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Bradycardia during Anesthesia in Infants

An Epidemiologic Study

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Background: The frequency and morbidity of bradycardia during anesthesia in infants are not well documented. This study sought to determine the frequency of bradycardia during anesthesia in infants (0 to 1 yr) compared to that in older children, describe causes and morbidity, and identify factors that influence its frequency.

***Methods:* Computerized information abstracted from 7,979 anesthetic records of patients ages 0–4 yr undergoing noncardiac surgery were examined for the presence or absence of intraoperative bradycardia. To study bradycardia in infants, 4,645 anesthetics in patients aged 0–1 yr were considered. Those with bradycardia to heart rates less than 100 beats/min were examined for causes, morbidity, and treatment of the bradycardia. For analysis of influencing factors, the frequency of bradycardia in infants was related to age, sex, race, ASA physical status, surgical site (body cavity), complexity (major or minor) and duration, type of primary anesthetist, type of supervising anesthesiologist, and anesthetic agents. Logistic regression was used to estimate the significance ($P < 0.05$) and odds ratios for each.**

***Results:* The frequency of bradycardia was 1.27% in the 1st yr of life, but only 0.65% in the third and 0.16% in the 4th yr, a significant difference. Causes of bradycardia in infants included disease or surgery in 35%, the dose of inhalation agent in 35%, and hypoxemia in 22%. Morbidity included hypotension in 30%, asystole or ventricular fibrillation in 10%, and death in 8%. Treatment involved epinephrine in 30% and chest compression in 25%. Associated factors included an ASA physical status of 3–5 (*vs.* 1 or 2) and longer (*vs.* shorter) surgery. Bradycardia was less than half as likely when the supervising anesthesiologist was a member of the Pediatric Anesthesia Service as with other anesthesiologists ($P < 0.001$).**

***Conclusions:* Bradycardia is more frequent in infants undergoing anesthesia compared to older children and is associated with substantial morbidity. It is more likely in sicker infants undergoing prolonged surgery and less likely when a pediatric anesthesiologist is present. (Key words: Anesthesia: adverse effects; pediatric. Complications: bradycardia. Epidemiology. Outcome.)**

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BECAUSE heart rate is the primary determinant of cardiac output in children during the 1st yr of life,[1] bradycardia during anesthesia in infants could represent an adverse event. Yet the frequency of bradycardia and associated morbidity during anesthesia, and factors which influence it, are not as well documented as are those for other dysrhythmias in children.[2] This epidemiologic study was designed to determine the frequency of bradycardia during anesthesia in infants compared to older children; explore causes and comorbidity of bradycardia experienced by infants during anesthesia; and identify possible factors that influence the frequency of bradycardia.

Materials and Methods

Frequency of Bradycardia in Children

A computerized clinical database containing information from all surgical anesthetics performed in the operating room suite of a large university hospital was used. The 7,979 consecutive records of children in the first 4 yr of life undergoing noncardiac surgery between the dates July 1, 1983, and February 29, 1992, were queried for the presence of bradycardia or asystole during anesthesia. Their presence or absence was determined in each case by the primary anesthesia care

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provider by indicating on a data sheet, either yes or no, whether in their judgment (with no additional definition) a clinically significant episode of bradycardia or asystole had occurred during the anesthetic. For each of 123 anesthetics in the database in which bradycardia or asystole was recorded, the written anesthetic record was obtained from departmental or hospital medical records files. The lowest recorded heart rate was determined for each. Bradycardia was redefined as a heart rate of less than 100 beats/min in the 1st yr of life, 98 beats/min in the 2nd and 3rd yr, and 65 beats/min in the 4th yr (at least two standard deviations less than normal for each age group)[3]; 84 records met these definitions. The incidence of bradycardia, thus defined, during anesthesia in children in each of the 1st 4 yr of life was calculated. A Pearson chi square analysis was used to determine if there were significant differences ($P < 0.05$) in the frequency of bradycardia with respect to age.

