An International, Multicenter, Observational Study of Cerebral Oxygenation during Infant and Neonatal Anesthesia

Vanessa A. Olbrecht, M.D., M.B.A., Justin Skowno, F.C.A., F.A.N.Z.C.A., Vanessa Marchesini, M.D., Lili Ding, Ph.D., Yifei Jiang, M.D., Ph.D., Christopher G. Ward, M.D., Gaofeng Yu, M.D., Huacheng Liu, M.D., Ph.D., Bernadette Schurink, M.D., Laszlo Vutskits, M.D., Ph.D., Jurgen C. de Graaff, M.D., Ph.D., Francis X. McGowan, Jr., M.D., Britta S. von Ungern-Sternberg, M.D., Ph.D., D.E.A.A., F.A.N.Z.C.A., Charles Dean Kurth, M.D., Andrew Davidson, M.B.B.S., M.D., F.A.N.Z.C.A.

ABSTRACT

Background: General anesthesia during infancy is associated with neurocognitive abnormalities. Potential mechanisms include anesthetic neurotoxicity, surgical disease, and cerebral hypoxia–ischemia. This study aimed to determine the incidence of low cerebral oxygenation and associated factors during general anesthesia in infants.

Methods: This multicenter study enrolled 453 infants aged less than 6 months having general anesthesia for 30 min or more. Regional cerebral oxygenation was measured by near-infrared spectroscopy. We defined events (more than 3 min) for low cerebral oxygenation as mild (60 to 69% or 11 to 20% below baseline), moderate (50 to 59% or 21 to 30% below baseline), or severe (less than 50% or more than 30% below baseline); for low mean arterial pressure as mild (36 to 45 mmHg), moderate (26 to 35 mmHg), or severe (less than 25 mmHg); and low pulse oximetry saturation as mild (80 to 89%), moderate (70 to 79%), or severe (less than 70%).

Results: The incidences of mild, moderate, and severe low cerebral oxygenation were 43%, 11%, and 2%, respectively; mild, moderate, and severe low mean arterial pressure were 62%, 36%, and 13%, respectively; and mild, moderate, and severe low arterial saturation were 15%, 4%, and 2%, respectively. Severe low oxygen saturation measured by pulse oximetry was associated with mild and moderate cerebral desaturation; American Society of Anesthesiology Physical Status III or IV *versus* I was associated with moderate cerebral desaturation. Severe low cerebral saturation events were too infrequent to analyze.

Conclusions: Mild and moderate low cerebral saturation occurred frequently, whereas severe low cerebral saturation was uncommon. Low mean arterial pressure was common and not well associated with low cerebral saturation. Unrecognized severe desaturation lasting 3 min or longer in infants seems unlikely to explain the subsequent development of neurocognitive abnormalities. **(Anesthesiology 2018; 128:85-96)**

NEUROLOGIC injury during pediatric anesthesia and surgery has always been a significant concern, especially during cardiovascular and neonatal surgery.[1,2] During the past few years, there has been concern for potential neurologic injury during anesthesia in infants without congenital heart disease related to potential neurotoxicity of anesthetic drugs[3] and cerebral hypoxia–ischemia related to hypotension and hypoxia during surgery.[4] Determining the incidence of low cerebral saturation during anesthesia in infants and neonates, as well as associated physiologic factors, such as hypotension and hypoxemia, could improve anesthetic safety, because these mechanisms may be preventable causes of neurologic injury.

In pediatric anesthesia, current standard monitoring includes electrocardiogram to monitor heart rate (HR) and rhythm, pulse oximetry saturation (Spo_2), arterial pressure, respiratory rate, and end-tidal carbon dioxide ($ETCO_2$). Real-time measurement of cerebral tissue hemoglobin oxygenation using near infrared spectroscopy (NIRS) is widely used in cardiac anesthesia and neonatal and pediatric intensive care units but is infrequently deployed outside of these areas. NIRS noninvasively measures cerebral oxygen

What We Know about This Topic

- Intraoperative cerebral hypoperfusion and ischemia in infants is a potential cause of later cognitive impairment
- The investigators thus evaluated cerebral saturation in 453 infants undergoing surgery
- Severe desaturation was rare and poorly associated with hypotension

What This Article Tells Us That Is New

- Cerebral desaturation seems an unlikely explanation for cognitive dysfunction
- Whether anesthesia provokes cognitive dysfunction in infants remains highly controversial
- But to the extent that it does, mechanisms other than cerebral desaturation should be considered

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of the work presented in this article has been presented at the Society for Pediatric Anesthesia in Colorado Springs, Colorado, April 2, 2016; American Society of Anesthesia in Chicago,

 Anesthesiology 2018; 128:85-96

<zdoi;10.1097/ALN.0000000000001920>

saturation ($rSco_2$) in a tissue volume approximately 1 to 2 cm below the sensor reflecting a weighted average saturation in gas-exchanging vessels (arterioles, venules, and capillaries).[5] Low regional cerebral $rSco_2$ (less than 50% for greater than 7 h in neonatal intensive care patients[6] and less than 45% for greater than 3 h in pediatric cardiac intensive care)[7] has been linked to adverse neurodevelopmental outcomes and to cerebral ischemic lesions on magnetic resonance imaging in neonatal and pediatric cardiac intensive care. In piglet models of hypoxia–ischemia, low regional cerebral $rSco_2$ (less than 50%) results in decreased brain tissue energetics, electroencephalogram slowing, brain ischemic lesions, and neurobehavioral impairment.[8] In pediatric cardiac surgery, $rSco_2$ monitoring is regarded as the standard of care by many institutions,[9] because perioperative $rSco_2$ has been associated with neurologic lesions and neurodevelopmental outcomes.[7,10,11]

Several studies have recently examined regional cerebral oxygenation in infants during pediatric, noncardiac, surgical procedures.[12–15] In children under age 2 yr, $rSco_2$ usually increased with sevoflurane induction of anesthesia, although decreased $rSco_2$ during induction was associated with very low mean arterial pressure and younger age.[12] These studies suggest that unrecognized cerebral desaturation during anesthesia of infants occurs not infrequently and is often associated with hypotension. However, these studies were conducted at a single center in low numbers of patients, reflecting local anesthesia practice for the definition and treatment of arterial pressure, as well as ventilation and arterial oxygenation. Thus, these observations may not be generalizable to infant anesthesia practices across the world.

In the present prospective, multicenter, observational study, we sought to determine the incidence of low regional cerebral oxygenation during anesthesia in a large cohort of infants receiving general anesthesia for noncardiac surgery in centers located in Australia, the United States, China, and Italy. Our secondary aims were to describe regional cerebral oxygenation during surgery and to identify factors associated with cerebral desaturation.

Material and Methods

Study Design

This prospective, observational study involved eight pediatric hospitals: Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio), the Children's Hospital of Philadelphia (Philadelphia, Pennsylvania), the Children's Hospital at Westmead (Sydney, New South Wales, Australia), the Royal Children's Hospital (Melbourne, Victoria, Australia), Princess Margaret Hospital for Children (Perth, Western Australia, Australia), Guangzhou Children's Hospital (Guangzhou, China), Yuying Children's Hospital of Wenzhou (Wenzhou, China), and the Giannina Gaslini Children's Hospital (Genoa, Italy). Each site obtained institutional review board approval for the study. All of the centers agreed to the plan for data collection and statistical analysis *a priori*. The primary aim of this study was to determine the incidence of low regional cerebral oxygenation using NIRS in infants during anesthesia for noncardiac surgery; the secondary aims were to characterize changes in cerebral oxygenation during surgery and to identify factors associated with low cerebral oxygenation.

Patients

Patients were eligible for enrollment if they were less than 6 months of age (corrected to term birth) and scheduled to undergo a general anesthetic for noncardiac surgery expected to last greater than 30 min. Postmenstrual age (PMA) and gestational age were recorded: PMA at the date of surgery in weeks was equal to (date of surgery – estimated date of delivery + 280 days)/7, and gestational age at birth was equal to 40 weeks – (expected date of delivery – date of birth). Patient recruitment began on December 11, 2014, and ended May 31, 2016. Patients were excluded if application of the NIRS monitor was impractical (*i.e.*, surgery on the head or neck of the child), if they were diagnosed with congenital heart disease involving major cardiovascular shunting, if they were diagnosed with a neurologic disease of the brain, or if they had structural malformations of the frontal brain, scalp, or skull by history or physical examination. Eligible children were identified at each of the individual sites from the operating room schedule, or, for emergency cases, the coordinating anesthesiologist contacted the study team. A member of the local study team approached families preoperatively to explain the project and to obtain informed written consent.

Illinois, October 25, 2016; and Society for Pediatric Anesthesia in Austin, Texas, March 4, 2017. V.A.O. and J.S. contributed equally to this article.

