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● *Original Contribution*

USE OF FOUR-DIMENSIONAL ANALYSIS OF POWER DOPPLER PERFUSION INDICES TO DEMONSTRATE CARDIAC CYCLE PULSATILITY IN FETOPLACENTAL FLOW

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Abstract—The aim of this study is to quantify fetoplacental cardiac cycle variation in virtual organ computer-aided analysis (VOCAL) power Doppler (PD) indices by novel application of spatio-temporal imaging correlation (STIC). We recruited 25 healthy women (20–34 weeks gestation) with uncomplicated, viable singleton pregnancies with anterior placentae. Three four-dimensional (4-D) STIC PD datasets of the fetoplacental circulation were obtained above the placental cord insertion. The vascularization index (VI), flow index (FI) and vascularization-flow index (VFI) were calculated offline using a standardized spherical sonobiopsy technique for all frames of the cardiac cycle. Clear maximum (systole) and minimum (diastole) values with progressive fluctuation were seen in the majority of datasets (VI 66/75 [88%]; FI 58/75 [77%]; VFI 68/75 [91%]). Variation from mean was: VI ± 3.33% (0.34%–9.69%); VFI ± 3.46% (0.27%–10.02%); FI ± 0.74% (0.14%–1.60%). All indices were significantly higher in systole than diastole ($p < 0.001$). Mean systolic:diastolic ratios were: VI 1.07 (SD 0.06), FI 1.01 (SD 0.01) and VFI 1.07 (SD 0.06). Intraclass correlation coefficients (ICCs) for the frames ascribed to systole and diastole and to the mean value across the cardiac cycle of the indices (95% confidence interval [CI]) were: systole VI 0.91 (0.83–0.96), FI 0.85 (0.72–0.92), VFI 0.92 (0.85–0.96); diastole VI 0.91 (0.84–0.96), FI 0.84 (0.71–0.92), VFI 0.92 (0.86–0.96); mean VI 0.91 (0.84–0.96), FI 0.84 (0.72–0.92), VFI 0.92 (0.86–0.96). There is clear cardiac cycle variation in VOCAL indices of fetoplacental blood flow, establishing the need to control for phase of the cardiac cycle, and raising the possibility of future 4-D evaluation of vascular flow change or impedance. (E-mail: alec.welsh@unsw.edu.au)

Key Words: **Power Doppler, Ultrasound STIC, VOCAL, Impedance, Placenta, Impedance index, Systolic:diastolic ratio, Flow quantification.**

INTRODUCTION AND LITERATURE

The potential for power Doppler (PD) to assess or quantify placental perfusion has been extensively researched to develop new tools for diagnosis or exclusion of placental pathology (Guiot et al. 2008; Welsh et al. 2001). Conventional two-dimensional (2-D) pulsed-wave Doppler generally restricts investigation of fetoplacental circulation to a single blood vessel, the umbilical artery, the flow conditions of which is purported to reflect downstream flow and placental impedance (Abramowicz and Sheiner 2008; Joern et al. 1996). Three-dimensional (3-D) ultrasound on the other hand allows assessment of Doppler signals throughout a whole organ or area so may be more reflective of vascularization and blood flow (Matijevic and Kurjak 2002; Pretorius et al. 1998). This has opened the way for the use of 3-D power Doppler (3-DPD), which may offer a more direct tool for assessing changes in villous numbers and flow in fetal growth restriction (Campbell 2007; Macara et al. 1996).

Three-dimensional PD has developed from a noninvasive tool for fine vascular depiction into one for semiquantification of flow or vascularity by generating the following 3-D vascular indices: vascularization index (VI), flow index (FI) and vascularization-flow index (VFI) using virtual organ computer-aided analysis (VOCAL) in four-dimensional (4-D) view, as seen in numerous precedent studies (Alcazar 2008; Martins 2010). Whilst the three "indices of vascularity" are not a direct measure of bloodflow, they have been shown to be related to volume

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flow and vessel number *in vitro* (Jones et al. 2009; Raine-Fenning et al. 2008a). Whilst promising, lack of standardization for attenuation, machine settings and sample volume as well as evidence for its true reproducibility (incorporating both data acquisition and analysis steps) have so far limited 3-DPD to the production of arbitrary values that cannot be used to compare examinations within or between subjects (Lai et al. 2010; Martins 2010; Martins and Nastri 2011). In addition, recent studies on the ovary and endometrium have suggested that 3-DPD VOCAL indices may be influenced significantly by blood-flow in different phases of the cardiac cycle (Kudla and Alcazar 2010; Martins et al. 2011b). There have been no previously published studies evaluating the presence of and quantifying the degree of fetoplacental cardiac cycle variation in quantified 3-DPD values.

