Chapter 17

Supravalvular Aortic Stenosis

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Case Scenario

A 2 ½-year-old male with Williams syndrome is evaluated preoperatively prior to dental rehabilitation. He presented last week to the preoperative clinic for evaluation prior to repair of his supravalvular aortic stenosis; however, on examination he was found to have multiple dental caries and his cardiac surgery was rescheduled to first optimize his dental health. Current vital signs are heart rate 105 beats/minute, respiratory rate 22 breaths/minute, SpO_2 98% on room air, and blood pressure 120/60 mm Hg. He is very friendly but appears anxious while his vital signs are being checked.

A transthoracic echocardiogram obtained last week showed the following:

- *Supravalvular aortic stenosis gradient of 65 mm Hg*
- *Mild peripheral pulmonary artery stenosis*
- *Mild right ventricular hypertrophy*
- *Moderate left ventricular hypertrophy*
- *Normal biventricular function*
- *Coronary arteries could not be visualized*

Key Objectives

- Describe the characteristic phenotype of Williams syndrome.
- Understand the cardiac anomalies common in patients with Williams syndrome.
- Understand why Williams syndrome patients are at high risk for cardiac events during sedation and general anesthesia.
- Describe the preoperative planning necessary for patients with Williams syndrome.
- Describe perioperative hemodynamic goals for patients with supravalvular aortic stenosis.

Pathophysiology

What is Williams syndrome?

Williams syndrome (WS), also known as Williams–Beuren syndrome, was first reported in 1961 by Williams and subsequently in 1962 by Beuren; each described four children with similar phenotypes consisting of supravalvular aortic stenosis (SVAS), characteristic facial features, and developmental delay [1, 2]. The incidence of WS is 1 in 7500 to 10,000, with an equal distribution among males and females [3].

The syndrome is a multisystem disorder with a variable clinical presentation resulting from a microdeletion on chromosome 7q11.23 encompassing 27 genes including the *ELN* gene that codes for the protein elastin [3]. The microdeletion is usually sporadic but can be familial [4]. Other genes that are deleted within the region of the microdeletion are responsible for the other features commonly associated with WS. The systems most affected in WS include cardiovascular, renal, endocrine, and psychiatric. Patients with WS have a high risk of cardiac events and sudden death, especially during sedation and general anesthesia [5].

What is the significance of the elastin deficiency in WS patients?

The elastin deficiency is caused by deletion of one elastin allele, resulting in a significant reduction in the quantity of elastin produced by affected patients. Consequently, an elastin arteriopathy develops as the elastin in arterial walls is replaced by a proliferation of smooth muscle cells in the vascular media that causes obstructive, hyperplastic intimal lesions of medium and large arteries. Abnormal circumferential growth of arteries also contributes to luminal narrowing. Elastin deficiency is responsible for many of the cardiovascular abnormalities associated with WS [6]. The aorta and coronary, carotid, renal, and pulmonary arteries can be affected [7]. Stenosis occurs most commonly at the sinotubular junction of the aorta, causing SVAS.

What cardiac abnormalities are associated with WS?

Eighty percent of patients with WS have cardiovascular abnormalities, which are the leading cause of morbidity and mortality [8]. The most common cardiac malformation

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is SVAS, occurring in 45%–70% of patients with WS. Supravalvular aortic stenosis occurs at the sinotubular junction of the aorta due to a circumferential ridge of tissue that causes luminal narrowing [4]. (See Figure 17.1A and B.) Other cardiovascular abnormalities associated with WS patients include supravalvular pulmonary artery stenosis (SVPS), peripheral pulmonary artery stenosis, coronary artery obstructions, aortic valve defects, hypoplasia of the aorta, coarctation of the aorta, and renal artery stenosis [8]. Forty to fifty percent of patients have systemic hypertension, which may be caused by renal artery stenosis [4].

