Congenital Supravalvular Aortic Stenosis and Sudden Death Associated with Anesthesia: What's the Mystery?

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Patients with congenital supravalvular aortic stenosis and associated peripheral pulmonary artery stenoses, the majority of whom have Williams-Beuren syndrome, are inherently at risk for development of myocardial ischemia. This is particularly true in the setting of procedural sedation and anesthesia. The biventricular hypertrophy that accompanies these lesions increases myocardial oxygen consumption and compromises oxygen delivery. In addition, these patients often have direct, multifactorial compromise of coronary blood flow. In this article, we review both the pathophysiology of congenital supravalvular aortic stenosis and the literature regarding sudden death in association with sedation and anesthesia. Recommendations as to preoperative assessment and management of these patients are made based on the best available evidence.

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Sudden death occurs in patients with congenital supravalvular aortic stenosis (SVAS) associated with Williams-Beuren syndrome (WS) and nonsyndromic SVAS at a rate higher than the general population. In addition, it is generally acknowledged that SVAS patients are at increased risk of sudden death when undergoing diagnostic or surgical procedures. We will review and analyze the literature addressing sudden death in the periprocedural and perioperative period in these patients. In addition, we will review the literature regarding the role of anesthesia and sedation in the genesis of these events and discuss the management of these patients.

PATHOPHYSIOLOGY OF CONGENITAL SVAS

The pathological features of congenital SVAS are demonstrated in Figures 1 and 2 and in Video Loops 1 and 2 (available at www.anesthesia-analgesia.org). The vast majority of cases of congenital SVAS are associated with WS. WS has an incidence of approximately 1:20,000 live births and is characterized by the presence of congenital SVAS in association with mental retardation, distinctive personality and behavioral traits, elfin facies and, in some instances, transient neonatal hypercalcemia.[1–3] Approximately 80% of patients have peripheral pulmonary artery stenoses as well. Nonsyndromic congenital SVAS is much less common, lacks the cognitive, behavioral and phenotypic abnormalities of WS, and occurs in a familial autosomal dominant form and in sporadic isolated cases. In addition, rare instances of isolated SVAS secondary to aortic hypoplasia and hyperplastic atherosclerotic plaques have been reported in association with homozygous familial hypercholesterolemia.[4]

It is now recognized that WS is the result of deletion of approximately 1.5 megabases of chromosome 7q11.23.[5,6] This deletion involves several genes, including the elastin gene. Elastin gene encodes for the elastin precursor, tropoelastin, which polymerizes and is laid down as concentric rings alternating with arterial smooth muscle cells during early development.[7] A number of different mutations leading to generation of null alleles in the gene encoding for production of elastin have been identified in patients with familial and sporadic forms of SVAS.[6,7] In patients with WS, it is the deletion of the other neighboring genes that is most likely responsible for the features of the syndrome other than SVAS and peripheral pulmonary artery stenoses.[7]

The vascular features of congenital SVAS are most accurately characterized as an elastin arteriopathy. A large quantity of elastin is normally present in the media of the great vessels, whereas smooth muscle and collagen are the primary components of smaller arteries. Smooth muscle cells from patients with isolated SVAS produce only 50% of the elastin produced by normal cells, whereas smooth muscle cells from patients with WS produce only 15% of the normal quantity of elastin.[7] The result is an arterial media with increased number of hypertrophied smooth

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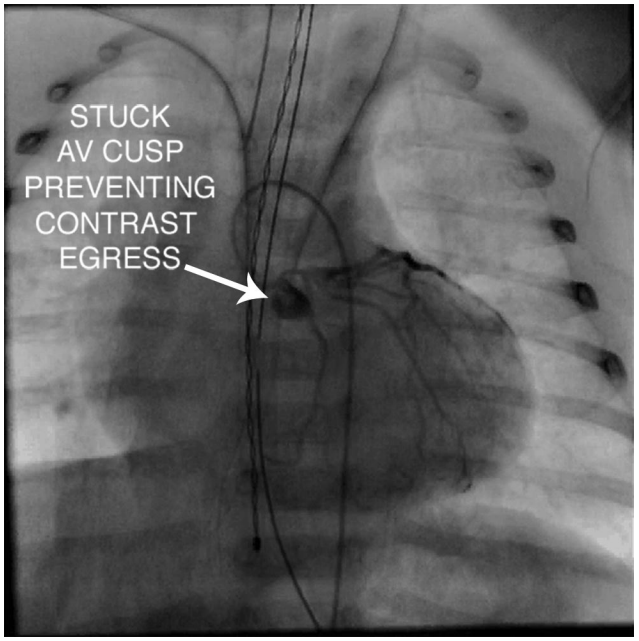

