Anesthetic Implications Of Intraarterial Chemotherapy For Retinoblastoma: A Literature Review

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Anesthetic Implications of Intraarterial Chemotherapy for Retinoblastoma: A Literature Review

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Abstract

Retinoblastoma (RB) is a rare pediatric cancer commonly diagnosed in patients at a very young age. New therapies for this disease are emerging that involve some degree of sedation, requiring anesthesia providers to be involved in their care. Intraarterial chemotherapy (IAC) is one of these new exciting treatment options and requires general anesthesia. Multiple studies and case reports have reported a sudden decrease in pulmonary compliance during IAC for RB and attribute this response to the trigemino-cardiac reflex (TCR). Once this event occurs, patients experience associated hypoxemia, hypotension, bradycardia, and cardiovascular collapse. A systematic literature review was aimed at educating the anesthesia provider on the signs and symptoms, pathophysiology, diagnosis and treatment options for patients with RB as well as identifying possible risk factors for developing this phenomenon.

*Keywords*: retinoblastoma, intraarterial chemotherapy, pulmonary compliance
Anesthetic implications of intraarterial chemotherapy for retinoblastoma

Retinoblastoma (RB) is a rare malignancy and is the most commonly diagnosed ocular cancer among pediatric patients. It can be a devastating disease that may lead to death if not treated effectively (Rao & Hanover, 2017). Intraarterial chemotherapy (IAC) is a relatively new treatment option for RB. It is performed in interventional neuroradiology and requires general anesthesia with tracheal intubation and muscle relaxation. Patients need to remain completely still as fluoroscopy is used to guide catheter placement in the ophthalmic artery. During this procedure, patients may develop a sudden and profound decrease in pulmonary compliance that can lead to hypoxemia, bradycardia, hypotension and ultimately cardiovascular collapse if not treated appropriately (Scharoun, Han & Gobin, 2016). In some case reports, this cardiorespiratory event was referred to as the trigemino-cardiac reflex (TCR). This systematic literature review will discuss RB and its anesthetic implications, define the TCR, and identify trends in the literature that may detect which patients may be at risk for developing this cardiorespiratory event. Finally, this paper will also educate the anesthesia provider on how to prepare, anticipate, identify and treat the sudden and profound decrease in pulmonary compliance that can occur during IAC for RB.

Methods

A systematic literature review was performed using PubMed and Cinahl databases. The following key words were used: intraarterial chemotherapy, retinoblastoma, trigemino-cardiac reflex, cardiopulmonary reflex, pulmonary compliance, pediatric anesthesia, and anesthesia outside of the operating room. Articles from 2014-2019 were evaluated for relevance. Two articles from 2013 were included as they were considered “landmark studies.”
Literature Review

Pathophysiology

RB is a rare pediatric cancer that results from mutations to specific genes during development. RB occurs in 1 in every 15,000 to 18,000 live births and represents 3% of all childhood cancers. The tumor begins in the retina and then extends outwards to surrounding structures (Rao & Hanover, 2017). Normal ocular anatomy can be seen in Figure 1. A tumor suppressor gene (RBL) has been identified in association with RB. The RBL gene is located on chromosome 13 (13q) and loss of function mutations to this gene causes nonsense codons or frameshifts. These changes cause overwhelming tumor cell growth. RB1 gene deletion syndrome may also occur. However, it is due to the complete lack of chromosome 13q and leads not only to RB, but also other neurodevelopment delays as well as varying degrees of physical abnormalities (Rao & Hanover, 2017).

While the RBL gene is responsible for the majority of cases, this type of cancer can also be due to a genetic mutation, 30-40% which are heritable and 60-70% which are sporadic. In what is considered "heritable" RB, there are two genetic mutations that occur that lead to the disease: 1) mutation of the germ cell, which makes all cells in the body prone to RB and other cancers, and/or 2) mutation of the retinal cell, which can only result in RB. The mutation of the retinal cell occurs on the same gene as the mutation of the germ cell, but on the paired chromosome. Patients with this diagnosis are usually diagnosed within the first month of life. In sporadic RB both mutations occur in the retinal cell, specifically and is diagnosed around the age of two (Rao & Hanover, 2017).

All of these mutations cause gene underactivity and create an environment in which cancer cell proliferation is promoted. Under normal conditions, the cell cycle has certain “check
points” that either allow the cell to continue to grow if developing normally or stops cell growth if there is some sort of malfunction in the cell structure or genetic coding. When these naturally occurring “check points” do not function as they are supposed to, such as in the case with the gene malfunctions that occur with RB, abnormal cell proliferation occurs at an uncontrolled rate, and therefore cancerous tumors develop (Grossman & Porth, 2014). This is exactly what occurs in patients with RB, and therefore tumor cells proliferate.

**Signs and Symptoms**

RB is usually diagnosed after significant disease progression has taken place. It can often go unrecognized by parents as children do not always have overt symptoms or exhibit any decline in vision or health (Almontaser, Ritchie, Madison & Jabbour, 2018). RB can affect only one or both eyes and is usually diagnosed by the age of 18, with 95% of diagnoses before the age of five (Rao & Hanover, 2017). The most
ANESTHETIC IMPLICATIONS OF INTRAARTERIAL CHEMO

common sign of RB is leukocoria, also known as the “white pupillary reflex”. This is most often first noticed by parents when using flash photography in which the child's pupils appear white. The second most common feature is strabismus, with other associated symptoms including poor vision, red painful eye, vitreous hemorrhage, phthisis bulbi, sterile orbital cellulitis, and proptosis (Rao & Hanover, 2017). The further the progression of the disease, the more overt the symptoms become.

