Plane-Wave Ultrasound Doppler of the Eye in Preeclampsia

Ronald H. Silverman¹, Raksha Urs¹, Ronald J. Wapner², and Srilaxmi Bearelly¹

¹ Department of Ophthalmology, Columbia University Irving Medical Center, New York, NY, USA
² Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, NY, USA

Correspondence: Ronald H. Silverman, Department of Ophthalmology, Columbia University Irving Medical Center, 635 West 165th St., Research Annex Room 711, New York, NY 10032, USA. e-mail: rs3072@cumc.columbia.edu

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Introduction

Pre-eclampsia (PE) is a rapidly progressive multisystem disorder characterized by the acute onset of hypertension occurring usually after 20 weeks of gestation and frequently associated with proteinuria and edema. Severe manifestations include reduced organ perfusion secondary to vasospasm and activation of the coagulation cascade.¹ It affects 4% to 7% of pregnant women and is one of the most serious complications of pregnancy. Despite extensive research, the cause of PE remains elusive.²

PE is fundamentally a disease of the vasculature and is directly implicated in an array of major maternal morbidities and adverse perinatal outcomes. Women destined to develop PE have increased vascular reactivity well before they become symptomatic. Identification of high-risk patients is based on clinical history, especially prior PE, diabetes, renal disease, and chronic hypertension.³

Presymptomatic warning of an elevated risk for development of PE would be a valuable clinical tool. A marker for severe progression could be crucial to the life and health of both mother and child. Severe complications of PE account for approximately 63,000 maternal deaths annually worldwide, with mortality rates especially high in less developed countries.⁴ In the United States, PE accounts for approximately 16% of all maternal deaths and risk of fetal death is highly elevated, especially for PE occurring in the preterm period.⁵,⁶ Women suffering PE are also at risk for high blood pressure, stroke, heart and renal disease, and vascular dementia later in life.⁷
While the placenta might be regarded as the most intuitive target for vascular imaging for assessment of PE risk, it is far less accessible to high-resolution imaging of the vasculature than is the eye, where the retinal microvasculature can be visualized optically. This is especially true given recent advances in ocular imaging, such as optical coherence tomography angiography (OCT-A). Whereas the placenta is poorly placed for routine, high-resolution imaging, the eye is superficial, has a rich retinal and choroidal vasculature, and can be imaged noninvasively in near-microscopic detail.

In ophthalmology, B-scan instruments generally consist of mechanically scanned single-element transducers. These emit a focused ultrasound beam, and images are produced by measurement of the probe orientation and range and amplitude of echoes. Ophthalmic B-scan instruments typically produce about 10 images/sec and provide no information on blood-flow.

Linear array probes are dominant in other clinical specialties. With electronic rather than mechanical scanning, scan rate is 10 times faster, and Doppler techniques can be used to produce color-flow images superimposing regions of flow over the gray-scale structural image. This technology, however, has made negligible impact in ophthalmology because such systems generally exceed Food and Drug Administration (FDA) guidelines for ophthalmic intensity thresholds.

Plane-wave ultrasound scanning is a recent technological advance that offers the advantages of linear arrays with compliance to FDA-guidelines. In this imaging mode, all array elements emit at once to produce an unfocused wavefront. Echo data received by the many elements are then brought into focus by postprocessing using a “delay-and-sum” algorithm, which is the inverse of how element firings would be timed to produce a converging, focused beam. Because the plane-wave is unfocused on transmit, ultrasound intensity is substantially lower than when using a standard scanned, focused beam, and because there is no scanning (electronic or mechanical), the imaging rate can be ~1000 times faster than with a mechanically scanned probe. Given the two-way pulse/echo transit time of the eye, roughly 15,000 B-scan images can be acquired per second.

We developed plane-wave ultrasound scanning for imaging of the eye and reported imaging and measurement of blood-flow in the major vessels and choroid.

In this study, we describe plane-wave ultrasound imaging and measurement of ocular blood-flow in 53 subjects scanned post-partum within 72 hours of delivery, 26 of whom had PE.