Figure 1. Anteroposterior projection of a left coronary artery angiogram demonstrating normal proximal and distal coronary anatomy with retention of contrast material in the left sinus of Valsalva due to adhesion of the left aortic valve leaflet to a ridge of tissue at the sinotubular junction (arrow).

muscle cells, increased collagen content, and reduced amounts of elastin that is largely in the form of broken and disorganized elastin fibers.

The normal presence of elastin is responsible for the distensibility of the aorta during systole and its subsequent recoil during diastole. This allows storage of hydrodynamic energy during systole and its release during diastole, a phenomena known as the windkessel effect. Loss of the windkessel effect, as occurs normally with aging, produces a wide pulse pressure with elevated systolic and reduced diastolic aortic pressures.[8] In addition, loss of aortic distensibility results in a reduction in the diastolic component of phasic coronary blood flow.[9] Although the loss of aortic distensibility alone is sufficient to elevate left ventricular (LV) afterload, the major impedance to LV ejection in SVAS is the development of obstructive aortic lesions. The reduced net deposition of arterial wall elastin leads to increased proliferation of arterial wall smooth muscle cells resulting in multilayer thickening of the media of large arteries and subsequent development of obstructive hyperplastic intimal lesions.[7] As a result, a characteristic hourglass narrowing of the aorta develops at the sinotubular junction; in approximately 30% of cases, there is diffuse tubular narrowing of the ascending aorta, often extending to the arch and the origin of the brachiocephalic vessels.[10,11] There may also be localized stenoses in the renal and mesenteric arteries.[11]

Although peripheral pulmonary artery stenoses are characteristically associated with SVAS, it is not uncommon for there to be central pulmonary artery (pulmonary artery proximal to the hilum) stenoses as well. The natural history of these pulmonary artery lesions is one in which there is a lessening in severity throughout childhood and adolescence.[12,13] Nonetheless, in approximately 40% of WS patients, there is severe pulmonary stenoses and right ventricular pressure overload and hypertrophy in conjunction with SVAS and LV pressure overload and hypertrophy.[11] These patients may have right ventricular systolic pressures as high 200 mg Hg and right ventricular to descending aortic pressure ratios as high as 2.0.

The aortic valve may also be pathologically involved in SVAS, creating an additional source of LV outflow tract obstruction. A tissue ridge at the sinotubular junction is the usual location of aortic wall constriction, and, importantly, it is also the peripheral attachment point of the aortic valve commissures. Partial adhesion of the valve leaflet hinge-points to the sinotubular junction generally makes this tissue ridge unresectable.[14] The sinotubular junction normally expands during systole, allowing the free edge of the leaflets to assume a position parallel to flow during ejection. The narrowed, nondistensible sinotubular junction renders the aortic valve leaflets redundant relative to the size of the aorta and inhibits alignment of the leaflets with blood flow. This mechanism is felt to be responsible for the development of the thickened aortic valve leaflets which have been reported in association with SVAS.[10]

Mechanical impairment of coronary blood flow is a frequent and often unappreciated feature of WS and nonsyndromic SVAS. Adhesion of the right or left aortic leaflet edge to the narrowed sinotubular junction can restrict coronary blood flow into the sinus of Valsalva. It has been suggested that the left coronary sinus of Valsalva is affected more frequently in this process than the right.[10,12] Cases of total isolation of the left and right coronary artery from the sinus of Valsalva as a result of complete fusion of a leaflet edge to a prominent sinotubular ridge have been reported.[15–17]

