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Association of Lower Age and Cardiorespiratory Events during Intra-Arterial Chemotherapy for Retinoblastoma: A Prospective Observational Study

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ABSTRACT

BACKGROUND AND PURPOSE: Retinoblastoma is the most common primary intraocular tumor in childhood. Intra-arterial chemotherapy is becoming the standard of care for both first-line and rescue therapy, thus improving survival rates and decreasing the adverse effects of retinoblastoma treatment. Cardiorespiratory adverse events during general anesthesia for intra-arterial chemotherapy, including decreased lung compliance and bradycardia, have been described, but data regarding associated factors are still lacking. We aimed to assess the characteristics of patients and procedures associated with cardiorespiratory events during intra-arterial chemotherapy.

MATERIALS AND METHODS: We performed a prospective monocenter observational study in children diagnosed with retinoblastoma undergoing intra-arterial chemotherapy under general anesthesia. The occurrence of cardiorespiratory events was registered. We also assessed clinical and procedural characteristics potentially associated with these events.

RESULTS: A cardiorespiratory event was observed in 22 (12.5%) procedures, predominantly a decrease in tidal volume observed in 16 (9%) procedures. The median age was lower in the procedures with a cardiorespiratory event (20.43 [SD, 11.76] months versus 30.11 [SD, 24.17] months) ($P < .05$). Other variables such as bilateral disease or a previous intra-arterial chemotherapy treatment were not associated with the occurrence of a cardiorespiratory event.

CONCLUSIONS: In children undergoing intra-arterial chemotherapy for retinoblastoma treatment, cardiorespiratory events were observed in 12.5% of procedures. Lower age was associated with this complication. Although predominantly mild, these events should have prompt diagnosis and treatment to prevent further deterioration and worse outcomes.

ABBREVIATIONS: $EtCO_2$ = end-tidal CO_2; IAC = intra-arterial chemotherapy; MAC = minimum alveolar concentration; SpO_2 = saturation of peripheral oxygen

Retinoblastoma is the most common primary intraocular tumor in childhood, occurring mostly in children younger than 2 years of age. If diagnosed early, the survival rate reaches near 100% in high-income countries.[1] During the past decades, retinoblastoma treatment has markedly advanced with a paradigm change from external beam radiation and systemic chemotherapy to more selective local therapies, increasing cure rates and decreasing adverse effects.[2]

Ophthalmic artery chemosurgery—also known as superselective ophthalmic artery chemotherapy—is a type of intra-arterial chemotherapy (IAC) and represents one of the treatment modalities for first-line or rescue therapy.[3] It involves the insertion of a microcatheter into the ophthalmic artery to deliver chemotherapy directly to the affected eye. Chemotherapy is delivered in high doses directly to the tumor, resulting in less systemic adverse effects and higher eye-salvage rates, becoming the standard of care in many centers.[4]

IAC is usually performed with the patient under general anesthesia, and adverse reactions involving the cardiac and respiratory systems have been consistently demonstrated.[5-10] Those cardiorespiratory events are probably secondary to an autonomic reflex whose mechanism remains to be elucidated. A broad spectrum of clinical manifestations can be observed such as an abrupt decrease in lung compliance, bradycardia, and cardiac arrest, thus posing specific challenges for anesthesiologists. Early detection and prompt treatment are of utmost importance in preventing further deterioration.[10]

Although some groups have reported these adverse cardiorespiratory reactions, associated factors remain to be demonstrated. We designed this study to describe our experience and assess the characteristics of patients and procedures associated with these cardiorespiratory events recorded during IAC.

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MATERIALS AND METHODS

This prospective, observational, monocenter study was conducted in a pediatric cancer center from March 2020 to December 2021. This center is a reference hospital for retinoblastoma treatment. This study was approved by the local research board (EXT 008/2019) and the local Ethics Committee (CAAE. 28598120.5.00005505) and registered at ClinicalTrials.gov (NCT04451304). Informed consent was obtained from the parents or guardians and children when appropriate. We enrolled consecutive children who underwent IAC for retinoblastoma under general anesthesia.

IAC was performed in children with retinoblastoma as first-line therapy or rescue therapy after local treatment or systemic chemotherapy. The choice of IAC drugs was based on disease severity and included combinations of melphalan, topotecan, and carboplatin.

