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REVIEW ARTICLE

WILEY Congenital Heart Disease

Peri-procedural risk stratification and management of patients with Williams syndrome

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Abstract

Williams syndrome (WS) is a congenital, multisystem disorder affecting the cardiovascular, connective tissue, and central nervous systems in 1 in 10 000 live births. Cardiovascular involvement is the most common cause of morbidity and mortality in patients with WS, and noninvasive and invasive procedures are common. Sudden cardiovascular collapse in patients with WS is a well-known phenomenon, especially in the peri-procedural period. Detailed guidelines for peri-procedural management of patients with WS are limited. The goal of this review is to provide thoughtful, safe and effective management strategies for the peri-procedural care of patients with WS with careful consideration of hemodynamic impacts of anesthetic strategies. In addition, an expanded risk stratification system for anesthetic administration is provided.

KEYWORDS

anesthesia, cardiac arrest, dentistry, perioperative care, surgery, Williams syndrome

1 | INTRODUCTION

Williams syndrome (WS), also referred to as Williams-Beuren syndrome (OMIM 194050), is a congenital, multisystem disorder involving the cardiovascular, connective tissue, and central nervous systems.[1] Williams syndrome occurs in approximately one in 10 000 live births[2] as a result of the de novo deletion of approximately 28 genes on chromosome 7q11.23, including the *ELN* gene, which codes for the protein elastin.[3] Haploinsufficiency of *ELN* has been demonstrated to be responsible for the vascular pathology in WS.[4]

Before developing peri-procedural management plans for patients with WS, it is imperative to have an understanding of the cardiovascular features of the syndrome that set it apart from other patient groups.

1.1 | Cardiovascular involvement

Cardiovascular defects are the most common cause of death in patients with WS.[3] Structural cardiovascular abnormalities occur in approximately 80% of all WS patients,[5] and are present in up to 93% of those presenting before 1 year of age.[6] A number of cardiovascular abnormalities are common to WS, but the majority consists of some form of arterial stenosis.[5] (Figure 1) Supravalvar aortic stenosis (SVAS) was the cardiovascular lesion first reported by Williams et al.,[7] and is the most common cardiovascular abnormality, occurring in 45–75%.[8] Pulmonary artery stenosis (PAS), especially of the branch pulmonary arteries, is the second most common cardiovascular abnormality in patients with WS.[5] (Figure 2) Coronary artery abnormalities, whether ostial stenosis or arterial dilation, are seen in up to 45% of patients with SVAS,[8] and likely contribute to some cases of sudden death in patients with WS.[9]

1.2 | Cardiovascular procedures in Williams syndrome

Approximately 20% of patients with WS undergo surgical or transcatheter interventions for cardiovascular abnormalities, with the large majority of those occurring by 15 years of age;[5,10] the likelihood of intervention is increased to approximately 30% in those who present before 1 year of age.[6]

When intervention is necessary in the setting of SVAS, surgical intervention is most commonly undertaken,[5,11] as transcatheter balloon angioplasty has been found to be ineffective.[10] In a surgical cohort in which 41% of patients had WS, the overall survival of patients with SVAS has been estimated at 90 ± 7%, 84 ± 9%, and 82 ± 10% at 5, 10, and 20 years, respectively, using a single-patch technique.[12] Freedom from late reoperation in the same cohort was estimated at 97 ± 4%,

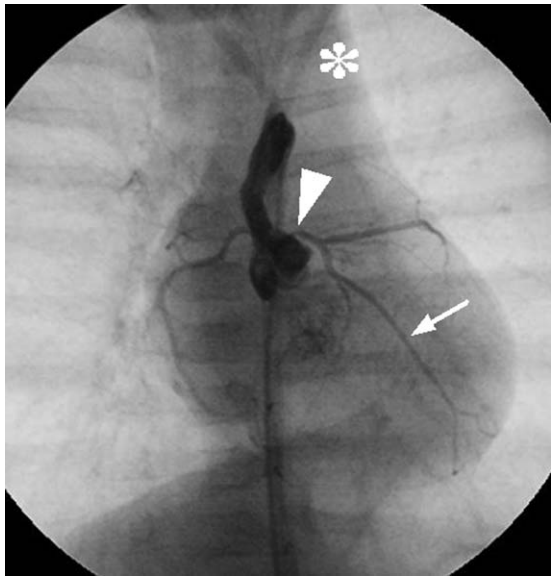

FIGURE 1 Multiple arterial stenoses in Williams syndrome. An anterior-posterior projection angiogram demonstrates severe supravalvar aortic stenosis. There is coronary ostial stenosis (arrowhead) and diffuse stenosis of the coronary arteries (arrow). The head and neck vessels are diffusely narrow (asterisk)

