular assessment across the range of PRFs.

Conclusions—Doppler cine clips provide a dynamic representation of the placental bed vasculature and a novel analytic approach to quantitatively evaluating the pulsatility of this critical vascular network. Further work is warranted to explore the reproducibility and clinical potential of this approach.

Keywords

placenta; spiral artery; power Doppler; ultrasound; pulsatility; cine

Introduction

A critical component of early placental development is the successful invasion and remodeling of the maternal spiral arteries by placental trophoblasts in order to convert the maternal vascular supply into a low resistance system. Inadequate spiral artery remodeling leads to an increased resistance and restriction of maternal flow to the placenta.^{1–5} The high resistance in the spiral arteries also leads to higher velocity flow into and within the placenta which can be traumatic to the sensitive villous tree developing from the fetal side of the placenta.³ This dysfunctional early placental vascular development has been associated with adverse pregnancy outcomes such as preeclampsia and fetal growth restriction.

Persistent resistance to flow in the uterine arteries has been associated with adverse pregnancy outcomes in multiple studies.^{6–10} However, this approach remains indirect and the clinical utility has been questioned.^{11,12} 3-dimensional power Doppler (3DPD) analysis has been studied to quantify the vascular signal within the placenta, however, the association with pregnancy outcomes have been inconsistent^{13–18} In addition, the technical difficulties in accurate and reliable 3DPD acquisition, particularly relating to standardization of machine settings, also impair the reliability of the 3DPD indices.^{19–25} Finally, 3DPD fails to consider the pulsatile nature of the placental vascular bed. Thus, we are left with no direct methods to assess this critical vascular bed in a clinically meaningful way. These recognized gaps in our ability to adequately assess and quantify the critical components of early placental development in real time has been the primary motivation behind the establishment of the Human Placenta Project by the NICHD.²⁶

In this study we seek to explore the potential to assess pulsatile variation in blood flow in the placental bed using 2-dimensional high resolution Doppler cine clips. The goal is to measure and characterize the changes in blood flow that occur over the cardiac cycle and how these measurements are influenced by two important Doppler parameters, the wall motion filter (WMF) and pulse repetition frequency (PRF). A modality that can capture and quantitatively assess the pulsatility of the placental vasculature would allow for a more robust evaluation of this critical vascular system and may open up opportunities to detect functional changes that reflect the placental development as well. Moreover, obtaining data at different points in the cardiac cycle at the same location may allow subjects to serve as their own controls during the analysis and improve inter-subject comparisons.^{27–29}

Materials and Methods

Singleton pregnancies with anterior placentas were recruited and consented to undergo a research ultrasound exam to evaluate the placental vascular bed. A GE Voluson E10 with a transabdominal eM6C probe (GE Healthcare, Austria) was used to locate the anterior placenta. An HD Flow Doppler box was used to evaluate the vascular signal at the utero-placental interface. In each case, the same investigator (NS), sonographically surveyed the sub-placental vascularity and subjectively identified an area with a strong Doppler signal. The Doppler box size was adjusted to include the placental bed, avoid fetal vessels, and ensure a minimum frame rate of 15Hz ensuring sufficient sampling of vascularity over the cardiac cycle. The subject was asked to take and hold a breath for 10 seconds while a cine

clip of the placental bed vasculature was recorded. Cine clip files were exported in .avi format for offline analysis.

As variations in machine settings has been identified as a significant pitfall in 3DPD studies, we designed this study to use the same machine settings (balance:225, smooth rise:4, fall:4, line density:8, ensemble:12, line filter:3, threshold:40) for all cases. The Doppler gain was set to the sub-noise in order to optimize the gain setting for each individual patient.^{22,23} While many machine settings impact Doppler imaging, the color image displayed is particularly sensitive Pulse repetition frequency (PRF) and wall motion filter (WMF).^{21,25} PRF sets the limits of velocity that can be unambiguously discriminated by the machine. A higher PRF will be more sensitive to higher velocities, but may miss lower velocity signals. The converse is true as well. WMF filters out low frequency signals that are often generated by vessel walls and surrounding tissues. Therefore, we investigated multiple combinations of these parameters by repeating the cine acquisition at the same spot on the placenta using six different PRF settings (0.9 KHz, 1.3 KHz, 1.8 KHz, 2.4 KHz, 3.2 KHz, and 4.0 KHz) and three different WMF settings (Low 2, Mid1, and High 1). Thus, each subject had 18 total cine clips analyzed offline.

