Reference Values for Noninvasive Blood Pressure in Children during Anesthesia

A Multicentered Retrospective Observational Cohort Study

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ABSTRACT

Background: Although noninvasive blood pressure (NIBP) monitoring during anesthesia is a standard of care, reference ranges for blood pressure in anesthetized children are not available. We developed sex- and age-specific reference ranges for NIBP in children during anesthesia and surgery.

Methods: In this retrospective observational cohort study, we included NIBP data of children with no or mild comorbidity younger than 18 yr old from the Multicenter Perioperative Outcomes Group data set. Sex-specific percentiles of the NIBP values for age were developed and extrapolated into diagrams and reference tables representing the 50th percentile (0 SD), +1 SD, −1 SD, and the upper (+2 SD) and lower reference ranges (−2 SD).

Results: In total, 116,362 cases from 10 centers were available for the construction of NIBP age- and sex-specific reference curves. The 0 SD of the mean NIBP during anesthesia varied from 33 mmHg at birth to 67 mmHg at 18 yr. The low cutoff NIBP (2 SD below the 50th percentile) varied from 17 mmHg at birth to 47 mmHg at 18 yr old.

Conclusions: This is the first study to present reference ranges for blood pressure in children during anesthesia. These reference ranges based on the variation of values obtained in daily care in children during anesthesia could be used for rapid screening of changes in blood pressure during anesthesia and may provide a consistent reference for future blood pressure–related pediatric anesthesia research. **(ANESTHESIOLOGY 2016; 125:904-13)**

MORE than six million patients under the age of 18, including 1.5 million infants, undergo procedures requiring sedation and anesthesia each year in the United States and Europe alone.[1] While concerns about potential neurotoxicity of general anesthesia have dominated the lay press and peer-reviewed literature, all pediatric patients undergoing surgery are at risk of complications related to anesthesia-induced cardiovascular depression. In fact, some have voiced concerns that neurotoxicity may be mediated by hypoperfusion.[2]

Monitoring of vital signs, such as heart rate and blood pressure, during anesthesia is a standard of care according to the American Society of Anesthesiologists (ASA) practice guidelines.[3] Although noninvasive blood pressure (NIBP) is obtained at least every 5 min in every patient, the interpretation of the values obtained in children is not guided by evidence because there are no valid reference ranges for NIBP in children during anesthesia. Current NIBP reference values are derived from population-based studies in healthy nonanesthetized children.[4–6] However, these references cannot be extrapolated to children during anesthesia because anesthetic drugs induce significant cardiovascular depression.[7]

What We Already Know about This Topic

- Gender- and age-specific reference ranges for oscillometric blood pressure measurements in children during anesthesia and surgery are poorly described

What This Article Tells Us That Is New

- The authors evaluated more than 116,000 children from 10 centers to determine blood pressure averages and ranges
- The analysis was restricted to two periods: (1) after anesthetic induction but before incision and (2) a brief initial stable portion of surgery
- Mean arterial pressure increased from about 40 mmHg at 1 month to 65 mmHg at 18 yr, with little difference in boys and girls.

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This gap in knowledge causes uncertainty, in particular, due to the known developmental physiologic spectrum of the pediatric patient. A recent case series of six healthy infants who developed severe encephalopathy after straightforward elective surgery, including one death and one with profound developmental delay, has refocused attention on pediatric anesthesia standards of care.[8] The exact cause of the encephalopathy could not be determined in any of these children, but hypotension during anesthesia was considered attributable. However, provider experience demonstrates that many infants with comparably hypotensive NIBP during anesthesia are doing well after surgery and do not develop any complications. The absence of evidence-based reference ranges exposes patients to nonstandardized care and providers to undue medicolegal risk while providing routine, reasonable care.

The purpose of the current study was to develop age- and sex-specific charts (percentile curves) of the natural variation of NIBP during anesthesia during the preparation and surgical phase. Availability of such reference curves and tables of NIBP measurements would aid physicians in detecting extreme values that justify further inquiry or action and would enable harmonization of diagnosis and treatment between anesthesiologists, hospitals, and countries.[9]

Materials and Methods

In the current retrospective observational cohort study, we used deidentified data from the Multicenter Perioperative Outcomes Group (MPOG) data set. The MPOG is a consortium of medical centers in the United States and Europe aggregating large volumes of observational perioperative electronic data, registry outcomes, and long-term administrative outcomes.[10] The study of deidentified patient data from the MPOG data set has been approved by the University of Michigan Institutional Review Board, Ann Arbor, Michigan (HUM00033894). Participation of the University Medical Center Utrecht (UMCU), Utrecht, The Netherlands, in the MPOG database has been approved by the Institutional Review Board of the UMCU (12.253-C). The protocol for the current study was approved by the MPOG Perioperative Clinical Research Committee (0018, February 10, 2014).

Data Source

The MPOG database has been described previously but is summarized as follows: each contributing member uses a modern intraoperative electronic health record (EHR). Data manually entered into the EHR include patient anthropometrics, intraoperative medications, surgical events, and clinical observations. Data collected using automated, validated interfaces include demographic information, laboratory values, and all physiologic monitor measurements, including heart rate and NIBP.[10] The database is growing over time and, at the time of data extraction, contained the automatically acquired data on vital signs and other EHR data of more than 3.5 million patients, including around 350,000 children from 17 centers. We included children with American Society of Anesthesia physical status (ASA PS) classes 1 and 2 who underwent anesthesia for surgical or diagnostic procedures in hospitals participating in the MPOG in the period from August 2007 up to and including December 2014. ASA PS 1 children are considered healthy, and ASA PS class 2 children have minor comorbidity not affecting daily life, such as controlled bronchial asthma.[11] We excluded cardiac surgery cases and cases for which the type of surgery was unknown.

