Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Cerebral oxygen saturation and autoregulation during hypotension in extremely preterm infants

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BACKGROUND: The impact of the permissive hypotension approach in clinically well infants on regional cerebral oxygen saturation ($rScO_2$) and autoregulatory capacity (CAR) remains unknown.
METHODS: Prospective cohort study of blinded $rScO_2$ measurements within a randomized controlled trial of management of hypotension (HIP trial) in extremely preterm infants. $rScO_2$, mean arterial blood pressure, duration of cerebral hypoxia, and transfer function (TF) gain inversely proportional to CAR, were compared between hypotensive infants randomized to receive dopamine or placebo and between hypotensive and non-hypotensive infants, and related to early intraventricular hemorrhage or death.
RESULTS: In 89 potentially eligible HIP trial patients with $rScO_2$ measurements, the duration of cerebral hypoxia was significantly higher in 36 hypotensive compared to 53 non-hypotensive infants. In 29/36 hypotensive infants (mean GA 25 weeks, 69% males) receiving the study drug, no significant difference in $rScO_2$ was observed after dopamine ($n = 13$) compared to placebo ($n = 16$). Duration of cerebral hypoxia was associated with early intraventricular hemorrhage or death. Calculated TF gain ($n = 49/89$) was significantly higher reflecting decreased CAR in 16 hypotensive compared to 33 non-hypotensive infants.
CONCLUSIONS: Dopamine had no effect on $rScO_2$ compared to placebo in hypotensive infants. Hypotension and cerebral hypoxia are associated with early intraventricular hemorrhage or death.

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IMPACT:

- Treatment of hypotension with dopamine in extremely preterm infants increases mean arterial blood pressure, but does not improve cerebral oxygenation.
- Hypotensive extremely preterm infants have increased duration of cerebral hypoxia and reduced cerebral autoregulatory capacity compared to non-hypotensive infants.
- Duration of cerebral hypoxia and hypotension are associated with early intraventricular hemorrhage or death in extremely preterm infants.
- Since systematic treatment of hypotension may not be associated with better outcomes, the diagnosis of cerebral hypoxia in hypotensive extremely preterm infants might guide treatment.

INTRODUCTION

Preterm birth remains an important risk factor for adverse neurological outcome.[1] Approximately 780,000 extremely preterm infants are born worldwide each year[2] and up to one-third of them will be diagnosed with or treated for hypotension. The most commonly used definition of a blood pressure threshold that warrants intervention is when an infant's mean arterial blood pressure (MABP) in mmHg is less than their gestational age (GA) in weeks.[3] Hypotension in preterm infants is associated with decreased cerebral blood flow (CBF),[4,5] intraventricular hemorrhage (IVH), ischemic lesions, and mortality.[6] Impaired cerebral autoregulatory capacity (CAR) may be an important pathophysiological mechanism in brain lesions in hypotensive preterm infants and has been associated with increased rates of IVH and mortality.[7,8] However, treatment for hypotension is also associated with poor neurodevelopmental outcome.[9] Dopamine, the most commonly used vasopressor in the neonatal intensive care unit (NICU), is known to increase MABP in preterm infants[10] and

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its use was associated with decreased CAR in a case–control study.[11]

It is uncertain whether, in the absence of signs of shock, low blood pressure should be treated in extremely preterm infants in the first days after birth.[12,13] The HIP trial was a randomized controlled trial studying the management of hypotension with dopamine or placebo. Near-infrared spectroscopy (NIRS)-derived cerebral oxygen saturation ($rScO_2$) is a surrogate for CBF that can be measured non-invasively and continuously at the bedside.[7,8] In a proportion of infants potentially eligible for the HIP trial, $rScO_2$ was measured. Our main hypothesis was that $rScO_2$ in hypotensive infants treated with dopamine would differ by more than 10% compared to hypotensive infants treated with placebo. Furthermore, we investigated the effect of hypotension on $rScO_2$ and CAR and evaluated the association between measures of $rScO_2$ and CAR and the composite outcome of IVH by day 7 or death before discharge.

METHODS

Study design

This is a prospective cohort study of infants potentially eligible for the HIP trial at NICU's in Cork, Dublin (Ireland); Antwerp, Leuven (Belgium); Prague (Czech Republic); and Edmonton (Canada). The study protocol has been previously published[14]. The central institutional review board, Cork Research Ethics Committee, University College Cork, and the human research ethics committees at each participating center approved the trial. All study sites were monitored by an independent clinical research associate.

Clinical trial registration

ClinicalTrials.gov (NCT01482559) with EudraCT 2010-023988-17.

