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Age-dependent changes in arterial blood pressure in neonates during the first week of life: reference values and development of a model

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Abstract

Background: Arterial pressure measurements are important to monitor vital function in neonates, and values are known to be dependent of gestational and postnatal age. Current reference ranges for mean arterial pressure in neonates have been derived from small samples and combined data of noninvasive and invasive measurements. We aimed to define reference values for noninvasive mean, systolic, and diastolic blood pressure during the first week of life in otherwise healthy preterm and term neonates defined by gestational and postnatal age.

Methods: In this retrospective cohort study in a neonatal intensive care unit (NICU) in a Dutch tertiary paediatric hospital, we included the noninvasive blood pressures of neonates admitted between 2016 and 2018, with exclusion of those with severe comorbidities (major cardiac malformations, intracerebral haemorrhage, and tracheal intubation >6 h). We defined the median (P50) with −2 standard deviations (SD) (P0.23), −1 SD (P16), +1 SD (P84), and +2 SD (P97.7) for gestational age and postnatal age using quantile regression, percentiles provided online (http://bloodpressure-neonate.com/).

Results: A total of 607 neonates, with 5885 measurements, fulfilled the inclusion criteria. The P50 values of mean noninvasive arterial blood pressure in extreme preterm infants steeply increased during the first day after birth and gradually increased within a week from 27 to 49 mm Hg at 24 h of gestational age, and from 49 to 61 mm Hg at 41 weeks of gestational age.

Conclusions: These reference values for noninvasive blood pressure in neonates in the NICU for various gestational age groups provide guidance for clinical decision-making in healthy and diseased neonates during anaesthesia and sedation.

Keywords: arterial pressure; haemodynamics; neonatal intensive care; paediatric anaesthesia; premature birth; reference values

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Editor's key pointss

- Arterial pressure measurement is an important physiological monitor of vital function in neonates, but current reference ranges are poorly defined.
- Reference values for noninvasive mean, systolic, and diastolic arterial pressure were analysed during the first week of life in otherwise healthy preterm and term neonates.
- Based on arterial pressure measurements from 607 neonates, mean noninvasive arterial pressure steeply increased during the first day after birth, and gradually increased within a week and more slowly after that based on gestational age.
- Reference values for changes in noninvasive blood pressure in neonates by gestational age provide guidance for clinical decision-making in healthy and diseased neonates.

Arterial blood pressure is an essential parameter in monitoring preterm and term newborns' cardiovascular function. Both hypotension and hypertension are associated with worse clinical outcome because of the risk for intracerebral ischaemia, haemorrhage, or both.[1,2] There are large variations in the definition of hypotension and hypertension in neonates in the neonatal intensive care unit (NICU).[3,4] Systematic reviews conclude that there is a paucity of reliable reference ranges owing to the limited validity because of current reference ranges based on small sample sizes, combined use of oscillometric noninvasive blood pressure (NIBP) and invasive arterial pressure measurements, and lack of consideration of factors such as gestational age, weight, medications, and maternal factors.[3,5,6] The commonly used guide for minimum mean arterial pressure (MAP) in sedated neonates in the NICU and during anaesthesia is equal to the postmenstrual age in weeks based on consensus.[4,7] Our group has defined reference values for arterial pressure for children between 0 and 18 years of age under anaesthesia in relation to weight, length, and age.[8] However, these reference values are not applicable to neonates because they were developed for patients at an older age and higher weight and did not consider potential influential factors such as gestational age at birth. We therefore conducted a study aimed to define evidence-based reference values for noninvasive mean, systolic and diastolic arterial pressures during the first week of life for neonates at various gestational ages in the NICU. We also make these results available through an open access online interactive calculator.

Methods

In this retrospective cohort study, we analysed arterial pressure measurements made in the first week of life in otherwise healthy preterm and term neonates. All neonates admitted to the NICU of a specialised paediatric tertiary referral university hospital (Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands) between July 1, 2016 and July 1, 2018 were screened for eligibility. The study was approved by the institutional medical ethics committee (MEC-2017-1114). Based on the observational nature of the study, a waiver for parental informed consent was given.

Patient characteristics were obtained from the electronic health records system (HiX, Chipsoft, Amsterdam, The Netherlands) and included gestational age, date and time of birth, sex, and weight. Gestational age had been established according to international consensus from ultrasound study or duration of amenorrhoea.[9] Inotropic usage, sedation, and tracheal intubation details were obtained from the NICU patient data management system (PICIS Clinical Solutions S.A., Barcelona, Spain).

Maternal factors relevant to the neonatal initial arterial pressures included occurrence of diabetes (mellitus and gravidarum), hypertension, pre-eclampsia (and HELLP syndrome), and antibiotic administration shortly before or during labour. Birth-related factors included mode of delivery (vaginal or Caesarean delivery), usage of vacuum extraction or forceps, APGAR scores at 1, 5, and 10 min postpartum, and umbilical arterial cord blood pH and base excess. From November 2017, protocol driven delayed cord clamping was gradually implemented at our institution.[10] This protocol comprised a 3 min delay in cord clamping in patients with gestational age ≥35 weeks and 1 min in patients with gestational age <35 weeks.

