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Title

Blood pressure in Danish children during general anaesthesia: Hypotension in a Paediatric Population Observational (HIPPO) Study

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None to declare

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Abstract

Background

In Denmark, thousands of infants and children require general anaesthesia annually. Hypotension during general anaesthesia might reduce cerebral blood flow and oxygen delivery to the brain. Safe lower limits of blood pressure are ill defined. The *Hypotension in Paediatric Populations Observational* study objective was to assess blood pressure in Danish children during general anaesthesia.

Methods

This study is a prospective observational multicentre study. Primary outcomes were mean arterial blood pressures in children aged 0 – 12 years. Lowest mean arterial blood pressure, intervention thresholds to increase blood pressure and type of intervention were secondary outcomes. Premature infants and children scheduled for cardio-thoracic surgery were excluded. Blood pressures were measured by oscillometry or invasively.

Results

In total, 726 patients were included. In children <1 year median arterial pressure was 51mmHg, (interquartile range; 43-58) and increased to 58mmHg (interquartile range; 52-65) for 12 year old children. In 32 patients 49 actions were taken to modulate blood pressure. Pre-induction blood pressures were recorded for 29%.

Conclusion

This study presents pragmatic, multicentre, prospectively collected observations of blood pressure in children undergoing general anaesthesia in usual practice. In the youngest infants, variability in blood pressure appears to be large. Measurement of blood pressure is recommended during every general anaesthesia and in children of all ages. Safe ranges of blood pressure remain to be defined.

Word count: 216

Editorial Comment:

Perioperative blood pressure levels, and low blood pressure related to general anesthesia in children continues to be a matter of concern for clinicians. In this prospective Danish multicenter observational study of children under going general anesthesia, mean arterial blood pressure was found to be highly variable, particularly in the youngest children.

Introduction

Each year, thousands of infants and children require general anaesthesia (GA) in Denmark. Although complications are rare, the occurrence of respiratory, cardiovascular, allergic and neurologic incidents might lead to major disability.(1, 2) In order to prevent detrimental effects occurring in the perioperative period, maintenance of physiologic homeostasis, i.e. normotension, is considered a key element. Low blood pressure (hypotension) during GA is suspected to reduce cerebral blood flow, decreasing oxygen delivery to the brain.(3) In 4-6 weeks old piglets, a reduction in partial pressure of oxygen in brain tissue ($PbtO_2$) was seen when mean arterial blood pressure (MAP) was decreased to 35-38 and 27-30 mmHg, described as ‘moderate’ and ‘severe’ arterial hypotension, respectively.(4)

In an observational multicentre study assessing the incidence of severe critical events in paediatric anaesthesia, hypotension was reported in 384 cases comprising 54.9% of specific cardiovascular adverse events. (5-7) Hypotension was identified as the plausible precursory cause in two infants out of nine suffering an episode of cardiac arrest. Of note, it was left to the clinicians in charge to decide which blood pressure levels resembled ‘hypotension’.

Based on these and similar findings, particular attention has been paid to potential consequences of perioperative low blood pressure in infants and children.(8) However, the safe lower limits of blood pressure are ill defined.

The *Hypotension In Paediatric Populations Observational* (HIPPO*)* study objective was to assess blood pressure in Danish children during GA. MAP in children aged 0 – 12 years were collected as primary outcome. Secondary outcomes were lowest MAP, MAP threshold for intervention and type of intervention done to increase blood pressure.

Methods

The study was designed as an observational, prospective multicentre trial.

Over a 15 week period in spring 2019 the study was conducted at 20 different Danish hospitals. During two consecutive weeks, paediatric patients aged 0 - 12 years scheduled at each site for emergency or elective procedures in sedation or GA were included. Exclusion criteria were prematurity at time of procedure and cardio-thoracic surgery. Preparation for surgery and anaesthesia, anaesthesia induction and –maintenance, and postoperative observation was conducted according to departmental standards and not influenced by data collection.

On arrival in the operating room, demographic data (age, weight, classification according to American Society of Anaesthesia (ASA), gender, status of prematurity at birth, means of airway management, type of anaesthesia induction and maintenance, type of surgery/procedure) of the child were recorded by the anaesthetist or nurse anaesthetist in charge of the patient. Pre-induction blood pressure was recorded according to the standard procedure of the different sites. Study data were recorded continuously during the procedure and collected by the local investigator after completion of the study period.

