

# Risk factors for bradycardia and desaturation in infants undergoing ophthalmological surgeries: a retrospective cohort study

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## Research Article

**Keywords:** Pediatric, respiratory depression, premature babies with retinopathy

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# Abstract

**Background:** Perioperative cardiac and respiratory adverse events remain major pediatric morbidity and mortality especially for children less than 1 year old. Physical status, anesthetic management and surgical profile are three main facets of perioperative setting and need to be investigated to identify useful predictors for perioperative adverse events in this population of fragile infants.

**Methods:** In this retrospective cohort study, all infants undergoing general anesthesia for ophthalmological surgeries at Peking University People's Hospital, Beijing, China from November 1, 2016 to October 31, 2017. Physical status, anesthesia and surgical management were analyzed by exploratory factor analysis and component matrix to explore risk factors for bradycardia and postoperative desaturation, the most commonly seen pediatric anesthesia related adverse events.

**Results:** After the 12 months, 350 cases were included, among whom 71 infants underwent two surgeries required by their ophthalmological conditions. The median post conceptual age at the time of surgery was 50 (42, 63) weeks. Bradycardia (31/350, 8.9%) and postoperative desaturation (36/350, 10.3%) were identified as major cardiac and respiratory adverse events. Preoperative Atropine, intubation and bigger body weight would prevent patients suffering from bradycardia, while longer duration of anesthesia was a risk factor for bradycardia. Low body weight was also a risk factor for postoperative desaturation. Body weight cut-off point identified was 3.15kg, which meant that, infants who were lighter than 3.15 kg, the chance of postoperative desaturation was significantly higher than who are heavier than 3.15kg (27.8% vs 4.2%,  $P=0.000$ ).

**Conclusion:** This study found that longer duration of anesthesia was related with a higher incidence of bradycardia and low body weight is a predictor for postoperative desaturation.

**Funding:** This study was supported by Research and Development Grant of Peking University People's Hospital, RDC2012-12.

**Keywords:** Pediatric, respiratory depression, premature babies with retinopathy.

## Introduction

Perioperative cardiac and respiratory adverse events remain major pediatric morbidity and mortality especially for children less than 1 year old, which is due to the relatively narrow infant airway together with the high incidence of respiratory tract infections in young children. Big annual caseload and experienced personnel are important to reduce pediatric morbidity and mortality<sup>1</sup>.

Anesthesia management of pediatric ophthalmologic surgeries is extremely challenging because covering and draping of the surgical field hinder direct access to patients' airway. There are several commonly seen ophthalmological diseases affecting infants, such as cataract, familial exudative vitreoretinopathy (FEVR) and retinopathy of prematurity (ROP). As a leading cause of childhood

blindness worldwide, ROP prompts early bedside screening and timely intervention. However, ROP screening guideline in China was not formulated until 2012, before which few infants suffering from ROP were identified and treated<sup>2,3</sup>. Fortunately, the guideline brought up several positive changes, but the epidemic of ROP in China is still characterized by advanced stage of ROP in more mature infants than those in the West<sup>3</sup>. Children suffering from complete retinal detachment (ROP stage 5) constitute 50% of severe ROP, which is rare in developed countries. Infants with stage 3-5 ROP will have to undergo ophthalmological procedures ranging from laser surgery to vitreoretinal surgery, the latter being the most complicated eye surgery. Actually prematurity is often related with underdevelopment of various systems and prone to suffer from high morbidity and mortality at surgery and prematurity is the strongest risk factor for desaturation among infants undergoing hernia repair<sup>4</sup>. Infants with post conceptual age (PCA) less than 46 weeks are advised to be transferred to intensive care unit (ICU) after general anesthesia<sup>5</sup>. However, with large loads of infants and limited ICU beds, it is not practical in developing countries. Reducing the risk of cardiac and respiratory adverse events and identifying infants at risk may make full use of limited medical resources.

In this study, we aimed to identify the risk factors for major cardiac and respiratory events related with eye surgeries in infants. Specifically, we studied 279 infant patients who received 350 surgeries to explore possible risk factors involved in physical status, anesthetic management and surgical profile.

## Methods

We conducted a retrospective cohort study on infants diagnosed as cataract, FEVR and ROP (stage 3-5) who received lensectomy, transpupillary laser treatment, vitreoretinal surgery with/without anterior segment surgery, collected demographic, surgical, and anesthetic features, and documented cardiac and respiratory adverse events associated with surgery. We analyzed the association between the features and the adverse events to reveal potential risk factors for each adverse event.