The etiology of coronary artery obstructions includes not only medial hypertrophy but also narrowing of the ostia by a thickened aortic wall, ostial obstruction due to superior displacement of the ostia to just below the sinotubular ridge of the aorta, fusion of the free edges of the coronary cusps to the site of SVAS, and accelerated atherosclerotic lesions and aneurysm formations due to exposure to high pressures in the presence of SVAS [9]. The degree of SVAS is not correlated to the degree of coronary artery involvement [10].

Clinical Pearl

Supravalvular aortic stenosis is the most common lesion in WS and occurs at the sinotubular junction. The degree of SVAS does not correlate with the degree of coronary involvement.

What abnormality of the electrical conduction system is common in WS patients?

Prolongation of the corrected QT (QTc) interval occurs in 13.6% of patients with WS [11]. Prolonged QTc may deteriorate into malignant ventricular arrhythmias, such as torsades de pointe or ventricular fibrillation, and may contribute to an increased risk of periprocedural morbidity and mortality. It is important to perform an electrocardiogram (ECG) on all patients with WS prior to an anesthetic to screen for evidence of QTc prolongation.

Clinical Pearl

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Does SVAS occur in patients without WS?

Supravalvular aortic stenosis can occur in patients without WS and is often due to point mutations in the *ELN* gene. Patients with nonsyndromic elastin arteriopathy can have the same cardiovascular manifestations as patients with WS but have a reduced incidence of prolonged QT interval [12].

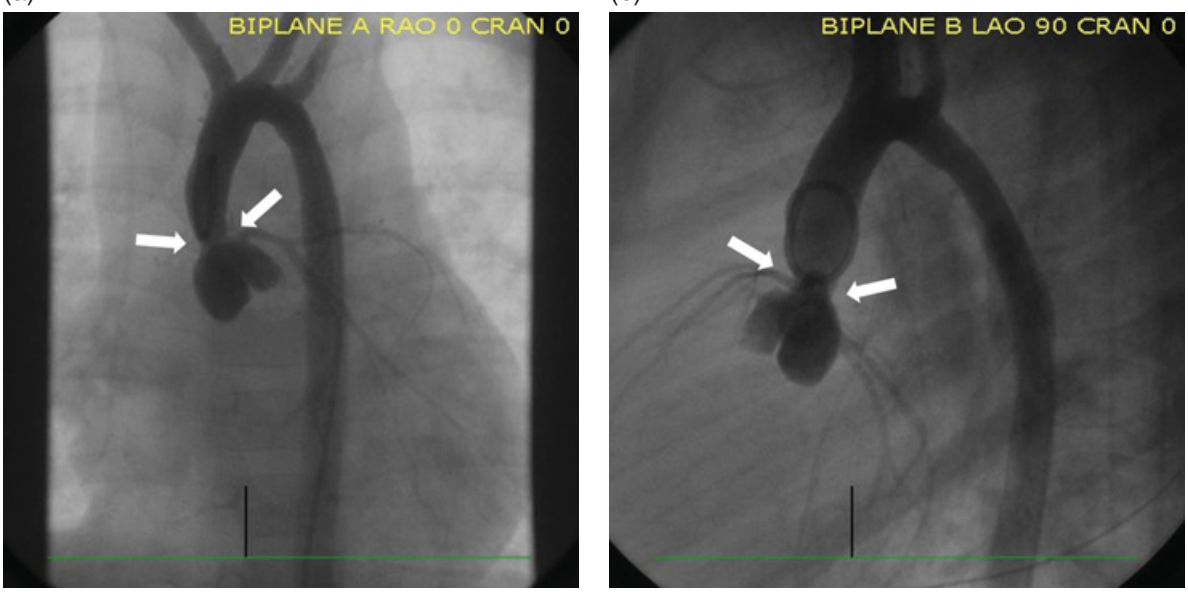

Figure 17.1 Supravalvular aortic stenosis: ascending aortic injection. An angiogram is performed in the ascending aorta in the AP (A) and lateral (B) projection. The arrows indicate the area of stenosis at the sinotubular junction. Courtesy of Russel Hirsch, MD.

