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The Effect of Maternal Antihypertensive Drugs on the Cerebral, Renal and Splanchnic Tissue Oxygen Extraction of Preterm Neonates

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Key Words
Antihypertensive drugs · Fractional tissue oxygen extractions · Neonatal oxygenation

Abstract
Background: Drugs with antihypertensive action are frequently used in obstetrics for the treatment of preeclampsia (labetalol) and tocolysis (nifedipine) or for neuroprotection ($MgSO_4$), and may affect the hemodynamics of preterm born neonates. ***Objective:*** The aim of this study was to assess whether maternal antihypertensive drugs affect multisite oxygenation levels of the neonate. ***Methods:*** Eighty preterm neonates of ≤32 weeks of gestational age were monitored using near-infrared spectroscopy. Mean cerebral, renal and splanchnic fractional tissue oxygen extractions (cFTOE, rFTOE and sFTOE) were calculated for the first 5 postnatal days. We determined the effect of various maternal antihypertensive drugs on cFTOE and rFTOE using multilevel analysis, and on sFTOE using Kruskal-Wallis and Mann-Whitney U tests. ***Results:*** Eleven infants were exposed to labetalol ± $MgSO_4$, 7 to nifedipine ± $MgSO_4$, 20 to $MgSO_4$ only, and 42 to no maternal antihypertensive drugs. The infants exposed to labetalol ± $MgSO_4$ had a lower cFTOE on days 1 (0.14, p = 0.031), 2 (0.13, p = 0.035) and 4 (0.18, p = 0.046) than nonexposed infants on the corresponding days (0.22, 0.20 and 0.24, respectively). On day 2, cFTOE was also lower in infants exposed to nifedipine ± $MgSO_4$ (0.11, p = 0.028) and to $MgSO_4$ only (0.15, p = 0.047). sFTOE was higher in infants exposed to labetalol ± $MgSO_4$ on days 1 (μ = 0.71) and 2 (μ = 0.82) than in nonexposed infants (μ = 0.26, p = 0.04 and μ = 0.55, p = 0.007, respectively). Maternal antihypertensive drugs did not affect rFTOE. ***Conclusions:*** Low neonatal cFTOE found with maternal antihypertensive drug exposure may relate to either increased cerebral perfusion or neurologic depression induced by the medication, or preferential brain perfusion associated with preeclampsia placental insufficiency. Concomitantly high sFTOE found with labetalol exposure supports the latter, while renal autoregulation may explain rFTOE stability.

Introduction

Hemodynamic instability is common in preterm infants and often linked to immaturity and transitional cardiovascular changes. Resulting changes in tissue perfusion may cause ischemia of still immature organs [1]. Nonvital organs, such as kidneys and intestines, are supposedly the first to be compromised, while the brain is relatively protected by cerebral autoregulation [1, 2]. Pos-

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sible consequences may be necrotizing enterocolitis (NEC) or dysregulation of the fluid-electrolyte balance [3, 4].

Maternal drugs with antihypertensive properties given shortly before preterm delivery may present hazards to the perfusion and oxygenation of these newborns. Labetalol, an α/β-blocker, is commonly used to treat emergent cases of preeclampsia [5]. Although the drug is considered safe and effective in reducing maternal blood pressure, it crosses the placenta and has a half-life of about 24 h in the newborn [5, 6]. Some have reported it to induce significant neonatal hypotension [7]. Nifedipine, a calcium channel-blocker commonly used as a tocolytic drug, is also known to have blood pressure-lowering effects, making it suitable for the treatment of maternal hypertension [5, 8]. Antihypertensive action is also seen for $MgSO_4$ (magnesium sulfate), a drug recently introduced for fetal neuroprotection during imminent preterm birth and able to directly block calcium channels [5, 9]. Both nifedipine and $MgSO_4$ have been associated with changes in cerebral blood flow (CBF) [10, 11].

Near-infrared spectroscopy (NIRS) is a widely approved, noninvasive method used to monitor regional tissue oxygen saturation (rSO_2) of the neonate and aids in the early detection of ischemic hypoxia [4, 12]. Simultaneous measurements of peripheral oxygen saturation (SpO_2) can be used to derive fractional tissue oxygen extraction (FTOE), reflecting not only changes in regional oxygen supply but also oxygen consumption [12]. As the global oxygenation status of the preterm neonate is vulnerable and may profoundly be affected by changes in perfusion [13], our aim was to investigate the influence of maternal antihypertensive drugs on cerebral (c), renal (r) and splanchnic (s)FTOE of preterm neonates using multisite NIRS.