**Methods**

This research followed the tenets of the Declaration of Helsinki and was approved by the Columbia institutional review board. Informed consent was obtained after explanation of the nature and possible consequences of the study.

**Subjects**

Human subjects were classified by one investigator (RW) into one of four groups: normal controls (n = 19), mild PE (mPE) (n = 7), severe PE (sPE) (n = 19), and chronic or gestational hypertension (HTN) (n = 8) based on criteria summarized in Table 1. Classifications were masked to investigators until ultrasound data analysis was complete.

Blood pressure (BP) was measured in the patient’s room before and after the ultrasound examination. Systolic and diastolic BP, pulse rate in beats per minute (BPM) were recorded. Mean arterial pressure (MAP) was calculated as (2*diastolic + systolic)/3. Pulse pressure was calculated as systolic − diastolic and pulse ratio as diastolic/systolic.

A dilated fundus examination was not performed as part of this study.

**Ultrasound System**

A Verasonics (Kirkland, WA, USA) Vantage-128 research ultrasound engine was used with a Verasonics L22-14vXLF 18 MHz linear array probe. The probe has a 12.8-mm aperture and elevation focus of about 18 mm.

**Imaging**

Patients were transported to the Harkness Eye Institute for ultrasound examination. Ophthalmic plane-wave ultrasound scanning was performed within 72 hours of delivery by a single investigator (RHS). Scanning was performed through closed eyelids with the subject in a seated position. GenTeal (Alcon, Geneva, Switzerland) ocular lubricant was applied to the probe surface as an acoustic coupling agent. Scanning was performed with minimum pressure to the eyelid to enable visualization and measurement of flow. For assessment of the retrobulbar vessels, the scan was in a horizontal plane encompassing the optic nerve. For the choroid, scans were in a horizontal plane just superior to the optic nerve. The dimension of the scanned region was approximately 12.8 mm laterally by 8 mm axially. Duplicate scans were acquired on both eyes. The scanning procedure had a duration of approximately five to ten minutes per eye.
We developed MATLAB (The MathWorks, Inc., Natick, MA, USA) programs to control transmit and receive of all transducer elements, enabling transmission of plane waves at multiple angles. Echo data received by the linear-array transducer elements were quadrature sampled at 62.5 MHz at 14-bits per sample.

In real-time “flash Doppler” mode,15 color-flow power Doppler was superimposed on grayscale plane-wave B-mode images. Although Doppler resolution and sensitivity are relatively modest in this mode, it allows identification of relevant ocular structures and flow, enabling orientation of the probe for data acquisition.

Once the probe was properly oriented, we acquired high-resolution data from the posterior pole for approximately three seconds at 6 kHz, compounding echo data from two angled transmissions at ±9°. At this acquisition rate, velocities of up to 140 mm/sec could be measured before reaching the alias limit. For choroidal “slow flow,” 10 angles were compounded and acquired at 1 kHz.

Postprocessing

All post-processing was performed by one investigator (RU). The first stage of data processing consisted of beamforming and coherent addition of each batch of angled plane-waves to form compound images. The data were subsequently processed using a singular value decomposition (SVD) filter,16 followed by a 10-Hz high-pass filter. The SVD filter exploits the different spatial coherence characteristics of bulk tissue motion caused by small movements of the eye or the hand-held probe versus blood flow, even when their velocities are comparable. The 10-Hz high-pass filter sets a threshold of ∼0.5 mm/sec for minimum detectable velocity and acts to improve distinction of flow from noise. These operations remove ‘clutter’, consisting of stationary or slow-moving tissue, leaving only blood-flow.

Spectrograms representing flow velocity as a function of time were generated from user-selected regions of interest: the central retinal artery (CRA), central retinal vein (CRV), short posterior ciliary arteries (SPCAs) and choroid. After application of phase unwrapping to the spectrogram to compensate for potential aliasing, the envelope of the spectrogram was automatically detected.17 The peak systolic velocity (PSV), end diastolic velocity (EDV) and average velocity (VMEAN) in two successive cardiac cycles were measured and the resistive index calculated as RI = (PSV-EDV)/PSV and pulsatility index as PI = (PSV-EDV)/VMEAN. Velocity values were cosine-corrected based on vessel angle with respect to the ultrasound axis. Doppler parameters for each vessel in the duplicate scans were averaged before subsequent statistical analysis. Figures 1 and 2 illustrate imaging and spectrograms at the posterior pole and choroid, respectively.