Although NIBP measurements are routinely acquired at least every 5 min during anesthesia, only measurements acquired during relatively stable hemodynamic periods were used to provide insight into reference values for NIBP. The analysis was therefore performed on data obtained during the preparation phase (within 20 min before procedure start) and during the initial surgical phase after the start of the procedure (between 15 and 35 min after procedure start). This was done in order to minimize the effect of patient positioning, initial surgical stimulus surge, and surgical bleeding on the reference values. Additionally, to estimate how often blood pressures during the remainder part of the surgical procedure were outside the range of the derived reference values, blood pressures obtained after the first 35 min were compared to the reference values.

We included only cases in which the start of the surgical procedure was clearly identified. For the preparation phase (20 min before procedure start), we calculated the mean of the last three measurements without artifacts, within this time frame. During the surgical phase, we calculated the mean of the first three measurements without artifacts, between 15 and 35 min after the start of the procedure. A case was included when at least two artifact-free measurements were available in the given time frame.

Although the management of artifact data is essential to provide meaningful reference ranges, no standardized definitions of blood pressure artifacts have been established for pediatric blood pressure measurements. Measurements were considered artifacts when the diastolic NIBP was lower than 3 mmHg, when the systolic NIBP was higher than or equal to 250 mmHg, when the pulse pressure (systolic NIBP minus diastolic NIBP) was lower than or equal to 5 mmHg, when the diastolic NIBP was higher than the mean NIBP, when the mean NIBP was higher than the systolic NIBP, or when the systolic, diastolic, or mean NIBP measurement was flagged as an artifact or was missing.

Outcomes

The primary outcome of the study was an estimate of the natural variation of systolic, mean, and diastolic NIBP in relation to age during the preparation and surgical phase of the procedure.[4] The variation was expressed as sex-specific percentile curves with the 50th percentile (0 SD), −1 SD, +1 SD, and highest (+2 SD) and lowest (−2 SD) reference ranges. Secondary outcomes were sex-specific plots of percentile curves and reference tables of systolic, mean, and diastolic NIBP in relation to weight.

Statistical Analysis

The NIBP values were analyzed according to the methods recommended by the World Health Organization for child growth standards.[12] For each outcome, a choice was made between the Box-Cox Cole-Green, the Box-Cox Power Exponential, and the Box-Cox t-family of distributions, aided by the worm plot and Q statistics as implemented in the generalized additive models for location, scale, and shape package for R software (version 3.2.3; https://www.r-project.org, accessed August 13, 2016).[13,14] Where needed, transformations of the variables were used to increase the fit. Differences between centers were estimated by adding dummy variables, as practiced in this context and evaluated with worm plots.[15] The results of systolic, diastolic, and mean NIBP are presented in graphs in relation to age and weight with a square root transformation of age for more detailed presentation for younger children. The R scripts to fit the models can be requested from the authors.

In order to compare the blood pressures during the remainder of the procedure with the proposed reference scales for age and weight, all NIBP measurements from 35 min after the start of the procedure until the end of anesthetic registration were gathered. These measurements were divided into epochs, each including three measurements. For each epoch, the median of the NIBP was calculated and compared with the preparation phase reference value of the same age or weight.

By including all surgical and diagnostic procedures on children under 18 yr old conducted between August 2007 and December 2014, we expected to include more than 100,000 cases. This sample is much larger than is customary in the field (typically n = 1,000 to 10,000).[12]

Results

Of a total of 327,123 anesthetics in patients younger than 18 yr old in the MPOG database, 221,202 cases with known ASA PS classes 1 and 2 and known sex were selected. Cardiac surgery cases, cases where the surgical procedure was unknown, and those without a documented “procedure start” timed event were excluded (fig. 1). In total, 116,362 cases across 10 centers with at least two valid blood pressure measurements in any of the periods of interest were used for analyses (University of Michigan Health System, Ann Arbor, Michigan; Oregon Health and Science University, Portland, Oregon; University of Colorado Denver, Denver, Colorado; University of Tennessee Medical Center, Knoxville, Tennessee; University of Virginia Health System, Charlottesville, Virginia; University of Florida, Gainesville, Florida; Washington University School of Medicine, St. Louis, Missouri; University of Vermont – Fletcher Allen Health Care, Burlington, Vermont; University of Washington Medical Center, Seattle, Washington; and University Medical Center Utrecht, Utrecht, The Netherlands). We used 108,179 cases for analysis of the preparation phase and 94,283 cases for analysis of the initial surgical phase. The age was known in all cases; in 104,977 cases (90%), the weight was known (table 1). The worm plots did not show significant differences between centers (data not presented).

