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Intracerebral regional distribution of blood flow in response to uterine contractions in growth-restricted human fetuses

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ABSTRACT

OBJECTIVE: To explore middle cerebral artery (MCA) and anterior cerebral artery (ACA) blood flow responses to superimposed acute hypoxemia in growth-restricted fetuses with and without established brain-sparing flow during basal conditions.

MATERIAL AND METHODS: 47 term fetuses suspected of growth restriction were exposed to an oxytocin challenge test with simultaneous cardiotocography and Doppler velocimetry in the umbilical artery, MCA and ACA. The MCA-to-ACA pulsatility index (PI) ratio was calculated during basal conditions, contractions and relaxations. Basal brain-sparing flow was defined as a MCA-to-umbilical artery PI ratio of < 1.08, *de novo* brainsparing flow in the MCA as a MCA PI decrease with ≥ 1 standard deviation during uterine contractions or relaxations compared with basal measurements, and *de novo* brain-sparing flow in the ACA as an ACA PI decrease with ≥ 1 standard deviation. Non-parametric statistical tests were used with $P < 0.05$ considered significant.

RESULTS: MCA and ACA PI were both significantly lower in the brain-sparing flow group (N = 8) during basal conditions ($P \leq 0.01$). During the oxytocin challenge test, MCA and ACA PI both decreased in the non-brain-sparing flow group (N = 39) ($P \leq 0.02$) but not in the brain-sparing flow group ($P \geq 0.4$). The MCA-to-ACA PI ratio remained unchanged in both groups. *de novo* brain-sparing flow calculations revealed no preferential flow to any cerebral artery.

CONCLUSION: Cerebral circulatory responses to acute hypoxemia are synchronized in the middle and anterior cerebral arteries without any preferential regional flow distribution.

INTRODUCTION

Redistribution of blood flow from the carcass to the brain and other vital organs is an important fetal defense mechanism to sustain hypoxia [1,2]. The fetal cerebral circulation can be estimated non-invasively with Doppler ultrasound flow velocimetry in the large cerebral arteries and veins, where an increase in the cerebral arterial circulation is characterized by an increment of diastolic flow velocity and a decrement of vascular flow resistance [3]. This 'brain-sparing' effect is a beneficial physiological adaptation for a limited period of time, but may ultimately not prevent brain lesions in case of sustained hypoxia [4].

In fetuses with intrauterine growth restriction (IUGR), the brain-sparing flow (BSF) phenomenon can be detected in both the middle cerebral artery (MCA) and anterior cerebral artery (ACA) [5,6]. There is evidence that during chronic hypoxia, a BSF in the ACA is more frequent, less transitory, and better indicates adverse perinatal outcomes than BSF in the middle or posterior cerebral arteries [7]. Dubiel *et al.* [7] speculate that during chronic hypoxia the cerebral regions nourished from the ACA is spared longer than regions nourished from other cerebral arteries. No study has yet addressed this issue during acute hypoxic stress.

In previous studies, using the oxytocin challenge test (OCT) as a clinical tool to reveal fetuses at increased risk of developing hypoxia in labor, and as an experimental human model to study fetal circulatory changes in response to acute oxygen deprivation, we

have found that fetuses with a normal cerebral circulation during basal conditions respond with a BSF during uterine contractions, whereas fetuses with an established BSF during basal conditions have a restrained capacity to further increase the cerebral perfusion [8,9]. As a further step of our previous observations, we wanted to elucidate whether some cerebral region has priority in blood supply during development of an acute BSF. For that purpose, we compared flows in the MCA and ACA.

MATERIAL AND METHODS

A consecutive series of 47 women with a singleton pregnancy at a gestational age of ≥ 36 weeks and with a fetus suspected of IUGR were exposed to an OCT on clinical indications, to decide the time and mode of delivery. The experiments with simultaneous Doppler velocimetry and electronic fetal heart rate (FHR) recordings during the OCT [10,11] were approved by the Lund University Research Ethics Committee and all women gave their informed consent to participate in the study. Umbilical artery (UA), MCA, and ACA flow velocity waveforms (FVWs) were recorded during basal conditions and during an OCT. The result of the basal UA measurements was revealed to the obstetrician in charge, but other flow results were concealed. Women with absent or reversed end-diastolic flow in the UA were not exposed to an OCT, but delivered by a cesarean section (CS).