The local protocol prescribes an arterial line in all patients <26 weeks of gestational age, for routine continuous invasive arterial blood pressure (IABP) measurement and blood sampling. Patients with gestational age ≥26 weeks only received arterial access based on individual indication at the discretion of the attending physician.

Inclusion criteria were all patients for whom vital sign data were available, who were not continuously administered sedatives, and were haemodynamically stable during the first week of life. As invasive arterial monitoring was routine in all patients with gestational age <26 weeks, invasive monitoring simultaneously with noninvasive monitoring was not an exclusion criterion in that group.

Exclusion criteria were neonates who met any of the following criteria: (septic) shock in the first 8 days of life requiring inotropes, major congenital cardiac malformations (defined as those with haemodynamic consequences on echocardiography), presence or high suspicion of genetic or other severe congenital disorders, severe intracerebral bleeding (intraventricular haemorrhage) with Papile-Burstein class II or higher,[11] necrotising enterocolitis Bell stage 2 or higher, heart rhythm disorders, asphyxia, maternal drug abuse, persistent pulmonary hypertension in the neonate, or surgery or death in the first week of life. Neonates with gestational age ≥26 weeks who had invasive arterial pressure measurements in the first 9 days of life were excluded, as haemodynamic instability is the most common indication for such monitoring in this group. The timeframes that the patients were intubated for surfactant administration according to the INSURE method were excluded.[12] Tracheal intubation with mechanical ventilation episodes was logged in the patient data management system, and these timeframes were excluded.

According to clinical local protocol, noninvasive arterial pressure measurements were made at least once every 2 h in the first 24 h after birth and once every 24 h after the first 24 h. Noninvasive arterial pressure was measured with an oscillometric method using Dräger Infinity® M540 monitors, and values were obtained from the patient monitoring system log files (*Dräger Infinity Acute Care System Medical Cockpit*, Drägerwerk, Lübeck, Germany). LabVIEW (National Instruments Corporation, Austin, TX, USA) software was used to process and sort patient monitor log files. Data were first extracted from the archives and filtered to contain only data from the first week of life.

In order to reduce the influence of outliers, we applied a median filter to reduce potential errors.[13] In clinical practice, unrealistic low or high values are usually followed by repeating the measurements. The nurse doing the measurement simply does not 'trust' the values and checks it again. To refrain from arbitrary and subjective definitions of outliers, we applied a median filter that is a well-known order statistical method with good performance to reduce noise.[14] If an individual patient provided more than one data point in 1 h, the median value was calculated and used in the analysis instead of a single value. Analysis was performed in the statistical package R (R Foundation for Statistical Computing, Vienna, Austria).

The reference curves for systolic, diastolic, and mean arterial pressures were based on quantile regression to estimate each quantile as a function of gestational age at birth, postnatal age, and so-called asymmetry, which determines the percentile being estimated. Mathematically quantile regression deals with optimisation in which the parameters of the quantile function are selected to minimise the weighted absolute distance between observations and quantiles by iteratively using a weighted quadratic approximation.[15,16] Quantiles were modelled as a product of B-spline bases of gestational age at birth, postnatal age, and the asymmetry, which is a statistical technique that allows incorporation of non-linearity and interactions between covariates. Smoothness[17] and monotonicity[18] constraints were enforced by placing penalties on the coefficients of the model. The optimal value of the penalties that regulate smoothness was estimated by cross-validation. Not all children received the same number of blood pressure measurements for the same time period. To limit bias by selective missingness, we used a form of inverse probability weighing in which we included the observation probabilities of gestational age at birth, postnatal age, birth weight, the trend and slope of individual blood pressure profiles, and previous blood pressure as covariates.[19] We present and plot the standard deviation scores (SD) based on European practice which corresponds with the percentile curves (P) for −2 SD (P02.3), −1 SD (P16), median (P50), +1 SD (P84), and +2 SD (P97.7) for systolic, mean, and diastolic noninvasive arterial pressure curves for the first 7 days for each full week of gestational age at birth. Patient characteristics are presented as median with inter-quartile rage (IQR) or as number with percentage (%).

Results

Of 1215 neonates admitted over 2 years, 141 were excluded because of insufficient data, and 467 neonates met the exclusion criteria (Fig 1), leaving 607 neonates, with gestational age ranging from 24 to 41 weeks, in the analysis. After exclusion of 175 h (2.5%) of INSURE time among 159 neonates, this resulted in 5885 NIBP measurements (Fig 2). Our sample consisted of 56% males and 22% multiple births, with a median gestational age of 33 weeks (IQR: 30–37, Fig 2). Birth weight ranged from 578 to 6310 g, median 1955 g (IQR: 1430–2890 g, Table 1); APGAR score at 10 min postpartum was 8 or higher in 89% of neonates. Median duration of admission to NICU was 4.4 days (IQR 2.5–7.5 days). The total admission duration of the study cohort by gestational age is presented in Supplementary Table S1.