The 50th percentile (0 SD) of the systolic NIBP during anesthesia for boys varies from 48 mmHg at birth to 100 mmHg at 18 yr, while the 50th percentile of the mean NIBP during anesthesia varies from 33 to 66 mmHg, respectively (fig. 2 and table 1 in Supplemental Digital Content 1, http://links.lww.com/ALN/B311). The reference value of the mean NIBP in the lowest age range in the preparation phase varies between 17 mmHg (–2 SD) and 71 mmHg (+2 SD) for boys and between 18 mmHg (–2 SD) and 59 mmHg (+2 SD) for girls (table 2 in Supplemental Digital Content 1, http://links.lww.com/ALN/B311).

Sex-specific percentile plots of systolic, mean, and diastolic NIBP are presented in relation to age during the preparation (fig. 2) and surgical phase (fig. 3) with associated reference tables (preparation phase: tables 1 to 3 in Supplemental Digital Content 1, http://links.lww.com/ALN/B311, and surgical phase: tables 4 to 6 in Supplemental Digital Content 1, http://links.lww.com/ALN/B311). The sex-specific percentile plots of systolic, mean, and diastolic NIBP in relation to weight are presented in figures 4 and 5 and tables 7 to 12 in Supplemental Digital Content 1, http://links.lww.com/ALN/B311. Detailed tables in relation to age, weight, and height are available on request from the corresponding author.

In 62,727 (58%) of the 108,179 cases, at least one epoch of three blood pressure measurements was available after the initial 35 min of the procedure start, *i.e.*, in these 62,727 cases, the procedure lasted longer than 35 min. In total, 405,417 epochs were identified, and the median NIBP of these epochs was compared to the corresponding reference value of NIBP. This resulted in 1.25% of the NIBP below the corresponding –2 SD and 1.79% of the NIBP above the 2 SD. Weight was known in 56,643 (90%) of these 62,727 cases. Similar comparison of NIBPs resulted in 1.34% and 1.24% epoch NIBPs below the –2 SD and 1.68% epoch NIBPs above the 2 SD using the weight-adjusted reference curves.

Discussion

Frequent monitoring of NIBP during anesthesia is a universal standard of care. However, reference values for NIBP in children during anesthesia did not previously exist. The present multicenter study produced age- and sex-specific NIBP reference values for children during anesthesia. The 50th percentile (0 SD) of the mean NIBP during the surgical preparation phase varies from 33 mmHg at birth to 66 mmHg at 18 yr during anesthesia for boys. The lower reference values in anesthetized children are considerably lower than those in nonanesthetized children. The –2 SD of the mean NIBP varies between 17 mmHg for the youngest and 47 mmHg for children of 18 yr old. More than 95% of the blood pressure values of the remaining part of the surgical procedure was within the obtained reference ranges, *i.e.*, values were above the –2 SD and below the +2 SD.