Bradycardia in Infants: Cause, Comorbidity, and Treatment

The 59 written anesthetic records of patients aged 1–365 days with episodes of bradycardia (heart rate < 100 beats/min) were examined for details of cause, comorbidity (hypotension to systolic pressures 30% < baseline, asystole or ventricular fibrillation, or death in the operating room), and treatment (atropine, epinephrine, or chest compression). Cause of bradycardia was determined by two of us (RLK and JHS) according to the following criteria: "hypoxemia" was considered the cause when the bradycardia episode was associated with a recorded oxygen saturation of less than 90% as determined by pulse oximetry; "the dose of anesthetic" if bradycardia occurred within 30 min of an increase in concentration of inhalation agent and in the absence of hypoxemia; "disease or surgery" if bradycardia occurred in the presence of severe illness (ASA physical status 4 or 5) with documented metabolic acidosis, or after surgical traction in the absence of hypoxemia or overdose; and "other anesthetic causes" in the absence of all the above.

For comparison, cardiovascular complications and treatment in the 4,586 anesthetics without bradycardia were determined from the database. The accuracy of the database regarding anesthetics without bradycardia was tested by selecting 59 patient records from the database, each matched to a bradycardia subject for type and length of surgery, ASA physical status, year and month of surgery, and type of supervising anesthesiologist, but without bradycardia. Their written anesthetic records were obtained and for each the lowest recorded heart rate was determined. Among these, the lowest rate was 110 beats/min, and none had evidence of serious intraoperative morbidity.

Factors Influencing Frequency

The 59 anesthetics with episodes of heart rates less than 100 beats/min were compared with the remaining 4,586 anesthetics in infants regarding factors that might influence the frequency of bradycardia. These included age (days), sex, race, ASA physical status (1–2 *vs.* 3–5), surgical type (emergency *vs.* elective), surgical site (body cavity involvement *vs.* noncavitary surgery) and complexity (major *vs.* minor), duration of procedure, type of primary anesthetist (resident or nurse anesthetist), whether or not the anesthetic method included halothane, and whether or not the supervising anesthesiologist was a member of the Pediatric Anesthesia Service ("pediatric" or "nonpediatric" anesthesiologist).

The Pediatric Anesthesia Service included 17 physicians during the period of study, of whom 2 were board certified in pediatrics and 10 had pediatric anesthesia "fellowship" training beyond anesthesiology residency. The remaining 5 had an interest, but no formal training beyond residency, in pediatric anesthesia. The case mix by age for a member of the Pediatric Anesthesia Service consisted of 33.8 ± 8.8% (mean ± SD) children aged 10 yr or less and 16.6 ± 5.9% children aged 1 yr or less. The remainder of the anesthesiology staff included 66 physicians whose pediatric case mix was 6.5 ± 4.9% children aged 10 yr or less and 2.1 ± 2.3% children aged 1 yr or less. The percentage of physicians certified by the American Board of Anesthesiology or the Royal College of Anaesthetists of England varied throughout the period but was never less than 75% for both pediatric and nonpediatric groups. Throughout the study, pediatric anesthesiologists, when available, were preferentially assigned to provide care to infants; however, the number of pediatric anesthesiologists was few early in the investigation and greater at the end, whereas the infant caseload was relatively constant. During the last 2 yr of study, pediatric anesthesiologists were mandatorily assigned to all infants.

The "primary anesthetist" was either the anesthesiology resident physician or a certified registered nurse anesthetist (CRNA) assigned to administer the anesthetic under the supervision of an attending anesthesiologist. In fewer than 2% of cases was the attending anesthesiologist the primary anesthetist. Because this element was added to the database on April 1, 1984, only records after that date were included in the analysis of this factor.