The study was approved by the Peking University People's Hospital Institutional Review Board, and parental consent was waived because of the retrospective design.

### Study population

We retrospectively included all infants who underwent ophthalmological procedures for cataract, FEVR and ROP at Peking University People's Hospital from November 1, 2016 to October 31, 2017. The majority of them were referred to our hospital where the National Pediatric Eye Center is located. Ophthalmological procedures included laser surgery, vitreoretinal and anterior segment surgery. Infants were excluded if they had a recent history (up to 2 weeks) of upper airway infection or their parents were unwilling to give consent.

We collected information regarding their demographic, anesthetic and surgical features. Gestation age at birth and PCA at the time of surgery would be recorded. Body weight at birth and body weight at the time of surgery would also be documented. Gestational age was determined by questioning the parents and

confirmed with documentation of physical examination at birth in previous medical records. PCA was the sum of the gestational and postnatal ages. A preoperative history of apnea would be recorded.

### **Anesthetic and Surgical management**

All patients were admitted to hospital on the day of surgery. All parents were instructed on applying topical anesthetic and mydriatic to their children preoperatively. In the preparation room, intravenous cannula was inserted and an intravenous infusion of 2-4 ml·kg<sup>-1</sup>·h<sup>-1</sup> ringer lactate was initiated and maintained during the surgery. Upon arrival at the operating room, standard monitor was established including electrocardiogram (ECG), non-invasive blood pressure, pulse saturation (SpO<sub>2</sub>) and end tidal carbon dioxide after anesthesia induction.

General anesthesia was induced either by intravenous propofol or inhalational sevoflurane. Airway management device could be either endotracheal tube or a face mask. If an endotracheal tube was used, pressure controlled ventilation was adopted, inspiratory pressure set as 20 cmH<sub>2</sub>O, and respiratory rate adjusted according to a target end tidal carbon dioxide of 35-45 cmH<sub>2</sub>O. Retrobulbar block with 0.5% ropivacaine 0.1 mL/kg was administered to all patients by an experienced ophthalmologic surgeon except for those undergoing laser surgery. Appropriate depth of anesthesia was ensured by central position of pupils<sup>6</sup>. Use of preoperative atropine, opioids, muscle relaxant or steroids was left to the discretion of the anesthesiologist in charge. After surgery, all infants were monitored in the ward for at least 12 hours.

Infants suffering from cataract would undergo lensectomy; laser coagulopathy or retinal cryotherapy was given to infants suffering from ROP stage 3 or threshold disease; scleral buckling would be applied to ROP stage 4a patients; vitrectomy with/without lensectomy would be applied to patients suffering from ROP stage 4b/ 5 and FEVR.

### **Outcome measurement**

All episodes of bradycardia (HR less than 100 bpm), laryngospasm, bronchospasm, airway obstruction, apnea, oxygen desaturation (less than 90%) were recorded as perioperative cardiac and respiratory adverse events in electronic anesthetic database. Bradycardia caused by oculocardiac reflex (OCR) was identified. Usually OCR was caused by pressing the globe or manipulation of extraocular muscles, which could often be corrected by cessation of surgical stimulus, or, if it did not work, atropine 0.01mg/kg should be administered. When surgical procedures were finished, all children who had recurrent desaturation (less than 90%) and could not be relieved by oxygen supply through a face mask would be admitted to intensive care unit (ICU) for further monitoring and treatment. Apnea was defined as a pause in breathing >10 seconds or a pause >5 seconds if associated with oxygen saturation <90% or bradycardia (HR less than 100 bpm). This definition was adapted from GAS study [12]. Pulse oximetry would be monitored for infants transferred to surgical ward, who would be discharged home 24 hours after surgery, and those transferred to ICU would stay there more than 24 hours.

## Statistical analysis

Statistical analysis was done with SPSS (version 20.0). We did univariate analysis with the student's t test or Mann-Whitney U test for continuous variables and the  $\chi^2$  test for categorical variables. For all analyses, we used two-sided tests, with *P* values less than 0.05 denoting statistical significance.