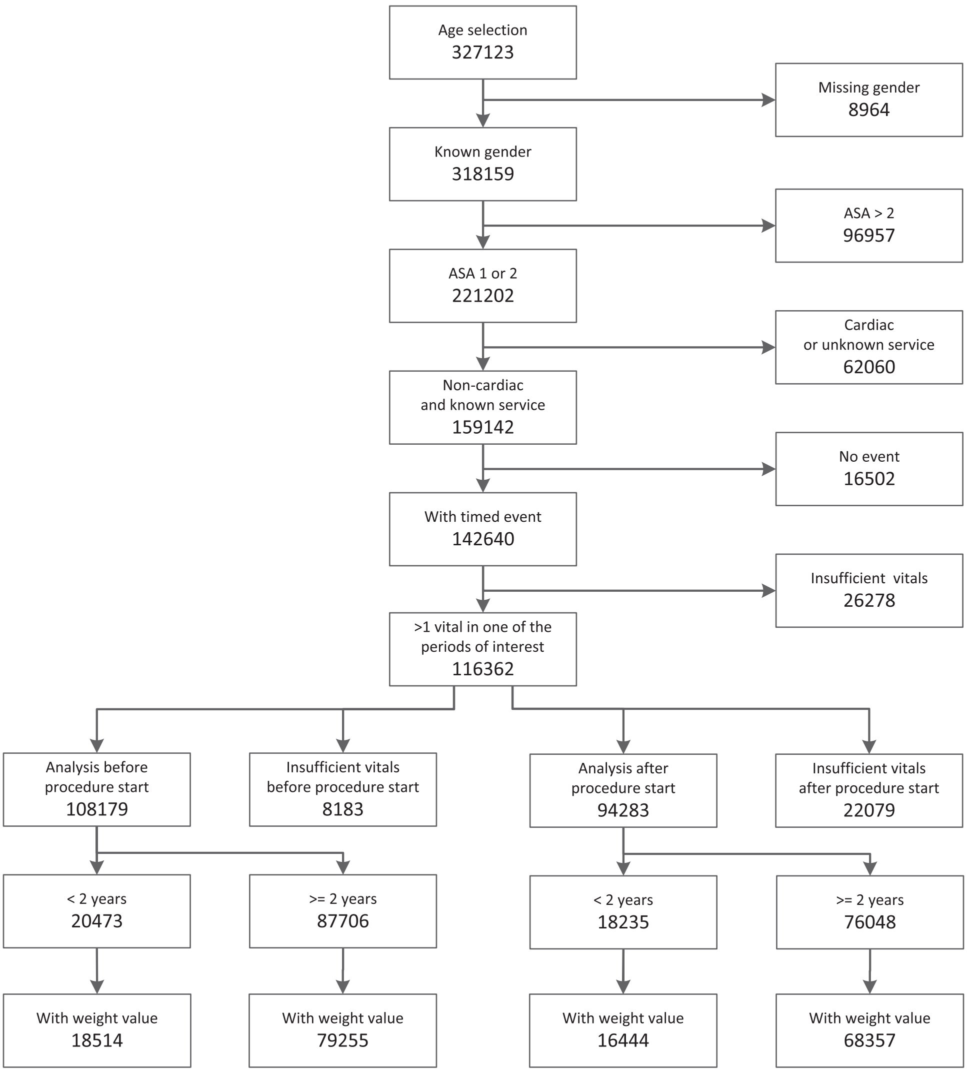

Fig. 1. Flow diagram of data inclusion from Multicenter Perioperative Outcomes Group data set.

Lack of Knowledge

Thus far, reference ranges for NIBP in children during anesthesia do not exist. Vital signs during anesthesia, in particular, NIBP measurements in adults, are often evaluated in reference to patient-specific baseline measurements. However, the clinical relevance of specific NIBP targets or thresholds is disputable, and even for adults, a clear definition of intraoperative hypotension does not exist.[16] The absence of reference values for NIBP during anesthesia causes a wide variation in diagnosis of potential derangement and subsequent treatment. For example, the threshold for intraoperative hypotension in children that is used in daily practice varies between anesthesiologists: some use a threshold at a 10% decrease from the baseline value, while others use a 40% decrease.[17] Furthermore, acceptable patient-specific baseline measurements are rarely available in children since obtaining a reliable NIBP measurement in uncooperative children in the operating room before anesthesia induction is almost impossible. This results in large discrepancies between definitions of intraoperative hypotension. Pediatric anesthesiologists from the Society of Pediatric Anesthesia and Association of Paediatric Anaesthetists reported definitions of intraoperative hypotension ranging from a systolic blood pressure of 25 to 70 mmHg for neonates and from 40 to 100 mmHg in children between 2 and 12 yr old.[17] This wide variation in clinician decision-making demands generalizable, multicenter data to inform practice.

Interpretation

The interpretation of the reference ranges of NIBP presented in our study is comparable to the reference ranges of growth standards for children presented by the World Health Organization, in which measurements of weight of a whole population are plotted into percentile curves.[12] Customarily, observations outside the 2.5th (–2 SD) and 97.5th (+2 SD) percentiles are considered unusually low or high.[12,18] The goal of the reference ranges presented is to provide a set of reference values for the practitioner enabling him or her

Table 1. Baseline Characteristics of Included Pediatric Cases (n = 116,362)

	All Participants	< 2 yr old
Cases	116,362	22,455
Age		
< 2 mo	2,122 (1.8)	2,122 (9.5)
2–12 mo	11,051 (9.5)	11,051 (49.2)
1 yr	9,282 (8.0)	9,282 (41.3)
2–5 yr	28,359 (24.4)	
6–8 yr	16,624 (14.3)	
9–11 yr	13,584 (11.7)	
≥ 12 yr	35,340 (30.4)	
ASA PS		
1	59,581 (51.2)	12,620 (56.2)
2	56,781 (48.8)	9,835 (43.8)
Vital signs available		
Only preprocedure start	22,079 (19.0)	4,220 (18.8)
Only postprocedure start	8,183 (7.0)	1,982 (8.8)
Both	86,100 (74.0)	16,253 (72.4)
Weight (median, IQR)	24.1 (14.0–50.0)	9.1 (6.9–10.9)
Weight known	104,977 (90.2)	20,240 (90.1)
Height (median, IQR)	127 (96–160)	73 (64–79)
Height known	78,242 (67.2)	13,358 (59.5)
Sex		
Male	67,501 (58.0)	15,190 (67.6)
Female	48,861 (42.0)	7,265 (32.4)
Surgical service		
Otolaryngology	21,636 (18.6)	3,255 (14.5)
Orthopedics	20,153 (17.3)	1,246 (5.5)
Urology	16,473 (14.2)	5,871 (26.1)
General	14,577 (12.5)	4,513 (20.1)
Ophthalmology	10,489 (9.0)	2,140 (9.5)
Plastics	7,898 (6.8)	2,125 (9.5)
Other	25,136 (21.6)	3,305 (14.7)

Values are given as the number of cases (n) and percentage of group (%), unless otherwise stated.

ASA PS = American Society of Anesthesia physical status; IQR = interquartile range.

to judge measurements acquired during clinical practice in relation to the variation within the reference population. The present reference curves should not be related to outcome, as they represent the variation in the population, as is the current practice with growth charts. An unusually low or high value relative to the reference alerts the medical practitioner, who can judge the measurement in the context of the clinical setting, patients' disease, the specific anesthetic medication, and the phase and type of the procedure for which the anesthetic is being administered after which appropriate treatment can be started, if judged necessary.[4]