The interplay between gestational age, postnatal age, and blood pressure is illustrated in a 3-dimensional mesh type plot (Fig 3). The median MAP increased from 23 mm Hg directly after birth to 35 mm Hg after 1 week of age at 24 weeks' gestational age, and from 46 mm Hg to 68 mm Hg at 41 weeks' gestational age (Fig 4). The range from P02.3 to P97.7 of MAP varied from 16 to 34 mm Hg at gestational age 24 weeks directly after birth, and from 56 mm Hg to 74 mm Hg at gestational age 41 weeks at Day 7.

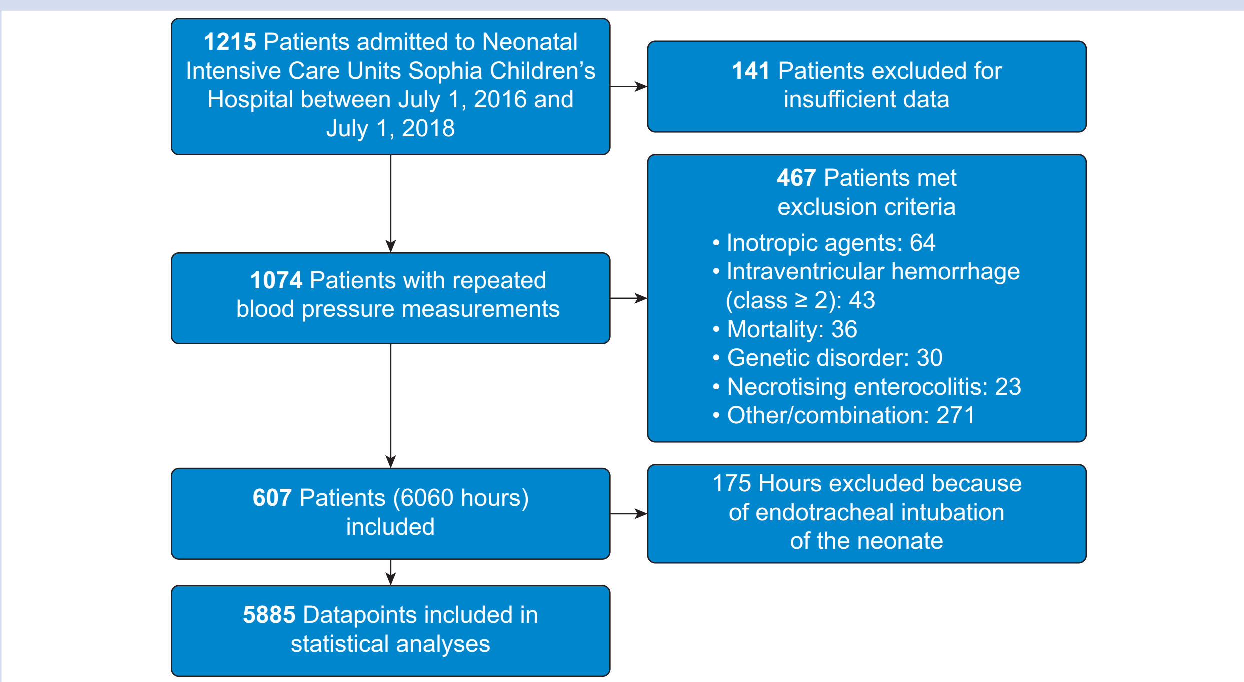

Fig 1. Flowchart of the study group and data included.

