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Original Article

Prospective Observational Study of Sympathetic Failure as a Mechanism Associated with Bradycardia During Induction of General Anesthesia in Children with Down Syndrome

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ABSTRACT

Aim: While bradycardia in children with Down syndrome (DS) during inhalation induction of anesthesia is characteristic, its mechanism is not well understood. This study investigated sympathetic failure as a potential (and modifiable) mechanism of bradycardia.

Materials and Methods: Ninety-three children with DS and 102 typically developing (TD) children underwent inhalation induction of anesthesia. These children were monitored for sympathetic activity, exposed to sevoflurane anesthetic and were observed for the development of bradycardia. The primary outcome was sympathetic failure in the context of normoxic bradycardia within the first 300 seconds of induction. Secondary outcome measures included hypotension and parasympathetic excess.

Results: During the first 300 seconds of induction, 54 DS children became bradycardic (54/93, 58%) while 22 TD children became bradycardic (22/102, 22%). In the DS group, 23 experienced hypotension (23/80, 29%). Of those who experienced hypotension, 15 also experienced sympathetic failure (15/28, 54%).

Conclusion: More than half of children with DS undergoing inhalation anesthesia induction with sevoflurane experienced bradycardia. Bradycardia and hypotension were associated with sympathetic failure. Sympathetic activity therefore appears to be a modifiable target in the prevention of bradycardia in children with DS.

Keywords: Down syndrome, pediatric anesthesia, autonomic nervous system diseases, sevoflurane

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Introduction

The risks of mask-inducing a child with Down syndrome (DS) to begin a general anesthetic include upper airway obstruction due to midface hypoplasia, large tongue and adenoids, small nares, potential atlantoaxial instability, and hypotonia leading to poor venous access. Children with DS are at much greater risk of bradycardia (1-7). Heart rate nadir occurs, on average, at around 190 seconds of inhalation induction with sevoflurane and autonomic contributions have been reviewed (8). This bradycardia competes for the attention of the anesthetist and is of variable clinical significance, ranging from mild to asystole (6). The mechanism of bradycardia, and therefore its prevention or goal-directed treatment, is unknown. Impaired autonomic cardiac regulation in individuals with DS may contribute (5,9,10).

Autonomic mechanisms, such as parasympathetic excess or sympathetic failure, have been postulated as a cause of normoxic bradycardia in children undergoing inhalation induction with sevoflurane. This study aimed to characterize sympathetic failure as a candidate mechanism of this bradycardia. Our bradycardia hypothesis states that sympathetic failure is associated with bradycardia in children with DS. Our related hypotension hypothesis states that sympathetic failure is related to hypotension in children with DS.

Materials and Methods

We conducted a prospective, pragmatic observational age-matched cohort study. All study procedures occurred at a tertiary children's hospital following institutional review board approval. Recruitment was from January 12th, 2022 to December 12th, 2023. This study adhered to the applicable strengthening of reporting of observational studies (11) and is registered at ClinicalTrials.gov (NCT05120531). Ethical approval for this study was obtained from the Cincinnati Children's Hospital Medical Center Institutional Review Board (2021-0643). Sevoflurane exposure was left to the discretion of the anesthetist.

Potential participants were screened using the operating room schedule. Eligible subjects were included if they were one month to 8 years of age (inclusive), undergoing inhalation induction of anesthesia with sevoflurane for a clinically indicated surgery, had a legally authorized representative to provide informed consent and were typically developing (TD) or had a diagnosis of DS (only for the DS cohort). Children with DS were matched to TD children by age groups based on percentile charts by Fleming et al. (12). The groups were: Infants (age 1-12 months), toddlers (age 1-3 years), preschool (age 4-5 years) and school age (age 5-8 years). Subjects were excluded if they had a contraindication to adhesive use or were receiving heart rate-altering therapy. Table I presents demographic data for the entire study population. Our rationale for including participants younger than eight years is that young children are at higher risk of morbidity from bradycardia as cardiac output is more dependent on heart rate, and by age eight, children safely have adult heart rates (13).