For each cine clip, the utero-placental interface was identified on the first frame and manually outlined as the region of interest (ROI). The same ROI was then replicated for each image frame of the clip to ensure that the same ROI size and location was used. By analyzing the color bar in the image, the computer program identified the colored pixels within the ROI of each frame. Doppler vascularity was determined by the ratio of the number of colored pixels to the total number of pixels in the ROI. All color pixels (i.e. red and blue) were analyzed in aggregate to assess total vascular area in the ROI. Except for the ROI selection, the vascularity analyses for all the images in the cine clip were completely automated. The minimum frame rate was set at 15fps and 18 clips of 10 second each, and a total of over 2700 images were analyzed per subject.

The Doppler vascularity analysis was repeated for each frame in the cine clip to generate tissue vascularity -time waveform. A 3-second segment containing three consecutive and similar-appearing cardiac cycles with strong, regular oscillations in the waveform was selected. The cine frame with the highest vascular area for each cycle in the waveform corresponded to peak systole (V_s); while the one with the “lowest” vascular area was at end-diastole (V_d). The vascularity-time waveform was used to measure time-average vascularity (V_{av}). We then calculated a vascular pulsatility index (VPI), representing the pulsatile change in tissue vascularity per unit vascularity, which was defined as the difference between the systolic (S) and diastolic (D) vascularity divided by the mean vascularity: $VPI = (V_s - V_d) / V_{av}$. Repeating the V_{av} and VPI analyses for each combination of PRF and WMF settings allowed us to observe the impact of these machine settings on the Doppler signal.

Finally, as mentioned above, the ability to quantify blood flow throughout the cardiac cycle may yield parameters that are more stable in the face of variations in machine settings, as the settings would have their impact on the Doppler signal throughout the cardiac cycle. To test this hypothesis, we calculated the ratio of systolic to diastolic vascularity across machine

settings (i.e. $SD = V_s/V_d$) to determine whether normalizing the systolic vascularity signal to the diastolic signal would demonstrate stability across variations in machine settings.

For this feasibility cohort, we recruited singleton gestations between 20 and 40 weeks of pregnancy with an anterior placenta. We chose a wide gestational age range to examine whether pulsatility in the placental vascular bed could be identified throughout the second and third trimesters. Women with a BMI > 35, non-anterior placentas, multiple gestations, and fibroids were excluded. The study protocol was approved by the Institutional Review Board at the Hospital of the University of Pennsylvania.

Results

A total of 10 cine clips were analyzed for this study. The mean maternal age was 30 years (range: 24-37) and five of the ten subjects were nulliparous. The mean gestational age at the time of the ultrasound was 25.7 weeks (range 20-35). Review of the video clips demonstrated visually apparent cyclical variation throughout the cardiac cycle. The graphical representation of the vascularity in each frame over a 3-second segment of the cine clip illustrates clear pulsatile waveforms of the Doppler signal within the placental bed. (Figure 1a) The cyclical pulsatility mimicking cardiac cycle at the maternal heart rate of approximately 72 beats per minute is apparent in the figure. The changes in the Doppler signal are illustrated in figure 1b which depicts 2 images chosen from the peak systole (S) and end-diastole (D) portions of the clip. A reduction in the proportion of color pixels within the ROI (i.e. vascularity) is visually apparent when comparing the end diastole frame to peak systole and can be quantified. In fact, at each PRF and WMF setting, the mean VA values were significantly higher at peak systole compared with end diastole (Table 1).

As increasing PRF reduces the sensitivity to lower velocity flow, fewer vascular pixels should be displayed, leading to a reduced vascularity. In fact, this is what we observed. At each WMF setting, the V_{av} gradually decreased as the PRF was increased. (Figure 2a) However, when calculating the vascular pulsatility index, there was a gradual increase in VPI with increasing PRF. (Figure 2b) Thus, as increasing the PRF leads to more of the Doppler signal being produced by larger and higher velocity vessels, we are able to detect a measurable increase in the pulsatility.