93 ± 7%, and 86 ± 10% at 5, 10, and 20 years, respectively. A more recent study of 28 WS patients cites 86% survival at 5, 10, and 15 years after repair with single and 3-patch repairs of SVAS.[13] In patients with the diffuse type of SVAS, as many as 35% will require reintervention.[14]

Transcatheter intervention is most commonly employed for peripheral PAS.[5] Geggel et al. have reported central pulmonary arteries do not respond well to balloon angioplasty, but the intrapulmonary segments do, especially when performed in a serial manner.[15] Transcatheter vascular stenting has been used infrequently in patients with WS.[5,15,16] Rapid failure of arterial stenting in patients with WS has been reported, and the resected arterial wall demonstrates extensive fibrosis and intimal and smooth muscle cell proliferation.[17,18]

1.3 | Sudden cardiovascular collapse

Sudden cardiac death in a patient with WS was first reported by Rashkind et al.[19] The risk of sudden cardiac death is reported to be 25-to-100 times greater than that in the general population.[9,20] The etiologies of the increased risk of sudden death have not been definitively determined. Cardiovascular collapse and death in the peri-procedural and peri-anesthetic setting has occurred in a significant number of patients.[21] The risk of sudden cardiovascular collapse appears to be greater in the presence of bilateral outflow tract obstruction,[16] especially when coronary arterial stenosis is present.[9] Coronary ostial stenoses, which can severely limit myocardial blood flow, occur in up to 45% of all surgical patients with SVAS (with and without WS).[22] It is possible that the report of severe coronary ostial stenosis in 5% of all patients with WS is an underestimate, as those data were derived only from surgical candidates.[8] Nevertheless, sudden death has been reported in the absence of autopsy evidence of outflow tract or coronary obstruction.[16,23]

Prolongation of the corrected QT interval (QTc) on electrocardiogram has been shown to be present in 13% of patients with WS, and may contribute to the increased risk of sudden death.[23] In addition, ventricular ectopic complexes and arrhythmias have been correlated with the presence of QTc prolongation in patients with WS, which may indicate a role for microvascular ischemia in the QTc prolongation.[24]

1.4 | Proposed mechanisms of cardiovascular collapse in Williams syndrome

While the complete etiology of the increased risk of sudden cardiovascular collapse in WS has not been elucidated,[8] it is clear the risk is

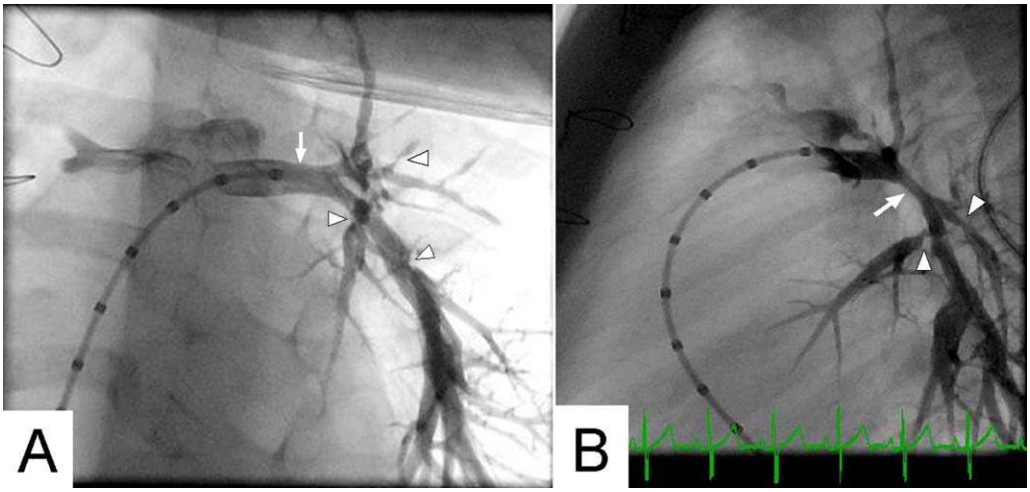

FIGURE 2 Peripheral pulmonary artery stenosis. (A) An anterior-posterior projection angiogram of the left pulmonary artery demonstrates severe peripheral pulmonary artery stenosis. The left pulmonary artery is diffusely stenotic (arrow) with multiple significant stenoses demonstrated at the origins of peripheral arteries (arrowheads). (B) A lateral projection angiogram in the left pulmonary artery taken at the same time as the image in frame A demonstrates diffuse stenosis (arrow) with severe stenosis at the origins of the branch pulmonary arteries (arrowheads)