Submitted for publication February 28, 2017. Accepted for publication September 11, 2017. From the Department of Anesthesiology (V.A.O., Y.J.) and Division of Biostatistics and Epidemiology (L.D.), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Department of Anaesthesia, Children's Hospital at Westmead, Sydney, New South Wales, Australia (J.S.); Discipline of Child and Adolescent Health, University of Sydney, Sydney, New South Wales, Australia (J.S.); Anaesthesia and Pain Management Research Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia (V.M., B.S., A.D.); Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (C.G.W., F.X.M., C.D.K.); Department of Anesthesiology, Guangzhou Women and Children's Medical Center, Guangzhou, China (G.Y.); Department of Anesthesiology, Second Affiliated Hospital and Yuying Children's Hospital of Whenzhou Medical University, Wenzhou, Zhejiang, China (H.L.); Department of Anaesthesia and Pain Management, Royal Children's Hospital, Melbourne, Victoria, Australia (B.S., A.D.); Department of Anesthesiology, Pharmacology, and Intensive Care, University Hospitals of Geneva, Geneva, Switzerland (L.V.); Department of Anesthesiology, Sophia Children's Hospital, Erasmus Medical Center, Rotterdam, The Netherlands (J.C.d.G.); School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia (B.S.v.U.-S.); and Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Western Australia, Australia (B.S.v.U.-S.).

Device

Cerebral oxygenation data for each institution were obtained using the SenSmart X-100 Regional Oximetry System (Nonin, USA). This device measures regional tissue hemoglobin oxygen saturation using spatially resolved spectroscopy principles and the modified Beer-Lambert law; absolute $rSco_2$ as measured by this device has been validated in neonates and infants over the range of $rSco_2$ 30 to 90% (average root mean square error = 4%).[16] Our study used the pediatric sensor containing light-emitting diodes at four wavelengths with photodiode detectors spaced 2 and 3 cm from the light source. The device captures $rSco_2$ every 3 s.

Data Collection

Preoperatively, medical history was obtained along with baseline physiologic data. The NIRS sensor was applied to the patient's forehead 2 cm above the supraorbital ridge lateral to midline before the induction of anesthesia. Apart from placing the NIRS sensor on the patient's forehead, the infants received standard care per the discretion of the anesthesia team. Baseline NIRS data were obtained before induction on room air. The sensor remained on the forehead throughout the anesthetic period and was removed after emergence from anesthesia in the operating room before transfer to the postoperative anesthesia care unit or the intensive care unit. Source data of the study were collected from the NIRS device, as well as from the perioperative anesthesia records. In the operating room, physiologic data were captured every 3 to 5 min in accordance with site standard of care *via* electronic medical chart or using the ICM+ physiologic data acquisition system (Cambridge University, United Kingdom). Timestamps were used to ensure data synchronization between NIRS and other physiologic data. At four sites, the anesthesia team was blinded to the NIRS values (Cincinnati Children's Hospital Medical Center, Children's Hospital of Philadelphia, Guangzhou Children's Hospital, and Yuying Children's Hospital of Wenzhou), whereas at the other four sites (Children's Hospital at Westmead, Royal Children's Hospital, Princess Margaret Hospital for Children, and Giannina Gaslini Children's Hospital) the team was not blinded; however, the unblinded group did not use the $rSco_2$ values to manage the anesthetic. Unblinded NIRS data were a requirement of the institutional review board at the unblinded institutions. Postoperatively, parents were contacted 7 days after the operation and asked whether their child had any seizures or other significant medical problems related to surgery.

Statistical Analysis and Definitions

Based on preliminary data of 50 patients from Cincinnati Children's Hospital Medical Center, the incidence of severe low cerebral oxygenation ($rScO_2$ less than 50%) was less than 2%. Given this incidence, which is a sample proportion of 0.010, a sample size of 450 patients would produce a two-sided 95% CI with a width equal to 0.020.

The following time points and definitions were defined *a priori* and used in data collection and analysis. *Baseline* included the time between placement of the NIRS probe on the patient's forehead before induction of anesthesia and administration of anesthetic drugs or supplemental oxygen to induce anesthesia. The average value during this time was used to define baseline $rSco_2$.

Induction included the time from administration of anesthetic induction drugs to the start of surgery (*e.g.*, incision). The average value during this time period was used to define induction $rSco_2$.

Surgery included the time from the start of surgery (*e.g.*, incision) until the last stitch or dressing was placed. The average value during this time period was used to define surgery $rSco_2$.

Emergence included the time from 3 to 5 min after the last stitch or dressing was placed and/or until the patient was extubated. The average value during this time period was used to define emergence $rSco_2$.

Prematurity was defined as infants born before 37 weeks' gestation. *Term* was defined as infants born at 37 weeks' gestation or later. *Expected date of delivery* was defined as the date mother expected the child to be born, calculated by 40 weeks after the first day of the last menstrual period, from an early ultrasound scan, or from date of conception plus 2 weeks.

Mild hypotension involved an arterial pressure event lasting greater than 3 min (mean arterial pressure of 36 to 45 mmHg or systolic blood pressure of 51 to 60 mmHg). *Moderate hypotension* included an arterial pressure event lasting greater than 3 min (mean arterial pressure of 26 to 35 mmHg or systolic blood pressure of 41 to 50 mmHg).[12] *Severe hypotension* involved an arterial pressure event lasting greater than 3 min (mean arterial pressure of 25 mmHg or less or systolic blood pressure of less than 40 mmHg).

Mild low arterial saturation included an arterial saturation event lasting greater than 3 min (Spo_2 80 to 89%). *Moderate low arterial saturation* included an arterial saturation event lasting greater than 3 min (Spo_2 70 to 79%). *Severe low arterial saturation* involved an arterial saturation event lasting greater than 3 min (Spo_2 less than 70%).

Mild low cerebral saturation involved an $rSco_2$ event lasting greater than 3 min (relative decrease in $rSco_2$ of 11 to 20% below baseline value or absolute $rSco_2$ 60 to 69%). *Moderate low cerebral saturation* included an $rSco_2$ event lasting greater than 3 min (relative decrease in $rSco_2$ of 21 to 30% below baseline value or absolute $rSco_2$ 50 to 59%).[17] *Severe low cerebral saturation* involved an $rSco_2$ event lasting greater than 3 min (relative decrease in $rSco_2$ greater than 30% below baseline value or absolute $rSco_2$ less than 50%).

Demographic and other data recorded on the paper Case Report Form were collated in an electronic REDCap database (hosted by the University of Sydney, Sydney, New South Wales, Australia) and then analyzed with R 2015 (R Core Team, Austria) and SAS version 9.3 (SAS Institute Inc., USA). Descriptive summary statistics of baseline and

intraoperative data for the patient population, as well as stratified by site, were presented as frequencies and percentages for categorical variables and mean and SD for continuous variables. Repeated measures of cerebral oxygenation and intraoperative data (*i.e.*, $rSco_2$, Spo_2, systolic blood pressure, mean arterial pressure, HR, and $ETCO_2$) were analyzed using mixed-effects models with surgery period as the fixed effect and subject nested within the study site as the random effect. Least square means and 95% CIs were estimated using the restricted maximum likelihood method. For the defined variables (low arterial pressure, low cerebral saturation, and low arterial saturation as defined above), incidence rate, frequency of events per patient, percentage of anesthesia time of each event, and percentage of total anesthesia time of all events were reported as median (range) or 95% CI.

For the primary outcomes, univariate regression models were run when incidence was not rare (greater than 5%). Predictors included patient demographics, intraoperative variables, and incidence of low arterial pressure and low arterial saturation based on variables identified *a priori* in our statistical analysis plan. $ETCO_2$ values were not included in regression analysis due to the unreliability of this measure in infants. Specifically, American Society of Anesthesiologists (ASA) physical status, history of prematurity, weight at the time of surgery, PMA at the time of surgery, and sex were demographic variables included in analysis; mild, moderate, and severe low arterial pressure and low arterial saturation were also included.

A *post hoc* area under the curve (AUC) analysis was conducted for time spent below absolute and relative regional cerebral saturation thresholds of any duration, measured in percentage of minutes of the anesthetic (100 times minutes below threshold/minutes of total anesthetic). This analysis includes all time below threshold (not just restricted to events lasting greater than 3 min in duration, as used in the remaining analyses). In addition, a *post hoc* description of the seven patients with severe cerebral desaturation was added per reviewer recommendation.

We compared patients from blinded and unblinded sites on demographics, intraoperative variables, and outcomes. A two-sample *t* test or Wilcoxon rank-sum test, as appropriate, was used for continuous variables, and chi-square test or Fisher exact test, as appropriate, was used for categorical variables. A *P* value of less than 0.05 was considered significant for all of the results.

