Cerebrovascular autoregulation in preterm fetal growth restricted neonates

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ABSTRACT

Objective To investigate the effect of fetal growth restriction (FGR) on cerebrovascular autoregulation in preterm neonates during the first 3 days of life.

Design Case-control study.

Setting Neonatal intensive care unit of the Wilhelmina Children's Hospital, The Netherlands.

Patients 57 FGR (birth weight <10th percentile) and 57 appropriate for gestational age (AGA) (birth weight 20th–80th percentiles) preterm neonates, matched for gender, gestational age, respiratory and blood pressure support.

Methods The correlation between continuously measured mean arterial blood pressure and regional cerebral oxygen saturation was calculated to generate the cerebral oximetry index (COx). Mean COx was calculated for each patient for each postnatal day.

The percentage of time with impaired autoregulation (COx>0.5) was also calculated.

Results FGR neonates had higher mean COx values than their AGA peers on day 2 (0.15 (95% CI 0.11 to 0.18) vs 0.09 (95% CI 0.06 to 0.13), p=0.029) and day 3 (0.17 (95% CI 0.13 to 0.20) vs 0.09 (95% CI 0.06 to 0.12), p=0.003) of life. FGR neonates spent more time with impaired autoregulation (COx value >0.5) than controls on postnatal day 2 (19% (95% CI 16% to 22%) vs 14% (95% CI 12% to 17%), p=0.035) and day 3 (20% (95% CI 17% to 24%) vs 15% (95% CI 12% to 18%), p=0.016).

Conclusion FGR preterm neonates more frequently display impaired cerebrovascular autoregulation compared with AGA peers on days 2 and 3 of life which may predispose them to brain injury. Further studies are required to investigate whether this impairment persists beyond the first few days of life and whether this impairment is linked to poor neurodevelopmental outcome.

INTRODUCTION

Cerebrovascular autoregulation is the ability to maintain stable cerebral perfusion despite fluctuations in arterial blood pressure.¹ The cerebral arterioles constrict as blood pressure increases to prevent hyperperfusion of the brain. A decrease in blood pressure is compensated for by dilation of the cerebral arterioles to prevent hypoperfusion.¹ Previous studies have indicated that cerebrovascular autoregulation may be dysfunctional in (sick) preterm neonates, predisposing them to haemorrhagic and ischaemic brain injury and neonatal death.^{2–6}

Compared with preterm appropriate for gestational age (AGA) neonates, preterm fetal growth

What is already known on this topic?

- ▶ Cerebrovascular autoregulation is the ability to maintain stable cerebral blood flow despite fluctuations in arterial blood pressure.
- ▶ Cerebrovascular autoregulation can be impaired in preterm appropriate for gestational age (AGA) neonates, which predisposes these neonates to neurological injury.

What this study adds?

- ▶ Fetal growth restricted (FGR) preterm neonates more frequently display impaired cerebrovascular autoregulation compared with AGA peers on days 2 and 3 of life.
- ▶ Further research is needed to investigate whether this impairment persists and whether this impairment increases the risk of neurological injury in preterm FGR neonates.

restricted (FGR) neonates demonstrate higher cerebral oxygenation throughout the first few postnatal days.^{7,8} This increase most likely reflects increased cerebral blood flow related to the brain-sparing phenomenon. Chronic fetal hypoxia and FGR have also been associated with cerebrovascular remodeling and altered cerebrovascular reactivity.^{9,10} These alterations in structural and functional properties of the cerebral vasculature may further impair cerebrovascular autoregulation and increase vulnerability of the brain to hypoperfusion and hyperperfusion within this subgroup of preterm neonates. To date, no studies have investigated cerebrovascular autoregulation in preterm FGR neonates. In this study, we thus aimed to investigate the effect of FGR on cerebrovascular autoregulation in preterm neonates throughout the first 3 days of life. We hypothesised that FGR would exacerbate the unfavourable effect of preterm birth on cerebrovascular autoregulation.