TABLE 1 Preprocedural management of patients with Williams syndrome

Cardiovascular assessment within 1 mo of procedure[a]
Consider hospital admission the night prior to the procedure to insure intravenous access and ability to maintain fluid hydration, especially in patients <5 years of age
Preprocedural evaluation by an anesthesiologist
Limit period without fluid intake to 2 h
Begin maintenance intravenous fluid replacement if period of NPO is to be >2 h
Coordinate procedure to be the first case of the day
Electrocardiogram within 2 h of start of the procedure

Abbreviation: NPO, nil per os.
[a]Assessment should include those steps previously published.[8]

increased in the peri-procedural setting, especially in the setting of anesthesia.[21] Because acute cardiovascular collapse in patients with WS seems most likely to be seen in patients with SVAS and coronary ostial stenosis, decreased myocardial perfusion with resultant ischemia has been suggested as an etiology.[21] In addition, because sudden decompensation events are prone to occur in patients with bilateral outflow tract obstruction,[16] microvascular ischemia in the setting of biventricular hypertrophy must be considered, a finding suggested by the correlation of ventricular ectopic complexes and QTc prolongation in patients with WS.[24]

2 | PREPROCEDURAL MANAGEMENT

2.1 | Recent cardiologist assessment

Because cardiovascular abnormalities are often a driving force for a given procedure in patients with WS, and because the nature and degree of involvement can evolve sometimes rapidly, an evaluation by a cardiologist within 1 month of the procedure should be considered. An unremarkable, recent anesthetic course prior to a procedure does not ensure the absence of current cardiovascular insufficiencies. A cardiologist will be able to assess the patient's current cardiovascular involvement, including structural and electrocardiographic abnormalities. Ironically, assessment of the cardiovascular status of the patient often requires the use of sedation or anesthesia, thereby creating a clinical quandary, and numerous reports of cardiac arrest have occurred during these assessments.[25,26] Recommendations on the management of cardiovascular disease in WS have been published previously.[8] Table 1 outlines our recommended preprocedural management strategy.

Obtaining an electrocardiogram should be considered shortly before—a couple of hours—the planned procedure. This will allow for a final determination of the rhythm, electrical conduction and repolarization (QTc) prior to the administration of medications that may alter conduction during anesthesia.

2.2 | Fluid management

For many patient populations, whether syndromic or nonsyndromic, preprocedural preparation begins the evening before the planned procedure, most notably as instructions for fluid intake and fasting. The American Society of Anesthesiologists Committee on Standards and Practice Parameters recommended a minimum fasting period of 2 h for clear liquids for healthy patients who are undergoing elective procedures[27] (Table 2). Modifications to these recommendations are necessary for conditions that may contraindicate enteral intake (e.g., bowel obstruction and severe gastroesophageal reflux) or require longer fasting intervals (e.g., conditions that may cause a delay in gastric emptying).

Careful consideration must be given to the preprocedural fluid status of patients with WS. Despite the minimum fasting period of only 2 h for clear liquids, it is still possible for many patients without WS to be nil per os (NPO) for 8–12 h prior to a procedure. In the otherwise healthy patient with WS, such long periods with no enteral intake may exist for the simplicity of instruction or for the convenience of potentially moving the procedure to a slightly earlier time. In contrast, long periods without hydration might occur simply because the patient with WS is not offered or encouraged to maintain enteral hydration with clear liquids. However because of the type of cardiovascular abnormalities most often seen in WS, namely arterial stenoses, and because acute cardiovascular collapse events often seem to be precipitated by hypotensive episodes,[21] extended periods without fluid intake should be avoided in WS. Maintaining adequate fluid hydration helps preserve myocardial preload and myocardial contractility, either of which may be compromised by sedatives or anesthetics that can impair the sympathetic nervous system responses, increase venous capacitance,

TABLE 2 Summary of fasting recommendations[27]

Ingested material	Minimum fasting period
Clear liquids	2 h
Breast milk	4 h
Infant formula	6 h
Nonhuman milk	6 h
Light meal	6 h

These recommendations are applicable to healthy patients of all ages who are to have elective procedures (but do not include women who are in labor). Light meals may include nonfatty solids such as toast and clear liquids. Meals that include foods that may lengthen gastric emptying time such as meats, fatty foods, or fried foods may require longer subsequent fasting periods of 8 h or more.

reduce systemic vascular resistance, or directly depress myocardial contractility. The overall goal in patients with WS is to minimize the NPO time and resultant relative dehydration as much as possible. Our practice is to administer maintenance intravenous (IV) fluids if a patient is to be NPO for longer than 2 h. In addition, coordinated efforts are undertaken to assure the patient is the first case of the day to reduce the chances of unexpected delays of the procedure and consequently longer fasting intervals. The highest risk patients (i.e. bilateral outflow tract obstruction) may benefit from preprocedural admission and IV hydration to further negate NPO effects.

