

Microcirculatory mechanisms in postnatal hypotension affecting premature infants

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BACKGROUND: Hypotension remains a common complication in preterm infants and is associated with high neonatal morbidity and mortality. The underlying mechanisms are still not fully understood. We studied the microcirculation in extremely low birth weight infants to understand the relationship between blood pressure and skin perfusion.

METHODS: In 21 patients (gestational age <30 wk, birth weight <1,225 g), functional vessel density (FVD) and diameter distribution were obtained prospectively by side stream dark-field imaging at the right arm in the first 48 h after birth. Infants with blood pressure below gestational age and receiving catecholamines were defined as hypotensive as compared with the remaining normotensive control group.

RESULTS: In the first 6 h after birth, FVD was significantly higher in the hypotensive group than in the control group. After 12 h, there were no significant differences in either blood pressure or FVD between the two groups. FVD did not change significantly during the observation period in either group.

CONCLUSION: Hypotensive infants have a higher FVD, possibly due to loss of microvascular tone leading to vasodilation and flow redistribution. However, the link between blood pressure and perfusion remains unclear, and no definitive correlation could be found.

Systemic hypotension is common in preterm infants and is associated with high neonatal morbidity and mortality. Failing to treat hypotension can lead to severe shock, characterized by acute circulatory failure, inadequate tissue oxygenation, and organ perfusion, resulting in metabolic acidosis (1–3). Hypotension is frequently first treated by repeated boluses of isotonic saline to fill the vasculature, followed by treatment with pressors (dopamine, epinephrine, norepinephrine) to tighten the vasculature, and inotrope agents (dobutamine) and/or hydrocortisone to compensate for the immature vasculature (4–7).

There is an ongoing debate regarding which is the lowest acceptable normal blood pressure (2,3,8–11). There is general agreement but no real scientific evidence to accept the equivalent of the gestational age as the lower limit for the mean arterial blood pressure (MAP) during the first postnatal

days (12). Conclusive data are lacking to determine which blood pressure levels actually harm extremely low birth weight infants. Therefore, treating low blood pressure values without evidence of metabolic acidosis—and therefore clear signs of inadequate tissue oxygenation—should be questioned. Because global hemodynamic parameters, such as blood pressure and heart rate, do not reflect adequate tissue oxygenation, it becomes essential to study the microcirculation (13).

Side dark field (SDF) imaging is a relatively new technique to visualize the microcirculation at the bedside (14,15). The technique consists of a handheld microscope with light-emitting diodes. The lens can be placed on the arm of the neonate and thus the microcirculation of the skin can be observed. The light (wavelength within the absorption spectrum of hemoglobin) is absorbed by erythrocytes but reflected by the tissue. Thus an *in vivo* image of perfused vessels can be obtained and subsequently analyzed by measuring the length of capillaries per image area and the diameter distribution of the vessels (16,17). Therefore, these measurements of the microcirculation can be compared at different time points and before and after treatment. This might add more information about the perfusion in neonates in health and disease.

The objective of this prospective study was to analyze microcirculatory mechanisms in postnatal hypotension in preterm infants in the first 48 h of life.

RESULTS

The data of 21 of 34 prospectively enrolled preterm infants could be analyzed, and 7 neonates had to be excluded due to infection. The data points of six neonates (one in the hypotensive group, five in the control group) were excluded retrospectively because they had a gestational age >30 wk. In each of the groups, one infant could not be measured in time for the first data point; two values at 48 h of life in the hypotensive group and two values in the control group are missing due to technical problems.

As can be seen in **Table 1**, the clinical data of 10 hypotensive and 11 normotensive neonates did not differ significantly, except for sex, with more males in the hypotensive group. Nine of the 10 hypotensive neonates had an umbilical arterial line placed as compared with only 3 of the 11 controls.

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At 6 h after birth, MAP was significantly lower in the hypotensive than in the control group (Table 2), with no significant difference at 12, 24, and 48 h. None of the other clinical variables, such as hematocrit, heart rate, or body temperature differed between the two groups. Dobutamine was started in the hypotensive group before 6 h of age in eight infants and between 6 and 12 h in two infants. At 12 h of life, 9 of the 10 hypotensive infants received dobutamine (2–10 $\mu\text{g}/\text{kg}/\text{min}$). In two infants, dopamine was added to the dobutamine for persistent hypotension (2–12 $\mu\text{g}/\text{kg}/\text{min}$). At 24 h only five infants required the continuation of dobutamine treatment (1–3.5 $\mu\text{g}/\text{kg}/\text{min}$), and one infant received only dopamine (5 $\mu\text{g}/\text{kg}/\text{min}$). At 48 h, in nine of the 10 hypotensive infants, catecholamines were stopped.

