PCRC Proposal Cover Sheet

Title: Development of reference ranges for vital signs for children during anesthesia

Principle Investigator: Jurgen C. de Graaff, M.D., Ph.D.

Co-Investigators: Wietze Pasma D.V.M., Wilton van Klei M.D., Ph.D, Stef van Buuren, Olubukola O. Nafiu, and others as appropriate

Approved by Mentor: Sachin Kheterpal, M.D., M.B.A.

Type of Study: Retrospective, observational cohort study

Hypothesis: To develop vital signs percentile curves for children under anesthesia

Number of Patients/Participants: 50,000 – 250,000 patients younger than 18 years

Power Analysis: NA

Proposed statistical test/analysis: To develop percentile curves with vital signs on the y-axis and the patient age on the x-axis using the Box-Cox family of distribution available in the generalized additive models for location, scale and shape (GAMLSS) package for R software.

Resources (Brief summary of resources for data collection, personnel, financial): Departmental sources only.

- Jurgen de Graaff M.D., Ph.D.: 20% protected time for dedicated research, Assistant Professor of Pediatric Anesthesia, University Medical Center Utrecht, The Netherlands.
- Wietze Pasma D.V.M. 100% data manager for research purposes and MPOG database manager.
- Wilton van Klei M.D., Ph.D. : mentor, 20% research protected time for dedicated research, Associate Professor of Anesthesiology and Head Department of Anesthesiology, Manager Research and Education Division of Anesthesiology, Intensive Care and Emergency Medicine, University Medical Center Utrecht, The Netherlands.
- Prof. Stef van Buuren, Netherlands Organisation for Applied Scientific Research TNO, Leiden
- Olubukola O. Nafiu, MD, FRCA
- Sachin Kheterpal, MD, MBA

Introduction

What is the significance of the clinical problem being addressed?

Monitoring of vital signs (blood pressure, heart rate, oxygen saturation, respiratory rate, and ETCO2) during anesthesia is standard care according to the American Society of Anesthesiologists (ASA) practice guidelines. In children, interpretation of vital signs is based on age and weight related reference ranges. A reference range represents the natural variation in measurements between children. An unusually low or high value relative to the reference alerts the medical practitioner, who can scrutinize the particular measurement, and take appropriate action if needed.[1] Customarily, observations outside the 5^{th} and 95^{th} percentiles at the patient's age are considered unusually low or high. References are known for many vital signs, but they are almost always calculated from measurements of subjects who are awake. Although vital signs are routinely monitored during anesthesia, there appear to be no reference ranges for children under anesthesia.[2]

Current reference values for vital signs are derived from population based studies in healthy children with ambulatory measurements.[1;3;4] Heart and respiratory rate percentile curves for hospitalized children became available recently.[5;6] However, these references cannot be generalized or extrapolated to children under anesthesia, because anesthetic drugs induce significant changes in vital signs values due to reduced respiratory function, cardiac output and vascular resistance.[2;7;8] Therefore, it is unknown which values are to be considered 'normal' within those circumstances, and which values are to be considered deviating and thus require further scrutiny or treatment.

