Session V: Whose Case Is It Anyway?

Williams Syndrome

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In 1961, Williams and colleagues described four children in whom a characteristic facial appearance was associated with supravalvar aortic stenosis (SVAS) and mental retardation. The facial resemblance among these children was so striking that the known diagnosis of SVAS in one prompted the search for and discovery of SVAS in the other three. [1] Subsequently, in 1962, Beuren and colleagues described three more children (and a fourth one in an addendum to their manuscript) with facial features like those in Williams' patients, again uniformly associated with SVAS. [2] These facial features consisted largely of soft tissue similarities such as broad foreheads, "heavy cheeks", wide mouths with "pouting lips", wide set eyes, blue irises, and mandibular hypoplasia, giving rise to an appearance often described as an "elfin facies". Other consistent features included a deep somewhat "metallic" voice, complex dental malformations, and strabismus. [1,3] Both authors postulated that this scenario might constitute a previously unrecognized clinical syndrome, one that has come to be known as Williams-Beuren Syndrome, or just Williams Syndrome (WS).

Over the ensuing years, much has been learned, often the hard way by unfortunate clinical experiences, about the cardiovascular malformations that accompany WS, and DNA analysis has determined the cause of these malformations. The genetic defect is the

submicroscopic deletion within chromosome subunit 7q11.23 of 1.5 megabase pairs of DNA containing alleles of at least 15 genes, including the gene that codes for elastin. [4,5,6] This deletion involves only one of the elastin alleles (hemizygous), usually occurs as a sporadic *de novo* event (rarely familial), and can involve the chromosome inherited from either parent. [7] A resulting "elastin arteriopathy" develops because of a significant reduction in the quantity of elastin produced by affected patients. [6] Consequently, the media of significant arteries contains not only a decreased amount of elastin that is mostly in the form of broken and disorganized fibers but also an increased number of hypertrophic smooth muscle cells and an increased amount of collagen. The resultant multilayer thickening and fibrosis of the media of large arteries leads to hyperplastic obstructive intimal lesions. The aorta and coronary, carotid, renal, and pulmonary arteries can be affected. [6,8,9] Cardiovascular abnormalities that have been described in patients with WS include SVAS, aortic valve defects, hypoplasia of the aorta, coarctation of the aorta, increased thickness of carotid arterial walls, renal artery stenosis, supravalvar pulmonary stenosis (SVPS), peripheral pulmonary stenosis (PPS), and coronary artery obstructions. [10,11,12] 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. [8,9,10,13]

The major potential pathophysiologic consequence of these vascular abnormalities is compromise of myocardial oxygen delivery. From one end, coronary blood flow may be limited by any of the mechanisms previously described. From the other end, elevated ventricular end diastolic pressures secondary to SVAS, SVPS, or PPS increase ventricular wall tension, compress subendocardial vessels, and hamper myocardial perfusion. [9,14] Systemic hypertension induced by renal artery stenosis, diffuse aortic narrowing, or decreased compliance of inelastic arterial walls [15,16] also serves to elevate ventricular end diastolic pressures and subsequently limit myocardial perfusion. As a result, the balance between myocardial oxygen supply and demand may be in a continually precarious state in patients with WS. In fact, there are several descriptions of myocardial infarction and/or ischemic cardiomyopathy being the presenting finding in children with WS. [8,13,17]

This precarious myocardial oxygen balance also explains why many procedural arrests occur during anesthetic induction or during invasive cath lab procedures. [10,18,19] Several drugs commonly administered during an anesthetic may decrease systemic vascular resistance (propofol, inhalation agents) and thus decrease coronary blood flow and myocardial oxygen delivery while others may increase heart rate (ketamine, atropine, glycopyrrolate) and thus increase myocardial oxygen demand. [9,10] 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 obstructions. [9] When it occurs, hemodynamic instability during anesthesia and

invasive procedures progresses rapidly from initial hypotension and bradycardia to cardiac arrest that many times fails to respond to aggressive resuscitation measures. [9,19]

Because of the cardiac and noncardiac issues that are associated with WS, these patients often have to undergo various diagnostic and/or interventional procedures. Twenty one percent of children with WS will require catheter-based interventions or surgical procedures to deal with cardiac abnormalities, usually by the age of five years. [12] Subsequent surveillance imaging procedures are likely to follow in many patients. In some children, correction of strabismus, hernia repairs, ENT procedures, or dental procedures will be deemed necessary. In most of these cases, anesthesiologists are going to be called upon to provide sedation or general anesthesia to allow the performance of these procedures.