In the hypotensive group and in the control group, functional vessel density (FVD) did not change during the first 48 h of life (Table 3). At 6 h after birth, FVD was significantly higher in infants treated with catecholamines than that in the control group infants (Figure 1 and Table 3), whereas MAP was significantly lower. At all other time points, FVD and blood pressure did not differ between the groups. Diameter distribution did not change during the first 48 h of life and did not differ between both groups (Table 4).

DISCUSSION

We demonstrated that hypotensive preterm infants requiring catecholamine treatment have a significantly lower MAP and a higher FVD at 6 h of life in comparison with normotensive infants. During successful treatment, leading to similar blood

pressure to that of the normotensive infants, FVD did not differ at 12, 24, or 48 h of life.

Contributing factors to low blood pressure in neonates—without evidence of shock—include abnormal peripheral vasoregulation due to immaturity of receptors and systems that regulate blood pressure, perinatal asphyxia, hemodynamically significant patent ductus arteriosus, infection, and relative adrenal insufficiency (3,18,19). Because we excluded asphyxia and infection in our study group and there were no differences in the prevalence of patent ductus arteriosus, the low blood pressure in our hypotensive group can possibly be explained by an abnormal peripheral vasoregulation and adrenal insufficiency. SDF imaging provides the technique to visualize abnormal peripheral vasoregulation by using a microscope at the bedside. In our study, we saw a higher FVD at 6 h of life in the hypotensive group, relatively soon after the start of antihypotension treatment. At this time point, blood pressure in the hypotensive group was significantly lower. Therefore, the increased FVD at 6 h of life could possibly be due to a loss in microvascular tone and resulting flow redistribution. This effect could be exacerbated by the use of dobutamine.

Because the vasoactive treatment has an effect on peripheral perfusion, this might also be an additional explanation for our findings. Treatment in the hypotensive group started with dobutamine, a relatively cardioselective amine with α and β receptor-mediated inotropic effects. In its most effective range (2–15 $\mu\text{g}/\text{kg}/\text{min}$), hypotension is treated by significantly increasing the left-ventricular output (10,20–22). On the other

Table 1. Clinical data

	Hypotensive	Control
Birth weight (g)	815 (636–994)	883 (725–1,041)
Gestational age (wk)	26.1 (24.8–27.5)	27.1 (25.9–28.3)
Apgar score		
Minute 1	6.1 (3.9–8.3)	6.5 (4.6–8.5)
Minute 5	7.9 (6.5–9.4)	8.3 (6.7–9.8)
Minute 10	8.7 (7.6–9.8)	8.8 (7.7–9.9)
Tracheal intubation (%)	90	45
Male (%)	87*	36*
hsPDA during hospital course (%)	50	81
Umbilical arterial catheter	90*	27*

Values are given as mean (95% CI) or as percentages.

CI, confidence interval; hsPDA, hemodynamically significant patent ductus arteriosus.

* $P < 0.05$ unpaired t -test.

Table 2. Mean arterial blood pressure at the four time points (in mmHg)

Group	Hour 6	Hour 12	Hour 24	Hour 48
Hypotensive	29.7 (25–34)*	31.7 (28–35)	32.1 (29–35)	32.9 (28–38)
Control	34.9 (31–39)*	36.1 (33–39)	34.8 (30–40)	38.1 (35–42)

Values are given as mean (95% CI).

CI, confidence interval.

* $P < 0.05$, hypotensive group vs. control (Mann–Whitney test).

Table 3. Functional vessel density (in 1/cm)

	Hour 6	Hour 12	Hour 24	Hour 48
Hypotensive	235 (222–249)*	230 (216–243)	219 (205–233)	224 (210–239)
Control	211 (197–225)*	215 (200–229)	219 (205–232)	229 (216–240)

Values are given as mean (95% CI).

CI, confidence interval.

* $P < 0.05$, hypotensive group vs. control group (unpaired t -test).

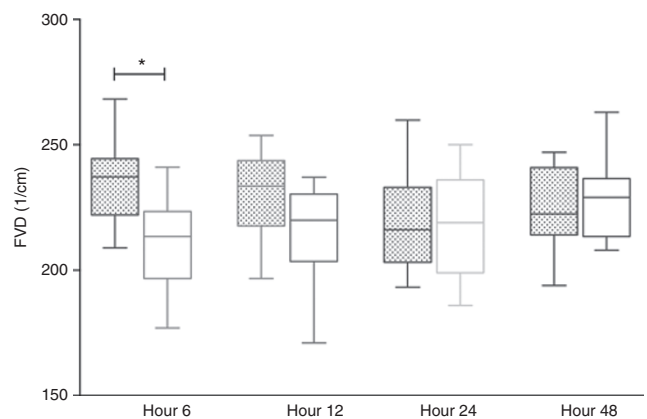


Figure 1. Functional vessel density (FVD) for the hypotensive (shaded) and control (unshaded) groups at 6, 12, 24, and 48 h of life. FVD is significantly (*) different between the two groups at 6 h of life.

