# 学位論文

# 3D power Doppler ultrasound assessment of placental perfusion during uterine contraction in labor

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# 3D power Doppler ultrasound assessment of placental perfusion during uterine contraction in labor

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## ARTICLE INFO

## ABSTRACT

*Introduction:* To assess placental perfusion during spontaneous or induced uterine contraction in labor at term using placental vascular sonobiopsy (PVS) by 3D power Doppler ultrasound with the VOCAL imaging analysis program.

*Method:* PVS was performed in 50 normal pregnancies (32 in spontaneous labor group [SLG], and 18 in induced labor group with oxytocin or prostaglandin $F_{2\alpha}$ [ILG]) at 37–41 weeks of gestation to assess placental perfusion during uterine contraction in labor. Only pregnancies with an entirely visualized anterior placenta were included in the study. Data acquisition was performed before, during (at the peak of contraction), and after uterine contraction. 3D power Doppler indices such as the vascularization index (VI), flow index (FI), and vascularization flow index (VFI) were calculated in each placenta.

*Results:* There were no abnormal fetal heart rate tracings during contraction in either group. VI and VFI values were significantly reduced during uterine contraction in both groups (SLG, −33.4% [−97.0–15.2%], and ILG, −49.6% [−78.2–−4.0%]), respectively ($P < 0.001$). The FI value in the ILG group was significantly lower during uterine contraction ($P = 0.035$), whereas it did not change during uterine contraction in the SLG group. After uterine contraction, all vascular indices returned almost to the same level as that before uterine contraction. However, the FI value in ILG (−8.6%, [−19.7–16.0%]) was significantly lower than that in SLG (2.4%, [−13.4–38.1%]) after uterine contraction ($P < 0.05$). All 3D power Doppler indices (VI, FI, and VFI) during uterine contraction (at the peak of contraction) showed a correlation greater than 0.7, with good intra- and inter-observer agreements.

*Discussion:* Our findings suggest that uterine contraction in both spontaneous and induced labors causes a significant reduction in placental perfusion. Reduced placental blood flow in induced uterine contraction has a tendency to be marked compared with that in spontaneous uterine contraction. To the best of our knowledge, this is the first study on the non-invasive assessment of placental perfusion during uterine contraction in labor using 3D power Doppler ultrasound. However, the data and their interpretation in the present study should be taken with some degree of caution because of the small number of subjects studied. Further studies involving a larger sample size are needed to assess placental perfusion and vascularity using PVS during normal and abnormal uterine contractions in normal and high-risk pregnancies.

## 1. Introduction

In spontaneous uterine contraction, maternal placental blood flow before labor was reported to be 4.5% of the cardiac output, decreasing to 2.9% (35.5% decrease) during uterine contraction, and increasing to 7.2% (60% increase) after contraction in pregnant rhesus monkeys [1]. Reduction of placental blood flow during spontaneous uterine contraction was also $30 \pm 8\%$ in dogs and $35 \pm 12\%$ in rabbits [2]. On the contrary, in induced uterine contraction with oxytocin and prostaglandin $E_2$, uterine contraction led to a marked reduction (average: 73%) of the placental blood flow in pregnant rhesus monkeys, and the placental blood flow partially recovered after the uterine contraction [3]. These reductions of placental blood flow on induced uterine contraction with oxytocin were $43 \pm 16\%$ in dogs, and $46 \pm 13\%$ in rabbits [2].

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However, to the best of our knowledge, there are no available data on the change in placental blood flow during uterine contraction in the human placenta.

Placental vascular sonobiopsy (PVS) using three-dimensional (3D) power Doppler ultrasound with VOCAL imaging histogram analysis is a novel technique to quantitatively and qualitatively assess the vascularization and blood flow in the placenta [4–6]. Moreover, PVS is a valid alternative for evaluation of the placental vascularity and blood flow when visualization of the entire placenta is not feasible [7]. In the present study, we assessed placental perfusion during spontaneous or induced uterine contraction in labor at term using PVS.

