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Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life

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ABSTRACT

Objective To evaluate lowest mean arterial blood pressure during the first 24 h of life (minMAP^{24}) in very-low-birthweight (VLBW) infants and to identify associations between hypotension and short-term outcome.

Design Retrospective cohort analysis of the minMAP^{24} of 4907 VLBW infants with a gestational age <32 weeks in correlation with clinical data. Hypotension was defined as minMAP^{24} being lower than the median value of all patients of the same gestational age.

Results MinMAP^{24} values correlated with gestational age. Median minMAP^{24} values of VLBW infants ≤29 weeks' gestation were 1–2 mm Hg lower than gestational age in completed weeks. Hypotensive infants had a higher rate of intraventricular haemorrhage (IVH, 20.3% vs 15.9%, p<0.001), bronchopulmonary dysplasia (BPD, 19.2% vs 15.1%, p<0.001) and death (5.2% vs 3.0%, p<0.001). Multivariate logistic regression analyses, including potential confounders, confirmed these data. MinMAP^{24} was an independent risk factor for IVH (OR 0.97/mm Hg, 95% CI 0.96 to 0.99, p=0.003), BPD (OR 0.96/mm Hg, 95% CI 0.94 to 0.98, p<0.001) and mortality (OR 0.94/mm Hg, 95% CI 0.90 to 0.98, p=0.003).

Conclusions Hypotension during the first 24 h of life is associated with adverse outcomes in VLBW infants. This underlines the need for randomised controlled trials on the use of vasoactive drugs in this vulnerable patient cohort.

What is already known on this topic

- Management of circulation and blood pressure in very preterm infants varies widely among neonatal intensive care units.
- Blood pressure in preterm infants correlates with gestational age, birth weight and postnatal age.

What this study adds

- In infants <29 weeks of gestation, the lowest mean arterial blood pressure during the first 24 h was 1–2 mm Hg below gestational age.
- Hypotension during the first 24 h was associated with higher mortality and higher rates of intraventricular haemorrhage and bronchopulmonary dysplasia.

INTRODUCTION

Birth weight, gestational age and postnatal age have been demonstrated to have a large impact on blood pressure (BP) levels.[1–5] However, the definition of hypotension in very-low-birthweight (VLBW, birth weight <1500 g) infants, its clinical significance and relevance for therapeutic strategies is controversial.[1] In line with that, the management of circulatory problems and BP in preterm infants varies widely among neonatal intensive care units (NICUs).[3 6]

BP is only one surrogate measure in a complex haemodynamic situation during the first 24 h of life. Many neonatologists do not necessarily consider hypotension itself as a factor that needs urgent intervention. On the other hand, hypotension is regarded as an indicator of circulatory failure and organ dysfunction. Low cerebral blood flow and clinical signs of shock such as reduced microcirculation are signs of a reduced cardiac output.[7] In clinical practice, many NICUs follow guidelines that define hypotension at the first day of life as mean arterial BP below the cut-off value of gestational age in weeks.[8] It is yet unknown whether there is a threshold of hypotension that enables clinical health professionals to discriminate between a 'physiological' and a 'pathological' condition with respect to short-term or long-term complications. Conflicting results have been obtained in smaller studies postulating the association between postnatal hypotension in very preterm infants and adverse short-term outcome as intraventricular haemorrhage (IVH) or death.[1 7 9 10] The evaluation of 945 surviving infants with a gestational age of ≤28 weeks in the context of the ELGAN (extremely low gestational age newborn) study found little evidence that early postnatal hypotension indicators are associated with developmental delay at 24 months' corrected gestational age,[2] but short-term outcome parameters such as mortality were not evaluated in this study.

In view of the limited information available, we analysed data from a large multicentre cohort of very preterm infants enrolled in the German Neonatal Network (GNN) regarding early BP values. Our aim was to evaluate the lowest mean arterial BP during the first 24 h of life (minMAP^{24}) in VLBW infants and to identify associations between hypotension and short-term outcome.