Results

A total of 453 patients were included in the final data analysis (fig. 1). Patients averaged a PMA of 50 weeks and weight of 5 kg at the time of surgery (table 1). The majority were ASA physical status I or II, term birth, and male sex. Most patients underwent general surgical and urologic procedures not using laparoscopic techniques (table 2). Nearly 85% of patients received inhalational induction with sevoflurane, and 40% also received propofol and opioids at induction; 60% received neuromuscular blocking agents. Nearly 96% were maintained with inhaled anesthesia, and approximately 50% received a local anesthetic for regional analgesia (table 2).

Missing data were present in 6.5% of the 59,466 physiologic data points (2.7% in $rSco_2$ data) captured every 3 to 5 min from before the induction of anesthesia to after emergence from anesthesia in the operating room. Table 3 displays the incidence of low cerebral oxygenation, arterial pressure, and arterial saturation events greater than 3 min during the study. During the anesthetic time, approximately 27% (n = 106) of patients experienced events of greater than 10% decline in rSco2 from baseline, with more than 40% (n = 196) having an absolute $rSco_2$ less than 70% lasting greater than 3 min during the anesthetic, representing approximately 4 and 10% of the total anesthetic time, respectively (table 3). Moderate low $rSco_2$ was less common, with 6% (n = 24) having a greater than 20% decline of $rSco_2$ from baseline and 11% (n = 51) having an absolute $rSco_2$ less than 60%, representing 0.8% and 1.0% of the total anesthetic time, respectively; severe low $rSco_2$ was rare, with only 1.0% (n = 4) experiencing a greater than 30% decline of $rSco_2$ from baseline and 1.6% (n = 7) having an absolute value less than 50%, representing 0.1% of the total anesthetic time in both cases. Nearly two thirds of patients had mild hypotension, more than one third moderate hypotension, and more than 12% (n = 57) severe hypotension. The average number of mild and moderate hypotension events per patient were 2.5 and 1.0, respectively; 1 in every 5 patients experienced severe hypotension. In addition, these mild, moderate, and severe hypotensive events lasted for approximately 20, 8, and 2% of the total duration of the anesthetic, respectively. Decreased arterial oxygen saturation was far less common than hypotension: only 15, 4, and 2% (n = 66, 19, and 7, respectively) of patients experienced mild, moderate, and severe events of decreased Spo_2. In contrast to hypotensive events, the low Spo_2 events were brief, the duration of which was less than 1% of total anesthesia time. The majority of hypotension occurred during induction and surgery, whereas a minority occurred during emergence (table 4). Similarly, the majority of arterial and cerebral desaturation events occurred during induction and surgery (table 4).

There were significant differences in $rSco_2$ during the different periods of the study: the $rSco_2$ increased during induction and remained increased during surgery and emergence (fig. 2). There were no significant changes from baseline in Spo_2 during induction, surgery, or emergence. Statistical differences also occurred in HR between baseline and these time periods. There were statistically significant decreases in arterial pressure during induction, surgery, and emergence (fig. 2). Baseline data were not included for $ETCO_2$ due to inaccuracy of measurement in the patient population.

Table 5 reports the AUC analysis for regional cerebral saturation. Across the whole study population, the median percentage of minutes below the various thresholds of total

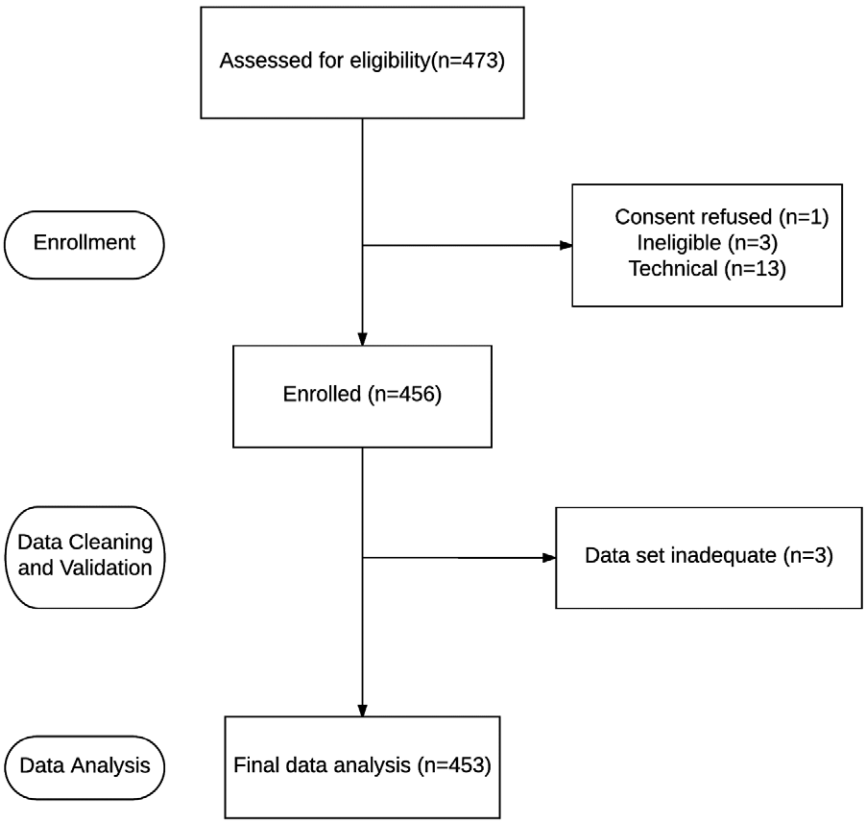

Fig. 1. Flow sheet documenting study recruitment, enrollment, and inclusion in final data analysis.

anesthetic minutes is minimal. A total of four patients experienced relative declines in $rSco_2$ of greater than 30% from baseline, for a median (95% CI) of 33% of minutes (1 to 100% of minutes). Eleven patients experienced absolute $rSco_2$ of less than 50% of any duration, for a median (95% CI) of 6% of minutes (22 to 76% of minutes).

Because severe cerebral desaturation events were uncommon (0.95% for greater than 30% decline of $rSco_2$ from baseline and 1.55% for absolute value less than 50%), the number of events was insufficient to conduct regression analysis. It was, however, possible to assess the factors associated with mild and moderate cerebral desaturation in univariate analysis (table 6). The factors with odds ratios greater than 3 for mild and moderate cerebral desaturation were severe low Spo_2 and ASA III or IV *versus* I. All of the other statistically significant factors had odds ratios less than 2 for mild or moderate cerebral desaturation.

A total of nine patients experienced severe cerebral desaturation: four patients had a greater than 30% decline from baseline, and seven patients had an absolute $rSco_2$ less than 50%; two patients met criteria that fit both definitions. See Supplemental Digital Content 1 (http://links.lww.com/ALN/B547), which is a table listing the nine cases and includes demographic information, operative details, degree of cerebral desaturation, duration of the cerebral desaturation, and details of the events.

A sensitivity analysis was conducted between blinded (USA and China) and unblinded (Australia and Europe) centers to assess the influence of blinding confounder. There were no differences between the centers for sex or incidence of prematurity. There was a disproportion of ASA I and II patients in blinded centers (ASA II = 50%; ASA I = 26%) *versus* unblinded centers (ASA II = 33%; ASA I = 41%; $P = 0.0024$). Weight and PMA at surgery were higher in blinded *versus* unblinded centers (median [interquartile range] = 6 [4 to 7] *vs.* median [interquartile range] = 5 [4 to 6], $P < 0.0001$ and 53 [45 to 59] *vs.* 48 [43 to 56], $P = 0.0002$, respectively). There were no differences between the centers for mild, moderate, or severe hypotension or incidence of greater than 20% decline of $rSco_2$ from baseline or absolute $rSco_2$ less than 60% or less than 50%. There were higher rates of mild, moderate, and severe low arterial saturation ($P < 0.0001$, $P < 0.0001$, and $P < 0.0201$, respectively) in blinded centers *versus* unblinded centers. There was also a higher rate of greater than 10% decline of $rSco_2$ from baseline and absolute $rSco_2$ less than 70% in blinded centers ($P = 0.0150$ and $P = 0.0014$, respectively). There were more infants having greater than 30% decline in $rSco_2$ from baseline in unblinded *versus* blinded centers (n = 4 *vs.* n = 0; $P = 0.0240$).

