ANESTHESIOLOGY

Hypoxemia, Bradycardia, and Multiple Laryngoscopy Attempts during Anesthetic Induction in Infants

A Single-center, Retrospective Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Successful tracheal intubation of an infant may be a challenging skill to acquire due to differing anatomy and physiology compared to older children and adults
- Multiple intubation attempts may be associated with increased complications

What This Article Tells Us That Is New

- In a quaternary pediatric academic center, 16% of healthy infants undergoing routine tracheal intubations had multiple laryngoscopies
- There was also a 35% incidence of hypoxemia, defined as an oxygen saturation measurement less than 90%, during induction of anesthesia
- There was evidence for an association between multiple laryngoscopies and hypoxemia

ABSTRACT

Background: The infant airway is particularly vulnerable to trauma from repeated laryngoscopy attempts. Complications associated with elective tracheal intubations in anesthetized infants may be underappreciated. We conducted this study of anesthetized infants to determine the incidence of multiple laryngoscopy attempts during routine tracheal intubation and assess the association of laryngoscopy attempts with hypoxemia and bradycardia.

Methods: We conducted a retrospective cross-sectional cohort study of anesthetized infants (age less than or equal to 12 months) who underwent direct laryngoscopy for oral endotracheal intubation between January 24, 2015, and August 1, 2016. We excluded patients with a history of difficult intubation and emergency procedures. Our primary outcome was the incidence of hypoxemia or bradycardia during induction of anesthesia. We evaluated the relationship between laryngoscopy attempts and our primary outcome, adjusting for age, weight, American Society of Anesthesiologists status, staffing model, and encounter location.

Results: A total of 1,341 patients met our inclusion criteria, and 16% (n = 208) had multiple laryngoscopy attempts. The incidence of hypoxemia was 35% (n = 469) and bradycardia was 8.9% (n = 119). Hypoxemia and bradycardia occurred in 3.7% (n = 50) of patients. Multiple laryngoscopy attempts were associated with an increased risk of hypoxemia (adjusted odds ratio: 1.78, 95% CI: 1.30 to 2.43, $P < 0.001$). There was no association between multiple laryngoscopy attempts and bradycardia (adjusted odds ratio: 1.23, 95% CI: 0.74 to 2.03, $P = 0.255$).

Conclusions: In a quaternary academic center, healthy infants undergoing routine tracheal intubations had a high incidence of multiple laryngoscopy attempts and associated hypoxemia episodes.

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Tracheal intubation of anesthetized infants is performed in operating rooms all over the world. Infants are more challenging to learn to intubate than adults because of anatomic and physiologic reasons, including a higher positioned glottis in the neck, angled vocal cords, smaller functional residual capacity, and significantly higher oxygen consumption.[1,2] Children with anatomically difficult airways are at increased risk for adverse airway events.[3] These adverse events include hypoxemia, bradycardia, cardiac arrest, severe airway trauma, and death.[4–7] Souza and Carvalho found an association between multiple tracheal intubation attempts

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version. 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). The work presented in this article has been presented at the Section of Biomedical Informatics Research meeting in the Department of Anesthesiology and Critical Care Medicine at The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, May 16, 2017. The preliminary data set for this article has been presented as a scholarly pursuit project by Dr. Acquah for the completion of his medical education at the Perelman University School of Medicine, Philadelphia, Pennsylvania, May 2017. The preliminary data set for this article has been presented in a grant application for the Anesthesia Patient Safety Foundation (Rochester, Minneapolis) grant in 2017. The Anesthesia Patient Safety Foundation awarded a grant to Dr. Fiadjoe to conduct the Videolaryngoscopy in Small Infants (VISI) Trial. The grant funding was not used to conduct the research presented in this manuscript.

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and both hypoxemia and bradycardia in a cross-sectional study of 147 children in an intensive care unit.[8]

Multiple laryngoscopy attempts in infants may be required for various reasons, including inexperience with the procedure and limited intubation time because of apnea intolerance. Novice learners from a variety of pediatric specialties obtain their early intubation experiences in operating rooms in healthy children. A possible reason for this common practice is that clinicians may believe that multiple intubation attempts in healthy children are innocuous. Core competency requirements for laryngoscopy training are poorly defined, and high variability in training requirements exists across training programs.[9,10] This is in stark contrast to the aviation industry, where competence is often demonstrated on simulators before actually flying an aircraft. The incidence of multiple tracheal intubation attempts for children classified as American Society of Anesthesiologists (ASA) physical status I or II during routine induction of anesthesia remains unknown, and complications in this population may be underreported.[7,11]

We designed this retrospective study to determine the incidence of multiple tracheal intubation attempts in anesthetized infants in an academic children's hospital and the associated risks of hypoxemia or bradycardia. We included patients managed in operating rooms, nonoperating room locations (interventional and diagnostic radiology), and ambulatory surgery centers. We hypothesized that normal infants requiring multiple laryngoscopy attempts for tracheal intubation would be more likely to experience hypoxemia or bradycardia during induction of anesthesia.

Materials and Methods

Study Population

This study adhered to strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.[12] The institutional review board (Committees for the Protection of Human Subjects, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania) granted a waiver of review for our protocol because we used a deidentified data set. We included children in the first year of life (age less than or equal to 12 months), ASA physical status I or II, who received general anesthesia between January 24, 2015, and August 1, 2016, and underwent elective tracheal intubation *via* direct laryngoscopy with a Macintosh, Miller, or Wis-Hipple laryngoscope (Heine Optotechnik, Germany).[11] We evaluated anesthetic records from our (1) main hospital operating rooms, (2) main hospital radiology suites, and (3) ambulatory surgery centers. If a patient had more than one anesthesia encounter during the study time period, only the first anesthesia encounter was included in the initial study sample. Our care model differs by location and consists of direct supervision of certified registered nurse anesthetists, fellows, and residents in the operating rooms and radiology suites at the main hospital. The ambulatory surgery centers use a direct provider model, and cases are staffed by an attending pediatric anesthesiologist. We excluded emergency cases, children with baseline hypoxemia (oxygen saturation measured by pulse oximetry [Spo_2] less than 90%), congenital heart disease, or a history of difficult intubation or critical airway (see Supplemental Digital Content 1, http://links.lww.com/ALN/B991, for institutional definitions of critical and difficult airway). We also excluded infants managed with laryngeal mask airways, nasotracheal tubes, and cases where an indirect laryngoscopy technique was attempted.