A similar trend was seen when examining how the WMF settings impact the Doppler signal. Increasing the WMF leads to a reduced sensitivity to the slower flow exhibited by blood that is at the periphery of the vessel lumen (i.e. near the vessel wall). Thus, increasing the WMF setting further reduces the detection of the Doppler signal, leading to a reduction in the V_{av} . (Figure 3a) However, the higher flow in the pixels detected at higher WMF settings is more affected by the changes in the cardiac cycle, leading to an increase in VPI. (Figure 3b)

When calculating the SD ratio of vascularity across machine settings, the slope of the linear fit line approached 0, indicating that this ratio appears to remain stable across machine settings. (Figure 4)

Discussion

A non-invasive and direct assessment of the placental bed vasculature would represent a significant advancement in the ability to study and understand placental development. In this study, we demonstrate how analysis of a Doppler cine clip can capture and quantify the pulsatile nature of this critical vasculature. We also demonstrated the impact that PRF and WMF settings have on these parameters and that a systolic-diastolic ratio may prove to be a PRF-independent strategy to allow each patient to serve as their own control and limit inter-subject variability.

Previous research aimed at developing a more direct evaluation of placental vascularity relied heavily on 3-dimensional power Doppler (3DPD) analysis to quantify the vascular signal within the placenta. While this approach has been partially validated in phantom and animal studies,^{30–33} the association with pregnancy outcomes have been inconsistent.^{13–18} In addition, the technical limitations in obtaining accurate and reliable 3DPD acquisitions, particularly relating to standardization of machine settings and inter-subject comparisons, have significantly impaired the utility of the 3DPD indices.^{19–24} While the use of sub-noise gain may help adjust for inter-subject differences in attenuation^{22,23}, the lack of an internal Doppler reference point makes it difficult to accurately compare data across patients. The vast majority of studies fail to specifically target the spiral arterial bed, but include either all intra-placental Doppler signal or spherical samples therein, including fetal vessels on the chorionic plate. In fact, Hafner et al³⁴ demonstrated improved clinical prediction when separately quantifying the myometrial vs the intra-placental 3DPD signal.

Recently, a 3-dimensional fractional moving blood volume (3DFMBV) approach has been developed to address some of these points.³⁵ This sophisticated technique helps control for variation in machine settings and inter-subject variation by automatically identifying a reference vessel at similar depth that is assumed to represent a maximum power Doppler signal from which a standardized fractional measure of vascularity can be calculated. The approach also allows the utero-placental interface to be targeted using a semi-automated segmentation algorithm. In fact, there is great promise in this approach as the analysis appears to be more reproducible than commercially available 3DPD parameters³⁵ and has demonstrated statistically significant reductions in Doppler signal in first trimester placentas of pregnancies that progressed to develop preeclampsia compared to controls.³⁶ However, more work is needed to validate the technique, fully automate the segmentation, and extend the reproducibility studies to include multiple 3DPD acquisitions. Moreover, while a validated FMBV may address the standardization of the Doppler signal amplitude, it is still sensitive to a loss of signal in low flow vessels, especially at increasing WMF.³⁷

Moreover, an inherent and significant limitation in both conventional 3DPD and 3DFMBV is that they utilize a static 3DPD acquisition, which captures the Doppler signal at varying times of the cardiac cycle as the transducer sequentially acquires 2D planes over image volume without accounting for the pulsatile nature of the placental bed vascularity. This inherently inserts a degree of variability between acquisitions as different areas of the placental bed will be caught at different points in the cardiac cycle.

Spatiotemporal image correlation (STIC), a 4-dimensional technique, may open new avenues to capture pulsatility within a 3D volume.^{27–29,38} Currently, the STIC acquisition of the placental bed is still being refined as the scanner must be able to detect the maternal heart rate within the placental bed in order to appropriately organize the numerous image slices acquired throughout the volume into the correct part of the cardiac cycle. Despite the proposed improvements³⁹, the acquisition remains far slower and more complex than a 2D approach. The volume angle is also limited, making acquiring an entire placenta currently infeasible. Finally, STIC analysis would require a 3DPD analysis for each 3D frame within the cardiac cycle, which is quite time-consuming.