2.3 | Electrolytes and metabolism

Generally, electrolyte dyscrasias are uncommon in patients with WS with the marked exception of hypercalcemia, which is reported to occur in 5–50%.[3] If present, hypercalcemia tends to be more pronounced in patients with WS during infancy.[28,29] Because of this risk of hypercalcemia in early childhood, regular evaluations of the serum calcium are recommended.[30] It is our practice to evaluate the serum calcium, ionized calcium and albumin prior to procedures requiring anesthesia. In addition, due to the effects of both hypercalcemia with subsequent hypercalciuria, as well as renovascular involvement in patients with WS, screening of the renal function with a serum BUN and creatinine are regularly performed in the preprocedural period.

Hypothyroidism occurs in 15–30% of patients with WS[31,32] and often has a subclinical presentation.[3] Clinical hypothyroidism may precipitate a number of unwanted physiological effects detrimental to patients undergoing anesthesia and surgery. Some of the effects of hypothyroidism include decreased myocardial function, decreased spontaneous ventilation, reduced plasma volume, anemia, hypoglycemia and impaired hepatic drug metabolism.[33,34] To avoid these effects of hypothyroidism, some of which could be significantly detrimental in patients with WS, preoperative screening of thyroid function has been recommended.[35] The general recommendations for thyroid screening are for biennial evaluation.[30] If no such screening has been obtained and can be verified, or if there is clinical evidence of hypothyroidism, our practice is to insure that both the thyroid stimulating hormone (TSH) and free T4 are checked and are normal prior to the anesthetic administration. If the patient is found to have hypothyroidism, appropriate therapy should be initiated prior to the planned procedure.

2.4 | Impaired glucose tolerance and type 2 diabetes mellitus

Patients with WS, irrespective of age, often manifest impaired glucose tolerance, as well as type 2 diabetes mellitus.[36,37] Adjustment of long- and intermediate-acting insulin preparations is necessary for the fasting period. We typically reduce the evening dose of long- or intermediate-acting insulin preparations by half, and then check the blood glucose in the morning prior to the procedure. Regular or short-acting insulin is given as needed after checking the morning glucose level. In addition, scheduling diabetic patients early in the day can simplify their glucose management.

2.5 | Antibiotic prophylaxis

Antibiotic prophylaxis is unnecessary in the large majority of patients with WS. With the exceptions of those who have undergone surgery or transcatheter device interventions within the last 6 months, those with residual defects after surgical closure of atrial or ventricular septal defects, and the very rare patient with cyanotic heart disease, antibiotics are no longer recommended.[38]

2.6 | Management of preprocedural anxiety

Significant anxiety and irritability are prominent features in patients with WS, occurring in over 80%.[39] Phobias are also common, including fears of loud noises, doctors or dentists, and blood tests or injections.[40] These unique psychosocial features of WS can be mitigated by using distraction, reframing and elements of hypnosis.

Preprocedural establishment of rapport and trust with care providers helps allay some of the fear and anxiety in patients with WS. In this situation, their hypersocial personalities facilitate the development of trust. Keeping syringes, needles, and equipment out of sight will prevent patients from becoming overly anxious and suspicious of the care team.

Patients with WS have a unique auditory profile. Auditory aversions such as odynacusis or auditory allodynia are common, resulting in easy disturbances of these patients from loud noises or other noises that may not be disturbing to most people.[41] A noise-free environment should be sought with specific attention paid to minimizing procedural noise (i.e. noise from instruments). Conversely, many patients with WS have an affinity for music, which can be utilized to lull them into relaxing.

Many patients with WS may respond well to nonpharmacological techniques, but some will also require a light anxiolytic or sedative in the preoperative period. For those patients averse to placement of an IV cannula, orally administered midazolam or diazepam are usually effective in relieving anxiety without adverse effects on blood pressure or heart rate.[42,43] A pharmacobehavioral approach combining distraction techniques with pharmacological anxiolysis is often very effective.[44] Intranasal dexmedetomidine, as another option, can induce a sedated sleep without tachycardia or significant hypotension.[45] This may be a viable alternative for patients who have not tolerated midazolam previously. Either dexmedetomidine or midazolam can help prevent anxiety-related tachycardia from occurring at the time of anesthesia induction,[43] averting tachycardia-related increases in myocardial oxygen requirements at the same time myocardial blood flow has the potential to be reduced from coronary artery stenosis and/or short diastolic filling times.