Statistical Analysis

Statistical analysis was performed with IBM SPSS, Version 25 (IBM Corp., Armonk, NY). Means and standard deviations of systemic BP parameters and ultrasound-determined flow parameters were deter-
mined for each group and analysis of variance (ANOVA) performed. Correlation coefficients between BP and flow parameters were determined. Correlation coefficients for all measurements between left and right eyes were determined. Focusing specifically on sPE, we compared Doppler parameters in control versus sPE eyes by vessel using a general linear model (GLM) repeated measures procedure in which values from fellow eyes were treated as repeated measures to control for potential correlation between fellow eyes. Last, we repeated the GLM analysis with MAP as a covariate.

Results

Table 2 summarizes mean systemic parameters by diagnostic group. PE and HTN groups had higher BP than controls, but the diastolic/systolic ratio and heart rate were not significantly different.

Significant correlations between systemic BP and Doppler parameters (considering all groups together) are listed in Table 3. The table demonstrates significant correlations between systolic and diastolic BP and MAP with ocular flow parameters, particularly resistance (PE and RI). This was particularly notable in the sPE group, where diastolic BP had correlation coefficients of $-0.562$ and $-0.529$ with PI in the CRA and SPCA, respectively. This negative correlation was also evident to a lesser degree in control subjects.

We also examined Doppler parameters for correlation with the time interval between delivery and the ultrasound examination. ANOVA showed no significant difference in the time interval between groups. We found positive correlations between the interval and
Table 2. Systemic Blood Pressure Parameters (in mm Hg) and ANOVA by Group

| DIAG     | Systolic | Diastolic | Pulse Pressure | Ratio | MAP    | BPM    |
|----------|----------|-----------|----------------|-------|--------|--------|
| Control (N = 19) | Mean: 111.05 | 71.21 | 39.84 | 0.640 | 84.49 | 76.37  |
|          | SD: 12.87 | 9.24 | 5.57 | 0.031 | 10.26 | 10.68  |
| mPE (N = 7)  | Mean: 132.29 | 80.14 | 52.14 | 0.606 | 97.52 | 78.37  |
|          | SD: 12.35 | 8.59 | 6.31 | 0.031 | 9.55  | 14.11  |
| sPE (N = 19) | Mean: 131.37 | 82.42 | 48.95 | 0.630 | 98.73 | 76.73  |
|          | SD: 13.68 | 7.46 | 9.62 | 0.046 | 8.88  | 13.19  |
| HTN N = 8  | Mean: 124.00 | 79.50 | 44.50 | 0.641 | 94.33 | 77.29  |
|          | SD: 10.25 | 8.79 | 5.88 | 0.043 | 8.89  | 15.70  |
| ANOVA     |          |         |     | 9.50  | 5.98 | 6.95 | 0.353 | 0.100 | 0.001 | 0.001 | 0.217 | <0.001 | 0.716 |

Ratio, diasystolic/systolic; MAP, mean arterial pressure; BPM, beats/minute.

Table 3. Statistically Significant Correlations of Ocular Flow Velocity Parameters with Systemic Blood-Pressure Variables in the CRA, CRV, and SPCA

| Systemic BP Variable | Vessel | Parameter | R     | P     |
|----------------------|--------|-----------|-------|-------|
| Systolic             | CRA    | PI        | -0.353| 0.010 |
|                      | SPCA   | RI        | -0.321| 0.019 |
|                      | SPCA   | PI        | -0.357| 0.009 |
|                      | CRV    | EDV       | -0.306| 0.039 |
| Diastolic            | CRA    | RI        | -0.314| 0.022 |
|                      | CRA    | PI        | -0.410| 0.002 |
|                      | SPCA   | RI        | -0.403| 0.003 |
|                      | SPCA   | PI        | -0.387| 0.004 |
|                      | CRV    | EDV       | -0.338| 0.022 |
|                      | CRV    | Vmean     | -0.293| 0.048 |
| Pulse pressure Ratio | SPCA   | PSV       | 0.275 | 0.046 |
|                      | SPCA   | EDV       | 0.317 | 0.021 |
| MAP                 | CRA    | RI        | -0.287| 0.037 |
|                      | CRA    | PI        | -0.397| 0.003 |
|                      | SPCA   | RI        | -0.379| 0.005 |
|                      | SPCA   | PI        | -0.386| 0.004 |
|                      | CRV    | EDV       | -0.335| 0.023 |
|                      | CRV    | Vmean     | -0.297| 0.045 |