MAP, systolic and diastolic pressure measured in mmHg, pulse frequency as beats per minute and oxygen saturation by pulse oximetry were measured at time points according to departmental standards and recorded on the HIPPO- datasheet at 5minute intervals. If boli of fluid (> 5 ml/kg) or vasoactive drugs were administered, the type and dose were recorded and the time point was marked. Adjustment of anaesthesia depth was not considered an intervention.

Source data were filed into a database by members of the study group. The input form included automated checks for e.g. double registration. If systolic and diastolic pressures but not mean arterial pressures were recorded, MAP was calculated using the formula: MAP = ((diastolic pressure x 2) + systolic pressure) / 3. The lowest MAP from each patient was used to calculate mean-low-MAPs for each age group. In case of a single measurement, this value was registered as the lowest MAP. We assumed that the values recorded were valid and that artefacts would have been corrected before logged on the data-sheet. Descriptive statistics were calculated using Microsoft Excel for Mac (version 16.27) and RStudio (version 1.1.463), count data were double checked and descriptive coding used. Results were presented as number (percentage), mean ± SD or median (interquartile range).

The study was initiated by the authors as part of the Inter-Nordic fellowship in Paediatric Anaesthesia & Intensive Care medicine 2017-19, organized by the Scandinavian Society of Anaesthesiology and Intensive Care (SSAI). Study conductance was in accordance with the Helsinki Declaration and all data were recorded anonymously. With reference to the ruling 'Act on Research Ethics Review of Health Research Projects' of Nov 13th 2018, this study did not comply with the definition of a health research project (Part 2 'Definitions', Section 2). Hence, no ethical approval or parental consent was required (Supplement 1). All expenses were covered by departmental funds.

Results

A total of 738 patients were included initially. Twelve patients were found to be ineligible (age limit exceeded, status of prematurity, source datasheets unreadable or age/weight mismatch) leaving data from 726 patients – a total of 7453 measurements, excluding pre-induction values - to be analysed. All age groups were homogenous with regard to demographic characteristics (Table 1) except for males being overrepresented in most groups. Procedures most frequently performed were otorhinolaryngological, gastrosurgical and orthopaedic (Table 2). Endotracheal tubes (ETT) were preferred in patients below 3 years of age (Table 1), and mask induction outnumbered intravenous induction in children 0 – 4 years, while intravenous maintenance predominated in all groups (Table 1).

Primary outcome: Median, interquartile ranges and outliers of blood pressures measured in each age group are presented in Figure 1.

Secondary outcomes: For patients < 1 year old median of ~~MAP (meanMAP) and~~ lowest MAP (~~mean~~MAP_{LOW}) was 47 mmHg (interquartile range; 38-58) (Figure 2). These readings increased to median MAP_{LOW} 51mmHg (interquartile range; 46-58) in 12 year old patients.

During the course of anaesthesia 32 patients (4.4%) received either one or more fluid boli (n=20) or vasoactive drugs (n=29) to adjust blood pressure (Table 3). Individual MAP at time points of intervention is illustrated in Figure 3.

Overall, blood pressure was not measured at any point during the anaesthesia in 81 patients (11%), predominantly among the youngest age groups (Table 4). In addition, the fraction of patients with missing pre-induction blood pressure measurement was higher in the lowest age groups, ranging from 95.1% in children < 1 year to 42% in children <13 years (Table 4).

Discussion

This observational study presents prospectively collected, multi-centre pragmatic MAP results in children undergoing GA in routine practice. Data from >700 children anaesthetized at a large number of Danish centres were included. In 89% of cases, blood pressure was measured as standard care. Of note, current blood pressure reference values are derived from population-based studies in healthy non-anaesthetized children. As a consequence, for children undergoing GA, safe ranges of blood pressure are not known. The lack of consensus on clear definitions of 'hypotension' might explain why, in the current data, the trigger values for intervention vary from MAP 25 to 45 mmHg in 0 year old children, MAP 50 to 75 mmHg in 7 year olds and 40 – 89 mmHg in children 11 years of age.

Recently, de Graaff et al reported reference values for non-invasive blood pressure (NIBP) of 116,362 anaesthetized children, derived in a register-based retrospective study conducted at multiple international centres.(9) Blood pressures were obtained by oscillometry and reported as systolic, diastolic and mean pressures. The 50th percentile of mean blood pressure ranged from 46 mmHg in the youngest (age 0 years) and increased throughout the age groups to reach 94 mmHg in children 12 years old. Current data lie well within these ranges.