Anesthesia

IAC was performed with the patient under general anesthesia in an operating room with angiography. Induction was accomplished with IV propofol or inhaled sevoflurane, and all patients had their tracheas intubated with an appropriate tube size. Other anesthetics choice, including a muscle relaxant, was at the discretion of the attending anesthesiologist. Maintenance was accomplished with oxygen 50%, air, and sevoflurane 1.0–1.5 minimum alveolar concentration (MAC) adjusted for age. Atropine was not prophylactically administered. Mechanical ventilation was set in a pressure-control mode to a volume of 8–10 mL/kg with positive end-expiratory pressure of 5 cm H_2O. The respiratory rate was adjusted to achieve an end-tidal CO_2 ($EtCO_2$) of 35 mm Hg.

The electrocardiogram, peripheral oxygen saturation, $EtCO_2$, and sevoflurane were continuously monitored. Noninvasive blood pressure was measured at 3-minute intervals.

Procedure

IAC was performed by a single experienced interventional neuroradiologist. With the patient under general anesthesia, an ultrasound-guided puncture of the common femoral artery was performed, and a 3F pediatric arterial sheath was introduced into the arterial lumen. A flow microcatheter of 1.2 or 1.5F with a microguide of 0.07 or 0.08 inch (Balt, Montmorency, France) was guided into the ICA under fluoroscopy and then to the ostium of the ophthalmic artery. As per protocol, the microcatheter was navigated into the ophthalmic artery. In case of a difficult approach to the ophthalmic artery ostium, the microcatheter was retrieved under roadmaps. After we ensured the correct microcatheter tip position with fluoroscopic confirmation by injecting iodine contrast media, chemotherapy was infused slowly. Systemic IV heparinization with an initial heparin bolus of 75 IU/kg was performed. When infusion was complete, the microcatheter and the arterial introducer were removed, and local hemostasis was achieved by manual compression for 5 minutes at the puncture site, followed by a pressure bandage for 4 hours. The patient remained in rest for 4–6 hours with the lower limbs in extension and was discharged from the hospital after this period.

Variables Collected

We collected demographic data and previous therapeutic interventions for retinoblastoma, including previous IAC, and data regarding anesthesia techniques and drugs. Data related to IAC were also registered such as catheter size and chemotherapy drugs. We collected vital signs and respiratory parameters at the following moments: immediately before femoral puncture, immediately after internal carotid catheterization, and during the cardiorespiratory event if observed.

Cardiorespiratory events were defined as any unexpected cardiac or respiratory event requiring treatment during IAC. We assessed the presence of decreased lung compliance (characterized by an abrupt decrease in tidal volume); hypoxia (a decrease in saturation of peripheral oxygen [SpO_2] of $>10\%$ from baseline or decrease in SpO_2 of $<90\%$); slow-rising nonplateauing capnography; hypotension (a decrease in systolic blood pressure of $>20\%$); bradycardia (a decrease in heart rate of $>20\%$); and cardiac arrest. Events occurring during anesthesia induction or emergence were not considered. If >1 event occurred concomitantly, all of them were registered. In the cases in which cardiorespiratory events were observed, we registered the time and the treatment to alleviate the symptoms.

Statistical Analysis

On the basis on the literature[5-10] and a previous retrospective pilot study with 100 cases at our institution, the expected percentage of cardiorespiratory events in this population was set at 10%. Considering the number of patients required for a logistic regression analysis with a minimum of 2 covariates in the model, we estimated that 200 patients were required to obtain 20 adverse cardiorespiratory events.

For descriptive purposes, categoric variables were presented through relative and absolute frequencies. According to their distributions, continuous variables were described as means and SDs or median and interquartile ranges. Normality was evaluated through skewness, kurtosis, and graphical methods.

Children with and without cardiorespiratory events were compared using the Pearson χ^2 test, the Fisher exact test, the Welch 2-sample t test, or the Wilcoxon rank-sum test, as appropriate. To identify independent predictors of the cardiorespiratory event, we performed a multivariable analysis using logistic regression based on prior knowledge and the results of univariate analysis. The following variables were considered a priori for inclusion in the multivariable models: age, previous procedures, catheter size, bilaterality, and procedural duration. The catheter size was strongly correlated with age, so the catheter size (considered a confounder) was excluded from the multivariable model. The results were expressed as ORs with 95% CIs.

Patients older than 84 months of age could be considered outliers ($n = 9$), so we repeated the analyses excluding them. The results were similar to those with the full sample, which was maintained as the primary analysis.