PATIENTS AND METHODS

Patients and data collection

We performed a retrospective case-control study on data from a large prospective cohort study investigating normative cerebral oxygen saturation (rScO₂) and cerebral fractional tissue oxygen extraction (cFTOE) values of prematurely born neonates (gestational age (GA) <32 weeks) admitted to the neonatal intensive care unit of the Wilhelmina

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Figure 1 Patient selection. AGA, appropriate for gestational age; FGR, fetal growth restriction; HSPDA, haemodynamically significant persistent ductus arteriosus; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; SGA, small for gestational age.

Children's Hospital between 2000 and 2013.¹¹ In this observational study rScO₂ was recorded by means of near-infrared spectroscopy during the first 3 days of life (INVOS 5100C with a small adult sensor, Covidien/Medtronic, Boulder, Colorado, USA). cFTOE was calculated as (SpO₂ – rScO₂)/SpO₂. In addition, physiological variables used for routine clinical monitoring were recorded. These data included continuous measurement of mean arterial blood pressure (MABP) by an indwelling arterial catheter and arterial oxygen saturation by pulse oximetry (SpO₂). Clinical data included a daily blood pressure support score adapted from Krediet *et al*¹² and a respiratory support score classified as non-invasive (spontaneously breathing with low flow or continuous/bilevel positive airway pressure) or invasive (synchronised intermittent mandatory ventilation or high-frequency oscillatory ventilation).

From the database, we identified all FGR neonates—defined as by having a birth weight below the 10th percentile for GA on the Fenton growth curve¹³—for whom simultaneous rScO₂ and MABP data were available (figure 1). Each FGR neonate was matched with an AGA control (birth weight between the 20th and 80th percentiles). Matching criteria were gender, GA (± 4 days) and similar blood pressure and respiratory support status. Neonates with chromosomal abnormalities, congenital abnormalities influencing the systemic and/or cerebral circulation (including congenital heart disease), confirmed haemodynamically significant persistent ductus arteriosus on echocardiography,¹⁴ proven perinatal sepsis and perinatal asphyxia¹⁵ were excluded. For eligible infants, we collected information regarding the last fetal Doppler measurements when available. A middle cerebral artery pulsatility index below the fifth percentile or a placental-cerebral ratio above 1.1 was considered abnormal and a sign of prenatal brain sparing.

Autoregulation analysis

Data were analysed using in-house developed software (Signal-Base, University Medical Centre Utrecht, The Netherlands). To estimate cerebrovascular autoregulation, the correlation between continuously measured MABP and rScO₂ was used.¹⁶ Data were visually inspected in 30 min epochs. Data that included MABP,

rScO₂ and/or SpO₂ artefacts were excluded from further analysis. Due to the fact that SpO₂ fluctuations influence rScO₂ irrespective of MABP changes, we excluded any SpO₂ fluctuations exceeding 10% compared with the epoch's baseline.¹⁷ It is estimated that the rScO₂ response to an MABP change occurs with a delay of approximately 10 s in neonates.¹⁸ To take this physiological delay into account, the MABP signal was subjected to a preprocessing time shift of +10 s.¹⁹ MABP and rScO₂ signals were filtered and subsequently down-sampled at 0.1 Hz to eliminate high-frequency noise.²⁰ A Pearson's correlation coefficient was calculated between 30 paired samples of MABP and rScO₂, generating the cerebral oximetry index (COx).^{20–21} The COx was updated every 10 s using a moving 300 s window (97% overlap).²⁰ The average MABP and the coefficient of variation (CV) of MABP were also calculated for each 300 s window. The MABP CV can be used as a measure of blood pressure variability^{22–23} and blood pressure variability has been shown to affect cerebrovascular autoregulation.²⁴

Mean COx was calculated for each patient for each postnatal day. A COx value >0.5 was considered to represent impaired cerebrovascular autoregulation.²⁰ The percentage of time spent with a COx >0.5 was also calculated for each patient for each postnatal day. Cerebrovascular autoregulation was further investigated relative to the neonate's MABP.²⁰ COx values were grouped and averaged in 5 mm Hg bins, where MABP was corrected for GA (MABP—GA in completed weeks).^{21–25} The mean COx and the time spent with a COx >0.5 were calculated for each MABP bin in each patient.