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What are the risk factors for cardiac arrest in WS?

Patients with WS have a 25- to 100-fold higher risk of sudden death compared to an age-matched normal population [13]. The risk of sudden death and major adverse cardiac events (MACE) – including cardiac arrest, need for postoperative mechanical circulatory support, and in-hospital mortality – are high during the perioperative period in patients with WS [5, 12]. An analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database in 2015 by Hornik et al. reported that 9% of WS patients undergoing cardiac surgery had MACE in the perioperative period with an in-hospital mortality rate of 5% [14]. Latham et al. reported cardiac arrest in 5% of WS patients undergoing an anesthetic [12].

The two conditions associated with a high risk of cardiac arrest are biventricular outflow tract obstructions and coronary artery obstruction by ostial or intraluminal stenosis [15]. Age <3 years and prolongation of the QTc interval have also been identified as risk factors for cardiac arrest. Biventricular outflow tract obstruction with right ventricular (RV) and left ventricular (LV) gradients >20 mm Hg increases the risk of cardiac arrest. The rate of cardiac arrest increases as the gradients of the biventricular outflow tract obstruction increase, with the highest risk with gradients >50 mm Hg [12].

Clinical Pearl

Risk factors for cardiac arrest in the perioperative period are biventricular outflow tract obstruction and coronary artery obstruction by ostial or intraluminal stenosis. The risk increases as the gradients of the biventricular outflow tract obstruction increase.

When is cardiac surgery indicated for patients with SVAS?

Supravalvular aortic stenosis repair is indicated when the patient develops symptoms related to the obstruction, there is a documented gradient >50 mm Hg, or there is evidence of coronary obstruction [16]. Approximately 30% of patients with WS who have SVAS will require surgical repair [4].

Anesthetic Implications

Why are patients with WS at high risk for cardiac arrest when undergoing anesthesia?

The balance between myocardial oxygen supply and demand may be in a continually precarious state in patients with WS, as the cardiovascular abnormalities associated with WS and their pathophysiologic consequences predispose patients to myocardial ischemia.

Factors that can negatively impact myocardial oxygen supply and demand in WS include the following:

- ***Reduced coronary blood flow*** can decrease myocardial oxygen supply. Stenotic lesions may be present within the coronary artery and at the ostium. Restriction of blood flow into the sinus of Valsalva can occur secondary to adhesion of aortic leaflets to the sinotubular junction.
- ***Ventricular hypertrophy*** secondary to ventricular outflow tract obstruction(s) can result in both decreases in coronary perfusion AND increases in oxygen demand. Decreases in subendocardial perfusion can occur due to increased left ventricular end-diastolic pressure (LVEDP) in the setting of decreased coronary perfusion pressure. Increased myocardial oxygen consumption leading to increased myocardial oxygen demand results from the increased muscle mass of ventricular hypertrophy.

Patients with WS are at high risk for cardiac arrest when undergoing anesthesia due to a further imbalance in myocardial oxygen supply and demand induced by anesthetic medications that alter hemodynamics. Several commonly utilized anesthetic medications may decrease systemic vascular resistance (SVR) and thus decrease coronary blood flow and myocardial oxygen delivery. Other anesthetic agents may increase heart rate and thus increase myocardial oxygen demand [9]. Changes in preload, afterload, contractility, and heart rate that occur during anesthesia may lead to myocardial ischemia and subsequent cardiovascular collapse in children with WS [12]. When hemodynamic instability occurs during anesthesia it progresses rapidly from initial hypotension and bradycardia to cardiac arrest that many times fails to respond to aggressive resuscitation measures [12, 15].

Clinical Pearl

Patients with WS are at high risk for cardiac arrest when undergoing sedation or general anesthesia due to an imbalance in myocardial oxygen supply and demand that can be further accentuated by anesthetic medications.