Study population

Infants born before 28 weeks GA and without signs of shock were eligible for inclusion in the HIP trial. Exclusion criteria were infants considered non-viable by attending clinicians, with life-threatening congenital abnormalities or with grade III or IV IVH[15] on pre-trial cranial ultrasound. At 7 of the 10 participating centers, blinded $rScO_2$ measurements were performed in potentially eligible infants if consent was provided by the parents. Eligible infants were randomly allocated to receive dopamine or placebo if invasively measured MABP in mmHg fell below a value equivalent to their GA in weeks for more than 15 min in the first 3 days after birth. A saline fluid bolus of 10 ml/kg was given as part of the intervention in both arms. Staff and investigators were blinded to the study medication received. The study medication was prepared by the local pharmacy or a caregiver not involved in patient care, according to the study protocol. Additional treatment was administered according to the study protocol.[14] Thus, both non-randomized, non-hypotensive infants and hypotensive infants randomly allocated to receive dopamine or placebo had $rScO_2$ measurements during the study period.

Interventions

$rScO_2$ (%) was measured by INVOS 5100 and the neonatal OxyAlert NIRSensor (Covidien, Mansfield, MA). Arterial oxygen saturation (SaO_2) and MABP were measured by neonatal monitors (IntelliVue MP70,Philips Healthcare, Best, The Netherlands, or equivalent). $rScO_2$ with or without SaO_2 and MABP data were saved on a central database, encrypted, and transferred for offline analysis in Belgium.

Signal processing and measurement of CAR

The investigators were blinded to the study medication received during data analysis and statistical analysis. The sample frequency and the amount of data points were identified for each center and infant, respectively. Artifact removal was applied using two different approaches. To remove movement artifacts or non-physiological variations in MABP data with a sample frequency of 1 Hz, segments with a variation of >3 SD in 10-s windows were removed. To remove signals outside the physiological domain, $rScO_2$ data below 30% and MABP data below 10 and above 70 mmHg were removed.

To measure CAR, $rScO_2$ is a valid surrogate for CBF under the assumption of stable SaO_2 and constant cerebral metabolism.[16] Oblique subspace projections were used to eliminate the contribution of SaO_2 in the $rScO_2$ signal.[17] CAR was studied using the inversely proportional parameter transfer function (TF) gain. TF gain values were explored in overlapping 20-min epochs (overlap of 19 min) with significant coherence (COH) between (SaO_2-corrected) $rScO_2$ and MABP in the very-low-frequency (VLF) range, which indicates that CAR is pressure passive.[18] TF gain quantifies the damping effect between the input (MABP) and the output (SaO_2-corrected $rScO_2$) and is expressed as % $rScO_2$ change/mmHg MABP change.[8,19] A higher TF gain indicates that moderate changes in MABP are associated with larger changes in CBF, reflecting decreased CAR. Significant COH was tested using Monte Carlo simulations.[20] Signal detrending and Welch's method (overlapping 10-min subwindows) were used to reduce edge effects and noise, respectively. Analysis was performed using MATLAB 2018b (The Mathworks, Natick, MA).

Study outcomes

The primary outcome was the difference in $rScO_2$ between dopamine- and placebo-treated hypotensive infants, for a period of 2 h following commencement of the study drug. For hypotensive infants receiving the study drug, mean values of $rScO_2$, MABP, and TF gain were calculated in 2-h epochs before, after start, and after stop of the study drug. Furthermore, the percentage of time with $rScO_2$ below 63% (% time $rScO_2 < 63\%$)[21] was calculated as a measure for cerebral hypoxia in the same time frames. Identical parameters were calculated for each infant, for days 1, 2, and 3 and the first 3 days after birth overall to compare between hypotensive and non-hypotensive infants. The relation of the parameters with the composite outcome of occurrence of IVH by day 7 or death before discharge from the hospital was assessed.

A post hoc exploratory analysis focused on the relation between multiple pairs of median MABP with TF gain and median $rScO_2$, respectively, per day and in all available 20-min pressure-passive epochs per patient, to investigate whether these relations would permit identification of adverse outcome.

Statistical analysis

To identify a difference of 10% (SD 12%)[22] in $rScO_2$ after dopamine therapy in comparison with placebo, with a type 1 error of 0.05 and type 2 error of 0.2, 23 randomized participants with $rScO_2$ monitoring in each group were needed. A multivariate linear model for longitudinal measures with an unstructured covariance matrix was used to compare the evolution of study parameters between groups over time. A direct likelihood approach was adopted such that cases with missing information were still included in the analysis. Least-squares means (and their 95% confidence interval (CI)) are reported. *P* values are given after Bonferroni Holm correction for multiple testing. Relation with outcome was assessed using univariable and bivariate logistic regression models. To characterize the relation between TF gain–MABP and $rScO_2$–MABP, spearman correlations were performed per day for all infants.