The study exposure was clinically indicated doses of sevoflurane for the induction of general anesthesia. Participants underwent autonomic monitoring using the Vrije Ambulatory Monitoring System (VU-AMS) beginning in the preoperative holding area during at least 300 seconds of induction of general anesthesia. Following this endpoint, the monitor was removed, skin was assessed for damage, and the child was discharged from this study.

Data collection included demographic, clinical data, and autonomic data. The VU-AMS monitor was used to collect autonomic data prospectively (14,15). Autonomic data were analyzed using the Vrije Universiteit-Data Analysis and Management Software (Amsterdam, Netherlands). As the usual pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA) parameters are undocumented in children with DS, each child's preoperative value was used as his or her baseline and the change for induction was computed. The deprivation index, a surrogate for socioeconomic status, was obtained by geocoding (16). Each data source was stored securely in REDCap® and de-identified using subject numbers (17,18).

The primary outcome is normoxic bradycardia within the first 300 seconds of induction. Those children who experience normoxic bradycardia during the induction of anesthesia were labeled as chronotropic incompetence due to sympathetic failure if the bradycardia occurred with a 10% or greater lengthening (increase) of the PEP compared to the preoperative measurement. Normoxic bradycardia, from now on called bradycardia, is defined as a heart rate less than the 10th percentile for age for children during the first 300 seconds of general anesthesia under normoxic (SpO_2 >90%) (12). Bradycardia thresholds for the infants age group are below 115 beats per minute, toddlers below 98, preschool age below 86, and school-age children below 70 beats per minute. Normoxia is defined as SpO_2 greater than 90%, measured by pulse oximetry. Ninety percent was chosen for the cut-off point as children rarely become bradycardic due to hypoxia when their oxygen saturation is above 90% (19).

The secondary outcome was hypotension. Hypotension is defined as systolic blood pressure one standard deviation (SD) below normal values for age in children under general anesthesia (20) while understanding that children with DS may safely experience lower blood pressure due to their DS status and short stature (21,22). Using this liberal definition, we expected that 16% of participants would meet our definition of hypotension (i.e., one SD).

Covariates comprised age for heart rate and age and sex for blood pressure. These confines were incorporated into our definitions of bradycardia and hypotension. Potential confounders to bradycardia status might include obstructive sleep apnea, nil per os duration, sevoflurane exposure, paralytics, and/or perioperative heart rate altering medications.

Autonomic parameters, PEP and RSA, were acquired. Impedance cardiogram scoring was performed manually by one author (JWS) according to published guidelines (23). PEP reflects sympathetic nervous system activity. Lower values of PEP indicate sympathetic stimulation, i.e., a shorter time in milliseconds from onset of ventricular depolarization to aortic valve opening. Given that parasympathetic excess has been posited to cause bradycardia, parasympathetic activity was also measured via RSA. RSA equals the longest inspiratory R-R interval minus the shortest expiratory R-R interval and is measured in milliseconds (24-26). RSA analysis ideally comprises at least four minutes or 240 seconds of continuous data. Therefore 300 seconds of data are required for this timing to fulfill both requirements.

Table I provides a demographic comparison between those participants with and those without DS. The presence of DS confers the development of bradycardia with an odds ratio of 9.56 (1). If we attribute all bradycardic episodes to autonomic dysfunction, we conservatively assumed that 6.8-9% (5) of controls and 25% of children with DS (5) will become bradycardic. With a total sample size of approximately 156 children, we would achieve 80% power to detect a difference in autonomic activity between the groups of greater than 19%. We had planned to enroll approximately 100 children with DS and 100 without DS to account for technical failures and data loss.