Our primary outcomes included hypoxemia, defined as an oxygen saturation measurement less than 90% for at least 1 min, and bradycardia, defined as a heart rate less than 100 beats per minute for patients younger than 1 month and a heart rate less than 80 beats per minute for infants 1 month or older as measured by continuous 3-lead electrocardiography.[13,14] We measured the length of the hypoxemic and bradycardia episodes in continuous minutes that occurred during the induction of anesthesia. These outcome variables were dichotomized indicating zero events *versus* at least one event. Per peer reviewer request, we performed a *post hoc* analysis and evaluated the study outcomes using an alternate definition for hypoxemia, Spo_2 less than 90%, for at least two consecutive minutes.

Measures

Clinical outcomes data are documented in our anesthesia information management system (Epic Systems, USA). Our routine clinical practice is to perform inhalational induction with facemask for the majority of our patients presenting for elective procedures. From demographic data, the following were extracted: age, weight, height, ASA status, and anesthesia location. We extracted baseline pulse oximetry measurements from preprocedure documentation. From the intraprocedure documentation record, the following were extracted: number of laryngoscopy attempts, type of airway device (endotracheal tube, laryngeal mask airway, or tracheostomy), laryngoscopy technique (direct laryngoscopy, video laryngoscopy, or fiberoptic laryngoscopy), and anesthesia timeline events (*i.e.*, from anesthesia start to anesthesia ready). From intraoperative medications, the following were extracted: name, dose, and time of administration of neuromuscular blocking agents and vasoactive drug use (atropine, glycopyrrolate, or epinephrine). From the postanesthesia documentation, the following were extracted: administration of racemic epinephrine, and orders for supplemental oxygen delivery after discharge from postanesthesia care unit.

We defined the period of anesthesia induction based on the intraprocedure event documentation. The anesthesia information management system marks the beginning of the anesthesia record with the event "anesthesia start." The anesthesiologist marks the completion of the induction phase as "anesthesia ready." We defined healthy infants as ASA status I or II infants who did not have significant hypoxemia or bradycardia at baseline.[11] Laryngoscopy attempts

were documented in the anesthesia information management system as 1, 2, 3, 4, 5, and Other. Our practice guidelines for airway management define a laryngoscopy attempt as the insertion of an airway device into the oropharynx until its removal. All of the anesthesia machines (Dräger Apollo, Fabiuos Tiro, and Fabious MRI, Dräger, USA) were configured with physiologic monitors (GE Carescape B650, B850, GE Healthcare, United Kingdom; and Invivo Expression IP5, Philips, Netherlands). Physiologic data were recorded in 1-min intervals and transferred from the monitors to the electronic health record *via* a medical device integration interface (Nuvon, Bernoulli Enterprise, USA). Pulse oximetry data were screened for outliers defined by the concurrent recording of a Spo_2 saturation of 0% and pulse rate of 0 beats per minute from the pulse oximetry monitor.

Statistical Analysis

The statistical analysis plan was defined before accessing the data. No statistical power calculation was conducted before the study. The sample size was based on the available data. Descriptive statistics were conducted as follows: categorical variables were reported as counts and percentages, and continuous variables were summarized as medians with interquartile ranges; chi-square test, Fisher exact test, and Mann–Whitney U test were used as appropriate. The multiple logistic regression was applied to estimate the risk of hypoxemia or bradycardia associated with multiple laryngoscopy attempts, after adjustment for age, weight, ASA status, encounter location, and staffing model. The association of laryngoscopy attempts with hypoxemia and bradycardia were further presented using stacked bar plots, where the rate of multiple laryngoscopy attempts was plotted against minutes of hypoxemia and bradycardia (as defined earlier), respectively. The number of laryngoscopy attempts and the rate of hypoxemia by age groups were also plotted. All statistical analysis was conducted using SAS (v. 9.3., SAS Institute, USA), and all figures were made using R 3.4.2 (R Foundation for Statistical Computing, Austria). A two-sided *P* value less than 0.05 was considered statistically significant.

Results

A total of 7,125 infants received general anesthesia between January 24, 2015, and August 1, 2016. A total of 1,341 infants met our inclusion criteria (fig. 1). Demographic and clinical information is shown in table 1 and figure 2. A total of 47 of 1,341 (3.5%) patients did not have a reported

