University of Szeged
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Investigation of neonatal blood pressure

PhD Thesis

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Contents

1. Publications

I.

Kiss, J. K., Gajda, A., Mari, J., Nemeth, J., & Bereczki, C. (2023)

Oscillometric arterial blood pressure in haemodynamically stable neonates in the first 2 weeks of life

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II.

Kiss, J. K., Gajda, A., Mari, J., & Bereczki, C. (2024)

Blood pressure in preterm infants with bronchopulmonary dysplasia in the first three months of life

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Impact factor (5 years): 3.4, rank: Q1

2. Abbreviations

11β-HSD2: 11β hydroxysteroid dehydrogenase

abn: abnormal

AKI: Acute kidney injury

ANS: Antenatal steroids

AWAKEN: Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates

BP: Blood pressure

BPD: Bronchopulmonary dysplasia

Bw: Birth weight

CHD: Congenital heart defect

Cs: Caesarean section

DEHP: di-(2-ethylhexyl) phthalate

DBP: Diastolic blood pressure

DCC: Delayed cord clamping

GA: Gestational age

GDM: Gestational diabetes mellitus

GW: Gestational week

HELLP: Haemolysis, Elevated Liver Enzymes and Low Platelets

HTN: Hypertension

IDDM: Insulin-dependent diabetes mellitus

IUGR: Intrauterine growth retardation

IVH: Intraventricular haemorrhage

MBP: Mean blood pressure

NICU: Neonatal Intensive Care Unit

NIV: Non-invasive ventilation

Pc: Percentile

PDA: Persistent ductus arteriosus Botalli

PHT: Pulmonary hypertension

PMA: Postmenstrual age

PN: Parenteral nutrition

SBP: Systolic blood pressure

SD: Standard deviation

SES: Socioeconomic status

3. Introduction

3.1. Preamble

Blood pressure measurements are essential to evaluate the cardiovascular stability of preterm and term infants. Diagnosing and treating hypotension and hypertension are important to reduce the lifelong consequences of prematurity [1]. Over the last 40 years, several studies have provided data on the blood pressure values of preterm and term neonatal patients [2-15]. However, defining normal blood pressure remains very challenging in this population. The difficulties arise from the different measurement methods, patient population and wide variety of prenatal and postnatal influencing factors examined by different studies [2-15]. Studies conducted to determine normal blood pressure differ fundamentally in terms of patient inclusion criteria. Some early studies examined all patients without exclusion criteria and tried to identify the influencing factors statistically. The other approach to conducting studies was to select a haemodynamically stable patient group to determine normal blood pressure.

3.2. Studies examining normal blood pressure in neonates

The Philadelphia Neonatal Blood Pressure Study Group (14 level 3 NICU in the Philadelphia area) conducted one of the most comprehensive early studies in this field [7]. Zubrow and colleagues included all the NICU admissions over three months and measured the blood pressure eight hourly. They analysed 24052 blood pressure measurements of 608 infants. Their investigation concluded that blood pressure strongly correlates with gestational age and birth weight. In the first five days of life, there is a rapid rise in blood pressure, followed by a more gradual increment. After the fifth day of life, postconceptional age is the most strong predictor of systolic and diastolic blood pressure. They collected 55 other variables, which, according to their results, only had a small effect on BP variance. Zubrow and his coworkers included all the NICU admissions, but other studies followed a different approach and selected a patient sample without the potential risk of blood pressure alterations. In 2009, Pejovic and his colleagues carried out a single-centre, prospective study to determine normal blood pressure in a healthy term and preterm patient group [5]. In this study, many exclusion criteria were used to exclude cardiovascular instability, the effect of medications, and the underlying health conditions of the newborn. Pejovic and coworkers included 373 patients in the study, of whom 292 were preterm, and 81 were term infants. They used oscillometric devices and recorded 12552 blood pressure measurements over the first month of life. According to their results, systolic and diastolic blood pressure increased during the first month of life. A more rapid BP

increase was visible in the preterm patients. Blood pressure increased with gestational age and was higher in the higher birth weight group on day 1 of life. Kent et al. conducted a comprehensive study to determine normal neonatal blood pressure, measured by an oscillometric method, in a preterm patient group. They involved 147 preterm infants (gestational age: 28-36 weeks) in the first month of life [3]. The patient population was homogenous, without ventilated patients or patients needing inotropic support for more than 24 hours. They excluded patients with maternal substance abuse but not with other risk factors for hypertension. They investigated blood pressure development over time and found a significant difference in blood pressure in preterm infants born less than 31 weeks gestation from day 1 to day 14. Pretems whose gestational age was above 31 weeks showed a significant difference in blood pressure only within the first week of life. Due to its clinical usefulness, Kent and coworkers provided nomograms with 10th and 90th percentiles for gestational age and birth weight. Dionne et al., from the previous studies' results [3-5, 7-8, 10], created a percentile table by postmenstrual age with the estimated 50th, 95th, and 99th biweekly blood pressures that can be used after two weeks postnatal age to determine normal blood pressure in clinical practice [16].

Several other early studies collected blood pressure data to determine normal neonatal blood pressure [2-10]. The main difficulty in comparing and utilising the results of these studies today arises from the fact that they investigated different patient groups and used different blood pressure measurement methods and investigation lengths. The complexity of collating studies has increased because today's routine antenatal and neonatal care and its possible impact on neonatal blood pressure differ significantly from what was offered previously. Therefore, selecting a patient group based on the inclusion criteria of the early studies in this field is not possible today. In recent years, the development of computer data processing has made it possible to carry out new studies processing large blood pressure databases, and studies determining normal neonatal blood pressure have again become the centre of attention. Considering the new patient care conditions and extensive data collection opportunities, the need to determine normal blood pressure and to create new percentile curves that can be easily used in everyday practice has been expressed once again.

Major studies examining normal neonatal blood pressure and their main characteristics are summarised in Table 1.

Table 1 Studies investigating normal blood pressure in neonates

Author, Publication date	**Measurement method**	**Measurement number (n), study length**	**Patient number (n) Patient group characteristics**
T Hegyi, 1994 prospective [2]	oscillometric, arterial, Doppler	hourly, first 3-6 hours	n=1105, Subgroups: preterm Bw: 501-2000g, healthy term, ventilated, mat.HTN, low Apgar
AB Zubrow, 1995 prospective [7]	oscillometric	n=24052 day 1 → 99	n= 608, all NICU patients without exclusion
MK Georgieff, 1996, prospective [9]	oscillometric	3/patient, day 7 → 4 month	n=61, 16 VLBW, 22 LBW, term Excluded: renal/renovascular anomaly, CHD, chrom. anomaly, BPD, diuretics
M de Swiet, 1980 prospective [10]	Doppler (SBP)	n=5573 4/patient day 4 → 1 year	n=1797 GA >38, healthy term
A Kent, 2007 prospective [4]	oscillometric	3/day day 1 → 4	n=406, healthy term Excluded: mat.HTN, IDDM, GDM, substance abuse, cong/chrom. anomaly, Bw <3rd Pc, sepsis, NICU admission
A Kent, 2007 prospective [14]	oscillometric	3/day until discharge → 6 & 12 month	n=406, healthy term Excluded: mat.HTN, IDDM, GDM, substance abuse, cong/chrom. anomaly, Bw <3rd Pc, sepsis, NICU admission
B Pejovic, 2007 prospective [5]	oscillometric	n=12552 1st month	n=373, 292 preterm, 81 term Excluded: Hgb abn., renal/renovascular anomaly, CHD, PDA, chrom. anomaly, indomethacin, steroids, diuretics, muscle relaxant, narcotics, ANS, PN, IUGR, inotropes, ventilation
E Lurbe, 2007 prospective [8]	oscillometric	day 2 → 1, 3, 6, 9, 12 month	n=149, healthy term, uncomplicated pregnancy
A Kent, 2009 prospective [3]	oscillometric	day 1, 2, 3, 4, 7, 14, 21, 28 1 month	n=147, GA: 28-36, stable, ventilation, inotropic support < 24 h, Excluded: chrom. anomaly, substance abuse
B Batton, 2014 prospective [6]	arterial	n=18 709 first 24 hrs	n=367, GA: 23-26, Excluded: died, cong. anomaly, withdrawal of care
ZA Vesoulis,2016 prospective [15]	arterial	n=11.9 million data, first 72 hrs	n=35, GA: 25±1.5, Bw: 865±200g, Excluded: inotropes, died, IVH gr 3-4
CJ Alonzo, 2019 retrospective [11]	arterial, oscillometric	n=2 billion, until 38 PMA	n=1708, GA: 23-34
AC Zadelhoff, 2023 retrospective [12]	oscillometric	n=5885 first week of life	n=607, GA: 24-41 Excluded: septic shock, major CHD, asphyxia, genetic disorders, NEC, IVH gr 2-4, PPHN, substance abuse, surgery, death, ventilated periods
Y Elsayed, 2024 prospective [13]	arterial	n=44496 first 3 days of life	n=206, GA <29 Tx, volume, inotropes, >FiO2 0,50, hsPDA, IVH gr 3-4, sepsis, death

abn: abnormal, ANS: antenatal steroid, Bw: Birth weight, CHD: congenital heart defect, chrom.: chromosomal, cong.: congenital, DBP: diastolic blood pressure, GA: gestational age, GDM: gestational diabetes mellitus, gr: grade, hrs: hours, hsPDA: haemodynamically significant persistent ductus arteriosus Botalli, IDDM: Insulin-dependent diabetes mellitus, IUGR: Intrauterine growth retardation, IVH: intraventricular haemorrhage, mat.HTN: maternal hypertension, MBP: mean blood pressure, n: number, Pc: percentile, PN: parenteral nutrition, SBP: systolic blood pressure, Tx: Blood transfusion

3.3. Blood pressure influencing factors

Several studies examined maternal health and therapy's influence on neonatal blood pressure, but the results are still controversial [4, 7, 8, 17, 18]. The significant studies examining maternal influencing factors on neonatal blood pressure are summarised in Table 2.

Table 2 Studies examining maternal influencing factors on neonatal blood pressure

Examined factor	Studies/date of publication	Number of patients involved	Results
Maternal sociodemographic factors			
Age	Gillman/2004 [19] Sedaghat/2008 [20]	1095 mother+newborn 406 term newborn	increasing age → BP ↑ no correlation
Ethnicity	Zinner/1980 [35] Schachter/1976 [36] Vesoulis/2016 [37]	837 mother+newborn 392 term newborn 35 preterm GA < 28	no difference no difference African American → BP ↑
Socioeconomic status	Sadoh/2010 [21]	473 mother+newborn	low SES → BP ↑
Maternal health history			
BMI	Sadoh/2010 [21]	473 mother+newborn	BMI > 30 → BP↑
Blood pressure	Gillman/2004 [19] Hegyi/1994 [2] Hegyi/1996 [22] Mausner/1983 [24]	1059 mother+newborn 47 infant 38 infant 391 + 190 mother	maternal HTN → SBP ↑ maternal HTN → SBP ↑ no difference no difference
Diabetes	Kent/2009 [23]	190 preterm GA:28-31	SBP, MBP, DBP ↑
Smoking	Beratis/1996 [25] Geerts/2007 [38]	369 (73 smoker) 456 (30 smoker)	15/more cigarettes/day→BP ↑ SBP ↑
Medications			
Antenatal steroids	Demarini/1999 [26] Moise/1995 [27] Been/2009 [28] Mildenhall/2009 [39] Vesoulis/2016 [37] LeFlore/2000 [29]	178 preterm GA < 31 240 preterm GA:23-27 271 preterm GA ≤ 32 145 preterm GA < 32 35 preterm GA < 28 70 preterm GA < 31	BP ↑ need for inotropes ↓ BP ↑ no difference (repeated ANS) BP↑ no difference
Delivery and birth			
MgSO4	Rantone/2002 [40]	40 preterm GA < 33	no difference
Anaesthesia	Sedaghat/2008 [20]	406 term newborn	spinal anaesthesia → SBP ↓ on day1, but not on days 2-3
Mode of delivery	Sedaghat/2008 [20]	406 term newborn	elective Cs → SBP ↓ on day1, but not on days 2-3
Chorio-amnionitis	Been/2009 [28] Yanowitz/2002 [41]	271 preterm GA < 32 55 preterm GA < 32	no difference MBP, DBP ↓
Early preeclampsia	Chourdakis/2020 [31]	106 newborn + 106 controls	BP ↑
HELLP syndrome	Dötch/1997 [30]	36 infants	BP ↓
Cord management	Cochrane/2019 [32] Shenone/2022 [33] Mercer/2003 [34]	5721 infants/48 studies 54 term newborn 32 GA: 24-32	DCC → BP ↑ DCC → BP ↑ DCC → MBP ↑

ANS: antenatal steroid, BP: blood pressure, Cs: cesarean section, DBP: diastolic blood pressure, DCC: delayed cord clamping, HTN: hypertension, MBP: mean blood pressure, SBP: systolic blood pressure, SES: socioeconomic status

3.3.1. Maternal demographic and social factors

Maternal sociodemographic factors, e.g., maternal age, ethnicity, socioeconomic class, and their effect on newborn blood pressure, were extensively studied, but a clear correlation could not have been demonstrated. An American cohort study [19] involved 1059 mother-newborn pairs and measured blood pressure in the first five days of life. They found that each five-year increase in maternal age results in a 0.8 mmHg increase in the newborn's systolic blood pressure. Segaquhat and his research group conducted a study involving 406 healthy, term infants [20]. In opposition to the results of previous studies, there was no significant correlation between maternal age and neonatal blood pressure in the first three days of life. According to a Nigerian study, low maternal socioeconomic status significantly influences neonatal blood pressure. Sadoh and colleagues collected blood pressure readings and maternal medical and socioeconomic data from 473 term infant-mother pairs. The newborns from low socioeconomic status had higher systolic blood pressure than term infants from a high or middle class [21].

3.3.2. Maternal health, delivery and medication influence on neonatal blood pressure

Different research groups studied the effect of maternal hypertension and preeclampsia on neonatal blood pressure, but most of the studies used small patient numbers, and their results are contradictory. In the investigation led by Gillman, there was a correlation between maternal hypertension and increased neonatal systolic blood pressure [19]. Hegyi et al. found higher systolic and diastolic blood pressure between 3-6 hours of life in the offspring of hypertensive mothers but not on days one and seven [2, 22]. Furthermore, neither an Australian study group [23] nor the investigation led by Mausner [24] found a difference in neonatal BP between the newborns of hypertensive mothers and the control group. Kent et al. [23] investigated 190 preterm and term infants to prove that pregnancy-associated conditions affect neonatal blood pressure. They found higher systolic, diastolic, and mean blood pressure in the first 28 days of life in the preterm offspring (28-31 weeks gestation) of diabetic mothers. The hypotensive effect of chorioamnionitis on neonatal blood pressure is still debated [28]. Dötch et al. found that patients whose mothers suffered from HELLP syndrome had significantly more hypotension and need for volume resuscitation [30]. According to one more recent study, maternal early-onset preeclampsia results in significantly higher blood pressure in the offspring's first month of life compared to the newborns born from normotensive mothers [31].

Several research groups have investigated the effects of maternal harmful habits, such as smoking, on newborns. Maternal heavy smoking (15 cigarettes/day) causes an increase in

neonatal blood pressure in the first 12 months of life compared to a nonsmoking control group [25].

Antenatal steroid administration and its effect on neonatal cardiovascular stability and blood pressure was extensively studied. Demarini led a prospective study investigating 178 infants with birth weights between 500-1499 grams [26]. They measured the blood pressure over the first day of life and found a significantly higher BP, with less need for inotropic support and volume. Another two studies concluded with similar results [27, 28]. Contrarily, an investigation done by LeFlore et al. could not show blood pressure difference between the antenatal steroid group and the controls [29].

Delayed cord clamping and its effect on neonatal circulation are among the most studied therapeutic interventions [32]. Delayed cord clamping is associated with haemodynamic stability, higher BP in the early hours after birth, and less need for inotropic support [32-34].

3.3.3. Neonatal factors influencing blood pressure

Gestational age, postnatal age and birth weight are known factors affecting the blood pressure of newborn infants. The blood pressure increases with gestational age and birth weight on the first day of life. In the first days, there is a rapid rise in blood pressure, which rises gradually further for the first two months of life. Within the first days of life, the rate of rise increases with decreasing gestational age.

Some studies examined gender's influence on neonatal blood pressure. Emery et al. found significantly lower blood pressure on the first day of life in male infants than in females, but there was no difference on the second day [42]. The study led by Kent did not find a difference in blood pressure by gender at six months of age [14].

Familiar and twin studies draw attention to the fact that, in some cases, the genetic background of the newborn can also influence blood pressure as early as the neonatal period. A study showed that the CYP2D6 CC genotype is associated with systolic hypertension during follow-up in preterm infants [43]. Another study examined a consanguineous family with early-onset neonatal hypertension, where the biallelic loss of function of the NPR1 gene was responsible for neonatal-onset systemic hypertension [44].