3 | PREPROCEDURAL RISK STRATIFICATION FOR ANESTHESIA ADMINISTRATION

Robust data on which to base procedural risk stratification algorithms are limited for patients with WS. As mentioned previously, Bird and

colleagues first reported the increased risk of sudden death in patients with WS, and they identified coronary artery stenosis and bilateral outflow tract obstruction as risk factors.[9] Subsequently, other investigators have corroborated those risk factors.[16,21] Matisoff and colleagues recently used these data and their own experience to create a risk classification system for anesthetic administration in patients with WS.[46]

Recent data from the Society of Thoracic Surgeons database have not only further corroborated the findings of Bird et al., but have also identified other risk factors for major adverse cardiovascular events, including death, cardiac arrest and mechanical circulatory support.[47] In that relatively large study, risk factors for such events in association with cardiac surgery included surgery to repair bilateral outflow tract obstruction; surgery involving any coronary artery repair; preoperative mechanical ventilation; younger age at the time of surgery; lower weight at the time of surgery; and, though the numbers were too small to reach statistical significance in the model, preoperative arrhythmia. We have used these important data, other data in the literature, and our large experience with WS to develop an expanded risk stratification system for anesthetic administration in patients with WS (Table 3).

4 | PROCEDURAL ANESTHESIA AND SEDATION

Patients with WS will present for a range of procedures requiring anything from mild anxiolysis to general anesthesia. The choice of level of sedation or anesthesia depends on patient and procedural factors. The patient must be able to cooperate for the procedure, such as remaining still for imaging studies or relaxing for dental examinations. Procedures that could be painful usually require analgesia and sedation or pharmacological hypnosis. In other cases such as surgical procedures, control of ventilation and/or muscle relaxation may be necessary.

Given that WS has been identified as a significant risk for sudden cardiac death under sedation and anesthesia,[25] providers may be hesitant to give any anxiolytics or anesthetics. Unfortunately, such an omission can result in unintended consequences such as failed procedures or inadequate imaging studies due to lack of patient cooperation. These experiences can be terrifying to the patient with WS, resulting in further anxiety at the next medical care encounter. Such anxiety is not innocuous—an increased stress response increases myocardial work that can be disastrous in patients who may have limited myocardial blood supply. Omission of an appropriate anxiolytic prior to a general anesthetic can also increase the risk for emergence delirium, further increasing myocardial work in the postanesthetic period.

For the most nonstimulating procedures, such as echocardiograms, radiological imaging, or dental examinations, the methods described to prepare the environment, establish rapport, and perhaps induce a mild pharmacological anxiolysis may be enough to allow for patient cooperation. For the more fearful patient, or those having potentially painful or invasive surgical procedures, an increased depth of sedation/anesthesia, such as moderate-to-deep sedation or general anesthesia, might be indicated.

For any anesthetic technique in a patient with WS the overall goal is to maintain hemodynamic stability by maximizing myocardial oxygen supply and minimizing myocardial oxygen demand. Preservation of cardiovascular function requires thoughtful consideration of the type of anesthesia/sedation required and the properties of the anesthetic agents available. Specifically, anesthetic agents at dosages that do not cause significantly increased myocardial oxygen demand and/or reduced coronary artery perfusion are ideal. Techniques that might induce significant myocardial depression, tachycardia, or decreased cardiac preload or systemic vascular resistance should be avoided. Advantages and disadvantages exist for every anesthetic agent/drug for the

TABLE 3 Risk stratification for anesthetic administration in patients with Williams syndrome

Low risk	Moderate risk	High risk
Age >20 years	Hypertension	Age <3 years
No cardiac involvement greater than mild supravalvar or branch pulmonary artery stenosis	Moderate supravalvar or branch pulmonary artery stenosis	History of adverse cardiovascular event
Normal ECG	Mild bilateral outflow tract obstruction	Preprocedural arrhythmia
No renal artery involvement	Renal artery stenosis	Bilateral outflow tract obstruction of ≥ moderate severity
	Renal dysfunction	SVAS gradient of ≥40 mmHg and the presence of left ventricular hypertrophy
	QTc on ECG >450 ms but <500 ms	Coronary artery involvement
	Airway abnormalities, lung disease, or severe gastroesophageal reflux	Diffuse stenosis of the thoracic aorta
		≥Moderate left or right ventricular hypertrophy Symptoms or ECG signs of ischemia
		QTc on ECG ≥500 ms

Abbreviations: ECG, electrocardiogram; ms, milliseconds; QTc, corrected QT interval on ECG.
Adapted from Matisoff et al.[46]