Statistical analysis

Data were statistically analysed using SPSS for Windows V.22 (IBM, Released 2013). To analyse demographic and clinical variables, X² test, Fisher's exact test or Mann-Whitney U test was used, as appropriate. These data are represented as n (%) or median (range).

Physiological variables (rScO₂, cFTOE, MABP and SpO₂), MABP CV and cerebrovascular autoregulation variables were analysed using a mixed model approach to explore the effect of postnatal age and group. These analyses were corrected for GA. A mixed model was also used to explore the effect of GA-corrected MABP bin and group on cerebrovascular autoregulation variables. Statistically significant overall group differences were followed up with single analysis of (co)variance to explore on which postnatal day, respectively, in which MABP bin, group differences occurred. These data are represented as mean with bootstrapped 95% CIs.

RESULTS

For a total of 57 (61% male) FGR neonates simultaneous and artefact-free MABP and rScO₂ data were available for cerebrovascular autoregulation analysis. Demographic and clinical data are presented in table 1. FGR pregnancies were more often associated with pre-eclampsia/Hemolysis Elevated Liver enzymes and Low Platelets (HELLP) and FGR fetuses were more frequently delivered by caesarean section. Prenatal Doppler measurements were available for 79% of the FGR fetuses. Of these, 91% showed signs of brain sparing. For the AGA population this information was lacking in the majority of cases (88%). There were no differences between the FGR and AGA group for antenatal corticosteroid administration or GA at birth. FGR neonates were born with a significantly lower birth weight and they had a higher lactate than AGA controls. Apgar score at 1 min was similar between the groups, however FGR neonates had slightly higher Apgar score at 5 min. There were no

Table 1 Demographics and clinical data

	FGR	AGA	P values
n (% male)	57 (61)	57 (61)	NA
Birth weight, g	840 (515–1235)	1345 (840–1940)	<0.001
Birth weight percentile	6 (1–10)	54 (21–79)	<0.001
Head circumference, cm	25 (20.5–27.3)	27.5 (23.2–31.0)	<0.001
Head circumference percentile	6 (0–63)	52 (11–99)	<0.001
Gestational age, weeks	30 (26 ⁴ / ₇ –32)	30 ¹ / ₇ (26 ⁴ / ₇ –31 ⁶ / ₇)	0.847
Pre-eclampsia/HELLP	31 (54%)	6 (11%)	<0.001
Doppler data available	45 (79%)	7 (12%)	<0.001
Prenatal brain-sparing (MCA-PI or PCR abnormal)	41 (91%)	2 (29%)	0.001
Antenatal corticosteroids	46 (81%)	45 (79%)	0.815
Delivery by caesarean section	55 (97%)	29 (51%)	<0.001
Apgar score at 1 min	7 (1–10)	7 (0–10)	0.722
Apgar score at 5 min	9 (6–10)	8 (4–10)	0.031
Lactate, mmol/L	5.5 (2.0–18.1)	3.8 (1.2–26.10)	<0.001
Umbilical artery pH	7.25 (6.95–7.37)	7.26 (7.06–7.41)	0.083
Predominant form of respiratory support			0.663
Low flow/CPAP/BIPAP	44 (77%)	42 (74%)	
SIMV/HFOV	13 (23%)	15 (26%)	
Predominant form of blood pressure support			0.802
No support	47 (83%)	49 (86%)	
Mild support	6 (10%)	4 (7%)	
Moderate to intensive support	4 (7%)	4 (7%)	
IVH	9 (16%)	10 (18%)	1
Grade I	7	4	
Grade II	3	5	
Grade III	0	0	
Grade IV	0	0	
Data available for autoregulation analysis, hour			
Overall	44.8 (2.1–64.0)	49.2 (19.7–62.2)	0.066
Day 1	13.65 (0.3–20.3)	14.5 (1.3–20.9)	0.528
Day 2	17.18 (0.6–22.4)	18.4 (6.0–21.7)	0.083
Day 3	16.9 (4.0–22.2)	17.6 (4.2–22.1)	0.88

Data are presented as median (range) or n (%).