Statistical Analysis

Descriptive statistics included medians with interquartile ranges or means with SDs for continuous variables and frequencies with percentages for categorical variables. In bivariate analysis, associations were tested using the Wilcoxon rank-sum test or t-test, and the chi-square or Fisher's exact test depending on variable type and distribution. Bivariate associations were also tested using simple logistic regression with or without Firth's bias reduced correction and an odds ratio with 95% confidence intervals. Statistical analysis was performed using RStudio version 2021.09.0 Build 351 (27). The sample size calculation was performed using PASS 15.0.13, release date 2/10/2020 (NCSS, LLC, Kaysville UT) (28).

Subjects were removed from this analysis if data were missing for the primary outcome, heart rate nadir or PEP. Excluded subjects had more frequent ASA 2 status and less frequent ASA 3 status, but no difference in ASA 1 or ASA 4 statuses or no other differences in demographic information. Missing data disqualified that participant from analysis in the field for which the data was missing. Missing values for oxygen saturation, and SpO2 data, were assumed to be non-hypoxic (≥90%).

Results

Two hundred forty-nine children met the inclusion criteria, of whom 195 comprised the final population. Fifty-four children were excluded as shown in Figure 1.

For the 195 participants with data for the primary outcome (93 DS, 102 TD), heart rate and PEP measurements were made for 300 seconds prior to induction (baseline) and during the first 300 seconds of anesthesia. Baseline PEP and RSA are consistent with the published normative values (26). Patients varied from one month to eight years and weighed from 2.8 to 48 kg. Baseline heart rates, systolic blood pressures, pre-ejection periods and respiratory sinus arrhythmias of the participants were no different regardless of their DS status (Table I). Each participant for whom a previous electrocardiogram was available was in normal sinus rhythm (including one participant whose pacemaker was set to DDD during the electrocardiogram and consent). The demographic information for those participants with DS stratified by bradycardia are listed in Table II.

Normoxic bradycardia in the setting of sympathetic failure was the primary outcome of this study. Bradycardia occurred with a frequency of 54/93 (58%) for children with DS and 22/102 (22%) for TD children. Preoperative PEP was similar for children with DS and for TD children (70, and 66 respectively, p=0.176). Following exposure to sevoflurane, PEP for children with DS was greater than for TD children (75 and 69 respectively, p=0.009). Consistent with PEP findings, sympathetic failure occurred in 30/93 (32%) children with DS and 29/102 (28%) TD. The specificity of sympathetic failure to predict bradycardia was 90% in children with