Methods

Study Design and Population

We analyzed the influence of maternal antihypertensive drugs on neonatal NIRS data, which were previously collected at the neonatal intensive care unit of the University Medical Center of Groningen (UMCG) in the context of a prospective observational cohort study aiming to find predictors of NEC in high-risk infants. It is registered in the Dutch Trial Registry (CALIFORNIA trial, NTR3239) and has been approved by the ethical review committee of the UMCG. Informed parental consent was obtained for each infant.

The inclusion criteria of the CALIFORNIA trial were preterm birth with a gestational age (GA) ≤30 weeks, a birth weight (BW) ≤1,000 g, or being born at a GA ≤32 weeks with a BW ≤1,200 g, antenatal indomethacin exposure or congenital heart disease interfering with intestinal perfusion. Exclusion criteria were chromosomal disorders and abdominal diseases other than NEC. For the purpose of the current sub-study, newborns with congenital heart defects were excluded.

Maternal Antihypertensive Drugs

Based on the antihypertensive drugs most commonly administered to the mothers of our study population, subjects were categorized into four groups: exposure to labetalol ± $MgSO_4$, exposure to nifedipine ± $MgSO_4$, exposure to $MgSO_4$ only, and no exposure to maternal antihypertensive drugs. Infants with no exposure were identified if the maternal medical chart had no record of the use of any of the drugs mentioned above, including methyldopa and dihydralazine. Labetalol treatment of emergent hypertension was administered intravenously, usually followed by cesarean delivery of the child shortly after. Nifedipine was used for tocolysis in preterm labor and $MgSO_4$ was given for either maternal or fetal neuroprotection, usually in combination with labetalol, nifedipine or another tocolytic. Antihypertensive treatment with methyldopa was infrequent, and will thus receive no further attention in our study.

Near-Infrared Spectroscopy

NIRS was performed using the INVOS 5100 near-infrared spectrometer (Somanetics Corp., Troy, Mich., USA) combined with the neonatal SomaSensor (Somanetics Corp.) to determine regional cerebral, renal and splanchnic oxygen saturation. Cerebral sensors were placed on the lateral forehead, renal sensors on the left or right flank just below the last costal arch, and splanchnic sensors below the umbilicus. Since a low BW often did not allow for abdominal sensor placement due to a lack of infraumbilical space, splanchnic measurements were less frequently performed. Otherwise, measurements took place every 5 s for a minimal period of 2 stable hours within the first day after birth if possible, followed by measurements on the subsequent days 2, 3, 4 and 5. SpO_2 measured simultaneously with pulse oximetry (Nellcor) enabled us to compute regional FTOE using the equation $FTOE = (SpO_2 - rSO_2)/SpO_2$ [4, 12]. FTOE can be used to assess organ perfusion [12].

Statistical Analysis

The mean cFTOE, rFTOE and sFTOE values were calculated per day for each newborn. The statistical program MLwiN version 2.15 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK) was used to determine the association between maternal antihypertensive drugs and both neonatal cFTOE and rFTOE using multilevel analysis. Multilevel analysis is more flexible than the standard repeated measures (M)ANOVA approach because it allows unequal numbers of observations per individual. Separate models were built for cFTOE and rFTOE with the infant as level 1 nested within the four groups of treatment at level 2. The intercept, also called the reference set, was day 1 in infants unexposed to maternal antihypertensive drugs and served as the baseline. As is standard for multilevel analysis [14], a Student t test was used to test for differences between the estimated mean on day 1 and the intercept, and to test for differences between estimated means on days 2–5 a χ^2 test with one degree of freedom was used. Potential confounders, such as GA, BW, head circumference (HC), hemodynamically significant patent ductus arteriosus (PDA), hemoglobin and arterial pCO_2, were included into the model if they had a statistically significant effect on the intercept.