## 2. Patients and methods

### 2.1. Patients

In the period from July 2012 to May 2015, 73 women with normal singleton pregnancies in labor at 37–41 weeks of gestation were studied cross-sectionally. The women were recruited randomly. The fetal age was calculated from the first day of the last menstrual period, with confirmation by first-trimester ultrasound. Women with gestational diabetes, chronic hypertension, maternal systemic disease, or taking antihypertensive medications were not enrolled. Of the 73 women, 23 (31.5%) were excluded because of insufficient data acquisition due to severe artifacts caused by uterine contraction or maternal movements. Therefore, 50 women (32 in a spontaneous labor group [SLG], and 18 in an induced labor group with oxytocin or prostaglandin $F_{2\alpha}$ [ILG]) underwent further investigation. Indications of induced labor were a weak labor in 11 women, and post-term pregnancy in 7 women. Clinical characteristics of the subjects in each group are shown in Table 1. The umbilical artery pulsatility index in all subjects was normal at 26 to 29 weeks of gestation. The growth of all fetuses was normal, and there were no abnormalities during pregnancy. This study was approved by the Kagawa University Graduate School of Medicine Ethics Committee, and standardized written informed consent was obtained from all women.

### 2.2. Ultrasound examination

A single experienced observer (M.S.) performed all 3D power Doppler ultrasound scans using a Voluson E8 A6 2.4 (GE Healthcare Japan, Tokyo, Japan) with a transabdominal 1–4 MHz transducer (RAB2-5-D) at the first stage of labor. At each examination, each placenta was confirmed to be located in an anterior position. 3D power Doppler ultrasound was employed for a representative placental vascular tree volume based on the following procedure, described in detail in our previous investigations [4–6]. The maximal sensitivity was ensured by setting the pulse repetition frequency (PRF) to 0.6 kHz and the wall motion filter to 'low'. The

following constant default instrument settings (corresponding to the manufacturer's Doppler power setting) were used throughout the examinations: frequency, mid; dynamic, balance, 225; smooth, 4/5; ensemble, 11; line density, 8; power Doppler map, 4; artifact suppression, on; power Doppler line filter, 3; quality, normal. The power Doppler window was placed over the placenta, including its total thickness, from the basal to chorionic plates. The 3D volume box was positioned over the placenta at a fixed 65° angle. Volume acquisition was carried out within 16 s before (at the start of contraction), during (at the peak of contraction), and after uterine contraction (at the end of contraction) (Fig. 1).

As presented in detail in our previous studies [4–6], the examination of placental perfusion was performed using PVS. In the measurement of PVS, the power Doppler window is placed over the placenta, including its total thickness, from the basal to chorionic plates (excluding both of them). The spherical 3D volume is obtained between the basal and chorionic plates (Fig. 1). The VOCAL program automatically calculates color values (vascularization index [VI], flow index [FI], and vascularization flow index [VFI]) from the acquired sphere. A sequence of six placental sections separated by successive rotations of 30° is obtained, and 1 to 3 spherical sampling sites are chosen in each plane. Each spherical volume was taken at approximately equidistant intervals along the length of the placental image. Each index was an average value from those of 6–13 spheres in each placenta. A single experienced observer (M.S.) conducted all 3D Doppler ultrasound histogram analyses with the VOCAL program.

### 2.3. Statistical analysis

All statistical analyses were performed with SPSS statistical software, version 23 for Windows (SPSS Inc., Chicago, IL, USA). Differences in the maternal age, birth age, cervical dilatation, interval of uterine contraction, birth weight, and umbilical artery blood pH between SLG and ILG groups were assessed by the unpaired $t$-test. Differences in Apgar scores between the groups were investigated with the Mann-Whitney $U$ test. The percent change of each index during uterine contraction was assessed by the Wilcoxon Signed-rank test. Differences in variables at each stage between SLG and ILG groups were investigated with the Mann-Whitney $U$ test. Intra- and inter-class correlation coefficients were used as an expression of reliability [8]. Intra- and inter-class correlation coefficients were defined as the correlation between any two measurements from the same data during uterine contraction (at the peak of contraction). Their values ranged from zero to one; the latter indicates maximum reliability. Intra- and inter-observer variability were calculated according to Bland and Altman's procedure [9] in 20 samples (11 in SLG and 9 in ILG). Intra-observer variation was examined by M.S., and inter-observer variation was assessed by M.S. and J.N. This analysis consisted of a graph, in which the difference between the measurements (y-axis)