TABLE 4 Summary of peri-procedural pharmacologic agents

Drug class	Examples	Advantages	Disadvantages	Summary
Vagolytic drugs	Atropine Glycopyrrolate	Maintain heart rate Useful for reversal of neuromuscular blocking drugs	May cause a supra-physiologic heart rate increase (increased myocardial oxygen demand and decreased diastolic perfusion time)	Best avoided (especially in combination with sympathomimetic activity drugs)
Neuromuscular blocking agents	Pancuronium[a] Rocuronium[a] Vecuronium Cisatracurium Atracurium Mivacurium	May be helpful in lowering minimal alveolar concentration values	[a]May have a deleterious effect by increasing heart rate	Best avoided (especially in combination with other vagolytic agents)
Induction agents	Propofol[b] Thiopental[b] Ketamine[c] Etomidate	Rapid induction of anesthesia	[b]May have deleterious cardiovascular effects (increased venous capacitance, decreased systemic vascular resistance and direct myocardial depression [c]May have a deleterious effect by increasing myocardial oxygen demand by increasing heart rate and blood pressure	[b]Best avoided altogether or given in small doses with a direct-acting alpha antagonist
Benzodiazepines	Midazolam Lorazepam Diazepam	Reliable amnestic agent Hemodynamically stable when used as a single agent	May cause hypotension and decreased systemic vascular resistance when used at higher doses or in combination with other medications	
Potent volatile anesthetic agents	Sevoflurane Isoflurane Desflurane	Titratable effects	May cause reduction in systemic vascular resistance and resultant hypotension Desflurane can cause an increase in heart rate	May be used judiciously. Hypotension must be treated aggressively.

patient with WS (Table 4). Selection of a combination of anesthetic/sedative agents in a "balanced" technique is optimal.

4.1 | Choice of sedation versus anesthesia

Sedation and anesthesia represent somewhat arbitrarily defined points on a continuum of induced states of altered consciousness and reduced sensitivity to pain and noxious stimuli. The appropriate point on the continuum must be selected for the patient with WS in a fashion that does not adversely impact hemodynamics, especially the myocardial oxygen supply and demand ratio. While it may be inconsequential to utilize a brief, mask-administered sevoflurane general anesthetic in a healthy patient without WS, it can be disastrous for the high-risk patient with WS who otherwise appears well outwardly; sevoflurane may result in precipitous decreases in the systemic vascular resistance with resultant hypotension. The sedation/anesthetic technique must be chosen to accommodate the needs of the procedure, as well as the physiologic limitations of the patient. In general, the goal is to maintain the hemodynamic state by providing the minimum effective level of sedation/anesthesia. It is imperative that the provider be well versed in the effects of the anesthetic agents and be prepared to treat hemodynamic perturbations aggressively.

4.2 | Monitoring

While the medication administration is carefully titrated to the procedure and cooperation of the patient, monitoring of these patients must not be overlooked, regardless of the depth of the anesthetic. Standard monitoring for sedation and anesthesia, based on American Society of Anesthesiologists guidelines, includes pulse oximetry, continuous electrocardiography, intermittent blood pressure measurement, temperature, and when at all possible, measurement of end-tidal carbon dioxide exhalation.[48] Lesser monitoring reduces the providers ability to recognize and respond quickly to signs of hemodynamic instability, reduced cardiac function, cardiac ischemia, or impaired ventilation/breathing. Monitoring of the electrocardiographic ST segments, especially when a 5-lead electrocardiograph is employed, can be useful in detection of coronary ischemia.

Because stenoses can occur in arteries supplying the limbs, adequate arterial flow must be ensured to the extremity being used for blood pressure monitoring, whether using a noninvasive cuff or invasive arterial catheter. Four-extremity blood pressure measurements, which may have to be done after sedation and/or induction, are recommended to help determine the presence of stenosis and the accuracy of clinical blood pressure measurements. The target for blood pressure in a sedated patient with WS should generally be similar to the blood pressure measured in that patient while at rest and calm, and should be measured in the same extremity with the same measurement modality (i.e. size and location of blood pressure cuff or invasive arterial monitoring catheter). In the event of discrepancies between the four-extremity blood pressure measurements, the extremity with the highest mean blood pressure may be closest to the aortic blood pressure. However, in the setting of SVAS, care must be taken to assess if blood pressure discrepancies in the upper extremities are due to stenoses or are the result of the Coanda effect.[49] A widened pulse pressure may help

differentiate the two as it can indicate proximal arterial stenosis in a given extremity. In the case of a widened pulse pressure, the measurement should be compared with one from another site.