Once diagnosed, in most cases, RB results in a uni- or multi-focal, dome-shaped retinal mass with dilated retinal vessels. The tumor starts as a small, transparent growth that is entirely intraretinal. In the retina, RB starts out as small tumors that are less than 3 mm. These tumors will then extend into the macula and vitreous body (Rao & Hanover, 2017.) These structures can be seen in Figure 1. RB is considered extensive when either 50% of the globe is occupied or it has invaded the optic nerve, choroid, sclera, orbit, or anterior chamber. As it grows, the tumor becomes opaque and white and extends away from the vitreous cavity or towards it. As the malignancy advances, clinical manifestations advance to the outside of the eye. (Rao & Hanover, 2017). Figure 2 shows the clinical presentation of RB. A) exophytic growth

Table 1: International Classification of Retinoblastoma

<table>
<thead>
<tr>
<th>Grouping:</th>
<th>Retinoblastoma ≤3 mm in size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: Small tumor</td>
<td>Rb &gt; 3 mm, Macular location (≤3 mm to foveola), Juxtapapillary location (≤1.5 mm to disc)</td>
</tr>
<tr>
<td>Group B: Larger tumor</td>
<td>Subretinal fluid ≤3 mm from margin</td>
</tr>
<tr>
<td>Group C: Focal seeds</td>
<td>Vitreous seeds ≤3 mm from retinal tumor</td>
</tr>
<tr>
<td>Group D: Diffuse seeds</td>
<td>Subretinal &amp; Vitreous seeds ≤3 mm from retinal tumor</td>
</tr>
<tr>
<td>Group E: Extensive retinoblastoma</td>
<td>Rb occupying 50% globe, Neovascular glaucoma, Opaque media (from hemorrhage in anterior chamber, vitreous, or subretinal space), Invasion of postlaminar optic nerve, choroid (2 mm), sclera, orbit, anterior chamber</td>
</tr>
</tbody>
</table>

Staging:

- Stage 0: Unilateral or bilateral retinoblastoma and no enucleation
- Stage I: Enucleation with complete histological resection
- Stage II: Enucleation with microscopic tumor residual (anterior chamber, choroid, optic nerve, sclera)
- Stage III: Regional extension
  - A. Overt orbital disease
  - B. Preauricular or cervical lymph node extension
- Stage IV: Metastatic disease
  - A. Hematogenous metastasis
  - 1. Single lesion
  - 2. Multiple lesions
  - B. CNS extension
    - 1. Prechiasmatic lesion
    - 2. CNS mass
    - 3. Leptomeningeal disease

Rb: Retinoblastoma

pattern with diffuse subretinal fluid; B) endophytic growth pattern with diffuse vitreous seeds, which are primary or secondary collections of tumor cells that are found in the avascular vitreous; C) advanced RB with neovascular glaucoma; and D) advanced RB with orbital cellulitis (Rao & Hanover, 2017). As the disease progresses, symptoms become more obvious and clinical manifestations more severe.

**Diagnosis**

Official diagnosis of RB is done through a routine eye exam by an ophthalmologist usually after leukocoria or other physical symptoms are noticed by parents. The extent of extraocular extension of RB is then evaluated with the use of imaging, including MRI and CT scan. Other tests include ultrasound, fluorescein angiography, and optical coherence tomography (Rao & Hanover, 2017). Pediatric patients do not generally undergo routine eye exams, unless under these circumstances. They are usually unable to cooperate or tolerate eye these exams or further imaging without some sort of sedation (Almontaser et al., 2018). Therefore, anesthesia providers are present for these cases and administer anesthetics ranging from moderate sedation to general anesthesia.

Once a diagnosis is made and extent of tumor extension is evaluated, the tumor is then grouped and staged. The grouping system evaluates the extent of tumor size, location, severity, and presence of subretinal and vitreous seeds. The staging system, however, helps to predict survival in patients with RB. Favorable outcomes for eye preservation exist for patients deemed stage 0 & I. While patients who have stage IV are predicted to lose their eye and even their life. The International Classification of Retinoblastoma (ICRB) was created in 2003 and includes both grouping and staging (Almontaser et al., 2018). The ICRB is listed in Table 1.
Treatment

After a diagnosis is made, treatment is aimed at vision optimization, eye salvage, and survival. Treatment options include intravenous chemotherapy, periocular chemotherapy, intravitreal chemotherapy, radiation therapy, focal therapy, and IAC (Rao & Hanover, 2017). Figure 3 depicts the administration of these types of chemotherapy.

**Intravenous chemotherapy** is a widely used form of chemotherapy and can be seen in Figure 3. Typically, six rounds of a combination of three drugs are administered: vincristine, etoposide, and carboplatin. This option has displayed very promising success rates, especially in less advanced cases. In ICRB groups A, B, and C, intravenous chemotherapy has success rates, defined as eye salvage, of 100%, 93%, and 90% respectively. In ICRB group D and E tumors, rates of regression and eye salvage with the standard triple-drug chemotherapy have been less than ideal. Fifty percent of group D eyes required additional treatments including external beam radiation therapy or enucleation (Rao & Hanover, 2017). While this is a promising treatment option for group A, B, and C eyes, effectiveness is less than ideal in group D and E eyes.

Intravenous chemotherapy, however, comes with many side effects. The systemic effects of agents like vincristine, doxorubicin, carboplatin, and etoposide include nephrotoxicity, hepatotoxicity, cardiomyopathy, ototoxicity, and myelosuppression. It even puts patients at risk for developing other types of malignancies, especially leukemias (Monroy et al., 2014). These side effects can be devastating and often leave patients with secondary life-long medical conditions.

Intravenous chemotherapy is usually administered via central vein through an indwelling port catheter or peripherally inserted central catheter. Placement of these lines requires
anesthesia, from moderate sedation to general anesthesia, and therefore pediatric anesthesia providers are very much involved in the care of these patients.

**Periocular chemotherapy** is a treatment option for ICRB group D and E tumors that also have vitreous seeds. Through this approach, seen in Figure 3, chemotherapeutic agent is administered via a posterior sub-tendon injection in the quadrant of the eye that is closest to the vitreous seeds. These patients require a larger concentration of chemotherapeutic agent locally which can be achieved by this route on administration. Periocular chemotherapy achieves rapid levels of chemotherapeutic agent in the vitreous cavity within 30 minutes at concentrations that are six to ten times higher than what intravenous chemotherapy may provide. When used in conjunction with high dose chemotherapy, this option has led to a 95% eye salvage rate in group C patients and a 70% eye salvage rate in group D patients (Rao & Hanover, 2017). Anesthesia providers are involved in these cases as the injection requires some degree of sedation or general anesthesia to ensure that the patient does not move and that the chemotherapeutic agent is not inadvertently injected in the wrong space.