diastolic ($R = 0.346, P = 0.020$) and mean velocity ($R = 0.324, P = 0.030$), but only in the short posterior ciliary artery. We repeated the analysis for just the sPE group and found no significant correlation between Doppler parameters and time interval.

Mean Doppler parameters by group and their standard deviations are presented for each vessel in Tables 4 to 7. ANOVA shows significant differences among groups. EDV, $V_{\text{MEAN}}$, RI, and PI were all significant in the choroid. PI was significant in all vessels with exception of the CRV (which has negligible pulsatility).

Although there was a trend toward increased flow velocities in the HTN group compared with controls, this was not statistically significant. The low number of cases in this group, however, makes this a tentative finding.

Table 8 provides correlation coefficients between left and right eyes of each measurement. In most cases, correlation was small to moderate ($R < 0.5$), but all measurements were highly correlated ($R > 0.6$) in the SPCA. This is a surprising finding given the irregular directionality of the SPCAs but perhaps reflects greater averaging, because often more than one SPCA was imaged per scan.

GLM findings comparing Doppler parameters in control versus sPE eyes are presented in Table 9. Significant differences in EDV were found in the choroid and CRA, for $V_{\text{MEAN}}$ in the CRA, and for RI and PI in all vessels other than the CRV. Table 10 repeats this analysis, but adding MAP as a covariate. When taking MAP into account, no variable attained statistical significance.

**Discussion**

From GLM comparison of controls with sPE and their means (shown in Tables 4–7), we find EDV to be significantly elevated in sPE with respect to controls in the choroid and CRA, and resistance indexes reduced. Resistance was also significantly reduced in the SPCA. These resistance indices were negatively correlated with BP parameters, particularly diastolic and mean arterial pressure.
Our findings are consistent with the observation of reduced vascular resistance in transcranial Doppler studies of the cerebral arteries of women with PE reported by Riskin-Mashiah et al.\textsuperscript{18} and in the ophthalmic artery by Hata et al.\textsuperscript{19,20} and Diniz et al.\textsuperscript{21} Sato et al.\textsuperscript{22} reported declining vascular resistance and an inverse correlation with MAP in the retinal vessels in late pregnancy in normal subjects using laser Doppler flowmetry. Alves Borges et al.\textsuperscript{23} reported reduced resistance in the ophthalmic artery in post-partum PE versus control subjects. Belfort et al.,\textsuperscript{24} however, reported that whereas resistance was negatively correlated with MAP in normal pregnancies, it was positively correlated with MAP in the CRA and ophthalmic artery in PE.

Our observation of decreased vascular resistance in PE and a negative correlation with BP are consistent with most of the above prior studies of cerebral, orbital, and retinal blood flow. It has been proposed that in PE, vascular hypertension and end-organ hypoperfusion are causal agents in tissue damage, e.g., proteinuria arising from kidney damage. It has been suggested that early-onset PE results from abnormal production of placental angiogenic proteins that, on entering the maternal circulation, disturb endothelial function\textsuperscript{25} and that late-onset PE is a compensatory response to ongoing fetal metabolic demands surpassing the placenta’s ability to sustain adequate fetal growth.\textsuperscript{26} In either case, angiogenic factors in the maternal circulation induce reduced vascular resistance and elevated end-organ perfusion.