When called upon, the challenge for anesthesiologists is being able to predict which of these children might experience hemodynamic instability on induction of anesthesia. Unfortunately, the substrate for myocardial ischemia can exist without much in the way of overt hemodynamic abnormalities. [9] The two conditions associated with a high risk of sudden death are severe biventricular outflow tract obstructions and coronary artery obstructions by ostial or intraluminal stenoses. [19] The preanesthetic workup, therefore, not only must attempt to identify any evidence of existing myocardial ischemia but also must attempt to assess these two predictive conditions.

Before anesthetic induction, an electrocardiogram (ECG) should be closely analyzed for changes indicative of myocardial ischemia as well as for evidence of ventricular hypertrophy suggestive of outflow obstructions. Additionally, repolarization abnormalities should be sought on the ECG since a prolonged QTc interval is six to seven times more common in patients with WS and places those affected at risk for ventricular dysrhythmias, especially upon exposure to certain drugs. [20] A transthoracic echocardiogram is useful in assessing the amount of biventricular outflow obstructions caused by SVAS and SVPS. While the contribution of PPS to right ventricular outflow obstruction may be more difficult to assess echocardiographically, a finding of right ventricular hypertrophy in the absence of obvious SVPS may prove insightful. Coronary artery obstructions are also difficult to assess noninvasively by echocardiography. However, ventricular wall motion abnormalities and evidence of endocardial fibroelastosis may be suggestive. Of note, the degree of SVAS is a poor predictor of the presence of coronary stenoses [10,19] and a poor predictor by itself of sudden death. [21] Indeed, significant coronary obstruction can occur in the absence of significant SVAS. [9] Magnetic resonance imaging is a promising modality to assess coronary blood flow. Cardiac catheterization is considered the "gold standard" for assessing coronary arterial anatomy but is risky, as previous described. [9,13,19,22] However, obtaining either an MRI or a cardiac catheterization as part of the workup of a child with WS often itself requires administration of an anesthetic! Therefore, the first time a child with WS requires an anesthetic, the anesthesia team may be required to proceed with limited and incomplete data and must plan an anesthetic as if the child's coronary blood flow and myocardial oxygen balance exist in a tenuous state. This makes dealing with children

with WS a daunting experience that should strike fear in the hearts of all knowledgeable healthcare providers!

Many anesthetic regimens have been used successfully in children with WS. Whatever recipe is concocted, certain physiologic variables should be carefully watched. An age-appropriate heart rate should be maintained, so vagolytic drugs (atropine, glycopyrrolate) and those with sympathomimetic activity (ketamine, pancuronium) should be used cautiously. Maintaining sinus rhythm is important in the face of hypertrophied, noncompliant ventricles. Supraventricular tachycardia should be quickly treated, preferably by cardioversion since pharmacologic therapy could also lower blood pressure. Adequate preload should be maintained, so drugs that increase venous capacitance (propofol) must be used judiciously. Myocardial contractility and systemic vascular resistance must also be preserved. Hypotension should be quickly and aggressively treated. Phenylephrine is probably the best choice. If the patient is bradycardic, low doses of epinephrine should be titrated. Finally, acute elevations in pulmonary vascular resistance from hypercarbia, hypoxemia, or high airway pressures should be avoided. [9,14] The best anesthetic regimen probably utilizes a combination of drugs with which the anesthesiologist is most familiar titrated in small incremental doses until the desired plane of sedation or anesthesia is reached. Elective procedures requiring anesthesia should be planned only after consideration by all participants of the potential extreme hazards of anesthetizing patients with WS. In children with unproven coronary anatomy and unknown myocardial oxygen supply and demand balance, consideration

should be given to administering anesthesia in a setting where knowledgeable help and the capability of providing ECMO support are readily available.