In nonanesthetized children, reference values are focused on hypertension and are defined in relation to age and sex.[19] Therefore, most reference tables for nonanesthetized children focus on the upper limits (+2 SD) of the reference values.[6] The upper reference range of the systolic NIBP differs only marginally between nonanesthetized and anesthetized children. The 98th percentiles of the systolic NIBP of boys 4 and 10 yr old when not anesthetized are 120 and 126 mmHg, respectively,[6] and are comparable to our observed results: systolic NIBP when anesthetized during the preparation phase (+2 SD: 117 and 128 mmHg, respectively) and during the surgical phase (+2 SD: 120 and 130 mmHg, respectively). In contrast, the 50th percentile (0 SD) and 2.5th percentile (−2 SD) NIBPs are much lower in anesthetized compared to nonanesthetized children. Published guidelines establish that the 50th percentiles (0 SD) of the systolic NIBP of boys 4 and 10 yr old when nonanesthetized are 103 and 108 mmHg, respectively.[6] However, our real-world data demonstrate that 50th percentile (0 SD) for the same type of patients during the preparation phase of surgery is approximately 15 mmHg lower (88 and 94 mmHg, respectively). These figures are 90 and 95 mmHg, respectively, during the surgical phase. The lowest reference ranges for anesthetized children are considerably lower (approximately 20 mmHg) than those for awake children; the 2.5th percentiles (−2 SD) of the systolic and mean NIBP of a 4-yr-old boy are 85 and 60 mmHg, respectively, when nonanesthetized,[17] and 68 and 38 mmHg, respectively, when anesthetized.

The variance of NIBPs found is rather large. The wide range is caused by the natural biologic variation, differential impact of anesthesia medication on cardiovascular depression, and variation in the measurement technique itself (*i.e.*, location, the circumference of limb being measured, the cuff size used, *etc.*). These confounding factors are not reliably available in the present multicenter retrospective cohort study data and therefore cannot be used to adjust the model. In contrast, the NIBP reference values in awake children are based on highly controlled ambulatory care settings enabling tight measurement criteria: auscultatory measurements, on the right arm, using appropriate cuff size (an inflatable bladder width that is at least 40% of the arm circumference at a point midway between the olecranon and the acromion) in a sitting position.[19] These ideal and systematic measurements are seldom possible in the operating room. In the current anesthesia standard of practice, an automatic oscillometric device is used, which measures mean arterial blood pressure and then calculates the systolic and diastolic values,[20] whereas the variation may be increased by the algorithms used for the devices, which may differ from company to company.[21] Furthermore, the location of the NIBP varies among both arms and legs, due to the placement of intravenous lines and surgical site. When every blood pressure value in this study was measured under ideal circumstances, the variability might have been smaller, but this ideal measurement circumstances generally are not present during anesthesia. Nevertheless, this wide variance represents the natural variation each pediatrician and anesthesiologist has to deal with in daily practice.

The current reference ranges have a wide variation in the lower end of the spectrum of age and weight ranges. This wide variation reflects the variation in clinical practice and is not caused by excluding incomplete data since the reasons for including or excluding patients were not dependent on