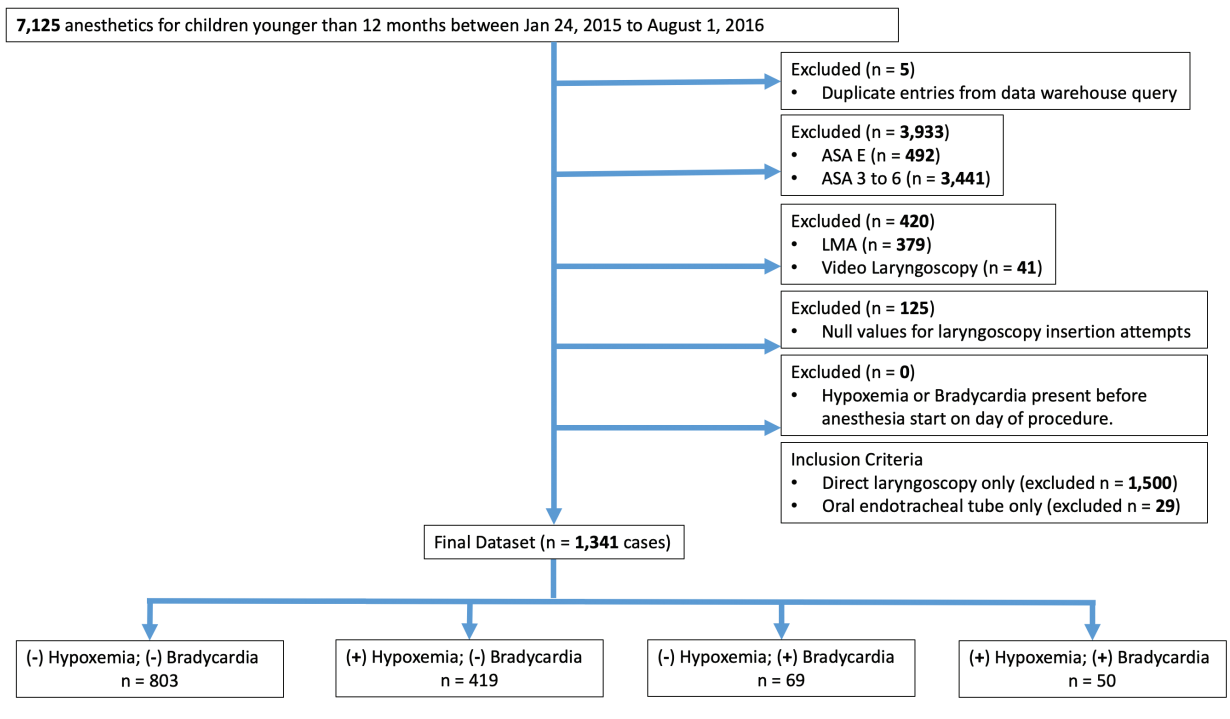

Fig. 1. Single-center retrospective observation study profile denoting inclusion and exclusion criteria. 7,125 patients had unique anesthesia encounters. If a patient had more than one anesthesia encounter during the study time period, only the first anesthesia encounter was included in the initial study sample. Primary outcomes were defined per study protocol: hypoxemia was defined as oxygen saturation measured by pulse oximetry less than 90% for at least 1 min. Bradycardia was defined with the age-specific definition (heart rate less than 100 beats per minute for infants younger than 1 month and a heart rate less than 80 beats per minute for infants one month or older). ASA, American Society of Anesthesiologists; LMA, laryngeal mask airway.

Table 1. Demographics

			Laryngoscopy attempt				
	Total (n = 1,341)		Single (n = 1,133)		Multiple (n = 208)		*P* Value
Age (months), median (IQR)	7	(3 to 9)	7	(3 to 9)	5	(3 to 8)	0.015
Sex, No. (%)							0.738
Male	967	(72.1)	819	(72.3)	148	(71.2)	
Female	374	(27.9)	314	(27.7)	60	(28.8)	
Weight (kg), median (IQR)	7.5	(5.7 to 8.7)	7.6	(5.9 to 8.8)	6.7	(4.8 to 8.4)	< 0.001
ASA classification, No. (%)							0.764
ASA I	366	(27.3)	311	(27.4)	55	(26.4)	
ASA II	975	(72.7)	822	(72.6)	153	(73.6)	
Baseline vital signs before induction							
Spo_2, median (IQR)	99	(97 to 100)	99	(97 to 100)	99	(96 to 100)	0.990
Heart rate, median (IQR)	142	(127 to 160)	141	(126 to 160)	147	(129 to 165)	0.076
Encounter location, No. (%)							0.021
Operating room	1,111	(82.8)	926	(81.7)	185	(88.9)	
Radiology	139	(10.4)	122	(10.8)	17	(8.2)	
Ambulatory surgery	91	(6.8)	85	(7.5)	6	(2.9)	
Staffing model, No. (%)							0.896
Supervision model	1,261	(94.0)	1,065	(94.0)	196	(94.2)	
Physician only	80	(6.0)	68	(6.0)	12	(5.8)	
Duration of induction (min), median (IQR)	18	(13 to 24)	17	(13 to 23)	23	(17 to 30)	< 0.001
Clinical events during induction of anesthesia							
Hypoxemia, n (%)							
Spo_2 < 90% at least 1 min	469	(35.0)	370	(32.7)	99	(47.6)	< 0.001
Spo_2 < 90% at least consecutive 2 min	172	(12.8)	136	(12.0)	36	(17.3)	0.035
Bradycardia, No. (%)	119	(8.9)	96	(8.5)	23	(11.1)	0.228
Medication administered during induction							
Neuromuscular blockade, No. (%)							0.429
None	973	(72.6)	824	(72.7)	149	(71.6)	
Depolarizing	36	(2.7)	27	(2.4)	9	(4.3)	
Nondepolarizing	330	(24.6)	280	(24.7)	50	(24.0)	
Nondepolarizing + depolarizing	2	(0.1)	2	(0.2)	0	(0)	
Anticholinergic agents							
Atropine, No. (%)	71	(5.3)	54	(4.8)	17	(8.2)	0.044
Glycopyrrolate, No. (%)	31	(2.3)	28	(2.5)	3	(1.4)	0.460
Anesthetic agents							
Dexmedetomidine, No. (%)	13	(1.0)	12	(1.1)	1	(0.5)	0.705
Medications administered during postanesthesia recovery care							
Supplemental oxygen, No. (%)	24	(1.8)	20	(1.8)	4	(1.9)	0.875
Racemic epinephrine, No. (%)	1	(0.1)	1	(0.1)	0	(0)	NA