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Whose Case Is It Anyway? The Cardiac Catheterization Lab

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Disclosure

I have no financial relationships with industry to disclose.

The Case

- 15 year old girl
- 126.5 kg
- Cardiac transplant at 11 years of age for idiopathic dilated cardiomyopathy

- Type II diabetes mellitus
- Obstructive sleep apnea

The Case

- History of grade 3R rejection 2 years ago
  - Ventricular fibrillation arrest in cath lab
- Has now been non-compliant with her anti-rejection medications for several weeks

The Case

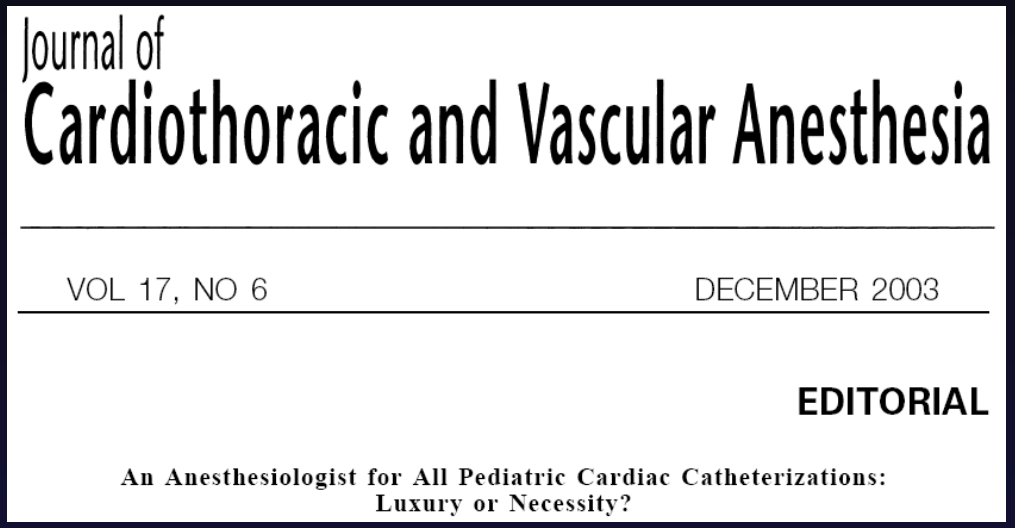
- Presents with:
  - Tachycardia
  - Tachypnea

- Cardiology would like to do cardiac cath with endomyocardial biopsy

Who in your institution provides anesthesia/sedation for the cardiac catheterization laboratory?

A. All anesthesia providers
B. Pediatric anesthesiologists
C. Pediatric cardiac anesthesiologists
D. Cardiology-directed sedation nurse

Anesthesia In the Catheterization Lab



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EDITORIAL

An Anesthesiologist for All Pediatric Cardiac Catheterizations: Luxury or Necessity?

- Increasing complexity of patient and interventions
- Risk of instability/complications due to procedure or sedation
- Need skilled practitioner in sedation, airway management, and resuscitation
- Allow cardiologist to concentrate on their technical task

Andropoulos D, Stayer S.

Complications In the Cath Lab

Pediatric Anesthesia 2005 **15**: 1083–1088 doi:10.1111/j.1460-9592.2005.01677.x

Incidents and complications during pediatric cardiac catheterization

Table 1
Summary of database information

	Number of cases	*Number of cases with event*	*Event rate (%)*
All cardiac catheterizations	4454	416	9.3
Diagnostic catheterizations	2274	212	9.3
PDA/ASD occlusions	572	24	4.2
Other interventional catheterizations	1254	145	11.6
Pacemakers and electrophysiological studies	354	35	9.9

Bennett D, et al. Ped Anes 2005; 15:1083-88.