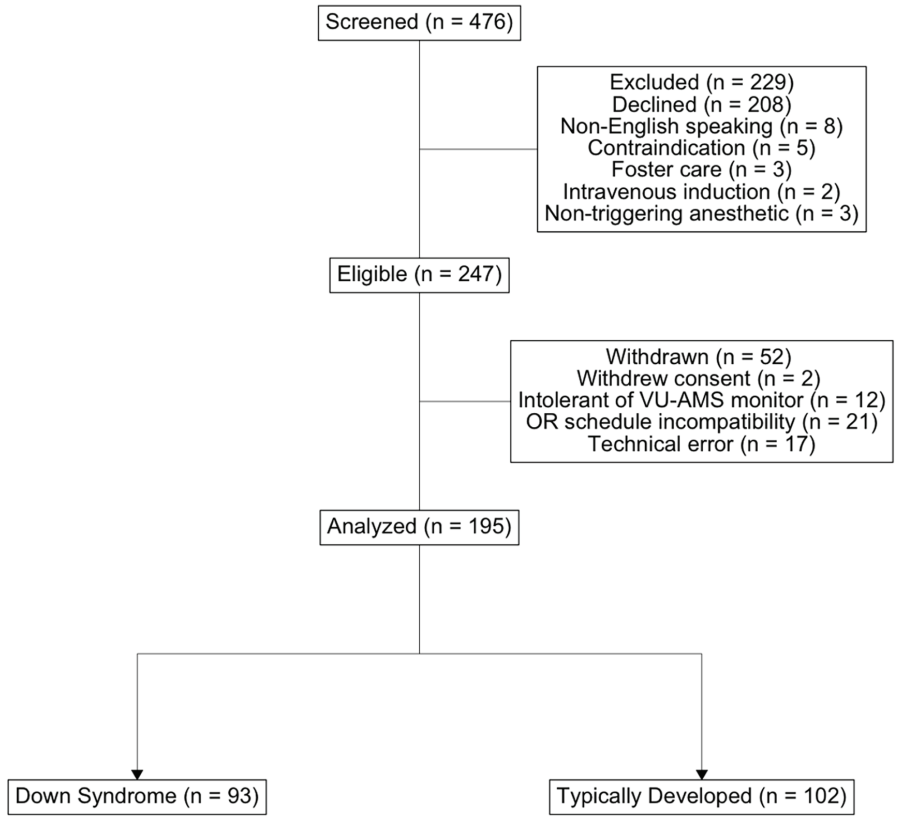

Figure 1. Participant flow through the study
VU-AMS: Vrije Ambulatory Monitoring System

DS and 76% in TD children and sympathetic failure was not sensitive in either DS or TD (48%, 45% respectively). Figure 2 shows Poincare plots of RR interval pre-induction and during induction. There were no statistically significant differences between the pre-induction and induction SD1 values for the DS children (p=0.466), or between the induction SD1 values for the DS vs TD children (p=0.329). Within the DS group, there were no differences in SD1 either pre- or during induction and bradycardia status.

The frequency of bradycardia among children with DS was (54/93, 58%) and the frequency of sympathetic failure was (30/93, 32%). We found that PEP increased significantly more in those children with DS who became bradycardic (6 milliseconds versus 1, p=0.003) than in those children with DS who did not become bradycardic. This association did not exist in TD children (p=0.083).

Factors associated with bradycardia included sympathetic failure (at least a 10% increase in PEP from baseline to induction), systolic hypotension, and the severity of hypotension. There was no difference in intraoperative administration of fentanyl, ondansetron, ketorolac, morphine, or hydromorphone among those children with DS based on bradycardia status.

Systolic hypotension occurred in 27/93 (29%) children with DS and in 9/102 (9%) TD children. Among those children with DS, bradycardia was associated with hypotension (p=0.003); in TD children, there was no association (p=0.401). In those children with DS, sympathetic failure was associated with hypotension (p=0.008). In contrast, for TD children, sympathetic failure was less common (29/102, 28%) and was not associated with hypotension (p=0.711).

We found associations between parasympathetic excess (an increase in RSA from baseline to induction) and bradycardia but not hypotension or sympathetic failure (p-values were 0.005, 0.94, and 0.14 respectively). Figure 3 shows a Venn diagram of children with DS who became bradycardic. Parasympathetic excess alone was associated with bradycardia in twenty percent of the study population (Figure 3). The independence of parasympathetic excess and sympathetic failure remains unproven. Figure 3 shows 15 children with DS and bradycardia with simultaneous parasympathetic excess and sympathetic failure supporting

