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Acute centralization of blood flow in compromised human fetuses evoked by uterine contractions

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Short title: Middle cerebral artery blood flow during the OCT

Key words: Cerebral; Doppler; Middle cerebral artery; Pregnancy; Pulsatility index; Umbilical

ABSTRACT

Background: During fetal hypoxia blood is redistributed to the brain ('brain-sparing'). Sequential changes of the cerebral and placental circulation in parallel in comparisons between basal conditions and acute hypoxic stress have not yet been thoroughly studied in human fetuses.

Aim: To explore acute fetal middle cerebral artery (MCA) circulatory changes relative to umbilical artery (UA) blood flow in a clinical experimental model with hypoxic stress provoked by uterine contractions during an oxytocin challenge test (OCT).

Study design: Prospective comparative between imminently compromised (OCT positive) and un-compromised (OCT negative) fetuses.

Subjects and methods: 82 term pregnancies suspected of intrauterine growth restriction were exposed to simultaneous electronic fetal heart rate monitoring and Doppler recordings of pulsatility index (PI) in the UA and MCA during basal conditions and during uterine contractions and relaxations at an OCT.

Outcome measures: Sequential changes of UA and MCA PI, OCT positive vs. negative cases. Nonparametric statistics with a $P < 0.05$ considered significant.

Results: The UA PI was significantly higher in OCT positive cases ($N = 10$) compared with OCT negative cases ($N = 72$) during uterine contractions and relaxations, but not during basal measurements. During contractions and relaxations the MCA PI decreased significantly in both groups (brain-sparing), but significantly more in OCT positive cases.

Conclusions: During acute hypoxic stress, changes towards a centralization of blood flow to the brain develop in imminently compromised (OCT positive) fetuses at an

expense of the umbilicoplacental blood flow, and the brain-sparing flow is more pronounced than in un-compromised (OCT negative) fetuses.

INTRODUCTION

Animal experiments have revealed that chronic as well as acute fetal hypoxia causes a centralization and priority of blood flow to vital organs, such as the brain, heart, and adrenal glands.¹⁻³ In human pregnancy with fetal intrauterine growth restriction (IUGR) this represents a chronic state.⁴ As part of the circulatory response to hypoxia, a decrease of vascular flow resistance in the fetal middle cerebral artery (MCA) has then been demonstrated.^{5,6} This redistribution of blood flow, a 'brain-sparing' effect, suggests an adaptation of the fetal circulation to hypoxemia.^{5,6}

In the human fetus redistribution of blood flow may be a response to chronic compromise rather than to an acute development of hypoxemia. During the first stage of labor and in the absence of fetal distress, Maesel *et al.*⁷ found no significant changes of fetal MCA blood flow in association with uterine contractions. Late in the first stage and in the second stage of labor increments of vascular resistance during uterine contractions have been demonstrated in other cerebral vessels, such as the internal carotid artery⁸ and anterior cerebral artery.⁹ However, such changes may be caused by persistent external pressure on the fetal head as the head is molded, since direct mechanical pressure on the fetal skull causes momentary blood flow reductions.^{10,11}

We have in previous studies demonstrated occurrence of acute and transient blood flow changes in the uterine and umbilical circulations in compromised fetuses exposed to short-lasting interruptions of oxygen delivery by uterine contractions.^{12,13} By performing Doppler velocimetry simultaneous to electronic fetal heart rate (FHR) monitoring during an oxytocin challenge test (OCT), we demonstrated a transient

increase of vascular flow resistance in the umbilical artery (UA) as well as in the uterine artery. The aim of the present study was to explore acute changes in the fetal cerebral circulation relative to placental flow by recording MCA and UA blood flows before and during uterine contractions in a series of IUGR fetuses at term.

MATERIAL AND METHODS

The study comprised a consecutive series of 82 women at a gestational age of at least 36 completed weeks with a suspicion of IUGR and no definite indication to perform an elective cesarean section (CS). The managing obstetricians' uncertainty about the optimal time and mode of delivery was a prerequisite, and hence, an increased UA vascular flow resistance ($> \text{mean} + 2 \text{ SD}$ according to reference values¹⁴) was then an additional indication in 26 cases. Since absent or reversed end-diastolic flow in the UA is an absolute indication for a CS at our unit, such cases were excluded.