Furthermore, using all available individual 20-min epoch data for each infant, linear mixed models with (correlated) random intercepts and slopes on (log-transformed) TF gain and $rScO_2$ values were used comparing the relation TF gain–MABP and $rScO_2$–MABP as a function of outcome. Restricted cubic splines with four knots[23] were used to allow a nonlinear relation between

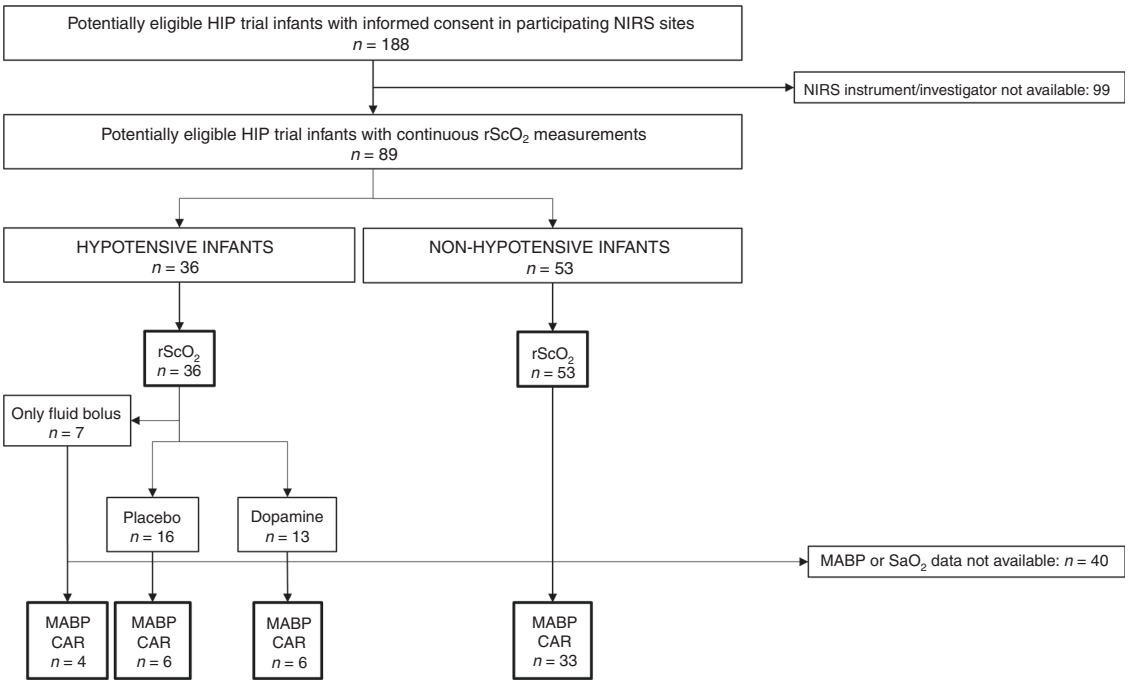

Fig. 1 Recruitment and participant flow. Recruitment, randomization, and participant flow in a trial of cerebrovascular measurements in (non)-hypotensive extremely preterm neonates with or without treatment with dopamine.

the pairs. The model contained terms for the spline basis (2 extra terms on top of the intercept and the linear slope), the main effect of group (i.e. the levels of the outcome), and additional terms referring to the interaction between group and MABP. The result is given of an overall test for any difference between both levels in the relation. Predicted mean outcomes were plotted with pointwise 95% confidence intervals. Empirical standard errors were used to correct for misspecification of the covariance structure. Analyses were performed on the information from the first day. GA was added as a continuous covariate in the model. A P value <0.05 was considered statistically significant. All reported P values are two sided. Analyses have been performed using SAS software, version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC) and SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY).

RESULTS

Study population and data collection

Data were collected only from the centers allocated to perform NIRS monitoring in infants with informed consent for the HIP trial. Between February 2015 and September 2017, $rScO_2$ was obtained in 89 potentially eligible HIP infants, 36 of whom were randomized to either placebo or dopamine (Fig. 1). Finally, 29/36 infants received the study drug (dopamine $n = 13$ versus placebo $n = 16$) because of persistent hypotension after one fluid bolus. In all, 30.6% of infants received additional treatment, but beyond the first 2 h after start of the study drug. Fifty-three infants were never hypotensive during the first 3 days after birth. In 49/89 infants, continuous MABP and SaO_2 data were available by which TF gain could be calculated. Acquisition sample frequency (f_s) varied from 1 Hz (down sampled to 1/30 Hz) to 1/60 Hz. Based on the Nyquist theorem, COH and TF gain were studied in the 0.003–0.017 (f_s 1/30 Hz, two centers) or 0.003–0.0083 (f_s 1/60 Hz, one center) VLF range. Median duration of the recordings and deleted data due to artifact reduction were 50.7 (interquartile range (IQR) 39.3–55.6) and 1.9 (IQR 0.7–5.5) h, respectively. Monte Carlo simulations detected the cut-off value for non-significant coherence at 0.5 ($f_s = 1/30$ Hz) and 0.55 ($f_s = 1/60$ Hz). Due to exclusion of the non-coherent 20-min epochs, median decrease in data points for TF gain values was 55.5 (IQR 52.1–66.1)%. Infant characteristics are summarized in Table 1 a + b.