No seizures were reported in any of the patients in the study population, nor did any experience other cerebral

Table 1. Study Population Demographic Information Reported by Study Site and as a Whole

Patient Characteristics	CCH (N = 79)	CHP (N = 76)	CHW (N = 50)	GEN (N = 6)	GZH (N = 71)	PMH (N = 58)	RCH (N = 84)	WZH (N = 29)	Total Values (N = 453)
Gestational age at birth, mean ± SD, weeks	37 ± 8	36 ± 5	37 ± 5	36 ± 3	40 ± 0	38 ± 4	38 ± 3	38 ± 3	38 ± 5
Postmenstrual age at surgery, mean ± SD, weeks	50 ± 9	50 ± 8	47 ± 8	48 ± 8	57 ± 5	51 ± 8	50 ± 9	53 ± 8	51 ± 9
Weight at surgery, mean ± SD, kg	5 ± 2	5 ± 2	5 ± 2	5 ± 2	7 ± 1	5 ± 2	5 ± 2	6 ± 3	5 ± 2
ASA physical status, n (%)									
I	11 (14)	15 (20)	17 (34)	0 (0)	17 (24)	32 (55)	20 (35)	23 (79)	135 (32)
II	34 (44)	37 (49)	19 (38)	1 (100)	50 (71)	16 (28)	19 (33)	6 (21)	182 (43)
III	24 (31)	24 (32)	12 (24)	0 (0)	3 (4)	10 (17)	15 (26)	0 (0)	88 (21)
IV	9 (11)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	4 (7)	0 (0)	15 (4)
Sex, n (%)									
Men	57 (72)	57 (75)	33 (66)	2 (33)	45 (63)	44 (76)	59 (70)	19 (66)	316 (70)
Women	22 (28)	19 (25)	17 (34)	4 (67)	26 (37)	14 (24)	25 (30)	10 (34)	137 (30)
Prematurity, n (%)	32 (41)	23 (20)	18 (36)	4 (67)	0 (0)	17 (29)	23 (27)	5 (17)	122 (27)

Postmenstrual age at surgery in weeks was defined as follows: (date of surgery – estimated date of delivery + 280 days)/7. Gestational age at birth was defined as follows: 40 weeks – (expected date of delivery – date of birth). Prematurity was defined as birth before 37 weeks' gestation.

ASA = American Society of Anesthesiologists; CCH = Cincinnati Children's Hospital Medical Center; CHP = Children's Hospital of Philadelphia; CHW = Children's Hospital at Westmead, Sydney; GEN = Giannina Gaslini Children's Hospital; GZH = Guangzhou Children's Hospital; PMH = Princess Margaret Children's Hospital; RCH = Royal Children's Hospital Melbourne; WZH = Yuying Children's Hospital of Wenzhou.

Table 2. Intraoperative Variables of the Study Population Reported by Site and as a Whole

Intraoperative Variables (Anesthetic, Surgical, and Physiologic)	CCH (N = 79)	CHP (N = 76)	CHW (N = 50)	GEN (N = 6)	GZH (N = 71)	PMH (N = 58)	RCH (N = 84)	WZH (N = 29)	Total Values (N = 453)
Type of surgery performed categorized by risk, n (%)									
Major risk surgery	22 (28)	16 (21)	17 (34)	3 (60)	20 (28)	12 (21)	32 (38)	12 (41)	134 (30)
Intermediate risk surgery	43 (54)	32 (42)	16 (32)	2 (40)	44 (62)	28 (48)	32 (38)	15 (52)	212 (47)
Minor risk surgery	14 (18)	28 (37)	17 (34)	0 (0)	7 (10)	18 (31)	20 (2)	2(7)	106 (23)
Type of surgery performed categorized by specialty, n (%)									
Otolaryngology	13 (16)	0 (0)	5 (10)	0 (0)	21 (27)	7 (12)	3 (4)	1 (3)	50 (11)
General surgery	50 (63)	51 (67)	34 (68)	2 (40)	28 (39)	31 (53)	49 (58)	15 (5)	260 (57)
Orthopedic surgery	3 (4)	1 (1)	2 (4)	2 (40)	8 (11)	8 (14)	2 (2)	7 (24)	33 (7)
Urology	13 (16)	18 (24)	7 (14)	0 (0)	14 (20)	10 (17)	25 (30)	4 (14)	91 (20)
Neurosurgery (spine)	0 (0)	6 (8)	0 (0)	1 (20)	0 (0)	1 (2)	0 (0)	0 (0)	8 (2)
Ophthalmology	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (1)	2 (7)	4 (1)
Radiology	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (17)	4 (5)	0 (0)	6 (1)
Laparoscopic technique, n (%)	26 (33)	36 (47)	4 (8)	2 (33)	14 (20)	5 (9)	9 (11)	1 (3)	97 (21)
Agents used at induction, n (%)									
Sevoflurane	73 (92)	72 (95)	49 (98)	6 (100)	18 (25)	54 (93)	79 (94)	28 (97)	379 (84)
Propofol	22 (28)	37 (49)	2 (4)	4 (67)	71 (100)	11 (19)	34 (40)	2 (7)	183 (40)
Neuromuscular blockers	50 (63)	49 (64)	33 (66)	1 (17)	71 (100)	22 (38)	34 (40)	16 (55)	276 (61)
Opioids	37 (47)	14 (18)	14 (28)	6 (100)	70 (99)	9 (16)	23 (27)	10 (34)	183 (40)
Agents used in maintenance, n (%)									
Inhaled anesthetic	73 (92)	68 (89)	50 (100)	5 (83)	70 (99)	58 (100)	81 (96)	29 (100)	434 (96)
Propofol	6 (8)	13 (17)	2 (4)	1 (17)	3 (4)	22 (38)	16 (19)	0 (0)	63 (14)
Neuromuscular blockers	45 (57)	15 (20)	9 (18)	2 (33)	12 (17)	23 (40)	26 (31)	0 (0)	132 (29)
Opioids	56 (71)	33 (43)	25 (50)	3 (50)	11 (15)	27 (47)	31 (37)	1 (3)	187 (41)
Regional anesthesia, n (%)	19 (24)	53 (70)	22 (44)	2 (33)	10 (14)	49 (84)	61 (73)	17 (59)	233 (51)

Major risk surgical procedures include anorectoplasty, laparotomies (including gastroschisis repair, omphalocele closure, exploratory laparotomy, and Kasai procedure), laminectomy for tethered cord release, major urogenital procedures (including ureteral reimplantation, adrenalectomy, partial nephrectomy, and complete nephrectomy), tracheoesophageal fistula repair, and thoracotomy. Intermediate risk surgical procedures include laparoscopic surgery, airway surgery (including microlaryngoscopy, bronchoscopy, and tracheostomy), oral surgery (including cleft lip and/or palate repair), cystoscopic surgery, minor orthopedic surgery (including shoulder arthroscopy, digit surgery, spica cast placement, and hip reduction), and pyloromyotomy (including open and laparoscopic). Minor risk surgical procedures include male urogenital surgery (including orchidopexy, circumcision, revision circumcision, hypospadias repair, and chordee release), inguinal hernia repair (both unilateral and bilateral), and esophagoscopy.

CCH = Cincinnati Children's Hospital Medical Center; CHP = Children's Hospital of Philadelphia; CHW = Children's Hospital at Westmead, Sydney; GEN = Giannina Gaslini Children's Hospital; GZH = Guangzhou Children's Hospital; PMH = Princess Margaret Children's Hospital; RCH = Royal Children's Hospital Melbourne; WZH = Yuying Children's Hospital of Wenzhou.

Table 3. Description of Low $rSco_2$, MAP, SBP, and Spo_2 Events for Greater Than 3 min during Anesthesia

	Incidence (%) (95% CI)	Frequency of Events per Patient, Median (Range)	Percentage of Anesthesia Time of Each Event, Median (Range)	Percentage of Anesthesia Time at Low Saturation or Hypotension, Median (Range)
11–20% Decline of $rSco_2$ from baseline	27 (22–31) n = 106	0 (0–9)	0 (0–9)	0 (0–85)
21–30% Decline of $rSco_2$ from baseline	6(4–8) n = 24	0 (0–8)	0 (0–19)	0 (0–50)
> 30% Decline of $rSco_2$ from baseline	1 (0–2) n = 4	0 (0–7)	0 (0–9)	0 (0–31)
Absolute $rSco_2$ 60–69%	43 (39–48) n = 196	0 (0–14)	0 (0–55)	0 (0–85)
Absolute $rSco_2$ 50–59%	11 (8–14) n = 51	0 (0–10)	0 (0–17)	0 (0–47)
Absolute $rSco_2$ < 50%	2 (0–3) n = 7	0 (0–4)	0 (0–6)	0 (0–24)
Mild low arterial pressure	62 (57–66) n = 279	1 (0–21)	3 (0–67)	8 (0–100)
Moderate low arterial pressure	36 (31–40) n = 161	0 (0–15)	0 (0–100)	0 (0–100)
Severe low arterial pressure	13 (10–16) n = 57	0 (0–12)	0 (0–40)	0 (0–74)
Mild low Spo_2	15 (11–18) n = 66	0 (0–8)	0 (0–20)	0 (0–63)
Moderate low Spo_2	4 (2–6) n = 19	0 (0–6)	0 (0–9)	0 (0–27)
Severe low Spo_2	2 (0–3) n = 7	0 (0–4)	0 (0–7)	0 (0–9)

Incidence is the number of patients experiencing event divided by total number of patients. Frequency of events per patient includes the number of events occurring per patient during course of anesthetic. Percentage of anesthesia time of each event includes the duration of each event (greater than 3 min) divided by total duration of anesthetic per patient. Percentage of anesthesia time at low saturation or hypotension includes the total amount of time spent below the threshold for low saturation or hypotension divided by the total anesthetic time per patient. N is the number of patients experiencing the event. Mild hypotension is defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 36 to 45 mmHg or SBP of 51 to 60 mmHg). Moderate hypotension is defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 26 to 35 mmHg or SBP of 41 to 50 mmHg). Severe hypotension is defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 25 mmHg or less or SBP of less than 40 mmHg). Mild low arterial saturation is defined as an arterial saturation event lasting greater than 3 min (Spo_2 80 to 89%). Moderate low arterial saturation is defined as an arterial saturation event lasting greater than 3 min (Spo_2 70 to 79%). Severe low arterial saturation is defined as an arterial saturation event lasting greater than 3 min (Spo_2 less than 70%).