**Table 1**
Clinical characteristics of subjects.

| Subject | n | Maternal age (yo) | Parity | Birth age (weeks) | Cervical dilatation (cm) | Uterine contraction interval (min) | Birth weight (g) | Apgar score | | UApH |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1 min | 5 min | |
| | | Mean (SD) | Median (range) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Median (range) | Median (range) | Mean (SD) |
| Spontaneous labor | 32 | 29.9 (5.4) | 0 (0–2) | 39.5 (0.9) | 6.1 (3.1) | 3.8 (0.9) | 3028.9 (230.3) | 8 (7–10) | 9 (7–10) | 7.31 (0.08) |
| Induced labor | 18 | 29.6 (3.9) | 0 (0–2) | 40.5 (0.9) | 5.9 (3.3) | 3.3 (0.6) | 3212.7 (295.8) | 8 (5–9) | 9 (7–10) | 7.28 (0.08) |
| Significance | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |

yo, years olds; min, minute; SD, standard deviation; NS, not significant; UApH, umbilical artery blood pH.
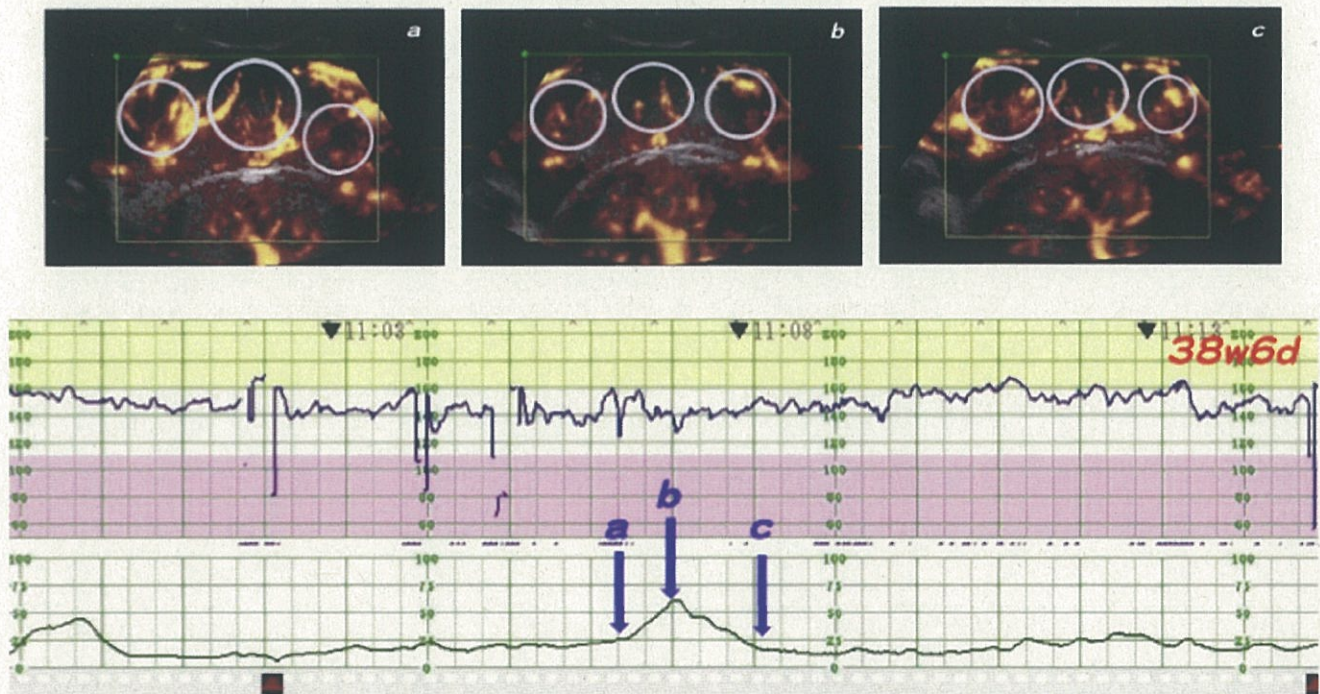
**Fig. 1.** CTG tracing and the timing of placental vascular sonobiopsy examination using 3D power Doppler ultrasound at 38 weeks and 6 days of gestation. Each sphere of placental tissue was obtained between the basal and chorionic plates. *a*, before uterine contraction (at the start of contraction); *b*, during uterine contraction (at the peak of contraction); *c*, after uterine contraction (at the end of contraction).

was plotted against their mean value (x-axis). The 95% limits of individual agreement between the two measurements were calculated as the mean difference between two measurements $\pm2.0$ standard deviations. Moreover, the difference between the mean difference and zero was assessed by a two-sample $t$-test. A $P$-value $< 0.05$ was considered significant.