Complications In the Cath Lab

Table 2
Summary of minor complications, as described contemporaneously by the anesthetist. A minor complication is defined as a transient event that had no long-term ill effect on the patient and resolved with specific treatment

	n
Respiratory	
Airway difficulties	22
Desaturation	14
Pulmonary problems	9
Tracheal tube displaced accidentally	1
Total	46
Cardio-vascular	
Arrhythmias	17
Hypotension	4
Infundibular spasm	1
Total	22
Procedure	
Pneumothorax	2
Hemothorax	1
Pulmonary hemorrhage	1
Total	4

Table 3
Summary of major complications, as described contemporaneously by the anesthetist. A major complication is defined as a potentially life-threatening event requiring immediate treatment

	n
Cardio-vascular	
Cardiac arrest	22
Inotropes required	14
Tetralogy 'spells'	10
Arrhythmia requiring cardioversion	9
Hypotension	3
Cardiac tamponade	2
Right ventricular failure	1
Total	61
Respiratory	
Laryngospasm	10
Failure to establish adequate self ventilation	4
Pulmonary hemorrhage	3
Low SpO_2 postprocedure	2
Bronchospasm	1
Lobar collapse	1
Total	21
Deaths (see Table 4 for details)	
Total	4
Other	
No recovery available: ICU admission	1
Premedication causing hypoxia	1
Drug overdose causing hypotension	1
Total	3
Equipment	
Ventilator failure causing hypoxia	1
Circuit wrongly assembled, unable to oxygenate	1
Total	2

Bennett D, et al. Ped Anes 2005; 15:1083-88.

Complications In the Cath Lab

- Increased incidence of complications in pediatric catheterization vs. surgery in general
- Increased incidence with:
  - Age < 1 y.o.
  - Therapeutic interventions excluding PDA/ASD closure

Bennett D, et al. Ped Anes 2005; 15:1083-88.

Cardiac Arrest in the Cath Lab

Table 4. Events and Demographics According to Technique

	Cardiac anesthesia service		Nurse sedation
	General anesthesia (n = 3843)	MAC (n = 642)	n = 2804
Cardiac arrests	51	4	15
Age (y), median (IQR)	2.6 (0.5–9.7)	9.6 (2.1–15.8)	13.6 (4.8–19.4)
Weight (kg), median (IQR)	12.0 (5.6–29.4)	28.5 (11.0–53.0)	45.0 (16.6–63.2)
Procedure type (%)			
Biopsy	538 (2)	172 (0)	710 (0)
Diagnostic	764 (5)	197 (1)	693 (4)
Intervention	2541 (44)	273 (3)	1401 (11)

CA = cardiac arrest; n = number; IQR = interquartile range; MAC = monitored anesthesia care; CAS = Cardiac Anesthesia Service.

P = 0.003 comparing cardiac arrests in CAS versus nurse-managed sedation.

P < 0.001 comparing proportion of interventional cases between CAS and nurse-managed cases.

Table 8. Frequency of Cardiac Arrests and Percentage of Cases Managed by the CAS Over Time

Year group	Total cases (n)	Cases managed by CAS*	Cardiac arrests†	ECMO (n)	Died before discharge (n)
2004–2005	2300	1163 (51%)	34 (1.5%)	7	7
2006–2009	4989	3322 (67%)	36 (0.7%)	10	8

Year 2004–2005: 15/100 catheterizations (99% confidence interval [CI], 10–20).

Year 2006–2009: 7/100 catheterizations (99% CI, 5–10).

CAS = Cardiac Anesthesia Service; ECMO = extracorporeal membrane oxygenation.

*P < 0.001 (compares proportions of cases in the 2 time periods).

†P = 0.002 (compares proportions of cardiac arrest in the 2 time periods).

Odegard K, et al. Anes Analg 2013; epub ahead of print.