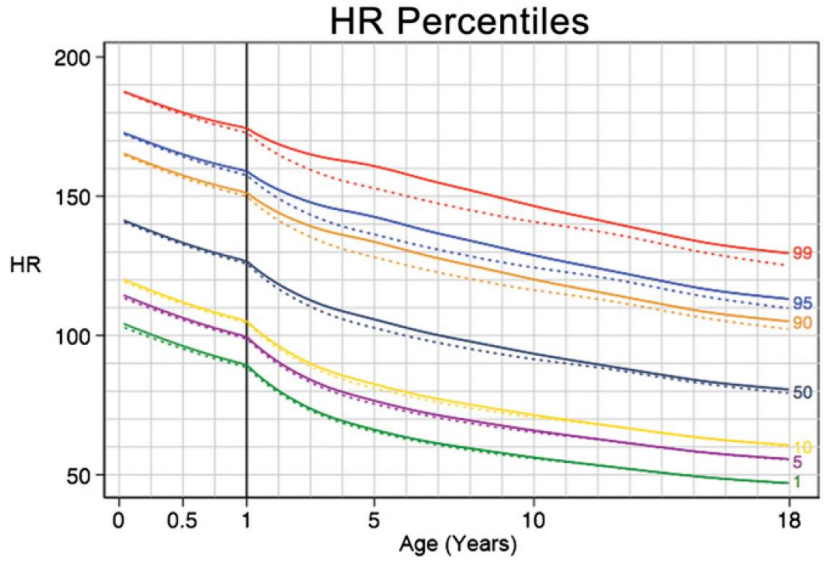

Figure 1: Sample of percentile curves for Heart Rate (HR) in hospitalized children. Dotted lines represent sensitivity analysis excluding diseases of the respiratory system. Solid vertical line at 1 year of age represents a change in scale of the x-axis.(4)

The absence of appropriate reference values for vital signs cause a wide variation in diagnosis and subsequent treatment of potential derangement. For example, the threshold for intraoperative hypotension used in practice varies substantially between anesthesiologists, where some set the threshold at a 10% decrease from the baseline value, while others take 40%.[2]

Reference ranges for vital signs in children would aid anesthesiologists in detecting extreme values that justify further inquiry or require action, and would harmonize diagnosis and treatment between anesthesiologists, hospitals, and countries. Therefore, the primary aim of this study is to present age- and weight- (for children younger than 1 year) specific reference ranges for vital signs in children during anesthesia. The present proposal focuses on non-invasive blood pressure (NIBP) and heart rate (HR) in children. Reference values for other vital signs (including invasive blood pressure, oxygen saturation, respiratory rate, ETCO2) are planned for a future proposal.

Methods

IRB statement

The study of de-identified patient data from the MPOG dataset has been approved by the Colorado Multiple Institutional Review Board, which governs research at our institution. Participation of the UMCU in the MPOG study has been approved by the Institutional Review Board of the University Medical Center Utrecht (12.253-C). The here proposed study protocol has been reviewed by the Institutional Review Board of the University Medical Center Utrecht, which waved the need for informed consent, as patients were not subjected to investigational actions (13-320/C, June 24th, 2013). Patient confidentiality was guaranteed according to the Dutch law on personal data protection.

Study type

We propose a multicenter retrospective cohort study using de-identified patient data from the MPOG data set.[9]

Primary outcome

Percentile curves for NIBP and HR in relation to gender, age, weight and height in healthy children under anesthesia will be developed.

Secondary outcome(s), where applicable

The variance and influence of comorbidities, medication and other determinants (including obesity, surgical specialty and center) will be evaluated.

Patient inclusion criteria

The population consists of all healthy children (ASA physical status class 1, ≤18 years old) who underwent anesthesia for elective surgery and/or diagnostic procedures in one of 5 academic pediatric hospitals in the period August 2007 and December 2013.

Patient exclusion criteria

- Emergency surgery
- ASA physical status class > 1
- Patients for cardiac surgery or percutaneous cardiac interventions or with hypertension, renal disease, or on use of steroids, diuretics, blood pressure medication or beta-blockers are likely excluded based on ASA score, but these parameters will be checked supplementary.

Data source

Automatically acquired data on NIBP and HR from the MPOG database will be used. Because a child could be included in the analyses more than once, the results are presented based on the level of cases. A case is defined as the registration of an anesthetic procedure from induction to end of anesthesia when the patient leaves the operating room or procedure suite.

To get insight into reference values for NIBP and HR, only measurements acquired during a stabilized period will be used. The analyses will be performed **during the preparation phase** (the period between end of anesthetic induction and start of surgery or intervention.