In those patients with WS who have decreased cardiac function, or who are otherwise deemed to be high-risk, additional less common noninvasive modalities may be beneficial. Transesophageal echocardiographic monitoring of cardiac function can provide real-time assessment of myocardial performance during the procedure,[50] and may be especially useful for procedures requiring deeper levels of anesthesia or those associated with greater hemodynamic disturbances. Near-infrared spectroscopy (NIRS) can be a useful noninvasive monitor of tissue oxygenation to the brain and somatic areas.[51] The bispectral index monitor allows for estimation and titration of the depth of anesthesia or sedation such that adequate but not excessive levels of sedatives and anesthetics are achieved.[52–54]

4.3 | Induction of anesthesia

The anesthetic plan begins with techniques for anxiolysis as described above. Topical local anesthetics (e.g., EMLA™, ELA-Max™, and Synera™) or other needleless local anesthetic applications (e.g., Zingo™ and J-Tip™) may be applied to areas likely to be used for IV catheter placement.[55] If IV access can be obtained prior to induction of anesthesia, early replacement of fluid deficits estimated from the NPO time can be initiated before anesthesia induction. Fluid replacement can offset a reduction in preload following the NPO period and subsequent anesthetic agents' effects. Hereafter, anesthesia induction can be accomplished in a gradual, balanced manner, allowing time to respond to more gradual hemodynamic consequences such as unintended hypotension and/or tachycardia. In the event mask-induction of general anesthesia is required prior to IV catheter insertion, we schedule the patients to ensure the cardiac anesthesiologist has an assistant skilled in vascular access or airway management such that expedient treatment of unintended hemodynamic effects can be quickly remedied.

Venipuncture causes severe anxiety in many patients with WS. In the United States, many children who undergo general anesthesia in a hospital have an IV catheter placed after induction of anesthesia with sevoflurane/nitrous oxide anesthesia. Such an approach in a patient with WS can result in cardiac arrest due to systemic hypotension and reduced coronary artery perfusion.[56] Unfortunately, such acute cardiovascular collapse can occur in patients with WS even in the most mundane of outpatient sedation settings, including routine dental care.[56] Some of the most common therapies used for dental sedation and anxiolysis include nitrous oxide and propofol. Nitrous oxide has been reported to be a myocardial depressant resulting in moderate decreases in the mean arterial pressure and left ventricular systolic function.[57] However, when administered as a single agent, nitrous oxide may preserve systemic blood pressure by stimulatory effects on the sympathetic nervous system.[58] In this regard, nitrous oxide (50% N_2O/50% O_2) may be a good choice when used alone for stage 1 anesthesia in patients with WS.

Propofol has also been shown to decrease mean arterial pressure —a result of vasodilation, decreased systemic vascular resistance, and inhibition of the sympathetic response,[59,60] effects that can be catastrophic in a patient with WS. In addition, propofol augments vagal tone and has been associated with heart block, bradycardia,[61] and asystole[62] when used in combination with agents that decrease chronotropic function, such as fentanyl or succinylcholine. We generally refrain from the use of propofol in all but the most controlled of environments.

Because of the potential for adverse hemodynamic consequences of sedation/anesthesia, our standard practice is to perform any procedure requiring anxiolysis or sedation for patients with WS under the direct supervision of a cardiac anesthesiologist familiar with the physiological aberrancies common in WS. Many centers may not have dedicated cardiac anesthesiologists, and in those situations, pediatric anesthesiologists are the providers most familiar with patients with WS and should be the ones guiding the procedural management of the patient. However, we recommend that consultation with a cardiac anesthesiologist with experience with patients with WS be sought prior to the case to ensure an appropriate plan is in place and that balanced anesthetic induction techniques are used to avoid high doses of any single anesthetic agent.

Unfortunately, there is no optimal recipe for sedation/anesthesia that is suitable for all patients with WS. As previously shown in Table 4, there are advantages and disadvantages to each class and tailoring of the regimen is imperative. For instance, while high-dose sevoflurane or propofol could have disastrous hemodynamic consequences due to the individual properties of these agents, judicious combinations of lower doses of these drugs with other agents can provide good anesthetic states. Used in balanced combinations in adequate but not excessive doses, effective and safe levels of sedation/anesthesia can be obtained.

In general, the goal of sedation/anesthesia determines the technique. For example, a nonstimulating, painless procedure may be accomplished with a single agent sedative alone, such as with no more than 0.5 mg/kg of oral midazolam or perhaps with inhaled 50% N_2O/50% O_2. A longer, more invasive procedure may require general anesthesia, muscle relaxation and subsequent control of ventilation.

4.4 | In-hospital sedation

As stated previously, patients with WS often require sedation for noninvasive procedures and diagnostic tests. Such procedures may include, but are not limited to simple venipuncture, computed tomography (CT), magnetic resonance imaging (MRI), dental exams and echocardiograms. For any anesthetic agent, even mild sedation, it is essential that the provider has the ability to monitor the patient closely and respond to any hemodynamic changes. This may require that procedures normally done in a clinic setting be brought to the operating room or a dedicated procedure room so adequate monitoring (see Section 4.2) is ensured.

For many noninvasive procedures, oral midazolam and/or intranasal dexmedetomidine may be sufficient. However, in all but the least stimulating and brief procedures, it is advisable to place an IV catheter to be able to respond to hemodynamic instability and provide IV fluids to replace deficits due to fasting and ongoing losses.