Vasospasm, however, has long been considered characteristic of PE onset and progression. In the case of the eye, this is supported by the narrowing of the retinal vessels in PE reported by Lupton et al.\textsuperscript{27} and Soma-Pillay et al.\textsuperscript{28} In both reports, however, retinal vessel caliber was corrected by dividing by MAP, which, given the elevated BP in PE, is a potentially confound-
Table 6. Short Posterior Ciliary Artery Flow Velocity Parameters With ANOVA by Group

| DIAG  | PSV   | EDV   | V_MEAN | RI    | PI    |
|-------|-------|-------|--------|-------|-------|
| Control (N = 19) | Mean  | 97.477 | 17.835 | 45.762 | .823  | 1.931 |
|       | SD    | 36.623 | 12.494 | 21.032 | .086  | .517  |
| mPE (N = 7)      | Mean  | 112.068| 21.045 | 54.879 | .812  | 1.774 |
|       | SD    | 32.681 | 7.321  | 18.797 | .053  | .277  |
| sPE (N = 19)     | Mean  | 96.242 | 24.393 | 50.387 | .749  | 1.547 |
|       | SD    | 28.825 | 12.523 | 17.726 | .088  | .388  |
| HTN (N = 8)      | Mean  | 92.774 | 22.966 | 52.234 | .765  | 1.471 |
|       | SD    | 41.752 | 18.184 | 30.492 | .06   | .269  |
| ANOVA |       |       |        |        |       |       |
| F     | .471  | .855  | .398   | 3.09  | 3.69  |
| p     | .704  | .471  | .755   | .035  | .018  |

Note that in some eyes the CRV was not visualized, so that N is less than the full cohort.

Table 7. Central Retinal Vein Flow Velocity Parameters With ANOVA by Group

| DIAG  | PSV   | EDV   | V_MEAN | RI    | PI    |
|-------|-------|-------|--------|-------|-------|
| Control (N = 15) | Mean  | −27.085 | −13.466 | −19.224 | .490  | .736  |
|       | SD    | 11.446 | 6.218  | 8.714  | .134  | .290  |
| mPE (N = 6)      | Mean  | −37.001 | −17.419 | −25.847 | .500  | .741  |
|       | SD    | 18.190 | 6.641  | 11.325 | .102  | .215  |
| sPE (N = 17)     | Mean  | −30.724 | −18.449 | −23.446 | .392  | .558  |
|       | SD    | 7.806  | 4.688  | 6.126  | .141  | .275  |
| HTN (N = 8)      | Mean  | −27.947 | −13.910 | −20.450 | .510  | .742  |
|       | SD    | 11.165 | 8.025  | 9.227  | .144  | .275  |
| ANOVA |       |       |        |        |       |       |
| F     | 1.22  | 2.19  | 1.25   | 2.21  | 1.57  |
| p     | .316  | .103  | .305   | .101  | .211  |

Table 8. Correlation Coefficients Between Right and Left Eye of Doppler Measurements by Vessel

| Vessel | PSV | EDV | V_MEAN | RI | PI |
|--------|-----|-----|--------|----|----|
| Choroid| 0.241 | 0.206 | 0.158 | 0.259 | 0.365* |
| CRA   | 0.314* | 0.310* | 0.432** | 0.248 | 0.464** |
| CRV   | 0.427** | 0.224 | 0.380* | 0.189 | 0.288 |
| SPCA  | 0.679** | 0.603** | 0.643** | 0.650** | 0.603** |

* P < 0.05.
** P < 0.01.

Table 9. GLM of Doppler Parameters for Controls Versus sPE

| Vessel | PSV | EDV | V_MEAN | RI | PI |
|--------|-----|-----|--------|----|----|
| Choroid| 0.094 | 5.84 | 3.12 | 4.46 | 5.23 |
| CRA   | 0.761 | 0.021 | 0.086 | 0.042 | 0.028 |
| CRV   | 1.56 | 6.29 | 9.03 | 6.47 | 9.74 |
| SPCA  | 0.219 | 0.017 | 0.005 | 0.015 | 0.004 |
| F     | 0.123 | 1.56 | 0.542 | 1.76 | 1.16 |
| P     | 0.730 | 0.228 | 0.471 | 0.201 | 0.296 |

Statistically significant differences are highlighted in bold.