A total of 1,341 patients met inclusion criteria. Study variables include American Society of Anesthesiologists classification of I (defined as a normal, healthy patient) and II (a patient with mild systemic disease). The encounter location represents the three procedure areas throughout the institution as follows: (1) operating room, (2) radiology consisting of diagnostic and interventional radiology, and (3) ambulatory surgery centers. The staffing model describes the attending supervision model categorized as supervision model (ratio 1:1 or 1:2) or physician-only. The neuromuscular blockade category indicates depolarizing (succinylcholine), nondepolarizing (cisatracurium, rocuronium and/or vecuronium), or nondepolarizing and depolarizing neuromuscular blockade agents administered during induction of anesthesia. Anticholinergic agents indicates administration of atropine or glycopyrrolate or epinephrine. The number of laryngoscopy attempts was extracted directly from clinical documentation. Hypoxemia was defined as oxygen saturation lower than 90% during induction of anesthesia (primary analysis 1 min or more; *post hoc* analysis at least two consecutive minutes). Bradycardia was defined as heart rate lower than 100 beats per minute for infants younger than 1 month and 80 beats per minute for patients 1 month or older. Supplemental oxygen order after discharge from postanesthesia recovery unit and racemic epinephrine administration in anesthesia recovery unit. The induction of anesthesia period was identified from electronic documentation time stamps defining "anesthesia start" and "anesthesia ready." Spo_2, oxygen saturation measured by pulse oximetry; IQR, interquartile range; NA, not applicable.

weight in the dataset. These patients were excluded from multivariable logistic regression model analysis. Patients in ambulatory surgery centers were older (8 months, 95% CI: 7 to 9, $P < 0.001$) compared to patients in the operating room (6 months, 95% CI: 3 to 9) and radiology (7 months, 95% CI: 3.5 to 8.5). Patients in ambulatory surgery also weighed more (8.5 kg, 95% CI: 7.8 to 9.5, $P < 0.001$) than those in operating room (7.4 kg, 95% CI: 5.5 to 8.7) and radiology (7.4 kg, 95% CI: 5.9 to 8.3) settings. Eighty-four percent were intubated with one attempt. The remaining 208 (16%) required two or more laryngoscopy attempts to achieve tracheal intubation. Hypoxemia occurred in 469 (35%) infants while 119 (9%) experienced bradycardia. Hypoxemia and bradycardia occurred in 50 (3.7%) infants but were not observed simultaneously. There were no cardiac arrests. A total of 378 (28%) patients received neuromuscular blocking drugs during the induction of anesthesia, 416 (31%) received intravenous atropine, 255 (19%) received glycopyrrolate, and 3 (0.2%) received intravenous epinephrine during induction.

Infants requiring two or more laryngoscopy attempts (n = 99 of 208, 48%) had a significantly higher rate of hypoxemia than patients requiring a single attempt (n = 370 of 1,133, 33%; $P < 0.001$). Infants with two or more laryngoscopy attempts (n = 23 of 208, 11.1%) had a slightly but statistically nonsignificant increase in bradycardia rate, compared with those with only a single attempt (n = 96 of 1,133, 8.5%; $P = 0.228$). There was no significant difference between the two groups when assessing sex, ASA status, staffing model, baseline Spo_2 and heart rate, and medication administered during induction (all $P > 0.05$). Infants with two or more laryngoscopy attempts were younger, had lower weight, and experienced longer induction than those with a single attempt (all $P < 0.05$); multiple laryngoscopy attempts were more common in operating rooms than in radiology suites and ambulatory surgery centers ($P = 0.021$). The number of laryngoscopy attempts by age in month is presented in Supplemental Digital Content 2 (http://links.lww.com/ALN/B992).

After controlling for confounding in the multivariable model (table 2), patients requiring multiple laryngoscopy attempts had a 78% higher risk of hypoxemia (adjusted odds ratio: 1.78, 95% CI: 1.30 to 2.43, $P < 0.001$). Multiple attempts were not associated with bradycardia (adjusted odds ratio: 1.23, 95% CI: 0.75 to 2.03, $P = 0.413$). A graph displaying the cumulative duration of hypoxemia (Spo_2 less than 90%) and bradycardia based on the classification of single *versus* multiple laryngoscopy attempts is shown in figure 3, where we observe an increasing trend in the proportion of patients requiring multiple laryngoscopy attempts with higher cumulative duration of hypoxemia or bradycardia.

The association between age and hypoxemia remained statistically significant in the multivariable model: each 1-month increase in age was associated with a 10% reduction in the risk of hypoxemia (adjusted odds ratio: 0.90, 95% CI: 0.84 to 0.96, $P = 0.002$). The decreased rates of hypoxemia by age in months is shown in figure 4, with the highest proportion of hypoxemia episodes observed in infants in the first 4 months of life (birth to 120 days old). There were no statistically significant associations between hypoxemia and other features such as weight, ASA status, encounter location, and staffing model in the multivariable model (all $P > 0.05$).

Post Hoc Analysis

The association between hypoxemia and multiple laryngoscopy attempts was reevaluated with the *post hoc* criteria for prolonged hypoxemia, at least 2 consecutive minutes with oxygen saturation less than 90%, in a multivariable model. The association between prolonged hypoxemia and multiple laryngoscopy attempts was not statistically significant (adjusted odds ratio: 1.45, 95% CI: 0.94 to 2.23, $P = 0.090$).