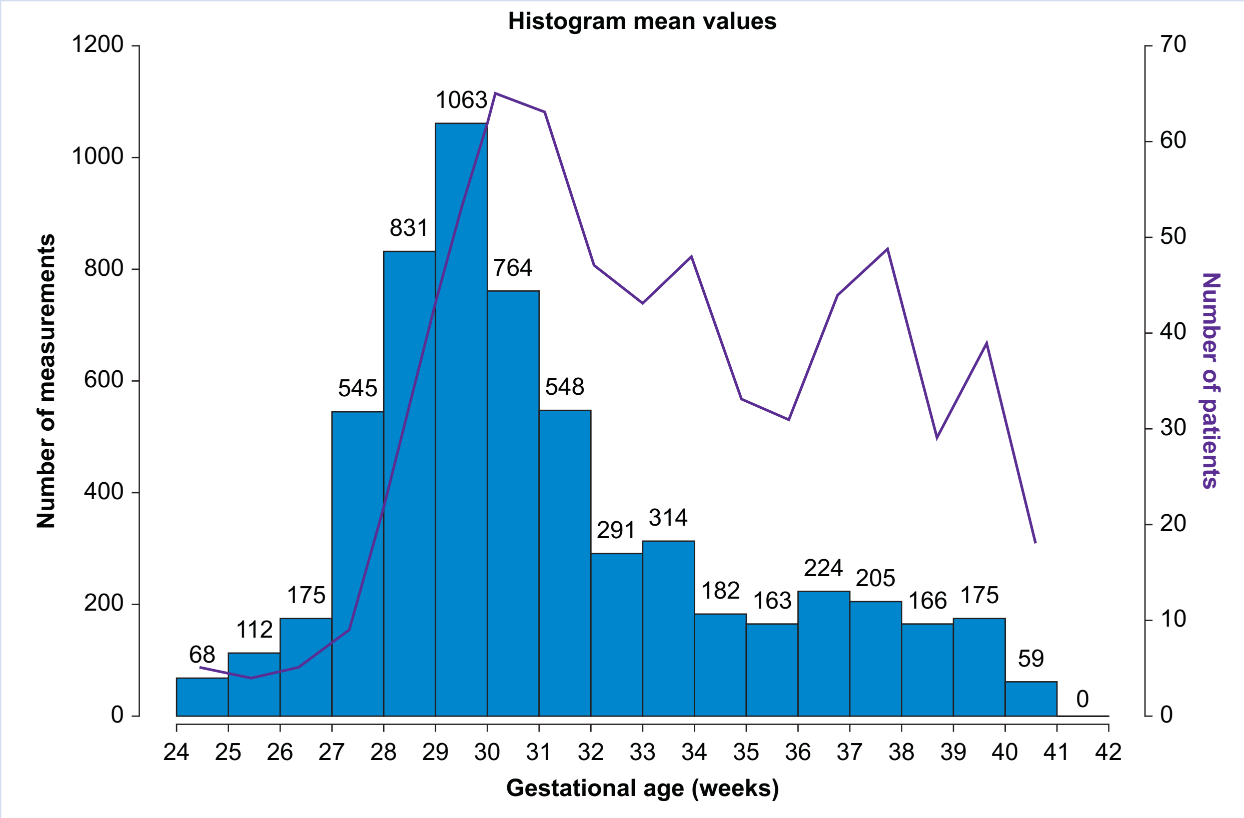

Fig 2. Histogram of number of patients and arterial pressure measurements. Number of measurement boxes on the left y-axis and number of patients in purple line on the right y-axis in relation to gestational age in weeks at birth.

Mean and diastolic arterial pressure rapidly increased within the first day in the lowest gestational age (24–32 weeks) group; the curves flatten thereafter. This observation was most pronounced in the patients with the lowest gestational age. The rapid increase in diastolic arterial pressure within the first hours after birth occurred in all gestational age groups. The systolic arterial pressure showed a more gradual increase within the first 48 h after birth in gestational age groups 24 until 33 weeks with a near linear increase in the older gestational age groups (Fig 4). The reference values for individual neonates according to our model can be found on a website incorporating gestational and chronologic age at http://bloodpressure-neonate.com/.

Discussion

The present model describes in detail the course of noninvasive arterial blood pressure during the first week of life in preterm and term infants born between 24 and 41 weeks of gestational age in the NICU. A website provides easily accessible data on the reference ranges, with percentile values for each gestational age for the first week of life. The sample represents blood pressure values of low acuity NICU patients and might therefore not be generalisable to infants with severe morbidity. Current standards for awake neonates of various ages will be helpful in determining what blood pressures are acceptable under anaesthesia and for diseased neonates in neonatal and paediatric intensive care. However, the reference values obtained in relatively healthy premature neonates cannot be directly converted to neonates under sedation or general anaesthesia.

Previous research has presented several reference tables or curves for blood pressure in neonates.[6,20–23] These papers have limited practical value to the preterm neonate population, because they were either based on small samples with few measurements, describe MAP of term infants only, include values of neonates who received vasoactive drugs, or were based on a mixture of invasive and noninvasive values, or were not translated to graphs. Therefore, in clinical practice many anaesthesiologists use, as a rule of thumb for minimum MAP, the postmenstrual age in weeks.[4,7] The present model shows that the lowest range for MAP at 24 h after birth matches pretty well with the gestational age in most gestational age groups. The −2 SD (P02.3) 24 h after birth at gestational age 24 weeks is 23 mm Hg, at gestational age 30 weeks 32 mm Hg, and at gestational age 36 weeks 37 mm Hg. However, our data show that the simple linear rule of thumb fails to predict blood pressure in many situations. It does not take into account the low values shortly after birth, the rapid increase in the first day, and the gradual increase thereafter in the more mature age groups. For example, at Day 4–7 of life, the rule of thumb underestimates the lower limit of MAP by 5 and 10 mm Hg in neonates born at 32 and 40 weeks of gestation, respectively. This suggests that blood pressure support should be more restrained in the first day of life and more aggressive in the course of the first week.