Table 1. Characteristics of the study population

	No exposure (n = 42)	Exposure to labetalol ± $MgSO_4$ (n = 11)	Exposure to nifedipine ± $MgSO_4$ (n = 7)	Exposure to $MgSO_4$ only (n = 20)
Neonatal factors				
Male/female, n	28/14	2/9*	4/3	9/11
Gestational age, weeks	28.2 [26.7; 29.3]	28.1 [26.7; 28.6]	25.3** [25.0; 29.3]	28.1 [27.7; 29.5]
BW corrected for age (z score)	–0.92 [–2.60; –0.14]	–2.04** [–2.78; –1.40]	–0.08* [–0.41; 0.72]	–1.05 [–1.94; –0.14]
HC corrected for age (z score)	–0.62 [–2.0; –0.07]	–1.58* [–2.2; –1.01]	–0.2 [–0.61; 0.2]	–0.75 [–1.70; –0.33]
MABP (first 48 h), mm Hg	37 [32; 44]	34 [30; 45]	36 [30; 38]	38 [34; 42]
Heart rate (first 48 h), beats/min	157 [150; 163]	149* [137; 155]	154 [150; 161]	148* [139; 156]
r_cSO_2 (first 48 h), %	75 [69; 82]	78 [75; 87]	78 [76; 87]	79 [73; 83]
r_rSO_2 (first 48 h), %	67 [56; 79]	72 [51; 87]	64 [48; 80]	63 [54; 75]
r_sSO_2 (first 48 h), %	52 [30; 64]	17.6 [15; 25]	73 (n = 2)	48 [18; 67]
Hb levels (first 48 h), mmol/l	9.3 [8.3; 10.4]	10.3* [9.8; 11.0]	8.2** [7.4; 9.9]	9.9 [9.0; 10.6]
Arterial pCO_2 levels (first 48 h), kPa	5.05 [4.61; 6.06]	6.30* [5.30; 7.05]	4.93 [3.67; 5.10]	5.50 [4.77; 5.92]
Ventilatory status (day 1)				
Mechanical ventilation	21 (50.0)	6 (54.5)	2 (28.6)	10 (50.0)
CPAP/SiPAP	21 (50.0)	5 (45.5)	4 (57.1)	9 (45.0)
Oxygen flow/no assistance	0 (0.0)	0 (0.0)	1 (14.3)	1 (5.0)
hsPDA	16 (38.1)	4 (36.4)	4 (57.1)	4 (20.0)
IUGR[1]	7 (16.7)	5 (45.5)*	0 (0.0)	2 (10.0)
Maternal factors				
Gestational hypertension[2]	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)
Preeclampsia[3]	1 (2.4)	9 (81.8)*	0 (0.0)	1 (5.0)
HELLP syndrome[4]	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)
Maternal vascular underperfusion[5]	11 (26.2)	8 (72.7)*	0 (0.0)	8 (33.8)
Indomethacin tocolysis	4 (9.5)	0 (0.0)	1 (14.3)	4 (20)

Data are presented as medians and interquartile ranges [25th percentile; 75th percentile] or n (%). * Indicates a difference to newborns unexposed to maternal antihypertensive drugs at a significance level of $p \leq 0.05$, tested using the Mann-Whitney U test or χ^2 test. ** Indicates a difference to newborns unexposed to maternal antihypertensive drugs at a significance level of $p \leq 0.1$, tested using the Mann-Whitney U test. Hb = Hemoglobin; CPAP = continuous positive airway pressure; SiPAP = synchronized inspiratory positive airway pressure; hsPDA = hemodynamically significant PDA; IUGR = intrauterine growth restriction; r_cSO_2 = regional cerebral tissue oxygen saturation; r_rSO_2 = regional renal tissue oxygen saturation; r_sSO_2 = regional splanchnic tissue oxygen saturation; MABP = mean arterial blood pressure.

[1] Defined as an echographically estimated fetal weight below the 10th percentile.

[2] Defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg occurring in the second half of a previously normotensive pregnancy.

[3] Defined as gestational hypertension with proteinuria of ≥0.3 g protein in 24-hour urine.

[4] Defined as a combination of hemolysis, elevated liver enzymes (ASAT >70 iU/l) and low platelets ($<100 \times 10^6$/l).

[5] As defined by Roescher et al. [22]; in summary decidual vasculopathy or thrombosis.

The statistical program SPSS version 22.0 (IBM Corp., Armonk, New York, N.Y., USA) was used for descriptive analyses and the exploration of the relationship between antihypertensive drugs and sFTOE. The Kruskal-Wallis and Mann-Whitney U test were used without the possibility to correct for confounders, as sFTOE measurements were less frequent and not normally distributed.

To test for differences in neonatal characteristics between the exposure groups, the Mann-Whitney U test and the χ^2 test were used. For all calculations a p value ≤0.05 was considered significant.

Results

Characteristics of the Study Population

Of 80 preterm infants included in this study, 11 were exposed to labetalol ± $MgSO_4$ (2 of which were exposed to labetalol alone), 7 to nifedipine ± $MgSO_4$ (2 of which were exposed to nifedipine alone) and 20 to $MgSO_4$ only. Table 1 presents the neonatal and maternal characteristics per exposure group and indicates significant differ-

Table 2. Effect of maternal antihypertensive drugs on cFTOE using multilevel analysis