Primary outcome and planned comparisons

Among 29 hypotensive infants treated with the study drug, there were no significant differences in $rScO_2$ between infants in the 2 h after receiving dopamine (estimated mean 77.7%; 95% CI 71.2–84.1) or placebo (75.8; 69.8–81.7) $P > 0.99$ (Fig. 2a). The evolution over time of % time $rScO_2 < 63\%$ was significantly different between groups (interaction effect $P = 0.017$) (Fig. 2b). The changes in the 2-h time frame after stop of the study drug versus before start were significantly higher ($P = 0.038$) in the dopamine group: values, expressed as ratios, in the 2-h time frame after stop of the study drug versus values before start were 4.90 (95% CI 1.82–13.3) and 1.08 (95% CI 0.71–1.67) times higher in the dopamine and placebo groups, respectively.

The evolution of MABP, available in 12/29 infants, was significantly different between groups (interaction effect $P = 0.035$) with MABP being significantly higher 2 h after start of dopamine (estimated mean 28.4 mmHg; 95% CI 25.5–31.4) compared to placebo (23.8; 20.8–26.7) $P = 0.019$ (Fig. 2c). There were no significant differences in TF gain, calculated in 12/29 infants, between treatment groups (Fig. 2d).

Secondly, comparisons were made between all 89 non-hypotensive and hypotensive infants—regardless of treatment allocation—in the first 3 days after birth. $rScO_2$ did not differ between 36 hypotensive (estimated mean 74.5%; 95% CI 71.2–77.8) and 53 non-hypotensive infants (75.8; 72.8–78.8) $P = 0.45$ over the first 3 days after birth overall (Fig. 3a). The % time $rScO_2 < 63\%$ was significantly higher in the hypotensive (estimated mean 3.2%; 95% CI 1.9–5.2) versus non-hypotensive infants (1.6; 1–2.5) $P = 0.048$ over the first 3 days after birth together (Fig. 3b). MABP, available in 49/89 infants, increased significantly over time in both groups, but was significantly lower in the 16 hypotensive infants on day 1 (estimated mean 29.6 mmHg; 95% CI 27.6–31.5), day 2 (32.1; 30.1–34.1), and day 3 (33.5; 31.2–35.9) compared to the 33 non-hypotensive infants on day 1 (35.2; 33.9–36.6) $P < 0.001$, day 2 (37.5; 36.1–38.9) $P < 0.001$, and day 3

Table 1. Infant characteristics and outcome of (a) hypotensive versus non-hypotensive infants and (b) hypotensive infants treated with dopamine versus placebo.

a

Infant characteristics and outcome	Hypotensive ($n = 36$)	Non-hypotensive ($n = 53$)	Total ($n = 89$)	P value
Male sex, *n* (%)	25 (69)	26 (49)	51 (57)	0.056
GA in weeks, median (IQR)	25.3 (24.7–26.5)	25.9 (25.1–26.9)	25.7 (24.9–26.6)	0.036
Birth weight in g, median (IQR)	755 (607–860)	800 (670–950)	770 (650–829)	0.037
Apgar 1 min, median (IQR)	4 (2–6) ($n = 35$)	5 (2–7) ($n = 48$)	4 (2–6) ($n = 83$)	0.237
Apgar 5 min, median (IQR)	7 (5–8) ($n = 35$)	6.5 (5–8.75) ($n = 48$)	7 (5–8) ($n = 83$)	0.826
CRIB score, median (IQR)	11 (7–13) ($n = 35$)	10 (7–12) ($n = 48$)	11 (7–12) ($n = 83$)	0.381
Study drug received, *n* (%)	29 (81)	0 (0)	29 (33)	
Additional treatment[a], *n* (%)	11 (31)	0 (0)	11 (12)	
IVH[b] by day 7, *n* (%)	13 (36)	12 (23)	25 (28)	0.165
Survival to discharge, *n* (%)	28 (78)	49 (93)	77 (87)	0.061