The presence of both ostial and diffuse left and right coronary artery stenoses must be considered as well. The etiology of direct coronary artery involvement seems to be multifactorial. The elastin arteriopathy may diffusely involve the coronary arteries while a thickened aortic wall can directly narrow the coronary ostia.[18] Displacement of the coronary ostia superiorly to a position just below the sinotubular ridge with subsequent obstruction has been reported in three cases of sudden cardiac death.[19] Coronary artery dilation and tortuosity due to exposure of the coronary arteries to high prestenotic pressures may lead to development of accelerated coronary atherosclerosis and coronary aneurysms.[20,21] It should be noted that significant obstruction to coronary blood flow with associated fatal myocardial infarction has been reported in both the presence and the absence of hemodynamically significant SVAS.[19,20,22–26] In other words, although these patients are typically followed and assessed by echocardiography, the possibility of

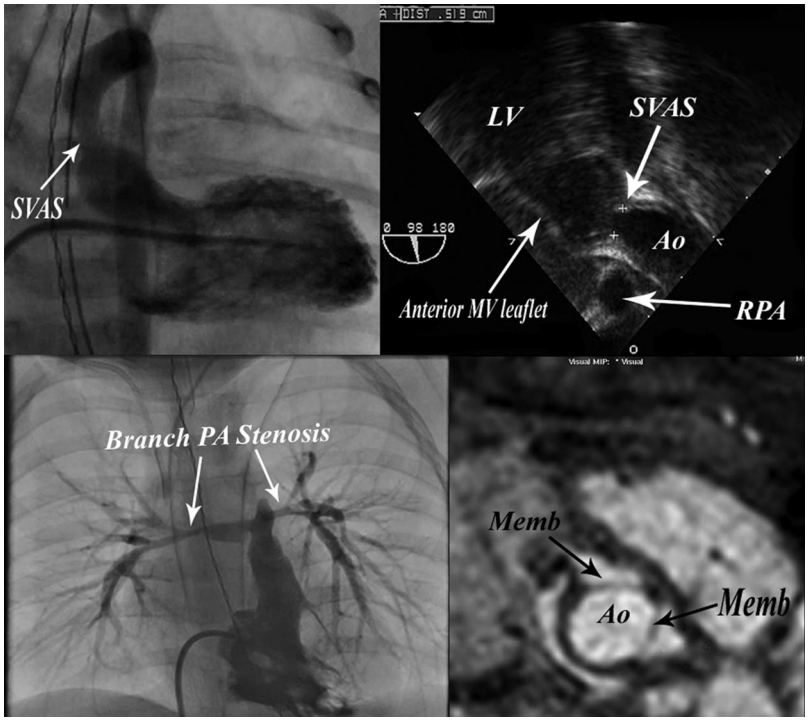

Figure 2. Top left: Anteroposterior projection of a left ventricular angiogram demonstrating significant supravalvular aortic stenosis (SVAS). Top right: Inverted transesophageal echocardiography mid-esophageal aortic valve long axis view demonstrating SVAS. Bottom left: Anteroposterior projection of a right ventricular angiogram demonstrating significant proximal branch pulmonary artery stenoses. Bottom right: Cardiac magnetic resonance image short axis view of the ascending aorta demonstrating an obstructive membrane arising from the sinotubular junction and extending in front of both the right and left coronary ostia in a patient with mild SVAS.

significant coronary obstruction via one or more of the mechanisms outlined can exist independent of the degree of arch obstruction.

Right ventricular and LV hypertrophy induced by outflow tract obstruction is a risk factor for development of subendocardial ischemia. Myocardial oxygen consumption is increased by the mass of the myocardium, the prolonged ejection phase and a high- pressure isovolumic contraction phase. Myocardial oxygen delivery is compromised by a reduced diastolic interval (prolonged ejection phase), absence of systolic coronary perfusion particularly in the right ventricle due to elevated right ventricular systolic pressure, elevated LV end diastolic pressure due to reduced LV compliance, low aortic diastolic pressure due to loss of the windkessel effect, and compression of subendocardial vessels. The presence of obstructed coronary blood flow via any of the mechanisms previously described further increases this risk.