	Unadjusted model (n = 347)			Adjusted model (n = 339)		
	cFTOE (SE)	difference (%)	p value	cFTOE (SE)	difference (%)	p value
Day 1						
No exposure (n = 22)	0.21 (0.02)			0.22 (0.02)		
Labetalol ± $MgSO_4$ (n = 6)	0.12 (0.04)	–0.09 (42.9)	0.018*	0.14 (0.04)	–0.08 (36.4)	0.031*
Nifedipine ± $MgSO_4$ (n = 5)	0.19 (0.04)	–0.02 (9.5)	0.324	0.19 (0.05)	–0.03 (13.6)	0.247
$MgSO_4$ only (n = 7)	0.19 (0.04)	–0.02 (9.5)	0.282	0.19 (0.04)	–0.03 (13.6)	0.260
Day 2						
No exposure (n = 39)	0.19 (0.02)			0.20 (0.02)		
Labetalol ± $MgSO_4$ (n = 9)	0.11 (0.05)	–0.08 (42.1)	0.010*	0.13 (0.05)	–0.07 (35.0)	0.035*
Nifedipine ± $MgSO_4$ (n = 9)	0.11 (0.06)	–0.08 (42.1)	0.023*	0.11 (0.06)	–0.09 (45.0)	0.028*
$MgSO_4$ only (n = 20)	0.14 (0.05)	–0.05 (26.3)	0.043*	0.15 (0.05)	–0.05 (25.0)	0.047*
Day 3						
No exposure (n = 39)	0.19 (0.02)			0.20 (0.02)		
Labetalol ± $MgSO_4$ (n = 11)	0.16 (0.05)	–0.03 (15.8)	0.367	0.18 (0.05)	–0.02 (10.0)	0.613
Nifedipine ± $MgSO_4$ (n = 7)	0.18 (0.06)	–0.01 (5.3)	0.815	0.19 (0.06)	–0.01 (5.0)	0.899
$MgSO_4$ only (n = 20)	0.18 (0.05)	–0.01 (5.3)	0.818	0.19 (0.05)	–0.01 (5.0)	0.843
Day 4						
No exposure (n = 40)	0.22 (0.02)			0.24 (0.02)		
Labetalol ± $MgSO_4$ (n = 11)	0.15 (0.05)	–0.07 (31.2)	0.016*	0.18 (0.05)	–0.06 (25.0)	0.046*
Nifedipine ± $MgSO_4$ (n = 6)	0.24 (0.06)	+0.02 (9.1)	0.612	0.27 (0.06)	+0.03 (12.5)	0.532
$MgSO_4$ only (n = 20)	0.19 (0.05)	–0.03 (13.6)	0.319	0.21 (0.05)	–0.03 (12.5)	0.304
Day 5						
No exposure (n = 42)	0.23 (0.02)			0.24 (0.02)		
Labetalol ± $MgSO_4$ (n = 10)	0.20 (0.05)	–0.03 (13.0)	0.299	0.21 (0.05)	–0.03 (12.5)	0.505
Nifedipine ± $MgSO_4$ (n = 7)	0.20 (0.06)	–0.03 (13.0)	0.386	0.21 (0.06)	–0.03 (12.5)	0.377
$MgSO_4$ only (n = 20)	0.21 (0.05)	–0.02 (8.7)	0.412	0.22 (0.05)	–0.02 (8.3)	0.426

cFTOE values are to be understood as weighted means. * Indicates a difference to newborns unexposed to maternal antihypertensive drugs on the corresponding day at a significance level of $p \leq 0.05$. The adjusted model includes a correction for HC, which was found to be a significant confounder.

ences between infants exposed and infants unexposed to maternal antihypertensive drugs.

Association between cFTOE and Exposure to Maternal Antihypertensive Drugs

Newborns exposed to maternal labetalol ± $MgSO_4$ had a significantly lower cFTOE than newborns not exposed to maternal antihypertensive drugs on days 1, 2 and 4 after birth (table 2; fig. 1). This did not change when adjusting for HC, which was found to significantly influence cFTOE (p = 0.002). Adjusted for HC, infants exposed to labetalol ± $MgSO_4$ had a cFTOE of 0.14 (standard error, SE 0.04) on day 1, 0.13 (SE 0.05) on day 2 and 0.18 (SE 0.05) on day 4. Compared to infants unexposed to maternal antihypertensive drugs, who had corresponding values of 0.22 (SE 0.02), 0.20 (SE 0.02) and 0.24 (SE 0.02), the cFTOE in infants exposed to labetalol ± $MgSO_4$ was thus 36.4% (p = 0.031) lower on day 1, 35.0% (p = 0.035) lower on day 2 and 25.0% (p = 0.046) lower on day 4.

Intrauterine exposure to nifedipine ± $MgSO_4$ and $MgSO_4$ alone resulted in a significantly lower cFTOE on day 2 (0.11, SE 0.06, and 0.15, SE 0.05, respectively, compared to 0.2 in unexposed infants), with a corresponding difference of 45% (p = 0.028) and 25% (p = 0.047).