Cardiac Arrest in the Cath Lab

Table 5. Cardiac Arrests Likely and Possibly Related to Anesthesia or Nurse-Managed Sedation

	Diagnosis	Procedure	Age (y)	Weight (kg)	Presumed etiology
Likely anesthesia-related					
1	PV stenosis	PV BD	0.5	5.4	GETA; respiratory arrest after extubation
2	SV s/p BDG and BTS	Shunt BD and stent placement	2.0	12.6	GETA; bradycardia and hypotension after induction of anesthesia
3	Congenital AS, s/p Ross procedure	Aortic valve BD	0.5	6.1	GETA; PEA after induction of anesthesia
Possibly anesthesia-related					
4	s/p Cardiac TX	Biopsy	1.2	7.8	Asystole after neostigmine, acute rejection on biopsy, ECMO cardiopulmonary resuscitation
Likely nurse-managed sedation-related					
5	Congenital PS	Pulmonary valve BD	1 day	2.9	Respiratory arrest after morphine and midazolam bolus
6	Heterotaxy, SV, PV stenosis s/p mBTS	PV BD, BTS dilation	18.1	63.2	Respiratory arrest at completion of the case, due to airway obstruction and pulmonary edema
7	Congenital PS	Pulmonary valve BD	0.25	6.0	Bradycardia and respiratory arrest after sedation bolus

PV = pulmonary vein; GETA = general endotracheal anesthesia; SV = single ventricle; BDG = bidirectional Glenn; BD = balloon dilation, ECMO = extracorporeal membrane oxygenation PS = pulmonary valve stenosis; mBTS = modified Blalock Taussig shunt; AS = aortic stenosis; TX = transplantation; PEA = pulseless electrical activity; s/p = status/post.

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Cardiac Arrest in the Cath Lab

- With low arrest rate, could not determine differences based on practitioner experience
- Cardiac anesthesia involvement in all stages of management has potentially decreased arrest rate
- With high complexity of cases and likelihood of arrest, need to be familiar with environment and challenges of these cases

Odegard K, et al. Anes Analg 2013; epub ahead of print.

STS Congenital Anesthesiology Report Non Operative Catheterization Anesthesia Operations