**Intravitreal chemotherapy** seen in Figure 3, is also a good option for patients who present with vitreous seeds. This method injects chemotherapeutic agent directly into the vitreous cavity, instead of the quadrant around it. Because of their lack of blood supply, vitreal

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Figure 3: Administration of Ocular Chemotherapy

seeds can be very resistant to intravenous chemotherapy. Ineffective chemotherapeutic concentration in the vitreous cavity can result in persistent vitreous seeds, making intravitreal chemotherapy the desired treatment route. Melphalan is the chemotherapeutic agent used in this technique. With its use, vitreous seed regression from 85-100% has been reported with associated globe salvage in 80-100% of eyes (Rao & Hanover, 2017). This procedure, however, is painful and requires some degree of sedation or general anesthesia.

**Radiation therapy** is also an effective, as well as a potentially curative, treatment option because RB is a highly radiosensitive tumor. It was once the primary modality of treatment for RB, but it was associated with too many side effects. These include cataract formation, inflammation of the cornea or conjunctiva, retinopathy, and bleeding (Rao & Hanover, 2017). These structures can be seen in Figure 1. Radiation is now only used in refractory cases of RB where intravenous chemotherapy has been unsuccessful or in multimodal treatment modalities, as it can shrink tumor size and make other treatments more successful (Rao & Hanover, 2017). Patients require general anesthesia for this type of treatment, as pediatric patients are unable to remain still enough for the duration of the procedure. Therefore, anesthesia providers are essential in their care.

**Focal therapy** includes cryotherapy, transpupillary thermotherapy, and laser therapy. These procedures allow for targeted therapy of smaller tumors, using probes or lasers that are able to kill the malignant cells. These options are usually used after tumor size has decreased after two to three cycles of chemotherapy or for treatment of small recurrent tumors or subretinal seeds (Rao & Hanover, 2017). These cases also require general anesthesia because they are painful, and the patient must remain completely still.
**Enucleation**, or the surgical removal of the eye, is the oldest form of treatment for RB. It best used for unilateral disease in which the patient has experienced complete loss of vision. This can completely remove all of the malignant tumors and immediately cure the patient. However, this is now only indicated in advanced cases (Rao & Hanover, 2017). While this is not as commonly performed, as other treatment options have been effective in globe salvage, when it is done the patient must be under general anesthesia.

**Intraarterial Chemotherapy (IAC)**

Intraarterial chemotherapy is a relatively new procedure that is used as a primary treatment of advanced RB or as a secondary treatment in recurrent cases. It has previously been described as selective ophthalmic artery chemotherapy or chemosurgery and is performed under general anesthesia. Using a sterile technique, a catheter is placed in the femoral artery and advanced through the ipsilateral internal carotid artery. The arterial anatomy is visualized with angiography and the catheter is then advanced into the ostium of the ophthalmic artery (Almontaser et al., 2018). It is there where the chemotherapeutic agent is then injected, as can be seen in Figure 4. This allows for selective administration of the chemotherapeutic agent as close to the malignancy as possible.

IAC was first used in the 1950s but is now rapidly becoming a popular treatment option for RB. It is particularly useful for advanced stage D and E RB and recurrent RB following intravenous chemotherapy. This type of delivery of chemotherapeutic agent minimizes systemic toxicity that occurs with intravenous chemotherapy. This is not only because a smaller dose is given but also because the selective administration decreases amount systemically absorbed (Almontaser et al., 2018). Melphalan and topotecan are the chemotherapeutic agents of choice. Melphalan is a cytotoxic nitrogen mustard derivative alkylating agent that inhibits both DNA and
RNA synthesis and topotecan is a topoisomerase inhibitor that prevents rapidly diving cells from repairing DNA damage (Almontaser et al., 2018). The specific chemotherapeutic agent used may vary from institution to institution and provider preference.

The efficacy of IAC, however, is largely due to a multidisciplinary approach. Patients with RB undergoing this type of treatment require frequent trips to and evaluations from pediatric oncologists, ophthalmologists, interventional neuroradiologists, nurse practitioners, and anesthesia providers, including nurse anesthetists. It is important that there is an open line of communication among all providers involved, particularly during the procedure itself, to ensure both safe delivery of the chemotherapeutic agent and proper care of the patient pre, intra, and post procedure. Any pertinent information regarding the patient’s care should be well documented. Patients will normally receive three treatments within 3-4-week intervals. Some patients may require as many as six treatments to eradicate the entire tumor (Knight, Stiffler, Nixon & Lajoie, 2017).

Information from all providers should be readily available to their multidisciplinary colleagues. This is often attainable through the use of electronic medical records.

Anesthesia outside of the operating room

IAC is performed outside of the operating room in interventional neuroradiology. When anesthesia is administered in settings outside of the operating room, anesthesia providers are faced with unique challenges that impact patient safety and care. For several reasons, patients

![Figure 4: Ophthalmic Artery Anatomy](image-url)
under anesthesia in these settings are more likely to suffer from adverse events due to poor monitoring. Older anesthesia equipment is often found in these locations and machinery used to create images to guide the proceduralist surrounds the patient (Landrigan-Ossar & McClain, 2014). This forces the anesthesia provider to be further away from the patient than they normally would be in the operating room and creates field avoidance. Communication between the anesthesia provider and the proceduralist of upmost concern to ensure the safety of the patient.

In most pediatric hospitals with large caseloads, 30%-40% of cases are performed in non-operating room anesthesia venues (Nelson & Bailey, 2017). Adverse events may occur in these settings that anesthesia providers must be able to anticipate and treat. Contrast media is often administered in these procedure areas and patients may develop reactions to this agent. Anaphylactoid reactions to contrast media usually occur within five minutes of exposure but can also occur within one hour. Patients will present with symptoms, including bronchospasm, urticaria, and cardiac instability. Patients at risk for allergic reactions to contrast dye include those with asthma, ectopic tendencies, and history of reactions to contrast dye (Nelson & Bailey, 2017). The anesthesia provider should have all medications to treat such a reaction available to him or her in interventional radiology, including epinephrine and intravenous fluids.

**Efficacy of intraarterial chemotherapy**

The side effects of intravenous chemotherapy include neutropenia, deafness, infection, and secondary leukemia. Because IAC is selectively administered to the ophthalmic artery, large amounts of chemotherapeutic agent do not enter systemic circulation, and therefore these unfortunate side effects do not occur. Selective administration also allows the chemotherapeutic agent to target the tumor directly. For these reasons, and to maximize the effectiveness of the chemotherapeutic agent, IAC is being performed at an increasing frequency (Scharoun, Han, &
Gobin, 2016). However, it is important to evaluate whether or not IAC is just as effective as intravenous chemotherapy for RB.