What physical characteristics are consistent with WS?

Patients with WS have distinct facial features, neurodevelopmental findings, and personalities, although considerable phenotypic variability exists. The facial features consistent with WS include a broad forehead, wide-set

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eyes, flat nasal bridge, short nose with a bulbous nasal tip, long philtrum, wide mouth with a thick vermillion of the lips, heavy cheeks, and a pointed chin [1, 17]. Children are often described as having pixie-like or elfin-like facial features. Many patients have a developmental delay, with an average IQ of 50–60; however, there are some patients who have IQs of 100 [17]. Patients have a distinct "cocktail party" personality, meaning that they do not display social anxiety and are very friendly. Despite this personality, patients often experience significant periprocedural anxiety that can evolve quickly into agitation in the setting of medical procedures. Most patients with WS have a normal airway exam; however, in some patients difficulty with mask ventilation and tracheal intubation may be noted secondary to a flattened midface, mild micrognathia, small teeth, and malocclusion [18].

What preoperative laboratory abnormalities might be expected?

Endocrine abnormalities frequently associated with WS include hypercalcemia, hypothyroidism, and diabetes mellitus type 2. Hypercalcemia is generally mild but can be severe during infancy. Subclinical hypothyroidism occurs in 15%–30% of patients with WS. Patients are often asymptomatic but general anesthesia may precipitate unwanted symptoms, including depression of myocardial function, poor temperature regulation, and impaired hepatic drug metabolism [17, 18]. Diabetes mellitus type 2 is more common in adults with WS than in children. A thyroid function panel and calcium and glucose levels should be checked at appropriate age intervals according to the American Academy of Pediatrics (AAP) guideline for patients with WS [19]. Additionally, these laboratory results should be checked preoperatively if there is clinical suspicion of an endocrinopathy or if they have not been recently measured.

What preoperative diagnostic studies should be reviewed?

Prior to an anesthetic, all available cardiac diagnostic studies should be reviewed, and a determination should be made as to whether additional studies need to be performed. At a minimum, an ECG and a transthoracic echocardiogram (TTE) should be performed.

- ***The electrocardiogram*** should be analyzed for changes indicative of prolonged QTc interval, evidence of ventricular hypertrophy suggestive of outflow tract obstructions, and changes indicative of myocardial ischemia, such as ST segment abnormalities.
- ***Transthoracic echocardiography*** should be reviewed and assessed for any degree of biventricular outflow tract obstruction caused by SVAS and/or SVPS. While the contribution of peripheral pulmonary artery stenosis to RV outflow tract obstruction may be more difficult to assess with echocardiography, a finding of RVH in the absence of obvious SVPS may prove insightful. ***Coronary artery obstructions are also difficult to assess by echocardiography, but ventricular wall motion abnormalities may be suggestive of coronary lesions.*** Echocardiography can also be used to assess cardiac function.
- ***Cardiac catheterization*** with coronary and aortic angiography is the gold standard for assessing coronary arterial anatomy but carries risk. Catheter manipulations during cardiac catheterization may further compromise myocardial oxygen supply and demand balance by blocking coronary blood flow, inducing valvular regurgitation, producing dysrhythmias, or acutely increasing ventricular outflow tract obstruction(s). Contrast injection into a stenotic coronary artery may cause acute myocardial ischemia secondary to the lack of oxygen carrying capacity in contrast.
- ***Cardiac magnetic resonance imaging*** (MRI) and ***computed tomography*** (CT) scans also provide valuable data on cardiovascular anatomy.

Patients often require sedation or general anesthesia when diagnostic studies are performed. Therefore, the anesthesia team may be required to proceed with limited and incomplete data. An anesthetic must be planned as if the child's coronary blood flow and myocardial oxygen balance exist in a tenuous state.

Clinical Pearl

An anesthetic must be planned as if the child's coronary blood flow and myocardial oxygen balance exist in a tenuous state.