Several factors in neonatal therapy have a hypotensive or hypertensive effect, but in most cases, the results from the studies are still controversial. Caffeine is widely used in preterm infants to prevent apnoea of prematurity. Some studies have shown increased blood pressure in preterm infants receiving caffeine [45-47]. However, another study with low patient

involvement did not find a difference in heart rate and blood pressure after caffeine administration [48]. Non-invasive ventilatory support and PEEP administration might cause reduced cardiac output and hypotension. One study by Waal found no superior vena cava flow change in non-invasively ventilated (PEEP 5-8 H_2Ocm) newborns [49]. An early study, investigating ventilated newborns, found significantly lower systolic and diastolic blood pressure compared to controls [2, 22]. Postnatal steroids are administered to preterm infants with bronchopulmonary dysplasia. An earlier study found a significant rise in blood pressure during dexamethasone therapy, which remained above baseline after treatment [50]. Based on the findings of a recent meta-analysis, a medium cumulative dose of postnatal dexamethasone has a risk of causing hypertension [51]. On the other hand, several studies investigating hypertension in BPD patients did not demonstrate a hypertensive effect of postnatal steroids on the studied patient groups [52-54]. Diuretics are frequently used in neonates during the treatment of acute kidney injury, hypertension or BPD; their administration might affect the results of certain studies investigating neonatal blood pressure [55-57].

Some recent studies have drawn attention to the change in the spectrum of hypertension in neonates and highlighted the potential role of environmental factors in neonatal hypertension [58, 59, 61]. A recent study by Jenkins and colleagues found that neonatal postnatal exposure to di-(2-ethylhexyl) phthalate (DEHP) can cause hypertension [59]. DEHP is commonly added to plastics to increase flexibility and can leach out from respiratory and intravenous tubing. They investigated 18 patients with idiopathic hypertension from birth to 8 months of life. The intravenous and respiratory DEHP exposure and the urinary DEHP metabolite were higher in hypertensive patients than in the normotensive control group. The metabolite of the DEHP is an inhibitor of the 11β-HSD2. The inhibition of 11β-HSD2 causes mineralocorticoid-mediated sodium retention and consequent hypertension.

3.4. Bronchopulmonary dysplasia effect on neonatal blood pressure

Particular diseases of premature infants can affect blood pressure development and cardiovascular outcome of the infant. BPD is one among these conditions, and several working groups have investigated its effect on blood pressure. Previous research has shown that preterm infants with BPD have a significantly higher risk of developing systemic hypertension [52-54, 60-62]. According to the literature, the incidence of hypertension varies widely, with rates between 12% and 43% in preterm infants with BPD [53, 60]. Despite improved neonatal care, BPD remains one of the most common complications of preterm birth, affecting 17-75% of preterm infants born before the 28th week of gestation worldwide [63, 64]. BPD and the

consequent hypertension can significantly affect premature infants' short- and long-term life outcomes.

Table 3 summarises the significant studies investigating the influence of BPD on neonatal blood pressure.

Table 3 Studies investigating BPD effect on blood pressure

Author, date	Total number (n) of patients, MGA	BPD definition	HTN definition	Increased BP in BPD
Abman, 1984, retrospective [60]	n=65 30 BPD MGA:30	* PPV in the first week At 1 month: * respiratory distress *O2 dependency * radiographic evidence	SBP > 113 mm Hg on three separate occasions	yes
Emery, 1992, prospective [65]	n=40 20 BPD MGA: 26	Oxygen-dependent at 28 days of age	none	no
Anderson, 1993, retrospective [53]	n=87 87 BPD 11 HTN MGA: 30	* PPV in the first week * persistent respiratory symptoms *O2 requirement > 28 days *abnormal chest Xray	SBP ≥ 113 mmHg on three separate occasions	yes
Greenough, 1993, prospective [66]	n=26 13 BPD MGA: 28	*O2 dependent at 28 days of age *abnormal chest Xray	SBP > 100 mmHg/ 113 mgHg	no
Alagappan, 1998, retrospective [52]	n=73 41 BPD MGA:28	*PPV in the first week * O2 requirement >28 days to maintain oxygenation, *abnormal chest XRay	SBP >105 mmHg (>90th Pc)	yes
Jenkins, 2017, retrospective [61]	n= 97 37 BPD MGA: 26.7	Needing oxygen after 36 weeks PMA	Daily average of SBP > 95th percentile, for 2 days	yes
Sehgal, 2022, retrospective [54]	n=171 57 BPD MGA: 27	Requirement for respiratory support at 36 weeks PMA	SBP and MBP ≥ 95th percentile for PMA	yes

BPD: Bronchopulmonary dysplasia, HTN: hypertension, MBP: mean blood pressure, MGA: mean gestational age, n: number, PPV positive pressure ventilation, PMA postmenstrual age, SBP: systolic blood pressure

3.5. Neonatal blood pressure measurement

The intra-arterial blood pressure measurement method is still considered the gold standard in the evaluation of neonatal blood pressure. However, arterial lines are associated with several side effects, such as thrombosis, ischaemia and infection. Therefore, their use is decreasing in non-critically ill neonatal patients. During arterial measurement, a catheter is placed in the

umbilical, or the radial artery, and a fluid-filled tubing connects it to a pressure transducer. The pressure transducer converts the arterial pulse to an electrical signal, and after processing, it is displayed as a blood pressure waveform [67].

As neonatology moves toward non-invasive procedures and monitoring, oscillometric measurements have become favourable in haemodynamically stable patients. Oscillometric blood pressure monitoring is based on the fact that the blood flowing through the artery creates oscillations on the vessel wall, which are transmitted to the cuff, detected and recorded by the transducer. The cuff is inflated above the systolic blood pressure during the oscillometric measurement. The artery begins to pulse when the cuff's pressure is lower than the systolic blood pressure. The maximal oscillations occur at the mean arterial pressure [68]. The device then uses a manufacturer-specific algorithm to calculate systolic and diastolic blood pressure. The main advantage of oscillometric measurement is its non-invasiveness and fewer complications than intra-arterial measurements. However, there could be a significant difference in accuracy between the devices of different manufacturers [68, 69]. The reliability of the oscillometric measurement and the correlation with the arterial measurement results were investigated in several studies. Shah et al. investigated 73 preterm infants (<37 weeks gestation) and 1703 paired arterial and oscillometric measurements. Concordance between arterial and non-invasive measurements in hypotensive preterm infants was low [70]. According to the meta-analysis and review of blood pressure measurement methods published by Dionne et al., oscillometric measurements are less accurate below 30 mmHg, so they should be used with appropriate caution [71]. Based on their findings, it is recommended to use MBP among oscillometric values because it gives the most reliable results [71]. The meta-analysis suggests that the blood pressure cuff width to arm circumference ratio should be 0.5 for oscillometric BP measurements [71, 72].

The difference between measurement locations was broadly studied [71]. Taking right arm blood pressure is recommended, but studies show that calf blood pressure could be used for measurements in the first days of life, giving comparable results to the right arm blood pressure [71, 72].

Some studies investigated the wakefulness state of the infant during blood pressure measurement [5, 73] and demonstrated that crying and feeding could increase blood pressure significantly. Therefore, taking the blood pressure measurement in sleep or a quiet awake state is recommended.

Based on previous research, Nwankwo and colleagues created a standard oscillometric blood pressure measurement protocol used in most NICUs worldwide [72]. The blood pressure

should be measured 1.5 hours after a feed or medical intervention, with an appropriately sized BP cuff on the right upper arm, and the infant should be lying prone or supine and should be asleep or in a quiet awake state. The blood pressure measurement should be repeated three times at 2-minute intervals.

Accurate blood pressure measurement and knowledge of normal values are essential in determining and appropriately treating neonatal hypotension. Circulatory instability detected in the first days of life and its consequences (e.g., intraventricular haemorrhage) can determine the patients' long-term quality of life. During their NICU stay, it is also important to recognize and treat neonatal hypertension.

3.6. Neonatal hypertension

The incidence of diagnosed neonatal hypertension varies between 0.2% and 3 % [1]. Neonates treated in neonatal intensive care units have a higher incidence, between 1% and 2.5%, than healthy-term infants [74, 75, 81]. The secondary analysis of the AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) study showed that 1.8% of the study patients had been diagnosed with hypertension, and a further 3.7% of the patients had undiagnosed hypertension [74]. It is important to note that patients with a severe malformation of the urinary tract and congenital heart defects requiring surgery were not included in the study.

Neonatal hypertension is defined as persistent systolic and/or diastolic measurements over the 95th percentile for postmenstrual age [76, 77]. After the second week of life, the 95th and 99th percentile blood pressure values, estimated from the results of previous studies by Dionne and colleagues, can be used to diagnose hypertension [16].

Several studies have investigated the causes of neonatal hypertension [61, 74], but the aetiology has still not been identified in several cases [61]. Recent publications have drawn attention to the change in the spectrum of hypertension [58, 59, 61]. Previously, umbilical artery-related thromboembolic events with high renin levels were one of the leading causes of neonatal hypertension. Recently, the environmental effect of DEHP was suspected in the background of BPD-related or idiopathic hypertension with low renin levels. The following table (see Table 4) shows the most common etiological factors behind neonatal hypertension [1, 16, 77, 78, 79].

Table 4 Most common causes of neonatal hypertension

Renal – Renovascular – Renal parenchymal disease	 – Thromboembolism, Renal artery stenosis, Renal venous thrombosis – Polycystic kidney disease, Multicystic-dysplastic kidney disease, Acute tubular necrosis, Cortical necrosis
Pulmonary	Bronchopulmonary dysplasia
Cardiac	Coarctation of the aorta
Endocrine	Congenital adrenal hyperplasia**,** Hyperaldosteronism**,** Hyperthyroidism
Medication/Intoxication	Dexamethasone, Inotropes, Caffeine, Vitamin D, Maternal substance abuse
Neoplasia	Wilms tumour, Mesoblastic nephroma, neuroblastoma
Neurologic	Pain, Intracranial hypertension, Seizures
Miscellaneous	Volume overload, Total parenteral nutrition, Closure of abdominal wall defect
Idiopathic	

3.7. Outcome and follow-up in neonatal hypertension

The outcome of hypertension in preterm and term infants has been investigated in several trials. An early study [80] followed 17 hypertensive neonates after discharge from the NICU. The antihypertensive medication was discontinued in all the patients by 24 months of age. Bowley et al. investigated the incidence of hypertension and the duration of treatment [81]. They found that 57% of the hypertensive patients received medication, and the median duration of the antihypertensive treatment was ten days. One recent retrospective, multicentre investigation on the treatment of idiopathic hypertension found that 60% of the patients received antihypertensive medication at six months of age [82]. However, in 93% of them, the treatment was discontinued by two years of age. In BPD patients, hypertension treatment could be weaned off by two years of age usually [1, 53].

The hypertensive NICU patients or patients with risk factors to develop hypertension should be followed up on an outpatient basis. More extended follow-up studies would be essential to know the later complications of NICU graduates with hypertension and related comorbidities.

4. Aims and questions

We conducted two single-centre studies to define normal neonatal blood pressure, investigate its influencing factors, and study the effect of bronchopulmonary dysplasia on neonatal blood pressure. We created a retrospective cohort of NICU patients and used extensive monitoring and clinical data in our research.

The main scientific questions of our research and the aims formulated based on the questions are as follows:

1. What is the normal blood pressure of a haemodynamically stable neonate? How do neonatal characteristics (birth weight, postnatal age, gestational age) affect neonatal blood pressure?

- We aimed to determine the normal average blood pressure in haemodynamically stable neonates according to different gestational ages and birth weights.
- We aimed to create a percentile table for the first five days of life for different gestational ages and birth weights.

2. Does antenatal steroid administration increase neonatal blood pressure after birth?

- We aimed to prove the antenatal steroid neonatal blood pressure stabilising effect.

3. Does the patient group with moderate and severe BPD have a different blood pressure than the control group?

- We aimed to compare the blood pressure of moderate and severe BPD patient group to the reference data.

4. Can we detect hypertension by performing individual examinations of BPD patients' blood pressure data?

- We aimed to examine the blood pressure variation of moderate to severe BPD patients in the first three months of life. We compared the individual patient's blood pressure to the 95th percentile.

5. Materials and methods

We conducted two retrospective single-centre studies at the Neonatal Intensive Care Unit of the University of Szeged, Hungary, to determine normal average neonatal blood pressure, the corresponding percentiles and the effect of BPD on neonatal blood pressure changes. Over a three-year period (from 01. January 2019 to 31. December 2021), relevant clinical data and all the blood pressure readings were collected from the entire patient group admitted to the unit.

5.1. Patient selection

5.1.1. Investigation of normal blood pressure in haemodynamically stable neonates

In our first study, we determined the normal average blood pressure and percentiles in haemodynamically stable neonates. In order to select the corresponding group of patients, we excluded all infants with a substantial risk of hypotension or hypertension from the study. The exclusion criteria [4, 5, 16, 76] were the following: (1) need for inotropic support, (2) postnatal steroid administration, (3) patients who required invasive ventilation for more than 24 hours, (4) renal parenchymal disease, renovascular abnormality and acute kidney injury, (5) major congenital heart defect, (6) chromosomal anomaly, (7) intracranial hypertension, (8) diagnosed hypertension of the newborn, (9) maternal substance abuse and withdrawal syndrome of the newborn, (10) use of an umbilical arterial catheter, (11) severe and moderate bronchopulmonary dysplasia, (12) endocrine disorder with a risk of hypertension and (13) death. Newborns with mild BPD who were not diagnosed with hypertension during their NICU stay were included in the study population since, in most BPD patients, hypertension starts at a later date than they have been discharged from the NICU [60].

As there have been changes in neonatal medicine since the earlier research, we have not excluded interventions that are part of routine care today. Therefore, patients ventilated on nasal CPAP, received caffeine or had short-term procedural analgesia were involved in the study. The neonates who received diuretics without the diagnosis of hypertension were included in our clinical investigation.

We also collected maternal medical data. However, we did not exclude patients based on the investigated maternal medical problems, as the results are still controversial on their effect on neonatal blood pressure [17]. Over the study period, the unit admitted 839 patients. After applying the exclusion criteria, we collected blood pressure data from 629 preterm and term infants for analysis in the study (see Fig. 1).

5.1.2. Investigation of blood pressure changes in moderate and severe BPD patients

All preterm infants born before 30 weeks gestation with moderate or severe BPD admitted to our NICU over three years (from 1 January 2019 to 31 December 2021) were included in our second investigation. We excluded the patients from the study who were transferred out or died before 36 weeks of postmenstrual age. Regarding the inclusion of the patients, there was no overlap between the BPD patient group and the patient group used to determine normal neonatal blood pressure.

5.2. Definitions used in our investigations

The gestational age determination was based on the last menstrual period and early ultrasound scans done by the obstetrics team.

A complete steroid course was defined as four times 6 mg doses of dexamethasone administered intramuscularly every 12 hours [83]. The steroid course was considered incomplete when the suggested dose was not entirely given.

We calculated the weight percentiles using the Fenton growth charts.

We independently reviewed and collected data on each patient's respiratory status and corresponding support, established a diagnosis based on the results and used the National Institute of Child Health and Human Development (NICHD) 2001 definition to diagnose moderate and severe BPD [84, 85]. Based on the NICHD criteria, we defined moderate BPD as an oxygen requirement less than 30%, while severe BPD was defined as an oxygen requirement of 30% or more and/or a positive pressure ventilation requirement at 36 weeks PMA. All patients in the studied population also met the criteria for Grade 1-3 BPD based on the NICHD 2019 study, which extended the definition to include the mode of respiratory support [86].

Neonatal hypertension was defined as persistent systolic and/or diastolic measurements above the 95th percentile for PMA [76, 77]. The definition of a persistent blood pressure increase was a high blood pressure above the 95th percentile for three or more days. Hypertensive periods lasting less than three days are more likely to be the result of a therapeutic intervention than more extended periods.

We used the modified Kidney Disease: Improving Global Outcomes (KDIGO) definition to diagnose neonatal acute kidney injury (AKI) [87]. According to the definition, both serum creatinine levels and urine output were checked to determine AKI.

5.3. Blood pressure measurement

Measurement method and device: Blood pressure was measured using an oscillometric device (GE Dash 3000 multiparameter monitor system with the GE DINAMAP blood pressure algorithm) with an appropriately sized cuff (cuff-width-to-arm-circumference ratio closest to 0.50) [71,72]. We used oscillometric measurements exclusively, except for the individual blood pressure analysis of three patients in our second study who had only intraarterial data for the first seven days of life.

Timing and number of the measurements: The blood pressure measurements were taken according to the unit's guideline in a quiet, awake state or during sleep. Generally, a single blood pressure measurement was taken. In our first study, on a daily average, the number of measures by patient varied between one and twelve in the study group's first two weeks of life. The medical team decided the frequency of the measurements based on the patient's condition. The aim was to avoid repeating measurements to ensure comfort and keep the settled states of the neonates under the measure. In case of invalid values or suspected hypo- or hypertension, the blood pressure was remeasured based on the medical team's decision. Data on the infants' wakefulness state were unavailable in the medical records. According to our protocol, the measurements were done during sleep or in a quiet awake state. In case of an unsuccessful measurement (e.g., the newborn wakes up during measurement and cries), the protocol is to remeasure the blood pressure in a settled state.

Measurement place: We preferably used the right upper arm to measure the blood pressure. Left arm or calf blood pressure measurements were used in case of contraindications such as right arm tissue injury, peripheral cannula or PICC-line [77, 88, 89]. According to the literature, calf blood pressure can be used during the first six months of life as the results are similar to upper limb blood pressure measurements [77]. Patients with a congenital heart defect (e.g., coarctation of aortae) were excluded from the patient group.