A meta-analysis by Chen et al. (2018) compared the efficacy of IAC to intravenous chemotherapy for RB. The authors found there was no statistical difference in globe salvage and overall success rate—defined as the avoidance of external beam radiation therapy or enucleation in patients with group A, B, C, and E eyes. However, patients with group D eyes who received IAC had significantly higher globe salvage rates compared to those who received intravenous chemotherapy. There was also a significantly higher rate of globe salvage in stage IV and V eyes among those who received IAC compared to intravenous chemotherapy, with no real difference in among stage I-III eyes. Between the two groups, there was no difference in tumor recurrence or metastasis rates but there was a higher overall success rate in IAC eyes compared to intravenous chemotherapy (Chen et al., 2018). This is especially encouraging for patients with advanced RB.

In a retrospective interventional case series by Shields et al. (2014), IAC for RB was analyzed as a primary and secondary treatment option after intravenous chemotherapy for patients with RB. This study examined a total of 70 eyes in 67 patients with a mean age of 30 months. Each patient received melphalan, with the addition of topotecan and/or carboplatin as necessary. During their follow up, each patient was assessed for regression of the solid tumor, subretinal seeds, vitreous seeds, and subretinal fluid. The authors found that globe salvage was achieved in 72% of eyes that were treated with primary IAC and 62% of eyes treated with secondary IAC (Shields et al., 2014). Eyes that were found to have failed treatment had an extensive recurrence of subretinal or vitreous seeds upon examination. Patients who received IAC as a secondary treatment option had all either failed intravenous chemotherapy or were
facing enucleation as a treatment option. Interestingly, there was no significant difference in tumor recurrence found between IAC and intravenous chemotherapy.

These results support the conclusion that IAC can be an effective treatment option for patients, both as a primary and secondary option. The results discussed by Chen et al. (2018) is similar to those by Shields et al. (2014), as both authors found higher success rates associated with IAC compared to intravenous chemotherapy. Patients may benefit from IAC, not only because of its successful outcome, but also because it is not associated with the same systemic side effects that accompany intravenous chemotherapy.

**Efficacy in young children**

RB is most frequently diagnosed in children less than 2 years. It may even be present at birth and require treatment at a very young age (Grossman & Porth, 2014). This makes it prudent to evaluate if IAC is a treatment option for children this young. In a retrospective case study by Chen et al. (2016), IAC was found to be effective in children with RB under the age of 3 months. The authors studied 10 patients with a mean age of 10.4 weeks who had a total of 28 collective procedures. One procedure was canceled after the patient developed an internal carotid artery spasm mid procedure. Of the 27 successful procedures, after a follow up of 28.3 months, tumor regression was found in 12 out of 13 eyes, all patients were alive, and none of them had developed metastatic disease (Chen et al., 2016). This is a relatively short follow up period, so it may not provide support for positive long-term outcomes and unfortunately, there are no other studies that evaluate IAC for RB in this age group. Furthermore, like most pediatric studies, there was no control group. Nonetheless, these results support that IAC is a feasible option even for children younger than 3 months old.
However, not all patients with primary indications for IAC can actually receive it. In a literature review by Manjandavaida, Stathopoulos, Zhang, Hanovar, and Shields (2019), the following are listed as contraindications: 1) patients with neovascular glaucoma, orbital cellulitis, hyphema or blood in the anterior chamber of the eye, 2) evidence of optic nerve, scleral, orbital or extraocular extension, 3) trilateral RB, 4) systemic metastasis, 5) tumors that may benefit from transpupillary cryotherapy, and/or intravitreous chemotherapy.

**Pediatric anesthesia for IAC for RB**

Patients require general anesthesia with endotracheal intubation and muscle relaxation to undergo IAC as they must remain completely still as the neuroradiologist guides a catheter into their ophthalmic artery under fluoroscopic visualization. Scharoun et al. (2016) discusses the anesthetic techniques used by anesthesia providers at Weil Cornell Medical Center in New York. General anesthesia can be maintained with volatile anesthetic and patients are mechanically ventilated using pressure control ventilation. Most importantly, the anesthesia provider must ensure complete immobility of the patient during catheter manipulations by the proceduralist. After intubation, oxymetazoline, a potent vasoconstrictor, is sprayed into the nare ipsilateral to the tumor. This causes constriction of vessels in the nose, to ensure that the chemotherapeutic agent stays in the ophthalmic artery and does not pass into collateral circulation. Dexamethasone is given to prevent periorbital edema if two chemotherapeutic agents are administered. Heparin is then administered by the anesthesia provier after the femoral catheter is placed by the proceduralist.

Once the procedure is completed, dexmedetomidine may be given after the femoral catheter is removed. The patient needs to remain supine without bending his or her leg to prevent hematoma formation over the femoral cannula site. Dexmedetomidine can be an excellent
sedative for this as it preserves respiration, unlike opioids which depress respirations. Muscle relaxation reversal should then be administered. Patients are then extubated and transported to PACU (Scharoun et al., 2016). Anesthesia providers should bring emergency medications and supplies for reintubation during transport if PACU is not in close proximity to interventional radiology.

**Complications of IAC**

The concept of delivering a chemotherapeutic agent through the ophthalmic artery to target the tumor is to limit the amount of agent delivered systemically. The previously discussed side effects associated with intravenous chemotherapy has pushed the new interest in implementing IAC as a primary treatment for RB (Monroy et al., 2014). However, IAC, like all RB treatments, is not a benign procedure and comes with its own effects and complications.

The intraocular complications with IAC discussed by Monroy et al. (2014), include ophthalmic artery thrombosis, retinal and vitreous hemorrhages, enucleation, orbital edema, retinal detachment, third cranial nerve palsy, and retinal pigment changes. The extraocular complications include transient femoral artery occlusion due to thrombus at the catheter insertion site and periorcular erythema. There have also been reports of reversible cerebral vasoconstriction, but this may have been due to other pharmacologic agents administered during the procedure, including oxymetazoline, mydriatics that contain phenylephrine, and albuterol. Despite its occurrence, no permanent sequelae have been reported from cerebral vasoconstriction. The most serious and pertinent extraocular complication reported by Monroy et al. (2014) is the transient hemodynamic instability and abrupt decrease in ventilation associated with ophthalmic artery cannulation. This cardiorespiratory event is the most important IAC side
effect for anesthesia providers to be aware of, as they need to be able to identify and treat it if it occurs.