All analyses were 2-sided, and the final P values $<.05$ were considered significant. All analyses were performed in SPSS statistical software (Version 26.0; IBM) or R statistical and computing software (http://www.r-project.org/).

RESULTS

We included 175 treatment sessions (11 bilateral) in 71 children during the study period. In 96 (55%) procedures, the children were female. Overall, the mean age was 29 (SD, 23.21) months. In 22

Table 1: Clinical and demographic characteristics

Characteristic	Overall (n = 175)[a]	No Cardiorespiratory Event (n = 153)[a]	Cardiorespiratory Event (n = 22)[a]	P Value[b]
Female sex	96 (55%)	82 (54%)	14 (64%)	.376
Age (m)	28.93 (23.21)	30.11 (24.17)	20.43 (11.76)	.004
Weight (kg)	13.00 (10.00–15.65)	13.00 (9.90–16.00)	11.30 (10.00–14.50)	.228
Bronchial hyperreactivity	19 (11%)	19 (12%)	0 (0%)	.136
Rhinitis	1 (1%)	1 (1%)	0 (0%)	>.999
Previous bronchiolitis	5 (3%)	5 (3%)	0 (0%)	>.999
Upper respiratory tract infections <15 days	8 (5%)	8 (5%)	0 (0%)	.598
Parental smoking	9 (5%)	7 (5%)	2 (9%)	.315
No clinical history	137 (78%)	117 (76%)	20 (91%)	.169

[a] Data are No. (%), mean (SD), median (25th–75th percentiles).
[b] Determined by the Pearson χ^2 test; Welch 2-sample t test; Fisher exact test; Wilcoxon rank-sum test.

procedures, we observed a cardiorespiratory event, and they occurred in children significantly younger (20.43 [SD, 11.76] months) than those without this complication (30.11 [SD, 24.17] months) ($P < .05$). This significant difference was not observed in the variable weight (Table 1). Figure 1 demonstrates the predicted risk of a cardiorespiratory event based on age. For a previous respiratory history or symptoms such as upper respiratory tract infection in the past 15 days, we did not find a difference between patients with or without cardiorespiratory events (Table 1).

In 23 (15%) procedures, children were premedicated to alleviate anxiety. The drug was predominantly midazolam. In 151 procedures (88%), children received sevoflurane inhalational induction combined with a propofol bolus and a fentanyl bolus. The total fentanyl mean dose was 3.6 (SD, 3.3) mcg/kg. A single dose of muscle relaxant was administered to facilitate intubation in 83 (48%) procedures. Anesthesia maintenance was achieved with sevoflurane 1.0–1.5 MAC. The mean IAC duration was 80 minutes (interquartile range, 70.00–95.00 minutes), while the mean anesthesia duration was 130.00 minutes (interquartile range, 115.00–150.00 minutes), with no difference observed between patients with or without cardiorespiratory events (Online Supplemental Data).

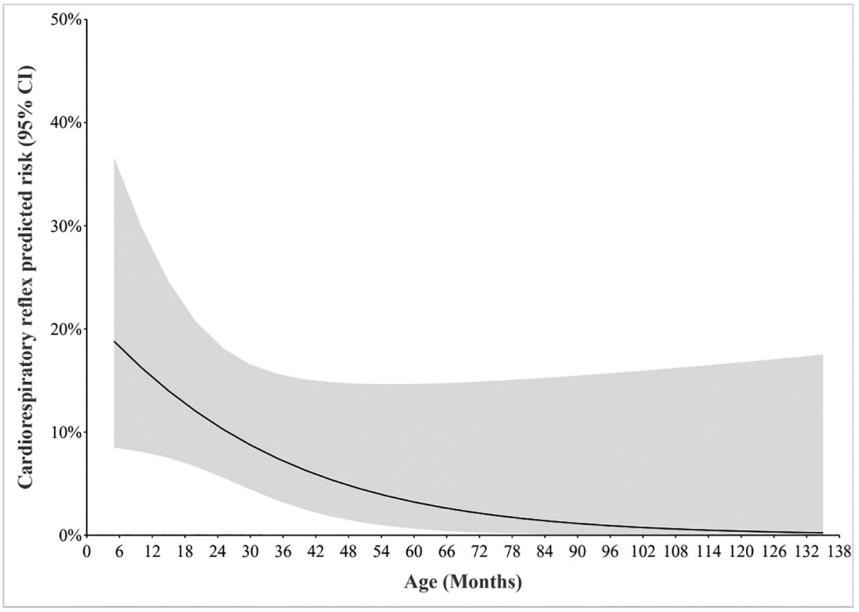

FIG 1. Predicted risk of a cardiorespiratory event based on age.