Association between rFTOE and Exposure to Maternal Antihypertensive Drugs

Multilevel analysis demonstrated no significant differences in renal oxygen extraction between newborns exposed and newborns unexposed to maternal antihypertensive drugs (table 3; fig. 2). Although GA and arterial pCO_2 had a significant influence on rFTOE ($p \leq 0.001$ and p = 0.004, respectively), the relation between mater-

Table 3. Effect of maternal antihypertensive drugs on rFTOE using multilevel analysis

	Unadjusted model (n = 336)			Adjusted model (n = 293)		
	rFTOE (SE)	difference (%)	p value	rFTOE (SE)	difference (%)	p value
Day 1						
No exposure (n = 22)	0.30 (0.04)			1.24 (0.21)		
Labetalol ± $MgSO_4$ (n = 6)	0.22 (0.09)	–0.08 (26.7)	0.170	1.13 (0.10)	–0.11 (8.9)	0.128
Nifedipine ± $MgSO_4$ (n = 5)	0.27 (0.10)	–0.03 (10.0)	0.384	1.12 (0.09)	–0.12 (9.7)	0.088**
$MgSO_4$ only (n = 7)	0.23 (0.08)	–0.07 (23.3)	0.194	1.19 (0.08)	–0.05 (4.0)	0.258
Day 2						
No exposure (n = 38)	0.30 (0.05)			1.23 (0.05)		
Labetalol ± $MgSO_4$ (n = 8)	0.24 (0.12)	–0.06 (20.0)	0.457	1.14 (0.13)	–0.09 (7.3)	0.279
Nifedipine ± $MgSO_4$ (n = 7)	0.32 (0.13)	+0.02 (6.7)	0.845	1.18 (0.11)	–0.05 (4.1)	0.497
$MgSO_4$ only (n = 19)	0.36 (0.10)	+0.06 (20.0)	0.265	1.29 (0.10)	+0.06 (4.9)	0.276
Day 3						
No exposure (n = 38)	0.39 (0.05)			1.32 (0.05)		
Labetalol ± $MgSO_4$ (n = 11)	0.41 (0.11)	+0.02 (5.1)	0.759	1.35 (0.13)	+0.03 (2.3)	0.647
Nifedipine ± $MgSO_4$ (n = 7)	0.54 (0.13)	+0.15 (38.5)	0.077**	1.40 (0.11)	+0.08 (6.1)	0.292
$MgSO_4$ only (n = 20)	0.41 (0.10)	+0.02 (5.1)	0.725	1.35 (0.10)	+0.03 (2.3)	0.554
Day 4						
No exposure (n = 36)	0.39 (0.05)			1.31 (0.05)		
Labetalol ± $MgSO_4$ (n = 11)	0.36 (0.11)	–0.03 (7.7)	0.629	1.32 (0.13)	+0.01 (0.8)	0.890
Nifedipine ± $MgSO_4$ (n = 5)	0.28 (0.14)	–0.11 (28.2)	0.268	1.17 (0.12)	–0.14 (10.7)	0.089**
$MgSO_4$ only (n = 19)	0.34 (0.10)	–0.05 (12.8)	0.378	1.30 (0.10)	–0.01 (0.8)	0.790
Day 5						
No exposure (n = 40)	0.42 (0.05)			1.34 (0.05)		
Labetalol ± $MgSO_4$ (n = 10)	0.35 (0.11)	–0.07 (16.39)	0.305	1.29 (0.13)	–0.05 (3.7)	0.465
Nifedipine ± $MgSO_4$ (n = 7)	0.53 (0.13)	+0.11 (26.17)	0.192	1.40 (0.11)	+0.06 (4.5)	0.391
$MgSO_4$ only (n = 20)	0.38 (0.10)	–0.04 (8.25)	0.496	1.32 (0.10)	–0.02 (1.5)	0.779

rFTOE values are to be understood as weighted means. ** Indicates a difference to newborns unexposed to maternal antihypertensive drugs on the corresponding day at a significance level of $p \leq 0.1$. The adjusted model includes a correction for GA and arterial pCO_2.