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METHODS

Study cohort

The GNN collects data in a prospective cohort study of currently 47 tertiary care centres focused on the long-term development of VLBW infants. Preterm infants (gestational age <37 completed weeks) with a birth weight <1500 g who are admitted to one of the participating study centres are eligible. After informed parental consent, a predefined clinical dataset is recorded for each patient. Additionally, a basic anonymous dataset of any infant who is eligible for the GNN, but was not enrolled, is recorded. Data quality is ensured by regular monitoring of participating centres. All data are entered in a database by health record administrators at the main GNN office at the University of Lübeck, Germany. The GNN study is approved by the Ethics Committee at the University of Lübeck and at each participating centre.

Definitions

Estimation of gestational age was based on ultrasound measurement of the fetus between week 8 and 12 of gestational age. If this information was not available, the best estimate, including all antenatal and postnatal data, was recorded. Birth weight was measured either directly after birth or on admission. Preterm infants with a birth weight <10th percentile were defined as small for gestational-age infants.[11]

Variables

We recorded >200 predefined antenatal and postnatal variables. Antenatal data were collected from maternal charts as well as information provided by mother and attending physician.

IVH was defined as localised bleeding in the germinal matrix (grade I), blood filling up to 50% of a ventricle (grade II), blood filling more than 50% of a ventricle (grade III) and IVH of any stage with additional periventricular haemorrhagic infarction (grade IV) according to Papile *et al*.[12] Periventricular leukomalacia (PVL) was defined as parenchymal cystic lesions in the periventricular region. Bronchopulmonary dysplasia (BPD) was defined as need of oxygen or respiratory support (continuous positive airway pressure (CPAP) or mechanical ventilation) at 36 weeks' postmenstrual gestational age. Early-onset sepsis was defined as blood-culture-proven clinical sepsis with at least two clinical signs, which occurred in the first 72 h of life. Death was defined as all-cause mortality during the primary hospital stay. Necrotising enterocolitis was defined as necrotising intestinal inflammation requiring surgery, and higher-stage retinopathy of prematurity (ROP) was defined as ROP requiring treatment.

Hypotension and treatment

BP increases over the first day of life,[1] and the incidence of hypotension is higher in the first 24 h of life than on subsequent days.[2] Therefore, we studied the minMAP^{24}, regardless of the mode of measurement (invasive or non-invasive). We did not collect data on the duration of hypotension. For our analyses, we used two definitions of hypotension:

1. minMAP^{24} lower than gestational age (in weeks)
2. minMAP^{24} lower than median minMAP^{24} of all patients of the corresponding gestational age in completed weeks.

According to the second definition, infants were post-hoc stratified in infants with hypotension (lower BP group) and infants with higher minMAP^{24} (higher BP group). Treatment with vasoactive drugs in the first 24 h was defined as early treatment with any of the following drugs: dopamine, dobutamine, epinephrine or norepinephrine. Information on volume therapy was not recorded.

Statistics

Data were analysed with SPSS Statistics V.20.0. We used χ^2, Fisher's exact test and Mann–Whitney U test for explorative analysis. Multivariate logistic regression models were used for retesting of associations. A p value <0.05 was considered as statistically significant.

RESULTS

Study cohort

During the study period from January 2009 to December 2012, 6091 VLBW infants were enrolled in 47 GNN centres, including 5348 infants with gestational age <32 weeks. Of these, 441 cases were excluded due to missing data on BP. The sample for this analysis consisted of the remaining 4907 infants.

Clinical characteristics

The clinical characteristics of the study group are described in table 1. As shown in table 2, the documented minMAP^{24} increased with gestational age. In 52% of the study population, minMAP^{24} values were below the gestational age of the infant, particularly in very premature infants.

In infants with a gestational age of ≤29 completed weeks, the median minMAP^{24} of all patients of the corresponding gestational age was 1–2 mm Hg lower than gestational age in completed weeks. BP in the lowest quartile of minMAP^{24} was at least 5 mm Hg lower than gestational age in completed weeks (table 2).