Interestingly, when paediatric anaesthetists were asked to define significant intraoperative hypotension, the reported threshold values varied significantly. (10) In the same survey study, members from two different paediatric anaesthesia societies disagreed on the importance of pre-induction baseline values of blood pressure and which rate of decrease from baseline should be considered important. In the existing literature, various definitions of 'hypotension' have been proposed based on cerebral perfusion and brain tissue oxygenation. Rhondali et al referred to hypotension during sevoflurane anaesthesia as a relative decrease of blood pressures obtained awake. Flow velocity in the cerebral middle artery as assessed by transcranial Doppler sonography was reduced if MAP decreased >20% in infants <6 months and >40% in infants >6 months).(11) In another study the same group of authors defined hypotension as absolute values of MAP <35 mmHg in patients <6 months and <43 mmHg in patients ≥6 months.(12) This was based on the finding, that regional cerebral saturation of oxygen (rSO_2) assessed by near-infrared spectroscopy

(NIRS) dropped significantly, if MAP was lowered below these values. Michelet et al considered a decrease of 20% as ‘hypotension’ in infants <3 months comparing awake values of systolic blood pressure (SBP) to values obtained after induction of GA.(13) In a preclinical setup on piglets of ages which approximate 18 months old children with regard to brain development, Ringer et al associated various MAP ranges with $PbtO_2$.(4) Mean arterial pressures of 35-38mmHg (= “moderate hypotension (mHT)”) and 27-30mmHg (= ”severe hypotension (sHT)”) were chosen. It was observed that PtO_2 decreased significantly immediately after inducing hypotension with no difference between mHT and sHT.
Comparing the current data with these ranges, 30 children would have been exposed to moderate and 11 to severe hypotension (Supplement 2), potentially associated with reduced brain oxygenation.

Overall, in our data, MAP was lower in the youngest age groups. This finding is in accordance with the results of a recent randomized controlled study. Infants less than 60 conceptual weeks were scheduled for herniorraphy and assigned to either GA or regional anaesthesia (caudal block). Eighty seven percent of infants had a MAP of less than 45 mmHg.(5) A study using transcranial Doppler sonography showed significant variation in cerebral blood flow following a decrease in MAP from 62 to 39 mmHg in infants less than 6 months old. This suggests cerebral autoregulation to be immature in young infants, who might be particularly vulnerable to variations in MAP.(11) Yet, current data show the variation in MAP to be largest in the youngest age groups. Among the 11% of children who did not have their blood pressure measured at any point during anaesthesia a large proportion were children < 4 years old. Based on the findings cited above, it is strongly recommended to measure blood pressure continuously during GA in the youngest infants and to counteract large variation in blood pressure. It should be noted, however, that numerous factors influence cerebral autoregulation in children (e.g. age, anaesthesia, use of vasopressors, gender, temperature, inflammation, carbon dioxide) in an unfavourable way, resulting in inter-intervidual variation.(14) It might hence be impossible to select uniform safe blood pressure goals for all children undergoing anaesthesia. Consequently, in the individual child, occult cerebral hypoperfusion must be avoided by monitoring and optimizing relevant factors (e.g. oxygenation, ventilation, peripheral perfusion) besides blood pressure.

The strength of this study is the comprehensive collection of data. As a consequence, data are truly representative of Danish clinical practice. However, the oscillometric or invasive method to measure blood pressure e.g. choice of appropriate size of inflatable cuff and site of measurement upper or lower extremity etc. was not standardized and data might have been under- or overestimated. Furthermore, we did not assess anaesthesia depth, amounts of analgesics administered or level of anxiety prior to induction. These variables are all known to influence blood pressure and might skew our results.

Organ specific outcomes were not assessed. In order to define ranges of blood pressure sufficient to meet oxygen demands of specific organs, their functions should have been properly evaluated and associated with levels of blood pressure. This was beyond the scope of this study. However, alleged complications of intraoperative hypotension comprise brain ischemia, kidney dysfunction, myocardial ischemia and multiple organ dysfunction.(15) All of these events are detrimental and hence the design of studies which assess appropriate outcomes in order to define safe limits of blood pressures are warranted.

Conclusion

This study has prospectively and pragmatically assessed blood pressure monitoring in children during GA in a range of routine practice. In the youngest and most vulnerable infants, the variability in mean arterial blood pressure appears to be large. In the same age group, measurement of blood pressure in practice appears to be inconsistent, although considered ‘standard-of-care’. In order to prevent perioperative detrimental effects following blood pressure variation or hypotension, measurement of blood pressure is recommended during every GA and in children of all ages. Safe ranges of blood pressure remain to be defined.