In our own experience, (uncorrected) retinal vessel calibers were not significantly different between 35 control and 31 sPE subjects.29 Retinal vessel narrowing, if present, would seemingly be in contradiction with the reduced vascular resistance in the orbital vessels and choroid observed in this and most other studies. One explanation is that in some eyes the CRV was not visualized, so that N is less than the full cohort.
Table 10. GLM of Doppler Parameters for Control Versus sPE Controlling for MAP

|       | PSV | EDV  | V_MEAN | RI   | PI   |
|-------|-----|------|--------|------|------|
| Choroid | F   | 0.027| 2.47   | 1.79 | 1.62 | 2.21 |
|       | P   | 0.900| 0.125  | 0.189| 0.211| 0.146|
| CRA   | F   | 0.558| 1.16   | 2.94 | 1.24 | 2.45 |
|       | P   | 0.460| 0.290  | 0.095| 0.272| 0.127|
| CRV   | F   | 0.771| 0.032  | 0.084| 2.42 | 1.29 |
|       | P   | 0.392| 0.860  | 0.775| 0.138| 0.273|
| SPCA  | F   | 0.269| 0.620  | 1.18 | 0.349| 0.887|
|       | P   | 0.607| 0.437  | 0.286| 0.559| 0.353|

A limitation of this study is that it was performed postpartum. However, although removal of the placenta is classically considered the cure for PE, it is well known that the vascular effects continue through the early and sometimes later postpartum period.

Another limitation is that Doppler measurements provide only velocity values rather than volumetric flow, which is very sensitive to lumen diameter changes. It has been shown that retinal arteriolar caliber tends to narrow as blood pressure increases, and that factors such as age, gender and smoking are significant covariates. Our findings confirm systemic blood pressure to be an important covariate of ocular flow velocity parameters in PE. Because the present study was comprised of female subjects of childbearing age, gender and age are unlikely to be significant as covariates.

Vessel caliber is a crucial element affecting perfusion. Lumen diameters of the vessels interrogated in this study are not revealed by ultrasound. Hence, while flow velocity was measured, volumetric flow is unknown and potentially affected by changes in velocity, lumen diameter, or both. The lumens of the CRA, SPCA and CRV have been variously reported to range from about 0.1 to 0.2 mm. Volumetric flow is determined by the pressure gradient between vessel input and outlet divided by resistance, which according to the Poiseuille equation, varies inversely with the fourth power of lumen diameter. Hence, a small change in diameter will result in a large change in flow. Assuming a constant pressure gradient, a 10% decrease in radius of the CRA or SPCA (just 5–10 μm) would result in a 36% decrease in volumetric flow to the retina or choroid, respectively.

Conclusions

In this study, we demonstrated the feasibility of imaging and measuring ocular blood flow in PE with plane-wave ultrasound scanning. We found significantly decreased flow resistance in sPE with respect to controls in the CRA, SPCA, and choroid. The seeming contradiction between our finding of decreased orbital and choroidal resistance with some reports of retinal vasoconstriction in PE might be addressed in future studies using ultrasound scanning in conjunction with OCT-A. Although OCT-A cannot at present measure flow dynamics, it has allowed demonstration of subtle structural changes in the retina and choriocapillaris in PE. Swept-source OCT-A is particularly adept in imaging and characterizing the choriocapillaris. Measurement of vascular density, voids and lumen cross sections in the choriocapillaris together with ultrasound-determination of flow resistance in the choroid and orbital vessels would offer new insights regarding flow in the eye and, possibly, generally in end-organs in pregnancy and PE. Spectral domain OCT or adaptive optics measurement of retinal vessel wall thickness and lumen diameter could also contribute to understanding ocular flow dynamic changes in PE.

Previous studies have shown that increased vascular reactivity occurs prior to the onset of PE, suggesting ophthalmic Doppler alterations could identify woman prior to the onset of clinical disease. To unambiguously determine the potential of the technique to assess risk of developing PE, longitudinal imaging of pregnant woman before the onset of symptoms would allow elucidation of the development of altered ocular flow as a precursor to development of PE.
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