Multiple measurements for NIBP and HR during the preparation phase per case will be available. For NIBP, the mean of the last three measurements before incision will be calculated and used for analyses. For HR, the mean of the last five minutes before incision will be calculated and used. NIBP and HR will only be included if a predefined number or minimum period of measurements is available to control for bias.

These definitions are:

For *blood pressure*: a minimum of 2 measurements, and > 0 mmHg with a pulse pressure > 5 mmHg and a systolic blood pressure greater than the mean arterial pressure, larger than the diastolic blood pressure and lower than 300 mm Hg will be included. To minimize the number of artifacts only NIBP > 0 mmHg

with a pulse pressure > 5 mmHg and a systolic blood pressure greater than the mean arterial pressure, larger than the diastolic blood pressure and lower than 300 mm Hg will be included.
For *Heart rate:* a minimum of 5 minutes recording, and measurements ranging between 10 and 300.

Statistical analysis

The HR and NIBP will be analyzed according to the methods recommended by the WHO for child growth standards, and be calculated in cooperation with the Netherlands Organization for Applied Scientific Research TNO (https://www.tno.nl/).[10] For each outcome a choice will be made between the Box-Cox Cole-Green (BCCG), the Box-Cox Power Exponential (BCPE) 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 (GAMLSS) package for R software.[11] Where needed transformations of the variables will be used to increase fit. Differences between centers will be estimated by adding dummy variables, as practiced in [12] in this context. Growth charts of the final solutions will be drawn and the reference values will be tabulated for publication.
The analyses will be performed during the preparation phase (the period between end of anesthetic induction and start of surgery or intervention. Any period used for defining reference values has advantages and disadvantage. Therefore, we propose a two-step approach:
1) an initial simple analyses performed in a relative stable period without interventions (intubation or detubation) and hemodynamic shifts (e.g. blood loss in the surgical phase): during the preparation phase (the period between end of anesthetic induction and start of surgery or intervention.
2) an intensive detailed analyses in which we develop reference ranges for subgroups with specific risk factors (co-morbidities, obesitas, medication, hypertension etc), type of surgery and phase of anesthesia (induction , maintenance, recovery phase). The influence of age, weight (including overweight and obesity), length and specific co-morbidities (e.g. actual use of blood pressure medication and beta-blocker) and progress of the vital NIBP and HR during the procedure will be investigated by regression analysis of Z-scores relative to the newly derived references. This will require intensive analyses and modeling of the data which specific techniques that will be developed specifically.

Power analysis

By including all surgical and diagnostic procedures on children under 18 years old conducted between August 2007 and December 2013, we expect to include 250,000 cases. This sample is much larger than is customary in the field (typically n = 1000 to n = 10000 children), so no issues of lack of power are expected.

Known Limitations/Questions for PCRC

The present study proposal is hampered by the validity of measurements in AIMS. Effects of measurement error are reduced by taking the mean over the measurement.

Study group

- Jurgen C. de Graaff, M.D., Ph.D., assistant professor, is pediatric anesthesiologist and epidemiologist and has background in institutional database analysis in perioperative variables, complications and outcome after anesthesia.
- Wietze Pasma ,D.V.M. Data manager for local MPOG database, Department of Anesthesia
- Wilton van Klei M.D., Ph.D., associate professor, is anesthesiologist and epidemiologist and head of Department of Anesthesiology and has background in institutional and national database analysis in perioperative variables, complications and outcome after anesthesia.
- Prof. Stef van Buuren is a statistician at the Netherlands Organisation for Applied Scientific Research TNO, and holds a chair as Professor in Applied Statistics in Prevention at the University of Utrecht. Van Buuren was the project leader of the Fifth Dutch Growth Study, developed the worm plot, has wide experience in modeling growth reference curves, and was a member of the WHO advisory committee for selecting appropriate methodology to calculate growth charts.
- Olubukola O. Nafiu MD, FRCA, is pediatric anesthesiologist and has experience in blood pressure analysis in pediatric anesthesia.
- Sachin Kheterpal MD, MBA, Assistant Professor of Anesthesiology, University of Michigan, developed and manages the MPOG dataset, and has a research background and interest in the intraoperative impact on patient outcomes.