Where should this procedure be performed?

All patients with WS are at high risk for major adverse cardiac events during the perioperative period. Morbidity and mortality may occur in patients with WS despite the most cautious anesthetic care [12]. Elective procedures requiring anesthesia should be planned only after consideration by all participants of the balance between the benefits of the procedure and the potential adverse events of anesthetizing patients with WS. All elective procedures requiring sedation or general anesthesia should be performed at a medical center with pediatric cardiac care subspecialists who are available for immediate consultation [4]. The facility must be equipped to handle unexpected cardiac

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emergencies, initiate extracorporeal membrane oxygenation (ECMO) immediately, and adequately monitor the patient post-procedure.

Clinical Pearl

Administration of sedation or general anesthesia for elective procedures should be performed at a medical center with immediate access to cardiac multidisciplinary specialists and the capability to provide ECMO support.

What preoperative preparations are necessary for patients with WS?

Thorough preoperative preparations should take place before every elective procedure in patients with WS [4]. Brown et al. reported a low rate of cardiac events in 75 patients with WS who each had a preanesthetic evaluation. The authors of this review concluded that high anesthetic risk can be mitigated with appropriate planning and adherence to hemodynamic goals [20]. Patients with WS should attend a preoperative anesthetic clinic at least 1–2 weeks before scheduled procedures. The preanesthetic evaluation should include the following:

- ***History and physical*** should be conducted with attention to any new symptoms or signs of cardiac disease progression.
- ***Cardiology consultation*** and new imaging studies should be completed if necessary due to the progressive nature of cardiac lesions. Recently obtained diagnostic studies, such as an ECG, echocardiogram, or cardiac catheterization report, should be reviewed. An updated ECG and TTE within the previous 6 months prior to an anesthetic should be available.
- ***Preoperative laboratory results*** should be reviewed and ordered according to the AAP guidelines to evaluate for hypercalcemia, hypothyroidism, and hyperglycemia [19].
- ***Fasting guidelines*** should include continuing hydration with clear fluids until 2 hours before the procedure to preserve myocardial preload. The procedure should be scheduled as a first start case to avoid unexpected delays that would increase fasting times and to ensure adequate personnel resources are available for assistance if needed. If there are any delays, an intravenous (IV) line should be placed preoperatively for fluid administration.
- ***The ECMO support team*** should be notified about patients with severe SVAS gradients or known involvement of the coronary arteries.
- ***Postoperative recovery location*** and intensive care unit availability should be discussed prior to all procedures requiring sedation or general anesthesia.

If appropriate, a ***child life*** specialist should explain perioperative events to the patient.

Clinical Pearl

The risk of perioperative cardiovascular events can likely be mitigated by proper planning, preparation, and coordination of resources. Ideally WS patients should attend a preoperative anesthetic clinic at least 1–2 weeks prior to the procedure.

What risks should be discussed with the patient's parents before the case?

The anesthetic plan, along with the risks and benefits of anesthesia, should be discussed with the patient's family before the case. The significant potential for cardiac arrest and the possibility of ECMO support should be discussed before the procedure. Many parents of patients with WS are well aware of the risks while undergoing anesthesia and should be given the proper time to ask questions.

What are the perioperative hemodynamic goals for patients with WS?

For patients with WS, the perioperative goal is to decrease the incidence of myocardial ischemia by maximizing the oxygen supply and minimizing the myocardial oxygen demand. The hemodynamic goals are to maintain an age-appropriate heart rate, sinus rhythm, adequate preload, contractility, and SVR. It is important to avoid tachycardia, hypotension, and increases in pulmonary vascular resistance (PVR). Tachycardia increases myocardial oxygen consumption and decreases diastolic perfusion time. A decrease in coronary perfusion pressure resulting from hypotension will be especially hazardous when coronary artery lesions are present or when myocardial hypertrophy has developed. Changes in the hemodynamic status of patients should be treated quickly to avoid deterioration that may lead to myocardial ischemia and cardiac arrest.