Table 2. Logistic Regression of Outcome between Hypoxemia or Bradycardia Events during Induction of Anesthesia *versus* Number of Laryngoscopy Attempts

	Hypoxemia (Spo_2 < 90%)					
	1 min		Consecutive 2 min		Bradycardia	
	AOR (95% CI)	*P* Value	AOR (95% CI)	*P* Value	AOR (95% CI)	*P* Value
Laryngoscopy attempt						
Multiple	1.78 (1.30 to 2.43)	< 0.001	1.45 (0.94 to 2.23)	0.090	1.23 (0.75 to 2.03)	0.413
Single	Reference		Reference		Reference	
Age in months	0.90 (0.84 to 0.96)	0.002	0.89 (0.81 to 0.99)	0.025	0.99 (0.89 to 1.11)	0.957
Weight in kg	0.99 (0.90 to 1.11)	0.986	1.07 (0.92 to 1.24)	0.366	0.92 (0.77 to 1.09)	0.308
ASA classification						
ASA I	0.87 (0.66 to 1.15)	0.322	0.79 (0.52 to 1.20)	0.261	0.59 (0.35 to 0.98)	0.041
ASA II	Reference		Reference		Reference	
Encounter location						
Operating room	1.26 (0.83 to 1.91)	0.281	1.53 (0.76 to 2.94)	0.203	0.70 (0.389 to 1.26)	0.236
Ambulatory surgery	1.03 (0.52 to 2.04)	0.936	0.65 (0.187 to 2.30)	0.508	1.13 (0.41 to 3.11)	0.812
Radiology	Reference		Reference		Reference	
Staffing model						
Physician-only	0.82 (0.46 to 1.45)	0.488	0.95 (0.379 to 2.37)	0.908	0.78 (0.309 to 2.07)	0.646
Supervision model	Reference		Reference		Reference	

Individual univariate logistic regression models were applied to assess association between study variables and hypoxemia events during induction of anesthesia. Hypoxemia was defined as oxygen saturation less than 90% for at least 1 min (*a priori* definition) and at least two consecutive minutes (*post hoc* definition per reviewer request). The multivariable logistic regression model includes age (months), weight (kg), laryngoscopy attempts (multiple *vs.* single), encounter location, staffing model, and American Society of Anesthesiologists (ASA) status. Hypoxemia events during induction of anesthesia were associated with multiple laryngoscopy attempts (2 or more) using the *a priori* definition of at least 1 min of hypoxemia, but not the *post hoc* definition of two or more consecutive minutes of hypoxemia. Age was associated with an increased risk of hypoxemia with both *a priori* and *post hoc* models. Weight, ASA status, encounter location, and staffing model were not associated with an increased risk of hypoxemia or bradycardia. The induction of anesthesia period was identified from electronic documentation timestamps defining "anesthesia start" and "anesthesia ready." AOR, adjusted odds ratio; Spo_2, oxygen saturation measured by pulse oximetry.

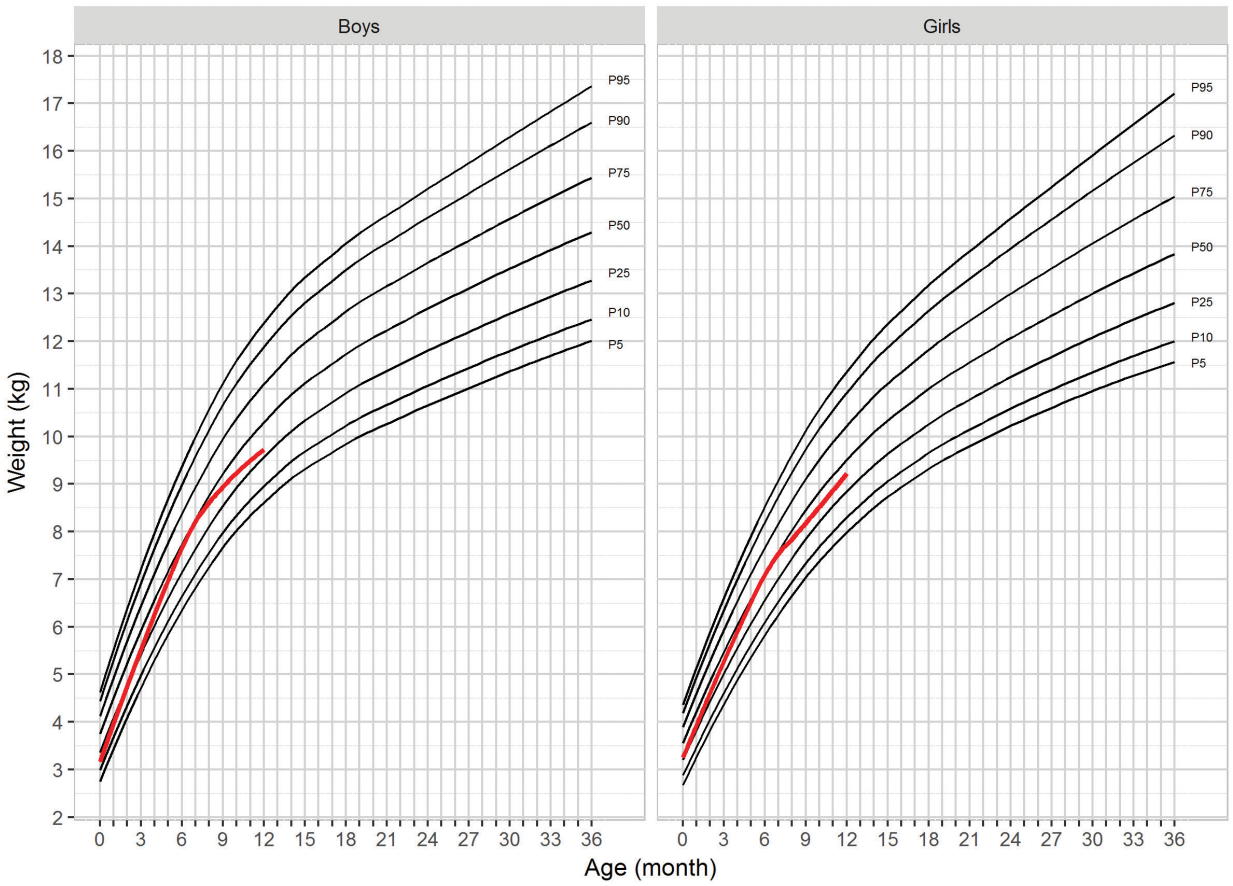

Fig. 2. Regression line to fit the weight-for-age growth curves for boys and girls based on the Centers for Disease Control growth curves for children age 0 to 36 months. P, percentile.