Our observational data define the range of actual arterial blood pressures in our population, but developing a new rule

Table 1 Baseline characteristics of the study group. Data are presented as median with inter-quartile rang [IQR], or as number (%).*27× amoxicillin/clavulanic acid, 9× penicillin, 9× amoxicillin.

	Noninvasive blood pressure (n=607)		N
Sex (male), *n* (%)	340	(56)	607
Twins, *n* (%)	135	(22)	607
Gestational age, weeks	33.6	[30.7–37.3]	605
Birth weight, g	1955	[1430-2890]	605
Delivery, *n* (%)			602
Caesarean delivery	314	(52)	
Vaginal	259	(43)	
Vacuum extraction/ forceps	29	(5)	
Meconium-stained amniotic fluid	45	(14)	326
Umbilical arterial cord blood gas analysis			
Base excess	−3.1	[−6.0 to 1.9]	340
pH	7.28	[7.22–7.33]	362
Median APGAR			
5 min postpartum	9	[8–9]	569
10 min postpartum	9	[8–10]	400
APGAR ≥8, *n* (%)			
5 Min postpartum	427	(75)	569
10 Min postpartum	356	(89)	400
Maternal, *n* (%)			
PE/HELLP	104	(17)	607
Diabetes mellitus/ diabetes gravidarum	62	(10)	607
Hypertension	11	(2)	607
Prepartum antibiotics*	45	(7)	606
Comorbidities, *n* (%)			
Intraventricular haemorrhage (class 1)	12	(2)	607
Infant respiratory distress syndrome	171	(28)	607
Cardiac (non-excluding)	18	(3)	607
NICU admission duration, days, *n* (%)			607
<1 Week	167	(27.5)	
≥1 Week	440	(72.5)	

APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HELLP: haemolysis, elevated liver enzymes, and a low platelet count syndrome; NICU, neonatal intensive care unit; PE: pre-eclampsia.

of thumb that is useful in clinical practice requires clinical intervention studies with data on organ perfusion and long-term outcomes, which cannot be inferred from descriptive data alone. Easily accessible reference ranges for both hypotension and hypertension are crucial for optimal treatment.[24] Our interactive website shows ranges for expected blood pressures, and the open source allows incorporation of the reference tables into electronic medical records.

The present model shows a rapid increase in mean and diastolic arterial pressure within the first day of life in the lowest gestational age groups, and a more gradual increase in systolic arterial pressure. Previous studies on the postnatal development of blood pressure in extremely premature infants have shown conflicting results.[20–22] Some studies report an initial decrease in blood pressure in extremely premature infants within the first 3 h after birth with an increase in the first 24 h thereafter,[20,22,25] and others report a rapid increase within the first few hours.[21,26] These differences might be ascribed to inclusion of patients receiving inotropes and vasopressors with dissimilar treatment protocols, and by differences in standardisation of measurements and data modelling. Our data are in line with previous studies showing a rapid increase in blood pressure in extremely premature neonates directly after birth, which suggests more rapid adaptation to extrauterine life, and a more gradual increase in those at greater gestational age.[21,26]

The reference values determined for NIBP are based on the most frequently used method for blood pressure measurement in the intensive care setting, a cuff and oscillometric determination. For MAP <30 mm Hg, IABP measurements are more accurate.[5] However, IABP measurement requires intra-arterial cannulation, which is avoided in neonates who are not critically ill and can be associated with severe complications.[27] Other studies have shown that in neonates, NIBP measurement shows fair agreement with IABP, irrespective of gestational age or birth weight.[28] We preferred to describe noninvasive blood pressure in otherwise healthy neonates. Because in our hospital only diseased neonates are monitored invasively, we could not perform a similar analysis for IABP in healthy neonates, and chose to present only NIBP nomograms.

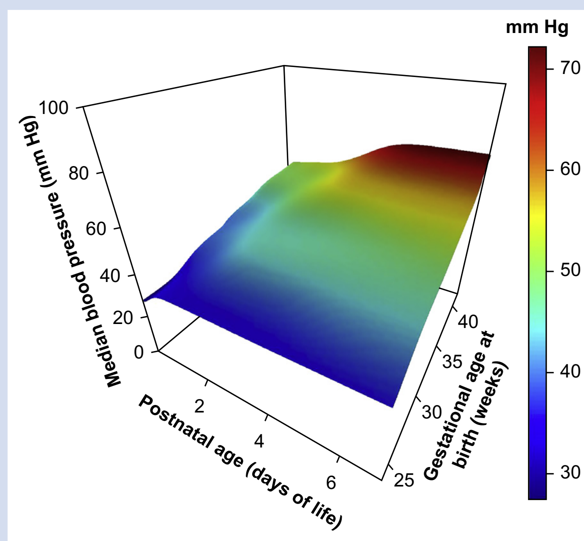

Fig 3. 3-Dimensional mesh plot of the interplay between gestational age in weeks, postnatal age in days, and median mean arterial pressure in mm Hg. The variance in colour corresponds with mean arterial pressure in mm Hg as depicted on the right side of the graph.