4.5 | General anesthesia

Many patients with WS will present for procedures requiring deep sedation or general anesthesia. These may include cardiac surgery, MRI, endoscopies, dental rehabilitation, cardiac catheterizations or a number of other surgical procedures. Preparation of the patient, minimization of NPO times, monitoring and induction should be carried out as outlined previously.

The overall goal for patients with WS is to achieve an adequate plan of anesthesia while maximizing myocardial oxygen supply and minimizing myocardial oxygen demand. First, the anesthetic must be titrated to the procedure. In a case with minimal stimulation but requiring a motionless patient (e.g. MRI), use of a neuromuscular blocking agent may be advised to lower overall anesthetic requirements and minimize the hemodynamic impact of higher anesthetic agent requirements. Second, the patient must be kept euvolemic—any intravascular loss (e.g. blood loss, urine output, and insensible losses) must be monitored closely and replaced carefully. Finally, the anesthetic depth must be easily titratable. This usually requires the use of short-acting agents that may be manipulated easily as the patient's status changes.

4.6 | Cardiovascular procedures

Patients with WS often undergo multiple cardiovascular procedures ranging from a noninvasive echocardiogram to a complicated cardiac surgery with cardiopulmonary bypass. General anesthesia is required for many of these procedures. Apart from the general considerations of anesthesia noted above, there are several specific concerns during cardiac procedures, especially with regard to cardiac catheterization. Arrhythmias, though usually short-lived, are common during cardiac catheterizations due to wire manipulations within the heart. However, even short runs of an unstable tachyarrhythmia, whether supraventricular or ventricular, may be poorly tolerated in this population. These arrhythmias may lead to myocardial ischemia, which can exacerbate myocardial irritability and arrhythmogenesis, and can worsen myocardial function.

Cardiac catheterizations are often performed in these patients to look specifically at the coronary arteries and ventricular outflow tracts, as well as to perform balloon angioplasty of the pulmonary arteries. Injection of angiographic contrast media into a stenotic coronary artery may cause acute myocardial ischemia, as the contrast material has no oxygen carrying capacity. This brief, but significant episode of ischemia may have catastrophic consequences leading to arrhythmias, myocardial depression and cardiovascular collapse.

4.7 | General surgical procedures

In addition to cardiovascular procedures, many patients with WS will present for various general surgical procedures ranging from simple tympanostomy tube placement to complex posterior spinal fusion. While the case severity may vary, the provider must maintain a high level of vigilance, and monitoring should be tailored to the individual case as previously discussed (see Section 4.2).

5 | POSTPROCEDURAL MANAGEMENT

Until the patient with WS has recovered to near baseline cognitive function after anesthesia/sedation, monitoring should be continued with ECG, pulse oximetry, and at least intermittent blood pressure measurement. Electrocardiographic ST segments should remain near baseline after the stimulation of the procedure has ended. Perfusion pressure can be reduced after procedural stimulation has ended and residual anesthetic or narcotic remains. In such a circumstance, blood pressure should be augmented to preprocedural levels if there is evidence of hypotension or myocardial ischemia (ST segment changes, persistently high lactic acid levels, metabolic acidosis, etc.).

Because of the aforementioned issues with anxiety, patients with WS may be comforted by the presence of familiar guardians soon after regaining consciousness and awareness of their surroundings.

6 | SUMMARY

Anesthesia and sedation for the patient with WS requires careful preprocedural evaluation of the patient's current cardiovascular condition. Consultation with the patient's cardiologist is essential. Preprocedural preparation to reduce fear and anxiety will reduce cardiovascular stress, while careful preprocedural hydration allows for adequate cardiac preload during induction of anesthesia or sedation. Careful, balanced titration of sedatives and anesthetic agents is imperative such that effective, but not excessive, levels of anesthesia and sedation are rendered without increasing myocardial oxygen requirements or reducing coronary artery perfusion. Attention to monitoring is essential to detect and prevent potential myocardial ischemia that could result from lowered systemic blood pressure due to reduced cardiac preload, tachycardia-related reduction of cardiac filling, anesthetic agents with myocardial depressant effects, and reduced systemic afterload. Monitoring should be continued until the patient has regained reasonable cognitive functioning and awareness. Such attention to detail enhances the safety and effectiveness of anesthesia and sedation for the patient with WS, and will prevent acute cardiovascular events in these patients.

CONFLICTS OF INTEREST

None of the authors have any conflicts of interest pertaining to this manuscript.

AUTHOR CONTRIBUTIONS

R. Thomas Collins, II, MD: Manuscript conception and design, manuscript authorship, approval of article.

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Justin T. Hamrick, MD: Manuscript design, manuscript authorship, approval of article.

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