**Decreased Pulmonary Compliance During IAC for RB**

When undergoing IAC for RB, patients may experience a sudden and profound decrease in pulmonary compliance. Patients become difficult to ventilate and develop hypoxemia very rapidly. Following this decrease in compliance, patients experience hemodynamic changes that may lead to adverse outcomes, including death, if not treated appropriately (Scharoun et al., 2016). Pediatric respiratory physiology may contribute to the sudden and profound cardiovascular manifestations.

**Pediatric Vulnerability to Hypoxia**

According to Hines & Marshall (2018), there are very important physiological differences between the adult and pediatric respiratory systems that make pediatric patients extremely vulnerable to life threatening problems if a decrease pulmonary compliance occurs. First, a pediatric patient’s oxygen consumption is two times greater than an adult on a per kilogram basis. This contributes to a rapid onset of hypoxemia when ventilation is compromised. Second, pediatric patients have higher compliance of their chest wall and lung parenchyma. This is especially true in newborns and predisposes them to alveolar collapse. Chest wall compliance is higher in the newborn because there is less ossification of their ribcage. This means that at the end of exhalation, the “spring” of the chest wall pulling outward to create the negative pressure that begins inhalation, is much weaker in a child than an adult. This causes a child’s functional residual capacity, which is the volume of air in the lung at the end of passive exhalation, to be much closer to closing capacity, which is the volume in the lungs at which the respiratory bronchioles collapse (Bhalla, Khemani, & Newth, 2017). Therefore, at the end of expiration,
small airways of the lung collapse and alveoli are not ventilated. This leads to a ventilation to perfusion mismatch and results in hypoxemia very quickly. Adults, however, do have excellent elasticity of their chest wall, and therefore and increased functional residual capacity compared to an infant or a child (Hines & Marshall, 2018). Extensive knowledge of pediatric respiratory physiology compared to that of the adult is crucial for pediatric anesthesia providers in providing safe anesthetics.

**Presentation of Decreased Pulmonary Compliance**

In a case report by Scharoun et al. (2016), the authors present a 2-year-old boy undergoing IAC for RB. The patient was placed under general anesthesia with muscle relaxation and mechanical ventilation. The femoral artery was cannulated, and the catheter advanced toward the internal carotid artery, the catheter was then further advanced to the orifice of the ophthalmic artery. This can be identified in Figure 4. At this time, the anesthesia provider noticed a sudden drop in tidal volume by 75%. Upon auscultation, there is no wheezing appreciated. Albuterol, however, was still administered. There was little improvement in tidal volume and the patient began to desaturate. The anesthesia provider then hand ventilated the patient, and after 3 minutes his tidal volumes began to recover. However, the patient then becomes bradycardic and hypotensive requiring epinephrine. After several doses, as well as crystalloid fluid administration for blood pressure support, the patient stabilized. The procedure continues, the patient is extubated, and recovered in the PACU unremarkably.

This cardiopulmonary event occurs in as much as 29% of IAC cases, despite the level of anesthesia or muscle relaxation (Scharoun et al., 2016). The phenomenon even occurs before anything is injected into the ophthalmic artery, including saline, contrast, or chemotherapeutic agent. It is always abrupt and is related to the initial positioning of the catheter in the internal...
carotid artery or the ophthalmic artery. Tidal volumes will decrease, and patients will quickly desaturate due to the normal pediatric lung physiology that was discussed earlier. This may lead to bradycardia, hypotension, and cardiovascular collapse (Scharoun et al., 2016). This event must be quickly identified by the anesthesia provider and treated appropriately.

**Risk Factors for Developing a Decrease in Pulmonary Compliance During IAC for RB**

As this is now a well-known occurrence with IAC, the question remains—who is at risk and can the depth of anesthetic effect its occurrence? In a retrospective study by Phillips et al. (2013), a total of 52 patients underwent a combined 143 rounds of intra-arterial chemotherapy. Each patient received super selective ophthalmic artery chemotherapy using a standard protocol for general anesthesia, ophthalmic artery catheterization, and pulsed infusion of melphalan as the chemotherapeutic agent. All patients were intubated and received volatile anesthetic with muscle paralysis. Patients who required treatment intraoperatively to maintain cardiac and respiratory stability were considered to have had an adverse reaction.

Adverse reactions occurred in 35 of the procedures, or 24% of cases (Phillips et al., 2013.) This finding is similar to the occurrence of 29% of cases as cited by Scharoun et al. (2016). All of the documented reactions occurred during the second or subsequent catheterization procedure and consisted of hypoxia, reduced lung compliance, systemic hypotension, and/or bradycardia. Out of the 143 procedures, only one was abandoned due to hemodynamic instability.

Two patients were discussed specifically by Phillips et al. (2013). In the case of a 15-month-old child weighting 11 kg, undergoing their second intraarterial chemotherapy procedure, immediately after microcatheter was flushed with 0.9% normal saline the patient experienced a 40% decrease in tidal volume from 130 mL to 70 mL. Following this decrease in lung
compliance the patient’s blood pressure decreased from 80/50 (58) mmHg to a minimum of 43/16 (25) mmHg. Additionally, the heart rate decreased from 160 to 141 bpm. The second patient was a six-year-old child weighing 25 kg undergoing their fifth procedure, immediately upon insertion of the microcatheter into the ophthalmic artery, the patient’s tidal volume decreased from 247 to 22 mL—a 90% decrease. Following this event, the patient experienced a decrease in blood pressure from 92/42 (57) mmHg to a nadir of 52/24 (32) mmHg (Phillips et al., 2013). Specific end-tidal CO₂ and peak airway pressure readings were not discussed in these cases, but this illustrates how drastic the hemodynamic changes can be during this procedure upon catheter insertion and manipulation.

Phillips et al. (2013) concluded that: 1) The clinical signs present in these patients are believed to be an autonomic reflex, similar to the TCR or oculocardiac reflex. 2) All of the documented reactions occurred during the second or subsequent procedures. This means that patients may become sensitized during initial procedures and then the phenomenon is evoked with subsequent procedures. 3) Finally, atropine does not alter the incidence or severity of these reactions. 4) These reactions are life-threatening.