Conflicts of interest

None of the authors have any conflicts of interest to report.

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Tables and Figures

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Tables 1 + 2 + 3 + 4 version 1.1

Table 1: Patient characteristics: age in years; number of patients in each group; mean weight in kg (±SD); ASA classification, total numbers per age group; gender (male/female); status of prematurity (i.e. number of patients born before week 37), total numbers; Intravenous (i.v.) induction in percent, Airway-management (percentage), Maintenance (inhalational, total intravenous anaesthesia (TIVA), regional (peripheral/central blok as adjuvant to general anaesthesia), percentages

Age in years	Number of children	Body-weight (kg ± SD)	ASA, total numbers				Gender (m/f)	Prematurity (status of)	I.v. Induction (%)	Maintenance			Airway management		
										Inhalation (%)	TIVA (%)	Regional (%)	LMA (%)	ETT (%)	Spontaneous (%)
0	61	7.1 (2.5)	26	20	7	2	28 / 23	5	35	48	51	2	17	66	17
1	68	11.1 (2.1)	38	19	6	0	42 / 25	12	32	30	65	5	31	58	10
2	61	13.3 (2.1)	36	15	8	1	42 / 18	5	43	36	62	2	43	31	26
3	61	16.5 (2.9)	32	14	9	1	42 / 19	5	40	28	67	4	44	24	32
4	69	17.7 (2.4)	45	14	7	1	38 / 31	3	46	15	82	3	58	26	17
5	58	20.4 (3.1)	37	15	4	0	36 / 22	3	60	4	92	4	55	26	19
6	42	24.2 (5.4)	33	3	3	0	19 / 22	4	48	13	77	10	46	29	24

7	53	27.2 (5.9)	38	10	4	0	34 / 19	2	69	13	81	6	56	31	13
8	50	30.6 (8.3)	30	15	3	0	34 / 16	1	59	13	83	4	52	28	20
9	45	35.6 (8.6)	29	15	1	0	26 / 19	3	67	5	93	2	51	35	14
10	57	37.0 (8.7)	46	5	5	0	34 / 20	3	86	0	95	5	64	34	2
11	50	40.5 (9.6)	36	8	2	0	31 / 19	2	90	13	85	2	49	39	12
12	51	45.2 (9.5)	37	8	5	0	29 / 22	1	84	14	80	6	38	48	14

Table 2: Number of children in each type of surgery, per age in years

Age	**ORL***	**Neurosurgical**	**Gastrosurgical**	**Urological**	**Orthopaedic**	**Diagnostic procedures**	**Dental**	**Plastics**	**Other**
0	7	1	19	4	2	12	0	4	13
1	18	2	11	16	5	7	2	1	11
2	13	0	10	7	4	13	3	1	12
3	14	0	13	3	11	8	0	0	13

4	14	2	10	9	12	6	4	1	10
5	7	0	11	3	12	12	2	1	12
6	8	0	2	4	16	3	1	0	9
7	9	0	6	4	16	6	3	1	10
8	5	2	5	8	13	10	0	0	9
9	6	0	4	3	18	3	3	1	7
10	6	0	8	6	30	2	2	0	4
11	7	1	6	8	14	2	3	2	8
12	10	1	6	3	19	3	3	2	4
Sum	**124**	**9**	**111**	**78**	**172**	**87**	**26**	**14**	**122**

*Otorhinolaryngological

Table 3: Blood pressure modulating interventions registered. For each age group in years number of patients and interventions is shown (absolute numbers); type of intervention is specified

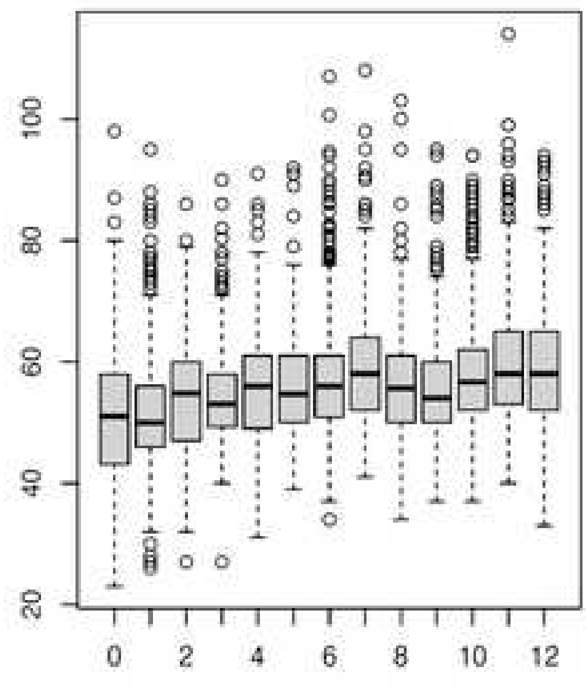
Age in years	Number of patients	Interventions	Fluid boli	Vasoactive medications, administration of
0	3	8	5	3
1	3	12	7	5
2	3	3	2	1
3	1	1	0	1
4	1	1	1	0
5	2	2	0	2
6	1	1	0	1