5.4. Data collection and handling

The blood pressure values and patient and maternal demographic and medical data were retrieved from the IntelliSpace Critical Care and Anesthesia (ICCA) electronic medical records by Phillips and the hospital information system Medsol. The ICCA hospital administration system automatically stores the monitoring data in databases. All non-invasive blood pressure values in the records of the ICCA's database were retrieved using relevant SQL queries and were output as CSV text files. After a data validity check, the text file with the data was transferred to an SQL database for further analyses in the study.

We developed a standalone software program, PDAnalyzer, to perform all the main calculations based on the measured numeric blood pressure values and relevant additional raw data in our database. This data management method prevented data quality problems and maintained data reliability and accuracy. Altogether, 360507 systolic, diastolic, and mean blood pressure data were analysed. The PDAnalyzer program calculated the daily average blood pressure values, the corresponding deviations, and the daily percentile values.

5.4.1. Handling data in haemodynamically stable neonates

In our first investigation, the collected data included all the blood pressure records, use of antenatal steroids, Apgar scores at 1 and 5 minutes of life, birth weights, number of ventilated days (either invasive or non-invasive), neonatal medications (caffeine-citrate, diuretics, ibuprofen, analgesia), maternal medical history (hypertension, gestational diabetes mellitus, insulin-dependent diabetes mellitus, smoking) and neonatal diagnoses (intraventricular haemorrhage, patent ductus arteriosus, bronchopulmonary dysplasia, necrotising enterocolitis, sepsis).

The PDAnalyzer program calculated the daily average blood pressure values, the corresponding deviations, and the daily percentile values. The blood pressure values of the first two weeks of life (see Fig. 2/a, 2/b, 2/c) were used for detailed calculations and statistical analyses. The results of the first five days have been presented with additional details (see Fig. 3/a, 3/b, 3/c and 4/a, 4/b, 4/c and Table 7).

In our first study, during the data analysis period, we calculated the normal average blood pressure for preterms less than 30 weeks gestation without moderate or severe BPD or other risk factors for hypertension and created percentile charts [76]. By linear regression analysis, we created the reference 95th-percentile trendlines at both weekly and daily resolutions. In our second study, these results served as a reference. Our reference group's 95th percentile curve indicated a statistically strong significant correlation ($R=0.785$, two-sided $p=0.012$) with the corresponding data previously presented by Dionne [16].

5.4.2. Handling data in patients with moderate and severe BPD

The collected data included all blood pressure records, demographic data, antenatal and postnatal steroids, diuretics, blood transfusions, fluid boluses, inotropic support, ibuprofen administration, and the number of invasive and non-invasive ventilation days.

In our second investigation, we examined the blood pressure data of the entire patient group with moderate and severe BPD. We compared the BPD patient group results to the

previously defined normal daily average from a preterm patient group born less than 30 weeks gestation, which served as a reference.

Since we found a difference between the daily average blood pressure curves of the two groups, in order to understand and explain this phenomenon, we examined the development of the patient's blood pressure individually on a daily and weekly basis. We calculated the daily and weekly average blood pressure values for all patients in the first 90 days of life. We used our previously determined 95th-percentile blood pressure values and trendlines as a reference for diagnosing hypertension. Hypertensive periods lasting less than three days are more likely to be the result of a therapeutic intervention than more extended periods. Therefore, our study examined two groups (infants with less than three hypertensive days and infants with three or more hypertensive days) separately.

5.5. Statistical analysis

In most cases, statistical analysis was carried out using the IBM SPSS Statistics program (version 29) and Microsoft Excel Data Analysis module. One Sample Kolmogorov-Smirnov test was performed to prove the normal distribution of the blood pressure data. We used paired samples T-test to compare paired samples with continuous variables, and in the case of discrete variables, we used a simple binomial test. For the verification, the significance level was usually set at $p < 0.05$. Linear regression analyses were used to determine trend lines to approximate the arithmetic means calculated from the raw blood pressure values. The graphs were created by Microsoft Excel version 2209.

5.6. Ethical approval

Ethical approval was granted by the local Ethics Committee of the University of Szeged and the Hungarian Medical Research Council Scientific and Research Ethics Committee. The number of ethical approvals: 78/2021-SZTE RKEB, BM/15221-1/2023.

6. Results

6.1. Investigation of normal neonatal blood pressure

We overviewed the main medical characteristics of our patients and blood pressure measurement numbers to investigate normal neonatal blood pressure.

6.1.1. Characteristics of the patients and measurement numbers

We admitted 839 patients in our neonatal intensive care unit over three years (2019-2021). From the total 839 patients, we excluded 136 patients who required inotropic support and mechanical ventilation longer than 24 hours, 27 patients who died and 28 patients for other reasons (e.g. diagnosed hypertension, withdrawal syndrome, genetic problems, hydrocephalus). Another 19 patients were excluded due to technical reasons (e.g., insufficient data) (see Fig. 1).

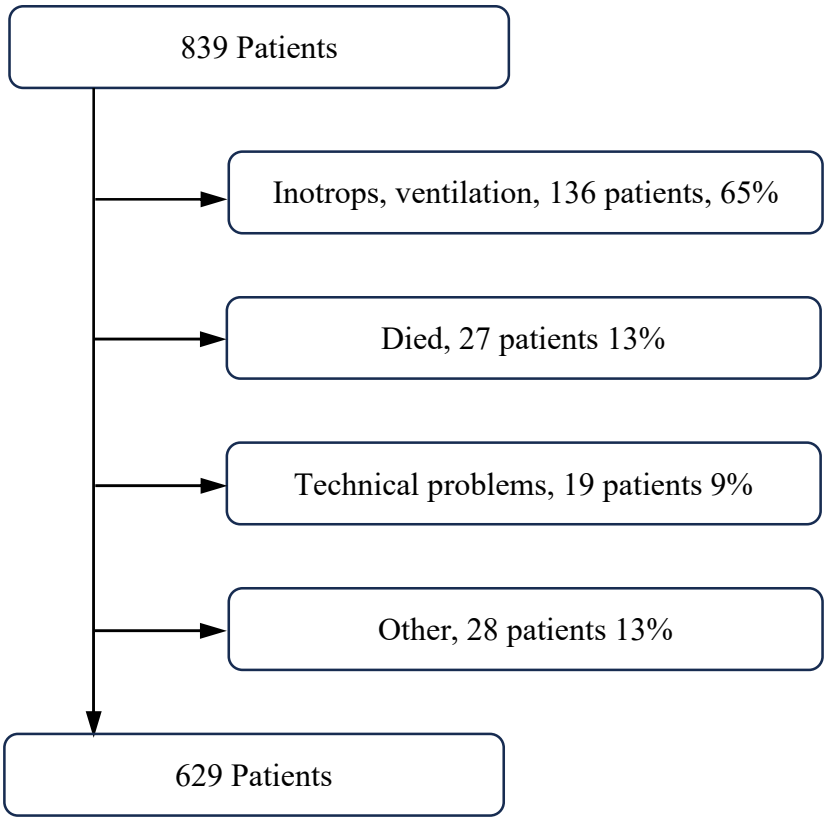

Fig. 1 Excluded patients in the first investigation

After applying the exclusion criteria, we included data from 629 infants in the study, of whom 378 (60%) were preterm and 251 (40%) were full-term patients. See the corresponding gestational age groups and BP measurement numbers in Table 5.

Table 5 Patient and measurement numbers in the different gestational age groups.

Gestational week	Number of patients	Percentage (%)	Number of measurements within the first 14 days of life		
			Systolic	Diastolic	Mean
25-28	27	4.3	2435	2435	2462
29	27	4.3	1916	1914	1930
30	27	4.3	1878	1878	1889
31	37	5.9	2309	2306	2312
32	59	9.4	3087	3087	3094
33	76	12.1	3252	3251	3269
34	53	8.4	2588	2588	2588
35	38	6.0	1746	1745	1745
36	34	5.4	1073	1073	1076
37	44	7.0	1628	1625	1628
38	49	7.8	1617	1617	1617
39	65	10.3	1974	1972	1972
40-42	93	14.8	2953	2953	2955
Total	629	100	28456	28444	28537

We also collected data on the medical conditions (hypertension, diabetes, smoking) of 594 affected mothers. Among them, 35% (n=207) had one of the above-mentioned medical conditions, but only 3.9% (n=23) had two or three investigated medical problems together. The maternal medical information was not processed with enough details in the ICCA and Medsol databases to let us draw a statistically valid conclusion on their effect on the newborn's blood pressure. The patient's demographic data and clinical characteristics are presented in Table 6.

The electronic patient records over the three years consisted of 119714 systolic, 119700 diastolic, and 121093 mean blood pressure data (i.e., 360507 data altogether). After applying the exclusion criteria, the remaining 629 patients had 44990 systolic, 44977 diastolic, and 44971 mean blood pressure values (i.e., altogether, 134938 data).

In this patient group, the average daily measurement count for one patient was 4.44, and the daily measurement numbers varied between 1 and 12. One-Sample Kolmogorov-Smirnov test has confirmed that the blood pressure data sample follows normal distribution.

Table 6 Neonatal and maternal clinical characteristics and demographic data

	All patients	25-28 GW	29-32 GW	33-36 GW	37-42 GW
Number of patients	629	27	150	201	251
Male/Female patients	380/249	15/12	88/62	124/77	153/98
Average birth weight (g)	2507	1013	1640	2275	3358
Birth weight range (g)	460-5340	460-1520	840-2710	840-2710	1190-5340
Birth weight	Number of patients				
Percentile < 3	36 (6%)	2	2	6	26
Percentile 3-10	47 (7%)	3	9	18	17
Percentile 10-90	479 (76%)	19	127	164	166
Percentile > 90	69 (11%)	3	12	13	41
Average Apgar scores					
Apgar 1 min (SD)	7.59 (±2.0)	6.3 (±1.8)	7.0 (±1.8)	7.4 (±1.7)	8.3 (±2.1)
Apgar 5 min (SD)	8.87(±1.3)	7.8 (±1.6)	8.6 (±1.2)	8.8 (±1.1)	9.2 (±1.5)
Neonatal therapy	Number of patients				
Diuretics	40 (6.3%)	9	12	7	12
Analgesia	118 (19%)	3	33	28	57
Caffeine citrate	244 (39%)	27	138	73	5
Ibuprofen	17 (2.6%)	5	8	3	1
Ventilatory therapy (<24h)					
Number of patients	40 (6.3%)	5	16	5	14
Length of ventilation (h)	3.3	2.0	2.9	3	5.3
Non-invasive ventilation					
Number of patients	375 (59%)	27	141	136	70
Length of ventilation (d)	5.74	26.5	6.55	3.2	2.18
Maternal data					
Number of mothers	594				
Hypertension	91 (15.3%)	7	20	41	23
IDDM/GDM	82 (13.8%)	2	24	30	26
Smoking	34 (5.7%)	5	11	10	8
Incomplete data	44 (7.4%)	1	7	11	25
Antenatal steroid	Patients	25-28 GW	29-32 GW	33-34 GW	
Incomplete course	82 (27%)	8	37	37	
Complete course	170 (55%)	15	86	69	
Not received	54 (18%)	4	27	23	

GW: gestational week, SD: standard deviation, IDDM: insulin-dependent diabetes mellitus, GDM: gestational diabetes mellitus

6.1.2. Average blood pressure values of the different gestational age groups in the first 14 days of life

The arithmetical average blood pressure values were determined in different gestational age groups in the first two weeks of life. Within the first 14 days of life, 63% of the total measurements (28456 systolic, 28444 diastolic and 28537 mean blood pressure data) were processed. The patient and measurement numbers in the different gestational age groups are presented in Table 5.

All the blood pressure curves representative of a certain gestational age were created. We calculated the daily arithmetical average blood pressure and the standard deviation for each

gestational age from the daily blood pressure measurements. Due to the low patient number in the very preterm group and the low measurement number in the term group, we investigated gestational weeks between 25-28 and 40-42 together, respectively. As a representative example, we presented the daily average systolic, diastolic and mean blood pressure curves as the function of time for different gestational age groups in the first two weeks of life (see Fig. 2/a, 2/b, 2/c).

The standard deviation was also calculated for the different gestational age groups. The average standard deviation for the systolic, diastolic and mean blood pressures are 9.7 mmHg, 7.9 mmHg and 8.5 mmHg, respectively. We found a statistically significant difference among the average blood pressure values of the different gestational age groups using the SPSS program paired samples T-test (p-value <0.001).

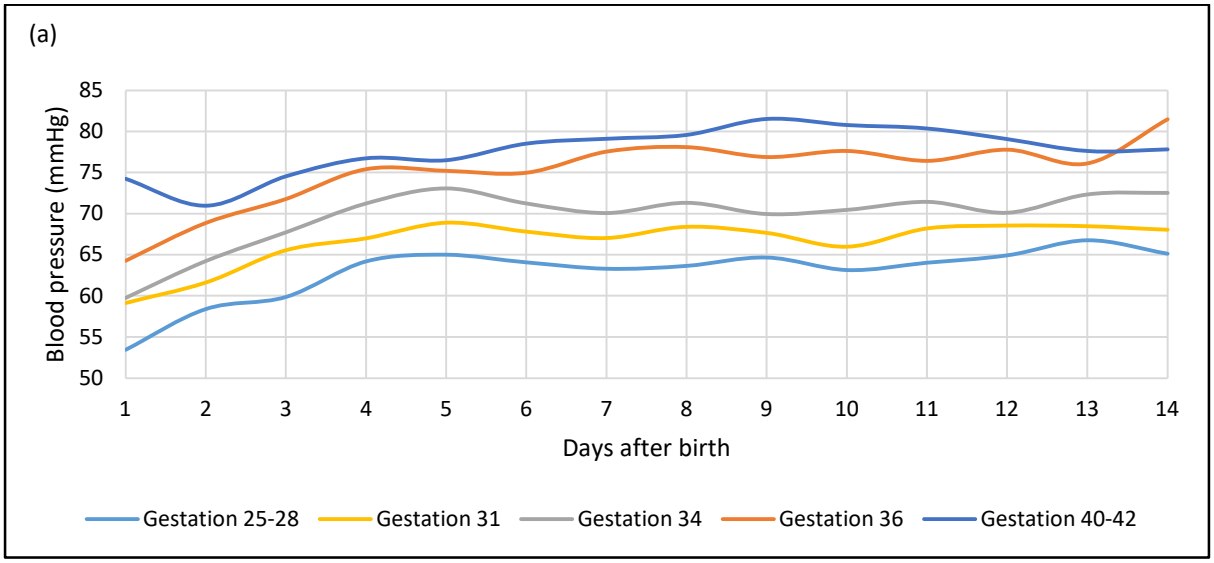

Fig. 2/a Systolic blood pressure curves for different gestational ages

We found that blood pressure increases with an increasing number of postnatal days and gestational age (see Fig. 2/a, 2/b and 2/c). According to our findings, the systolic blood pressure rise over the first three days of life is steeper in preterm infants (25-36 weeks gestation) than in the term infant group. The systolic blood pressure increased by 3.75 mmHg/day in preterm infants and 1.60 mmHg/day in the term infants in the first three days. After the first five days, the average systolic blood pressure values might show a mild decrease (see Fig. 2/a), but the trend remains increasing within the first two weeks of life.

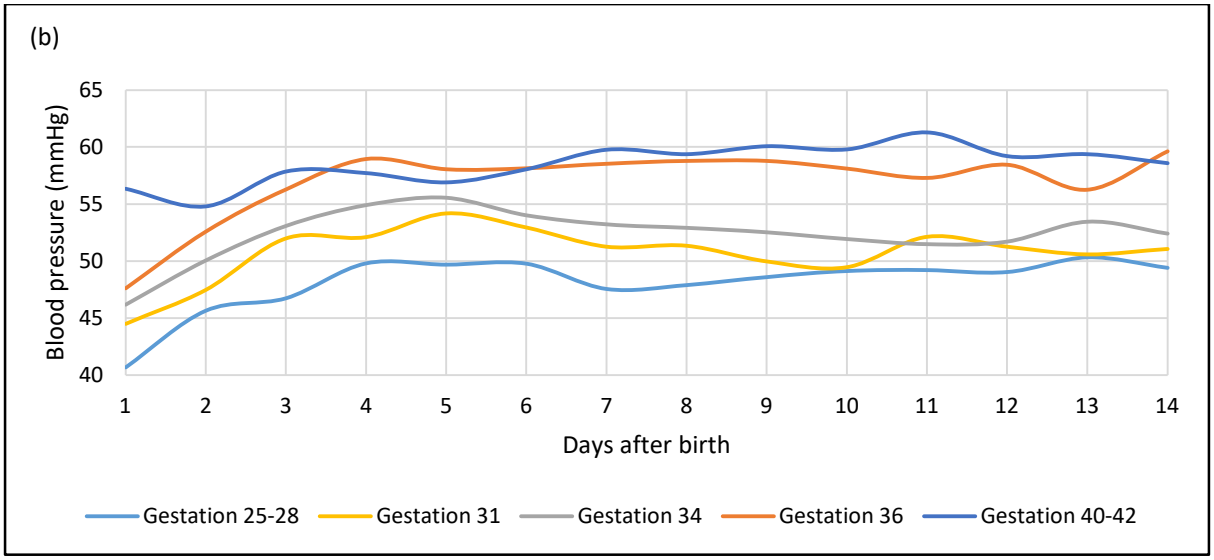

Fig. 2/b Mean blood pressure curves for different gestational ages

We experienced a similar pattern examining the diastolic and mean blood pressure data (see Fig. 2/c, 2/b). In the first three days, the daily diastolic blood pressure increase was 3.57 mmHg in preterm infants and 1.95 mmHg in term newborns, and the mean blood pressure elevation per day was 3.73 mmHg in the preterm and 1.93 mmHg in the term group.