We hypothesized that although fetoplacental blood-flow has low velocity, changes in flow with systole and diastole would result in variation in VOCAL parameters with the cardiac cycle. To test this, we modified spatial temporal image correlation (STIC) 4-D cardiac evaluation technology and applied this to the placental circulation to generate volumes representing separate phases of the cardiac cycle. To our understanding, this is a first use of STIC technology to demonstrate cyclical pulsation in fetoplacental power Doppler signals.

MATERIALS AND METHODS

We recruited 30 healthy women aged 18 years or over between 20–34 weeks gestation with uncomplicated, singleton pregnancy and an anterior placenta after local ethics committee approval (HREC Reference Number: 10/205) and obtained written, informed consent. Women with medical complications, those affected by hypertension/pre-eclampsia, intrauterine growth restriction or diabetes or pregnancies found to have a structural or chromosomal anomaly were excluded. Gestational age was confirmed by dates and/or first trimester ultrasound. Ultrasound was performed using a Voluson E8 (GE Medical Systems, Zipf, Austria) with a transabdominal RAB4-8-D 3-D/4-D curved array transducer. A single observer (N.M.) performed all the scans. Initial 2-D ultrasound assessment was performed to determine viability, fetal biometry, amniotic fluid volume and umbilical artery Doppler velocimetry. Only fetuses with normal measurements including estimated fetal weights of 10th–90th centile were included.

After baseline 2-D sonography, the placental cord insertion was identified and the STIC PD mode was activated. The region-of-interest was defined as the area directly adjacent to or above the cord insertion. Volumes were captured during periods of fetal quiescence with minimal maternal and transducer movement. Machine settings were derived from previous endometrial (Martins et al. 2011b) and ovarian STIC studies (Kudla and Alcazar 2010), a literature review of static 3-DPD studies and in collaboration with a GE Medical Systems Ultrasound Application Specialist. The following detailed settings were kept identical for all examinations since modification within subjects is known to affect resultant VOCAL indices (Raine-Fenning et al. 2008b): Gain "sub-noise gain" (median −2.7 dB, range −7.2 to −2.2 dB) as previously described (Collins et al. 2011a; Welsh et al. 2010); Power "100%"; wall motion filter "low 1"; PRF 0.6KHz; frequency "mid"; flow resolution "high"; balance "225"; smooth (rise/fall) "6/6"; ensemble "7"; line density "5"; PD map "5"; gently colour "off"; line filter "2"; quality "norm". STIC acquisition time was set to maximal "15 seconds" to maximize image resolution (Chaoui et al. 2004; DeVore 2010; DeVore et al. 2003) and volume angle was set to maximal "40 degrees." After data acquisition, the volume was checked to exclude movement artifact or noise and to ensure STIC-estimated fetal heart rate was 110–160 beats per minute. Three volumes were stored per case.

Offline data analysis of acquired volumes using a spherical sonobiopsy was performed by a second observer (M.H.) using 4-D View (Version 10.2; GE Healthcare, Sydney, NSW, Australia) for VOCAL automated analysis. The sphere was placed at the centre of the volume and enlarged to include as much placental tissue as possible (Fig. 1), then, through use of the "histogram" facility, VI, FI and VFI were recorded. Each STIC volume contained multiple static 3-DPD volumes at different phases of the cardiac cycle. These volumes were sequentially analysed by scrolling through using the "autocine" function and with the aforementioned spherical technique (Fig. 2).

The VOCAL indices were graphically plotted by frame number and their maximum (assumed corresponding to systole), minimum (assumed corresponding to diastole) and mean values were recorded for the three volumes stored per patient, with statistical analysis performed using PASW Statistics v.19 (SPSS Inc., Chicago, IL, USA). Difference between mean VOCAL indices ascribed to the different phases of the cardiac cycle from the three STIC PD datasets per patient were assessed with paired *t*-tests, with statistical significance set as $p < 0.05$. Consistency of values per subject for systolic, diastolic and mean phases of the cardiac cycle relative to the population were compared using intraclass correlation coefficients (ICC; single measures, two-way random effects model for absolute agreement) (McGraw 1996; Shrout and Fleiss 1979). Percentage variation of each VOCAL index from their means of the STIC datasets acquired for each patient was also calculated and recorded.