Ultrasound screening for dating was performed in the early second trimester and for fetal growth in weeks 32-33 in all cases. Suspected IUGR was defined as an ultrasonically estimated fetal weight deviation (WD) below the gestational age-adjusted mean weight minus 22 %, corresponding to mean -2 standard deviations (SD) according to reference values [12], or a fall of ≥ 10 % WD between two ultrasound measurements.

To mimic labor contractions, an intravenous oxytocin infusion was started from 6 mL/h (5 units of oxytocin in 500 mL 5.5% glucose) and doubled every 10 minutes until three

uterine contractions per 10-minute period occurred repeatedly. The OCT was classified positive (late FHR decelerations) or negative according to Freeman's criteria [13]. Although the OCT may occasionally be false positive, at our department a CS is promptly performed in cases of positive OCT. In cases of negative OCT, labor was induced or spontaneous labor was awaited. The median time from OCT to delivery in the latter group was 1 day (range 0-21; 0-1 day in 29 cases, 2-9 days in 12 cases, 14 days and 21 days in 1 case each).

During the OCT, FVWs were recorded during the peak of contractions and during relaxations. In each examined vessel, the mean pulsatility index (PI) of three consecutive FVWs was calculated from optimal quality recordings performed during basal conditions, during one uterine contraction, and during one relaxation period.

The blood flow measurements were performed with an Acuson Sequoia 512 real-time ultrasound scanner (Acuson, Mountain View, CA, USA), using an automatic step-less 2.5 to 6 MHz probe with pulsed and color Doppler flow options. This equipment has an automatic adjustment of the high-pass filter. The mechanical index and thermal index were both under 1 for exposure to Doppler output energy. Signals during basal conditions were recorded during fetal and uterine quiescence. UA FVWs were recorded from a free loop of the cord. By color Doppler imaging, the circle of Willis was identified in a transverse view of the fetal head at the level of the cerebral peduncles, with the MCA identified as a major lateral branch running anterior-laterally, and the

ACA as a branch running anterior. In the MCA the sampling volume was placed in the middle portion of the vessel at an insonation angle close to 0˚, and in the ACA the sampling volume was placed approximately 1 cm from the branching off the circle of Willis at an insonation angle of less than 30˚.

The MCA supplies the central and lateral areas of the frontal, parietal, and temporal lobes, plus insula, claustrum, basal ganglia (including caudate nucleus, putamen and globus pallidus) and internal capsule in the central parts of the hemispheres (Fig. 1a-c). The internal capsule is a white matter structure between thalamus and caudate nucleus on the medial side and the globus pallidus and putamen laterally; it contains largely myelinated pathways passing to and from the cerebral cortex. A functional impairment of cortical tissues supplied by the MCA will then strike large parts of motor, somatosensory and auditory centers, and important areas for language. A functional impairment of the basal ganglia will result in a variety of dysfunctions among which motor dysfunctions are the most obvious. Involvement of the internal capsule will result in interrupted cortical-subcortical connections.

The ACA nourishes the antero-medial cerebral cortex, from the frontal lobe to the parietal lobe all the way to sulcus parieto-occipitalis (Fig. 1a,b). It sweeps around the frontal and anterior aspects of the corpus callosum, whose main parts it also supplies. Moreover, it supplies some anterior parts of the internal capsule and caudate nucleus, and finally, the septal and preoptic areas. Dysfunction of areas nourished by the ACA

may cause motor and sensory losses in the contralateral leg, and disturbances in the dedicated 'mentalizing' brain network localized in the medial frontal cortex with disabilities of cognitive and emotional functions [14].