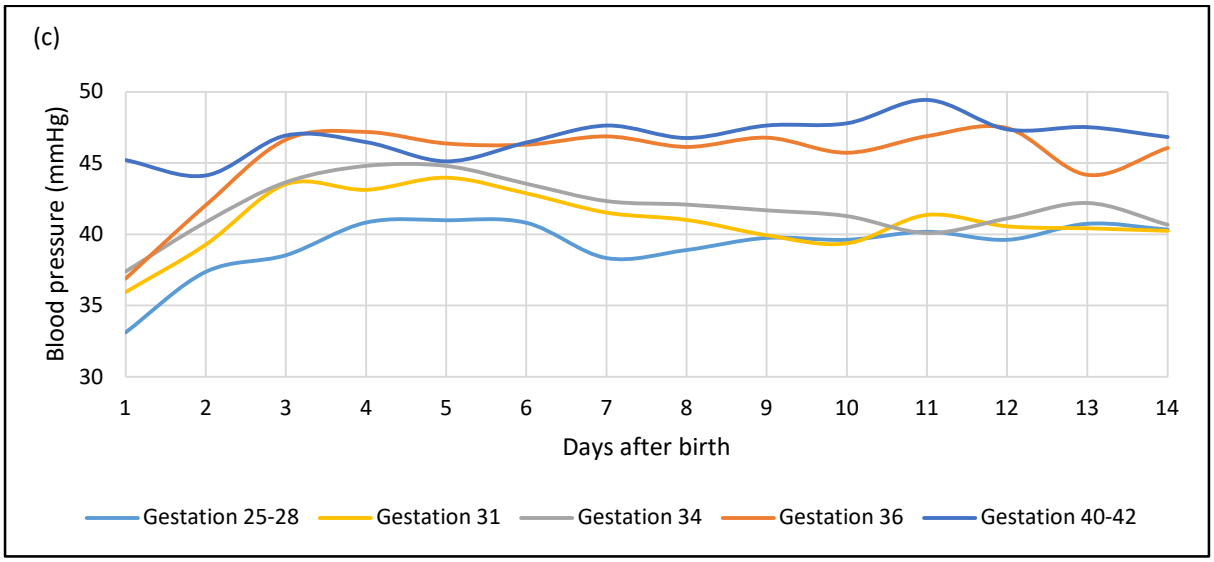

Fig. 2/c Diastolic blood pressure curves for different gestational ages

Term infants have a reduction in blood pressure over the first day of life before increasing (see Fig. 2/a, 2/b, 2/c). This indicates the possibility of different physiologic responses between term and preterm infants that need further study.

6.1.3. Blood pressure in the first five days of life by gestational age

As the blood pressure changes are most pronounced in the first week of life, the average daily blood pressure has been calculated on the first, third and fifth days, and the results are graphically presented (see Fig. 3/a, 3/b, 3/c).

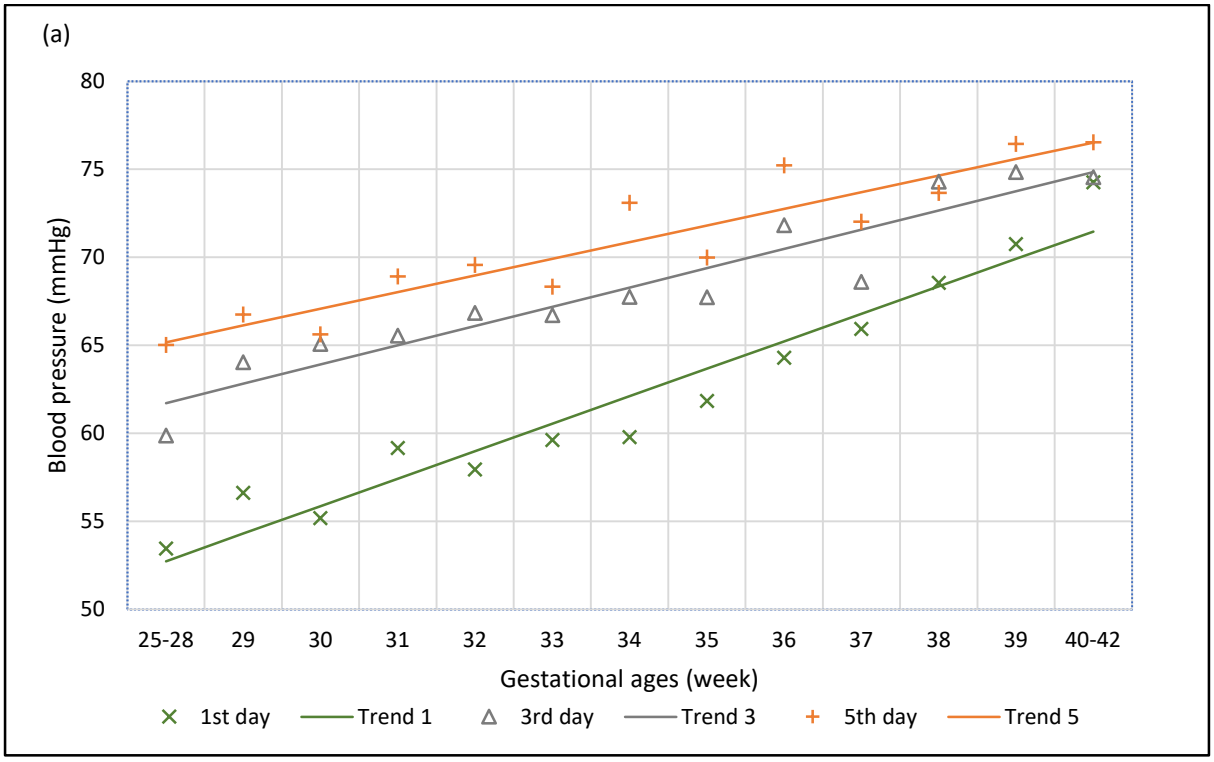

Fig. 3/a Systolic blood pressure by gestational ages on the first, third and fifth day of life

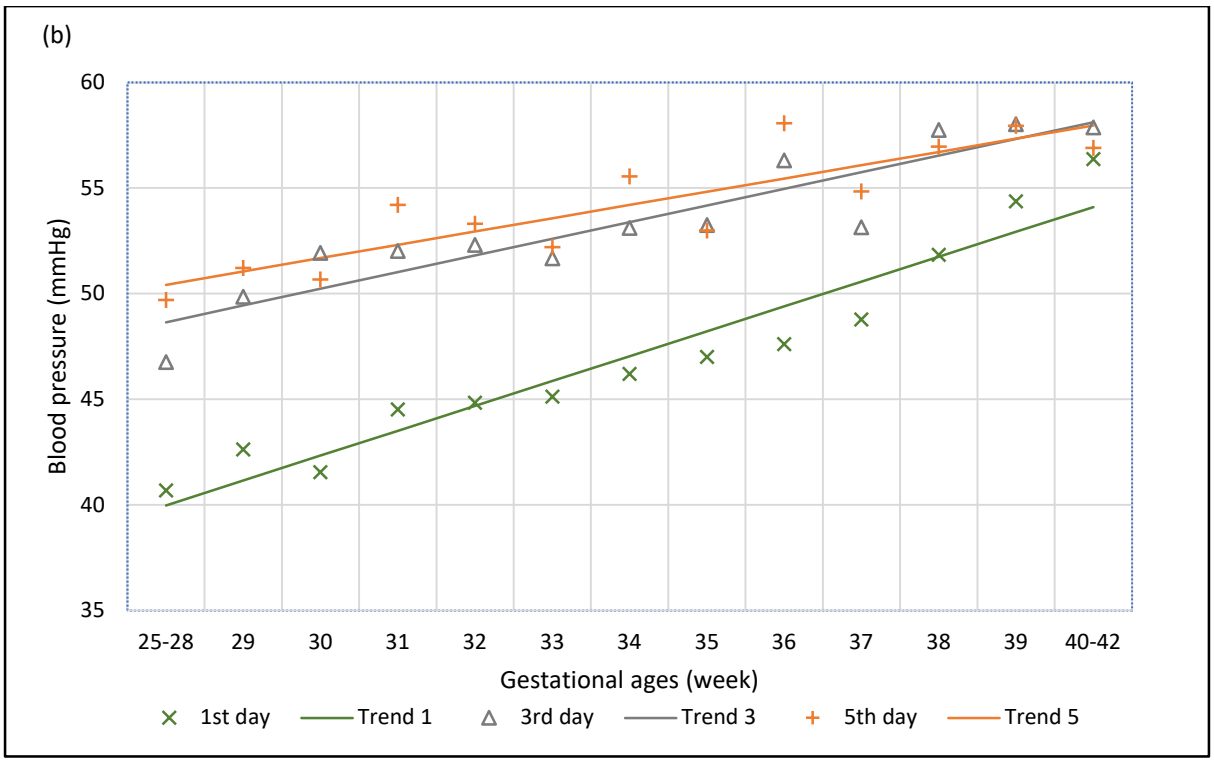

Fig. 3/b Mean blood pressure by gestational ages on the first, third and fifth day of life

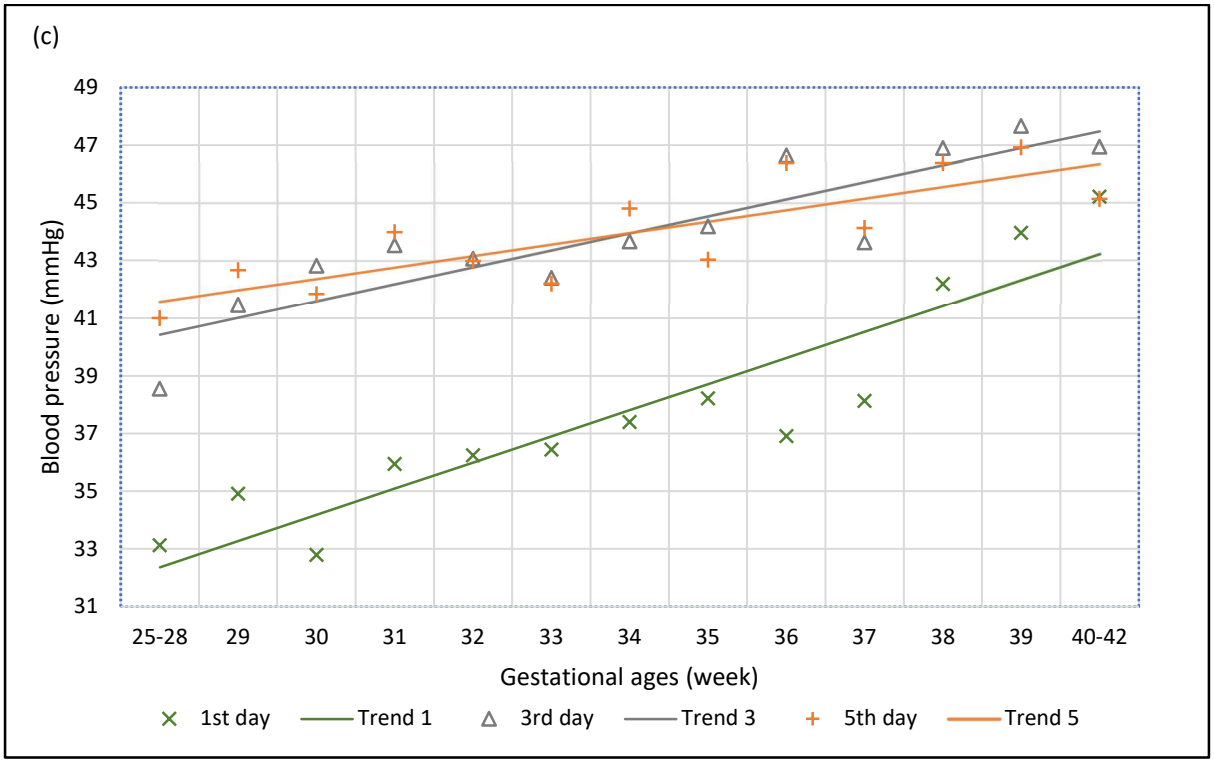

Fig. 3/c Diastolic blood pressure by gestational ages on the first, third and fifth day of life

Figure 3 shows the systolic, mean and diastolic blood pressure values and linear regression lines in different gestational ages on the first (Trend 1), third (Trend 3) and fifth (Trend 5) day of life. According to our analysis, the linear regression lines strongly correlate (systolic: Trend 1 $R^2 = 0.9364$, Trend 3 $R^2 = 0.8975$, Trend 5 $R^2 = 0.8662$, diastolic: Trend 1 $R^2 = 0.8483$, Trend 3 $R^2 = 0.7959$, Trend 5 $R^2 = 0.6761$, mean: Trend 1 $R^2 = 0.9244$, Trend 3 $R^2 = 0.8483$, Trend 5 $R^2 = 0.7631$) with the daily average blood pressure data. The calculated $p < 0.001$ value shows a significant correlation between them.

As shown in the figures above (see Fig. 3/a, 3/b, 3/c) the trendlines increase steeper in the first than in the third or fifth day of life. It means the blood pressure difference between the first, third and fifth days of life decreases as the gestational age increases. Based on trendline values, the average rates of change of the systolic blood pressure in the first five days for the 25-28, 32, 36 week gestational age groups are 3.11 mmHg/day, 2.49 mmHg/day and 1.88 mmHg/day, respectively. Considering the mean blood pressure, the corresponding values are 2.61 mmHg/day, 2.06 mmHg/day and 1.51 mmHg/day. Regarding diastolic blood pressure, the corresponding values are 2.30 mmHg/day, 1.79 mmHg/day and 1.28 mmHg/day.

The average blood pressure of the different gestational age groups increased rapidly over the first three days of life (systolic 3.08 mmHg/day, mean 3.17 mmHg/day, diastolic 3.07 mmHg/day). The following two days, there was a less pronounced increase in the systolic blood

pressure (1.28 mmHg/day) and the mean and the diastolic blood pressures did not increase further (mean 0.41 mmHg/day, diastolic 0.0 mmHg/day).

The following table (see Table 7) provides data on the daily average blood pressure values and percentiles in different gestational age groups on the first, third and fifth day of life.

Table 7 Average blood pressure values and 10th, 50th and 90th percentiles on the first, third and fifth day of life

Gestational age		**Day 1 BP**				**Day 3 BP**				**Day 5 BP**			
		Average	10th Pc	50th Pc	90th Pc	Average	10th Pc	50th Pc	90th Pc	Average	10th Pc	50th Pc	90th Pc
25-28	SBP	53	40	54	66	60	47	59	73	65	52	64	80
	DBP	33	21	33	45	39	28	38	50	41	31	41	52
	MBP	41	28	40	53	47	36	46	58	50	38	50	61
29-30	SBP	56	43	55	69	65	53	64	78	66	54	67	77
	DBP	34	24	34	44	42	31	42	52	42	32	42	54
	MBP	42	31	41	53	51	40	50	62	51	40	52	61
31-32	SBP	58	48	58	72	66	54	66	78	69	56	70	83
	DBP	36	27	36	46	43	34	43	53	43	34	43	54
	MBP	45	34	44	56	52	43	52	62	54	42	53	65
33-34	SBP	60	50	59	70	67	57	67	78	71	58	70	85
	DBP	37	27	37	46	43	34	43	52	43	33	43	55
	MBP	45	36	45	55	52	43	52	62	54	43	53	67
35-36	SBP	63	52	62	75	69	56	68	84	72	60	72	86
	DBP	38	29	38	47	45	35	44	56	44	34	44	56
	MBP	47	37	47	58	54	44	54	67	55	44	55	67
37-39	SBP	68	57	67	81	73	60	72	85	74	64	74	87
	DBP	41	31	41	51	46	36	45	57	46	36	45	57
	MBP	52	42	51	63	56	45	56	68	57	45	56	68
40-42	SBP	74	61	73	90	75	62	74	87	77	65	76	90
	DBP	45	33	43	62	47	35	46	59	45	37	44	57
	MBP	56	44	54	73	58	45	58	70	57	47	56	68

SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure

6.1.4. Blood pressure by birth weight

We investigated the change in neonatal blood pressure by increasing birth weight and generated eight patient groups; every patient group had a 500g difference in birth weight. The blood pressure data of 613 patients were included in the analysis. The data of 16 patients with a weight higher than 4500g was not used for calculation due to the low number of measurements and short hospital stay. We used 18370 systolic, 18363 diastolic and 18439 mean blood pressure data in the analysis.

The systolic, diastolic, and mean blood pressure values and linear regression lines are shown in the figure (see Fig. 4/a, 4/b, 4/c).