To minimise the potential confounding effect of gestational age, we used the definition of hypotension as minMAP^{24} lower than median minMAP^{24} of the corresponding gestational age in completed weeks for post-hoc stratification as lower BP group (n=2288) while infants with minMAP^{24} equal or higher than median minMAP^{24} of the corresponding gestational age in completed weeks were defined as higher BP group (n=2620).

Table 1 Clinical characteristics of the VLBW cohort with gestational age 22+0–31+6 weeks stratified to arterial hypotension (lower BP, minMAP^{24} lower than the median minMAP^{24} of gestational age) in the first 24 h of life

	Higher BP* (n=2619)	Lower BP (n=2288)	p Value†
minMAP^{24} in mm Hg (mean, SD)	30.87 (5.1)	22.84 (3.9)	
Gestational age in weeks (mean, SD)	28.02 (2.29)	28.10 (2.23)	0.213
Birth weight in g (mean, SD)	1013 (295)	1015 (305)	0.692
Gender, male (%)	51.8	51.5	0.820
Small for gestational age (%)	12.4	12.7	0.734
Multiples (%)	31.4	34.9	**0.01**
Inborn (%)	97.6	97.4	0.618
Mode of delivery (%)			
Elective caesarean section (%)	77.4	77.4	**<0.001**
Emergency caesarean section	8.4	11.9	
Early-onset sepsis (%)	1.5	1.8	0.476
Umbilical cord pH (mean, SD)	7.32 (0.09)	7.31 (0.10)	0.73
5 min Apgar score <7 (%)	16.0	20.8	**<0.001**
Mechanical ventilation (%)	48	61	**<0.001**

p Values<0.05 are given in bold.
*The number of infants in the higher BP group is higher than the number of infants in the low BP group since higher BP was defined as BP ≥median BP of the according week of gestational age.
†Mann–Whitney U test for gestational age, birth weight and umbilical cord pH; χ^2 test for all other variables.
BP, blood pressure; minMAP^{24}, lowest mean arterial blood pressure during the first 24 h of life; VLBW, very-low birth weight.

Table 2 Lowest mean arterial blood pressure during the first 24 h and gestational age (completed weeks)

Gestational age (weeks)	Number of infants with data	Lowest mean arterial blood pressure (mm Hg; median (IQR))
22	25	21 (18–25)
23	178	21 (19–24)
24	339	22 (20–25)
25	431	24 (21–26)
26	583	24 (21–28)
27	666	26 (22–29)
28	725	27 (24–31)
29	725	29 (25–32)
30	709	30 (27–34)
31	526	31 (27–35)
All	4907	27 (23–31)

In the lower BP group, more infants had invasive and continuous BP assessment (15.1% vs 13.0%, p=0.026).

Risk factors for hypotension

With regard to antenatal data, higher BP group and lower BP group did not differ in administration of antenatal steroids (91% vs 90%), tocolytic therapy (52% vs 53%), antenatal antibiotics (52% vs 53%), maternal age (mean±SD; 30±6 vs 31 ±6 years), maternal ethnicity (84% vs 85% Caucasian) or causes of preterm delivery apart from a trend to a higher rate of placental abruption in the lower BP group (7% vs 9%, p=0.07).

Emergency caesarean section, low Apgar scores, mechanical ventilation and multiple births were associated with hypotension (table 1). Data on placentofetal transfusion were not collected.

Outcome parameters

Infants with hypotension had a higher risk of mortality, BPD and IVH of any grade with a trend to increased need for ventriculoperitoneal shunt systems and operative closure of persistent ductus arteriosus (PDA). The incidences of PVL and necrotising enterocolitis requiring surgery or higher stage ROP were not associated with hypotension (table 3). Data stratified for mode of BP measurement and vasoactive treatment during the first 24 h of life are given as online supplementary tables S1–S3.

Infants with minMAP^{24} in the lowest quartile for gestational age (in weeks) had a higher risk for death (OR 1.90, 95% CI 1.41 to 2.58, p<0.001), IVH (OR 1.62, 95% CI 1.38 to 1.92, p<0.001) or BPD (OR 1.34, 95% CI 1.21 to 1.70, p<0.001; χ^2 test, ORs not adjusted for other risks than BP stratified to gestational age) compared with infants with minMAP^{24} ≥25th percentile (table 4).