AGA, appropriate for gestational age; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FGR, fetal growth restriction; HELLP, Hemolysis Elevated Liver enzymes and Low Platelets; HFOV, high-frequency oscillatory ventilation; IVH, intraventricular haemorrhage; MCA-PI, middle cerebral artery pulsatility index; NA, not applicable; PCR, placental-cerebral ratio; SIMV, synchronised intermittent mandatory ventilation.

differences between the groups regarding respiratory and blood pressure support scores.

Cerebrovascular autoregulation

Cerebrovascular autoregulation results are shown in [figures 2 and 3](#).

Figure 2 Mean COx (A) and time spent with impaired autoregulation (B). Fetal growth restricted (FGR) neonates are represented by the closed circles and appropriate for gestational age (AGA) neonates are represented by the open circles. Error bars represent bootstrapped 95% CIs. *P<0.05; **P<0.01. COx, cerebral oximetry index.

Postnatal age had no significant effect on cerebrovascular autoregulation variables, yet a significant group effect was found for these variables. Further testing revealed that FGR neonates had higher COx values than their AGA peers on day 2 (p=0.029, r=0.20) and day 3 (p=0.003, r=0.28) ([figure 1A](#)) and FGR neonates also spent more time with a COx value >0.5 than controls on postnatal day 2 (p=0.035, r=0.20) and day 3 (p=0.016, r=0.23) ([figure 1B](#)).

A significant group effect was also demonstrated when cerebrovascular autoregulation variables were examined in relation to GA-adjusted MABP bins. FGR neonates had significantly higher COx values and spent significantly more time with a COx value >0.5 at the 10–15 mm Hg (COx: p=0.006, r=0.26, COx>0.5: p=0.008, r=0.25) and 15–20 mm Hg bins (COx: p=0.004, r=0.28, COx>0.5: p=0.006, r=0.27) ([figure 2](#)).

Physiological variables and blood pressure variability

Physiological variables and blood pressure variability are shown in [table 2](#). rScO₂ was higher and cFTOE was lower in FGR compared with AGA neonates, reaching statistical significance on day 2 and day 3. SpO₂ was comparable between the groups. MABP and MABP CV increased significantly with advancing

Figure 3 Mean COx (A) and time spent with impaired autoregulation (B) for each gestational age-adjusted MABP bin. FGR neonates are represented by the closed circles and AGA neonates are represented by the open circles. Error bars represent bootstrapped 95% CIs. **P<0.01. AGA, appropriate for gestational age; COx, cerebral oximetry index; FGR, fetal growth restriction; GA, gestational age; MABP, mean arterial blood pressure.

postnatal age, however no group differences were detected for these variables.

DISCUSSION

To our knowledge, this is the first study to investigate the effect of FGR on cerebrovascular autoregulation in preterm neonates throughout the first postnatal days. This study uses a convenience sample based on data from an existing cohort study.¹¹ Infants with FGR were considered cases, and appropriately

matched controls were selected from the same cohort. With this sample we were able to demonstrate a significant difference in cerebrovascular autoregulation between the two groups. FGR neonates showed higher mean COx values than their AGA peers. Although mean COx did not exceed the threshold of impaired cerebrovascular autoregulation, FGR neonates did spend significantly more time with impaired cerebrovascular autoregulation (COx>0.5) than AGA neonates on days 2 and 3 of life.

In developed countries, FGR is most commonly caused by placental insufficiency leading to chronic fetal hypoxia.²⁶ Studies performed in adults at high altitude have established that chronic hypoxia significantly impairs cerebrovascular autoregulation.^{27–29} Although these changes appear to be functional and reversible after reoxygenation,²⁹ exposure to chronic hypoxia during a critical window of brain development may more permanently alter cerebrovascular structure and function resulting in lasting impairments in cerebrovascular autoregulation. In fact, animal studies have demonstrated that chronic fetal hypoxia promotes cerebrovascular remodelling, resulting in altered arterial wall structure and function.^{30–32} Although it has been hypothesised that some of these alterations aim to preserve energy while still maintaining basic contractile function during exposure to chronic intrauterine hypoxia,³¹ the consequences on postnatal cerebrovascular function are unknown. A recent study demonstrated significant structural changes within the cerebral vasculature of FGR lambs, including reduced endothelial proliferation,³² which may contribute to pressure passivity.³³ These authors also reported increased permeability of the blood–brain barrier and a higher incidence of haemorrhages in their FGR lambs.³² Moreover, Soul *et al* reported that human neonates born from pregnancies complicated by pregnancy-induced hypertension or placental infarction spent more time with impaired cerebrovascular autoregulation than neonates born from pregnancies without these complications.²³ Although these authors did not aim to investigate the effect of FGR, it is plausible that these pregnancy complications were associated with placental insufficiency resulting in chronic fetal hypoxia and FGR.