In order to avoid problems of multicollinearity, exploratory factor analysis was used to reduce dimension of the confounders and to find the underlying factors with clinical significance which could extract at least 70% of squared loadings from the initial components cumulatively. Scores of those underlying factors were saved as the new variables to be used in the multivariate logistic regression models with other uncorrelated covariates. The method of backward stepwise (Likelihood Ratio), which meant variables remained in the model if they improved the model fit with the likelihood ratio test, was used in the logistic regressions models to result in selected factors.

If any underlying factor from the factor analysis was selected, all of its main components, which extracted more than 50% of loadings in the rotated component matrix, were used as selected covariates. These selected covariates would construct a new logistic regression model with other selected initial confounders. Thus by using the method of backward stepwise (Likelihood Ratio), RRs of the observable factors could be calculated. Hosmer-Lemeshow statistic and Area Under the ROC Curve (AUC) were used to measure the calibration and discrimination of the logistic regression model, and the outliers, whose absolute value of standardized residuals were greater than 2.3, were excluded from the final analysis.

In order to facilitate clinical application of our research findings, we converted the continuous variables, which are predictors for various adverse events, to binary variables. Therefore we could figure out the cut-off point for different risk variables, through Decision Tree Analysis, i.e. Classification and Regression Trees.

## Patient and public involvement

Patients were not involved in setting the research questions or planning the study. Investigators do not know the identity of study participants.

## Data sharing

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## Results

During the 12 months, 279 infants (median PCA being 50 weeks) undergoing 350 surgeries were included in this study. Seventy-one infants received a second ophthalmological procedure as needed.

There was no death or cardiac arrest in all the cases. The median gestational age at birth was 31 (29, 36) weeks, while the median post conceptual age at time of surgery being 50 (42, 63) weeks. The number of

prematurely born (born at less than 37 weeks) infants was 267 (76.3%). For cardiac and respiratory complications, 31 (8.9%) cases suffered from intraoperative bradycardia, two of which were due to OCR and all bradycardia was resolved with intravenous atropine. After surgery, 36 (10.3%) cases had recurrent desaturation (less than 90%), which could not be relieved by oxygen supply through a face mask, and were admitted to intensive care unit (ICU) for further monitoring and treatment, among whom 3 cases suffered from laryngospasm after extubation, others suffered from apnea (Table 1).

### ***Exploratory factor analysis***

All variables, among which potential collinearity was considered, were analyzed with factor analysis. Five underlying factors were found: anesthesia managements (preoperative atropine and steroid, muscle relaxant, airway management device and intravenous/inhalational induction), current status of growth (postconceptual age and body weight at surgery), status of birth (gestation age and body weight at birth), duration of surgery and current physical status (hemoglobin concentration).

### ***Risk assessment of adverse events***

Intraoperative bradycardia, occurred in 31 (8.9%) infants. All bradycardia was resolved with intravenous atropine. In multivariate analysis, anesthesia managements [OR: 0.278 (0.186-0.416)], and duration of the procedures in operation room [OR: 1.788 (1.193-2.680)] were selected for constructing further logistic regression models. After 9 outliers were excluded, the significant risk factor for bradycardia was duration of anesthesia (Table 2). The final logistic regression model exhibited excellent discrimination and acceptable calibration. The AUC was 0.984 (0.972-0.996), and the Hosmer-Lemeshow statistic was 0.377 (P = 1.000).

For convenience of clinical application of our research findings, decision tree analysis was adopted, Bradycardia was set as a dependent variable, duration of anesthesia as an independent variable. Three terminal nodes were found through Decision Tree Analysis, i.e. Classification and Regression Trees. When duration of anesthesia  $\leq 128.5$  minutes, the incidence of Bradycardia was 10.9%. When duration of anesthesia last between 128.6 to 155.5 minutes, Bradycardia incidence was 0. When anesthesia duration went longer than 155.5 minutes, 11.7% of infants would suffer from Bradycardia (Fig.1).

For postoperative desaturation, Anesthesia management [OR: 0.570 (0.408-0.797)], current status of growth [OR: 0.410 (0.216-0.777)] and current physical status [OR: 0.471 (0.331-0.669)] were selected for constructing further logistic regression models. After 6 outliers and 38 cases (due to lack of Hb datum) were excluded, the significant risk factors for ICU events were Body weight at surgery. The final logistic regression model exhibited excellent discrimination and acceptable calibration. The AUC was 0.914 (0.875-0.953), and the Hosmer-Lemeshow statistic was 1.168 (P = 0.992). For convenience of clinical application of our research results, decision tree analysis was adopted, which revealed, for those who are lighter than 3.15 kg, the chance of ICU admittance was significantly higher than who are heavier than 3.15kg (27.8% vs 4.2%, OR being 6.57, 95% CI being (3.37-12.80)  $\square$  P=0.000) (Table 3, Fig 2).