## 3. Results

There were no significant differences in the maternal age, parity, birth age, cervical dilatation at examination (SLG: mean, 6.1 cm [SD: $\pm$ 3.1], and ILG, 5.9 cm [$\pm$ 3.3]), interval of uterine contraction at examination (SLG: mean, 3.8 min [SD: $\pm$ 0.9], and ILG, 3.3 min [$\pm$ 0.6]), birth weight, Apgar scores at 1 and 5 min, or umbilical artery blood pH between the two groups (Table 1). There was no fever-up during delivery. All women had a normal vaginal delivery. Within 24 h after delivery, an extensive pediatric assessment was performed of each neonate. No neonate was found to have congenital anomalies or genetic disorders.

There were no abnormal fetal heart rate tracings during contraction in either group. The percent change of each vascular index value during uterine contraction in both groups is shown in Table 2. VI (SLG: median, −30.4% [range: −95.6–9.7%], and ILG, −45.1% [−76.0–3.5%]) and VFI (SLG, −33.4% [−97.0–15.2%], and ILG, −49.6% [−78.2–−4.0%]) values were significantly reduced during uterine contraction in both groups, respectively ($P < 0.001$). The FI value in the ILG group was significantly lower during uterine contraction ($P = 0.035$), whereas it did not change during uterine contraction in the SLG group. After uterine contraction, all vascular indices returned almost to the same level at that before uterine contraction. However, the FI value in ILG (−8.6%, [−19.7–16.0%]) was significantly lower than that in SLG (2.4%, [−13.4–38.1%]) after uterine contraction ($P < 0.05$). There were no significant differences in any vascular index values during uterine contraction, nor any significant differences in VI or VFI values after uterine contraction between SLG and ILG groups.

### 3.1. Intra-observer agreement

The mean difference between measurements and the limits of agreement for each of the parameters studied during uterine contraction (at the peak of contraction) are shown in Table 3. The mean difference and 95% limits of intra-observer agreements for VI, FI, and VFI were 0.296% (5.997, −5.404), 1.597 (8.209, −5.016), and 0.567 (4.258, −3.125), respectively. The difference between the mean difference and zero was not significant for VI or VFI, but was weakly significant for FI ($P = 0.048$). Intra-class correlation coefficients for each of the parameters studied are also shown in Table 3. VI, FI, and VFI had intra-class correlation coefficients of 0.940, 0.711, and 0.925, respectively ($P < 0.0001$).

### 3.2. Inter-observer agreement

The mean difference between the two investigators (M.S. and J.N.) and the limits of agreement for each of the parameters studied during uterine contraction (at the peak of contraction) are shown in Table 4. The mean difference and 95% limits of inter-observer agreements for VI, FI, and VFI were −1.149% (5.644, −7.942), 0.481 (5.813, −4.852), and −0.156 (3.317, −3.628), respectively. The difference between the mean difference and zero was not significant for each 3D power Doppler vascularity index. Inter-class correlation coefficients for each of the parameters studied are also shown in Table 4. VI, FI, and VFI had inter-class correlation coefficients of 0.923, 0.836, and 0.908, respectively ($P < 0.0001$).

In this study, good intra- and inter-class correlation coefficients and intra- and inter-observer agreements were confirmed.

**Table 2**
Percent change of each index value during uterine contraction.

| Subject | n | Parameter | Percent change | |
|---|---|---|---|---|
| | | | Median (range) | |
| | | | During | After |
| Spontaneous labor | 32 | VI | −30.4[a] (−95.6−9.7) | −2.4 (−65.2−209.6) |
| | | FI | −2.9 (−28.7−20.1) | 2.4[c] (−13.4−38.1) |
| | | VFI | −33.4[a] (−97.0−15.2) | 2.7 (−69.6−296.9) |
| Induced labor | 18 | VI | −45.1[a] (−76.0−3.5) | −4.5 (−55.2−79.9) |
| | | FI | −4.6[b] (−36.3−10.9) | −8.6[c] (−19.7−16.0) |
| | | VFI | −49.6[a] (−78.2−−4.0) | −11.9 (−61.2−68.3) |

VI, vascularization index; FI, flow index; VFI, vascularization flow index; a, $p < 0.001$; b, $p = 0.035$; c, $p = 0.014$. Data are presented as percent change compared with the value before uterine contraction.