Table I. Demographic information for DANSIB participants

Characteristic	n	Overall, n=195	DS, n=93	No DS, n=102	p value
Age	195	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	2.50 (1.00, 4.00)	0.410
Male gender	195	123 (63%)	64 (69%)	59 (58%)	0.113
Weight	195	13 (10, 18)	13 (10, 17)	14 (10, 20)	0.055
Non-white race	195	31 (16%)	19 (20%)	12 (12%)	0.098
ASA PS	195				**<0.001**
1		26 (13%)	0 (0%)	26 (25%)	
2		66 (34%)	11 (12%)	55 (54%)	
3		99 (51%)	79 (85%)	20 (20%)	
4		4 (2.1%)	3 (3.2%)	1 (1.0%)	
Hispanic ethnicity		4 (2.1%)	3 (3.2%)	1 (1.0%)	0.349
Public insurance		78 (40%)	32 (34%)	46 (45%)	0.128
Congenital heart surgery	113	22 (19%)	21 (29%)	1 (2.4%)	**<0.001**
Missing		82	21	61	
Hypothyroidism	195	21 (11%)	20 (22%)	1 (1%)	**<0.001**
OSA	195	57 (29%)	47 (51%)	10 (9.8%)	**<0.001**
Deprivation index	178	0.31 (0.26, 0.42)	0.30 (0.25, 0.39)	0.34 (0.26, 0.43)	0.279
Missing		17	12	5	
Baseline HR	195	113.6 (19.29)	112.6 (19.6)	114.6 (19.04)	0.480
Baseline systolic BP	133	103.5 (13.43)	103.0 (15.64)	104 (11.32)	0.696
Missing		62	32	30	
Baseline PEP	195	68 (60, 77)	70 (61, 80)	66 (60, 74)	0.176
Baseline RSA	195	39 (25, 65)	41 (29, 63)	37 (25, 65)	0.352
Sevoflurane exposure	195	4.56 (3.61, 5.41)	3.70 (3.06, 4.30)	5.28 (4.67, 5.62)	**<0.001**

DANSIB: Down syndrome autonomic nervous system induction bradycardia, ASA PS: American Society of Anesthesiologists' Physical Status, OSA: Obstructive sleep apnea, Deprivation index: Material community deprivation (2019 Brokamp), Preop dexmedetomidine: Preoperative (sedative) intranasal dexmedetomidine, HR: Heart rate, BP: Blood pressure, PEP: Pre-ejection period, RSA: Respiratory sinus arrhythmia

a modern understanding of autonomic physiology. Systolic hypotension and/or sympathetic failure was present in 33 of the 54 (61%) instances of bradycardia. The 10 children with intact sympathetic and parasympathetic activity and who maintained their blood pressures spanned all age groups: Infants (2), toddlers (3), preschool (3), and school age (2), which is in contradiction to the idea that the physiology of bradycardia and hypotension relates to chronological age.

Sevoflurane exposure was lower among DS and yet bradycardia was more common. Figure 4 shows sevoflurane exposure over each of the five minutes of induction. There was no significant correlation with heart rate for end tidal sevoflurane during any minute.

Those factors anticipated to impact bradycardia and/or sympathetic failure included nil per os time for clear liquids, preoperative heart rate altering medications, sevoflurane exposure, and obstructive sleep apnea.

Preoperative albuterol was given to 6 DS and 4 TD individuals. Obstructive sleep apnea (OSA) was present in 47/93 (51%) of DS patients and 10/201 (9.8%) of TD children. We found no relationship between OSA and bradycardia.

Discussion

Our objective was to evaluate sympathetic failure as a mechanism for bradycardia during inhalation induction with sevoflurane. We found an association between sympathetic failure and bradycardia in children with DS but not in TD children. Unlike our findings, another observational study of children with a mean age of 8.6 years found no association of hypotension with bradycardia in children with DS (29). However, our participants had a mean age of 3.5 years,