Table 2 Physiological variables and blood pressure variability

	FGR	AGA	P values
rScO ₂ , %			
Postnatal day 1	71 (69 to 73)	69 (68 to 71)	0.311
Postnatal day 2	74 (72 to 75)	69 (68 to 71)	0.002
Postnatal day 3	71 (69 to 73)	69 (67 to 70)	0.042
cFTOE			
Postnatal day 1	0.26 (0.24 to 0.29)	0.29 (0.27 to –0.31)	0.152
Postnatal day 2	0.23 (0.22 to 0.25)	0.29 (0.26 to 0.31)	0.001
Postnatal day 3	0.26 (0.25 to 0.28)	0.30 (0.27 to 0.33)	0.032
SpO ₂			
Postnatal day 1	96 (95 to 96)	96 (95 to 96)	0.399
Postnatal day 2	96 (96 to 97)	96 (95 to 96)	0.404
Postnatal day 3	96 (96 to 97)	96 (95 to 97)	0.215
MABP			
Postnatal day 1*	37(36 to 38)	38 (37 to 39)	0.164
Postnatal day 2†	41 (40 to 43)	40 (39 to 42)	0.471
Postnatal day 3	43 (41 to 45)	42 (41 to 44)	0.461
MABP CV			
Postnatal day 1‡	3.8 (3.6 to 4.1)	4.1 (3.9 to 4.3)	0.179
Postnatal day 2‡	4.0 (3.8 to 4.2)	4.1 (3.9 to 4.4)	0.539
Postnatal day 3	4.3 (4.1 to 4.6)	4.4 (4.2 to 4.6)	0.609

Data are presented as mean (bootstrapped 95% CI). All variables were corrected for gestational age.

*Versus day 3 p<0.001.

†Versus day 3 p<0.01.

‡Versus day 3 p<0.05.

AGA, appropriate for gestational age; cFTOE, cerebral fractional tissue oxygen extraction; CV, coefficient of variation; FGR, fetal growth restriction; MABP, mean arterial blood pressure.

It is likely that the altered cerebrovascular reactivity of our FGR neonates is related to adaptations of the cerebral vasculature to the unfavourable prenatal environment. Surprisingly, however, cerebrovascular dysfunction only became apparent from day 2 of life. Our method to investigate cerebrovascular autoregulation requires spontaneous fluctuations in blood pressure. Dysfunctional autoregulation may only become detectable when there is sufficient blood pressure variability.^{23 24} In our study, blood pressure variability increased significantly with advancing postnatal age, which may explain why dysfunctional autoregulation became apparent from day 2 of life.

Cerebrovascular autoregulation is believed to have limited capacity. Within a specific range of blood pressures, the cerebral vasculature is able to maintain stable cerebral perfusion. This is referred to as the autoregulatory plateau.¹ When blood pressure falls below a lower threshold, cerebral blood flow will decrease. Similarly, when blood pressure exceeds an upper threshold, cerebral blood flow will increase.¹ Most of the preterm AGA studies focus on the effect of hypotension on cerebrovascular autoregulation. Gilmore *et al* suggested that dysfunctional autoregulation was more likely to occur during hypotensive rather than hypertensive episodes.²⁰ However, the autoregulatory ability of our AGA neonates did not vary over the range of blood pressures studied. Cerebrovascular autoregulation of FGR neonates, on the other hand, appeared to mainly be affected at mid to high blood pressures. When relating these findings to the autoregulatory plateau theorem, the findings suggest dysfunctional cerebral vasoconstriction of the FGR neonates at high cerebral perfusion pressure, which may be related to long-standing cerebral vasodilation due to the brain-sparing effect. Smaller numbers (n) and large variation within the data at the extreme upper end of the blood pressure range may explain why no significant group differences occurred here. The fact that only a limited number of neonates were exposed to (relatively mild) hypotension may explain why we did not observe a relationship between cerebrovascular autoregulation and hypotension.