To identify statistically significant independent variables that influenced the frequency of bradycardia, chi square analysis was initially applied to the proportions of cases with and without bradycardia (heart rate < 100 beats/min) for each factor considered. No adjustment to the P value was made for multiple comparisons. Factors whose proportions in the two groups were significantly different ($P < 0.05$), as well as those that might be clinically relevant but whose differences did not achieve statistical significance, were then applied as input variables to a multiple logistic regression model, with bradycardia set as the dependent, or output, variable. The method described by Hosmer and Lemeshow to derive and test a valid logistic model was used.[4] Odds ratios were then calculated for the input variables in the final model. Details of this procedure are provided in the Appendix.

Results

The frequency of bradycardia during noncardiac anesthesia was 1.27% for patients in the 1st yr of life, 0.98% in the 2nd, 0.65% in the 3rd, and 0.16% in the 4th (table 1). The decline in frequency with increasing age was statistically significant ($P = 0.041$).

The causes, comorbidity, and treatment of 59 bradycardia episodes in infants (1st yr of life) are summarized in table 2. Hypoxemia was the cause of bradycardia in 13 (22%), of which 12 involved infants of ASA physical status 3, 4, or 5. Anesthesia-related problems accounted for 8, 2 during induction involving difficult airways and 6 during transit to the recovery area. Surgical factors during thoracotomy or bronchoscopy were the cause of 5. Atropine was used in 9, epinephrine in 2, and chest compression in 1. A pediatric anesthesiologist was present in 8 (62%).

The dose of inhalation anesthetic agent was judged a factor in 21 (35%) episodes of bradycardia. Of these, 11 involved patients of ASA physical status 3, 4, or 5. The median time of occurrence after start of anesthesia was 15 min, with a range of 4–300 min. Halothane was used in 20; the inspired concentration was 1.7 ± 1.1% (mean ± SD) at the time of bradycardia. Isoflurane was involved in 1 episode, in which the vaporizer had been mistakenly set at 5%. Atropine was used to treat 19; 5 required epinephrine and chest compression. A pediatric anesthesiologist was present in 4 (19%).

Table 1. Frequency of Bradycardia during Anesthesia in Children, by Age

	0–1 yr	1–2 yr	2–3 yr	3–4 yr
Total anesthetics	4,645	1,932	774	628
With bradycardia	59	19	5	1
% Bradycardia	1.27	0.98	0.65	0.16

The observed decrease in frequency with age is significant ($P = 0.041$, chi-square).

Severe disease or surgical factors were the cause in 21 (35%) episodes of bradycardia. Of these, 17 involved patients of ASA physical status 3, 4, or 5. Severe intraabdominal disorders (such as necrotizing enterocolitis or diaphragmatic hernia) were present in 14, who were typically hypotensive and acidemic on arrival. Reflex bradycardia from surgical stimulation occurred in 6; hemorrhage accounted for 1. Halothane was used in 8 and isoflurane in 2; intravenous opioids with or without nitrous oxide were used in 11. Treatment of bradycardia included intravenous epinephrine and sodium bicarbonate in 11. All 5 intraoperative deaths in this study were in this group. Of the 21 cases, 10 (48%) were attended by a pediatric anesthesiologist.

Other anesthesia-related causes accounted for four episodes of bradycardia. Two occurred after the administration of a muscle relaxant antagonist (pyridostigmine) and the other two after the administration of spinal anesthesia. All responded to atropine. A pediatric anesthesiologist was present in three (75%).

Of the 59 patients with bradycardia, 15 (25%) had received atropine either as a preanesthetic medication or intravenously before the episode of bradycardia. Of the 25 in which a pediatric anesthesiologist was present, 9 (36%) had received atropine, compared to 6 of 34 (18%) when a nonpediatric anesthesiologist was present.

Among 4,586 anesthetics without bradycardia, cardiovascular complications occurred in 132 (2.87%). Hypotension was recorded in 64 and tachycardia in 28. No instance of asystole, ventricular fibrillation, the use of chest compression or epinephrine, or intraoperative death was recorded.