## Discussion

In this retrospective cohort study, bradycardia (8.9%) and postoperative desaturation (10.3%) were identified as major cardiac and respiratory adverse events in 350 cases of pediatric ophthalmological treatment. Risk factors analysis revealed that, longer anesthesia was related with a higher incidence of bradycardia and lower body weight is a better predictor for postoperative desaturation and consequential ICU admittance than post conceptual age.

Anaesthesia-related mortality and morbidity is known to be higher at the extremes of age than in other age groups. There is still a relative higher rate of adverse events in infants compared with older children even in a teaching paediatric hospital with a high annual caseload according to Murat<sup>1</sup>. Eye surgeries also hinder direct access to airway due to covering and draping of surgical field, therefore administering anesthesia to infants undergoing eye surgeries needs special attention especially when ex-preterm infants were involved.

Anesthesia management varied between developed and developing countries due to different screening program and epidemic of ROP. In developed countries, bedside ROP screening is performed under oral sucrose or anesthetic eye drops, which were considered insufficient to relieve the discomfort of ROP examination<sup>7</sup>. Cryotherapy could be accomplished under general anesthesia with endotracheal tube in place administered by a neonatologist in neonatal intensive care unit<sup>8</sup>. For surgical treatment of ROP involving laser or cryotherapy, anesthetic choices range from intravenous sedation to general anesthesia with endotracheal intubation<sup>9</sup>. In our center, laser treatment was performed under sevoflurane inhalation with spontaneous ventilation through a face mask<sup>10</sup>. All intraoperative apneic episodes were resolved by cessation of surgical procedure and bag-mask ventilation. For more complicated posterior segment surgery, retrobulbar block could be a useful adjunct for analgesia using endotracheal tube<sup>11</sup>. Many patients needing ROP surgery have been weaned from mechanical ventilation days or weeks before the surgery, but are then electively re-intubated for the surgery. Retrobulbar block and sevoflurane inhalation could be an alternative to endotracheal intubation general anesthesia for laser coagulopathy and some anterior segment surgery.

In our infants only study, cardiac and respiratory complications remained the major adverse events, which was similar to an observational study involving 24,165 cases of pediatric anesthesia the incidence being 12.5% and 53% respectively<sup>1</sup>. Risk predictor related with intraoperative bradycardia (HR<100 bpm) was the duration of anesthesia. With the prolongation of anesthesia duration, the prevalence of bradycardia would increase. It could be postulated that for longer surgeries and anesthesia, accumulation of anesthetic may inhibit cardiovascular system. Patients with a recent history of upper airway infection (n=5, data not shown) was not included in our study, but were safely managed by intravenous induction and use of laryngeal mask airway in accordance with a newly implemented guideline<sup>12</sup>.

As for postoperative apnea, a smaller body weight is a stronger indicator instead of postconceptual age. Infants with a body weight less than 3.15 kg have a significantly higher chance of ICU admittance after

ophthalmological surgeries (27.8% vs 4.2%,  $P=0.000$ ). Analyzed from 8 prospective studies, Cote found that the overall risk of apnea in patients less than 48 weeks post conceptual age is 5%, and this risk does not decrease to less than 1% until patients reach 54 weeks post conceptual age after inguinal herniorrhaphy<sup>13</sup>. Actually 3.15 kg is cutoff from PCA 35 to 41 weeks, it could be concluded that we need to take both body weight and post conceptual age into consideration when we apply anesthesia to these premature infants.

Furthermore, we did not witness the beneficial effect of dexamethasone, maybe because laryngospasm was too rare (3/350) in this study in contrast to a beneficial effect of steroids in one-lung ventilation children<sup>14</sup>. Use of muscle relaxant or opioids did not increase the prevalence of desaturation of ICU admittance, which is maybe due to minimizing doses, giving muscle relaxant antagonist at the end of surgery and our attempt to achieve opioid-sparing regimen.