The most frequent cardiorespiratory event was a decrease in tidal volume, observed in 16 (9%) procedures. This event was primarily treated by improving ventilation with manual or mechanical increases in inspiratory pressure as well as discontinuing the catheterization maneuver. Other cardiorespiratory events and interventions are described in Table 2. Hemodynamic complications such as hypotension or bradycardia were less common. In addition, none of the procedures were interrupted and postponed due to these complications.

Baseline vital signs, measured just before femoral puncture, were similar among patients with or without cardiorespiratory events. Vital signs, $EtCO_2$, and tidal volume variations before and during the cardiorespiratory event are presented in Fig 2.

Cardiorespiratory events occurred predominantly during internal carotid artery catheterization—primarily in the supraclinoid and carvernous segments—in 14/22 (64%) procedures, followed by ophthalmic artery catheterization in 3/22 (14%) and chemotherapy administration in 4/22 (18%) procedures.

In this study, the median number of previous procedures for IAC was 2.00 (interquartile range, 0.00–3.00). Having undergone a previous IAC did not differ between patients with a cardiorespiratory event (19, 86%) and without this complication (106, 72%). Among the patients with a cardiorespiratory event, 3/22 had never undergone an IAC.

The logistic regression model showed an association between lower age and the cardiorespiratory event, though it was not statistically significant. IAC duration, bilateral procedure, and previous IAC were not predictive variables in this model (Table 3).

DISCUSSION

In this study, a cardiorespiratory event was observed in 12.5% of procedures in children with retinoblastoma undergoing IAC. These complications were primarily mild and had a rapid resolution. The median age was lower in the patients with a cardiorespiratory event. Other variables such as bilateral disease

or a previous IAC treatment were not associated with the occurrence of a cardiorespiratory event.

Severe cardiorespiratory events during IAC were demonstrated in 2011 when Gobin et al[10] described reflex bronchospasm during artery catheterization. Lately, some authors have reported an incidence of 10%–25% of severe cardiorespiratory events.[5,7,8,10] In this study, all procedures were performed by a single experienced interventional neuroradiologist who has performed >1500 IAC procedures in children with retinoblastoma. We believe this long learning curve may have contributed to our incidence in the lower range (12.5%), particularly if mechanoreceptors play a role in triggering cardiorespiratory events. In our center, anesthesiologists are also trained and experienced in this specific procedure. Therefore, the team can diagnose such complications early, preventing further deterioration.[10]

We found an association between younger age and cardiorespiratory events, which was different from the results in other studies.[8] The older median age of our population (29 versus 20 months) may have led to this finding. Considering that this complication is probably an autonomic reflex response, such as the trigeminal-cardiac and oculorespiratory reflexes, a higher resting vagal tone in young children may justify this finding. The lack of association between weight and a cardiorespiratory event reinforces the role of autonomic immaturity in the occurrence of this complication.

Some authors have proposed a sensitization of the reflex arc mechanism because patients present with this complication only in the second or subsequent procedures.[5] In our study, this complication occurred in 3 of the 22 patients who had never undergone this treatment before. This finding is in line with findings in a previous case series.[11]

In common with Philips et al[5] and Gobin et al,[10] cardiorespiratory events occurred predominantly during carotid, at the supraclinoid and cavernous segments, and ophthalmic catheterization. We did not observe an association between the type of event (respiratory or cardiovascular) and the catheter site at the moment it was detected.

The protective role of a high anesthetic depth on the occurrence of autonomic reflexes is well-established.[12,13] However, Nghe et al[8] observed a high incidence (20%) of serious cardiorespiratory events during IAC, despite deep anesthesia. Unfortunately, we did not assess the depth of anesthesia in this study, though patients received standardized sevoflurane maintenance with 1.0–1.5 MAC adjusted for age.

The cardiorespiratory events were predominantly an abrupt decrease in lung compliance followed by a mild decrease in the SpO_2 treated with manual positive pressure with resolution in seconds or a few minutes. None of the IACs were interrupted and postponed after a severe cardiorespiratory event, different from the situation in other case series.[5,8]

This study confirms earlier findings that may help to predict cardiorespiratory events during IAC, such as the most probable moment (carotid and ophthalmic catheterization). Therefore, anesthesiologists can be aware and ready to treat this potentially life-threatening condition. The lower age in patients who developed this event and a trend toward an association between lower age and the event also help to identify patients at risk.