Data from other studies, however, have countered the conclusion that patients become sensitized and only experience this autonomic respiratory compromise on subsequent procedures. In a retrospective study by Kato et al. (2014), 122 patients undergoing a total of 468 procedures were studied. Intraoperative peak inspiratory pressure, positive end-expiratory pressure, tidal volume, oxygen saturation, and end-tidal carbon dioxide were analyzed. Any change in compliance, decrease in end-tidal carbon dioxide, and clinical outcomes were assessed. Compliance was defined as \( \frac{\Delta \text{volume}}{\Delta \text{pressure}} \) and computed as tidal volume/ (peak inspiratory pressure- positive end expiratory pressure). Out of the entire subject
population, 64% experienced a severe compliance event which was defined as a decrease in lung compliance of 40% (Kato et al., 2014). This means that if a 20 kg child had a normal tidal volume of 120-180 mL (6-8 ml/kg), their tidal volume would drop to as low as 72-108 mL. In the group of patients that experienced a severe respiratory compliance event, 20% experienced oxygen desaturation below 90%. Six of these patients experienced desaturation below 60%. Similarly, a sudden drop of end-tidal CO₂ by 30% occurred in 34% of patients in this subset (Kato et al., 2014). These are very dramatic hemodynamic changes that would be of upmost concern to the anesthesia provider.

Out of the 122 patients in this study, 27% experienced this significant decrease in compliance during their first exposure and 73% experienced the event in a subsequent case. Out of a subset of 94 patients who had their first and subsequent procedures identified, 67% experienced at least one severe respiratory event. Of this 67%, 18% of patients experienced a decrease in compliance during their first procedure (Kato et al., 2014). While the first case incidence is much smaller than subsequent case incidence, this finding rebuts Phillips et al. (2013) conclusion that patients become sensitized to the phenomenon after their first procedure. Kato et al. (2013) also found that the respiratory compromise is abrupt and always temporarily related to the initial positioning of the catheter in the internal carotid artery or the ophthalmic artery. This was found to be the case in every procedure where a respiratory event occurred.

The authors concluded that occurrence of a cardiopulmonary events during the first procedure is not predictive of it reoccurring in subsequent procedures. However, these events occur at a predictable stage of the procedure and are self-limiting (Kato et al., 2014). This allows the anesthesia provider to be prepared for when a decrease in compliance does occur so they can properly manage it. There should always be clear and open communication between the
anesthesia provider and neuroradiologist, so when this event does occur, the neuroradiologist can be notified and pause catheter manipulations until the problem resolves. Patients should immediately be placed on 100% oxygen and hand ventilated by the anesthesia provider (Kato et al., 2014). The authors also suggest that this most likely occurs due to a vascular to pulmonary reflex, which has not been described yet. While other reports suggest it is due to the oculocardiac reflex or trigemino-cardiac reflex, Kato et al. (2014) disagrees.

A retrospective study by Harris & Gaynor (2014) described what they believe is the TCR occurrence in patients undergoing IAC for RB and the objective change in compliance and vital signs experienced by those with a positive TCR. Harris & Gaynor (2014) studied 49 patients who underwent a collective 199 procedures. The authors define a positive TCR as the presentation of two of the following clinical features: 1) drop in systolic, diastolic, and/or mean blood pressure by 20% or greater, 2) a drop in pulse oximetry reading of 20% or greater, 3) a decrease in end-tidal carbon dioxide measurement of 20% or greater, indicative of a severe decrease in ventilation related to perfusion, and 4) an increase in peak inspiratory pressure of 20% or greater.

Harris & Gaynor (2014) found a total of 28 TCR events occurred in 18 out of 49 patents undergoing IAC for RB. In 21 of these cases, the TCR occurred during angiography of the ophthalmic artery and in seven cases it occurred during flushing or infusion through the catheter. The TCR did not occur during insertion of the catheter into the internal carotid artery or cavernous sinus, but only during microcatheter insertion into the ophthalmic artery. Only one of the TCR events was prolonged as it lasted three minutes and the procedure was aborted. All other cases were transient, and the procedure was able to continue after the stabilization of vital signs. Out of the 28 cases, seven received one dose of phenylephrine (1 mcg/kg) to support their
blood pressure and two patients received epinephrine (1 mcg/kg), not only to support blood pressure but to also produce bronchodilation (Harris & Gaynor, 2014).

This study found that among all cases with a positive TCR, 85.7% experienced a rise in peak inspiratory pressure, 75% experienced a decrease in their end-tidal carbon dioxide, and 64.3% experienced a decrease in their systolic blood pressure. The average rise in peak inspiratory pressure among all cases was 83.3% (Harris & Gaynor, 2014). This means that if a patient had a normal peak inspiratory pressure of 18 cm H2O, then an 83.3% increase would calculate to be 33 cm H2O. This is a notable increase that would be concerning to anesthesia providers, especially if the patient was paralyzed, not experiencing a change in position, and not coughing. The average drop in end-tidal CO2 among all cases was by 37.4% (Harris & Gaynor, 2014). This means that a normal reading of 40 mmHg would decrease to 25 mmHg. This would also be very concerning to anesthesia providers as it indicates a severe decrease in perfusion or ventilation. Finally, systolic blood pressure decreased by an average of 26.4% (Harris & Gaynor, 2014). To put this into context, a normal systolic blood pressure in a 5-year-old would be 100 mmHg. Of course, under general anesthesia, it may be lower, but a 26.4% decrease from a systolic blood pressure reading of 100 mmHg would be 74 mmHg. Also, a very concerning sign for an anesthesia provider.

These studies tell the reader four things. First, a decrease in pulmonary compliance may occur during IAC in 24-29% of cases. Second, all patients undergoing IAC for RB are at risk of this event, whether it’s the patients first or subsequent treatment. Third, the timing of the event is predictable, and will most likely occur during cannulation of the ophthalmic artery. Fourth, this event is usually transient, but emergency medications, including phenylephrine and epinephrine should be readily available.
Trigemino-cardiac Reflex

As the trigemino-cardiac reflex (TCR) and the oculo-cardiac reflex have both been mentioned in studies and publications describing the pulmonary compromise in patients undergoing IAC for RB, it is important to discuss and define the reflexes. In an article by Meuwly et. al (2017), the authors' goal was to improve the definition of the trigemino-cardiac reflex. They found that the TCR is triggered by a physical and/or chemical stimulation of any part or branch of the fifth cranial nerve, also known as the trigeminal nerve. Once these nerves are activated, an afferent signal is sent to the sensory nucleus of the trigeminal nerve, which is located on the floor of the fourth ventricle. The afferent pathway is connected to the efferent pathway via the reticular formation. The efferent premotor neurons are located in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve. These fibers activate the cardioinhibitory parasympathetic fibers which cause the clinical symptoms.