Univariate analysis of possible factors influencing the frequency of bradycardia identified five with P values < 0.05: ASA physical status, surgical type (elective *vs.* emergency), duration of surgery, primary anesthesia

Table 2. Causes, Comorbidity, and Treatment of Bradycardia (heart rate <100 beats/min) Occurring in Infants (newborn to 1 year) during Anesthesia

	Total (n = 59)	Hypoxemia (n = 13)	Excessive Dose of Inhalation Agent (n = 21)	Disease or Surgery (n = 21)	Other Anesthesia Cause (n = 4)
Comorbidity					
Hypotension	19	2	6	11	0
Asystole/ventricular fibrillation	8	0	2	6	0
Operating room death	5	0	0	5	0
Therapy					
Atropine	46	9	19	15	3
Epinephrine	18	2	5	11	0
Chest compression	15	1	5	9	0

provider (resident *vs.* CRNA), and supervising anesthesiologist (table 3). The following had *P* values > 0.05 but were also included in the initial logistic regression model: surgical complexity (major *vs.* minor), body cavity, anesthetic (halothane *vs.* no halothane), age within the 1st yr, and race.

With the logistic regression model, four significant variables were found: ASA physical status, type of supervising anesthesiologist, duration of the procedure, and type of surgery (emergency *vs.* elective). Table 4 lists their odds ratios with 95% confidence limits. Variables found not to be significant by logistic regression included complexity of surgery (major *vs.* minor), body cavity, and type of primary anesthetist (resident *vs.* CRNA).

Table 3. Univariate Analysis of Possible Factors Influencing the Frequency of Bradycardia in Infants (heart rate <100 beats/min), with Chi Square Results

Variable	Total	Bradycardia	%	*P* Value
ASA physical status				
3–5	2,049	41	2.00	
1–2	2,596	18	0.69	<0.001
Surgical type				
Emergency	601	16	2.66	
Elective	4,044	43	1.06	<0.001
Duration				
>4 h	378	14	3.70	
≤4 h	4,267	45	1.05	<0.001
Primary provider				
Resident	3,295	33	1.00	
CRNA	1,008	18	1.79	<0.044
Anesthesiologist				
Pediatric	3,043	25	0.82	
Nonpediatric	1,602	34	2.12	<0.001

One variable, the choice of anesthetic (halothane *vs.* no halothane), proved to be nearly colinear with another variable, ASA physical status. Because the model requires elimination of one or the other of such variables, choice of anesthetic was eliminated in favor of ASA physical status, because it seemed most likely that ASA physical status influenced the choice of anesthetic, rather than *vice versa.*

Discussion

This study found the frequency of bradycardia during anesthesia in the 1st yr of childhood, at 1.3%, was greater than that in the 3rd and 4th yr, at 0.6% and 0.2%, respectively. The decrease in frequency with increasing age proved to be significant. Thus, the observation in unanesthetized children that bradycardia is more likely to occur in infants than in older children[5] is true of anesthetized children as well. Furthermore, that the frequency of bradycardia did not vary signifi-

Table 4. Results of Logistic Regression

Variable	Odds Ratio	95% Confidence Interval	*P* Value
ASA physical status			
3–5 *versus* 1–2	2.49	1.41–4.41	0.0017
Supervising anesthesiologist			
Pediatric *versus* nonpediatric	0.41	0.24–0.69	0.0008
Surgical type			
Emergency *versus* elective	1.88	1.03–3.44	0.0392
Procedure duration			
Each additional hour	1.11	1.06–1.16	0.0001

cantly with age within the 1st yr ($P > 0.25$, logistic regression) suggests that the increased likelihood of bradycardia is present for the entire 1st yr of childhood.