A BSF during basal conditions was defined as a MCA PI-to-UA PI ratio of < 1.08 [15]. Since the UA PI is likely to increase during uterine contractions in OCT positive cases [10,11], this definition is valid only for basal recordings and not for the dynamic changes during the OCT. Thus, during uterine contractions and relaxations a change of MCA PI of ≥ 1 SD (= 0.24 according to reference values [15]) was arbitrary chosen to imply a significant change, i.e., a decrease of ≥ 0.24 implied *de novo* BSF in the MCA (BSF^{MCA}). A corresponding definition of flow changes in the ACA (*de novo* BSF^{ACA}) was created with a limit of 1 SD = 0.14 units, as estimated from van den Wijngaard *et al*. [5]. An UA PI change of ≥ 1 SD (≥ 0.08 units according to reference values [16]) was similarly chosen to imply a significant change compared with basal measurements. The basal UA PI was classified according to gestational age-adjusted reference values [16].

The FHR correlates negatively with the UA PI [17,18], and to allow statistical comparisons, the PI values of UA, MCA and ACA were adjusted for changes of heart rate 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 PI was in individual cases adjusted to a FHR that represented the mean value in the group.

The results were analyzed with regard to OCT result (positive/negative), BSF (present/absent) at basal conditions and *de novo* BSF, basal UA PI (normal/high) and UA PI changes during the OCT, PI measurements performed longitudinally (basal – contraction - relaxation), and neonatal distress (present/absent). A composite 'neonatal distress' group comprised fetuses not fully withstanding the exposure to hypoxic stress during the OCT or labor: positive OCT or operative delivery for fetal distress during labor (emergency CS, ventouse or forceps as indicated by an ominous FHR pattern or ST events at ST-analysis of the fetal ECG) and/or a 5-minute Apgar score < 7 and/or an umbilical cord arterial pH < 7.10 at birth and/or a venous pH < 7.15.

Statistical analyses: The Chi-square test and Fisher's exact test were used for comparison of discrete variables, the Mann-Whitney *U* test for comparison of cross-sectional non-paired continuous variables, and the Wilcoxon matched-pairs signed-rank test ('Wilcoxon's test') for comparison of continuous variables recorded longitudinally. Simple linear regression analysis was used to show relationships between variables. *P* values were corrected for ties and a two-tailed *P* value < 0.05 was considered significant. Although non-parametric tests were used, for didactic reasons we report mean values ± SD together with median and range. Statistics were performed with aid of StatView® (SAS Institute, Cary, NC, U.S.A.) and MedCalc® (MedCalc Software, Mariakerke, Belgium) computer softwares.

RESULTS

A basal BSF was present in 8 fetuses, the OCT was positive in 4 cases, and neonatal distress occurred in 13 cases. The number of OCT positive cases was then too small to allow statistical comparisons. In comparisons between cases with and without BSF and neonatal distress, respectively, no significant differences were found for gestational age, birthweight, or WD (Mann-Whitney *U* test; $P \geq 0.5$). No relationship was found between BSF and neonatal distress (Fisher's exact test; $P = 0.2$).

A significant relationship between FHR and PI was found only in the MCA during uterine contractions (simple linear regression; $P = 0.01$), and the PI was adjusted accordingly.

By definition the basal MCA PI was lower in the BSF group, and the same relationship was found for ACA PI (Table 1). The differences disappeared during the OCT, except for the MCA PI during uterine relaxation. The longitudinal analyses revealed a decrease of PI during the OCT in both vessels when compared in the whole group (N = 47) and in the non-BSF group (N = 39), but not in the BSF group (N = 8). For the MCA-to-ACA PI ratio, overall no significant differences were found.

The creation of *de novo* BSF in the MCA and ACA, respectively, revealed that in cases of *de novo* BSF^{MCA} (N = 20) the ACA PI and MCA-to-ACA PI ratio both decreased during contractions and relaxations compared with basal measurements (Wilcoxon's

test; $P \leq 0.01$), and in cases of *de novo* BSF^{ACA} (N = 21) the MCA PI decreased ($P \leq 0.005$) but the MCA-to-ACA PI ratio was unchanged or increased ($P = 0.3$ and 0.01) (tables not shown). An increase of the PIs > 1 SD were found in 7-11 fetuses (15-23 %). For MCA and ACA as well as for UA, no relationships between a decreased/unchanged/increased PI, respectively, and neonatal distress were found when compared in four-field tables (Fisher's test; $P \geq 0.1$).