There are several limitations of this study. Firstly, after dimension deduction, there are 6 potential risk factors, almost each of which were combinations of several observational variables. Thereafter, when converting to measurable regression equation, confidence interval was enlarged, which meant a low accuracy. Even though the combined risk factors could predict postoperative complications more precisely, we calculated the odd ratio for each observational variable in order to apply the results in clinical guidance. Secondly, collinearity test showed that there was no multicollinearity, but the confidence interval was enlarged, which could be caused by small sample size in this study. Thirdly, despite of the continuous variables determined as risk factors for different complications, a cut-off point should be ideally ascertained. In this scenario, RR value was based on univariate analysis, because almost no more significant factor was found in the regression models. Finally, this is not an interventional study, which could not eliminate bias or confounding factors. The advantage of less invasive airway,<sup>15</sup> LMA was not examined in our study, which would be studied in the future.

In conclusion, longer anesthesia was related with a higher incidence of bradycardia and lower body weight is a better predictor for intraoperative bradycardia, apnea and consequential ICU admittance than post conceptual age undergoing pediatric eye surgeries.

## **Declarations**

### **Ethics approval and consent to participate:**

The study was approved by the Peking University People's Hospital Institutional Review Board.

### **Consent for publication:**

Parental consent was waived because of the retrospective design.

## Availability of data and material

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## Competing interests:

All authors declare no competing interests.

## Funding:

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## Authors' Contribution:

All authors have read and approved the manuscript.

B.J.: Data analysis.

L.Y.: Study design.

H.Z.: Study design, patient recruitment, data collection and writing of the paper.

J.L.: Patient recruitment and data collection.

Y.F.: Study design.

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## Tables

Table 1. Demographics and measurement outcomes

Items	Data
<i>Demographic features</i>	
Male (n)	243 (69.4%)
Post conceptual age (weeks)	50 (42, 63)
Gestation age at birth (weeks)	31 (29, 36)
Body weight at surgery	6.0 (3.0, 8.0)
Body weight at birth	2.0 (1.0, 2.7)
Hemoglobin concentration (g/L)	110 (97, 120)
Cataract	48 (13.7%)
FEVR	35 (10%)
ROP	267 (76.3%)
<i>Surgical features</i>	
Laser surgery	53 (11.5%)
Vitreoretinal	249 (71.2%)
Lensectomy	48 (13.7%)
Second surgery (n)	71 (20.2%)
Duration of surgery (min)	66.0±29.6
<i>Anesthetic features</i>	
Duration of anesthesia (min)	116.2±43.7
Number of cases with preoperative Atropine	267 (76.3%)
Number of cases with preoperative Steroid	246 (70.3%)
Number of cases with Opioids	25 (7.1%)
Number of cases with Muscle relaxant	210 (60%)
Number of cases receiving Intubation	267 (76.3%)
Number of cases receiving Intravenous induction	187 (53.4%)
<i>Cardiac and respiratory adverse events</i>	
Number of cases suffering from Intraoperative bradycardia	31 (8.9%)
Number of cases of ICU admittance	36 (10.3%)

Data were shown by n (%), Median (interquartile range) or Mean±Standard Deviation.

FEVR, familial exudative vitreoretinopathy; ROP, retinopathy of prematurity.

Table 2. Risk factors associated with intraoperative bradycardia

	Univariate (n=350)		p value	Multivariate (n=341)	
	Yes	No		OR	p value
	total	value	total	value	
Preoperative Atropine	267	9(3.4%)	83	22(26.5%)	0.000
Preoperative Steroid	246	9(3.7%)	104	22(21.2%)	0.000
Muscle relaxant	210	5(2.4%)	140	26(18.6%)	0.000
Duration of surgery	70.3±29.1		65.5±29.6		0.346
Duration of anesthesia	113.9±41.7		116.5±43.9		0.501
					1.045 (1.019-1.072) 0.001*