b

	Dopamine ($n = 13$)	Placebo ($n = 16$)	Total ($n = 29$)	P value
Male sex, *n* (%)	9 (69)	11 (69)	20 (69)	1.000
GA in weeks, median (IQR)	25.1 (24.9–26.4)	25.6 (25–26.6)	25.4 (24.9–26.4)	0.449
Birth weight in g, median (IQR)	760 (639–815)	705 (613–938)	750 (639–860)	0.779
Apgar 1 min, median (IQR)	3 (2–5.5)	4 (3–6) ($n = 15$)	4 (2–6) ($n = 28$)	0.340
Apgar 5 min, median (IQR)	7 (6–8)	7 (5–8) ($n = 15$)	7 (6–8) ($n = 28$)	0.524
CRIB score, median (IQR)	8 (4.5–13)	12 (10–13) ($n = 15$)	11 (5.5–13) ($n = 28$)	0.317
Study drug received, *n* (%)	13 (100)	16 (100)	29 (100)	1.000
Additional treatment[a], *n* (%)	4 (31)	7 (44)	11 (38)	0.702
IVH[b] by day 7, *n* (%)	6 (46)	5 (31)	11 (38)	0.466
Survival to discharge, *n* (%)	12 (92)	12 (75)	24 (83)	0.343

[a]Adrenaline.
[b] IVH was defined as grade I–IV (15) and assessed at day 7 after birth.

(38.2; 36.6–39.9) $P = 0.001$, respectively (Fig. 3c). TF gain, calculated in 49/89 infants, significantly decreased over time in both groups and was significantly higher in the 16 hypotensive infants on day 1 (estimated mean 1.07%/mmHg; 95% CI 0.89–1.24), day 2 (0.96; 0.81–1.11), and day 3 (0.89; 0.74–1.05) compared to the 33 non-hypotensive infants on day 1 (0.87; 0.72–1.01) $P = 0.011$, day 2 (0.79; 0.66–0.92) $P = 0.007$, and day 3 (0.71; 0.57–0.84) $P = 0.005$, respectively (Fig. 3d).

After univariable logistic regression, significant odds ratios for occurrence of IVH by day 7 or death before discharge were obtained for % time $rScO_2 < 63\%$ on day 3 [odds ratio 1.027 (95% CI 1.004–1.051), $P = 0.023$] and day 1–3 overall [1.036 (1.004–1.069), $P = 0.026$], MABP on day 1 [0.853 (0.740–0.984), $P = 0.029$], GA [0.441 (0.283–0.687), $P < 0.001$], and clinical risk index for babies (CRIB) score[24] [1.291 (1.110–1.501), $P < 0.001$]. After correction for GA, no factor remained significant.

Hypothesis generating post hoc analyses

The correlation between mean TF gain and MABP for each day per infant was analyzed. TF gain increased significant with decreasing MABP on day 1 ($\rho = -0.306$), $P = 0.035$; day 2 ($\rho = -0.375$), $P = 0.008$; and day 3 ($\rho = -0.402$), $P = 0.006$ (Fig. 4a). This significant correlation was not observed between mean $rScO_2$ and MABP (Fig. 4b). Using all available individual 20-min epochs in the linear mixed model, a significant difference was found in the TF gain–MABP relation on day 1 in infants with IVH by day 7 or death before discharge ($P = 0.017$) (Fig. 4c). The $rScO_2$–MABP relation on day 1 was not significantly different between outcome groups (Fig. 4d).

DISCUSSION

In this study, treatment of hypotension—defined as MABP less than GA in mmHg—with dopamine compared to placebo is described in extremely preterm infants. Dopamine was found to increase MABP without associated significant difference in $rScO_2$ or TF gain compared to placebo in a time frame of 2 h following commencement of the study drug. The planned sample size was not reached due to a lower than anticipated inclusion rate. The power to detect a difference of 10% in $rScO_2$ equaled 80% since the observed standard deviation was lower than anticipated.