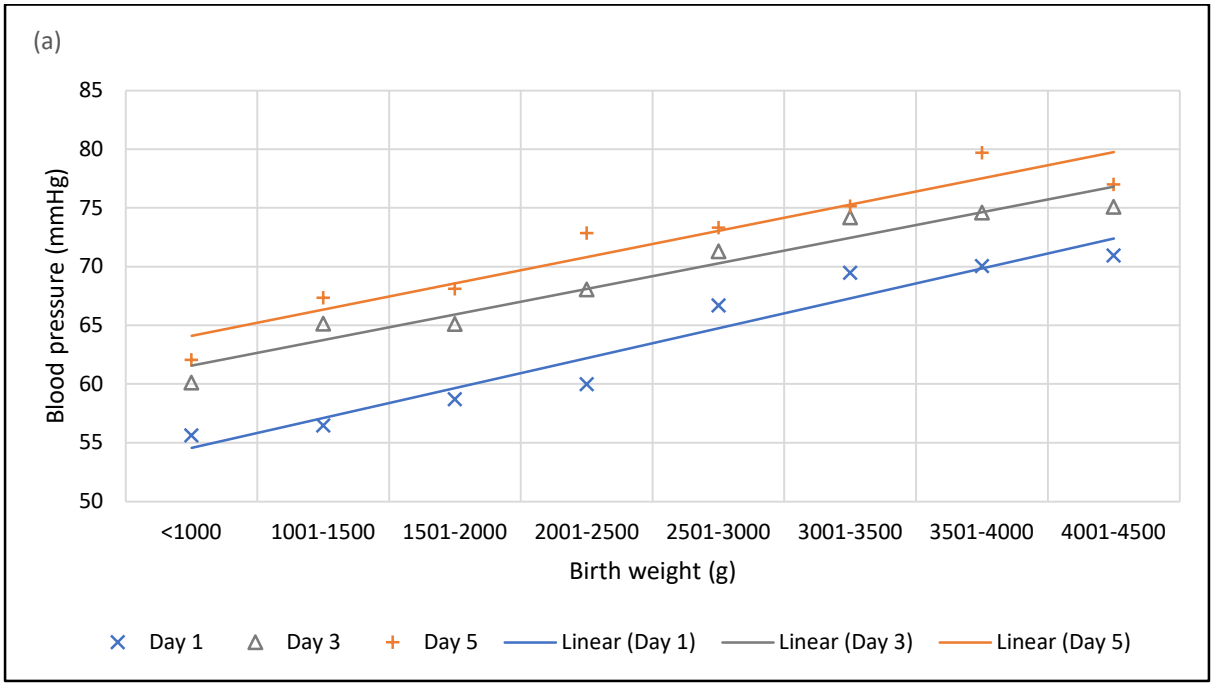

Fig. 4/a Systolic blood pressure by birth weight

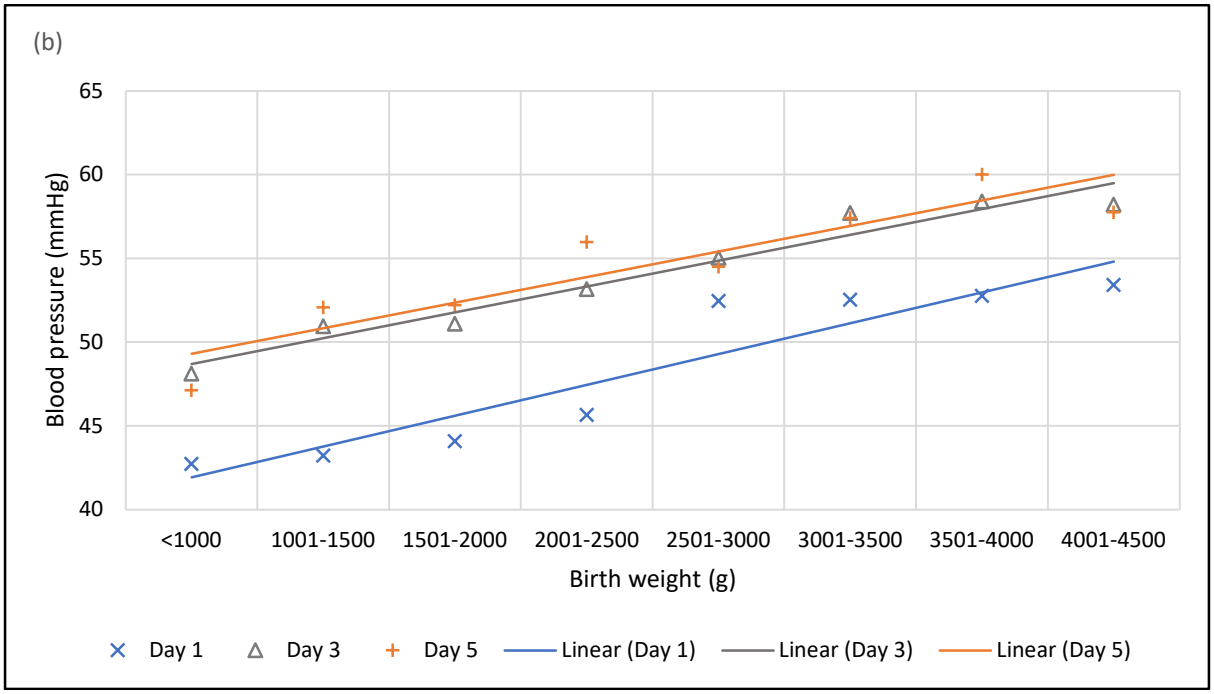

Fig. 4/b Mean blood pressure by birth weight

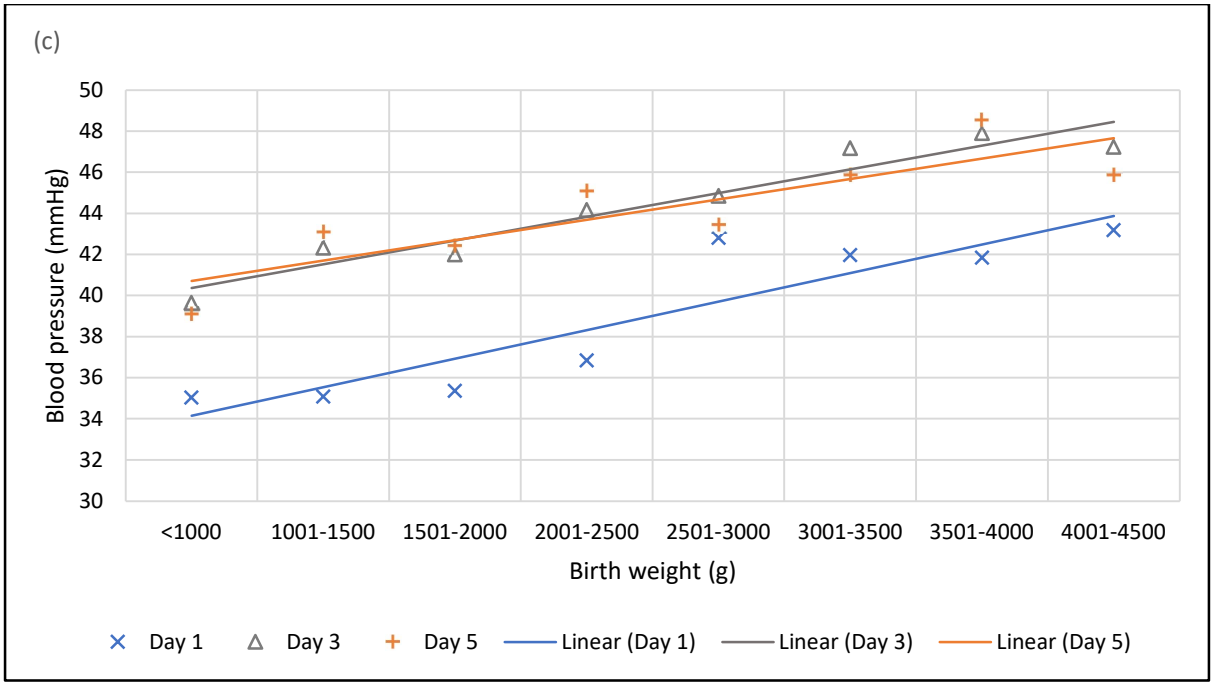

Fig. 4/c Diastolic blood pressure by birth weight

There is a positive linear correlation between birth weight and blood pressure on the first, third and fifth day of life (see Fig. 4/a, 4/b, 4/c). In the case of systolic blood pressure, the correlation coefficients are R(day1, day3) = 0.968, R(day1, day5) = 0.913, and R(day3, day5) = 0.966. The correlation coefficients calculated for the diastolic blood pressure are R(day1, day3) = 0.880, R(day1, day5) = 0.683, R(day3, day5) = 0.938 and for the mean blood pressure are R(day1, day3) = 0.947, R(day1, day5) = 0.816, R(day3, day5) = 0.946. The blood pressure differences are significant in the different birth weight groups (Paired Sample T-test: significance $p<0.001$).

The systolic blood pressure increased by 8.44 mmHg in the first five days. The daily average increment was 2.85 mmHg in the first three days and 1.36 mmHg over the following two days. The mean and diastolic blood pressure showed a similar pattern in the first three days of life; the calculated average daily increment was 2.86 mmHg and 2.69 mmHg, respectively. The blood pressure was almost static over the following two days.

The following table (see Table 8) contains the average blood pressure values and percentiles of the different birth weight groups on the first, third and fifth days of life.

Table 8 Average blood pressure values and 10th, 50th and 90th percentile by birth weight on the first, third and fifth day of life.

Birth weight (g)		Day 1 BP				Day 3 BP				Day 5 BP			
		Average	10th Pc	50th Pc	90th Pc	Average	10th Pc	50th Pc	90th Pc	Average	10th Pc	50th Pc	90th Pc
≤1000	SBP	56	40	55	72	60	46	59	77	62	49	62	77
	DBP	35	21	36	48	40	27	38	56	39	29	38	51
	MBP	43	27	41	56	48	35	46	64	47	36	47	59
1001-1500	SBP	56	43	55	71	65	53	65	78	67	54	68	79
	DBP	35	24	36	45	42	32	42	53	43	33	43	54
	MBP	43	31	43	56	51	40	51	61	52	41	52	62
1501-2000	SBP	59	48	58	70	65	54	65	77	68	57	68	81
	DBP	35	26	35	44	42	33	41	52	42	32	42	53
	MBP	44	34	44	54	51	42	51	60	52	42	52	64
2001-2500	SBP	60	50	59	72	68	58	68	79	73	60	73	86
	DBP	37	27	36	46	44	35	44	53	45	35	44	57
	MBP	46	36	45	55	53	44	53	62	56	45	55	69
2501-3000	SBP	67	54	64	82	71	59	71	84	73	63	74	83
	DBP	43	30	41	58	45	34	44	56	43	35	42	54
	MBP	52	40	50	68	55	44	54	67	55	45	54	66
3001-3500	SBP	69	56	69	82	74	62	73	87	75	63	75	88
	DBP	42	32	42	52	47	37	46	58	46	37	45	56
	MBP	52	42	52	63	58	46	57	70	57	48	57	68
3501-4000	SBP	70	59	70	81	75	62	74	86	80	69	80	91
	DBP	42	32	41	52	48	37	47	59	48	39	48	59
	MBP	53	43	52	64	58	46	58	70	60	50	60	71
4001-4500	SBP	71	58	70	88	75	62	75	88	77	61	78	90
	DBP	43	35	42	54	47	36	45	59	46	36	44	58
	MBP	53	43	52	66	58	45	58	71	58	45	58	69

SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, BP: blood pressure, Pc: percentile

6.2. Investigation of antenatal steroid administration effect on neonatal blood pressure

Based on the blood pressures of the first two weeks of life, we compared the average blood pressure values of the preterm patients (gestational age: 25-34 weeks, n=306) who received a complete course of antenatal steroids (n=170, 55%) to the patient group who had an incomplete antenatal steroid course (n=82, 27%) or did not receive steroid prophylaxis (n=54, 18%). A possibly significant difference between the groups above was refused because the applied paired sample T-test calculated significance as $p = 0.191$.

6.3. Investigation of blood pressure changes in moderate and severe BPD patients

Despite several studies on this topic, there are unanswered questions regarding the blood pressure changes in premature infants with BPD [52-54, 60-62, 65, 66, 89]. Among these questions, the most important ones are the onset and frequency of hypertensive periods in BPD patients. Previous studies applied different definitions for hypertension and BPD and took less frequent blood pressure measurements or used relatively short continuous time intervals in their investigations. These differences make it difficult to interpret and utilise their results in patient care today. Considering these reasons, our study aimed to investigate the changes in blood pressure in the premature BPD patient group during the first three months of life.

The next question of the study was to investigate the number of hypertensive periods and other blood pressure characteristics in individual patients. We used recent definitions of hypertension and BPD and utilised a large amount of measured data and a relatively long time interval. This kind of investigation may be the first step towards a systematic analysis of this phenomenon.

6.3.1. Patient group characteristics and measurement numbers

Over three years, our unit admitted 126 patients born at less than 30 weeks gestation, of whom 26 had moderate to severe BPD.

Table 9 lists the demographic characteristics and the general therapies applied to the BPD patient group. Patients were not given antihypertensive medications other than those listed in the table.

Our database comprised 19481 measured blood pressure data separately for systolic blood pressure, diastolic blood pressure and mean blood pressure in the first 90 days of life. Therefore, the average number of raw data points per patient was 749.3 for each blood pressure category. This amounted to an average of 8.3 daily blood pressure measurements per patient. For the investigated period, the median of the measurement numbers was 180 (IQR 318.5-125).

Table 9 Characteristics of moderate to severe BPD patients and BPD patients with three or more or less than three hypertensive days

	BPD patient group	≥3 days with HTN	<3 days with HTN
Patient number, n(%)	26 (100)	11 (42)	15 (58)
Mean GA (range)	26.1 (23-29)	26.2 (23-29)	26.1 (24-29)
Birth weight, (g)	696 (300-1390)	685 (300-1390)	705 (350-1360)
Male/female, n(%)	14/12 (54/46)	5/6	9/6
Severe BPD, n(%)	12 (46.2)	6 (54.5)	6 (40)
Postnatal steroids, n(%)	16 (61.5)	7 (63.6)	9 (60)
Diuretics, n(%)	23 (88.5)	10 (90.9)	13 (86.6)
Ibuprofen, n(%)	11 (42.3)	6 (54.5)	5 (33.3)
Inv. Vent. (days)	22.9	28.2	19.1
NIV (days)	39.2	36.9	40.9
Antenatal steroids, n(%)	17 (65.4)	9 (81.8)	8 (53.3)
AKI, n(%)	8 (30.7)	6 (54.5)	2 (13.3)
IVH (grade III-IV), n(%)	5 (19.2)	3 (27.3)	2 (13.3)
PDA, n(%)	17 (65.4)	8 (72.7)	9 (60)
PHT (on sildenafil), n(%)	2 (7.7)	2 (18.2)	0
NICU stay (days)	120.7	121.8	119.9

The percentages for therapy and comorbidities refer to the patient group in the same column. GA: gestational age, HTN: hypertension, BPD: bronchopulmonary dysplasia, AKI: acute kidney injury, IVH: intraventricular haemorrhage, PDA: persistent ductus arteriosus, PHT: pulmonary hypertension, Inv. vent.: invasive ventilation, NIV: non-invasive ventilation, n: number

6.3.2. The evolution of the average systolic, diastolic and mean blood pressures in the BPD patient group compared to the reference blood pressure data

We calculated the daily average systolic, diastolic and mean blood pressure values of the BPD patient group. Based on the daily average blood pressure data, we generated two trendlines: one for the BPD group and the other for the reference data. We compared the blood pressure curve and the corresponding trendline to the reference group's average daily blood pressure. The BPD patients' SBP trendline initially had lower values and rose gradually until around the 70th day of life, when it crossed the reference trendline (see Fig. 5/a). The DBP and the MBP showed similar trends to that of the SBP, but they reached the reference trendline around the 30th and the 45th days of life, respectively (see Fig. 5/b and Fig. 5/c). We performed a separate statistical analysis for the time intervals before and after the intersection of the trendlines. The calculations revealed a significant correlation between the BPD-related data and the reference data (SBP: $R1=0.732$, $R2=0.754$, $p<0.001$; DBP: $R1=0.454$, $R2=0.625$, $p<0.005$; MBP: $R1=0.371$, $R2=0.699$, $p<0.012$). However, there was a significant difference between the paired SBP, DBP and MBP curves (the calculated averages of the differences were as follows: SBP: $M1=-1.681$, $p<0.001$, $M2=-0.542$, $p=0.139$; DBP: $M1=-1.235$, $M2=1.627$, $p< 0.001$; and MBP: $M1=-1.454$, $M2=1.502$ $p<0.001$).