Clinical Pearl

The perioperative goal is to decrease the incidence of myocardial ischemia by maximizing the oxygen supply and minimizing the myocardial oxygen demand. Hemodynamic goals include maintaining an age-appropriate heart rate, sinus rhythm, preload, contractility, and SVR. Tachycardia and hypotension should be avoided.

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Does this patient need premedication for anxiolysis?

Despite the "cocktail party" personality of patients with WS, many patients have significant periprocedural anxiety and will require premedication for anxiolysis. It is important to avoid tachycardia related to anxiety because this increases myocardial oxygen demand, decreases the time needed for coronary perfusion in diastole, and may contribute to potential hemodynamic instability caused by anesthetic medications [4]. It is important for the anesthesiologist to develop rapport with the patient and family to establish trust. A calm environment should be created and maintained in the preoperative area. Many children with WS have hyperacusis and therefore loud noises should be avoided. Patients with WS have a near universal enjoyment of music, which can serve as a distraction [17]. Child life specialists can work with patients to create additional distractions. In addition to nonpharmacologic methods of anxiolysis, medications are often needed. Midazolam and dexmedetomidine are well tolerated and do not induce tachycardia.

What type of anesthetic should be performed – sedation, monitored anesthesia care, or general anesthesia?

Both patient and procedural factors should guide the depth of sedation and anesthesia [4]. Many patients with WS will require sedation or general anesthesia for noninvasive diagnostic studies. General anesthesia is the best plan for dental rehabilitation in this patient due to his age and likely inability to cooperate with the duration and discomfort of the procedure.

How should anesthetic induction be conducted for this patient?

Following premedication, establishment of a peripheral IV prior to induction of anesthesia not only allows for the careful titration of induction medications but also secures a route for the immediate treatment of any potentially adverse hemodynamic changes that may occur during induction. Thus, ***an intravenous induction is strongly preferred over an inhalational induction*** [21]. Topical local anesthetics or needleless local anesthetic applications can be used to minimize pain during placement of an awake IV line. Prior to induction, American Society of Anesthesiologists (ASA) standard monitors should be placed on the patient to provide continuous monitoring during induction. The ECG should be carefully monitored for any changes in the appearance of the ST segments. During induction of anesthesia a balanced technique should be used in which small incremental doses of a combination of medications are given until the desired plane of sedation or anesthesia is reached. Anesthetic medications should be selected that avoid tachycardia, hypotension, and myocardial depression to minimize the risk of myocardial ischemia. Narcotics, such as fentanyl, have been successfully used for induction. Ketamine maintains SVR and contractility but when used in larger doses may increase the heart rate. Nevertheless, ketamine has been used successfully for induction of patients with WS. In this case the use of neuromuscular blockade would be useful to facilitate placement of a nasal endotracheal tube for a dental procedure. Care should be taken to achieve an adequate anesthetic depth prior to intubation to avoid undue tachycardia.

If a patient is uncooperative and an IV is unable to be placed prior to induction, an inhalational induction is possible; however, a greater chance for hemodynamic instability exists. Inhalational anesthetics cause a decrease in the SVR and subsequent hypotension. Propofol should also be avoided for this reason. If an inhalational induction is necessary, additional anesthesia providers should be readily available to assist if needed. If a patient decompensates with loss of a perfusing heart rhythm during induction or any time during the perioperative period, Pediatric Advanced Life Support protocols should be initiated, advancing to ECMO if necessary.

Clinical Pearl

Careful intravenous titration of small incremental doses of a combination of medications seems to be the safest technique for induction of general anesthesia. The ECG should be carefully monitored for any changes in the appearance of the ST segments.

In addition to standard ASA monitoring, what other monitors should be available for this patient?