Although the known effect of dopamine on MABP is almost invariably positive, the cerebral effect of dopamine to treat hypotension differs among studies. Using Doppler ultrasound, no difference or a (short lasting) increase of mean blood velocity and decrease of resistance index in the anterior cerebral artery was seen in several observational studies.[25–28] Munro et al.[4] reported an increase in NIRS derived CBF in dopamine treated hypotensive infants. In a meta-analysis by Seri et al.,[10] dopamine was found to be associated with increases in CBF in hypotensive preterm infants. Pellicer et al. were the first to perform a blinded, randomized study to describe the effect of dopamine compared to epinephrine in hypotensive infants. A dose-dependent increase in NIRS derived cerebral blood volume and perfusion after escalation of therapy

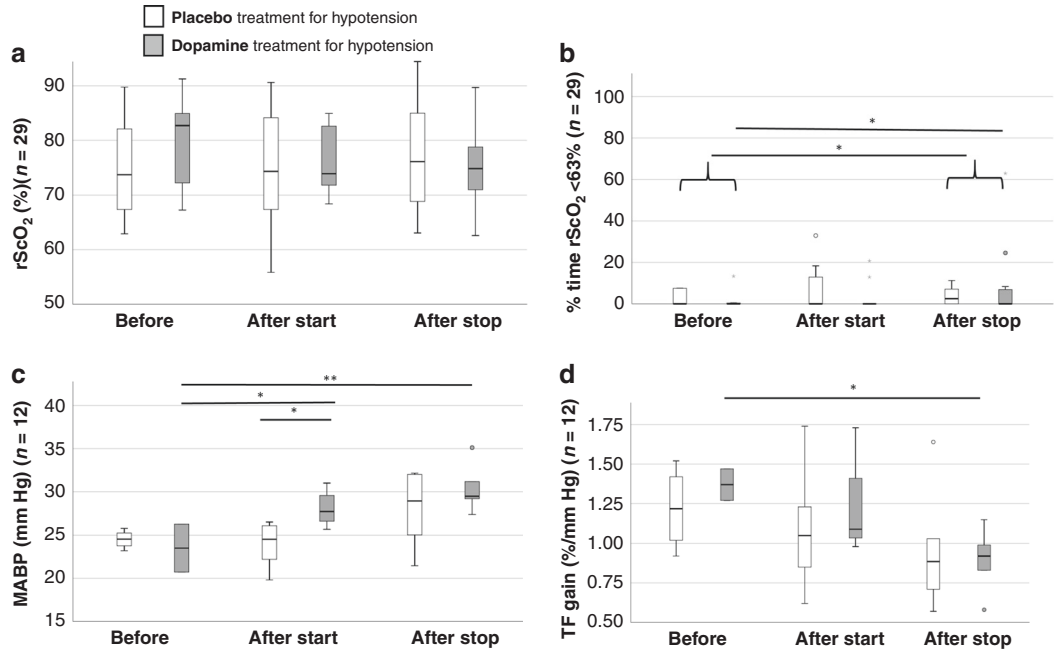

Fig. 2 Evolution of outcome parameters in hypotensive infants randomized to receive dopamine or placebo. Boxplots (middle: median; end of boxes: 25th and 75th percentile; whiskers: 1½ IQR) indicating evolution of $rScO_2$ (**a**), percentage of time with $rScO_2$ below 63% (**b**), MABP (**c**), and TF gain (**d**) in 2-h time epochs before, after start, and after stop of placebo or dopamine. *$P < 0.05$. **$P < 0.01$.