The experiment with simultaneous Doppler velocimetry and electronic FHR recordings during the OCT was approved by the Lund University Research Ethics Committee and all participating women gave their informed consent. The results of the basal UA blood flow measurements were revealed to the obstetricians whereas other flow results were concealed.

According to our routines, all 82 pregnancies were dated with an early second trimester ultrasound fetometry and all scanned again at 32 weeks. IUGR was defined as an ultrasonically estimated fetal weight below the gestational age-adjusted mean value minus 2 SD ($N = 72$), or a fall of $\geq 1 \text{ SD}$ between two fetometries ($N = 10$).

The procedure of simultaneous Doppler velocimetry and OCT has previously been described.^{12,13,15} By using an Acuson Sequoia 512 real-time ultrasound scanner (Acuson, Mountain View, CA, USA) equipped with an automatic step-less 2.5 to 6 MHz probe with pulsed and color flow Doppler options, Doppler velocimetry for basal UA and MCA measurements was performed immediately before the OCT

started. The apparatus has an automatic adjustment of the high-pass filter. Flow velocity waveforms (FVW) in the UA were recorded from a free-floating part of the cord. By color Doppler ultrasound, the MCA was identified as a major lateral branch of the Circle of Willis running antero-laterally towards the lateral edge of the orbit on a transverse section of the fetal head at the level of the cerebral peduncles. Pulsations in the MCA in the Sylvian fissure were identified. The pulse Doppler gate was applied to the middle portion of the lateral branch. FVWs were recorded at an insonation angle close to 0°. The mean pulsatility index (PI) was calculated from three consecutive FVWs of optimal quality.

The OCT was started with an intravenous oxytocin infusion at a rate of 6 mL/h (corresponding to 1 milli-unit/min when 5 units of oxytocin is diluted in 500 mL 5.5 % glucose). The infusion rate was doubled every 10 minutes until three uterine contractions per 10-minute window occurred and then maintained during the whole procedure. The maximal infusion rate was set at 96 mL/h (16 milli-units/min). The FHR patterns were interpreted relative to contractions and the OCT classified positive (late FHR decelerations) or negative according to Freeman's criteria.¹⁶ Although positive OCT cases may be optioned for a trial of vaginal delivery at other delivery units, such cases were delivered by a CS on the same day at our department, whereas in cases of negative OCT labor was induced or spontaneous labor awaited. The median time from OCT to delivery in the latter group was 1 day (range 0 - 21).

During the OCT, FVWs were recorded during the peak of contractions and during relaxations between uterine contractions. For each vessel, FVWs were recorded during one contraction and one relaxation and the mean PI was calculated as for basal

measurements. During tachycardia or bradycardia the FHR may influence the diastolic flow velocity and the calculation of PI, and FHR may then correlate negatively with the UA PI. To allow statistical comparisons, the PI values for both the UA and MCA were adjusted for changes of FHR according to the equation: Corrected PI = observed PI - constant • (mean FHR – observed FHR) in case a significant linear correlation existed between FHR and PI. At such relationships, the individual PI was adjusted to a FHR that represented the mean value in the group.

The PI was classified normal when within mean \pm 2 SD according to reference values for UA¹⁴ and MCA.¹⁷ The normal range (mean \pm 2 SD) of MCA PI at term is 0.93 to 1.89. The cerebral-to-umbilical vascular resistance ratio was expressed as the MCA PI/UA PI ratio. Brain-sparing was defined as a ratio of $<$ 1.08 according to Gramellini *et al.*¹⁷ However, this definition is valid only for basal measurements and not for the dynamic changes during the OCT, since the UA PI is likely to increase during uterine contractions in OCT positive cases.^{12,13} Thus, during uterine contractions and relaxations a decrease of MCA PI of \geq 1 SD was arbitrary chosen to imply a *de novo* brain-sparing effect. According to Gramellini *et al.*¹⁷, 1 SD corresponds to a MCA PI value of 0.24 at term. This level of change was also chosen to define an increase of MCA PI, i.e., changes within \pm 0.23 were regarded as no significant change.

The UA and MCA PI changes during the OCT were compared with regard to the OCT result (positive or negative OCT), birthweight cohorts (appropriate-for-gestational age = AGA = mean \pm 2 SD; small-for-gestational age = SGA = below mean – 2 SD; large-for-gestational age = LGA = above mean + 2 SD)¹⁸, operative delivery for fetal distress (ODFD; CS, ventouse or forceps delivery due to abnormal

FHR pattern¹⁹ in labor) in cases of negative OCT allowed a trial of labor, and neonatal distress (5-minute Apgar score < 7 and/or umbilical cord arterial blood pH < 7.10 and/or venous blood pH < 7.15).