Variables to be collected

Data Column	Source table	Column or concept	Concept ID	Remarks	AIMS UMCU
Age in years	AIMS_intraopcaseinfo	AIMS_age_Years			
Gender	AIMS_patient	AIMS_sex			
Type of surgery	AIMS_intraopcaseinfo	AIMS_Scheduled_Procedure_Text		not used in UMCU	
Type of surgery	AIMS_intraopcaseinfo	AIMS_Actual_Procedure_Text			Requires to be categorized by local anesthesists, medical specialism is registered
Age in months	AIMS_intraopcaseinfo	AIMS_Age_Months			
Age in weeks	AIMS_intraopcaseinfo	IMS_Age_Weeks			
Post-conceptional age	AIMS_preop	General - Post conceptual age	70424		Available age < 1 yr.
Weight	AIMS_preop	Physical Exam - Weight (kg)	70264		In KG measured at date of surgery
Weight	AIMS_preop	Physical Exam - Weight (lb)	70265	Value not used in UMCU	Can be calculated from 70264
ASA PS	AIMS_preop	Assessment and Plan - ASA Physical Status	70233		
Anesthesia technique (GA, Epidural/caudal, spinal, locoregional and Combinations)	AIMS_preop	Assessment and Plan - Anesthesia Technique	70220	Calculated value	
Heart rate (HR) during	AIMS_intraopphysiologic	SpO2 Pulse Rate	3010		

Data Column	Source table	Column or concept	Concept ID	Remarks	AIMS UMCU
anesthesia	AIMS_intraopphysiologic	EKG Pulse Rate	3005		
NIBP Systolic Blood pressure	AIMS_intraopphysiologic	BP Sys Non-invasive	3015		
NIBP Mean Blood pressure	AIMS_intraopphysiologic	BP Mean Non-invasive	3025		
NIBP Diastolic Blood pressure	AIMS_intraopphysiologic	BP Dias Non-invasive	3020		
Respiratory rate (RR)	AIMS_intraopphysiologic	Respiratory Rate Actual from EtCO2 tracing	3230		
	AIMS_intraopphysiologic	Respiratory Rate by EKG Bioimpedence	3180	not used in UMCU	Comparable with 3230
Type of anesthesia (general, general with locoregional anesthesia, spinal anesthesia)	AIMS_preop	Assessment and Plan - Anesthesia Technique	70220		Calculated from other values in UMCU
Type of ventilation (spontaneous, mechanical)					Calculated from other values in UMCU
End tidal CO2	AIMS_intraophysiologic	End Tidal CO2 %	3236		
	AIMS_intraophysiologic	End Tidal CO2 (mmHg)	3235	not used in UMCU	Calculated from 3236
Peripheral oxygen saturation	AIMS_intraophysiologic	SpO2 %	3045		

Data Column	Source table	Column or concept	Concept ID	Remarks	AIMS UMCU
Institution	Aims_IntraopCaseInfo_DI	MPOG_Institution_ID			
Start anesthesia	AIMS_IntraopNotes	AACD Anesthesia Start Date/Time	50002		
Induction time	AIMS_IntraopNotes	AACD Induction Start Date/Time	50004		
End of anesthetic induction time	AIMS_IntraopNotes	ACCD Induction End Date/Time	50005		
Surgical incision time	AIMS_IntraopNotes	ACCD Procedure Start Date/Time	50006		
End of surgical procedure	AIMS_IntraopNotes	ACCD Procedure Finish Date/Time	50007		
End anesthesia	AIMS_IntraopNotes	AACD Anesthesia End Date/Time	50009		

Management of missing data

Cases with missing data will not be included in the analyses.

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