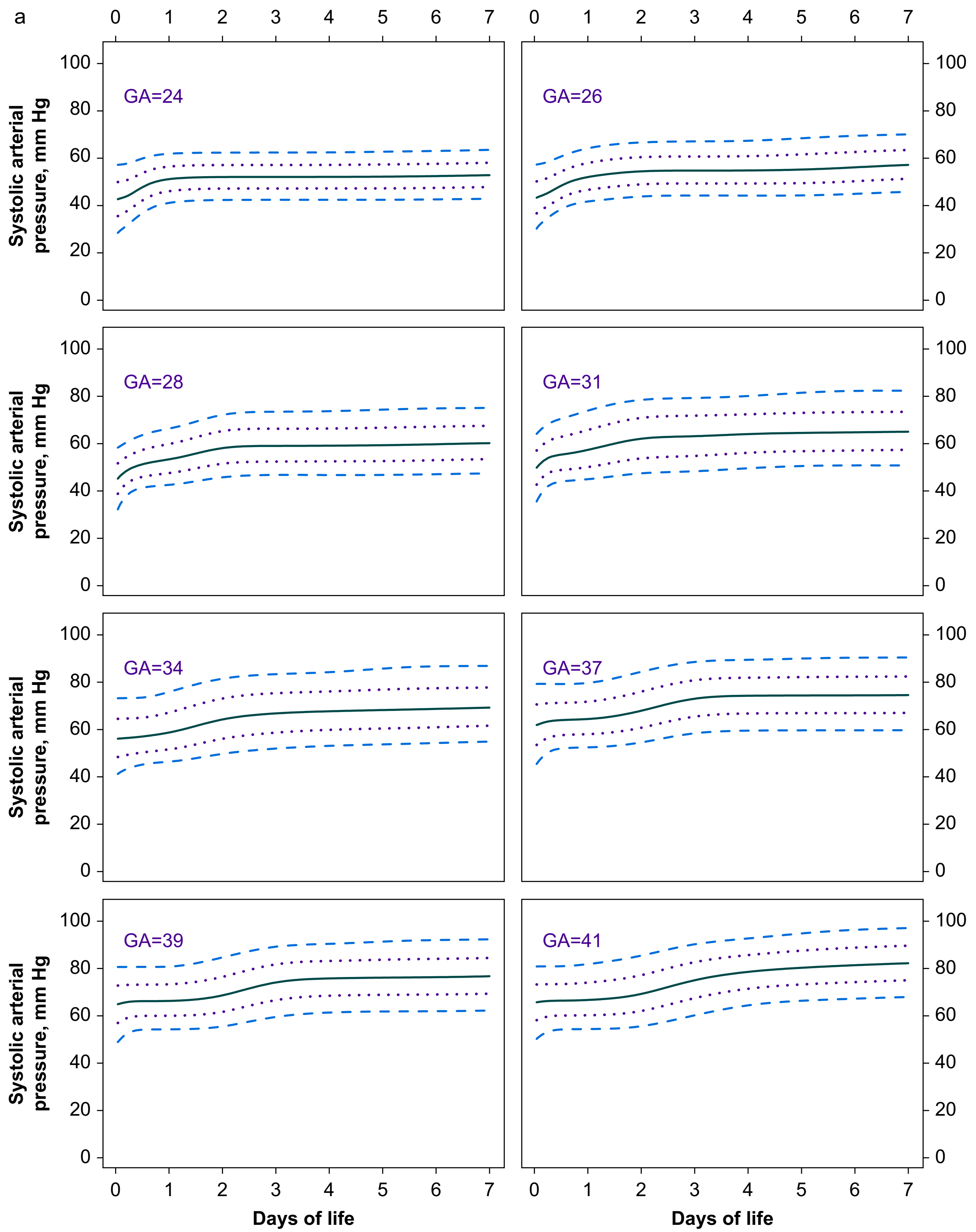

Fig 4. Plots of noninvasive blood pressure curves *vs* gestational age. Course of systolic arterial pressure (a), mean arterial pressure (b), and diastolic arterial pressure (c) by gestational age. Percentiles of noninvasive blood pressure (mm Hg, *y*-axis) for the first 7 days after birth (*x*-axis, in days) for each full week of gestation at birth (from 24 to 41 weeks), representing the −2 SD (P2.3): lower dashed purple line; −1 SD (P16): lower dotted blue line; median or 0 SD (P50): solid black line; +1 SD (P84): upper dotted purple line; and +2 SD (P97.7): upper dashed blue line. For percentile values for gestational age and postnatal age in weeks plus days, visit http://bloodpressure-neonate.com/. GA, gestational age (weeks); P, percentile; SD, standard deviation.