We also evaluated the independent association between hypoxemia and bradycardia using each definition of hypoxemia: (1) *a priori*, 1 min or longer, and (2) *post hoc* definition, at least two consecutive minutes of hypoxemia. When hypoxemia was defined as Spo_2 less than 90 for 1 min, 50 patients had hypoxemia and bradycardia during induction, and 803 patients did not experience hypoxemia or bradycardia. The association between hypoxemia and bradycardia was statistically nonsignificant (odds ratio: 1.39, 95% CI: 0.95 to 2.04, $P = 0.093$). Using the prolonged hypoxemia definition, Spo_2 less than 90% for at least two consecutive minutes, 24 patients had hypoxemia and bradycardia during induction, and 1,074 patients did not experience hypoxemia or bradycardia. Prolonged hypoxemia was significantly associated with more than 80% increase in the risk of bradycardia (odds ratio: 1.83, 95% CI: 1.13 to 2.96, $P = 0.013$). This suggests that prolonged low oxygen saturation may lead to bradycardia among anesthetized infants.

Discussion

The main finding of this single-center, retrospective cross-sectional study was that the rate of multiple laryngoscopy attempts in children ages 12 months and younger was surprisingly high (16%; table 1). Furthermore, hypoxemia occurred more frequently when more than one laryngoscopy attempt was required (table 2). These observations suggest that duration of tracheal intubation may be an independent predictor of hypoxemia independent of intubating conditions. Although the risk of prolonged hypoxemia (at least two consecutive minutes of hypoxemia) with multiple laryngoscopy attempts was not statistically significant, the magnitude of the association, a 45% increase in risk of hypoxemia, remains clinically important (table 2). The *post hoc* analysis also demonstrated an association between prolonged hypoxemia, defined as at least two consecutive minutes of Spo_2 less than 90%, and bradycardia, affecting 24 (1.8%) of patients in our study. We also observed that infants between birth and 120 days of life had the highest rate of hypoxemia (fig. 4).

The cause of hypoxemia observed in this study could be multifactorial and may not be directly linked to laryngoscopy. Hypoxemia may result from prolonged laryngoscopy, atelectasis, bronchospasm, laryngospasm, mucus obstruction, and coughing.[15] Hypoxemia as a result of hypoventilation may