Therefore, our 2D approach remains a promising and appealing strategy. First and foremost, this technique is a 2-dimensional technique that does not require 3D/4D equipment or capabilities, making it more easily incorporated into clinical care and research protocols. However, the most significant strength of the 2D cine approach is the ability to capture and analyze data from throughout the cardiac cycle. As we have demonstrated, placental bed vascularity varies significantly over the maternal cardiac cycle (Figure 1a). The difference between peak systolic and diastolic was significant for all PRFs (Table 1). This pulsatility is a function of the vascular remodeling and resistance, making it an attractive physiologic parameter by which to evaluate placental development. This pulsatility data is lost in both 3DPD and 3DFMBV analyses which rely on snapshots in time for each plane.

Capturing the Doppler signal throughout the cardiac cycle also yields systolic and diastolic data from the same plane in the same patient. As both data points are subject to the same acoustic environment, subjects can now serve as their own controls, enhancing any inter-subject comparisons. This is akin to how vascular indices, such as pulsatility index and SD ratios, remain stable from patient to patient despite variability of the insonation angles. This is illustrated by the fact that the SD ratio remains relatively unchanged with increasing PRF (Figure 4). While this stability makes the SD ratio promising, it would require that some Doppler signal is still detected in diastole. If the entire diastolic signal is filtered out, this ratio would become impossible to interpret.

Finally, we have shown that pulsatility increased linearly with PRF for all wall filters studied (Figure 3). This is consistent with the expectation that increasing the PRF and WMF excludes small and low velocity vessels thereby enabling visualization of larger and higher velocity blood vessels with stronger pulsatility. In addition, a higher WMF means that more of the lower amplitude signals will fall below the filter and not be displayed. Thus, it may be that the degree of the changes in vascularity and VPI with increasing PRF may reflect the vascular impedance characteristics of the spiral artery population of a particular placenta.³⁷

The limitation of a 2D technique will always be the inability to interrogate the entire placental bed at once. This is important to consider given the observed variability in placental pathology and histology. However, with the simplicity and speed of the 2D cine acquisitions and the potential automation of the analysis, there is potential to devise a standardized protocol for acquiring multiple 2D clips for each placenta to ensure of reasonable representation of the overall placental bed.

Another limitation to our technique is related to the variability in identifying the placental region to interrogate as well the manual tracing of the ROI, both of which can impact the applicability and reproducibility of this technique. Therefore, future work must include exploration of the variability between different regions of the placenta as well as reproducibility studies examining the impact that variations in the ROI tracing can have on the measurements.

For the purposes of exploring the feasibility of this technique, we limited our study to anterior placentas to optimize the imaging of the placental bed vessels. It may be that acquiring similar cine clips for posterior placentas may be more challenging. However, the dozens of studies investigating 3DPD of the placenta have successfully included posterior placentas. Notwithstanding the general limitations of 3DPD quantification briefly alluded to above, there are reassuring data regarding the ability to acquire the Doppler signal of posterior placentas.⁴⁰ Nonetheless, further studies to establish the feasibility of this technique on posterior placentas is warranted.

This study focused on HD-Flow due to its enhanced spatial resolution, vessel definition and reduced bloom artifact compared with conventional power Doppler or color Doppler. These features are appealing when attempting to quantify the often subtle changes in Doppler signal that occurs in the small vessels of the placental bed. However, we also attempted to exploit the fact that this modality encodes directionality of flow. Given that we studied anterior placentas, it would follow that the blue signal (flow away from the transducer) would be mostly comprised of arterial flow from the myometrium to the placenta; while red signal (flow towards the transducer) would be mostly comprised of venous flow from the placenta back to the myometrium. In fact, this is largely the case as illustrated by the larger prevalence of blue pixels within the color pixel population as well as the more distinct pulsatility noted on the color analysis (see Figure 1a). However, it was surprising to find a degree of pulsatility in the red pixel population (flow away from the placenta towards the uterus and transducer) in each cine clip. There are several possible explanations for this, such as pulse transmission to nearby veins or inclusion of myometrial arterioles with some vector of flow towards the transducer. However, it seems to us that the main contributor to this observation is signal aliasing, a phenomenon in Doppler when the velocity of flow is beyond the limits of the scale (i.e. PRF). In HD-Flow, misallocation of direction due to aliasing cannot be identified, an important drawback to this modality. Therefore, some of the observed pulsatile red signal is likely from arterial flow towards the placenta that is beyond the PRF scale. Therefore, while we have demonstrated this aliasing phenomenon in Figure 1a, we performed the quantitative analyses using the total, combined Doppler signal.