Table II. Comparison by bradycardia or not among children with DS

Characteristic	n	Overall, n=93	No, n=39	Yes, n=54	p value
Age	93	3.00 (1.00, 5.00)	3.00 (0.00, 5.00)	3.00 (1.00, 4.00)	0.651
Male gender	93	64 (69%)	26 (67%)	38 (70%)	0.704
Weight (kg)	93	13 (10, 17)	13 (7, 17)	12 (10, 17)	0.843
Non-white race	93	19 (20%)	12 (31%)	7 (13%)	**0.036**
ASA PS	93				0.240
2		11 (12%)	2 (5.1%)	9 (17%)	
3		79 (85%)	36 (92%)	43 (80%)	
4		3 (3.2%)	1 (2.6%)	2 (3.7%)	
Hispanic ethnicity	93	3 (3.2%)	2 (5.1%)	1 (1.9%)	0.570
Public insurance	93	32 (34%)	11 (28%)	21 (39%)	0.285
Deprivation index	81	0.30 (0.25, 0.39)	0.31 (0.26, 0.41)	0.30 (0.25, 0.37)	0.624
Missing		12	8	4	
Prior cardiac surgery	93	21 (23%)	7 (18%)	14 (26%)	0.364
Hypothyroidism	93	20 (22%)	9 (23%)	11 (20%)	0.754
Preoperative midazolam	93	12 (13%)	8 (21%)	4 (7.4%)	0.063
OSA	93	47 (51%)	19 (49%)	28 (52%)	0.765
Documented PCP	93	90 (97%)	37 (95%)	53 (98%)	0.570
Preoperative dex	21	2 (9.5%)	1 (7.7%)	1 (13%)	>0.999
Missing		72	26	46	
Preoperative albuterol	21	6 (29%)	3 (23%)	3 (38%)	0.631
Missing		72	26	46	
PEP baseline (msec)	93	70 (61, 80)	74 (59, 81)	68 (61, 78)	0.624
RSA baseline (msec)	93	41 (29, 63)	38 (21, 57)	46 (32, 72)	0.066
Heart rate baseline	93	112.6 (19.61)	116.7 (23.67)	109.7 (15.64)	0.110
Mean end tidal sevoflurane	93	3.70 (3.06, 4.30)	3.90 (3.12, 4.91)	3.66 (3.02, 4.03)	0.108
1st minute sevoflurane	84	3.70 (2.50, 4.80)	3.55 (1.90, 4.60)	3.75 (2.65, 4.90)	0.483
Missing		9	3	6	
2nd minute sevoflurane	79	4.00 (3.15, 4.95)	4.25 (3.43, 5.20)	3.80 (3.00, 4.70)	0.191
Missing		14	9	5	
3rd minute sevoflurane	86	4.10 (2.83, 4.78)	4.40 (3.03, 5.33)	4.00 (2.83, 4.60)	0.164
Missing		7	3	4	
4th minute sevoflurane	84	3.55 (2.90, 4.70)	4.35 (3.18, 5.10)	3.40 (2.75, 4.10)	**0.013**
Missing		9	3	6	
5th minute sevoflurane	89	3.20 (2.40, 4.20)	3.80 (2.83, 4.60)	2.90 (2.25, 3.70)	**0.005**
Missing		4	1	3	
Blood pressure baseline documented	92	61 (66%)	26 (68%)	35 (65%)	0.719
Systolic baseline	61	103.0 (15.64)	104.4 (14.39)	102.0 (16.63)	0.541
Missing		32	13	19	
Intra-op PIV placed	93	84 (90%)	32 (82%)	52 (96%)	**0.032**

Table II. Continued

Characteristic	n	Overall, n=93	No, n=39	Yes, n=54	p value
High-risk PRAP	13	1 (7.7%)	1 (17%)	0 (0%)	0.462
Missing		80	33	47	
Intra-op muscle relaxation	93	12 (13%)	7 (18%)	5 (9.3%)	0.217
Intra-op propofol admin	93	44 (47%)	23 (59%)	21 (39%)	0.056
Int propofol mg/kg dose	44	1.45 (1.09, 2.07)	1.32 (0.98, 1.82)	1.58 (1.22, 2.08)	0.290
Missing		49	16	33	
PEP induction	93	75 (64, 84)	74 (60, 83)	76 (67, 86)	0.129
Delta PEP	93	3 (0, 10)	1 (-2, 4)	6 (1, 15)	**0.003**
Systolic hypotension	93	27 (29%)	5 (13%)	22 (41%)	**0.003**
Severity of hypotension	93	7 (-2, 15)	13 (8, 23)	3 (-8, 8)	**<0.001**