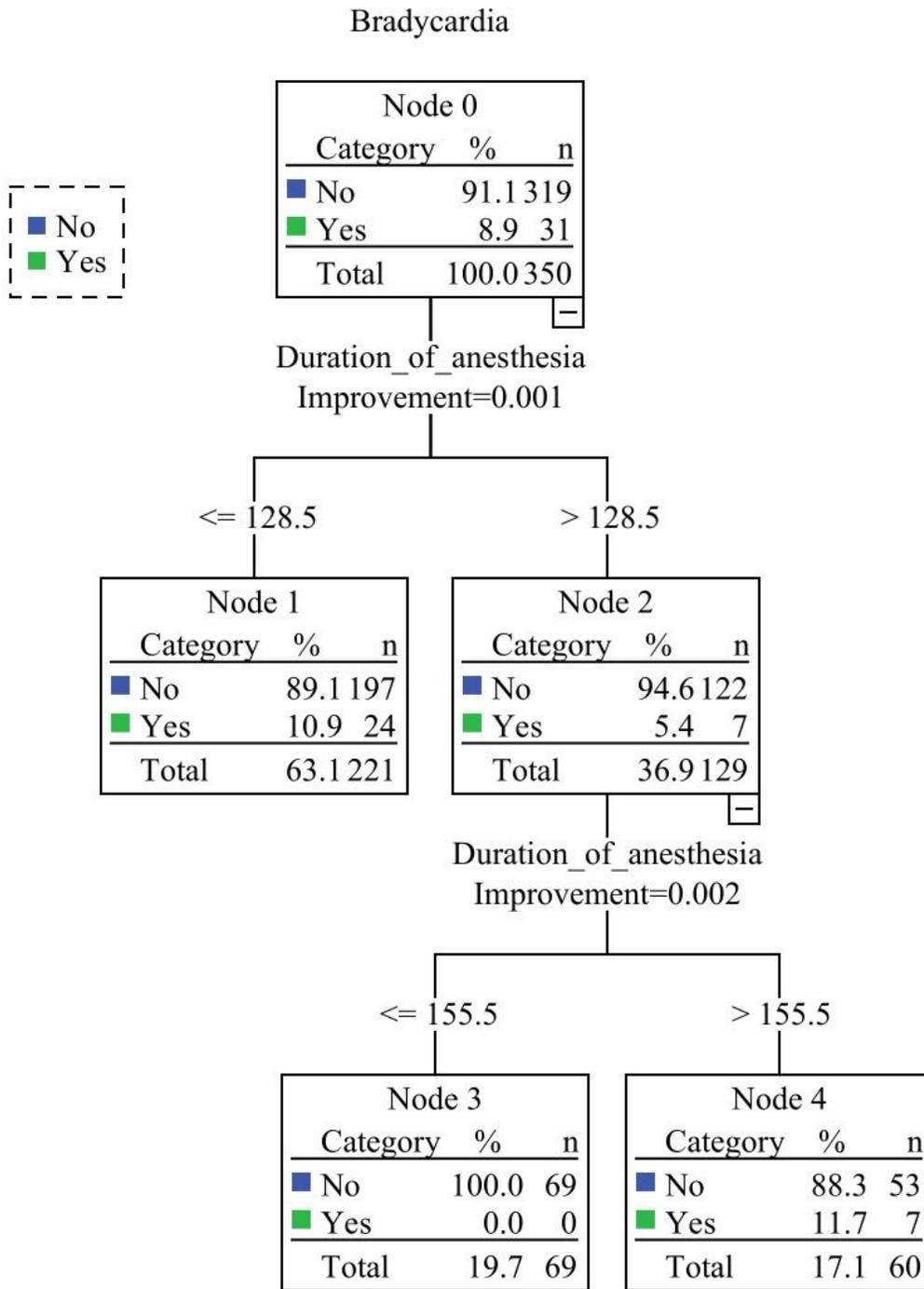
\*P<0.05

Table 3. Risk factors associated with ICU admittance

	Univariate (n=350)				p value	OR	Multivariate (n=306)	
	Yes		No				p value	
	total	value	total	value				
Preoperative Atropine	267	20 (7.5%)	83	16 (19.3%)	0.002			
Preoperative Steroid	246	21 (8.5%)	104	15 (14.4%)	0.098			
Muscle relaxant	210	11 (5.2%)	140	25 (17.9%)	0.000			
Hemoglobin level (g/L)	100(83,103)		111(98,121)		0.005			
Gestational age at birth	30(28,32)		31(30,38)		0.000			
Post conceptual age	40(37,43)		52(44,65)		0.004			
Body weight at birth	1.1(1.0,2.0)		2.0(1.0,3.0)		0.000			
Body weight	2.0(2.0,4.0)		6.0(4.0,8.0)		0.000	0.368		0.000*
							(0.222-0.609)	