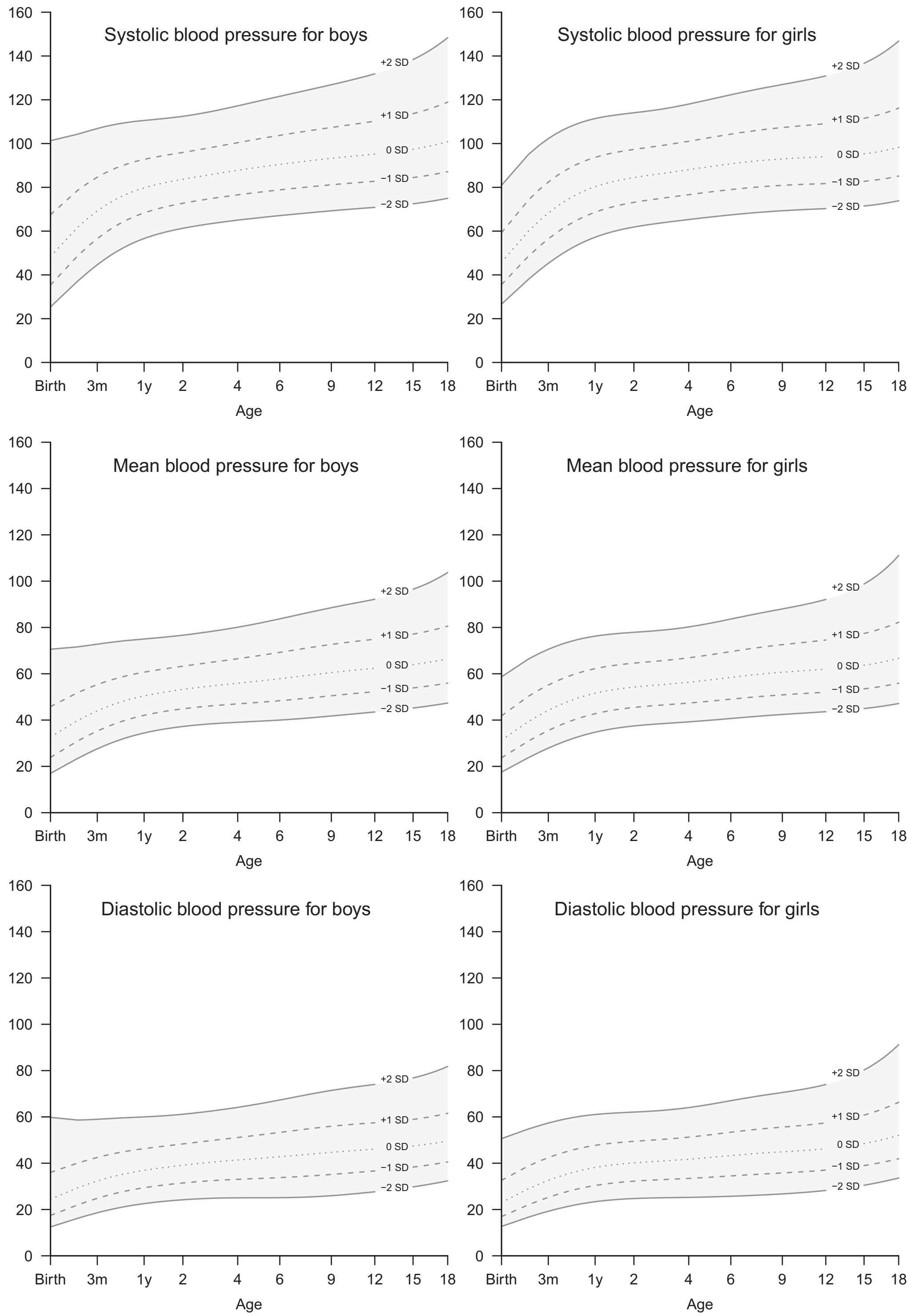

Fig. 2. Reference curves for noninvasive blood pressure for boys and girls during anesthesia during the preparation phase in relation to age.

blood pressure. Therefore, analysis of the complete cases will not introduce bias in the estimated distributions.[22] We excluded severely diseased children (ASA PS 3 and higher) to limit the influence of these sicker children on the blood pressure reference to focus on the initial research question (healthy children).

To give insight into the pressure ranges during the remaining part of the procedures, we compared these blood pressures with the reference standards proposed here. These results show that more than 95% of these measurements were within these limits, and only a very limited number of measurements were outside the reference range. Short procedures are not represented in this

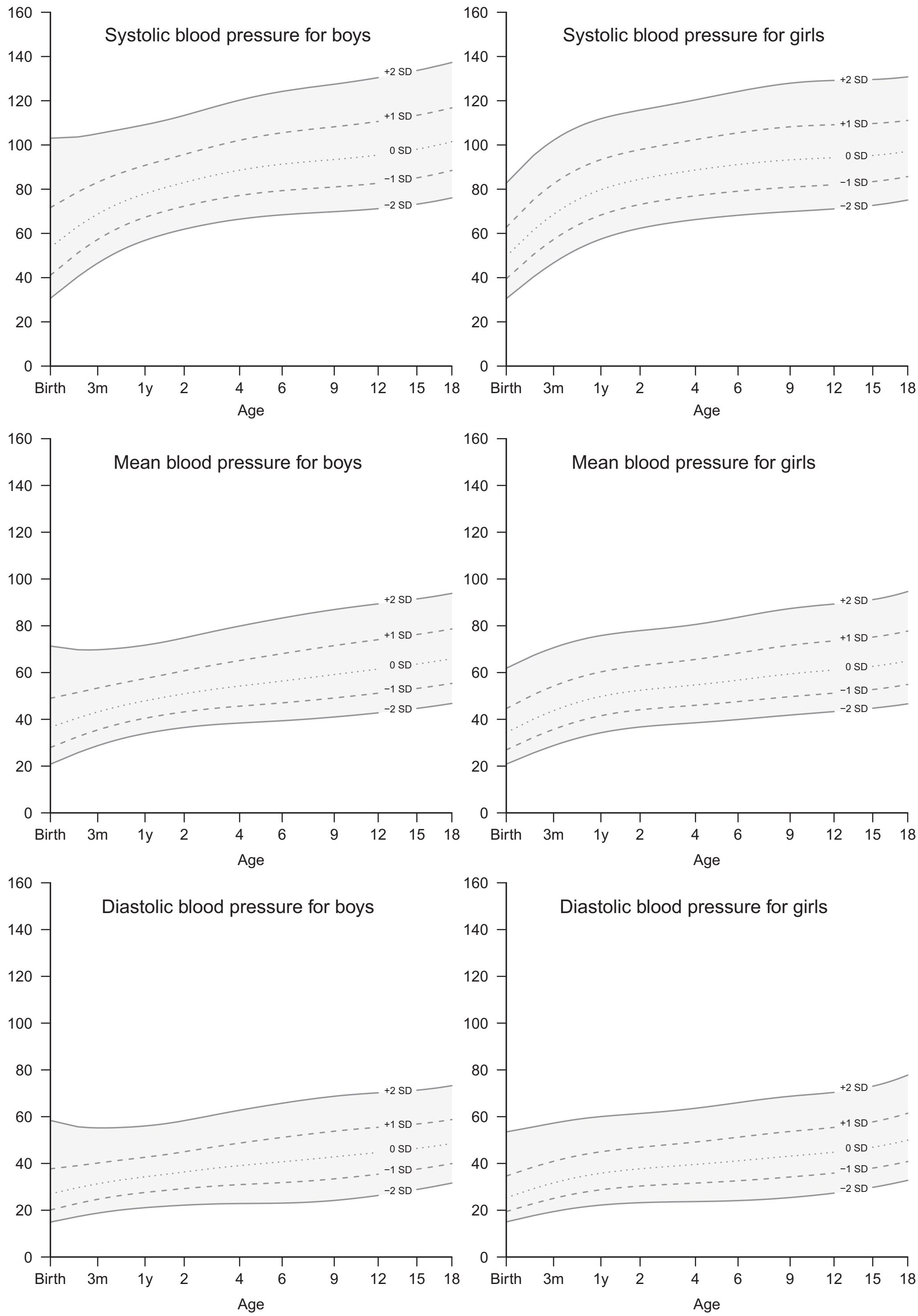

Fig. 3. Reference curves for noninvasive blood pressure for boys and girls during anesthesia during the surgical phase in relation to age.

last analysis because of the method of data collection, which could have led to under- or overestimation of the percentages.