MAP = mean arterial pressure; $rSco_2$ = cerebral saturation; SBP = systolic blood pressure; Spo_2 = arterial saturation.

complications at the 7-day follow-up point. One patient died secondary to complications of intestinal obstruction, one patient was still on extracorporeal membrane oxygenation after inadequate oxygenation secondary to omphalocele closure, and two patients were still ventilated after their operations due to septic complications.

Discussion

In this international, multicenter study of infants during general anesthesia, we found that mild and moderate cerebral and arterial desaturation and mild, moderate, and severe hypotension occurred frequently, whereas severe cerebral desaturation was rare. An AUC analysis was conducted *post hoc* to quantify the exposure to cerebral desaturation as a percentage of the anesthetic, which confirmed the cerebral desaturation findings. The incidence and exposure to these events were similar among the eight study institutions. Based on sensitivity analysis, whereas mild cerebral desaturation events were more common in blinded centers, there were no differences between the centers for moderate and severe cerebral desaturation events. Thus, whereas there were differences between the centers, there was no clear directional influence of blinding on incidence or exposure to cerebral desaturation, thereby rendering the effect of blinding as incidental. Although our univariate regression indicated that mild and moderate low $rSco_2$ were associated with many variables, the correlations were weak overall with the exception of severe low Spo_2. Thus, arterial hypotension and mild-to-moderate arterial desaturation were not major contributors to mild or moderate cerebral desaturation or clinically useful to predict low $rSco_2$.

Our definition of an event includes both duration and magnitude of decline of $rSco_2$, Spo_2, and arterial pressure. These event definitions were based on clinical practice, published consensus at the time of study design,[18] and previous definitions in the literature.[8,19–21] The 3-min time window was chosen as the shortest period of time over which these events may be clinically relevant and detectable during a standard anesthetic by using a noninvasive blood pressure cuff. In addition, the cerebral oxygenation events were a

Table 4. Incidence of Low $rSco_2$, MAP, SBP, and Spo_2 per Patient for Greater Than 3 min during Anesthesia Categorized by Time Periods

	Baseline, % (95% CI)	Induction, % (95% CI)	Surgery, % (95% CI)	Emergence, % (95% CI)
11–20% Decline of $rSco_2$ from baseline	–	8 (6–11) n = 33	19 (15–23) n = 74	10 (7–13) n = 37
21–30% Decline of $rSco_2$ from baseline	–	2 (1–3) n = 8	5 (1–7) n = 20	1 (0–1) n = 2
> 30% Decline of $rScO_2$ from baseline	–	0 (0–1) n = 1	1 (0–2) n = 3	0 (0–1) n = 1
Absolute $rSco_2$ 60–69%	15 (12–19) n = 60	16 (13–20) n = 73	29 (25–33) n = 130	15 (12–19) n = 67
Absolute $rSco_2$ 50–59%	1 (0–2) n = 5	3 (2–5) n = 15	7 (5–10) n = 33	3 (1–4) n = 12
Absolute $rSco_2$ < 50%	0 (0–0) n = 0	0 (0–1) n = 2	1 (0–2) n = 4	1 (0–1) n = 2
Mild low arterial pressure	2 (0–3) n = 4	43 (39–48) n = 191	53 (49–58) n = 235	24 (20–29) n = 101
Moderate low arterial pressure	2 (0–2) n = 2	24 (20–28) n = 105	27 (22–30) n = 117	8 (5–11) n = 33
Severe low arterial pressure	0 (0–0) n = 0	8 (6–11) n = 37	7 (5–10) n = 32	1 (0–2) n = 4
Mild low Spo_2	2 (0–3) n = 5	8 (5–10) n = 35	4 (2–6) n = 18	5 (3–7) n = 23
Moderate low Spo_2	0 (0–1) n = 1	2 (1–3) n = 9	1 (0–2) n = 4	1 (0–3) n = 6
Severe low Spo_2	0 (0–0) n = 0	0 (0–1) n = 2	1 (0–2) n = 4	0 (0–1) n = 1

N is the number of patients experiencing the event. Baseline is defined as the time between placement of the near infrared spectroscopy probe on the patient's forehead before induction of anesthesia and administration of anesthetic drugs or supplemental oxygen to induce anesthesia. The average value during this time was used to define baseline $rSco_2$. Induction was defined as the time between administration of anesthetic induction drugs to the start of surgery (*e.g.*, incision). The average value during this time period was used to define induction $rSco_2$. Surgery was defined as the time from the start of surgery (*e.g.*, incision) until the last stitch or dressing was placed. The average value during this time period was used to define surgery $rSco_2$. Emergence was defined as the time from 3 to 5 min after the last stitch or dressing was placed and/or until the patient was extubated. The average value during this time period was used to define emergence $rSco_2$. Mild hypotension was defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 36 to 45 mmHg or SBP of 51 to 60 mmHg). Moderate hypotension was defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 26 to 35 mmHg or SBP of 41 to 50 mmHg). Severe Hypotension was defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 25 mmHg or less or SBP of less than 40 mmHg). Mild low arterial saturation was defined as an arterial saturation event lasting greater than 3 min (Spo_2 80 to 89%). Moderate low arterial saturation was defined as an arterial saturation event lasting greater than 3 min (Spo_2 70 to 79%). Severe low arterial saturation was defined as an arterial saturation event lasting greater than 3 min (SpO_2 less than 70%).

MAP = mean arterial pressure; $rSco_2$ = cerebral saturation; SBP = systolic blood pressure; Spo_2 = arterial saturation.

combination of both relative (percentage below baseline) and absolute to draw comparisons with previous studies that had only reported relative desaturation and newer studies that have been able to report absolute values.[16]

Michelet *et al.*[13] investigated the relationship between relative $rSco_2$ and arterial pressure in term anesthetized infants and found an association between decreased arterial pressure and relative cerebral desaturation: a decrease of systolic blood pressure and mean arterial pressure of greater than 37.5% and 44.5%, respectively, had the strongest predictive value of cerebral desaturation greater than 20% below baseline. Consistent with our findings, decreases in arterial pressure were poorly correlated with decreases in relative $rSco_2$. In a study of cerebral and renal NIRS in neonates, Koch and Hansen[14] demonstrated a 2.8% intraoperative incidence of relative cerebral desaturation greater than 20% from baseline that was moderately correlated with decreased Spo_2 (ϕ = 0.371) and weakly correlated with decreased arterial pressure (ϕ = 0.231). Although similar to our findings, the interpretation and generalizability of the decreased $rSco_2$ remained in question.

Similar to our observations, several studies have reported a high incidence of low arterial pressure in infants during general anesthesia.[22–24] Because the autoregulatory thresholds for cerebral blood flow in infants are unknown,[25] there has been concern that putative learning and behavioral abnormalities in infants after anesthesia and surgery might be a result of cerebral ischemic events and not a direct effect of the anesthetic on the brain.[4] Our results show that cerebral oxygenation remains unchanged or is mildly decreased during these low arterial pressure events, suggesting that these arterial pressures are within cerebral autoregulation or that the tissue oxygen supply demand relationship is preserved, a result of a reduction in cerebral metabolic rate under general anesthesia resulting in less oxygen requirements in the brain than the awake state.