SUDDEN DEATH AND CONGENITAL SVAS

The natural history of WS suggests that the risk of sudden cardiac death is high. The most comprehensive analysis to date involves a cohort of 293 WS patients followed for 43 yr at two institutions (for a total of 5190 patient years).[27] During this time period, 10 patients died with 5 of the deaths deemed to be both cardiac in origin and unrelated to cardiac surgical procedures. Based on this analysis, the risk of sudden cardiac death was estimated to be 1/1000 patient years as compared to 0.01–0.04/1000 patient years in the age-matched normal population.[27] In another cohort of 104 WS patients followed for a mean duration of 13 yr, 3 patients with known SVAS died suddenly after syncopal episodes.[28] There are numerous other reports of sudden cardiac death in WS patients and, in the most of these cases, myocardial ischemia was directly implicated.[19,29,30]

Although it is likely cardiac arrest is underreported in association with procedures requiring either sedation or anesthesia in patients with WS, some insight can be gained from the cases that have been reported.[19,20,22,23,26,31–33] All cases in which sudden death was clearly temporally related to administration of sedative or anesthetic drugs are summarized in Table 1. Cases involving death after cardiac surgical procedures are not included.

In the largest series of sudden cardiac death cases in WS, 19 cases were collected from multiple sources.[19] Eleven of these cases were associated with administration of sedative or anesthetic drugs for cardiac catheterization or noncardiac surgical procedures.[19] Autopsy data regarding the severity of outflow tract obstruction and coronary artery anatomy were available in 15 of 19 cases. Coronary artery abnormalities were present in 14 cases, bilateral outflow tract obstruction in 9 cases, and both abnormalities in 7 cases. The authors concluded that the presence of biventricular outflow tract obstruction in combination with coronary artery abnormalities carried the highest risk of sudden cardiac death. A consistent hemodynamic feature before the onset of cardiac arrest in this series was the development of bradycardia and hypotension. In addition, in all cases of witnessed arrest resuscitative efforts were unsuccessful. In this series, the details of sedation and anesthesia management, apart from the name of the drugs used, were not presented.

Table 1. Cases of Cardiac Arrest Associated with Procedural Sedation or Anesthesia

Pt	Age	Anesthetic agents	Location	LVOTO	RVOTO	Autopsy	Ref
1	6 wk	Not described	General OR	−	+	(Survived event) Died at home at 6 yr; ostial obstruction	19
2	9 mo	Ketamine	Cath Lab	+	−	MI, SVAS, Ostial obstruction	19
3	6 mo	Diazepam	Cath Lab			SVAS, MI, PS	19
4	10 mo	Chloral hydrate, morphine	Cath Lab	++	+	SVAS, MI, RVOTO	19
5	9 mo	Morphine, midazolam	Cath Lab	+	+++	SVAS, RVOTO	19
6	5 mo	Not described	General OR	?	?	(Survived event)	19
	2 yr	Halothane	Cath Lab	−	+++	Not performed	
7	21 mo	Meperidine, promethazine chlorpromazine	Cath Lab	++	+++	Not performed	19
8	3 yr	Sevo, N_2O, propofol	General OR	?	?	Not performed	32
9	6 yr	Meperidine, promethazine chlorpromazine	Cath Lab	?	?	Not performed	31
10	3 yr	Ketamine, pancuronium	Cardiac OR	+++	?	Not performed	31
11	18 mo	Not described	General OR	?	?	Not performed	33
12	16 mo	Not described	Cath Lab	+++	++	MI, severe SVAS, sinus of Valsalva occlusion, CA involvement	23
13	5 yr	Not described	Cath Lab	+++	−	MI, moderate SVAS, sinus of Valsalva occlusion, CA involvement	23
14	8 mo	Not described	72 hr post Cath Lab	++	+++	MI, moderate SVAS, sinus of Valsalva occlusion, CA involvement	23
15	5 yr	Not described	General OR	+++	?	SVAS, AV dysplasia	20