ASA PS: American Society of Anesthesiologists' Physical Status, OSA: Obstructive sleep apnea, PCP: Primary care physician, Dex: Dexmedetomidine, PEP: Pre-ejection period which reflects sympathetic nervous system activity, RSA: Respiratory sinus arrhythmia which reflects parasympathetic nervous system activity, Intra-op: Intraoperative, PIV: Peripheral intravenous line placement, PRAP: Psychological risk assessment in pediatrics, Delta PEP: Change in PEP from baseline to induction, severity of hypotension - difference between systolic threshold and intraoperative systolic nadir, a greater difference indicates more severe hypotension
Descriptive statistics use n (%) for categorical variables and mean (standard deviation) if normally distributed and median (interquartile range) if not normally distributed for continuous variables

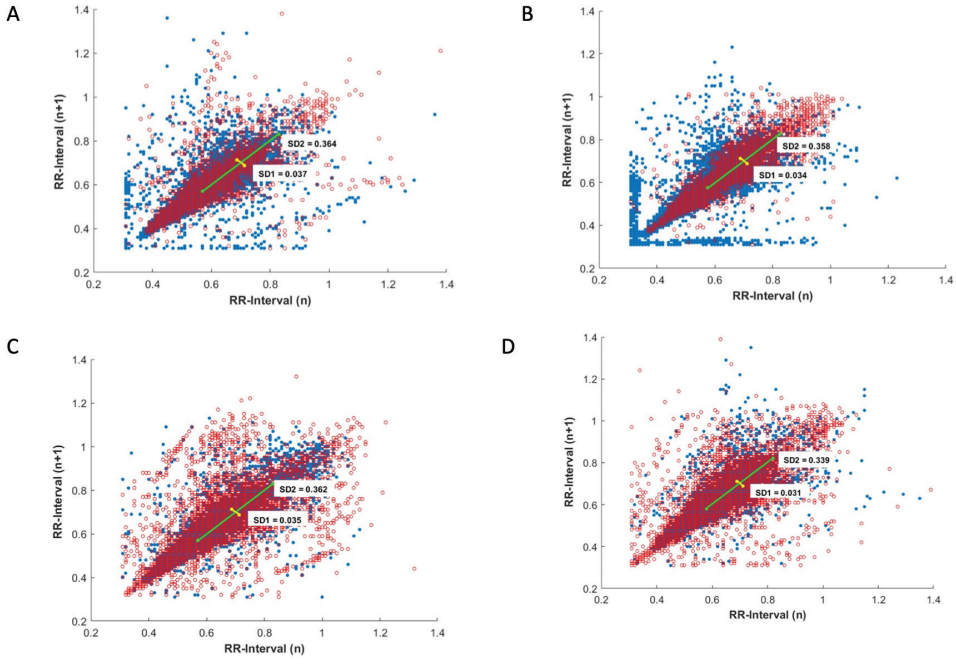

Figure 2. (Panels A and B). Poincare plots of RR Interval during induction. Children with Down syndrome, Panel A, those who became bradycardic had a larger SD1 (standard deviation perpendicular to the long axis of the plot) compared with TD children, Panel B. SD1 comprises the standard deviation of the difference between an RR interval and its predecessor, then the square root of that value. SD2 indicates the square root of the standard deviation of an RR interval
TD: Typically developing, SD: Standard deviation

and so age and heart rate dependence for cardiac output may explain this difference. A child with DS is expected to have blood pressure around the 37th percentile for age in children under five years (22). Therefore, our estimation of hypotension in children with DS may be inflated; however, there was no difference in preoperative blood pressures between the DS and TD children and so we used the same blood pressure thresholds in both groups.