The last 15 yr of anesthesia research has seen a substantial body of evidence from infant animal studies pointing toward drug neurotoxicity and abnormal learning and behavior later in life after anesthesia, but human evidence of neurodevelopmental compromise remains equivocal.[3] This research,

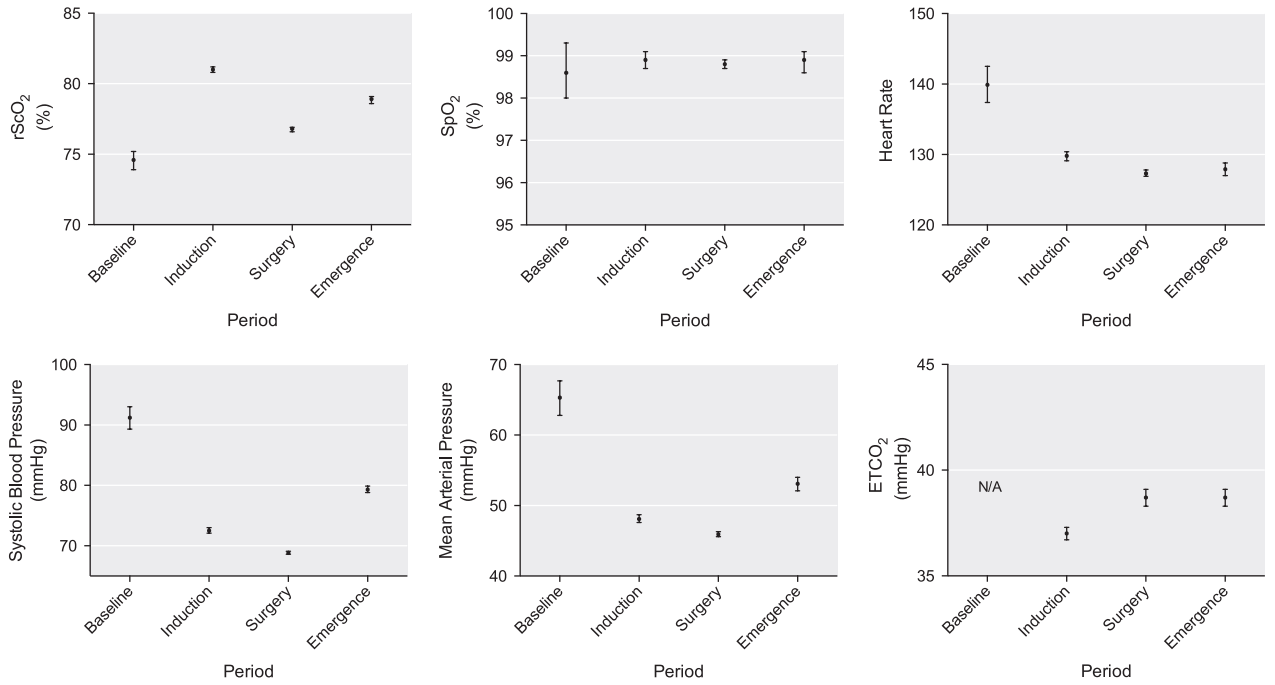

Fig. 2. Cerebral saturation ($rSco_2$), arterial saturation (Spo_2), heart rate, systolic and mean arterial blood pressure, and end tidal carbon dioxide ($ETCO_2$) for the study population, categorized by time periods. Data are presented as least square means and 95% CIs.

Table 5. AUC for Time Spent below Absolute and Relative $rSco_2$ Thresholds

Threshold	Patients, n	Incidence, % (95% CI)	AUC threshold-time % minutes total anesthetic, median (range)
11–20% Relative decline of $rSco_2$ from baseline	120	30 (26–35)	0 (0–85)
21–30% Relative decline of $rSco_2$ from baseline	30	8 (5–10)	0 (0–53)
> 30% relative decline of $rSco_2$ from baseline	7	2 (0–3)	0 (0–32)
Absolute $rSco_2$ 60–69%	238	53 (48–57)	2 (0–85)
Absolute $rSco_2$ 50–59%	60	13 (10–16)	0 (0–50)
Absolute $rSco_2$ < 50%	11	2 (1–4)	0 (0–24)

AUC is the total number of minutes below the threshold of any duration divided by the total minutes of the anesthetic, expressed as threshold-time percentage of minutes, using the relevant threshold definition. These incidence calculations differ from Table 3 in that all cerebral desaturation events are included in these calculations and not just those greater than 3 min. AUC data are presented as median (range).

AUC = area under the curve; $rSco_2$ = cerebral saturation.

and the discussions on its relevance in clinical practice, have refocused the specialty on anesthetic practice[26] and clarification of safe physiologic limits relating to blood pressure and oxygenation. Case reports and clinical experience suggest that substantial and prolonged hypotension and/or arterial desaturation may be associated with neurologic compromise and death.[27] What is less certain is the severity duration of this relationship with neurologic injury and the cerebral buffer to provide neuroprotection by anesthesia. Reference ranges for arterial blood pressure in children during general anesthesia that preserve blood flow and oxygen delivery to the organs do not currently exist. Although de Graaff *et al.*[28] have reported arterial pressure values in a large population of infants during anesthesia, the corresponding oxygenation of the organs is unknown.

The relationship of decreased $rSco_2$ to neurologic injury remains uncertain in infants. In neonatal piglets, neurophysiologic function does not become impaired until $rSco_2$ is less than 50%, and neurologic injury does not develop until $rSco_2$ is less than 50% for greater than 2 h, followed by a linear increase in the incidence of neurologic injury of approximately 15% per hour thereafter.[8] In a study of premature infants, Verhagen *et al.*[29] showed an association between both high and low cerebral $rSco_2$ (less than 50%) in the first 2 weeks of life and developmental outcome as measured by the Bayley Scales of Infant and Toddler Development at 2 to 3 yr of age. This finding adds to that of a similar study by Alderliesten *et al.*,[6] where neurodevelopmental outcome was compared with cerebral $rSco_2$ and blood pressure in a preterm neonatal group. They found an association between low $rSco_2$ and lower neurodevelopmental scores but no association between hypotension and neurodevelopment. This may indicate the separate use of $rSco_2$ monitoring in

Table 6. Anesthetic and Patient Factors Associated with Mild and Moderate Cerebral Desaturation

	Mild Cerebral Desaturation		Moderate Cerebral Desaturation	
	10–20% Decline of $rSco_2$ from Baseline, OR (95% CI)	Absolute $rSco_2$ 60–70%, OR (95% CI)	20–30% Decline of $rSco_2$ from Baseline, OR (95% CI)	Absolute $rSco_2$ 50–60%, OR (95% CI)
Sevoflurane not used during induction	1.5 (0.9–2.6)	2.2 (1.3–3.6)*	1.2 (0.4–3.4)	1.7 (0.8–3.4)
Propofol used during induction	0.9 (0.6–1.5)	1.6 (1.1–2.4)†	1.0 (0.4–2.3)	1.2 (0.6–2.2)
Opioids used during induction	2.0 (1.3–3.1)*	2.2 (1.5–3.2)‡	0.6 (0.2–1.3)	0.6 (0.3–1.0)
Muscle relaxants used during induction	1.7 (1.0–2.7)*	1.7 (1.1–2.5)*	0.8 (0.3–1.9)	0.6 (0.3–1.2)
Absence of locoregional block	0.7 (0.5–1.1)	1.8 (1.2–2.6)*	0.7 (0.3–1.6)	0.6 (0.3–1.0)
Laparoscopy performed	1.2 (0.7–2.0)	1.4 (0.9–2.2)	0.7 (0.2–2.0)	1.3 (0.7–2.5)
Sevoflurane used during maintenance	0.5 (0.2–1.4)	0.7 (0.3–1.7)	0.5 (0.1–2.1)	1.1 (0.2–4.8)
Propofol used during maintenance	1.2 (0.6–2.4)	1.3 (0.7–2.2)	1.7 (0.4–7.3)	2.0 (0.7–5.8)
Opioids used during maintenance	1.6 (1.1–2.5)	0.7 (0.5–1.0)	0.7 (0.3–1.5)	0.6 (0.4–1.2)
Muscle relaxants used during maintenance	1.6 (1.0–2.5)*	0.8 (0.6–1.3)	0.6 (0.2–1.3)	1.8 (1.0–3.3)†
Male sex	1.7 (1.0–2.9)†	1.6 (1.0–2.4)†	2.3 (0.8–6.9)	1.7 (0.8–3.3)
ASA II *vs*. I	1.0 (0.5–1.7)	1.4 (0.9–2.3)	1.1 (0.2–6.5)	0.9 (0.4–2.2)
ASA III *vs*. I	2.6 (1.4–4.8)*	2.4 (1.4–4.1)*	9.4 (2.0–43.2)*	4.7 (2.0–11)*
ASA IV *vs*. I	6.7 (2.0–22)*	1.6 (0.6–4.8)	9.3 (1.2–72)†	5.1 (1.3–19)†
ASA III or IV *vs*. I	3.0 (1.6–5.4)*	2.2 (1.3–3.8)*	9.4 (2.1–42)*	4.7 (2.1–11)*
Prematurity	1.8 (1.1–2.9)†	1.2 (0.8–1.8)	2.2 (1.0–5.2)	1.7 (0.9–3.2)
Mild low arterial pressure	2.6 (1.5–4.3)*	1.4 (1.0–2.1)	2.3 (0.8–6.2)	3.2 (1.5–6.8)*
Moderate low arterial pressure	2.1 (1.4–3.4)*	1.3 (0.9–1.9)	1.6 (0.7–3.6)	1.9 (1.0–3.4)†
Severe low arterial pressure	2.5 (1.4–4.6)*	1.4 (0.8–2.5)	1.3 (0.4–4.1)	2.1 (1.0–4.4)†
Mild low Spo_2	3.9 (2.2–6.9)‡	3.1 (1.8–5.4)‡	5.5 (2.3–13)*	2.9 (1.5–5.6)*
Moderate low Spo_2	5.0 (1.8–14)*	1.9 (0.7–4.7)	6.0 (1.8–20)*	4.0 (1.5–11)*
Severe low Spo_2	14.4 (1.7–124)†	3.3 (0.6–17)	8.4 (1.5–48)†	21.7 (4.1–115)*
Younger gestational age at birth	1.1 (1.0–1.1)*	1.0 (0.9–1.0)	1.1 (1.1–1.2)*	1.1 (1.0–1.1)†
Smaller weight at surgery	0.9 (0.8–1.0)	0.9 (0.8–1.0)	1.7 (1.3–2.2)*	1.3 (1.1–1.6)*
Younger postmenstrual age at surgery	1.0 (1.0–1.1)*	1.0 (1.0–1.0)	1.0 (0.9–1.0)	1.0 (1.0–1.1)†