Pt = patient; OR = operating room; STD = ST depression; yr = year old; mo = month old; Cath Lab = catheterization laboratory; MI = myocardial infarction; SVAS = supravalvular aortic stenosis; OO = ostial obstruction; LVOTO = left ventricular outflow tract obstruction; RVOTO = right ventricular outflow tract obstruction; ECG = electrocardiogram; Ref = reference number of the reported incident; + = mild; ++ = moderate; +++ = severe; PS = pulmonary stenosis; CA = coronary artery; AV = aortic valve.

The details of sudden cardiac arrest after induction of anesthesia in a 3-yr-old, 17.3 kg male with WS were reported.[32] Preoperative echocardiographic evaluation revealed mild supravalvular aortic and pulmonary stenosis with good biventricular function without evidence of ventricular hypertrophy. The child, who was to undergo bilateral myringotomy and tubes and repair of an undescended testicle, was nil *per os* for 13 h before induction of anesthesia. After an inhaled induction with 6% sevoflurane and nitrous oxide, IV access was obtained and a bolus of 20 mL/kg of Ringer's lactate solution was administered. Propofol 30 mg and glycopyrrolate 0.1 mg were then given for placement of a laryngeal mask airway. Shortly after a single-shot caudal with 8 mL of 0.25% bupivicaine the patient developed tachycardia (120 bpm) in association with severe ST segment depression and an unrecordable arterial blood pressure. This was followed rapidly by development of bradycardia, hypotension, and pulseless electrical activity (PEA). After chest compressions and administration of atropine and epinephrine, the patient was resuscitated. After a period of stabilization, the patient again developed bradycardia, hypotension, and PEA. Resuscitation was again successful and the patient underwent cardiac catheterization the following day after stabilization overnight on infusions of epinephrine and nitroglycerin. Catheterization revealed mild to moderate SVAS (gradient not reported) and near complete occlusion of the left main coronary ostium, with further compromise of coronary perfusion caused by fusion of the left aortic valve cusp to the supra-aortic ridge. Measurement of LV pressure via the retrograde route (across the aortic valve) resulted in bradycardia and hypotension that was persistent and refractory even after withdrawal of the catheter into the descending aorta. Extracorporeal membrane oxygenation (ECMO) was initiated and the patient was taken emergently to the operating room where surgical repair of the left main coronary ostium and SVAS was successfully undertaken.

Two cases of sudden periprocedural death in WS patients have been described by another group.[31] A 6-yr-old, 16 kg child was sedated for a diagnostic cardiac catheterization with IM meperidine 10 mg, promethazine 10 mg, and chlorpromazine 10 mg. Twenty minutes after the diagnostic catheters were removed the patient developed bradycardia, apnea, and complete heart block culminating in ventricular fibrillation and death. In the second case a 3-yr-old, 10.8 kg girl with WS was to undergo surgical relief of SVAS. Preoperative evaluation was notable for an electrocardiogram that revealed severe LV hypertrophy with a strain pattern. In addition, echocardiography revealed a peak instantaneous aortic supravalvular gradient of 150 mm Hg, severe LV hypertrophy, and tethering of the aortic

valve leaflets to the area of the SVAS in close proximity to the area of the left coronary ostium. After oral premedication with 6 mg of midazolam and an IV induction with 40 mg of ketamine and 2 mg of pancuronium, anesthesia was maintained with 0.2% isoflurane in 100% oxygen. The heart rate was reported to be 150 bpm and arterial blood pressure was not reported. Five minutes later, during placement of a central venous catheter in the internal jugular vein, the patient's heart rate slowed from 150 to 75 bpm followed by development of PEA. Transesophageal echocardiography at this time showed new global LV hypokinesis. Aggressive resuscitation with bolus injections of atropine, phenylephrine, and epinephrine followed by infusions of isoproterenol, dopamine, and epinephrine resulted in stabilization of the patient long enough to allow emergent cannulation for cardiopulmonary bypass. Despite an adequate surgical repair, the patient required a LV assist device (LVAD). After 3 days of LVAD support, there was no substantial recovery of LV function and the patient died when LVAD support was withdrawn. These authors acknowledged that in this second case an anesthetic technique that did not induce hypertension and tachycardia might have prevented this outcome.