Confounding factors and treatment

We, furthermore, did multivariate logistic regression analyses, including gestational age, gender, multiple birth, small for gestational age, antenatal treatment with steroids, tocolytics or antibiotics, birth due to suspected amniotic infection, birth due to placental abruption, inborn, Apgar score <7, umbilical cord pH <7.1, early-onset sepsis, minMAP^{24} and treatment with inotropes during the first 24 h of life as independent variables and IVH, BPD and death as dependent variables (table 5). However, the association between minMAP^{24} and IVH, BPD and death remained significant (table 5). This was also true if the centre where the infant was treated was added to the multivariate logistic regression analysis.

14.9% of the infants with lower BP received vasoactive treatment within the first 24 h compared with 3.7% in the higher BP group (p<0.001); 27.3% of hypotensive infants received vasoactive drugs during the whole duration of hospital stay compared with 13.4% in the higher BP group (p<0.001).

As expected, infants who were treated with inotropes during the first 24 h of life had a higher risk for complications (table 5). To rule out a possible confounding effect of treatment with vasoactive drugs, we analysed the subgroup of infants who were not treated with vasoactive drugs on the first day of life (n=4260). In this group of infants, lower BP was also associated with higher risk of development of IVH (16.5% vs 13.9%, p=0.019). This was also true if infants with minMAP^{24} in the lowest quartile for gestational age were compared with infants with minMAP^{24} ≥25th percentile (IVH 18.4% vs 14.3%, p=0.004). In a multivariate regression model, including potential confounding factors described above, minMAP^{24} was a significant predictor for the occurrence of IVH (OR 0.97/mm Hg, 95% CI 0.95 to 0.99, p=0.006), BPD (OR 0.96/mm Hg, 95% CI 0.94 to 0.98, p<0.001) and death (OR 0.95/mm Hg, 95% CI 0.90 to 0.99, p=0.026) in infants who were not treated with vasoactive drugs on the first day of life.

DISCUSSION

In the past, several definitions of hypotension have been published.[1 10] As our data confirm previous studies showing a strong correlation between gestational age and birth weight with BP,[2–5] we suggest to use a definition of hypotension, which is adjusted to gestational age. The definition of hypotension, which is based

Table 3 Outcome parameters of preterm infants with higher and lower blood pressure

Outcome*	Infants with higher blood pressure %	Infants with lower blood pressure %	p Value‡
IVH, any grade (2593/2275)	15.9	20.3	**<0.001**
IVH grade III or IV (2584/2269)	5.1	8.3	**<0.001**
Ventricular-peritoneal shunt (2572/2255)	1.3	2.4	**0.003**
PVL (2554/2230)	3.0	3.9	0.078
Death (2619/2288)	3.0	5.2	**<0.001**
BPD (2591/2271)	15.1	19.2	**<0.001**
Surgery for necrotising enterocolitis (2582/2263)	3.5	2.6	0.063
Surgical closure of PDA (2583/2263)	4.3	5.7	**0.029**
ROP treatment (2492/2178)	3.4	2.9	0.359

*Number of infants with data is given in brackets.
‡χ^2 test.
BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; PDA, persistent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Table 4 Outcome and lowest BP percentile

	Lowest BP on day one <25th percentile* N=1064 (%)	Lowest BP on day one 25–49th percentile N=1224 (%)	Lowest BP on day one 50–75th percentile N=1520 (%)	Lowest BP on day one >75th percentile N=1099 (%)
IVH	24.0	17.1	17.1	14.2
BPD	21.3	17.4	16.2	13.6
Death	6.3	4.3	3.6	2.1

*BP below the 25th percentile, which can be calculated by (gestational age in weeks—5=BP in mm Hg), had worst outcome for IVH, BPD and death if compared with infants with BP above this threshold. p<0.001 for all endpoints, χ^2 test. Results were confirmed by multivariate logistic regression (table 5).
BP, blood pressure; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage.

on BP below gestational age in completed weeks, is a poor predictor of treatment.[13] In our cohort, VLBW infants <29 gestational weeks had median minMAP[24] values of 1–2 mm Hg below gestational age in completed weeks. Our findings confirm the results of the ELGAN study,[2] analysing 945 infants with a gestational age <28 weeks of gestation and finding approximately the same median for minMAP[24] values for each gestational age.