Given the exploratory nature of this analysis, no adjustments were made for multiple comparisons. Mild hypotension was defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 36 to 45 mmHg or SBP of 51 to 60 mmHg). Moderate hypotension was defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 26 to 35 mmHg or SBP of 41 to 50 mmHg). Severe hypotension was defined as an arterial pressure event lasting greater than 3 min (mean arterial pressure of 25 mmHg or less or SBP of less than 40 mmHg). Mild low arterial saturation was defined as an arterial saturation event lasting greater than 3 min (Spo_2 80 to 89%). Moderate low arterial saturation was defined as an arterial saturation event lasting greater than 3 min (Spo_2 70 to 79%). Severe low arterial saturation was defined as an arterial saturation event lasting greater than 3 min (Spo_2 less than 70%).

*Data show statistical significance at $P < 0.01$. †Data show statistical significance at $P < 0.05$. ‡Data show statistical significance at $P < 0.0001$.

ASA = American Society of Anesthesiologists; OR = odds ratio; SBP = systolic blood pressure; Spo_2 = arterial saturation.

addition to standard parameters of arterial pressure, pulse oximetry, and arterial blood gasses.

In pediatric cardiac anesthesia, several studies have demonstrated links between cerebral $rSco_2$ and cerebral ischemia lesions on magnetic resonance imaging[7] and short-[30,31] and long-term[10,30,32] neurodevelopmental outcomes. Dent *et al.*[7] found an association between cerebral ischemic lesions and $rSco_2$ less than 50% for greater than 3 h. In addition, postoperative lower cerebral tissue oxygenation index has been noted to be associated with longer durations of stay in the intensive care unit, longer durations of intubation, and a higher probability of death.[30] However, a potential confounder is that cerebral $rSco_2$ may be affected by cardiovascular functional status and act as a marker for it rather than for cerebral specific injury that causes neurologic damage. The SafeBoosC trial in neonatal intensive care units in Europe has demonstrated that a tailored intervention strategy in NIRS-monitored patients can reduce the exposure to cerebral desaturation[33] in extremely premature infants. Analyses of secondary outcomes are ongoing but do not as yet show any differences between the treatment and control groups.[34,35] No studies have examined the potential relationship between cerebral desaturation and long-term neurodevelopmental outcomes in neonates and infants undergoing general anesthesia for noncardiac surgery.

The incidence of moderate or severe cerebral desaturation noted in this study is lower than that noted in four other recent studies that all used the INVOS 5100 NIRS device (Medtronic, USA). There are differences in precision and bias between NIRS devices that could contribute to the difference in incidences between our study and these studies.[36,37] The fact that the INVOS 5100, the oximeter with the highest variance, also reports a higher rate of desaturation must be kept in mind when interpreting results.

Although our study is the largest to date, it had several limitations. First, the study did not control for anesthesia technique; however, there were no significant differences among techniques across the study institutions. In addition,

half of the sites were blinded to the NIRS monitor, whereas half of the sites were unblinded. Although there was potential for bias relating to monitor-driven interventions, there were no significant differences noted in the incidence of moderate or severe low $rSco_2$ across any of the sites regardless of blinding status. Our event definitions were developed to the best of our ability. The lack of true standardized definitions of these events makes these definitions subjective and open to debate. We also would have hoped to understand the relationship between $ETCO_2$ and our outcomes. However, given the difficulty in accurate measurements in infants, we did not include this variable in analysis. Lastly, NIRS is limited to measurement of oxygenation beneath the sensor. The possibility exists for low cerebral oxygenation to occur in other areas of the brain that were not being studied or deeper in the brain than the source of the optical signal. However, during general anesthesia, imaging studies show a uniform change in blood flow and metabolism throughout the brain, suggesting that this possibility is unlikely.[38] Despite these limitations, this study provides a useful insight into the incidence of low cerebral saturation from major pediatric centers in the world.

In summary, mild cerebral deoxygenation is common during anesthesia of infants, whereas severe cerebral desaturation is uncommon. Low arterial pressure was very common and not well associated with low $rSco_2$. Although severe cerebral deoxygenation does occur during infant anesthesia, it is both rare and brief, and thus is unlikely to explain the reported learning and behavioral abnormalities associated with general anesthesia and surgery. Only by performing longer-term neurodevelopmental outcome studies would any association with later learning and behavioral difficulties be ascertained.

Acknowledgments

The authors thank Christopher Brasher, F.A.N.Z.C.A. (Department of Anesthesia and Pain Management, Royal Children's Hospital, Melbourne, Victoria, Australia); Jack Luxford, B.A. (Sydney Medical School, Sydney, New South Wales, Australia); Michaela Turancova, B.Sc. (University of Sydney, Sydney, New South Wales, Australia); Lara Oversby, R.N. (Department of Anesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Western Australia, Australia); Thomas Drake-Brockman, B.Phil. (Hons.) (Department of Anesthesia and Pain Management, Princess Margaret Hospital for Children and School of Medicine, University of Western Australia, Perth, Western Australia, Australia); and Lliana Slevin, B.Sc. (Hons.) Pharmacology (Department of Anesthesia and Pain Management, Princess Margaret Hospital for Children and Children's Lung Group, Telethon Kids Institute, Perth, Western Australia, Australia).