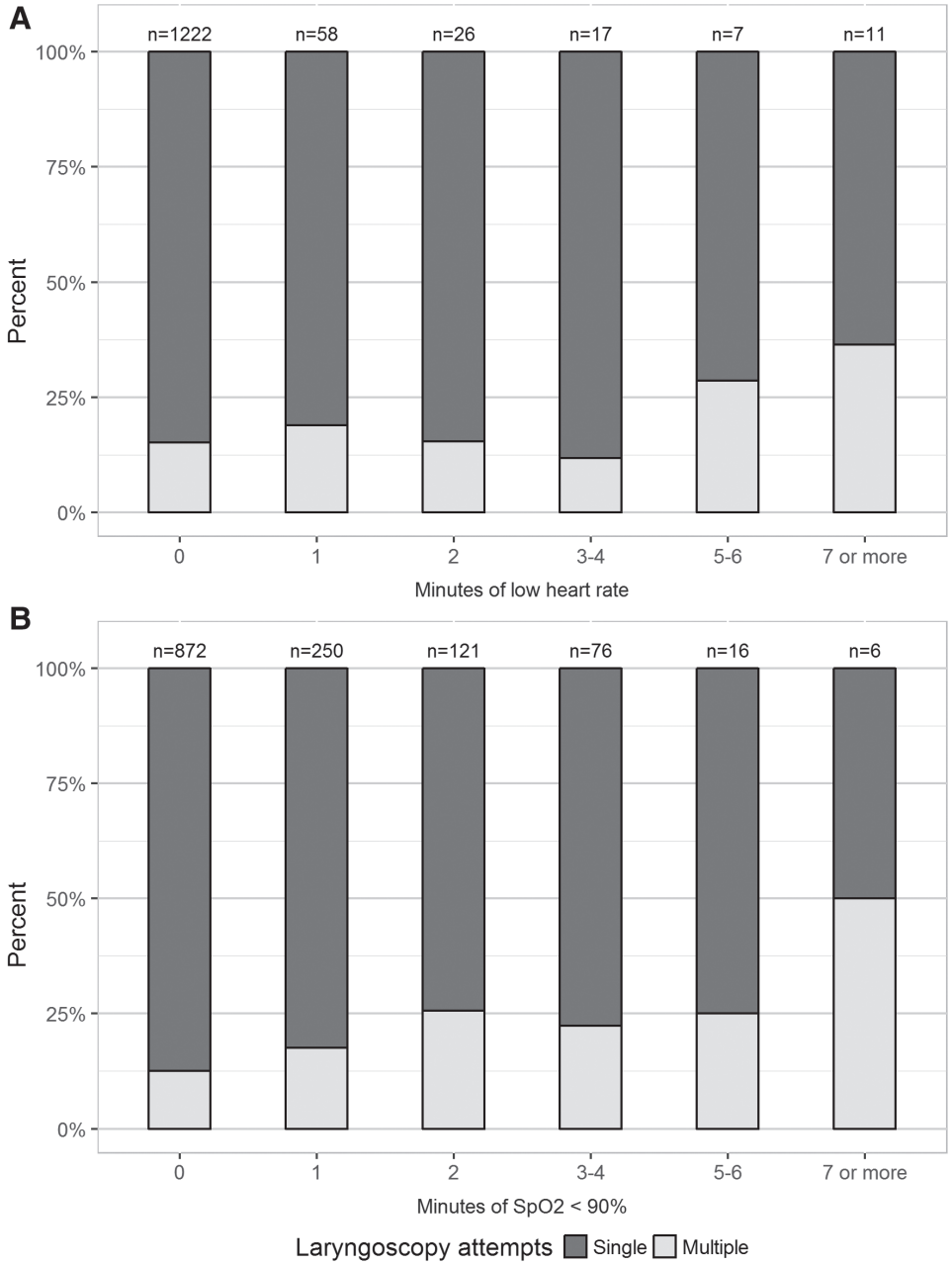

Fig. 3. Measurements for oxygen saturation and heart rate were obtained during induction of anesthesia, as identified from electronic documentation timestamps defining "anesthesia start" and "anesthesia ready." (*A*) Proportion of patients with single (*dark gray*) *versus* multiple laryngoscopy attempts (*light gray*) plotted against the cumulative minutes of bradycardia using the age-specific definition (heart rate less than 100 beats per minute for infants younger than 1 month and a heart rate less than 80 beats per minute for infants 1 month or older). Heart rate was measured with continuous 3-lead electrocardiogram over the course of induction of anesthesia. (*B*) Proportion of patients with single (*dark gray*) *versus* multiple laryngoscopy attempts (*light gray*) plotted against the cumulative minutes of hypoxemia (defined as oxygen saturation measured by pulse oximetry [Spo_2] less than 90%). A total of 469 patients developed hypoxemia during induction, with a larger proportion of patients requiring two or more laryngoscopy attempts (n = 99 of 208, 48%) experiencing hypoxemia compared to patients requiring only one laryngoscopy attempt (n = 370 of 1,133, 33%).

lead to bradycardia is a leading cause of cardiopulmonary arrests in children.[16,17] Bradycardia may also result from sedatives and analgesics, as well as the laryngeal vagal reflex.[18] We observed a low incidence of bradycardia (9%) and no cardiac arrests. None of the patients experienced concurrent episodes of hypoxemia and bradycardia, suggesting that the majority

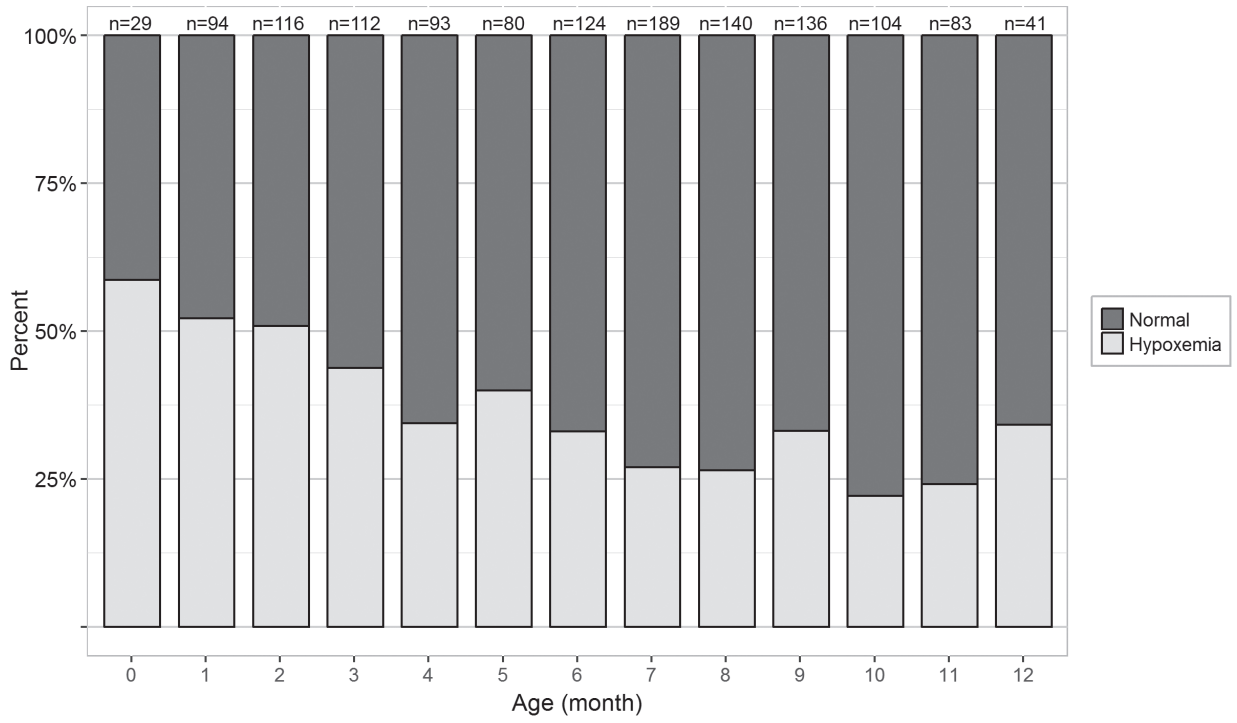

Fig. 4. The proportion of patients who developed hypoxemia during induction of anesthesia by age in months (0 = first month of life; 1 = second month of life; 2 = third month of life; 3 = fourth month of life; 4 = fifth month of life; 5 = sixth month of life; 6 = seventh month of life; 7 = eighth month of life; 8 = ninth month of life; 9 = tenth month of life; 10 = eleventh month of life; 11 = twelfth month of life; 12 = 1 yr of age). The induction of anesthesia period was identified from electronic documentation time stamps defining "anesthesia start" and "anesthesia ready."

of these hypoxemia episodes did not result in serious harm. Some clinicians argue that transient hypoxemia is of little concern, yet predicting the evolution from a transient event to one that leads to life-threatening conditions remains elusive. Furthermore, our previous work demonstrates that hypoxemia is the common event that leads to more severe complications such as cardiac arrest, neurologic injury, and death.[3]

Our results may facilitate benchmarking, quality improvement interventions, and establish baselines for future studies. The Pediatric Perioperative Cardiac Arrest registry reports a rate of 1.4 cardiac arrests in 10,000 anesthetics.[16] Based on these data, it was unlikely that we would observe cardiac arrests in our study of 1,341 patients presenting for elective procedures. Our study did not control for the administration of atropine, glycopyrrolate, or epinephrine during induction, which would limit our ability to detect the actual incidence of bradycardia in this cohort.