Organ Perfusion

The present data set does not allow a comparison of NIBP in relation to the clinical outcome related to organ perfusion, such as cerebral encephalopathy, kidney failure, or even surrogate outcome measures, such as hospital length of stay and mortality. Clear symptoms are very rare in these group of patients, and if present, they would not affect the results of the current study.

A cerebral ischemic infarct is a rare but devastating complication in pediatric anesthesia caused by low

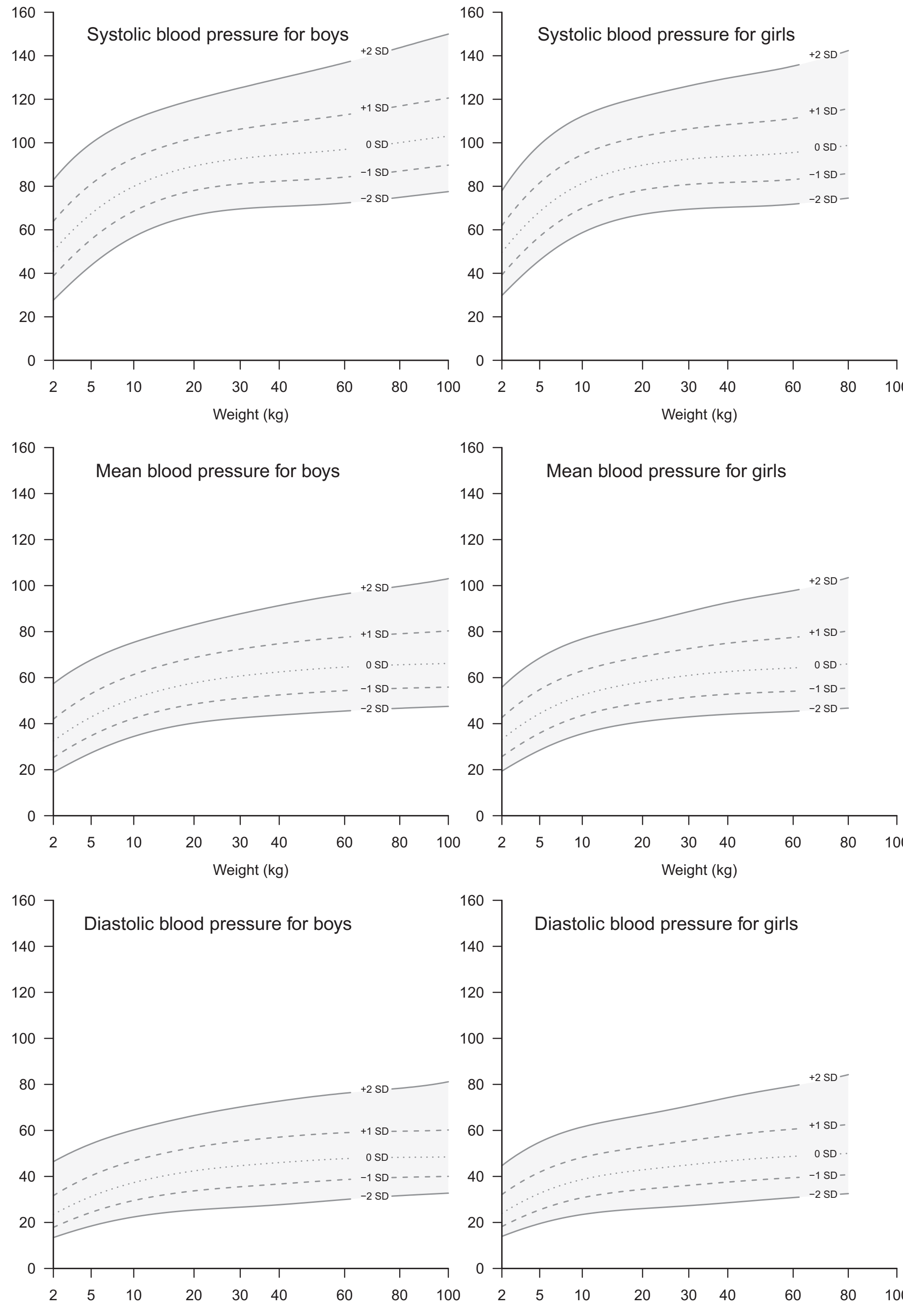

Fig. 4. Reference curves for noninvasive blood pressure for boys and girls during anesthesia during the preparation phase in relation to weight.