Statistical analyses: The Chi-square test and Fisher's exact test were used for comparison of categorical variables, the Mann-Whitney *U* test for comparison of cross-sectional non-paired variables, and the Wilcoxon matched-pairs signed-rank test ('Wilcoxon's test') for variables recorded longitudinally. Simple linear regression analysis was used to show relationships between variables. Odds ratios (OR) with 95 % confidence intervals (CI) were calculated. *P* values were corrected for ties and a two-tailed *P* < 0.05 was considered significant. Statistics were performed with aid of StatView[®] (SAS Institute, Cary, NC, U.S.A.) and MedCalc[®] (MedCalc Software, Mariakerke, Belgium) computer softwares.

RESULTS

The OCT was positive in 10 cases and negative in 72 cases. There was no difference in gestational age between OCT positive and negative cases (Mann-Whitney U test; $P = 0.4$), or between SGA ($N = 50$) and AGA ($N = 32$) cases ($P = 0.7$).

A significant negative correlation between FHR and PI was found only for MCA PI during contractions (simple linear regression; $P = 0.005$), and the MCA PI was corrected accordingly.

An UA PI above the reference range ($> \text{mean} + 2 \text{SD}$) was more common in OCT positive than in OCT negative cases, but the difference did not reach statistical significance (6/10 vs. 20/72; Fisher's test, $P = 0.06$). The UA PI was higher in OCT positive cases compared with OCT negative cases during contractions and relaxations (Mann-Whitney U test; $P = 0.03$ and 0.07 , respectively), but not during basal measurements ($P = 0.2$) (Figure 1). In neither the OCT positive nor the OCT negative group did the UA PI change significantly between basal measurements and measurements during the OCT (Wilcoxon's test; $P \geq 0.2$).

The changes of MCA PI relative to OCT outcome are shown in Figure 2. During basal conditions the PI was not different between the two groups, and during contractions and relaxations the PI decreased significantly in both groups. The MCA PI in OCT positive cases was significantly lower than in negative cases during uterine contractions and relaxations.

In the 26 cases of high basal UA PI, the MCA PI was neither during basal measurements, contractions, nor relaxations higher than in the 56 cases with normal basal UA PI (Mann-Whitney U test; $P \geq 0.4$).

There was no significant difference between the OCT groups regarding the prevalence of neonatal distress or SGA (Table 1). No newborn in the series had a 5-min Apgar score < 7 , so both cases of neonatal distress were due to low cord blood pH.

In comparisons between the ODFD ($N = 9$) and non-ODFD group ($N = 63$), there were no significant differences for UA PI or MCA PI during basal measurements, contractions or relaxations (Mann-Whitney U test; $P \geq 0.3$ and ≥ 0.2 , respectively). In neither the ODFD nor the non-ODFD group did the UA PI change significantly during contractions and relaxations compared with basal measurements (Wilcoxon's test; $P \geq 0.2$). During contractions and relaxations, the MCA PI decreased significantly in the non-ODFD group but not in the ODFD group ($P = 0.002$ and 0.007 , respectively, and 0.7 and 0.3 , respectively). A MCA PI decrease of ≥ 0.24 was found in three cases in the ODFD group and in 28 cases in the non-ODFD group (Fishers exact test; $P = 0.7$).

Table 1 also shows MCA PI data related to the OCT outcome. All five cases of low basal MCA PI belonged to the OCT negative group. Brain-sparing flow during basal conditions (MCA/UA PI < 1.08) and a *de novo* brain-sparing flow during contractions (MCA PI decrease ≥ 0.24) were equally common in the groups. Altogether 14 fetuses, all OCT negative, showed an increase of ≥ 0.24 during uterine contractions. None of these babies suffered neonatal distress but two ODFD.