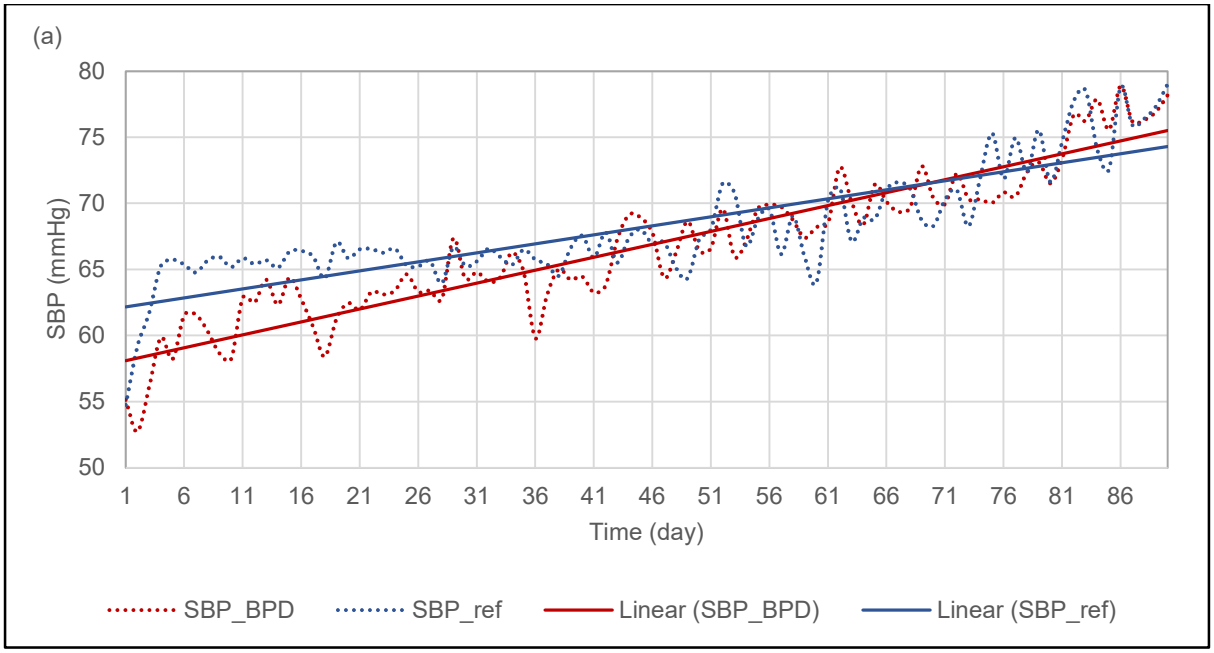

Fig. 5/a Systolic blood pressure curves and linear trendlines of the BPD group and the reference group as a function of time. SBP: systolic blood pressure, BPD: bronchopulmonary dysplasia, ref: reference group

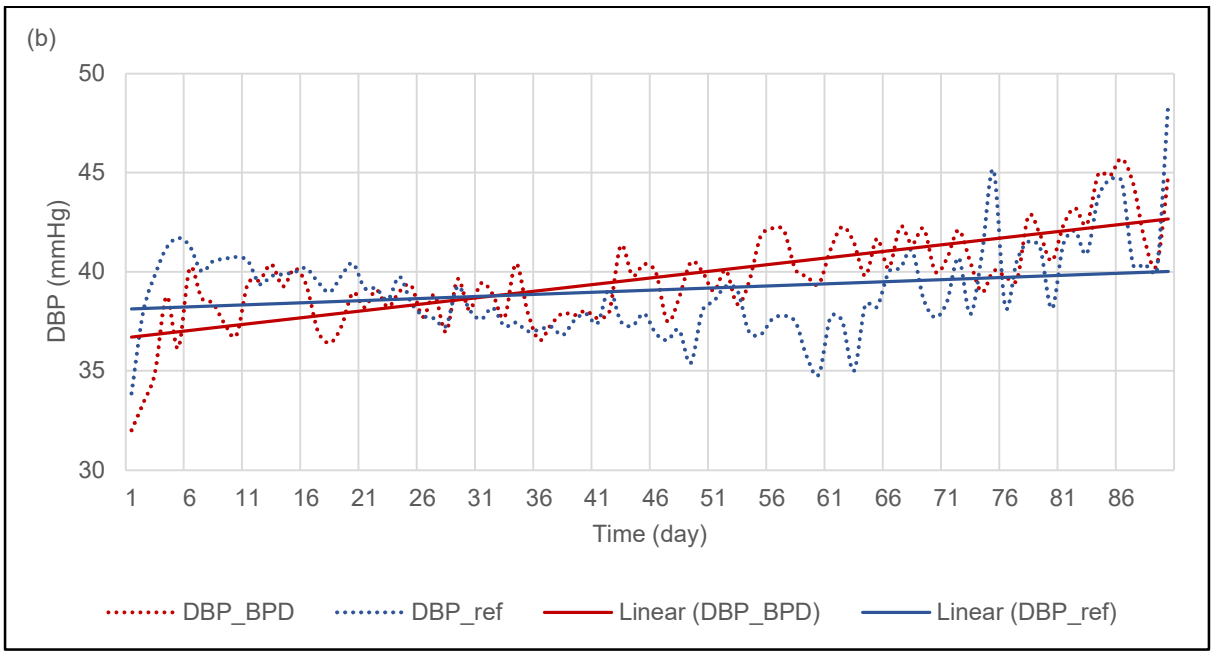

Fig. 5/b Diastolic blood pressure curves and linear trendlines of the BPD group and the reference group as a function of time. DBP: diastolic blood pressure, BPD: bronchopulmonary dysplasia, ref: reference group

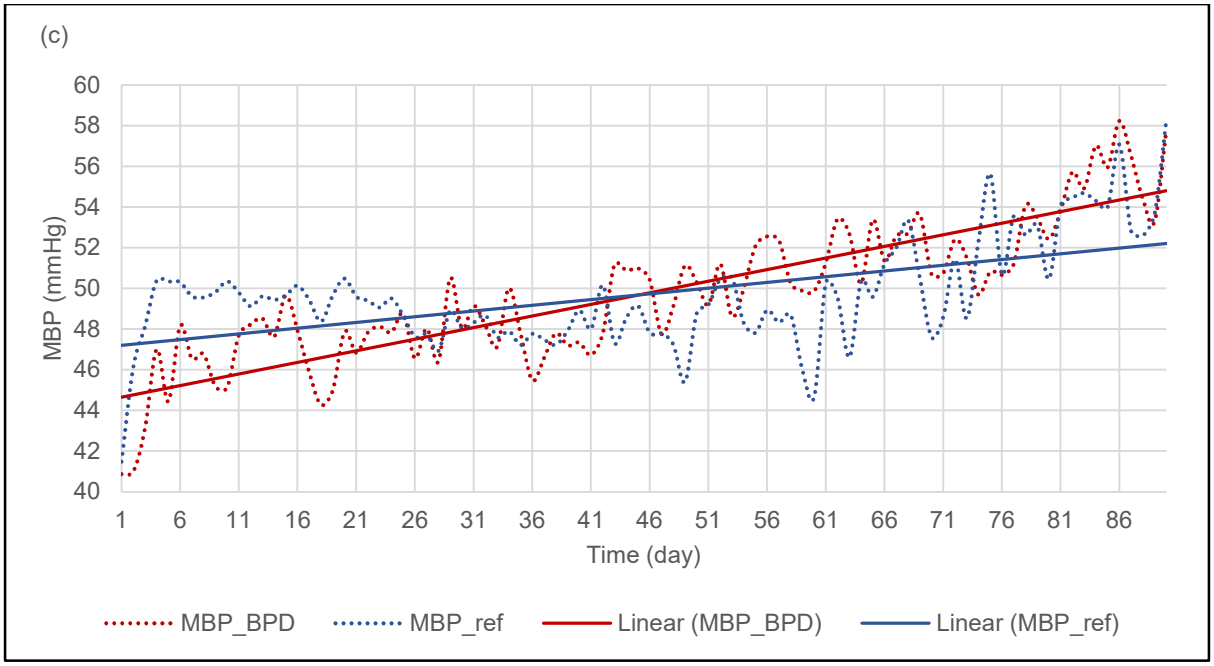

Fig. 5/c Mean blood pressure curves and linear trendlines of the BPD group and the reference group as a function of time. MBP: mean blood pressure, BPD: bronchopulmonary dysplasia, ref: reference group

6.3.3 Comparison of the daily average blood pressure to the 95th percentile blood pressure trendline

We calculated and compared each patient's daily average blood pressure to the 95th-percentile trendline. The average number of daily blood pressure measurements per patient was 8.3. At least three daily measurements were taken for all patients, ensuring that a single higher measurement was not used to diagnose hypertension. The average daily measurement numbers per patient during the hypertensive episodes were 9.2 and 9.4 for the SBP and DBP, respectively. Considering the 2340 patient days, we found 38 systolic (1.6%) and 50 diastolic (2.1%) daily average measurements above the 95th percentile. In our whole sample, only nine patients had no daily average blood pressure spikes (i.e., a systolic or diastolic daily average blood pressure above the 95th percentile), and 65% (n=17) had at least one day with a hypertensive average daily blood pressure in the first three months of life. We found 13 patients (50%) who had average daily SBP and 16 patients (61.5%) who had average daily DBP values that exceeded the 95th percentile. Most of them had occasional daily blood pressure spikes. Eleven patients (42%) had three or more days with an average blood pressure above the 95th percentile.

We compared the patients with elevated blood pressure values for three or more days to the remaining patients (see Table 9). Our detailed statistical analysis showed that patients with three or more hypertensive days had a 25% chance of having AKI (H_0: TP=0.25, exact sig.= 0.034). AKI episodes (91.6%) mainly occurred within the first two weeks of life. All the investigated BPD patients had normal renal function (i.e. age-appropriate serum creatinine levels and urine output) after the fifth week of life.

We also examined the onset of the blood pressure increase. Most daily average hypertensive blood pressure measurements occurred at the 2nd, 9th, 12th, and 13th weeks of life, corresponding to the 28th, 35th, 38th, and 39th week of corrected gestational age, respectively (see Fig. 6). We found that 34%, 22%, and 44% of the hypertensive daily average blood pressures occurred in the first, second, and third months of life, respectively.

We investigated data on fluid boluses, blood transfusions and inotropes in the database and found that the duration of administration did not coincide with periods of high blood pressure. Inotropic support was administered to 73% of the patients. All patients received blood transfusions, and the average transfusion number was 7.6 per patient for 90 days. A fluid bolus was administered to 16 patients. The average number of treatments administered was 1.75 per patient. These therapies were given mainly within the first three weeks of life: 44% of blood transfusions, 88% of fluid boluses and 62% of inotropes. The use of these particular therapies was limited compared to the entire investigated time interval. Therefore, these factors should not influence the results of our blood pressure analysis.

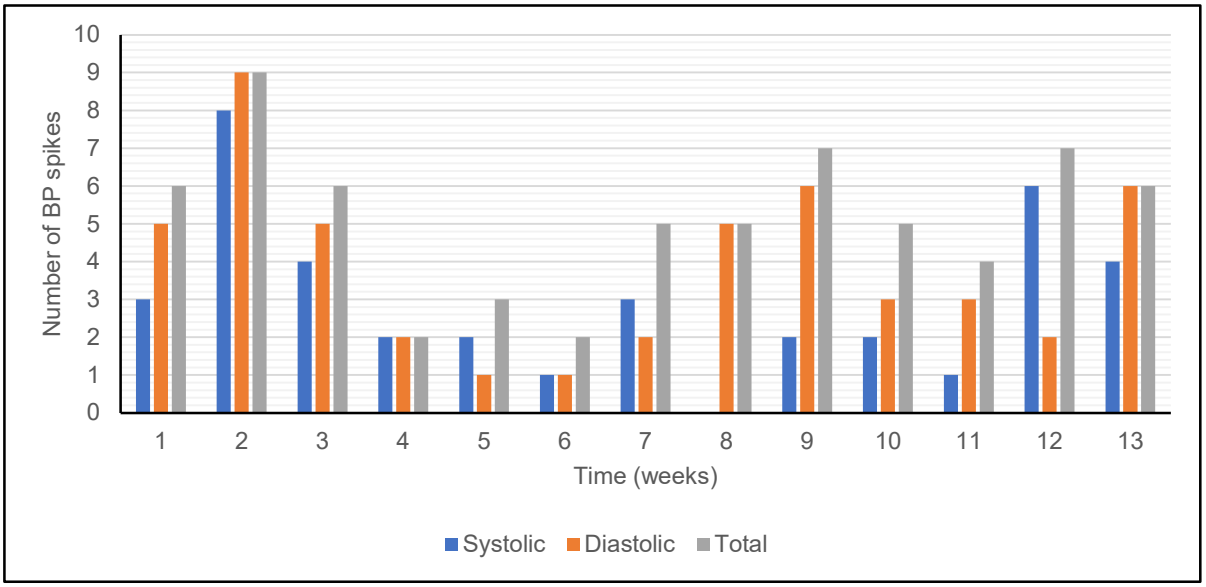

Fig. 6 Number of systolic, diastolic, and total blood pressure spikes over 13 weeks
BP: blood pressure, total: systolic and/or diastolic BP spikes

6.3.4. Comparison of the weekly average blood pressure to the 95th-percentile blood pressure trendline

We calculated the weekly average blood pressure values for every BPD patient. The weekly average SBP and DBP values were above the 95th percentile in 3 (11.5%) of the 26 patients for one week only. These results indicate that some of the shorter hypertensive periods may remain hidden when weekly averages or averages from longer time intervals are used to obtain blood pressure measurements.

7. Discussion

7.1. Overview of research aims and key findings

We conducted two single-centre retrospective studies to provide oscillometric blood pressure measurement data on normal neonatal blood pressure and its influencing factors with particular reference to BPD as one of the most common complications of extreme prematurity.

In our first study, we set up a NICU patient cohort and collected data from a haemodynamically stable term and preterm patient group without substantial hypotension or hypertension risks. The exclusion criteria described above were applied after collecting all the diagnoses and treatment data of the patients (see Table 6). We defined the normal average blood pressure in different gestational ages, postnatal age and birth weight groups. We also created percentile tables for different gestational age and birth weight groups. The percentile table for birth weight groups in the first five days of life was not previously available. We also examined the effect of antenatal steroids on neonatal blood pressure.

Our second study aimed to examine blood pressure changes in BPD patients during the first three months of life. The results of our detailed analysis using average daily blood pressure values show that BPD patients' blood pressure starts lower and ends higher than the reference value. To explain this phenomenon, we examined individual blood pressure changes in BPD patients with attention given to the influencing therapies. The individual daily average blood pressure calculations highlighted short periods with elevated blood pressure values. These blood pressure variations might partly explain the general blood pressure characteristics of the BPD patient group. We examined several factors influencing blood pressure, and our detailed statistical analysis showed that patients with three or more hypertensive days had a 25% chance of having AKI.

7.2. Contextualisation of results

In our first investigation, both our patient number and the volume of our measured data were comparable to the largest previous investigations done in this field of research. As a novel method, a large number of blood pressure data was retrieved from electronic hospital records and analysed further with the help of a standalone software. This retrospective approach enabled the use of large data sets and significantly reduced the possibility of errors due to data inaccuracies.

Most of the other clinical studies investigated healthy patient populations by excluding cardiovascularly compromised patients, but infants with a risk of hypertension were just partly

excluded [3, 5]. The Philadelphia neonatal blood pressure study is one of the most extensive investigations to determine normal neonatal blood pressure [7]. Zubrow and his associates involved 608 NICU patients without selection in their prospective multicentre study. They found a strong correlation between blood pressure and gestational age. However, they found that other diagnosis and treatment variables had only a small influence on blood pressure variance. Since earlier research work [3-10, 16], several improvements have arisen in neonatal therapy, and the patient's survival has improved. These changes also increased the importance of performing new studies and investigating a patient population without severe morbidities and major therapeutic interventions. To meet this target, we omitted patients from our study corresponding to the criteria described above. Parts of the exclusion criteria used in some earlier research work cannot be applied nowadays because they may not be appropriate in the current clinical practice [6].

We compared our results to studies carried out previously by using oscillometric blood pressure measurement methods. Kent and colleagues investigated a homogenous preterm patient group without ventilated patients or patients needing inotropic support [3]. Their published blood pressure values by gestational age are close to our results on the second day of life. They also provided blood pressure percentiles by birth weight, similar to our calculated average blood pressure findings. Another study led by Pejovic also published data to estimate normal blood pressure values in neonates. As a comparison, our patient group's blood pressure values were consequently higher than Pejovic's findings [5]. We assumed that the difference might be caused by the different patient populations and oscillometric devices.

The importance and actuality of the topic are shown by the fact that since our first publication, two more original research studies have been published, which have aimed to determine normal blood pressure values. A Canadian research group determined the normal neonatal blood pressure in a preterm group (less than 29 weeks of gestation) within the first three days of life when significant haemodynamic changes occur. Elsayed et al. used umbilical arterial measurement data and processed the 44469 individual blood pressure measurements of 206 preterm patients in their analysis [13]. They generated the estimated blood pressure curves and percentile tables for preterm infants less than 29 weeks gestation. Similarly to our study, they used a selected, haemodynamically stable population in their research. Their results are essential to know extreme preterm infants' normal arterial blood pressure values. However, in clinical practice, the use of the umbilical arterial line is limited in haemodynamically stable preterms due to the risk of complications and insertion difficulties.