Table 2 shows the significance of flow changes in the MCA and ACA relative to dynamic changes of UA PI within and without the range ± 1 SD (0.08). When the UA PI decreased ≥ 0.08, the MCA PI decreased during uterine relaxations, and when UA PI increased ≥ 0.08 the ACA PI decreased during both contractions and relaxations. Trends towards lower PI in both the MCA and ACA were found when UA PI remained unchanged. No significant changes of the MCA-to-ACA PI ratio were found.

In cases of a normal basal UA PI (N = 33), decreases of both the MCA PI and ACA PI were found during the OCT (Wilcoxon's test; $P = 0.03$-0.1), but in cases of a high basal UA PI (N = 14) the only significant change was a decrease of MCA PI during relaxation ($P = 0.04$) (table not shown). In neither group was there any significant change of MCA-to-ACA PI ratio or UA PI ($P \geq 0.2$).

DISCUSSION

Due to the more crucial functions of brain structures supplied from the middle cerebral artery (see MATERIAL & METHODS and below), it would be logic if in the brain-sparing phenomenon the middle cerebral artery blood flow has priority over the anterior cerebral artery flow. However, this study shows that both when brain-sparing flow is chronic and when dynamic flow changes occur during an OCT, the changes of vascular resistance occur in parallel in the two vessels, without altering the balance between them. During an OCT, the resistance decreases in both vessels, but only in fetuses with an intact cerebral circulation during basal conditions. As previously demonstrated, fetuses with an established brain-sparing flow show no further cerebral hyperperfusion in response to a superimposed hypoxemia [9]. The identical findings in the anterior and middle cerebral arteries indicate a global cerebral exhausted capacity for further circulatory responses in these fetuses. With numerous statistical comparisons we assessed the dynamic balance between the anterior and middle cerebral artery flows relative to various circulatory conditions, including basal and dynamic flows in the umbilical artery, development of *de novo* brain-sparing flow, and presence or absence of neonatal distress, and found no indication of preferential flow to any of the cerebral vessels. We therefore conclude that there is no evidence of an intracerebral regional redistribution of flow during acute hypoxemia provoked by an OCT.

In congruence with the present findings, animal studies have shown spatial and temporal homogeneity of flow changes in cerebral cortex areas in response to induced

acute hypoxia, and the homogeneity increases during hypoxia [19]. However, evidence of preferential flow changes exists in other structures of the central nervous system: hypoxia-induced vasodilatation is most robust in the brain stem, and the brain stem is more resistant to hypoxic injury than other brain areas [20].

In a previous study, we demonstrated not only a decrease of the middle cerebral artery PI in an acute sequence, but also that some fetuses respond to hypoxic stress with a marked increase of the PI [9]. An increase of the cerebral vascular resistance is an ominous sign when occurring during chronic hypoxia [21,22], but in our previous studies we have found that fetuses with an increase during acute hypoxic stress do well [9,23]. In the present study, 15-23 % of the fetuses showed such a 'brain-restricting' flow response in cerebral arteries. The increase was of the same magnitude in both vessels, and there was no association with neonatal distress. These observations indicate that not only a decrease but also an increase of vascular resistance in the large cerebral arteries occur in parallel, and that there is no compensatory mechanism working between the middle and anterior cerebral artery circulations. If blood flow is reduced in one vessel there is no compensatory supply from the other vessel. This was expected, since branches of cerebral arteries have no collaterals with each other, except tiny ones on the cerebral cortex surface. Both the middle and the anterior cerebral artery are therefore almost complete end-arteries, and at an occlusion of either the other artery will not be able to compensate and supply the core cortex territories, only the border zones. Since the middle cerebral artery nourishes a major part of the deep white matter of the

cerebral hemispheres, which connect cortical areas to each other and cortical areas to subcortical structures, this vessel has ‘veto power’ over the functions of the entire hemisphere. Tissue damage in areas supplied by the middle cerebral artery will therefore produce catastrophic losses of critical functions of the hemisphere, despite the fact that much tissue may remain anatomically intact.