Our study is focused on the short-term outcome of very preterm infants with a lower BP than median compared with infants with higher BP. We found an association between hypotension, higher mortality and the occurrence of IVH and BPD, suggesting a negative effect of hypotension. These findings contrast with several studies,[1 2 7] but agree with others.[4–6 9 14–17] Most of them were small single-centre studies,[1 4 5 7 9 15 17] or did not control for important potential confounders, in particular, gestational age and vasoactive treatment.[6 16] This is important given the fact that several studies have shown that infants receiving treatment with vasoactive drugs during the first 24 h have a higher mortality, and are less likely to survive without major morbidity.[1] We, therefore, analysed the effect of low BP in infants who did not receive vasoactive drugs on the first day of life. Again, IVH rate was high in the group with lower BP and low in group with higher BP. We also included treatment with vasoactive substances on the first day of life in our multivariate logistic regression analysis. Treatment with inotropes was associated with a higher rate of IVH. However, it is important to consider that vasoactive treatment might be due to complications, and is, therefore, not a completely independent cofactor.

Table 5 Multivariate logistic regression models predicting intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD) and death as dependent variables

	Dependent variable		
Independent variable	**IVH**	**BPD**	**Death**
Gestational age (week)	**0.76 (0.72 to 0.80) <0.001**	**0.71 (0.67 to 0.75) <0.001**	**0.69 (0.62 to 0.77) <0.001**
Female gender	0.86 (0.72 to 1.03) 0.100	**0.61 (0.51 to 0.75) <0.001**	**0.64 (0.44 to 0.94) 0.022**
Multiple birth	**1.28 (1.05 to 1.55) 0.013**	**0.75 (0.60 to 0.93) 0.008**	1.32 (0.88 to 1.97) 0.177
Small for gestational age (<10th percentile)	**0.65 (0.47 to 0.88) 0.006**	**2.59 (2.00 to 3.37) <0.001**	**2.86 (1.80 to 4.55) <0.001**
Maternal steroid treatment	**0.64 (0.47 to 0.87) 0.004**	1.13 (0.80 to 1.60) 0.488	0.68 (0.38 to 1.24) 0.206
Maternal treatment with antibiotics	0.86 (0.69 to 1.06) 0.160	0.88 (0.70 to 1.11) 0.266	1.07 (0.68 to 1.69) 0.779
Maternal treatment with tocolytics	1.14 (0.93 to 1.40) 0.220	0.93 (0.75 to 1.15) 0.498	1.13 (0.73 to 1.75) 0.574
Birth due to amniotic infection	0.90 (0.72 to 1.13) 0.382	**0.71 (0.55 to 0.91) 0.006**	0.70 (0.43 to 1.13) 0.574
Birth due to placental abruption	**1.40 (1.02 to 1.90) 0.036**	1.00 (0.70 to 1.42) 0.987	0.78 (0.38 to 1.59) 0.487
Inborn	1.01 (0.55 to 1.85) 0.982	1.14 (0.56 to 2.31) 0.721	1.03 (0.32 to 3.35) 0.964
Apgar <7 at 5 min of age	**1.54 (1.24 to 1.91) <0.001**	1.08 (0.85 to 1.37) 0.516	**1.63 (1.08 to 2.44) 0.020**
Umbilical artery pH <7.1	1.43 (0.89 to 2.31) 0.140	0.76 (0.43 to 1.33) 0.330	1.12 (1.09 to 5.60) 0.801
Early-onset sepsis	**2.06 (1.16 to 3.67) 0.014**	1.32 (0.71 to 2.45) 0.378	**2.47 (1.09 to 5.60) 0.031**
Treatment with inotropes during the first 24 h of life	**1.86 (1.43 to 2.42) <0.001**	**2.40 (1.82 to 3.16) <0.001**	1.48 (0.92 to 2.38) 0.109
Lowest mean arterial blood pressure during the first 24 h of life (mm Hg)	**0.97 (0.96 to 0.99) 0.003**	**0.96 (0.94 to 0.98) <0.001**	**0.94 (0.90 to 0.98) 0.003**

All data are given as 'OR (95% CI) p'. ORs <1.00 indicate a protective effect of the independent variable. Higher gestational age and higher values for the 'lowest mean arterial blood pressure during the first 24 h' were protective. p Values <0.05 are given in bold.