A positive TCR is defined as a sudden drop in heart rate and mean arterial blood pressure. The authors defined the TCR as having two major (plausibility and reversibility) and two minor (repetition and prevention) criteria. There has to be a direct link of time and action between stimulation and clinical manifestations and termination of the stimulus should also cease the manifestations (Meuwly et. al, 2017). The minor criteria suggest that the reflex should occur every time the stimulus is repeated. Due to ethical reasons, this is not something that can be done in every TCR case.

Chowdhury & Schaller (2016) define the TCR as a sudden onset of bradycardia with associated hypotension, apnea or gastric hypermotility during stimulation of any of the sensory
branches of the trigeminal, or fifth cranial nerve. The decrease in heart rate and blood pressure must be more than 20% from baseline and must be due to manipulation of the trigeminal nerve during surgery. Symptoms are transient when stimulation is removed (Chowdhury & Schaller, 2016). The authors presented four cases in which they believe the symptoms exhibited by the patient were due to the TCR. Only two of the cases will be included in this paper, due to a lack of relevance in the remaining cases. Neither of the cases that will be presented was due to IAC, but for this paper, the role of the TCR in their outcomes will be discussed.

The first two cases presented by Chowdhury & Schaller (2016) identify nasal packing to treat epistaxis as the precipitating factor before developing bradycardia, respiratory distress with a concomitant decrease in oxygen saturation, and hypotension. Both patients were intubated and provided advanced cardiac life support. Both patients, unfortunately, died as a result. Interestingly, nasal packings were not removed during resuscitation. This highlights that the TCR is not just limited to direct surgical stimulation and can result from indirect manipulation of the trigeminal nerve (Chowdhury & Schaller, 2016). Either direct or indirect, the TCR can be devastating if not treated appropriately, leading to death.

While this case series is very limited with its small sample size and lack of evidence if the nasal packings were the exact cause, it highlights the importance of the occurrence of identifying the TCR and treating it appropriately.

In a case study published by Klumpp, Jorge, and Azix-Sultan (2013), a 2-year-old presenting with RB in his right eye was referred for IAC using melphalan. After general anesthesia was induced, the patient was given muscle paralysis, intubated, and ventilated using pressure-controlled ventilation. Sevoflurane was used to maintain general anesthesia, mixed with 50% oxygen and air. After his femoral artery was cannulated, a microcatheter was advanced
through the internal carotid artery and into the ostium of the ophthalmic artery. Two minutes later, the patient's end-tidal CO\textsubscript{2} decreased by 14 mmHg and the patient experienced a precipitous fall in his oxygen saturation to a nadir of 40%. The anesthesia provider alerted the neuroradiologist who withdrew the catheter and the patient was ventilated with 100% oxygen. Wheezing was not heard upon auscultation. After four minutes, end-tidal measurements returned to normal, but the patient became hypotensive and phenylephrine (2 mcg/kg) was administered along with a fluid bolus over 30 minutes. Once the patient was stabilized the neuroradiologist was able to continue with the procedure without any further adverse events.

While there was no discussion of the adequacy of tidal volume administration during the time of this hemodynamic instability, the decrease in end-tidal CO\textsubscript{2} is indicative of dead space ventilation (Klumpp, Jorge, and Azix-Sultan, 2013). The patient was noted to become tachycardic, not bradycardic as previous other studies have mentioned. And therefore, we cannot say that this patient experienced the trigemino-cardiac reflex. Klumpp et al. (2013) continue to account that in their series of case studies evaluating this phenomenon, it occurred among 8 out of 30 patients of which experienced similar responses. Not one of their patients ever became bradycardic and therefore the TCR cannot be blamed.

This literature does not support that the TCR is what occurs during IAC. Based on the research conducted for this paper, it seems that bradycardia associated with IAC is directly related to an inability to ventilate, causing hypoxia, and resulting in bradycardia. So why is the TCR being blamed? And if it is not the TCR causing these symptoms, then what is? Unfortunately, the afferent and efferent signaling for this phenomenon has not been established, and the reason as to why this happens remains unknown.
Diving Reflex

Another autonomic reflex that may explain this cardiorespiratory event, is the diving reflex. Out of all the research conducted for this literature review, the diving reflex was only briefly mentioned by Scharoun et al. (2017). Most mammals have an intact diving reflex. It triggered by immersion of the face in cool water and is a protective mechanism to prevent aspiration while underwater. This reflex results in bradycardia, apnea, and peripheral vasoconstriction. While bradycardia occurs with immersion, alone, it is even further exaggerated by simultaneous apnea. This reflex is mediated by the ophthalmic branch of the fifth cranial nerve, or trigeminal nerve, via the anterior ethmoid nerve (Scharoun et al., 2017.) Studies mentioned by Scharoun et al. (2017) have found that direct stimulation of the anterior ethmoid nerve in muskrats causes bradycardia, hypotension, and apnea. This pathway can be seen in Figure 5. Interestingly, cutting the anterior ethmoid nerve completely abolishes the apnea triggered by nasal stimulation. According to Scharoun et al. (2017), anesthetized and spontaneously breathing dogs experience a decrease in dynamic lung compliance from 25.5 to 13.7 mL/cm H₂O and decrease in heart rate when given intranasal capsaicin. Could this be what is occurring in patients undergoing IAC for RB? It is unclear. It is also not mentioned in any

Figure 5: Diving Reflex

Adapted from “Anesthesia for Ophthalmic Artery Chemotherapy, by J. Scharoun, J. Han, & P. Gobin, 2016, Anesthesiology, 126(1).
other literature related to IAC for RB, except for the case report by Scharoun et al. (2017). More research is needed to determine if this is the cause of the sudden cardiorespiratory event during IAC for RB.

**Anesthetic Influence**

The previously mentioned studies all conclude that a decrease in respiratory compliance does indeed occur during ophthalmic artery chemotherapy for RB. It is presumed this is due to some sort of autonomic reflex, but the exact mechanism remains unclear. None of these studies, however, have evaluated what anesthetic factors may attribute to this occurrence. In a prospective, observational, single-arm study by Nghe et al. (2018), the authors hypothesized that the level of anesthetic depth may influence the occurrence of this respiratory phenomenon. A total of 115 procedures were analyzed on 32 patients. Other variables, including age and weight, medical history of asthma or upper respiratory tract infection within four weeks, and exposure to secondhand smoke were also assessed in hopes to find a possible association with severe intraoperative cardiopulmonary events.