Table 4. Vessel diameter distribution (in %)

		Hour 6	Hour 12	Hour 24	Hour 48
Small vessels (<10 μ m)	Hypotensive	36 (29–43)	34 (25–42)	30 (20–40)	37 (29–45)
	Control	35 (26–42)	32 (27–37)	34 (27–41)	40 (34–46)
Medium vessels (10–20 μ m)	Hypotensive	56 (52–61)	58 (52–65)	59 (52–67)	55 (49–62)
	Control	56 (52–60)	61 (58–65)	59 (54–63)	53 (50–57)
Large vessels (>20 μ m)	Hypotensive	8 (5–11)	8 (5–10)	11 (7–15)	8 (5–10)
	Control	10 (3–16)	7 (5–9)	7 (5–10)	6 (3–9)

Values are given as mean (95% CI).

CI, confidence interval.

hand, dobutamine is associated with a variable decrease in peripheral vascular resistance, mediated through β_2 peripheral adrenergic and dopaminergic vascular receptors, resulting in peripheral vasodilatation. This could explain an increased FVD due to dobutamine treatment (23–25).

However, some of our children also received dopamine. Dopamine has very contrary effects on peripheral perfusion; it increases blood pressure by influencing preload, myocardial contractility, and afterload. Its most important effect results from peripheral vasoconstriction, an effect derived from stimulating peripheral α_1/α_2 adrenergic and dopaminergic receptors. This effect could be further intensified by dobutamine (23–25). Therefore, one would expect a reduced FVD in the skin. In our opinion, our results could derive from a mixture of different effects: on one hand, an abnormal vasoregulation and vasodilatory mechanism could be the main cause for low blood pressure in the hypotensive group and thus explain a higher FVD in the first 12 h of life (26). These could be intensified by dobutamine, which was the main treatment for arterial hypotension in our hypotensive group. We had only three patients who were treated with very low-dose dopamine in addition to dobutamine, so its vasoconstrictive effects might not be visible in our observational study.

Peripheral oxygenation management is essential for the outcome of the child. However, central blood pressure is only a poor indicator for oxygen delivery to the demanding tissues (27,28). Therefore, measuring microcirculatory blood flow could be regarded as an important addition to the usual macrocirculatory parameters. Microcirculatory parameters have been shown to be able to visualize dysfunctional microcirculation in septic shock in children, effects of inhaled nitric oxide in children with hypoxemic respiratory failure, and in children receiving extracorporeal membrane oxygenation (29–31).

Possibly, microcirculatory parameters could help to assess the effect of hypotension on the microcirculation on an individual level and might help to derive specific, individual treatment decisions. We concentrated on the skin of preterm infants. At the moment, it is not possible to assess the microcirculation in central organs (brain, lungs, and intestine).

The predominance of boys in the hypotensive group and of girls in the control group is not surprising but is of great interest. We know that male preterm infants have a higher risk for mortality and morbidity (32). Preterm females have significantly higher catecholamine levels than males; this might be an important reason for a higher prevalence of males in our

hypotensive group (33). Our results in regard to gender are in agreement with data from Stark *et al.* (34). Using laser Doppler flowmetry, they found higher baseline flow during the first 24 h in extremely preterm boys with gestational age 24–28 wk, with a significant relationship to the vasodilatory effect of acetylcholine. There are many limitations to our study. The microcirculation in preterm infants is affected by many factors, such as hemoglobin level, incubator temperature, and maturity. Due to the retrospective exclusion of neonates of >30 wk of gestation, most clinical variables did not differ between our two groups.

The hypotensive group had a higher percentage of infants in whom arterial blood pressure was measured by an umbilical arterial catheter. Because blood pressure values are lower when obtained from an umbilical arterial catheter vs. cuff, this could be an important bias in our data. However, because the umbilical arterial catheter was not removed before the 48th h of life in our patients and we did not observe a significant difference in MAP at the later time points, it is unlikely that the difference in blood pressure at the 6th h of life is solely due to this.

Finally, because of the very time-consuming methods and analysis, as well as a strict time frame, the number of our patients is low and the statistical power is limited.

Conclusion

In conclusion, our results demonstrate significant differences in the microcirculation between hypotensive and normotensive premature infants. At 6 h after birth, FVD is higher in the hypotensive group, whereas blood pressure is significantly lower than that in the control group. There are no differences in blood pressure and FVD after 12 h of age.

The increased FVD could possibly be due to a loss in microvascular tone and flow distribution causing the hypotension. This effect could further be intensified by dobutamine.

However, the link between blood pressure and perfusion remains unclear, and no definitive correlation could be found. SDF imaging could nevertheless be an excellent method to study the effects of arterial hypotension on microcirculation *in vivo* and help to assess potential benefits of antihypotensive therapy.