In conclusion, we report the feasibility of 2D cine clip analysis of directional power Doppler signal of the placental bed and have demonstrated the ability to quantify the changes in Doppler signal that occur with the maternal cardiac cycle. Additional work is needed to help further standardize the technique and examine its reproducibility.

In addition, future work will explore whether this approach can shed light on the vascular remodeling of the placental bed, which is critical to normal placental development. One can speculate that a functional assessment of the placental bed vasculature at 11-14 weeks, after

the spiral artery remodeling is largely complete, may improve a new tool in the prediction of adverse pregnancy outcomes and allow for appropriate surveillance and investigation of potential interventions. Alternatively, there may be a role in later pregnancy to examine maternal blood supply to the placenta in women at risk for placental malperfusion (e.g. chronic hypertension, diabetes, fetal growth restriction). However, further work will be required to explore and validate the physiologic and clinical applicability of this technique.

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Figure 1.

(a): Graphical representation of the vascular area as a function of time for 3 consecutive cardiac cycles. Lines (s) and (d) correspond to the vascular areas obtained from the peak systole and end-diastole frames. (b): Image frames corresponding to peak systole (s) and end diastole (d). The region of interest is manually traced in red. The reduction in the Doppler signal between systole and diastole is visually apparent; however, vascularity (V) analysis quantifies this change as the systolic (V_s) was 15.5%, while the diastolic vascularity (V_d) was 8.4%. Note: The velocity limit on the color bar represents the Nyquist limit for velocity, but does not relate to the intensity of the color signal displayed as HD Flow is still an amplitude-based power Doppler modality and not velocity-based color Doppler.

Figure 2.

(a): Time-average vascularity (V_{av}) gradually decreases with increasing pulse repetition frequency (PRF) at (a) low, (b) medium, and (c) high wall motion filter (WMF) setting. The bars represent the range of values among the 10 cases. (b): Vascular pulsatility Index (VPI) by pulse repetition frequency (PRF) setting for (a) low, (b) medium, and (c) high wall motion filter (WMF) settings. The bars represent the range of values among the 10 cases.

Figure 3.

(a) Time-average vascularity (V_{av}) of color pixels by wall motion filter (WMF) setting. (b) Vascular pulsatility index (VPI) values according to WMF setting. The bars represent the range of values among the 10 cases

Figure 4.

Mean systolic-to-diastolic ratios (SD) of vascularity at each pulse repetition frequency (PRF) and wall motion filter (WMF) setting. SD remains fairly stable with increasing PRF as indicated by near-zero slopes of the linear fit lines.

Table 1

Mean systolic and diastolic vascular area values for each wall motion filter and pulse repetition frequency setting

WMF	PRF (KHz)	Peak Systolic vascular area (SD)	End Diastolic vascular area (SD)	p [*]
Low	0.90	18.4 ± 8.3	11.4 ± 5.2	0.002
	1.30	14.5 ± 5.5	9.2 ± 3.7	<0.001
	1.80	12.4 ± 6.6	7.1 ± 4.2	0.002
	2.40	10.0 ± 4.1	6.4 ± 3.1	<0.001
	3.20	7.2 ± 4.6	4 ± 2.5	0.007
	4.00	8.8 ± 5.7	5.2 ± 3.8	0.002
mid	0.90	17.5 ± 7.0	11.1 ± 5.5	<0.001
	1.30	11.5 ± 7.2	7.1 ± 4.9	<0.001
	1.80	11 ± 6.4	5.0 ± 3.4	0.014
	2.40	8.9 ± 6.1	5.0 ± 4.6	<0.001
	3.20	7.1 ± 4.7	3.6 ± 2.6	0.001
	4.00	7.1 ± 4.5	4.4 ± 3.6	<0.001
High	0.90	11.4 ± 5.2	5.2 ± 4.9	0.007
	1.30	10.1 ± 4.6	4.6 ± 3.5	0.012
	1.80	7.8 ± 4.1	4.1 ± 3.6	0.006
	2.40	4.1 ± 2.2	2.2 ± 2.0	0.002
	3.20	3.2 ± 1.5	1.5 ± 1.2	0.005
	4.00	3.3 ± 1.6	1.6 ± 1.4	0.007

N= 10 sets of Doppler cine clips

*
p - paired two tailed

WMF: wall motion filter

PRF: pulse repetition frequency