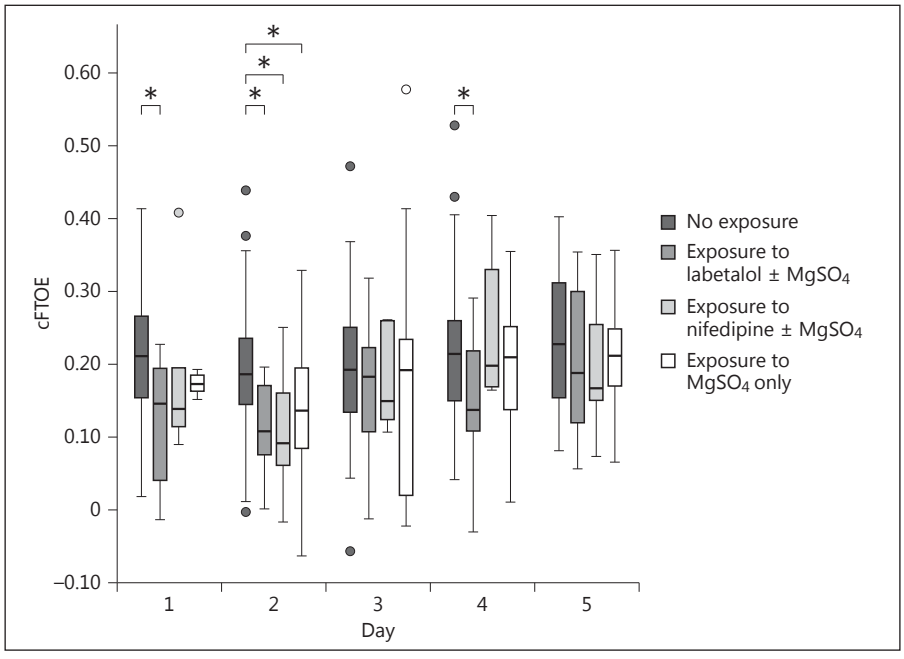

Fig. 1. Maternal antihypertensive drugs and cFTOE, presented per postnatal day and group of exposure in a box-and-whisker plot. The boxes present interquartile ranges and whiskers present the total range of values excluding outliers; circles represent outliers. Asterisks (*) indicate a difference between groups at a significance level of $p \leq 0.05$.

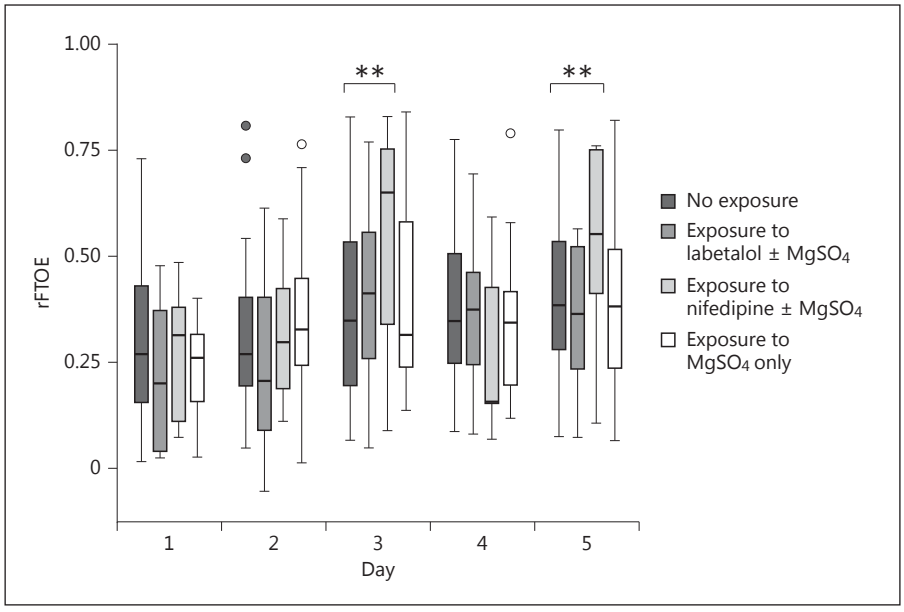

Fig. 2. Maternal antihypertensive drugs and rFTOE, presented per postnatal day and group of exposure in a box-and-whisker plot. The boxes present interquartile ranges and whiskers present the total range of values excluding outliers; circles represent outliers. Double asterisks (**) indicate a difference between groups at a significance level of $p \leq 0.1$.