The method used in this study analyses cerebrovascular autoregulation in the time domain. This technique allows quantification of the relationship between blood pressure and cerebral oxygenation but does not specify at which frequency of blood pressure fluctuations cerebrovascular autoregulation may be impaired. Cerebrovascular autoregulation is believed to prevent transmission of slow MABP fluctuations to the cerebral circulation.²⁰ By downsampling our data to 0.1 Hz we ensured that oscillations below 0.05 Hz were investigated (according to the Nyquist sampling theorem).²⁰ Nevertheless, previous studies have indicated that prematurity affects cerebrovascular autoregulation predominantly in the ultralow frequencies (0.003–0.01 Hz).^{4 24} Analysis in the frequency domain, which enables the distinction between low and ultralow frequencies, may thus provide additional information. Moreover, cerebrovascular autoregulation may depend on the magnitude of blood pressure changes, which can be incorporated in frequency domain analysis.²⁴ Also, it is plausible that the delay in rScO₂ response following an MABP change varies between patients. Frequency domain analysis eliminates the effect of this delay.³⁴ Future studies employing this technique to further investigate cerebrovascular autoregulation in preterm FGR neonates would be valuable. Nevertheless, analysis in the time domain has been found to be more robust.³⁵

We acknowledge the limitations of this study. First, it is important to note that rScO₂ can only accurately reflect fluctuations in cerebral blood flow (CBF) if arterial oxygenation and cerebral metabolic demand remain constant. Moreover,

cerebrovascular reactivity is influenced by oxygen and carbon dioxide concentrations, metabolic demand and neuronal factors.¹ We only analysed data with stable SpO₂, to minimise the effect of SpO₂ as a potential confounding factor. However, we were unable to correct for other potentially confounding factors, such as hypocapnia or hypercapnia and hypoglycaemia or hyperglycaemia. Actually, FGR neonates and infants can present with altered acid base status³⁶ and sympathetic tone,^{37 38} and they may have different cerebral metabolism.⁸ Moreover, there is evidence that vasoreactivity to some of these factors is altered in fetuses exposed to chronic hypoxia.^{30 31} Mechanistic studies exploring the interplay between these factors, vasoreactivity and cerebrovascular autoregulation in the FGR brain—and whether this differs from the AGA brain—would provide important information. Second, we cannot conclude whether the observed differences in cerebrovascular autoregulation between FGR and AGA neonates are of clinical importance. Our results showed a true, yet small to medium effect of FGR on cerebrovascular autoregulation.³⁹ Previous studies have related impaired cerebrovascular autoregulation to ultrasonographic evidence of brain damage in AGA preterm neonates.^{4 5 24 40} Our findings raise caution regarding the use of inotropic agents to significantly increase blood pressure in FGR neonates. Appropriately powered longitudinal studies investigating whether the observed differences in cerebrovascular autoregulation result in altered neurodevelopmental outcome would be very pertinent.

CONCLUSIONS

FGR neonates more frequently display impaired cerebrovascular autoregulation compared with AGA peers on days 2 and 3 of life. This may predispose them to brain injury. Longitudinal studies that extend beyond the first few days of life are warranted to investigate whether this impairment persists and whether it contributes to the increased risk of abnormal neurodevelopmental outcome of the FGR population. It is crucial that this topic is further investigated, as this will provide us with important insights to improve clinical care for FGR neonates.

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Contributors EC carried out all data analyses, interpreted and critically appraised the data and drafted the initial manuscript. FvB, WB and PMAL were responsible for data collection, contributed substantially to interpretation and critical appraisal of the data and critically reviewed the manuscript. ACD and GN contributed substantially to interpretation and critical appraisal of the data and critically reviewed the manuscript. All authors have seen and approved the final version of the manuscript as submitted.

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