\*P<0.05

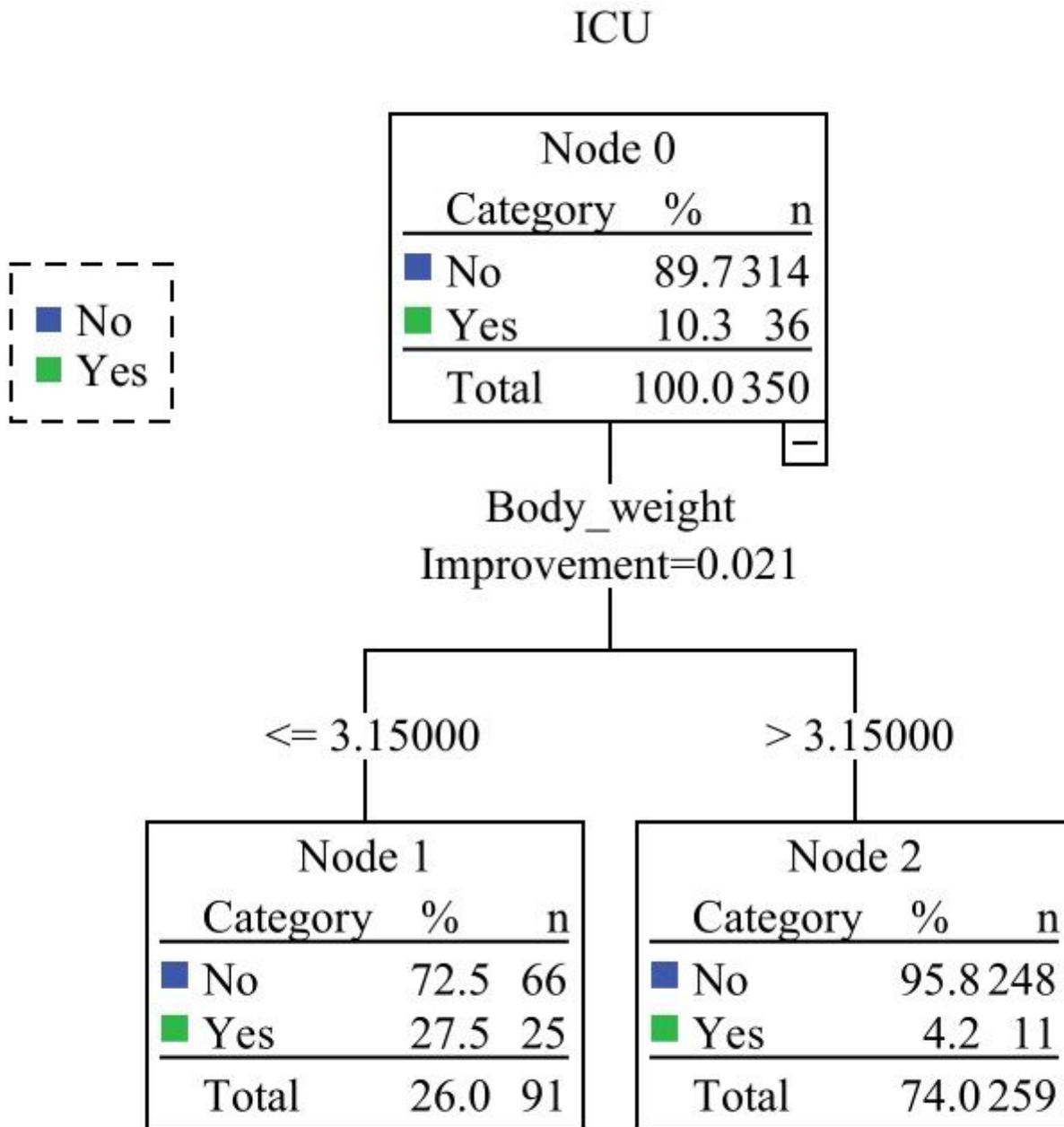
## Figures



**Fig.1. Duration of anesthesia cut-off point for Bradycardia**

Figure 1

Duration of anesthesia cut-off point for Bradycardia.



**Fig.2. Body weight cut-off point for ICU admittance**

Figure 2

Body weight cut-off point for ICU admittance .