cerebral perfusion.[8] The symptoms of low cerebral perfusion (syncope, nausea, *etc.*) are not signaled during general anesthesia. The lowest systolic NIBP of the patients with severe postoperative encephalopathy in the case series by McCann *et al.*[8] ranged from 22 to 40 mmHg. The current study shows considerably lower reference ranges (−2 SD) of the systolic and mean NIBP in the youngest boys of 25 and 17 mmHg during the preparation phase and 30 and 22 mmHg during the surgical phase. This lower range (−2 SD) corresponds with the lower 10th percentiles of the definition of systolic NIBP for significant hypotension (25 mmHg) that pediatric anesthesiologists from the United States and United

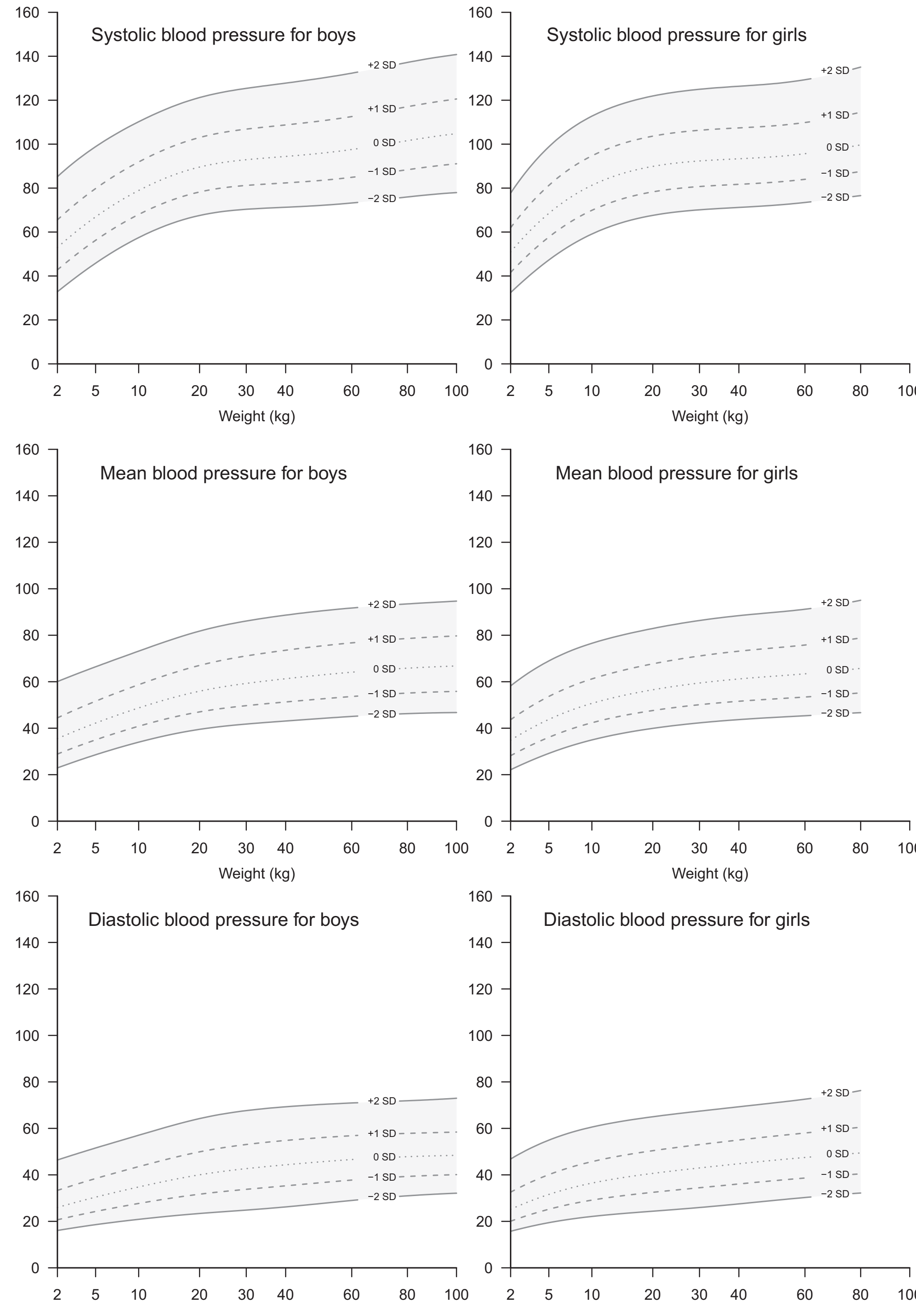

Fig. 5. Reference curves for noninvasive blood pressure for boys and girls during anesthesia during the surgical phase in relation to weight.

Kingdom reported.[17] These differences underscore the variation and uncertainty of current clinical practice.

Conclusions

Clinicians providing care to millions of pediatric patients during anesthesia each year lack the normative data needed to guide interpretation and treatment of intraoperative NIBP measurements. With more than 100,000 patients across 11 medical centers, our data provide the real-world context necessary to establish reference ranges for a pediatric anesthesia blood pressure. We have demonstrated that the 50th percentile (0SD) and lower bound (−2 SD) NIBPs observed during anesthesia are markedly lower in anesthetized children than in idealized data collected on awake patients. These data may help inform daily practice and decision-making for thousands of clinicians—anesthesiologists, surgeons, pediatricians, and pediatric specialists. Furthermore, the external validity of studies of anesthetized children can be calibrated to these reference tables.

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Competing Interests

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