Blood flow results relative to birthweight are shown in Table 2. There was no case of LGA in the series. During basal conditions the MCA PI was lower in SGA cases, but otherwise no significant differences were found. The MCA PI decreased from basal measurements to contractions and relaxations both in the AGA group (Wilcoxon's test; $P = 0.002, 0.04$) and the SGA group ($P = 0.01, 0.003$). No difference in UA PI was found between the groups during any condition (results not shown, Mann-Whitney U test; $P \geq 0.5$). ODFD was more common in SGA than AGA babies, though not significantly different (8/45 vs. 1/27, Fisher's test; $P = 0.1$)

DISCUSSION

The fetal arteriolar oxygen saturation falls to 5-10 % below baseline levels during uterine contractions.²⁰ During the OCT, an already imminently compromised fetus with a restricted oxygen reserve may have difficulties to cope with this hypoxemia. The fetus is then likely to unveil itself by late FHR decelerations as a classical sign of impending hypoxia. In such fetuses, represented by OCT positive cases in the present study, the response to contractions was a decrease of the vascular flow resistance in the MCA. However, also fetuses better resisting hypoxemia, i.e., those with a negative OCT, showed a decrease of MCA PI. This 'brain-sparing flow' phenomenon has previously been demonstrated during labor contractions in healthy fetuses²¹ and in fetal lambs exposed to hypoxia²², suggesting it is a normal physiological response to acute hypoxemia.

The response with a lowered cerebral vascular flow resistance was more pronounced in fetuses with a positive OCT than in OCT negative cases. In addition, umbilical artery vascular resistance became higher in OCT positive than in OCT negative cases during uterine contractions and relaxations, suggesting a circulatory redistribution with a centralization of blood flow to the brain at an expense of the umbilicoplacental blood flow in OCT positive cases.

During the early development of hypoxia there is a good correlation between the oxygen content in blood and the cerebral vascular impedance to flow, but by sustained hypoxia acidosis subsequently develops and then the cerebral vascular resistance increases.²³ In severely asphyxiated fetal sheep, an increase of cerebral vascular flow resistance is a sign of decentralization of flow and leads to fetal demise if sustained.²²

It is interesting that in the present cases of impending hypoxia, i.e., in cases with positive OCT, ODFD, or neonatal distress, there was no fetus with a significant increase of MCA PI during contractions. All fetuses with increasing cerebral vascular flow resistance belonged to the OCT negative group and did well during the neonatal period. Although the series included no fetus with signs of severe hypoxia, the disconcert results in sheep and human experiments may in part be explained by the inability in animal experiments to perfectly mimic a clinical situation with an acutely superimposed hypoxic challenge to a chronically hypoxic fetus. According to the present study, an acute increase of cerebral flow resistance during contractions is not a rare response and seems to be an innocent sign in the absence of severe hypoxia and acidosis.

The low cerebral flow impedance induced by uterine contractions did not return to baseline levels during relaxations, neither in OCT positive nor in negative cases. Indeed, the MCA PI remained in between contractions at the same lowered magnitude as during contractions. This suggests that after the initial cerebral vasodilatory response to contractions, there are no major changes of cerebral vascular flow resistance. These findings are in concordance with other studies on fetal cerebral blood flow during labor. In healthy fetuses, Yagel *et al.*²¹ measured MCA flow between uterine contractions in labor and found a lower resistance compared with controls measured during basal conditions, and Maesel *et al.*⁷ found no difference between measurements performed during contractions and relaxations. These and our results suggest that in both healthy and moderately compromised fetuses at term, once labor has started there are no large oscillatory changes of MCA flow resistance related to the contraction pattern, at least not in the early stages of labor. It takes

approximately 2 minutes for the oxygen saturation to fully recover after a contraction²⁰ and in fetal sheep exposed to acute short-lasting hypoxia it takes up to 5 minutes before the cerebral vascular flow resistance has returned to the baseline level.²⁴ Hypoxia and hypercapnia are potent and rapid stimuli for cerebral vasodilatation²⁵, and with repetitive uterine contractions it is likely that carbon dioxide will accumulate in fetal blood and the oxygen supply will remain at suboptimal levels also during a substantial time of the uterine relaxations.

The study included an evaluation of blood flow changes relative to fetal growth restriction, ODFD, and neonatal distress. Only two newborns suffered neonatal distress and this outcome parameter could then not be evaluated. Poor fetal growth is commonly associated with hypoxia and centralization of blood flow⁴, and as expected the MCA PI was significantly lower in SGA fetuses than AGA fetuses during basal conditions. During contractions and relaxations the MCA PI decreased in both groups, and then the difference between the groups disappeared. These results indicate that a low MCA PI is a hallmark of fetal growth restriction when performed during basal conditions, but not when performed during uterine contractions.