A case of sudden death in a WS patient immediately after tonsillectomy and bilateral tympanoplasty has been described.[33] The patient was an 18-mo-old boy (weight undocumented) with obstructive sleep apnea and SVAS as well as pulmonary stenosis. The severity of these lesions and the anesthetic technique were not specified. After tracheal extubation and administration of an unspecified dose of fentanyl for pain, the patient was noted to be bradycardic and cyanotic during transfer from the operating room table to a stretcher. The patient was then found to be pulseless despite provision of adequate ventilation. Despite an aggressive 53-min resuscitative effort involving administration of atropine, epinephrine, volume boluses, and defibrillation, there was no resumption of electrical or mechanical cardiac activity.

CONCLUSIONS

In congenital SVAS, myocardial ischemia has been implicated in the majority of cases of sudden death occurring in conjunction with anesthesia or sedation. Features common to the reported cases are sudden, rapid hemodynamic deterioration associated with hypotension and bradycardia, and a lack of response to aggressive resuscitative measures. It should also be recognized that catheter manipulation during cardiac catheterization can produce hemodynamic instability due to induction of dysrhythmias, exacerbation of outflow tract obstruction, creation of semilunar and atrioventricular valve insufficiency, and exacerbation of compromised coronary blood flow during aortic and coronary angiography. These problems can of course occur regardless of the sedation or anesthetic technique.[26] Furthermore, while some fatalities during cardiac catheterization have been associated with catheter manipulation, others have occurred before the procedure had begun or after apparently successful completion.

Identifying those patients with congenital SVAS at risk for myocardial ischemia is challenging. Echocardiography is useful in assessing ventricular outflow tract gradients, ventricular hypertrophy, and wall motion abnormalities but is an insensitive method for detecting and delineating compromise of ostial, proximal, and distal coronary blood flow. Of particular concern in this regard is the fact that significant coronary arterial flow impairment can occur in the absence of significant SVAS. Therefore, while the absence of significant SVAS (as identified by echocardiographic imaging and/or the presence of "only" minimal or mild LV to aorta pressure gradients) may be reassuring to the clinician, in actuality it does not exclude the possibility that there is significant impairment of coronary blood flow. Cardiac magnetic resonance imaging and computer tomography show increasing promise as noninvasive imaging modalities capable of delineating obstruction to coronary blood flow.[34] However, at present, cardiac catheterization with coronary and aortic angiography remains the "gold standard" for delineation of aortic leaflet tethering and assessment of coronary artery lumen caliber. Obviously, cardiac catheterization carries its own risks in these patients. Thus, evaluation and risk assessment of these patients, particularly as pertains to elective or noncardiac procedures in patients with varying degrees of SVAS, remains problematic.

Clearly patients with bilateral outflow tract obstruction and/or those with known coronary blood flow compromise represent a high-risk subset of patients. These patients may require intervention to relieve outflow tract obstruction prior to noncardiac surgical procedures. Percutaneous balloon dilation of SVAS is usually ineffective whereas outcome after surgery for SVAS is generally good with a 10 yr survival of 96% and a 20 yr survival of 77%.[14] Techniques which provide symmetrical reconstruction of the aortic root result in a reduced incidence of a residual gradient and of aortic insufficiency, as well as reductions in both mortality rate and need for reoperation as compared to surgical augmentation of a single aortic sinus.[14] In instances where there is diffuse tubular hypoplasia of the aorta and arch, symmetrical reconstruction of the ascending aorta with extension of the patch to the underside of the aortic arch is necessary. In some circumstances, surgical relief of coronary ostial stenosis may be necessary; in others long segment coronary stenosis may require coronary revascularization, usually with an internal thoracic arterial conduit.[14]