**Table 3**
Intra-class correlation coefficient and intra-observer agreement for placental vascularity indices.

| Parameter | Mean difference | 95% CI | Limits of agreement | P value | ICC | P value |
|---|---|---|---|---|---|---|
| VI (%) | 0.296 | −1.065 to 1.657 | 5.997 to −5.404 | 0.654 | 0.940 | <0.0001 |
| FI | 1.597 | 0.018 to 3.176 | 8.209 to −5.016 | 0.048 | 0.711 | <0.0001 |
| VFI | 0.567 | −0.315 to 1.448 | 4.258 to −3.125 | 0.194 | 0.925 | <0.0001 |

VI, vascularization index; FI, flow index; VFI, vascularization flow index; 95% CI, 95% confidence interval; ICC, intra-class correlation coefficient.

**Table 4**
Inter-class correlation coefficient and inter-observer agreement for placental vascularity indices.

| Parameter | Mean difference | 95% CI | Limits of agreement | P value | ICC | P value |
|---|---|---|---|---|---|---|
| VI (%) | −1.149 | −2.771 to 0.473 | −7.942 to 5.644 | 0.155 | 0.923 | <0.0001 |
| FI | 0.481 | −0.793 to 1.754 | −4.852 to 5.813 | 0.439 | 0.836 | <0.0001 |
| VFI | −0.156 | −0.985 to 0.673 | −3.628 to 3.317 | 0.698 | 0.908 | <0.0001 |

VI, vascularization index; FI, flow index; VFI, vascularization flow index; 95% CI, 95% confidence interval; ICC, inter-class correlation coefficient.

Therefore, the measurement values from only one examiner (M.S.) were used for statistical analysis.

## 4. Discussion

In the present study, uterine contraction in both spontaneous and induced labors led to a significant reduction in placental perfusion. The main reason for this significant reduction in placental perfusion during uterine contraction is that uterine contractions prevent blood flow into the intervillous space [10,11]. Interestingly, the reduced placental blood flow in induced uterine contraction had a tendency to be more marked compared with that in spontaneous uterine contraction. Similar findings have also been obtained in animal experiments [1–3]. Moreover, the recovery of placental blood flow after uterine contraction was rapid in spontaneous labor compared with induced labor. The explanation for these discrepancies between spontaneous and induced uterine contractions may be the significantly higher intensity of labor produced by oxytocin and prostaglandins [2,3]. Another explanation is that prostaglandin $F_{2\alpha}$ has a strong vasoconstrictive effect on both uterine and umbilical circulations [12]. This may explain the differences between the groups. Therefore, these results suggest that we may have to pay attention to the use of oxytocin and prostaglandin $F_{2\alpha}$ for the induction of labor due to the significantly higher intensity of uterine contractions produced by these agents.

Fetal heart rate tracings during uterine contraction in SLG and ILG groups showed no decelerations in this study, although there was a significant reduction in placental blood flow during uterine contraction in both groups. Stuart et al. [13] reported that placental vascular resistance to feto-placental blood flow was not altered by uterine contractions nor the infusion of oxytocin during uncomplicated labor. There was no difference in fetal oxygenation in the intervillous spaces between spontaneous and oxytocin-induced labors [14]. Subjects enrolled in the present study all had normal pregnancies, and normal vaginal deliveries. Moreover, umbilical artery data in all subjects were normal during pregnancy. Neonatal outcomes were also very favorable. Therefore, feto-placental functions in all pregnancies in this study were good, and each fetus was suggested to have a good reserve capacity to compensate for uterine contractions in labor.

In the present study, we only examined an entirely visualized anterior placenta to keep the maximum depth of the placenta constant [4,5], because there was a significant reduction in each vascular index value assessed by 3D power Doppler as the distance between the transducer and vascular tree volume increased [15]. Zalud and Shaha [16] stated that only anterior placentas should be included in 3D power Doppler studies to avoid the risk of Doppler signal attenuation. This limitation and disadvantage of 3D power Doppler histogram analysis will be resolved as further technical advances are made.

To the best of our knowledge, this is the first study on non-invasive assessment of placental perfusion during spontaneous and induced uterine contractions in labor using PVS by 3D power Doppler ultrasound with the VOCAL imaging histogram analysis. However, the data and their interpretation in the present study should be taken with some degree of caution because of the small number of subjects studied. Further studies involving a larger sample size are needed to evaluate placental blood flow and vascularity using PVS during normal and abnormal uterine contractions in normal and high-risk pregnancies.

## Conflict of interest

The authors have no conflict of interest.

## Acknowledgements

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