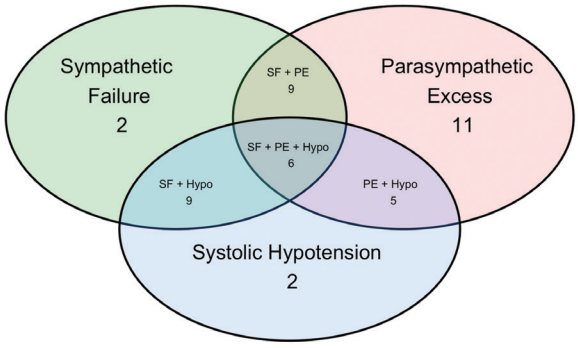

Figure 3. Venn Ddagram of children with Down syndrome who developed bradycardia during inhalation induction of anesthesia.

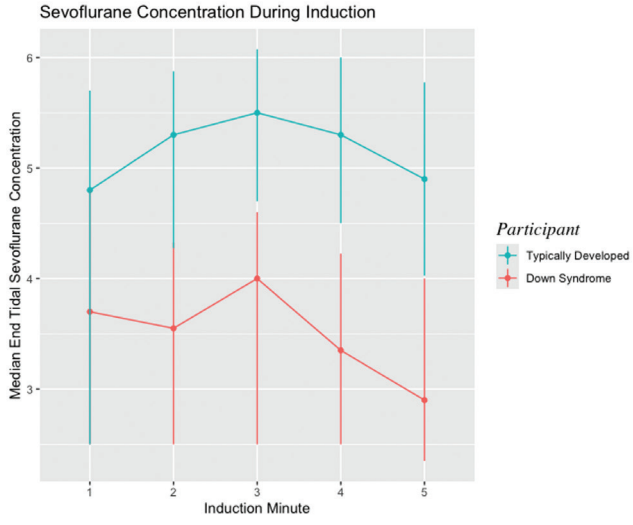

Figure 4. End tidal sevoflurane concentration over each of the first five minutes of inhalation induction in typically developed versus children with Down syndrome

The time course of development of bradycardia is rapid but not instantaneous suggesting a sympathetic (slower) rather than parasympathetic (over a single heart beat) mechanism (30).

The causation of bradycardia is unproven and likely multifactorial. Other factors include activity of the renin angiotensin aldosterone system, baroreceptor function, endocrine function and the physical pressure of the mask on the child's face (9,31). This study was the first to document separate sympathetic and parasympathetic measures of autonomic activity in young children exposed to sevoflurane, so there are no sevoflurane-exposed values for comparison. Sevoflurane has a vagolytic effect (32) and therefore should have been protective against bradycardia.

Study Limitations

The primary limitations of this study are methodological and statistical. We were unable to dictate the child's posture during baseline autonomic measurements and heart rate altering exposures such as sevoflurane. Ideally, baseline data would have been obtained with the participant supine; however, the hydrostatic pressure gradient effects of posture on cardiac output are less significant on shorter individuals such as children (21). The anesthetic technique and method of induction were not controlled. Experienced anesthetists may modify their technique of mask induction on children with DS.

Conclusion

In sevoflurane-induced bradycardia in children with DS, sympathetic failure and systolic hypotension predominate. When exposure to sevoflurane is associated with failure to maintain sympathetic tone, bradycardia and hypotension are frequent. Implications for the care of children with DS undergoing inhalation induction with sevoflurane include a search for other mechanisms to explain this phenotype. Further study of the use of a sympathomimetic agent for bradycardia prophylaxis prior to induction could be considered.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Cincinnati Children's Hospital Medical Center Institutional Review Board (2021-0643).

Informed Consent: A signed consent form was obtained from each study participant.

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Footnotes

Authorship Contributions

Concept: J.W.S., Design: J.W.S., S.M., J.M.D., L.D., D.C., Data Collection or Processing: J.W.S., J.M., K.G., L.D., Analysis or Interpretation: J.W.S., J.M., J.M.D., L.G., Q.D., D.C., S.W., Literature Search: J.W.S., K.G., Writing: J.W.S., S.M., J.M.D., L.D., D.C., S.W.

Conflict of Interest: No conflict of interest was declared by the authors.

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