Clinicians are often challenged whether to treat a hypotensive preterm infant with vasoactive therapy or not. Apart from BP, other factors such as clinical signs (eg, poor perfusion, metabolic acidosis or oliguria) or echocardiographic data (eg, superior vena cava flow) may influence this decision.[7] Despite the potential limitations of BP as surrogate parameter of haemodynamic adaptation, our descriptive data indicate that early hypotension is associated with adverse outcome, for example, mortality and risk for IVH. Our study was not designed to assess the effect of vasoactive drugs like dopamine and dobutamine on short-term outcomes of preterm infants. This should be done in randomised controlled trials.

Studies analysing the effect of BP on long-term outcome are contradictive. In a large multicentre cohort controlling for gestational age and treatment, Logan found no significant differences with regard to neurological outcome in the surviving infants.[2 18] However, he did not analyse short-term outcomes such as mortality and IVH. In a smaller, but very premature, group of infants, Batton *et al*[14] reported a high rate of short-term and long-term complications in infants with low BP, regardless of treatment in a case–control study.

The strengths of our study are represented by the size and data quality of the analysed cohort, defined by birth weight and gestational age.

Several limitations of our study must be considered, including the punctual collection of mean arterial pressure (MAP) data together with the use of two different methods of BP measurement. This could lead to a systematic overestimation of BP in relatively stable infants, as these are more often monitored non-invasively, potentially overestimating the BP.[19] Additionally, the monitoring of BP in stable infants is usually performed intermittently, which includes the risk of missing short episodes of hypotension. Furthermore, in stable infants, BP may be less often documented during continuous measurement than in sick infants. Finally, nurses may be biased to write down the 'better' BPs in well infants and the 'lower' BPs in sick. As we registered only the lowest MAP, we could not include the duration of hypotension or the variation of BP in our analysis. Both parameters were associated with poorer outcome parameters in smaller studies.[4 20]

Another reason for a falsely positive association between hypotension and mortality could be the exclusion of infants dying during the first day of life, due to missing parental consent. This hypothesis implies the assumption that these 'early' dying infants had higher low-MAP compared with the infants included in our study. This seems unlikely, as in our cohort, the lifespan of the infants dying during hospital stay was shorter when the infant was hypotensive during the first 24 h. Echocardiographic data were not available to us, so, potential causes of low BP (ie, low systemic vascular resistance, decreased cardiac output, large shunting through a PDA) could not be determined.[14]

Finally, it is important to emphasise that causation cannot be proven by our study design.[17] Whether hypotension during the first 24 h of life predicts IVH, BPD and death or is just an indicator of, for example, a difficult delivery room management or other confounders, which might be associated with IVH, BPD and death, cannot be answered in this study.

However, the high rate of IVH underlines the potential importance of hypotension as a surrogate marker for adverse outcomes. Large-scale randomised trials like the HIP (http://www.hip-trial.com) and NEO-CIRC trials (http://www.neocirculation.eu) focusing on BP-related treatments are needed to answer the question whether the outcome of preterm infants can be improved by treating hypotension.

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Contributors WG and KF conceptualised and designed the study, carried out the initial data analyses, supervised and coordinated the data collection, drafted the initial manuscript and approved the final manuscript as submitted. CR, CH, ME, CW and EH supported and coordinated data collection, drafted the initial manuscript and approved the final manuscript as submitted. MP supported data collection and data analysis, drafted the initial manuscript and approved the final manuscript as submitted. HR and MS supported the study design and the development of data collection instruments, critically reviewed the manuscript and approved the final manuscript as submitted.

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Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life

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