Depending on the degree of ventricular outflow tract obstruction(s) and coronary artery involvement, additional monitoring may be needed. A 5-lead continuous ECG should be used for all patients with WS and ST segments monitored closely for any change. External defibrillation pads should be available. Placement of an arterial line should be considered for all patients with WS, with the decision for placement based on the severity of cardiac disease, hemodynamic status during induction, and procedure to be performed. Placement

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of an arterial line prior to induction may be considered in patients with severe biventricular outflow tract obstructions and coronary artery stenosis. This should be placed after an IV line has been established, and sedation may be given for its placement. The patient in this case is at high risk for cardiac arrest because his SVAS gradient is >50 mm Hg, and therefore placement of an arterial line before induction would not be unreasonable, if feasible.

How should anesthetic maintenance be conducted for this patient?

After a hemodynamically stable induction, low concentrations of volatile anesthetics can be used for maintenance as part of a balanced anesthetic technique. If hypotension develops, phenylephrine, norepinephrine, and vasopressin infusions or boluses can be used to improve blood pressure without increasing the heart rate. Medications that prolong the QT interval, such as ondansetron, should be avoided in patients with prolonged QTc to prevent further deterioration into malignant ventricular arrhythmias. (See Chapter 49.) Narcotic medications should be titrated to blunt painful procedural stimuli to prevent tachycardia. Regional anesthesia techniques should be considered for postoperative pain management for appropriate procedure. A multimodal approach to analgesia is also helpful, utilizing IV acetaminophen and other nonnarcotic modalities.

Where should this patient recover after the procedure? Can this case be performed as an outpatient?

Regardless of the type of procedure performed, WS patients may need to be admitted for postoperative monitoring depending on the severity of cardiac involvement and any intraoperative events. Patients with WS should have continuous monitoring with ECG, pulse oximetry, and blood pressure until the patient recovers their baseline level of cognition [21]. Parental presence in the postanesthesia care unit may help to relieve anxiety. Patients with known risk factors for perioperative cardiac arrest – biventricular outflow tract obstructions and/or coronary artery stenosis – should be admitted for postoperative monitoring in a unit with continuous telemetry. Patients with severe biventricular outflow tract obstruction and coronary artery stenosis should be admitted to an intensive care unit for monitoring. Patients without significant cardiac involvement may be discharged after low-risk procedures, such as dental rehabilitation or an esophagoduodenoscopy, after return to baseline.

If a patient has had previous uneventful anesthetics, does this impact the approach to anesthetic care?

All patients with WS are considered high-risk for cardiac events during sedation or general anesthesia regardless of past anesthetic history. The natural history of cardiac lesions in WS includes progression of SVAS lesions and possible spontaneous resolution of branch or peripheral pulmonary artery stenosis lesions [8]. Cardiac lesions may have worsened since the last anesthetic placing the patient at higher risk for myocardial ischemia. ***Therefore, the same resources should be available for all patients with WS during every anesthetic.***

Clinical Pearl

All patients with WS are considered high risk for cardiac events during sedation or general anesthesia regardless of past anesthetic history. The natural history of cardiac lesions in WS includes progression of SVAS lesions.

What if the child has had prior cardiac surgery and the coronaries are "fixed"?

If a child has had an anatomic repair of known coronary defects, a recent CT or MRI may provide reassurance; however, it is important to remain vigilant. Patients with WS may have occult coronary artery abnormalities even with the absence of echocardiographic or angiographic evidence [12]. All patients with WS have the possibility of undiagnosed coronary artery disease.

Is it acceptable to perform a subsequent procedure at a community hospital?

All patients with WS are at high risk for major adverse cardiac events while undergoing a general anesthetic [12, 20]. Since cardiac morbidity and mortality may occur despite careful planning and the most cautious vigilant care, patients with WS should receive anesthetic care at tertiary care medical centers where immediate access to cardiac multidisciplinary specialists and the capability to provide ECMO support exists[12].

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Suggested Reading

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