For these reasons, developing appropriate percentile tables and curves based on oscillometric measurements is essential. Another recent study with a similar aim, led by Zadelhoff, developed normal blood pressure curves for different gestational age groups and percentiles [12]. They retrospectively analysed 5885 oscillometric measurements from 607 infants without major comorbidities in the first week of life. Our study analysed extensive oscillometric data and calculated the normal average values and percentiles for different gestational age and birth weight groups. An educational article about common hypertensive scenarios recommended using the percentile table for different birth weight groups generated in our first study [78]. We also calculated trendline values that might replace daily average blood pressure results in practice and be used to estimate expected blood pressure results in gestational age groups outside of the time interval presented in this paper.

The blood pressure stabilising effect of antenatal steroids is still controversial, although most of the studies show that antenatal steroid increases neonatal blood pressure [15, 26]. However, some studies have not found a significant difference between those who received antenatal steroids and those who have not [29]. Our study shows no essential difference between the complete antenatal steroid group and the group of patients with incomplete or no steroid administration. In our study, we could not examine the effect of partial steroid administration separately due to patient and measurement numbers. It would be interesting to investigate partial steroid administration's blood pressure stabilizing effect on a larger group of patients with more data.

In our second article, we presented the blood pressure changes of BPD patients in the first three months of life. The length of the investigated period, the frequency of data collection, and the high number of blood pressure measurements make our second study different from other related studies. Several clinical studies have confirmed the increased risk of hypertension in BPD patients [52-54, 60-62], while other studies have not shown a risk of high blood pressure in premature infants with BPD [65, 66]. In addition to the different diagnostic criteria used for BPD and hypertension, this difference may arise from the various and short periods during which blood pressure measurements were taken.

The most likely onset time of hypertension varies widely, from 0.5 to 15 months of life [52, 53, 60]. Jenkins and colleagues reported that hypertension began at a mean age of 11.3 ± 3.2 chronological weeks, corresponding to 39.6 ± 3.6 weeks PMA [61]. In our patient group, the likelihood of a blood pressure increase was high in the 2nd, 9th, and 12th to 13th weeks of life. The latter corresponds to 38-39 weeks of corrected gestational age. In our investigation,

an early increase in blood pressure might be related to other pathologies, such as AKI. However, a blood pressure increase beginning in the third month of life can be associated with BPD.

The aetiology of hypertension in BPD patients is still unknown, but several conditions likely contribute to its development. As pulmonary hypertension is frequently present in BPD patients, consequent hypertension of the infant to maintain adequate pulmonary perfusion and oxygenation could be one of the possible explanations. Some studies have investigated the association between pulmonary and systemic hypertension, but no correlation has been verified [53]. One study described worse left ventricular function and increased pulmonary vascular resistance among hypertensive BPD patients compared to controls based on echocardiographic measurements [90]. Another investigated explanation is the impaired elastogenesis in preterm infants, which leads to arterial rigidity and impaired vasodilatation [91, 92]. One of the most studied explanations is that the systemic effects of kidney failure negatively affect the developing lungs [94, 95]. The secondary analyses of the AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) and the PENUT (Preterm Erythropoietin Neuroprotection Trial) trials confirmed that preterm infants with AKI have a higher risk of developing BPD. AKI contributes to the development of chronic lung disease through different mechanisms. A discrepancy in fluid and electrolyte homeostasis, extravascular fluid retention and increased capillary alveolar permeability can lead to impaired gas exchange and worsening lung disease. The systemic inflammatory insult caused by AKI can contribute to pulmonary injury and fibrosis. Animal studies also have shown that AKI affects angiogenesis and alveolarisation, leading to a BPD phenotype in experimental animals [96]. Neonates with AKI also have a nearly two times higher risk of developing neonatal hypertension [74]. In our study, the incidence of AKI was significantly greater among patients with three or more hypertensive days, which confirms the role of AKI in the development of BPD and hypertension. Medications commonly used in the treatment of BPD patients might also contribute to the development of systemic hypertension. Nephrocalcinosis as a result of long-term diuretics use or dexamethasone therapy could also lead to systemic hypertension.

A recent study by Farnbach et al. investigated the changing spectrum of neonatal hypertension. Their research showed that most hypertensive neonates with pulmonary and miscellaneous causes had low plasma renin activity and potentially high DEHP exposure [58]. DHEP is used to increase softness and flexibility in plastics. During the treatment of a preterm infant, DEHP can leach out from intravenous bags, infusion and respiratory tubing. MEHP

(Mono(2-ethylhexyl) phthalate), the metabolite of DEHP, inhibits the 11βHSD2 enzyme, resulting in the inhibition of cortisol conversion to cortisone. The consequent mineralocorticoid receptor activation leads to fluid retention and sodium reabsorption, potentially playing a role in the development of hypertension in BPD patients.

7.3. Limitations of the studies

The investigation of normal neonatal blood pressure has some limitations, coming from its retrospective nature. The infants' wakefulness state and the measurement's place are not documented in our electronic records. However, data are collected in natural life circumstances, where the schedule and the quality of the measurements are ensured by following the NICU's corresponding protocols.

Some therapeutic interventions have uncertain effects on blood pressure (e.g., caffeine, nasal CPAP), but they are part of the routine neonatal treatment; therefore, patients receiving them could not have been excluded from the study. We also could not further divide the patients' groups based on non-invasive ventilation data because it would result in several groups with insufficient patients and blood pressure data for a statistical valuation.

Since our data were retrospective, we could only draw limited conclusions on the effect of medications and therapy on blood pressure. An earlier study found a significant increase in blood pressure during dexamethasone therapy, which remained above baseline after treatment [50]. Based on the findings of a recent meta-analysis, a medium cumulative dose of postnatal dexamethasone is associated with a risk of hypertension [51]. On the other hand, several studies investigating hypertension in BPD patients did not demonstrate a hypertensive effect of postnatal steroids on the studied patient groups [52-54]. Most of our BPD patients received postnatal steroids, which might have affected their blood pressure. Since 88.5% of the patients received diuretics due to BPD, this may have influenced the number and length of hypertensive episodes. Previous research on BPD-related blood pressure changes has not detailed the frequency and effect of diuretic therapy on the development of blood pressure changes. There are several general therapies (e.g., blood transfusions, fluid boluses, inotropic support) used during the treatment of preterm infants with BPD, which might cause changes in blood pressure. An extensive and prospective study would be useful to further clarify the effect of these influencing factors. Another limitation of our research is that we had to exclude patients who died from the study since it was not possible to determine their BPD status.

7.4. Suggestion for future research

Although several studies [4-7, 16] investigated normal blood pressure data on newborns, further research is still needed on how maternal and neonatal therapeutic factors and diagnoses affect blood pressure. The retrospective cohort we generated in our first study enables the examination of other factors influencing blood pressure. The previously collected data could be supplemented further by maternal, environmental and neonatal factors. The program developed for data processing and calculation makes it possible to determine the average blood pressure and percentile values of patient groups selected according to other aspects. In the future, we plan to compare our current results with the patient group who received inotropic support and add follow-up data.

The partial steroid administration and its effect on neonatal haemodynamic stability also needs further research.

One of the most exciting questions in investigating neonatal hypertension is the role of environmental factors, such as phthalate. A prospective multicenter study with a large case number would be of great importance in newborn care to be able to eliminate substances causing potentially serious side effects.

A larger, prospective study is needed to investigate the relationship between AKI, BPD, hypertension, and cardiac function. Collecting blood pressure follow-up data from the BPD patient group and investigating daily blood pressure changes in AKI could also improve our understanding of blood pressure changes in preterm infants with different underlying disorders.

8. Conclusions

Based on the results of our two studies, the summary of our key findings is the following:

1. What is the normal blood pressure of a haemodynamically stable neonate? How do neonatal characteristics (birth weight, postnatal age, gestational age) affect neonatal blood pressure?
- We have calculated the normal average blood pressure by gestational age and birth weight for haemodynamically stable preterm and term infants for their first two weeks of life. We found a significant difference between the blood pressure of each gestational age group. Our study provides additional data on how blood pressure varies with birth weight. There is a positive linear correlation between birth weight and blood pressure on the first, third and fifth day of life. The blood pressure differences are significant in the different birth weight groups.
- We generated percentile tables for different gestational ages and birth weights to show 10th, 50th and 90th blood pressure percentiles on the first five days of life. The percentile tables bring new information, as the tables previously calculated by Dionne used the blood pressure measurements only after the second week of life.

2. Does antenatal steroid administration increase neonatal blood pressure after birth?
- No significant blood pressure differences were found between the group with a complete antenatal steroid course and those who received incomplete steroid prophylaxis or did not receive antenatal steroids. We could not prove the antenatal steroid neonatal blood pressure stabilising effect.

3. Does the patient group with moderate and severe BPD have a different blood pressure than the reference data?
- We found a statistically significant correlation between the blood pressure values of the BPD patient group and the reference data. The difference between the blood pressure curve of the group with BPD and the reference group was also statistically significant.

4. Can we detect hypertension by performing individual examinations of BPD patients' blood pressure data?
- We compared the individual BPD patients' average daily blood pressure to the 95th percentile and found that 11 patients (42%) had hypertensive blood pressure values for three or more days within the first 90 days of life. Our statistical analysis showed a 25% chance of acute kidney injury within this group.

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10. References

1. Harer MW, Kent AL (2019) Neonatal hypertension: an educational review. Pediatr Nephrol 34:1009–1018. https://doi.org/10.1007/s00467-018-3996-1
2. Hegyi T, Carbone MT, Anwar M, Ostfeld B, Hiatt M, Koons A, Pinto-Martin J, Paneth N (1994) Blood pressure ranges in premature infants. I. The first hours of life. J Pediatr, 124:627–633. https://doi.org/10.1016/s0022-3476(05)83146-4
3. Kent AL, Meskell S, Falk MC, Shadbolt B (2009) Normative blood pressure data in non-ventilated premature neonates from 28–36 weeks gestation. Pediatr Nephrol 24:141–146. https://doi.org/10.1007/s00467-008-0916-9
4. Kent AL, Kecskes Z, Shadbolt B, Falk MC (2007) Normative blood pressure data in the early neonatal period. Pediatr Nephrol 22:1335–1341. https://doi.org/10.1007/s00467-007-0480-8
5. Pejovic B, Peco-Antic A, Marinkovic-Eric J (2007) Blood pressure in non-critically ill preterm and full-term neonates. Pediatr Nephrol 22:249–257. https://doi.org/10.1007/s00467-006-0311-3
6. Batton B, Li L, Newman N, Das A, Watterberg KL, Yoder BA, Faix RG, Laughon MM, Stoll BJ, Higgins RD, Walsh MC, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (2014) Evolving blood pressure dynamics for extremely preterm infants. J Perinatol 34:301–305. https://doi.org/10.1038/jp.2014.6
7. Zubrow AB, Hulman S, Kushner H, Falkner B (1995) Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. J Perinatol 15:470–479. PMID: 864
8. Lurbe E, Garcia-Vicent C, Torro I, Fayos JL, Aguilar F, de Llano JM, Fuertes G, Redon J (2007) First-year blood pressure increase steepest in low birthweight newborns. J Hypertension 25: 81-86. https://doi: 10.1097/HJH.0b013e32801040ec
9. Georgieff MK, Mills MM, Gómez-Marín O, Sinaiko AR (1996) Rate of change of blood pressure in premature and full term infants from birth to 4 months. Pediatr Nephrol 10:152-155. https://doi:10.1007/BF00862059
10. de Swiet M, Fayers P, Shinebourne EA (1980) Systolic Blood Pressure in a Population of Infants in the First Year of Life: The Brompton Study. Pediatrics 65:1028-1035. PMID: 7367116.
11. Alonzo CJ, Nagraj VP, Zschaebitz JV, Lake DE, Moorman JR, Spaeder MC (2020) Blood pressure ranges via non-invasive and invasive monitoring techniques in premature neonates using high resolution physiologic data. J Neonatal Perinatal Med 13:351–358. https://doi.org/10.3233/NPM-190260
12. van Zadelhoff AC, Poppe JA, Willemsen S, Mauff K, van Weteringen W, Goos TG, Reiss IKM, Vermeulen MJ, de Graaff JC (2023) Age-dependent changes in arterial blood pressure in neonates during the first week of life: reference values and development of a model. Br Journal Anaesth 130:585–594. https://doi.org/10.1016/j.bja.2023.01.024
13. Elsayed Y, Ahmed F (2024) Blood pressure normative values in preterm infants during postnatal transition. Pediatr Res 95:698–704. https://doi.org/10.1038/s41390-023-02788-8
14. Kent AL, Kecskes Z, Shadbolt B, Falk MC (2007) Blood pressure in the first year of life in healthy infants born at term. Pediatr Nephrol 22:1743–1749. https://doi.org/10.1007/s00467-007-0561-8

15. Vesoulis ZA, El Ters NM, Wallendorf M, Mathur AM (2016) Empirical estimation of the normative blood pressure in infants <28 weeks gestation using a massive data approach. J Perinatol 36:291–295. https://doi.org/10.1038/jp.2015.185
16. Dionne JM, Abitbol CL, Flynn JT (2012) Hypertension in infancy: diagnosis, management and outcome. Pediatr Nephrol 27:17–32. https://doi.org/10.1007/s00467-010-1755-z
17. Rabe H Bhatt-Mehta V, Bremner SA, Ahluwalia A, Mcfarlane R, Baygani S, Batton B, Klein A, Ergenekon E, Koplowitz LP, Dempsey E, Apele-Freimane D, Iwami H, Dionne JM, International Neonatal Consortium (2021) Antenatal and perinatal factors influencing neonatal blood pressure: a systematic review. J Perinatol 41:2317–2329. https://doi.org/10.1038/s41372-021-01169-5
18. Batton B. (2020) Neonatal Blood Pressure Standards: What Is "Normal"? Clin Perinatol 47:469–485. https://doi.org/10.1016/j.clp.2020.05.008
19. Gillman MW, Rich-Edwards JW, Rifas-Shiman SL, Lieberman ES, Kleinman KP, Lipshultz SE (2004) Maternal age and other predictors of newborn blood pressure. J Pediatr 144:240-245. https://doi:10.1016/j.jpeds.2003.10.064
20. Sedaghat N, Ellwood D, Shadbolt B, et al. (2008) The effect of mode of delivery and anaesthesia on neonatal blood pressure. Aust N Z J Obstet Gynaecol 48:172-178. https://doi:10.1111/j.1479-828X.2008.00832.x
21. Sadoh WE, Ibhanesehbor SE, Monguno AM, Gubler DJ (2010) Predictors of newborn systolic blood pressure. West Afr J Med. 29:86-90.
22. Hegyi T, Anwar M, Carbone MT, et al. (1996) Blood pressure ranges in premature infants: II. The first week of life. Pediatrics 97:336-342.
23. Kent AL, Shadbolt B, Hu E, Meskell S, Falk MC, Dahlstrom JE (2009) Do maternal- or pregnancy-associated disease states affect blood pressure in the early neonatal period? Aust N Z J Obstet Gynaecol 49:364-370. https://doi:10.1111/j.1479-828X.2009.01018.x
24. Mausner JS, Hiner LB, Hediger ML, Gabrielson MO, Levison SP (1983) Blood pressure of infants of hypertensive mothers: a two-year follow-up. Int J Pediatr Nephrol 4:255-261.
25. Beratis NG, Panagoulias D, Varvarigou A (1996) Increased blood pressure in neonates and infants whose mothers smoked during pregnancy. J Pediatr 128:806-812. https://doi:10.1016/s0022-3476(96)70333-5
26. Demarini S, Dollberg S, Hoath SB, Ho M, Donovan EF (1999) Effects of antenatal corticosteroids on blood pressure in very low birth weight infants during the first 24 hours of life. J Perinatol 19:419-425. https://doi.org/10.1038/sj.jp.7200245
27. Moïse AA, Wearden ME, Kozinetz CA, Gest AL, Welty SE, Hansen TN (1995) Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. Pediatrics 95:845-850.
28. Been JV, Kornelisse RF, Rours IG, Lima Passos V, De Krijger RR, Zimmermann LJ (2009) Early postnatal blood pressure in preterm infants: effects of chorioamnionitis and timing of antenatal steroids. Pediatr Res 66:571-576. https://doi:10.1203/PDR.0b013e3181b7c4da
29. LeFlore JL, Engle WD, Rosenfeld CR (2000) Determinants of blood pressure in very low birth weight neonates: lack of effect of antenatal steroids. Early Hum Dev 59:37–50. https://doi:10.1016/s0378-3782(00)00083-9
30. Dötsch J, Hohmann M, Kühl PG (1997) Neonatal morbidity and mortality associated with maternal haemolysis elevated liver enzymes and low platelets syndrome. Eur J Pediatr 156:389-391. https://doi:10.1007/s004310050621