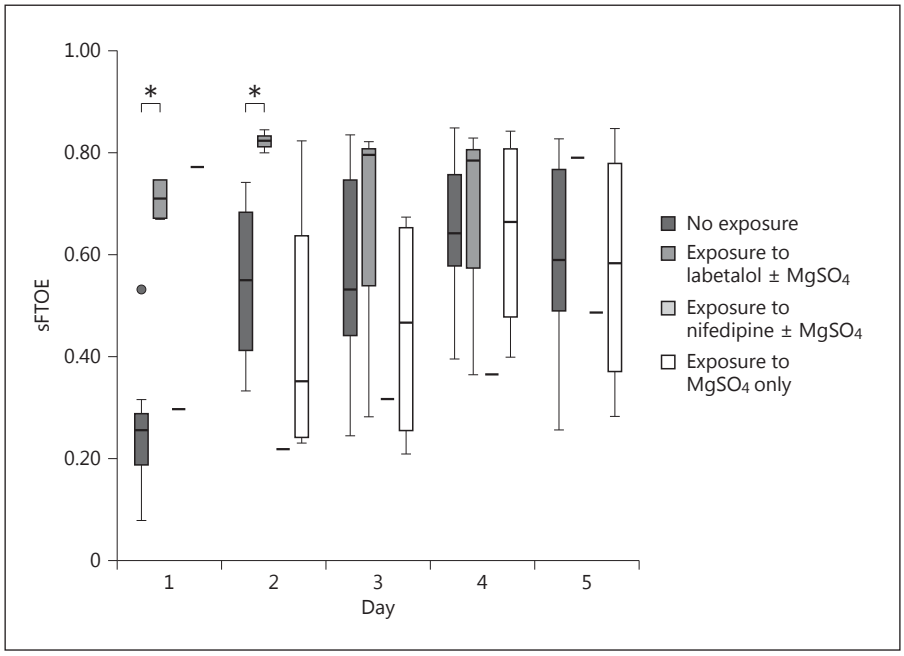

Fig. 3. Maternal antihypertensive drugs and sFTOE, presented per postnatal day and group of exposure in a box-and-whisker plot. The boxes present interquartile ranges and whiskers present the total range of values; dots represent outliers. Asterisks (*) indicate a difference between groups at a significance level of $p \leq 0.5$.

nal antihypertensive drugs and rFTOE was not altered much by their inclusion into the model (table 3).

Association between sFTOE and Exposure to Maternal Antihypertensive Drugs

The differences in sFTOE between exposure groups reached significance on day 2 after birth (Kruskal-Wallis H = 9.323, p = 0.025). While differences on day 1 almost reached significance (Kruskal-Wallis H = 6.370, p = 0.095), they demonstrated a p value above 0.1 on all other days (fig. 3).

Using the Mann-Whitney U test, we found that it was the group of infants exposed to labetalol ± $MgSO_4$ in whom sFTOE proved to be significantly higher on day 1 ($\mu = 0.71$, SD 0.05, n = 2) than in infants unexposed to maternal antihypertensive drugs ($\mu = 0.26$, SD 0.14, n = 7; p = 0.040). This was again the case on day 2, with the sFTOE of labetalol-exposed infants still significantly

higher than that of the controls (μ = 0.82, SD 0.02, n = 3 and μ = 0.55, SD 0.14, n = 16, respectively; p = 0.007). The differences between these two groups became insignificant by day 3 ($n_{day\ 3–4}$ = 3, and $n_{day\ 5}$ = 1). Exposure to $MgSO_4$ only ($n_{day\ 1}$ = 1 and $n_{day\ 2–5}$ = 4) or nifedipine ± $MgSO_4$ ($n_{day\ 1–5}$ = 1) did not result in significantly different sFTOE values compared to the values of nonexposed newborns on any of the 5 days after birth.

Discussion

We found that compared to unexposed infants, the cFTOE of infants exposed to maternal labetalol was significantly lower on days 1, 2 and 4, while the sFTOE was higher on days 1 and 2. Additionally, a significantly lower cFTOE was detected in newborns exposed to maternal nifedipine and/or $MgSO_4$ on day 2 after birth. rFTOE was not influenced by maternal antihypertensive drugs.

A decreased neonatal cFTOE may be explained by an increase in cerebral oxygen supply or by a decrease in cerebral oxygen consumption. An increase in oxygen supply may be a result of direct vasodilative drug action or cerebrovascular autoregulation. Kluckow and Evans [15] and Evans et al. [16] found maternal antihypertensive drugs to be associated with a temporary increase of postnatal blood flow through the superior vena cava, which represents an indirect measure of CBF. A possible explanation for this increase may be labetalol-induced vasodilation impairing cerebral autoregulation, as proposed by Caicedo et al. [17]. Other studies on fetal and maternal CBF were not able to demonstrate labetalol-induced changes [18, 19]. However, a decrease in maternal cerebral perfusion pressure was found and suggested to result from an autoregulatory cerebral response to systemically lowered blood pressure by labetalol [19].

The high sFTOE in labetalol-exposed infants may also be explained by vasodilative drug action. If excessive, vasodilation may be strong enough to decrease the effective circulating volume supplying the intestines, which are not protected by autoregulatory mechanisms. Studies and case reports relating hypotension in newborns to maternal labetalol support this theory [7, 20]. Other studies were unable to find an association between clinically significant hypotension and labetalol [21]. Furthermore, we found mean arterial blood pressure not to be significantly lower in labetalol-exposed infants (table 1).