Nghe et al. (2018) defined severe cardiorespiratory events as arterial hypotension, bradycardia, and a severe decrease in lung compliance. Out of the 115 procedures, 24 resulted in adverse cardiorespiratory events—20 experienced a severe decrease in lung compliance, one experienced bradycardia, and arterial hypotension was seen in nine procedures. All events occurred within two minutes of catheter insertion into the ophthalmic artery with a median occurrence of one minute. No events occurred while the catheter was in the carotid artery or after chemotherapy injection. For patients that experience a severe decrease in lung compliance, their peak inspiratory pressures gradually rose within the first minute of catheter insertion. Following
this rise, oxygen saturation decreased and some experienced hemodynamic instability (Nghe et al., 2018).

Unfortunately, none of the demographic data or medical history was significant in association with serious adverse cardiorespiratory events. Furthermore, all patients were maintained under general anesthesia using sevoflurane with mean alveolar concentration (MAC) values between 1.5 and 1.7, high enough to blunt autonomic reflexes. Patients also received a bolus of sufentanil 0.2 mcg/kg on induction and additional boluses of 0.1 mcg/kg after femoral artery puncture. Their bispectral index (BIS) was maintained between 40-50, a value encouraging of adequate depth of general anesthesia (Nghe et al., 2018).

Nghe et al. (2018), concluded that neither demographic values nor medical history can predict the occurrence of severe cardiorespiratory events during ophthalmic artery chemotherapy. Furthermore, this phenomenon can occur despite an adequate depth of general anesthesia, in which autonomic reflexes should be attenuated.

**Treatment of Intraoperative Decrease in Pulmonary Compliance During IAC for RB**

While the actual physiology of what causes the decrease in pulmonary compliance during IAC for RB is unknown, the treatment of possible physiological mechanisms will be discussed. It is speculated that patients may develop acute bronchospasm due to stimulation of the ophthalmic artery, causing a decrease in respiratory compliance due to the TCR. This causes a release of acetylcholine on the muscarinic receptors on the bronchial smooth muscle, resulting in bronchoconstriction. However, studies have documented the lack of wheezing heard upon auscultation and furthermore the administration of bronchodilators, like albuterol, do not improve symptoms. Pediatric intraoperative bronchospasm has an occurrence rate of 0.2-4.1% in the general population. There are three major triggers for perioperative bronchospasm including
mechanical airway manipulation, anaphylactoid reactions, and immunological anaphylaxis. Treatment includes reducing the level of stimulus, deepening the anesthetic, and administration of 100% oxygen. Pharmacologic intervention includes the administration of beta-2 agonists like albuterol. If severe airflow limitation persists, intravenous beta-2 agonists like salbutamol and epinephrine can be administered. Other medications include atropine, glycopyrrolate, and magnesium, all of which may provide further bronchodilation. Anesthesia providers should do their best to provide protective lung ventilation and avoid high peak airway pressures to avoid hyperinflation and barotrauma (Regli & von Ungern-Sternberg, 2015).

Anesthetic Management of Patients with RB

Some level of sedation or general anesthesia is needed for the large array of treatment options for RB. Therefore, anesthesia providers are becoming more involved in the care of patients with RB as IAC is becoming a more frequently used treatment option for these patients. Not only do anesthesia providers need to be well versed in the physiology of the disease but they also need to well-educated on the potential complications that can occur intraoperatively. The decrease in pulmonary compliance associated with ophthalmic artery cannulation is well reported with occurrence rates of 24-29%. Anesthesia providers should anticipate this event to occur with every anesthetic provided for IAC for RB and have the available tools to treat these patients readily available.

The Johns Hopkins Hospital IAC for RB and Pediatric Anesthesia

At The Johns Hopkins Hospital in Baltimore, Maryland, IAC is a commonly administered treatment for RB. Pediatric anesthesia providers are well educated on the disease and pulmonary manifestations that may occur during the procedure. Dr. Monica Pearl is a neuroradiologist at JHH and administers IAC to this patient population. From an anecdotal
perspective, Dr. Pearl discusses the decrease in pulmonary compliance that occurs during this procedure during her “time out”. She instructs the anesthesia provider to immediately let her know if this event occurs so that she can retract the cannula from the ophthalmic artery and halts the procedure until the patient recovers. Anesthesia providers prepare a syringe of epinephrine diluted to 10 mcg/ml and are prepared to administer it immediately if this event occurs. All patients are maintained under general anesthesia with sevoflurane and maintain muscle paralysis with rocuronium. Mechanical ventilation is supported with pressure support ventilation so that if there is a decrease in pulmonary compliance, the anesthesia provider can be immediately alerted when there is a decrease in tidal volume. This open line of communication between the proceduralist and the anesthesia provider ensures that everyone in the room is educated and prepared for this intraoperative event and have the ability to treat it immediately. This is exactly what Dr. Monica Pearl does during her “time out.”

**Conclusion**

RB is a difficult diagnosis for a family to deal with. New therapies like IAC provide treatment options that are just as effective as intravenous chemotherapy with far fewer side effects. While these patients do not suffer from the nephrotoxicity, hepatotoxicity, cardiomyopathy, ototoxicity, and myelosuppression associated with intravenous chemotherapy, it is far from a benign procedure. The intraoperative cardiorespiratory event associated with IAC can be devastating. However, it can be anticipated by anesthesia providers and treated effectively. This can only be attainable by educating the anesthesia provider on how to prepare, anticipate, identify, and treat this event effectively.

While the exact mechanism that causes such profound cardiorespiratory event during IAC for RB is not fully known, it is important for the anesthesia provider to be aware that its
occurrence is a possibility. Further research should be aimed at identifying risk factors for
developing this adverse event as well as the impact of the anesthetic provided. Furthermore, if
this is an autonomic mechanism, research should be aimed at identifying the afferent and efferent
limbs. In the meantime, providers should be aware that when the event does occur, it is prudent
to have an open line of communication with the neuroradiologist. When the catheter
manipulation is stopped, the symptoms usually resolve. As always, patients’ hemodynamics
should be supported by the anesthesia provider throughout the case, and emergency medications
should always be available.
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