In a review of the records of 59 infants with episodes of bradycardia to heart rates less than 100 beats/min, substantial morbidity was found. Hypotension occurred in 32%, asystole or ventricular fibrillation in 14%, and intraoperative death in 8%. Chest compression was required in 25%. In contrast, among infants without episodes of heart rates less than 100 beats/min, cardiovascular complications were recorded in less than 3%; none required epinephrine or chest compression. These data support the view that a heart rate of less than 100 beats/min in infants may be considered an adverse event.

The cause of bradycardia in infants could be assigned to one of four categories. Approximately one third were due to patient disease or surgical factors; most were very ill, and all of the intraoperative deaths in the study occurred in this group. The dose of inhalation anesthetic was deemed responsible for another third. Most of these were relatively healthy subjects receiving halothane who developed bradycardia early in the procedure. Most responded to discontinuation of agent and intravenous atropine, although five required epinephrine and chest compression. A nonpediatric anesthesiologist was present in 80% of these cases, but present in only 34% of all cases. Hypoxemia caused bradycardia in 13 (22%), of which 8 were anesthesia related. Hypoxemia was recognized in all and successfully treated with oxygenation and atropine in most cases, although chest compression was required in 1. Intraoperative pulse oximetry was used routinely in infants throughout all but the first 6 months of this 8-yr study.

In examining factors that might influence the frequency of bradycardia in infants, this study found ASA physical status, not surprisingly, to be important. ASA physical status 3, 4, and 5, as a group, was associated with a bradycardia rate three times greater than that in the group with ASA physical status 1 and 2. Logistic regression analysis revealed that bradycardia is 2.5 times more likely in patients of the higher ASA physical status categories, all other relevant factors being equal. Similarly, logistic regression showed the likelihood of bradycardia to increase by 11% for each hour of surgery. Surprisingly, the site (cavitary *vs.* noncavitary) and type (major *vs.* minor) of surgery were not significant factors.

Although the type of provider (resident *vs.* nurse anesthetist) appeared to be related to bradycardia by univariate analysis, other confounding variables were present that, when taken into account by multiple logistic regression, revealed this variable to be nonsignificant. On the other hand, whether the supervising anesthesiologist was pediatric or nonpediatric—also significant with univariate analysis—was even more significant ($P = 0.0008$) when the same confounding variables were taken into account by multiple logistic regression. All other factors considered being equal, bradycardia is less than half as likely (odds ratio 0.41) in infants during anesthesia with a pediatric anesthesiologist as with a nonpediatric anesthesiologist.

A limitation of this study was its retrospective nature; it was conceived after the database had been initiated. It was therefore confined to items in the database, and randomization of subjects was not possible. These limitations illustrate two important problems of retrospective studies: the problem of incomplete, inaccurate, or missing data and the problem of confounding variables. The problem of missing data (familiar to those who have attempted medical record reviews) can be overcome in part with an extensive database incorporating mechanisms to ensure that no records are missed and that all entries are complete and accurate. In addition, testing for accuracy is necessary, as was done in this study for all records of infants with bradycardia and for a representative sample of infants without bradycardia. Even then, desirable information may not be available. For instance, it would have been useful to know how many infants without bradycardia had received an anticholinergic agent as preanesthetic medication, but because this information was not kept in the database, we could not assess atropine's effectiveness in preventing bradycardia. Thus, the more extensive the available information, the more likely the success of a retrospective study.

For the problem of confounding variables, multiple logistic regression is a partial solution used increasingly in retrospective studies by epidemiologists[6] and health services researchers.[7] This form of multifactorial analysis can identify significant independent variables and assign them relative weights (odds ratios), provided their numbers are available. However, there is never the certainty that all important variables are known. Furthermore, variables not independent of one another (such as halothane and ASA physical status in this study) may limit the usefulness of logistic regression in identifying confounding variables.