In summary, blood flow changes occur synchronized in the middle and anterior cerebral arteries when fetuses with an intact cerebral circulation are exposed to uterine contractions with acute oxygen depletion – decreases, increases and no changes of vascular resistance are seen in parallel in the two vessels. In consequence, when fetuses with established brain-sparing flow show no further changes in the middle cerebral artery PI during the OCT, no changes are found in the anterior cerebral artery either. Despite several statistical comparisons from different physiological and pathophysiological circulatory viewpoints, we found no conclusive evidence of an intracerebral regional preferential brain-sparing blood flow that in the acute sequence would secure blood supply to hemispheric brain structures with the most vital functions.

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LEGEND TO FIGURE

Figure 1

The courses and blood supplies of the anterior (light gray color), middle (white color), and posterior (dark gray color) cerebral arteries. (a) Lateral view of the right cerebral hemisphere; (b) Medial view of the right cerebral hemisphere; (c) Schematic view from behind of a mid-brain cut through a frontal plane of the left cerebral hemisphere, showing the course of the left middle cerebral artery in the lateral sulcus and its branches supplying the basal ganglia (gray color). Illustrations modified from Heimer[24] and published with permission.

Table 1

Changes of middle cerebral artery (MCA) and anterior cerebral artery (ACA) pulsatility index (PI) before (basal measurements) and during an oxytocin challenge test (uterine contractions and relaxations) in growth restricted fetuses with (N = 8) and without (N = 39) brain-sparing flow (BSF) during basal conditions. Values are mean ± standard deviation (median, range). Statistical analyses performed with the Mann-Whitney *U* test for cross-sectional data and the Wilcoxon matched-pairs signed-ranks test for longitudinal data (basal – contraction – relaxation)..

	Basal	Contraction	Relaxation	Basal vs. contraction (*P*)	Basal vs. relaxation (*P*)	Contraction vs. relaxation (*P*)
Whole series (N = 47)						
MCA PI	1.51± 0.35 (1.52, 0.90-2.29)	1.35 ± 0.36 (1.32, 0.74-2.32)	1.39 ± 0.36 (1.34,0.67-2.42)	0.02	0.01	0.2
ACA PI	1.26 ± 0.31 (1.21, 0.75-1.90)	1.17 ± 0.29 (1.17, 0.62-1.86)	1.17 ± 0.31 (1.10, 0.64-2.04)	0.03	0.02	0.7
MCA/ACA PI ratio	1.22 ± 0.24 (1.19, 0.8-1.98)	1.18 ± 0.24 (1.20, 0.76-1.83)	1.21 ± 0.25 (1.19, 0.76-1.99)	0.5	0.7	0.5
BSF group (N = 8)						
MCA PI	1.13 ± 0.13	1.18 ± 0.21	1.13 ± 0.19	0.4	0.4	0.7

	(1.15, 0.9-1.32)	(1.18, 0.80-1.49)	(1.12, 0.87-1.39)			
ACA PI	1.02 ± 0.21	1.07 ± 0.31	1.02 ± 0.22	0.7	0.8	0.8
	(1.04, 0.78-1.34)	(1.01, 0.76-1.60)	(0.93, 0.8-1.38)			
MCA/ACA PI ratio	1.14 ± 0.19	1.15 ± 0.27	1.12 ± 0.16	0.9	0.8	0.7
	(1.12, 0.83-1.42)	(1.12, 0.87-1.55)	(1.14, 0.94 -1.44)			
Non-BSF group (N = 39)						
MCA PI	1.59 ± 0.34	1.39± 0.38	1.44 ± 0.36	0.01	0.02	0.09
	(1.56, 1.07-2.29)	(1.36, 0.74-2.32)	(1.44, 0.67-2.42)			
ACA PI	1.31 ± 0.30	1.19± 0.29	1.20 ± 0.32	0.01	0.02	0.7
	(0.5,0.3-0.8)	(1.18, 0.62-1.86)	(1.18, 0.64-2.04)			
MCA/ACA PI ratio	1.24 ± 0.24	1.19 ± 0.24	1.23 ± 0.26	0.4	0.8	0.4
	(1.20, 0.80-1.98)	(1.20, 0.76-1.83)	(1.24, 0.76-1.99)			
BSF vs. non-BSF (*P*)						
MCA PI	0.0005	0.1	0.02			
ACA PI	0.01	0.2	0.2			
MCA/ACA PI ratio	0.4	0.7	0.2			