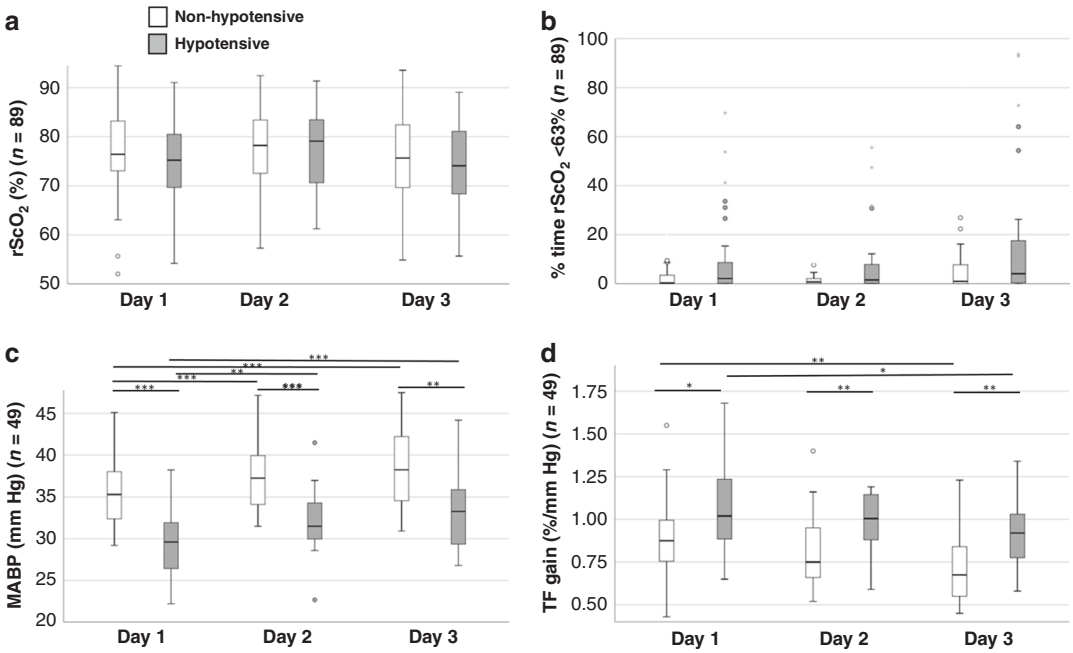

Fig. 3 Evolution of outcome parameters in hypotensive versus non-hypotensive infants. Boxplots (middle: median; end of boxes: 25th and 75th percentile; whiskers: 1½ IQR) indicating evolution of $rScO_2$ (**a**), percentage of time with $rScO_2$ below 63% (**b**), MABP (**c**), and TF gain (**d**) over the first 3 days after birth in hypotensive versus non-hypotensive infants. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

with dopamine was observed.[29] However, there was a wide range of responses among participants. The current study differs from Pellicer by describing not the response after the inotrope dose increments, but the mean cerebral oxygen saturation in the full time frame during these increments. According to the study protocol, the dose of dopamine or placebo was to be increased after each 30 min. Thus, after the 2-h time frame the maximum dose of dopamine (20 µg/kg min) was reached if MABP was not increased to or above a value equivalent to the GA. As a potentially more robust parameter to measure cerebral hypoxia, the % time with $rScO_2$ below 63% was calculated. This value corresponds to the hypoxic threshold used in the SafeBoosC 3 trial.[21,30,31] Although a greater increase (i.e. longer duration of cerebral hypoxia) in the dopamine group compared to the placebo group after stopping the study medication was observed, no significant differences between study groups were found.

Decreased CAR defined as a significant correlation between $rScO_2$ and MABP was found to be associated with dopamine

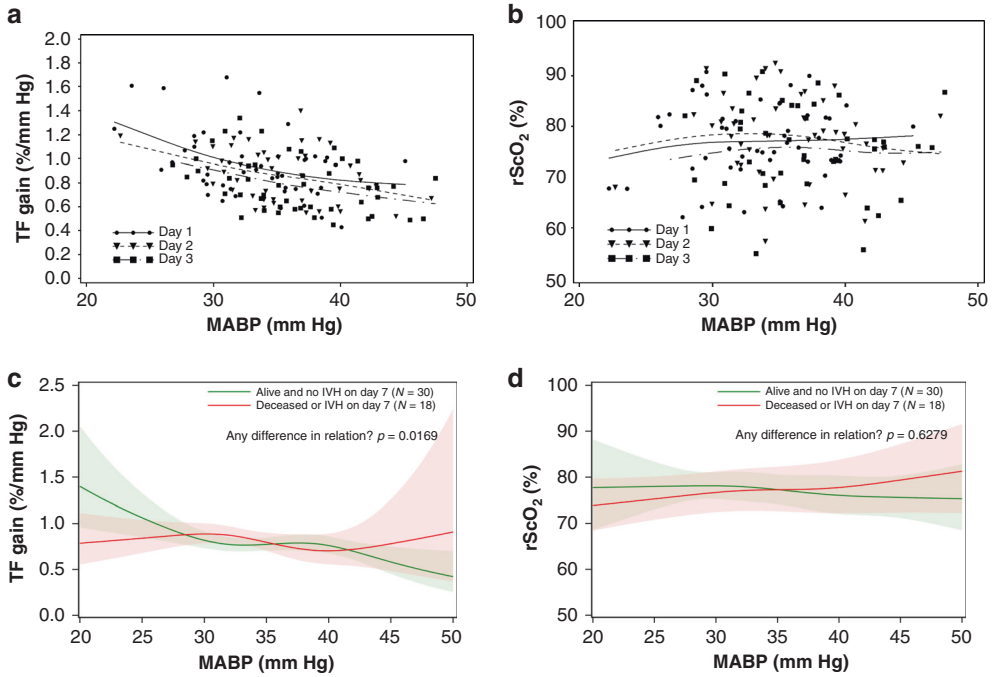

Fig. 4 Relations between MABP/TF gain and MABP/rScO$_2$. Scatterplot of each patient MABP with TF gain (**a**) and rScO$_2$ (**b**) in the first 3 days after birth. Predicted mean individual TF gain–MABP (**c**) and rScO$_2$–MABP (**d**) pairs with pointwise 95% CI during the first day after birth in infants with good (green) versus adverse (red) short-term outcome.

compared to non-dopamine treatment in three case–control studies.[11,32,33] With our patient group, we can conclude that there were concordant changes between MABP and rScO$_2$ in hypotensive infants (as described by Tsuji et al.[7]), but the magnitude of the change was not significantly different for dopamine versus placebo.