Research Support

Supported by Australian and New Zealand College of Anaesthetists Project Grant 15/021 (West End, Queensland, Australia) and Society of Pediatric Anaesthetists of New Zealand and Australia Research Grant 2016 (Morrisett, New South Wales, Australia), as well as the Princess Margaret Hospital Foundation (to Dr. von Ungern-Sternberg; Perth, Western Australia, Australia), the Callahan Estate (to Dr. von Ungern-Sternberg; Perth, Western Australia, Australia), and the Stan Perron Fellowship (to Dr. von Ungern-Sternberg; Perth, Western Australia, Australia).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Olbrecht: Department of Anesthesiology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 2001, Cincinnati, Ohio 45229. Vanessa.Olbrecht@cchmc.org. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. McCann ME, Schouten AN, Dobija N, Munoz C, Stephenson L, Poussaint TY, Kalkman CJ, Hickey PR, de Vries LS, Tasker RC: Infantile postoperative encephalopathy: Perioperative factors as a cause for concern. Pediatrics 2014; 133:e751–7
2. Stolwijk LJ, Lemmers PM, Harmsen M, Groenendaal F, de Vries LS, van der Zee DC, Benders MJ, van Herwaarden-Lindeboom MY: Neurodevelopmental outcomes after neonatal surgery for major noncardiac anomalies. Pediatrics 2016; 137:e20151728
3. Vutskits L, Xie Z: Lasting impact of general anaesthesia on the brain: Mechanisms and relevance. Nat Rev Neurosci 2016; 17:705–17
4. Wu B, Yu Z, You S, Zheng Y, Liu J, Gao Y, Lin H, Lian Q: Physiological disturbance may contribute to neurodegeneration induced by isoflurane or sevoflurane in 14 day old rats. PLoS One 2014; 9:e84622
5. Pellicer A, Bravo Mdel C: Near-infrared spectroscopy: A methodology-focused review. Semin Fetal Neonatal Med 2011; 16:42–9
6. Alderliesten T, Lemmers PM, van Haastert IC, de Vries LS, Bonestroo HJ, Baerts W, van Bel F: Hypotension in preterm neonates: Low blood pressure alone does not affect neurodevelopmental outcome. J Pediatr 2014; 164:986–91
7. Dent CL, Spaeth JP, Jones BV, Schwartz SM, Glauser TA, Hallinan B, Pearl JM, Khoury PR, Kurth CD: Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion. J Thorac Cardiovasc Surg 2006; 131:190–7
8. Kurth CD, McCann JC, Wu J, Miles L, Loepke AW: Cerebral oxygen saturation-time threshold for hypoxic-ischemic injury in piglets. Anesth Analg 2009; 108:1268–77
9. Scott JP, Hoffman GM: Near-infrared spectroscopy: Exposing the dark (venous) side of the circulation. Paediatr Anaesth 2014; 24:74–88
10. Sood ED, Benzaquen JS, Davies RR, Woodford E, Pizarro C: Predictive value of perioperative near-infrared spectroscopy for neurodevelopmental outcomes after cardiac surgery in infancy. J Thorac Cardiovasc Surg 2013; 145:438–45 e1
11. Andropoulos DB, Easley RB, Brady K, McKenzie ED, Heinle JS, Dickerson HA, Shekerdemian LS, Meador M, Eisenman C, Hunter JV, Turcich M, Voigt RG, Fraser CD Jr: Neurodevelopmental outcomes after regional cerebral perfusion with neuromonitoring for neonatal aortic arch reconstruction. Ann Thorac Surg 2013; 95:648–55
12. Rhondali O, Juhel S, Mathews S, Cellier Q, Desgranges FP, Mahr A, De Queiroz M, Pouyau A, Rhzioual-Berrada K, Chassard D: Impact of sevoflurane anesthesia on brain oxygenation in children younger than 2 years. Paediatr Anaesth 2014; 24:734–40
13. Michelet D, Arslan O, Hilly J, Mangalsuren N, Brasher C, Grace R, Bonnard A, Malbezin S, Nivoche Y, Dahmani S:

Intraoperative changes in blood pressure associated with cerebral desaturation in infants. Paediatr Anaesth 2015; 25:681–8

14. Koch HW, Hansen TG: Perioperative use of cerebral and renal near-infrared spectroscopy in neonates: A 24-h observational study. Paediatr Anaesth 2016; 26:190–8
15. Suskeviciene I, Rugyte DC, Bukauskas T, Vilke A, Bilskiene D, Macas A: Near-infrared spectroscopy in newborns and infants under general anesthesia. Acta Medica Lituanica 2012; 19:5
16. Kreeger RN, Ramamoorthy C, Nicolson SC, Ames WA, Hirsch R, Peng LF, Glatz AC, Hill KD, Hoffman J, Tomasson J, Kurth CD: Evaluation of pediatric near-infrared cerebral oximeter for cardiac disease. Ann Thorac Surg 2012; 94:1527–33
17. Denault A, Deschamps A, Murkin JM: A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth 2007; 11:274–81
18. Nafiu OO, Voepel-Lewis T, Morris M, Chimbira WT, Malviya S, Reynolds PI, Tremper KK: How do pediatric anesthesiologists define intraoperative hypotension? Paediatr Anaesth 2009; 19:1048–53
19. Rhondali O, André C, Pouyau A, Mahr A, Juhel S, De Queiroz M, Rhzioual-Berrada K, Mathews S, Chassard D: Sevoflurane anesthesia and brain perfusion. Paediatr Anaesth 2015; 25:180–5
20. McCann ME, Soriano SG: Perioperative central nervous system injury in neonates. Br J Anaesth 2012; 109(suppl 1):i60–7
21. Jevtovic-Todorovic V, Absalom AR, Blomgren K, Brambrink A, Crosby G, Culley DJ, Fiskum G, Giffard RG, Herold KF, Loepke AW, Ma D, Orser BA, Planel E, Slikker W Jr, Soriano SG, Stratmann G, Vutskits L, Xie Z, Hemmings HC Jr: Anaesthetic neurotoxicity and neuroplasticity: An expert group report and statement based on the BJA Salzburg Seminar. Br J Anaesth 2013; 111:143–51
22. Weber F, Honing GH, Scoones GP: Arterial blood pressure in anesthetized neonates and infants: A retrospective analysis of 1091 cases. Paediatr Anaesth 2016; 26:815–22
23. Sottas CE, Cumin D, Anderson BJ: Blood pressure and heart rates in neonates and preschool children: An analysis from 10 years of electronic recording. Paediatr Anaesth 2016; 26:1064–70
24. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME; GAS consortium: Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): An international multicentre, randomised controlled trial. Lancet 2016; 387:239–50
25. Williams M, Lee JK: Intraoperative blood pressure and cerebral perfusion: Strategies to clarify hemodynamic goals. Paediatr Anaesth 2014; 24:657–67
26. Weiss M, Vutskits L, Hansen TG, Engelhardt T: Safe anesthesia for every tot: The SAFETOTS initiative. Curr Opin Anaesthesiol 2015; 28:302–7
27. McCann ME, Schouten AN: Beyond survival: Influences of blood pressure, cerebral perfusion and anesthesia on neurodevelopment. Paediatr Anaesth 2014; 24:68–73
28. de Graaff JC, Pasma W, van Buuren S, Duijghuisen JJ, Nafiu OO, Kheterpal S, van Klei WA: Reference values for noninvasive blood pressure in children during anesthesia: A multicentered retrospective observational cohort study. Anesthesiology 2016; 125:904–13
29. Verhagen EA, Van Braeckel KN, van der Veere CN, Groen H, Dijk PH, Hulzebos CV, Bos AF: Cerebral oxygenation is associated with neurodevelopmental outcome of preterm children at age 2 to 3 years. Dev Med Child Neurol 2015; 57:449–55
30. Suemori T, Skowno J, Horton S, Bottrell S, Butt W, Davidson AJ: Cerebral oxygen saturation and tissue hemoglobin concentration as predictive markers of early postoperative outcomes after pediatric cardiac surgery. Paediatr Anaesth 2016; 26:182–9
31. Vida VL, Tessari C, Cristante A, Nori R, Pittarello D, Ori C, Cogo PE, Perissinotto E, Stellin G: The role of regional oxygen saturation using near-infrared spectroscopy and blood lactate levels as early predictors of outcome after pediatric cardiac surgery. Can J Cardiol 2016; 32:970–7
32. Hoffman GM, Brosig CL, Mussatto KA, Tweddell JS, Ghanayem NS: Perioperative cerebral oxygen saturation in neonates with hypoplastic left heart syndrome and childhood neurodevelopmental outcome. J Thorac Cardiovasc Surg 2013; 146:1153–64
33. Hyttel-Sorensen S, Pellicer A, Alderliesten T, Austin T, van Bel F, Benders M, Claris O, Dempsey E, Franz AR, Fumagalli M, Gluud C, Grevstad B, Hagmann C, Lemmers P, van Oeveren W, Pichler G, Plomgaard AM, Riera J, Sanchez L, Winkel P, Wolf M, Greisen G: Cerebral near infrared spectroscopy oximetry in extremely preterm infants: Phase II randomised clinical trial. BMJ 2015; 350:g7635
34. Plomgaard AM, Hagmann C, Alderliesten T, Austin T, van Bel F, Claris O, Dempsey E, Franz A, Fumagalli M, Gluud C, Greisen G, Hyttel-Sorensen S, Lemmers P, Pellicer A, Pichler G, Benders M: Brain injury in the international multicenter randomized SafeBoosC phase II feasibility trial: Cranial ultrasound and magnetic resonance imaging assessments. Pediatr Res 2016; 79:466–72
35. Plomgaard AM, van Oeveren W, Petersen TH, Alderliesten T, Austin T, van Bel F, Benders M, Claris O, Dempsey E, Franz A, Fumagalli M, Gluud C, Hagmann C, Hyttel-Sorensen S, Lemmers P, Pellicer A, Pichler G, Winkel P, Greisen G: The SafeBoosC II randomized trial: Treatment guided by near-infrared spectroscopy reduces cerebral hypoxia without changing early biomarkers of brain injury. Pediatr Res 2016; 79:528–35
36. Davie SN, Grocott HP: Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116:834–40
37. Bickler PE, Feiner JR, Rollins MD: Factors affecting the performance of 5 cerebral oximeters during hypoxia in healthy volunteers. Anesth Analg 2013; 117:813–23
38. Alkire MT, Pomfrett CJ, Haier RJ, Gianzero MV, Chan CM, Jacobsen BP, Fallon JH: Functional brain imaging during anesthesia in humans: Effects of halothane on global and regional cerebral glucose metabolism. Anesthesiology 1999; 90:701–9