Table 2

Changes of MCA and ACA PI during an oxytocin challenge test relative to a decreased (decrease ≥ 0.08 from basal), unchanged (± 0.07), or increased (increase ≥ 0.08) umbilical artery PI. Displayed figures are *P* values as calculated with the Wilcoxon matched-pairs signed-ranks test.

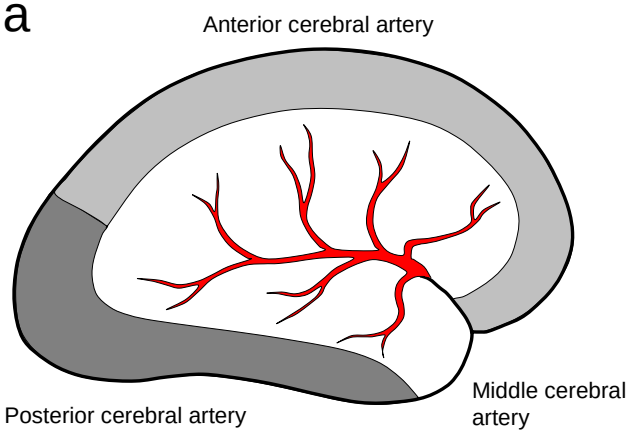
	Umbilical artery PI changes		
	Decrease	Unchanged	Increase
Change basal to uterine contraction	N = 14	N = 14	N = 19
MCA PI	0.3	0.06	0.3
ACA PI	0.8	0.07	0.04*
MCA/ACA PI ratio	0.2	0.3	0.3
Change basal to uterine relaxation	N = 10	N = 23	N = 14
MCA PI	0.01†	0.6	0.2
ACA PI	0.2	0.6	0.02‡
MCA/ACA PI ratio	0.1	0.7	0.2

* Basal 1.26 ± 0.31, contraction 1.09 ± 0.25

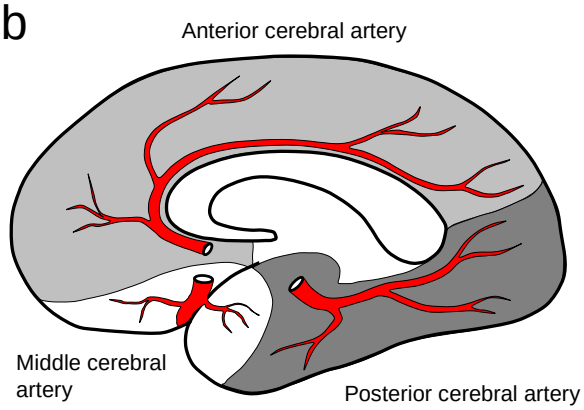
† Basal 1.70 ± 0.45, relaxation 1.37 ± 0.40

‡ Basal 1.34 ± 0.27, relaxation 1.11 ± 0.23

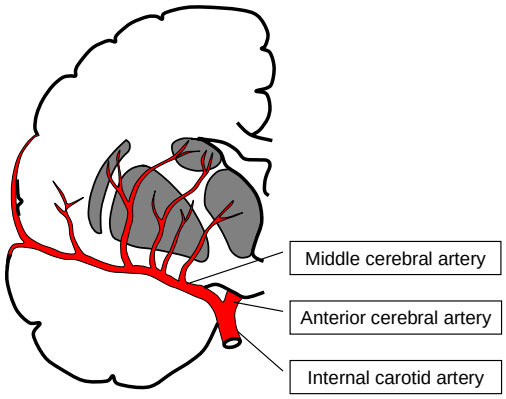
a


Anterior cerebral artery
Posterior cerebral artery
Middle cerebral artery

b


Anterior cerebral artery
Middle cerebral artery
Posterior cerebral artery

c


Middle cerebral artery
Anterior cerebral artery
Internal carotid artery