We also examined the differences in parameters between hypotensive and non-hypotensive infants. Notwithstanding initial treatment allocation and additional treatment, MABP significantly increased over time, as earlier described,[34] but remained significantly lower in hypotensive compared to non-hypotensive infants during the first 3 days. However, increased duration of cerebral hypoxia was found in hypotensive infants. Lower rScO$_2$ values are associated with lower GA[35] and with impaired neurodevelopmental outcome.[32,36] In univariable analysis, increased duration of cerebral hypoxia on day 3 and on days 1–3 overall and lower MABP on day 1 were associated with the occurrence of IVH by day 7 or death before discharge. However, this association was strongly related to GA. Since treatment of hypotension may not be associated with improved outcomes,[9] the diagnosis of cerebral hypoxia during hypotension, and also perhaps normotension, especially in the infants with youngest GA, might be of added value in determining the need for intervention but remain to be determined. The avoidance of cerebral hypoxia during (treatment of) hypotension as a means to improve neurodevelopmental outcome also remains to be elucidated.[37]

This study is the first NIRS derived study (as compared to Doppler flow measurements[38]) to describe improving CAR, but significantly lower in hypotensive compared to non-hypotensive infants, in the first 3 days after birth. We postulate this to be a maturational effect, equivalent to the increasing MABP but with a steeper slope of the autoregulation curve in hypotensive infants.[39]

In the constructed model between TF gain, rScO$_2$, and MABP (Fig. 4c, d), an estimate of the autoregulation curve in our cohort can be observed. TF gain on day 1 in both the normal and adverse outcome groups is between 0.5 and 1 in the 30–40 mmHg MABP range, reflecting the slightly negative slope of the autoregulatory plateau, as described by Greisen.[39] As we do not expect a perfect CAR system with zero-level influence of MABP on CBF/rScO$_2$, then MABP will always be somewhat related (even if weakly) to CBF/rScO$_2$. Taking into account the more extreme MABP ranges, the relation between TF gain and MABP was significantly different between outcome groups. This finding in the model is affirmative for the postulation that decreased CAR on day 1 in the higher MABP ranges is associated with IVH by day 7. In the low MABP ranges, decreased CAR was identified in infants with a good outcome. Different factors can play a role in the group with an adverse outcome. Vasodilation due to hypoxia,[40] hypercapnia,[41–44] perinatal asphyxia,[45–47] brain sparing,[48] or medication might explain the absent change in TF gain in the low MABP range since the maximum adaptation is already reached.

This study has limitations. Patient numbers were low due to the difficulties with recruitment. Patient numbers could be too small to detect a difference in cerebral oxygenation below 10% or a difference in TF gain between hypotensive infants treated with dopamine versus placebo. Changes in pCO$_2$, pO$_2$, pH, neurogenic factors, and metabolic demands, known to influence the cerebrovascular tone, were considered stable during the time of assessment. The data sampling frequency between centers was not uniform, leading to a unstandardized VLF band for CAR analysis. This is a reality in multicenter studies but requires attention to collect high-quality data for CAR research in the future. This study indicates that continuous measurement of rScO$_2$ combined with TF gain, inversely proportional to CAR, in the first days after birth is possible and indicative of adverse outcome. However, better determination of intact or impaired CAR by TF gain or other mathematical methods and the concordance between the different methods remain the subject of further research.

CONCLUSION

Dopamine significantly increased MABP compared to placebo without associated differences in rScO$_2$ or TF gain in hypotensive extremely preterm infants. Increased duration of cerebral hypoxia

and lower MABP were predictive for occurrence of IVH by day 7 or death before discharge. Decreased CAR was present in hypotensive compared to non-hypotensive infants and CAR correlated with MABP.

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AUTHOR CONTRIBUTIONS

L.T. conceptualized and designed the study, collected data, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript for important intellectual content. G.N. and E.D. conceptualized and designed the study, collected data, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content. D.H. and A.C. conceptualized and designed the study, performed the data analysis, and reviewed and revised the manuscript for important intellectual content. K.B., G.B., P.-Y.C., D.C., A.E.-K., A.G., J.M., N.M., J.M., C.P.F.O'D., J.M.O'T., Z.S., D.V.L., and H.W. conceptualized and designed the study, collected data, and reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

Competing interests: N.M. reports consultancy for Novartis and Shire, and is member of the Advisory Committee of GSK. The remaining authors declare no competing interests.

Consent statement: Parental informed consent was required for inclusion of infants in this study.

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