Some limitations of this study are inherent to its observational nature, so we cannot assume the associated factor as causative. Additionally, we believe anesthesia management may affect the incidence of cardiorespiratory events, and the lack of anesthesia standardization in our study may hamper its reproducibility. A clinical trial testing the effect of a

Table 2: Adverse cardiorespiratory events and treatment during intra-arterial chemotherapy

Events and Treatment	
Characteristic ($n = 175$)[a]	
Uneventful	153 (87%)
Reduced tidal volume (>10% from baseline)	16 (9%)
SpO_2 drop (>10% or below 90% even if transient)	7 (4%)
Change in the capnography curve to an ascending pattern	3 (2%)
Hypotension	5 (3%)
Bradycardia	2 (1%)
Cardiorespiratory arrest	0 (0%)
Treatment ($n = 22$)[a]	
Manual ventilation	13 (59%)
Increased inspiratory pressure	8 (36%)
Increase in FiO_2	12 (55%)
Crystalloid bolus	5 (23%)
Atropine	0 (0%)
Epinephrine	4 (18%)
Propofol bolus	2 (9%)
Increased sevoflurane	0 (0%)
Interruption of the procedure	1 (5%)
Neuromuscular blocker administration	0 (0%)
Spontaneous resolution	2 (9%)

Note:–FiO_2 indicates fraction of inspired oxygen.
[a] Data are No.

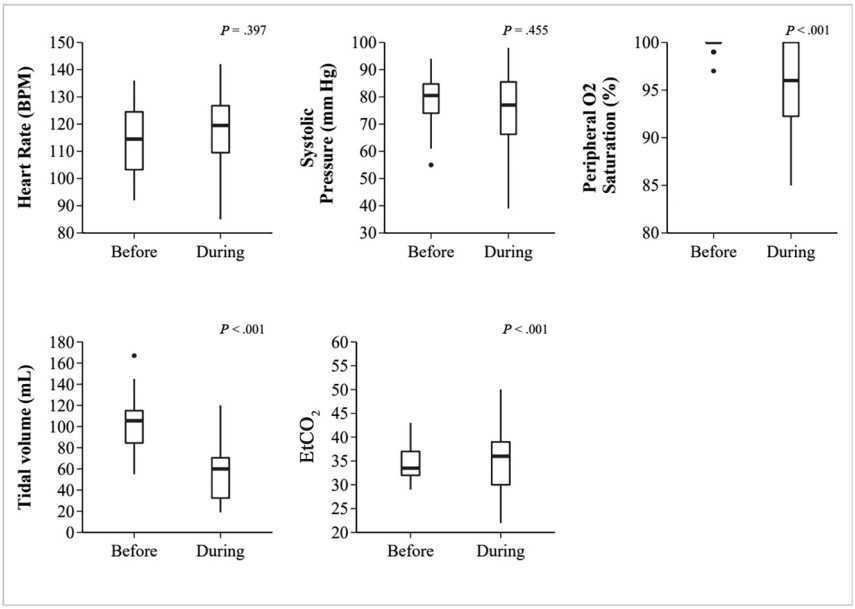

FIG 2. Vital signs and respiratory parameters measured before (immediately before femoral puncture) and during the cardiorespiratory event. BPM indicates beats per minute.

Table 3: Logistic regression model assessing age, IAC duration, bilateral procedure, and previous IAC as risk factors for cardiorespiratory events

Characteristic	OR	95% CI	*P* Value
Age (mo)	0.96	0.92–1.00	.079
IAC duration	1.00	0.98–1.02	.825
Bilateral IAC	0.63	0.03–3.85	.672
Previous IAC	2.69	0.84–12.1	.133

neuromuscular blockade on the incidence of cardiorespiratory events would also provide further elucidation about cause-effect mechanisms.

CONCLUSIONS

In children undergoing IAC for retinoblastoma treatment, cardiorespiratory events were observed in 12.5% of procedures. Lower ages were associated with this complication occurrence. Although predominantly mild and with a rapid resolution, these events should have prompt diagnosis and treatment to prevent further deterioration and worse outcomes.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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