Surgical therapy for relief of proximal pulmonary artery obstructions tends to be palliative in that reoperation or catheter-based intervention is commonly needed.[13] Percutaneous balloon dilation of peripheral

Table 2. Anesthetic Goals in Patients with Supravalvular Aortic Stenosis

Maintain an age-appropriate heart rate
Use of vagolytic drugs (atropine, glycopyrrolate) and drugs with sympathomimetic activity (pancuronium, ketamine) should be avoided, particularly in combination
The dose of atropine or glycopyrrolate given in conjunction with neostigmine for reversal of neuromuscular blockade should be chosen so as to avoid excessive tachycardia
Maintain sinus rhythm
Aggressive treatment of supraventricular tachycardia is necessary; cardioversion (regardless of systemic blood pressure) may be preferable to pharmacologic interventions (esmolol, adenosine) which may cause hypotension in this situation
Maintain preload
Drugs that increase venous capacitance (propofol, sodium thiopental) should be used with consideration given to drug-specific dose-related effect
In the presence of severe left ventricular hypertrophy rapid intravascular volume augmentation may cause a precipitous increase in left atrial pressure resulting in pulmonary vascular congestion
Maintain contractility
Drugs with negative inotropic effects (propofol, sodium pentathol, sevoflurane, isoflurane, desflurane) should be used with consideration given to drug-specific dose-related effect
Maintain systemic vascular resistance
Drugs that reduce system vascular resistance (propofol, sodium pentathol, sevoflurane, isoflurane, desflurane) should be used with consideration given to drug-specific dose-related effect
Hypotension should be treated aggressively. A pure α-adrenergic drug (phenylephrine) may be most appropriate unless significant bradycardia is also present in which case ephedrine or low dose epinephrine (0.1–1.0 μg/kg is appropriate
Avoid increases in pulmonary vascular resistance
Avoid hypercarbia and hypoxemia and maintain the lowest mean airway pressures consistent with adequate minute ventilation, particularly in patients with right ventricular outflow tract obstruction

pulmonary artery stenoses plays an important role in long-term treatment of these patients. In addition, balloon dilation of significant peripheral pulmonary artery stenoses is indicated to reduce right ventricular afterload before surgical relief of SVAS, regardless of whether surgical relief of more proximal pulmonary artery stenoses is also anticipated.[13] The hypertrophied right ventricle is particularly susceptible to ischemic injury after cardioplegic arrest and presurgical reduction of afterload is likely to improve right ventricular function in this setting.

In summary, there is a particularly tenuous myocardial oxygen supply: demand relationship in these patients. In addition, the incidence of impaired coronary blood flow has probably been underestimated. As such, all patients with congenital SVAS should be considered at risk for myocardial ischemia on multiple bases and treated accordingly. Although there are insufficient data to recommend a specific anesthetic technique in these patients a prudent approach would involve meticulous attention to balancing myocardial supply and demand. Tachycardia will increase myocardial oxygen consumption while simultaneously reducing diastolic perfusion time with the combination of hypotension and tachycardia being particularly deleterious. In either case, the presence of ventricular hypertrophy will further jeopardize subendocardial perfusion. The anesthetic goals for these patients are summarized in Table 2. As with coronary insufficiency patients, the best approach is one that uses a combination of drugs with offsetting hemodynamic effects used judiciously in small doses. Elective procedures should be performed in institutions capable of providing ECMO in the event that resuscitation using standard Pediatric Advanced Life Support protocols after cardiac arrest is unsuccessful.[35,36] The availability of a rapid-response ECMO team would be desirable.

It is worth re-emphasizing that the substrate for myocardial ischemia (i.e., coronary obstruction) can exist without much in the way of other overt hemodynamic abnormalities, and that routine screening (e.g., symptoms, activity, echocardiography) is likely to be insensitive for detection or prediction of this possibility. Completely elective surgery needs to be carefully considered against this background. The need for more definitive, invasive evaluations (which as noted carry risks of their own) before necessary noncardiac procedures should be considered.

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