7	4	4	0	4
8	1	1	0	1
9	7	7	1	6
10	3	6	4	2
11	3	3	0	3
12	0	0	0	0
Sum	32	49	20	29

Table 4: Sum of individual mean arterial pressure (MAP) measurements; fractions of children with MAP available before or at any time during anaesthesia, per age group

Age in years	Number of children	Sum of individual MAP measurements	Availability of pre-induction MAP, percent %	Unavailability of MAP measurements at any time absolute numbers and percent % of children
0	61	492	3 (4.9)	10 (16)
1	68	641	7 (10.3)	7 (10)
2	61	370	3 (4.9)	14 (23)

3	61	476	10 (16.4)	12 (20)
4	69	664	15 (21.7)	6 (9)
5	58	549	16 (27.6)	8 (14)
6	42	452	11 (26)	4 (10)
7	53	508	17 (32)	5 (9)
8	50	478	13 (26)	8 (16)
9	45	646	27 (60)	3 (7)
10	57	829	36 (63)	0 (0)
11	50	622	24 (48)	1 (2)
12	51	726	30 (58)	3 (6)
Total	726	7453	212 (29)	81 (11)



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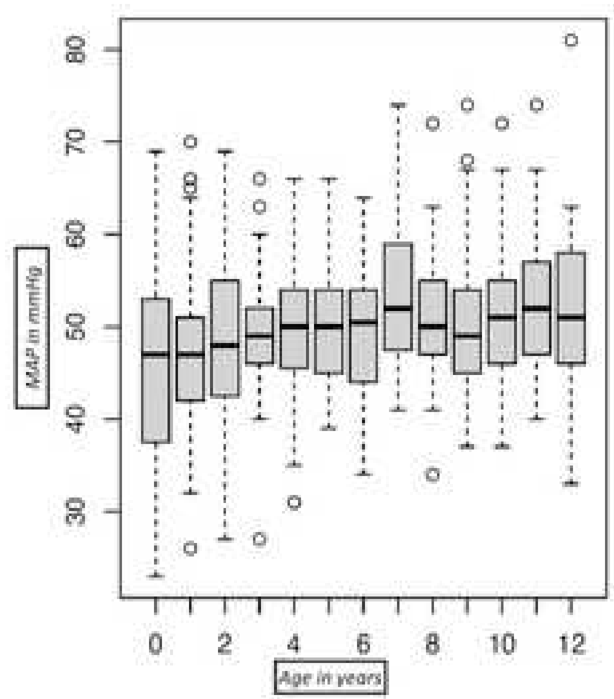

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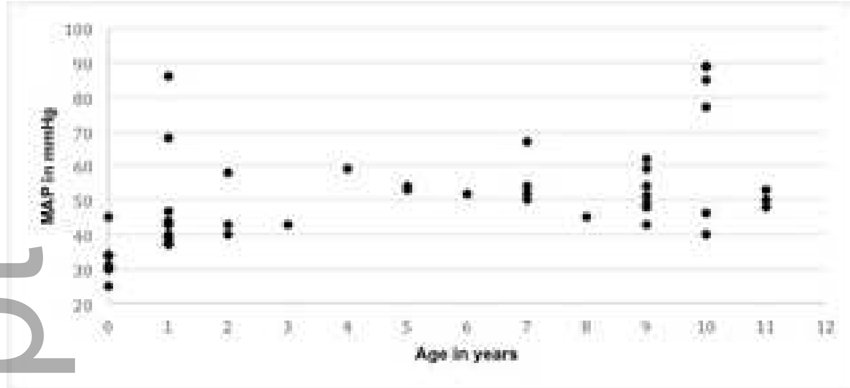

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