However, especially in association with labetalol, we need to consider another important aspect. Oxygenation may also be influenced by underlying maternal disease, as in our study labetalol was only given in cases of maternal hypertension, preeclampsia or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. Preeclampsia has been linked to placental abnormalities consistent with maternal vascular underperfusion, which was shown to have a tendency towards association with a lower cFTOE on day 2 after birth [8, 22]. Associated chronic hypoxemia of the fetus commonly results in intrauterine growth restriction and redistribution of cardiac output to the brain as a compensatory, 'brain-sparing' mechanism preventing cerebral ischemia [23]. Indeed, sub-analysis showed intrauterine growth restriction, defined as an echographically estimated fetal weight below the 10th percentile, and placental abnormalities consistent with maternal vascular underperfusion as defined by Roescher et al. [22], to be significantly more frequent in neonates exposed to maternal labetalol than in neonates unexposed to maternal antihypertensive drugs (table 1). We were, however, unable to investigate evident fetal brain sparing as cerebroplacental pulsality index ratios were infrequently measured. Verhagen et al. [24], who explored the effect of maternal labetalol on only cFTOE with similar results, also suspected preeclampsia-associated brain sparing as a possible cause. Our study further supports this theory as we found a concomitant increase in sFTOE in these newborns, which may be caused by an increase in vascular resistance of the splanchnic circulation associated with vasoconstriction of nonvital viscera. Unfortunately, we were unable to determine whether the associations found were related to labetalol or to preeclampsia of the mothers in this observational study. As these two factors always co-occurred in our study, future studies should elucidate which factor is mainly responsible for our cFTOE and sFTOE findings.

With regards to nifedipine, Harake et al. [25] demonstrated a 30–50% increase of fetal CBF upon low-dose nifedipine infusion in pregnant sheep. Others have reported significantly decreased pulsatility and resistance indices of the fetal middle cerebral artery in the first 24–48 h after tocolysis with nifedipine [10, 26]. However, Verhagen et al. [24] and Grzesiak et al. [27] did not find an effect of nifedipine on neonatal cFTOE or fetal CBF, respectively. It may therefore be possible that $MgSO_4$, which in our study was given to mothers in conjunction with nifedipine in 6 of the 7 subjects included, had a greater influence on our results. While studies on the effect of $MgSO_4$ on cerebral brain perfusion are inconsistent, a temporarily decreased oxygen consumption in the face of an unaltered CBF may be responsible for a reduction in cFTOE, as demonstrated in fetal sheep after the maternal

infusion of $MgSO_4$ [28]. Neurological depression due to $MgSO_4$ may be responsible [5], and this effect also needs to be considered when interpreting the association found between FTOE and labetalol, since most of the infants exposed to labetalol were also exposed to $MgSO_4$.

No significant association between rFTOE and maternal antihypertensive drugs was found. This was surprising since we expected rFTOE to be increased due to hypoperfusion of the kidney associated with vasodilative drug action or brain-sparing perfusion. However, Petrova et al. [29], who investigated the association between PDA size and regional oxygenation values, demonstrated a similar phenomenon. While cerebral and renal oxygenation was not affected by PDA size, mesenteric oxygenation was reduced in the presence of a large PDA combined with nasal continuous positive airway pressure. A possible cause for the stability of renal oxygenation may be intrinsic renal autoregulatory mechanisms [2, 3]. Although renal autoregulation seems to be impaired in advance of cerebral autoregulation during conditions of hypotension or arterial desaturation [2, 30], it may not be affected by exposure to maternal labetalol (or associated preeclampsia), nifedipine or $MgSO_4$. Another explanation for the stability of rFTOE values may be a failure to correctly place the NIRS sensor above the area of the kidney. The values may therefore represent not only the tissue oxygen extraction of the kidney, but possibly that of surrounding tissue other than intestinal tissue.

The limitations of this study include the small sample size of newborns in whom splanchnic NIRS were performed due to a lack of infraumbilical space in very low BW infants and the resulting inability to correct for confounders. The differences found, however, were large and significant, and should not be discarded. Further studies are recommended to confirm the findings or possibly detect other significant differences that may have been missed due to the small sample sizes. Furthermore, we were unable to adequately study the effect of dosage and pharmacodynamics on FTOE values due to the retrospective nature of the collection of data concerning dosage and maternal size. Finally, we did not correct for maternal indomethacin use, which may have been of influence on FTOE. However, its use was infrequent and did not significantly differ between groups.

In summary, this was the first study to globally analyze the postnatal effects of maternal antihypertensive drugs on multisite tissue oxygen extraction in preterm neonates using NIRS. Using this technique at multiple sites allowed us to observe regional oxygenation differences within the exposure groups. Our results show that preterm newborns exposed to maternal antihypertensive drugs, particularly labetalol, have significantly lower cerebral but higher splanchnic oxygen extraction than unexposed newborns, underlining the importance of monitoring the cerebral and abdominal tissue oxygenation in these newborns during their first days of life. The exact underlying pathogenesis needs to be studied further, as well as the clinical significance of our findings on neurological outcome and gastrointestinal function.

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