All patients in our cohort had a baseline oxygen saturation higher than 90%. Therefore, measurements less than 90% were likely acute hypoxemia rather than baseline hypoxemia. Analyzing data from between "anesthesia start" and "anesthesia ready" ensured that the complications observed were most likely unrelated to surgical events. However, we were not able to determine if the observation of hypoxemia between "anesthesia start" and "anesthesia ready" happened precisely as a result of laryngoscopy, despite searching for events that could also cause hypoxemia such as laryngospasm. It is possible that the hypoxemia episodes occurred as a result of data artifacts such as tourniquet application for intravenous line insertion on the same extremity as the pulse oximetry probe, patient movement, or other causes of signal interference. Pulse oximetry and heart rate from continuous electrocardiography data recorded automatically have been demonstrated to be reliable, although artifacts may still be recorded. Hoorweg *et al.* studied an automated anesthesia system and observed a rate of artifacts recorded in the electronic health record of 1% for heart rate and 4.6% for oxygen saturation during the induction phase.[19] Kool *et al.* also evaluated the incidence of artifacts recorded in anesthesia information management systems and found a low rate for heart rate (n = 9,442 measurements, 0%; 95% CI: 0 to 0.1%) and oxygen saturation (9,415 measurements, 0.3%; 95% CI: 0.2 to 0.5%), though they observed a higher rate of artifact measurements before surgical incision.[20] Our data suggests that multiple intubation attempts are potentially harmful even in infants with ASA physical status class I or II.

Our study had a few limitations. First, we are unable to determine causality and can only determine associations in this retrospective study. The dataset does not allow the evaluation of the primary outcome on a per laryngoscopy attempt basis because we rely on the clinical documentation that only lists the total number of laryngoscopy attempts. A reasonable interpretation of our results could be that hypoxemia led to multiple attempts *i.e.*, rapid oxygen consumption led the clinicians to abort the first intubation attempt in order to oxygenate. Hypoxemia could have also occurred as a result of difficulty with mask ventilation, airway obstruction, laryngospasm, or even events after the tracheal intubation such as breath holding or circuit disconnection. Second, we were unable to control for factors such as preoxygenation, tobacco exposure, or underlying pulmonary disease because the data are not easily retrievable from the electronic medical record. Passive oxygenation was not part of the clinical practice for routine intubations during the study period. These differences are unlikely to explain our findings because our routine practice is to maximize oxygen delivery before laryngoscopy. Furthermore, only patients with mild pulmonary disease were included in the study, which is less likely to impact our outcomes of interest. We did not control for history of prematurity because the data are not readily available in the electronic health record. We relied on designation of ASA physical status I or II to exclude premature infants. We also included weight in the analysis, which can be a surrogate marker for prematurity as preterm infants lag in growth during the first year of life.[21]

Third, the electronic anesthesia record system records pulse oximetry data points in 1-min intervals. Patients in our study could have developed brief episodes of hypoxemia with a duration of less than 60 s that were not recorded. Conversely, it is possible that brief episodes of hypoxemia (less than 60 s) were classified as hypoxemia cases because the data measurement may have taken place exactly when the patient experienced hypoxemia. This phenomenon is likely to be distributed evenly across the study population.

Finally, the anesthesia information management system only allows identification of one individual performing laryngoscopy. In our practice, this is the provider who successfully intubates the patient. For example, a patient who had three laryngoscopy attempts, where provider A attempts two times and provider B successfully intubates, would list provider B as the successful provider in setting of three laryngoscopy attempts. Therefore, it is not possible to accurately evaluate the effect of the training level of the individuals performing the laryngoscopy in this study. However, there was no difference in the incidence of multiple attempts across the encounter locations in our study, which do represent different care models. The odds ratio of hypoxemia rates between encounter locations was not statistically significant in either univariate or multivariable models (table 2). This observation could be due to unbalanced groups based on the care setting. The main operating room was the largest group, followed by radiology and the ambulatory surgery centers, respectively (table 1).

In summary, we present evidence supporting the association between multiple sequential direct laryngoscopy attempts and hypoxemia during induction of anesthesia. This adds to the growing body of evidence that multiple laryngoscopy attempts are undesirable, and should be a key target of quality improvement efforts.[3,4,6,7] First pass success should be the goal, and more attention is needed to minimize the risk for adverse events during tracheal intubation and to enhance the safety of anesthetized infants. Administering passive oxygen during routine intubations may delay the onset of hypoxemia and provide more time to perform laryngoscopy on the first attempt. Based on our observations that hypoxemia occurs frequently during induction of anesthesia in infants with normal airways, future research should explore using passive oxygen during intubation attempts in routine airway management. While our study was performed in a large, academic, pediatric health system that cares for complex patients, our analysis focused on a population of infants classified as ASA physical status class I or II without baseline hypoxemia and bradycardia. We expect our results to be generalizable to other pediatric teaching centers that care for infants with ASA physical status class I or II undergoing elective surgical procedures.

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Competing Interests

The authors declare no competing interests.

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