The finding that infants are significantly less likely to experience bradycardia during anesthesia in the hands of pediatric anesthesiologists should be interpreted in light of the above. Expected confounding variables would include severity of illness and complexity of surgery. Logistic regression did in fact identify ASA physical status, emergency *versus* elective surgery, and length of surgery as such, and controlled for these variables in calculating the odds ratio for pediatric anesthesiologists. Other possible confounding variables such as surgical site and primary provider proved not to be significant.

A question of bias due to self-reporting may be raised because the information in the database was collected by those providing the anesthesia care. It could be argued that pediatric anesthesiologists were less sensitive to episodes of bradycardia than were their nonpediatric colleagues. However, intraoperative data were recorded by the primary anesthesia provider and not the supervising physician. Furthermore, review of a representative sample of written anesthetic records of patients in whom no bradycardia had been recorded found no episode of bradycardia.

The results of this study might provide a clue as to why patients of pediatric anesthesiologists had fewer episodes of bradycardia. Of 21 episodes of bradycardia related to the dose of inhalation agent, only 4 involved a pediatric anesthesiologist. This, and the observation that this provider group had had more extensive experience with infants than their nonpediatric colleagues, suggests that they may be more familiar with the depressant effects of volatile agents (notably halothane) on the heart of infants than are their colleagues. It also suggests that it was the actual experience of the anesthesiologist, rather than his or her training, that made a difference.

The substantial morbidity associated with bradycardia found in this study should be considered in the context of currently available anesthetic morbidity rates. At least four studies of anesthetic cardiac arrest within the last decade have demonstrated an excess morbidity in children in the 1st yr of life compared with older children and adults.[8-11] Although the cause of this morbidity is not clear, one of these studies (by our group) indicated that the infant cardiac arrest rate, which was nine times higher than for adults, decreased to that for adults when a pediatric anesthesiologist was in attendance.[11] Recently in the United Kingdom, a recommendation was made that "anaesthetists should not undertake occasional paediatric practice."[12] To the extent that bradycardia is considered an adverse event, our findings do suggest that "occasional paediatric practice" may not be the ideal for providing anesthesia to infants.

Appendix

Multiple logistic regression may be used to express the proportion of a group of subjects in which an outcome variable (*e.g.*, bradycardia) can be expected, given the presence of certain independent variables (*e.g.*, ASA physical status of 3–5):

$$\pi = \frac{e^{(\beta_0+\beta_1 x_1+\beta_2 x_2+\cdots+\beta_n x_n)}}{1 + e^{(\beta_0+\beta_1 x_1+\beta_2 x_2+\cdots+\beta_n x_n)}}$$

where π is the proportion of subjects in which the outcome variable is present; β_0 is the intercept; β_n are parameter estimates of the independent variables; and X_n are the proportions of subjects exhibiting the independent variables.

A logit transformation is applied to π:

$$g = \ln \frac{\pi}{1 - \pi}$$

where g is the logit of π. By combining the two equations the mathematics is simplified:

$$g = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

The logit has additional advantages in that it is linear in its parameters, may be continuous, and may range from −infinity to +infinity.

A logistic regression model is fitted to the observed data by a method analogous to that used for multiple linear regression. Details of this method may be found in Hosmer and Lemeshow.[4]

The maximum number of independent variables is included in the initial model. Chi square is calculated for each parameter estimate and for the model as a whole, from which *P* values are determined. Variables with parameter estimates associated with P values > 0.25 are then removed and the model recalculated. This usually results in a larger chi square and an improved *P* value for the model as a whole. Other variables with *P* values 0.05 or greater are then removed sequentially and the model recalculated until the minimum number of significant variables provides a maximum chi square. For this study, chi square for the final model was 45.132, with four degrees of freedom, and $P = 0.0001$. Finally, the odds ratio, ψ, is calculated for each independent variable by using its parameter estimate, β_n:

$$\psi_n = e^{\beta_n}$$

For this study the logistic regression procedure was performed with the SAS System (Version 6, 1990, SAS Institute, Cary, NC) software running on the same computer as the database (Microvax 3500, Digital Equipment Corporation).

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