ODFD occurred in 14 % of women allowed a trial of labor, i.e., in those with a negative OCT. No difference in MCA vascular flow resistance was found during any condition in comparison between cases with and without ODFD. During contractions and relaxations, the MCA PI decreased significantly in the latter group but not in the former, opening a theoretical possibility to distinguish between the groups by performing MCA Doppler velocimetry before and during labor. However, when cases

showing a PI decrease of 1 SD or more during the OCT were compared, there was no difference between the groups with and without ODFD.

In summary, fetuses showing an impaired ability to resist hypoxic stress during the OCT responded with a more profound cerebral vasodilatation during the test than fetuses resisting hypoxemia well. Once the cerebral vasodilatation was established during the OCT it remained unaffected relative to the contraction pattern. In contrast to OCT negative cases, OCT positive cases showed a centralization of blood flow at the expense of placental blood flow. During chronic hypoxia, a decentralization of blood flow is regarded an ominous sign of fetal distress, but in this study fetuses responding to contractions with an acute increase of cerebral vascular flow resistance all did well.

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Table 1

Outcome measures relative to the result of the oxytocin challenge test (OCT).

	OCT positive		OCT negative		Significance of difference (<i>P</i>)	Odds ratio	95 % confidence interval
	N = 10	%	N = 72	%			
Neonatal distress	0	0	2	2.8	1.0	-	-
ODFD ^a	-	-	9	12.5	-	-	-
SGA ^b	5	50.0	45	62.5	0.7	0.60	0.16-2.26
MCA PI < 0.93 ^c	0	0	5	6.9	1.0	-	-
MCA/UA PI ratio < 1.08 ^d	3	30.0	12	16.7	0.4	2.14	0.48-9.49
MCA PI change during contractions							
Decrease $\geq 0.24^e$	7	70.0	31	43.1	0.2 ^f	3.09	0.74-12.90
Unchanged $\pm 0.23^e$	3	30.0	27	37.5			
Increase $\geq 0.24^e$	0	0	14	19.4			

ODFD = operative delivery for fetal distress (trial of labor allowed only in OCT negative cases); SGA = small-for-gestational age; MCA = middle cerebral artery; PI = pulsatility index; UA = umbilical artery.

- a) Cesarean section, ventouse or forceps delivery performed during labor due to impending fetal distress
- b) Birthweight < mean – 2 SD; Statistics in comparison with appropriate-for gestational age neonates (no cases of large-for-gestational age)
- c) MCA PI = 0.93 corresponds to the mean – 2 SD in term pregnancy at basal measurements
- d) MCA/UA PI ratio < 1.08 is the definition for redistribution of blood flow with priority for cerebral flow ('brain-sparing')
- e) 0.24 PI unit corresponds to 1 SD in term pregnancy at basal measurements
- f) Fisher's exact test on merged data: cases with decrease of PI compared with cases with unchanged plus increase of PI

Table 2

Blood flow results relative to birthweight.

	SGA		AGA		Significance of	Odds ratio	95 % confidence
	N = 50	%	N = 32	%	difference (<i>P</i>)		interval
MCA PI < 0.93	5	10.0	0	0	0.2	-	-
MCA/UA PI ratio < 1.08	11	22.0	4	12.5	0.4	1.97	0.57-6.84
MCA PI (mean \pm SD)							
Basal measurement	1.42 \pm 0.41		1.58 \pm 0.34		0.046		
Contraction	1.27 \pm 0.34		1.36 \pm 0.40		0.3		
Relaxation	1.26 \pm 0.33		1.44 \pm 0.49		0.1		

AGA = appropriate-for-gestational age

LEGENDS TO FIGURES

Figure 1

Umbilical artery pulsatility index during basal conditions and during the oxytocin challenge test (OCT). A positive OCT represents late fetal heart rate decelerations relative to uterine contractions. Mean and standard deviation values are indicated. Double-pointing arrows indicate the statistical difference (Mann-Whitney U test or Wilcoxon matched-pairs signed-ranks test).

Figure 2

Middle cerebral artery pulsatility index during basal conditions and during the OCT. Mean and standard deviation values are indicated. Double-pointing arrows indicate a statistically significant difference of $P < 0.05$ (Mann-Whitney U test or Wilcoxon matched-pairs signed-ranks test).