31. Chourdakis E, Fouzas S, Papadopoulou C, et al. (2020) Effect of Early-Onset Preeclampsia on Offspring's Blood Pressure during the First Month of Life. J Pediatr 220:21-26.e1. https://doi:10.1016/j.jpeds.2020.01.033
32. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L (2019) Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. The Cochrane database of systematic reviews, 9(9), CD003248. https://doi.org/10.1002/14651858.CD003248.pub4
33. Schenone CV, Argoti P, Goedecke P, Mari G (2022) Neonatal blood pressure before and after delayed umbilical cord clamping. J Matern Fetal Neonatal Med 35:5260-5264. https://doi:10.1080/14767058.2021.1876656
34. Mercer JS, McGrath MM, Hensman A, Silver H, Oh W (2003) Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. J Perinatol 23:466-472. https://doi:10.1038/sj.jp.7210970
35. Zinner SH, Lee YH, Rosner B, Oh W, Kass EH (1980) Factors affecting blood pressures in newborn infants. Hypertension 2:99-101.
36. Schachter J, Kuller LH, Perfetti C (1982) Blood pressure during the first two years of life. Am J Epidemiol 116:29-41. https://doi:10.1093/oxfordjournals.aje.a113400
37. Vesoulis ZA, El Ters NM, Wallendorf M, Mathur AM (2016) Empirical estimation of the normative blood pressure in infants <28 weeks gestation using a massive data approach. J Perinatol 36:291-295. https://doi:10.1038/jp.2015.185
38. Geerts CC, Grobbee DE, van der Ent CK, et al. (2007) Tobacco smoke exposure of pregnant mothers and blood pressure in their newborns: results from the wheezing illnesses study Leidsche Rijn birth cohort. Hypertension 50:572-578. https://doi:10.1161/HYPERTENSIONAHA.107.091462
39. Mildenhall L, Battin M, Bevan C, Kuschel C, Harding JE (2009) Repeat prenatal corticosteroid doses do not alter neonatal blood pressure or myocardial thickness: randomized, controlled trial. Pediatrics 123:646-652. https://doi:10.1542/peds.2008-1931
40. Rantone TH, Grönlund JU, Jalonen JO, et al. (2002) Comparison of the effects of antenatal magnesium sulphate and ritodrine exposure on circulatory adaptation in preterm infants. Clin Physiol Funct Imaging 22:13-17. https://doi:10.1046/j.1475-097x.2002.00387.x
41. Yanowitz TD, Jordan JA, Gilmour CH, et al. (2002) Hemodynamic disturbances in premature infants born after chorioamnionitis: association with cord blood cytokine concentrations. Pediatr Res 51:310-316. https://doi:10.1203/00006450-200203000-00008
42. Emery EF, Greenough A, Yuksel B (1993) Effect of gender on blood pressure levels of very low birthweight infants in the first 48 hours of life. Early Hum Dev 31:209–216. https://doi.org/10.1016/0378-3782(93)90196-2
43. Dagle JM, Fisher TJ, Haynes SE, Berends SK, Brophy PD, Morriss FH, Jr Murray JC (2011) Cytochrome P450 (CYP2D6) genotype is associated with elevated systolic blood pressure in preterm infants after discharge from the neonatal intensive care unit. J Pediatr 159:104–109. https://doi.org/10.1016/j.jpeds.2011.01.002
44. Capri Y, Kwon T, Boyer O, Bourmance L, Testa N, Baudouin V, Bonnefoy R, Couderc A, Meziane C, Tournier-Lasserve E, Heidet L, Melki J (2023) Biallelic NPR1 loss of function variants are responsible for neonatal systemic hypertension. J Med Genet 60:993–998. https://doi.org/10.1136/jmg-2023-109176
45. Soloveychik V, Bin-Nun A, Ionchev A, Sriram S, Meadow W (2009) Acute hemodynamic effects of caffeine administration in premature infants. J Perinatol 29:205-208. https://doi:10.1038/jp.2008.193

46. Hassanein SM, Gad GI, Ismail RI, Diab M (2015) Effect of caffeine on preterm infants' cerebral cortical activity: an observational study. J Matern Fetal Neonatal Med 28:2090-2095. https://doi:10.3109/14767058.2014.978757
47. Walther FJ, Erickson R, Sims ME (1990) Cardiovascular effects of caffeine therapy in preterm infants. Am J Dis Child. 144:1164-1166. https://doi:10.1001/archpedi.1990.02150340110035
48. Hoecker C, Nelle M, Poeschl J, Beedgen B, Linderkamp O (2002) Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. Pediatrics 109:784-787. https://doi:10.1542/peds.109.5.784
49. de Waal KA, Evans N, Osborn DA, Kluckow M (2007) Cardiorespiratory effects of changes in end expiratory pressure in ventilated newborns. Arch Dis Child Fetal Neonatal Ed 92:F444–F448. https://doi.org/10.1136/adc.2006.103929
50. Marinelli KA, Burke GS, Herson VC (1997) Effects of dexamethasone on blood pressure in premature infants with bronchopulmonary dysplasia. J Pediatr 130:594–602. https://doi.org/10.1016/s0022-3476(97)70244-0
51. Ramaswamy VV, Bandyopadhyay T, Nanda D, Bandiya P, Ahmed J, Garg A, Roehr CC, Nangia S (2021) Assessment of Postnatal Corticosteroids for the Prevention of Bronchopulmonary Dysplasia in Preterm Neonates: A Systematic Review and Network Meta-analysis. JAMA Pediatr 175:e206826. https://doi.org/10.1001/jamapediatrics.2020.6826
52. Alagappan A, Malloy MH (1998) Systemic hypertension in very low-birth weight infants with bronchopulmonary dysplasia: incidence and risk factors. Am J Perinatol 15:3–8. https://doi.org/10.1055/s-2007-993889
53. Anderson AH, Warady BA, Daily DK, Johnson JA, Thomas MK (1993) Systemic hypertension in infants with severe bronchopulmonary dysplasia: associated clinical factors. Am J Perinatol 10:190–193. https://doi.org/10.1055/s-2007-994716
54. Sehgal A, Elsayed K, Nugent M, Varma S (2022) Sequelae associated with systemic hypertension in infants with severe bronchopulmonary dysplasia. J Perinatol 42:775–780. https://doi.org/10.1038/s41372-022-01372-y
55. Mohamed TH, Klamer B, Mahan JD, Spencer JD, Slaughter JL (2021) Diuretic therapy and acute kidney injury in preterm neonates and infants. Pediatr Nephrol 36:3981–3991. https://doi.org/10.1007/s00467-021-05132-6
56. Segar J, Jetton JG (2021) Diuretic use, acute kidney injury, and premature infants: the call for evidence-based guidelines. Pediatr Nephrol 36:3807–3811. https://doi.org/10.1007/s00467-021-05201-w
57. Guignard JP, Iacobelli S (2021) Use of diuretics in the neonatal period. Pediatr Nephrol 36:2687–2695. https://doi.org/10.1007/s00467-021-04921-3
58. Farnbach K, Iragorri S, Al-Uzri A, Rozansky D, Forbush R, Jenkins R (2019) The changing spectrum of hypertension in premature infants. J Perinatol 39:1528–1534. https://doi.org/10.1038/s41372-019-0457-z
59. Jenkins R, Tackitt S, Gievers L, Iragorri S, Sage K, Cornwall T, O'Riordan D, Merchant J, Rozansky D (2019) Phthalate-associated hypertension in premature infants: a prospective mechanistic cohort study. Pediatr Nephrol 34:1413–1424. https://doi.org/10.1007/s00467-019-04244-4
60. Abman SH, Warady BA, Lum GM, Koops BL (1984) Systemic hypertension in infants with bronchopulmonary dysplasia. J Pediatr 104:928–931. https://doi.org/10.1016/s0022-3476(84)80501-6
61. Jenkins RD, Aziz JK, Gievers LL, Mooers HM, Fino N, Rozansky DJ (2017) Characteristics of hypertension in premature infants with and without chronic lung

disease: a long-term multi-center study. Pediatr Nephrol 32:2115–2124. https://doi.org/10.1007/s00467-017-3722-4
62. Starr MC, Wilson AC (2022) Systemic Hypertension in Infants with Bronchopulmonary Dysplasia. Curr Hypertens Rep 24:193–203. https://doi.org/10.1007/s11906-022-01179-4
63. Siffel C, Kistler KD, Lewis JFM, Sarda SP (2021) Global incidence of bronchopulmonary dysplasia among extremely preterm infants: a systematic literature review. J Matern Fetal Neonatal Med 34:1721–1731. https://doi.org/10.1080/14767058.2019.1646240
64. Szabó H, Baraldi E, Colin AA (2022) Corticosteroids in the prevention and treatment of infants with bronchopulmonary dysplasia: Part I. systemic corticosteroids. Pediatr Pulmonol 57:600–608. https://doi.org/10.1002/ppul.25805
65. Emery EF, Greenough A (1992) Neonatal blood pressure levels of preterm infants who did and did not develop chronic lung disease. Early Hum Dev 31:149–156. https://doi.org/10.1016/0378-3782(92)90041-e
66. Greenough A, Emery EF (1993) Effect of chronic lung disease on blood pressure levels at follow up. Eur J Pediatr 152:516–518. https://doi.org/10.1007/BF01955063
67. Butt WW, Whyte H (1984) Blood pressure monitoring in neonates: comparison of umbilical and peripheral artery catheter measurements. J Pediatr 105:630-632. https://doi:10.1016/s0022-3476(84)80437-0
68. O'Shea J, Dempsey EM (2009) A comparison of blood pressure measurements in newborns. Am J Perinatol 26:113–116. https://doi.org/10.1055/s-0028-1091391
69. Dannevig I, Dale HC, Liestøl K, Lindemann R (2005) Blood pressure in the neonate: three non-invasive oscillometric pressure monitors compared with invasively measured blood pressure. Acta Paediatr. 94:191-196. https://doi:10.1111/j.1651-2227.2005.tb01889.x
70. Shah S, Kaul A, Khandare J, Dhalait S (2021) Comparison of Invasive Arterial Blood Pressure Monitoring vs. Non-Invasive Blood Pressure Monitoring in Preterm Infants < 37 Weeks in the Neonatal Intensive Care Unit- A Prospective Observational Study. J Trop Pediatr 67:fmab109. https://doi.org/10.1093/tropej/fmab109
71. Dionne JM, Bremner SA, Baygani SK, Batton B, Ergenekon E, Bhatt-Mehta V, Dempsey E, Kluckow M, Pesco Koplowitz L, Apele-Freimane D, Iwami H, Klein A, Turner M, Rabe H, International Neonatal Consortium (2020) Method of Blood Pressure Measurement in Neonates and Infants: A Systematic Review and Analysis. J Pediatr 221: 23–31.e5. https://doi.org/10.1016/j.jpeds.2020.02.072
72. Nwankwo MU, Lorenz JM, Gardiner JC (1997) A standard protocol for blood pressure measurement in the newborn. Pediatrics 99:E10. https://doi.org/10.1542/peds.99.6.e10
73. Gupta JM, Scopes JW (1965) Observations on blood pressure in newborn infants. Arch Dis Child. 40:637-644. https://doi:10.1136/adc.40.214.637
74. Kraut EJ, Boohaker LJ, Askenazi DJ, Fletcher J, Kent AL, Neonatal Kidney Collaborative (NKC) (2018) Incidence of neonatal hypertension from a large multicenter study [Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates-AWAKEN]. Pediatr Res 84:279–289. https://doi.org/10.1038/s41390-018-0018-8
75. Singh HP, Hurley RM, Myers TF (1992) Neonatal hypertension. Incidence and risk factors. Am J Hypertens 5:51–55. https://doi.org/10.1093/ajh/5.2.51
76. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM, SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN (2017) Clinical Practice Guideline for Screening and Management of High Blood

Pressure in Children and Adolescents. Pediatrics 140:e20171904. https://doi.org/10.1542/peds.2017-1904
77. Flynn J (2019) Neonatal hypertension: Diagnosis and Management. In: Oh W, Baum M, Polin RA (eds.) Neonatology questions and controversies: Nephrology and fluid/electrolyte physiology, 3rd edn. Elsevier, Philadelphia, pp 255–270
78. Gaffar S, Ramanathan R, Easterlin MC (2024) Common Clinical Scenarios of Systemic Hypertension in the NICU. NeoReviews 25:e36–e49. https://doi.org/10.1542/neo.25-1-e36
79. Hjorten R, Flynn JT (2022) Neonatal Hypertension. Clin Perinatol 49:27–42. https://doi.org/10.1016/j.clp.2021.11.003
80. Friedman AL, Hustead VA (1987) Hypertension in babies following discharge from a neonatal intensive care unit. A 3-year follow-up. Pediatr Nephrol 1:30-34. https://doi:10.1007/BF00866881
81. Blowey DL, Duda PJ, Stokes P, Hall M (2011) Incidence and treatment of hypertension in the neonatal intensive care unit. J Am Soc Hypertens. 5:478-483. https://doi:10.1016/j.jash.2011.08.001
82. Xiao N, Starr M, Stolfi A, Hamdani G, Hashmat S, Kiessling SG, Sethna C, Kallash M, Matloff R, Woroniecki R, Sanderson K, Yamaguchi I, Cha SD, Semanik MG, Chanchlani R, Flynn JT, Mitsnefes M (2024) Blood Pressure Outcomes in NICU-Admitted Infants with Neonatal Hypertension: A Pediatric Nephrology Research Consortium Study. J Pediatr 264:113765. https://doi.org/10.1016/j.jpeds.2023.113765
83. Committee on Obstetric Practice (2017) Committee Opinion No. 713:Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol 130:e102-e109. https://doi.org/10.1097/AOG.0000000000002237
84. Jobe AH, Bancalari E (2001) Bronchopulmonary dysplasia. Am J Respir Crit Care Med 163:1723–1729. https://doi.org/10.1164/ajrccm.163.7.2011060
85. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K, National Institutes of Child Health and Human Development Neonatal Research Network (2005) Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 116:1353–1360. https://doi.org/10.1542/peds.2005-0249
86. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, Kirpalani H, Laughon MM, Poindexter BB, Duncan AF, Yoder BA, Eichenwald EC, DeMauro SB (2019) The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. Am J Respir Crit Care Med 200:751–759. https://doi.org/10.1164/rccm.201812-2348OC
87. Starr MC, Charlton JR, Guillet R, Reidy K, Tipple TE, Jetton JG, Kent AL, Abitbol CL, Ambalavanan N, Mhanna MJ, Askenazi DJ, Selewski DT, Harer MW, Neonatal Kidney Collaborative Board (2021) Advances in Neonatal Acute Kidney Injury. Pediatrics 148:e2021051220. https://doi.org/10.1542/peds.2021-051220
88. Baker MD, Maisels MJ, Marks KH. (1984) Indirect BP monitoring in the newborn. Evaluation of a new oscillometer and comparison of upper- and lower-limb measurements. Am J Dis Child 138:775-778. https://doi:10.1001/archpedi.1984.02140460065021
89. Crossland DS, Furness JC, Abu-Harb M, Sadagopan SN, Wren C (2004) Variability of four limb blood pressure in normal neonates. Arch Dis Child Fetal Neonatal Ed 89:F325-F327. https://doi:10.1136/adc.2003.034322
90. Reyes-Hernandez ME, Bischoff AR, Giesinger RE, Rios DR, Stanford AH, McNamara PJ (2024) Echocardiography Assessment of Left Ventricular Function in Extremely Preterm Infants, Born at Less Than 28 Weeks' Gestation, With Bronchopulmonary

Dysplasia and Systemic Hypertension. J Am Soc Echocardiogr 37:237–247. https://doi.org/10.1016/j.echo.2023.08.013
91. Sehgal A, Malikiwi A, Paul E, Tan K, Menahem S (2016) Systemic arterial stiffness in infants with bronchopulmonary dysplasia: potential cause of systemic hypertension. J Perinatol 36:564–569. https://doi.org/10.1038/jp.2016.10
92. Crisafulli A, Bassareo PP, Kelleher S, Calcaterra G, Mercuro G (2020) Factors Predisposing to Hypertension in Subjects Formerly Born Preterm: Renal Impairment, Arterial Stiffness, Endothelial Dysfunction or Something Else? Curr Hypertens Rev 16:82–90. https://doi.org/10.2174/1573402115666190627140523
93. Gievers LL, Jenkins RD, Laird A, Macedo MC, Schilling D, McEvoy CT (2019) Pulmonary Function and Systolic Blood Pressure in Very Low Birth Weight Infants at 34 - 36 Weeks of Corrected Age. Res Rep Neonatol 9:21–30. https://doi.org/10.2147/rrn.s208194
94. Starr MC, Boohaker L, Eldredge LC, Menon S, Griffin R, Mayock DE, Li L, Askenazi D, Hingorani S, Neonatal Kidney Collaborative (2020) Acute Kidney Injury and Bronchopulmonary Dysplasia in Premature Neonates Born Less than 32 Weeks' Gestation. Am J Perinatol 37:341–348. https://doi.org/10.1055/s-0039-3400311
95. Starr MC, Schmicker RH, Halloran BA, Heagerty P, Brophy P, Goldstein SL, Juul SE, Hingorani S, Askenazi DJ, PENUT Trial Consortium (2023) Premature infants born <28 weeks with acute kidney injury have increased bronchopulmonary dysplasia rates. Pediatr Res 94:676–682. https://doi.org/10.1038/s41390-023-02514-4
96. Liberio BM, Seedorf G, Soranno DE, Montford JR, Faubel SG, Hernandez A, Abman SH, Gien J (2023) Acute kidney injury decreases pulmonary vascular growth and alveolarisation in neonatal rat pups. Pediatr Res 10.1038/s41390-023-02625-y. *94*:1308–1316. https://doi.org/10.1038/s41390-023-02625-y