METHODS

Our single-center, prospective, observational study was conducted between October 2006 and October 2008 at the neonatal intensive care unit of the Children's University Hospital Munich, Munich, Germany. Preterm inborn infants with gestational ages <32 wk and a birth weight <1,500 g admitted to the neonatal intensive care unit

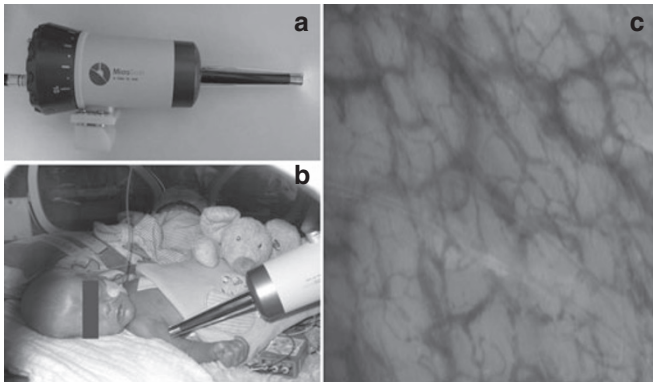


Figure 2. Measurement of the microcirculation. (a) Presentation of the side dark field (SDF) imaging device, (b) a measurement on a preterm neonate, and (c) the resulting photograph.

were consecutively included after written and oral parental consent. Neonates who received pressor or positive inotrope treatment for arterial hypotension within 12 h after birth were assigned to the hypotensive group, and infants needing no support to maintain their arterial blood pressure in the physiologic range were assigned to the control group. Exclusion criteria were signs of infection—defined as a C-reactive protein level >1.0 mg/dl—or congenital malformations. The institutional review board of the Medical Faculty of the Ludwig Maximilians University approved the study protocol and the consent forms.

Because only one neonate with a gestational age above 30 wk received treatment for hypotension, the data of infants with a gestational age above 30 wk were excluded to avoid bias of the results.

Infants were monitored according to standard procedure of the intensive care nursery, and treatment was independent from the study and at the discretion of the attending neonatologist. Blood pressure measurements were obtained continuously if an umbilical arterial line was in place; otherwise, measurements were obtained every 5–15 min with an oscillatory device (Dinamap Critikon Vital Data Monitor; Critikon, Norderstedt, Germany) until the infant's MAP was constantly in the physiologic range and thereafter every 2 h. Hypotension was defined as MAP below the equivalent of the gestational age and was treated with a volume bolus of 10–20 ml/kg body weight over 30–60 min. If this did not result in normotension, catecholamine treatment was started, usually with dobutamine (starting dose 5 μ g/kg/min); this was increased, if necessary, to 10 μ g/kg/min. If hypotension persisted, dopamine infusion was added (starting with 5 μ g/kg/min).

As described in the introduction, SDF imaging (Microvision Medical, Wallingford, PA) is a noninvasive video microscopic method to visualize microcirculation and has been previously used for assessing the microcirculation in very premature infants (35). Green light (530 nm) is emitted by light-emitting diodes and absorbed by the hemoglobin in erythrocytes but scattered by other structures of the tissue. Therefore, a noninvasive, functional image is obtained. In **Figure 2a–c**, a picture of the handheld video microscope, a measurement on a preterm neonate, and the resulting microcirculatory measurements are shown.

In this study, we used the video microscope MicroScan with $\times 5$ magnification. SDF images of 10 s were obtained on three different spots of the right inner upper arm (preductal arm). As we have shown previously, the upper region of the arm provides a good image quality and is easy to access (36–38).

Microcirculatory measurements were performed at four time points, specifically at 6, 12, 24, and 48 h of life. Measurements and analyses were performed by two investigators. Images underwent blinded off-line analysis with Microvision analysis software (Microscan BV, Amsterdam, The Netherlands). This software semiautomatically detects vessels on the screen and allows manual correction for artifacts such as lanugo hair. Accordingly, microcirculatory parameters such as FVD and the distribution of vessel diameters are calculated.

FVD represents the total vessel length in centimeters per image area in square centimeters. The distribution of vessels in small (<10 μ m), medium (10–20 μ m), and large vessels (>20 μ m) is calculated according to the percentage of total vessel length. Statistical analysis was performed with GraphPrism 6.0 (GraphPad Software, La Jolla, CA). Data are presented as mean values with 95% confidence intervals. For each time point, three video scans were analyzed, and the mean value of a variable was used for statistical analysis. Intergroup comparison was performed with the unpaired *t*-test after having passed normality test for parametric data. A *P* value of <0.05 was considered to be significant. The two investigators analyzing the scans trained together on 10 examples. Then, 10 new video scans were tested for interindividual variance, which was not significantly different.

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