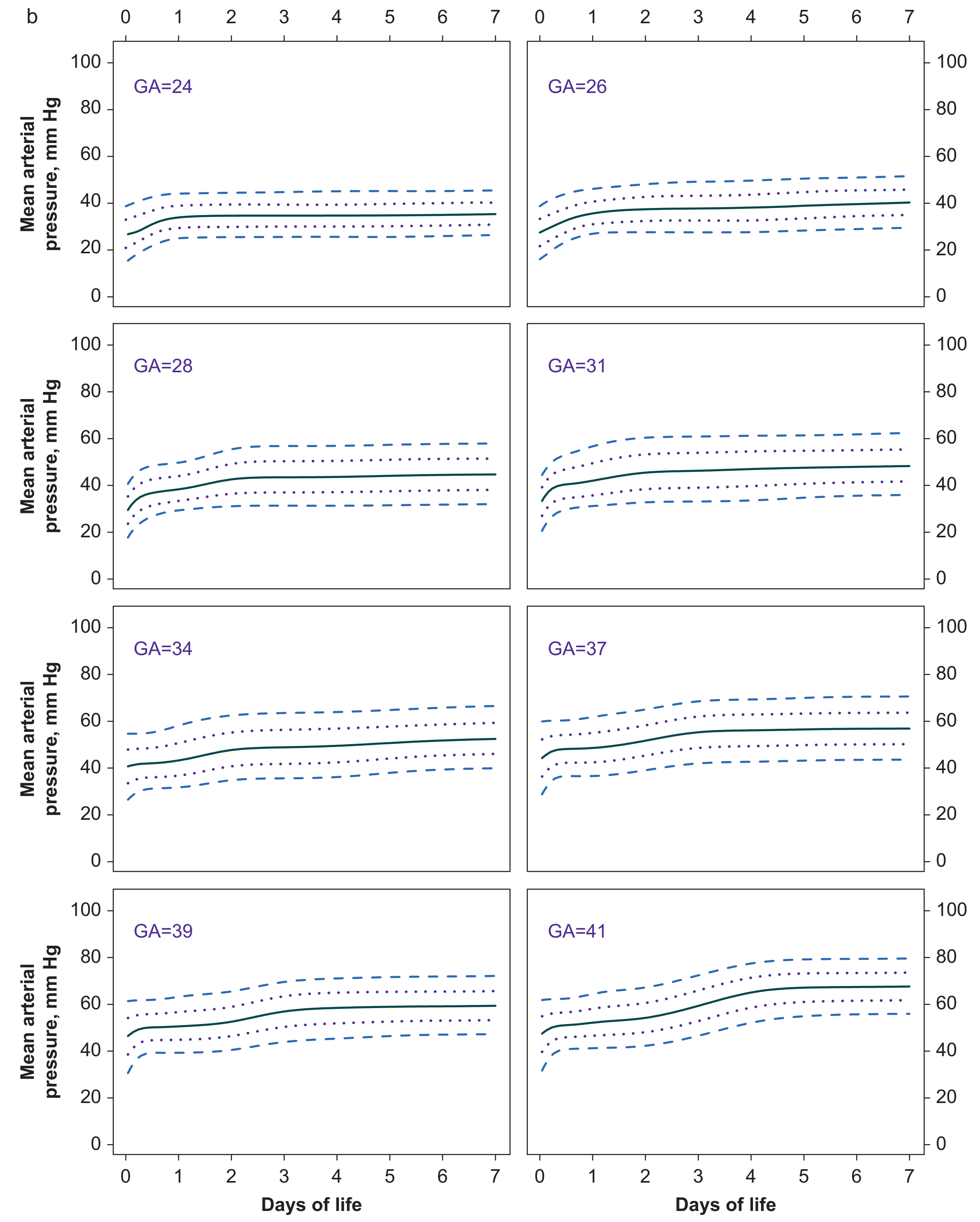

Fig 4. continued

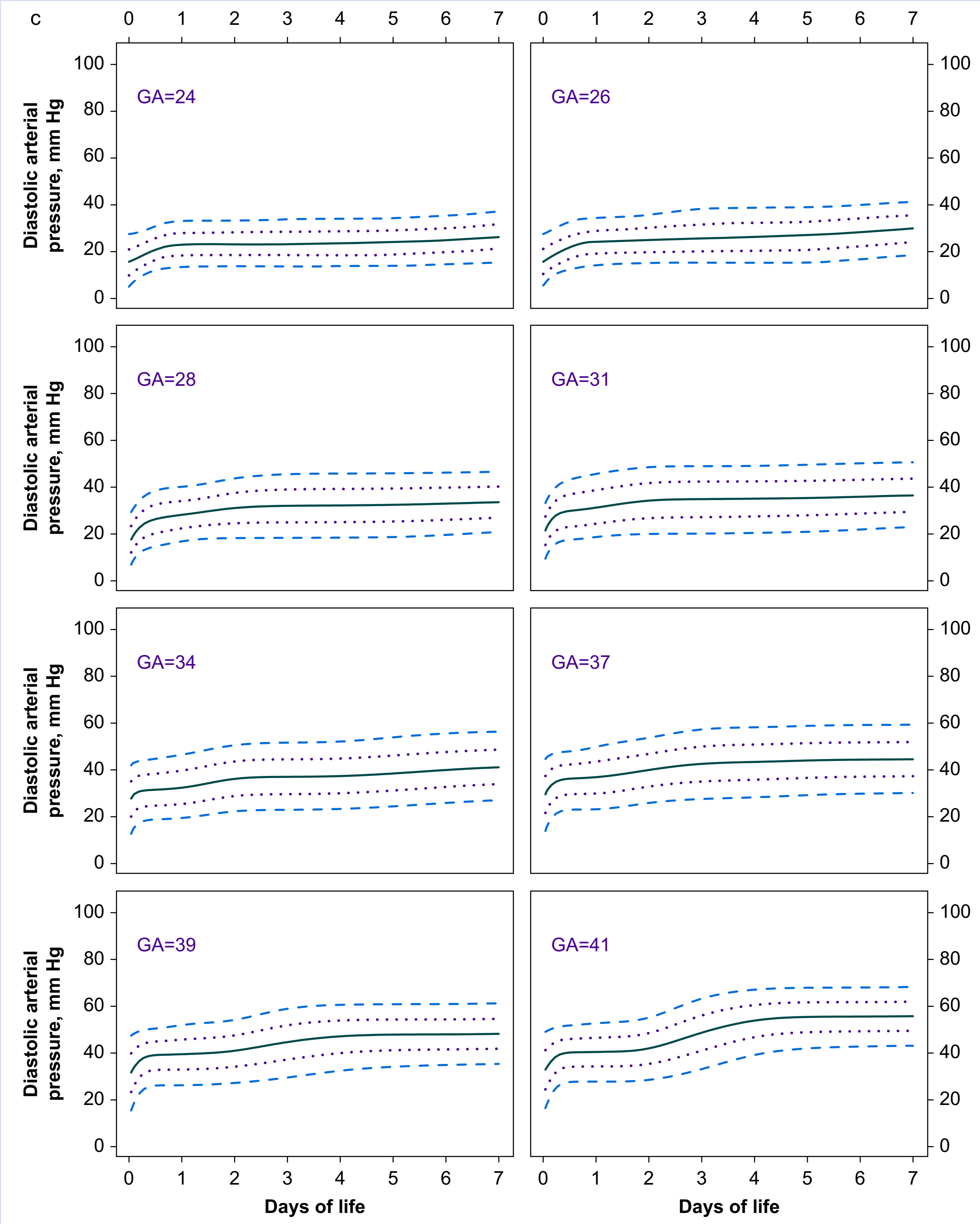

Fig 4. continued

Neonatal arterial blood pressure depends in part on gestational age and other factors such as sex, birth weight, ethnic background, delayed cord clamping, and maternal factors (such as maternal hypertension, pre-eclampsia and drug use). The latter were not included in our models since retrospective data were incomplete and the sample size was inadequate.[5,21,29,30] The issue of cord clamping is interesting in that as long as the baby is breathing, a 1-min delay will transfuse ~80 ml and a 3-min delay ~100 ml into the baby's circulation, which in turn increases cardiac filling and subsequently arterial pressure.[31]

Other limitations include the sensitivity of oscillometric NIBP measurements to artifacts (movement and crying) and the influence of incorrect cuff size and measurement location. The location of the measurement (upper or lower extremity) and cuff size was performed according to standard practice, but was not registered and could therefore not be incorporated in the analyses. We suggest that future studies could benefit from a prospective multicentre design, inclusion of a larger sample of healthy neonates with registration of potentially relevant maternal and neonatal factors, and a highly standardised NIBP measurement protocol carried out by trained staff. Expanding the observation period beyond the first week of life in such studies would be valuable.

In conclusion, reference values for noninvasive blood pressure for various age groups presented here will be useful in guiding clinical decision-making for preterm and term born neonates in the first week of life in intensive care units and by inference during anaesthesia.

Authors' contributions

Conceptualised the study: ACvZ, WvW, TGG, IKMR, MJV, JCdG
Designed the study: ACvZ, MJV, JCdG
Designed the database: ACvZ
Collected data: ACvZ, JAP, WvW
Carried out the analyses: ACvZ, JAP
Drafted the manuscript: ACvZ
Reviewed the manuscript: JAP, SW, KM, WvW, TGG, JCdG
Revised the manuscript: JAP, SW, KM, TGG, IKMR, MJV, JCdG
Designed and performed the statistical analyses: SW, KM
Designed the data collection instruments: WvW, TGG
Responsible for the clinical data collection and critically reviewed the manuscript: IKMR
Critically reviewed the analyses: MJV
Coordinated and supervised data collection: JCdG
Approved the final manuscript as submitted and agree to be accountable for all aspects of the work: all authors

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Declaration of interest

The authors declare they have no financial relationships relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.01.024.

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