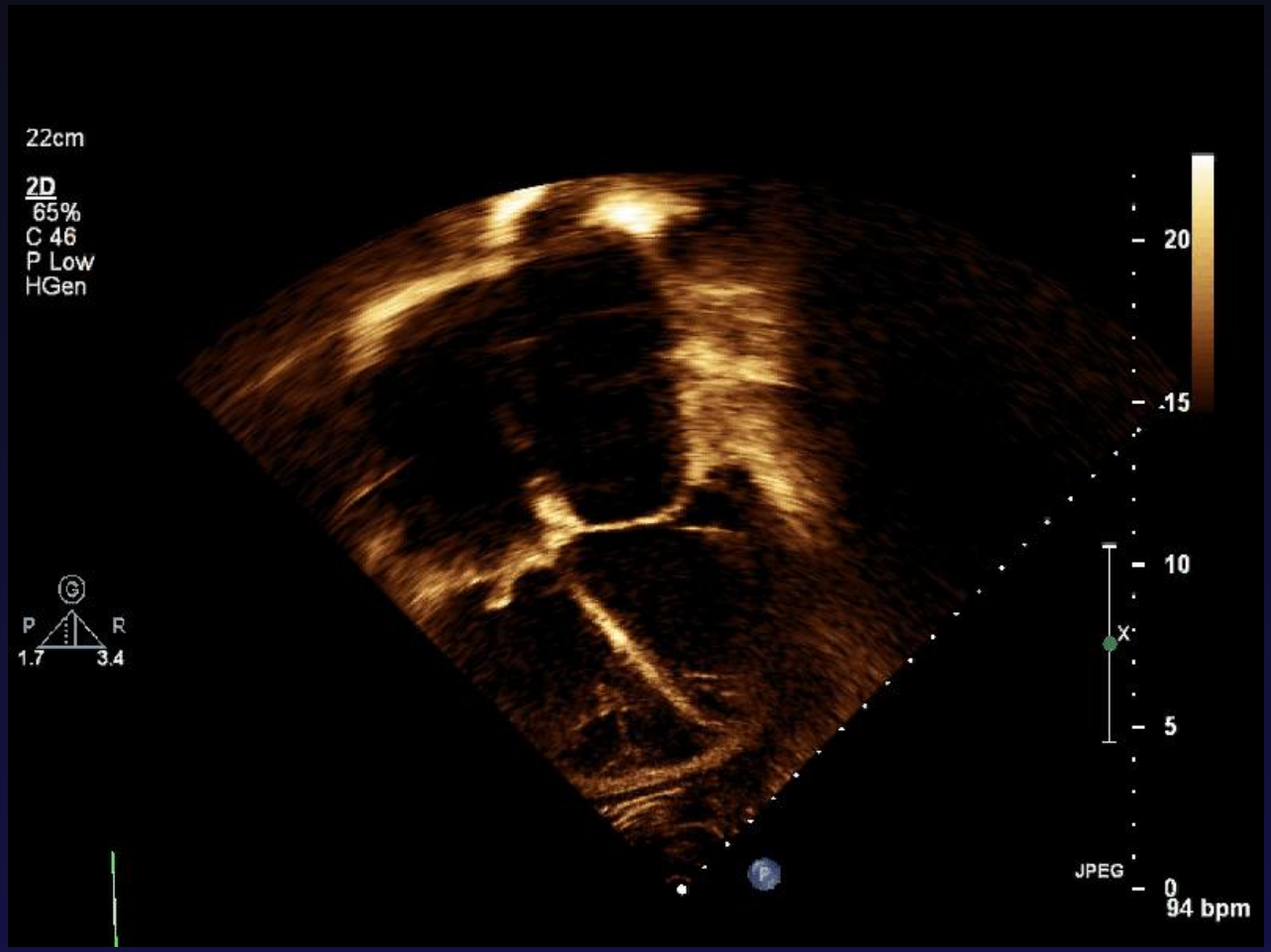
	STS N	STS %
Adverse Events		
None/Missing	3,009	98.5%
Any Adverse Event	45	1.5%
Dental Injury	0	0.0%
Respiratory Arrest	5	0.2%
Difficult Intubation/Reintubation	10	0.3%
Stridor / Sub-glottic Stenosis	7	0.2%
Extubation	1	0.0%
Endotracheal Tube Migration	2	0.1%
Airway Injury	3	0.1%
Arrhythmia - Central Venous Line Placement	0	0.0%
Myocardial Injury - Central Venous Line Placement	0	0.0%
Vascular Compromise - Central Venous Line Placement	0	0.0%
Pneumothorax - Central Venous Line Placement	0	0.0%
Vascular Access	1	0.0%
Hematoma	1	0.0%
Arterial Puncture	2	0.1%
Intravenous/Intra-arterial Air Embolism	0	0.0%
Bleeding - Regional Anesthetic Site	0	0.0%
Intrathecal Puncture - Regional	0	0.0%
Local Anesthetic Toxicity - Regional	0	0.0%
Neurologic Injury - Regional	0	0.0%
Anaphylaxis/Anaphylactoid Reaction	3	0.1%
Non-allergic Drug Reaction	1	0.0%
Medication Administration	1	0.0%
Medication Dosage	0	0.0%
Intraoperative Recall	0	0.0%
Malignant Hyperthermia	0	0.0%
Protamine Reaction	0	0.0%
Cardiac Arrest - Unrelated to Surgery	8	0.3%
Esophageal Bleeding / Rupture	0	0.0%
Esophageal Chemical Burn	0	0.0%
Airway Compromise	0	0.0%
TEE Related-Extubation	0	0.0%
Patient Transfer Event	0	0.0%
Neurologic Injury	1	0.0%

CCAS Database, Courtesy of Vener D.

The Case

- Last cath was 6 months ago
  - CVP = 12
  - RVp = 40/12
  - PCWP = 16
  - LV = 130/16
  - Ao = 130/80
  - Grade 0 rejection and normal CAs
- Ordered echo and found …..

Current Echocardiogram



How would you approach anesthetizing this child?

A. General anesthesia
B. MAC
C. I refuse to touch this child

Recipient Survival

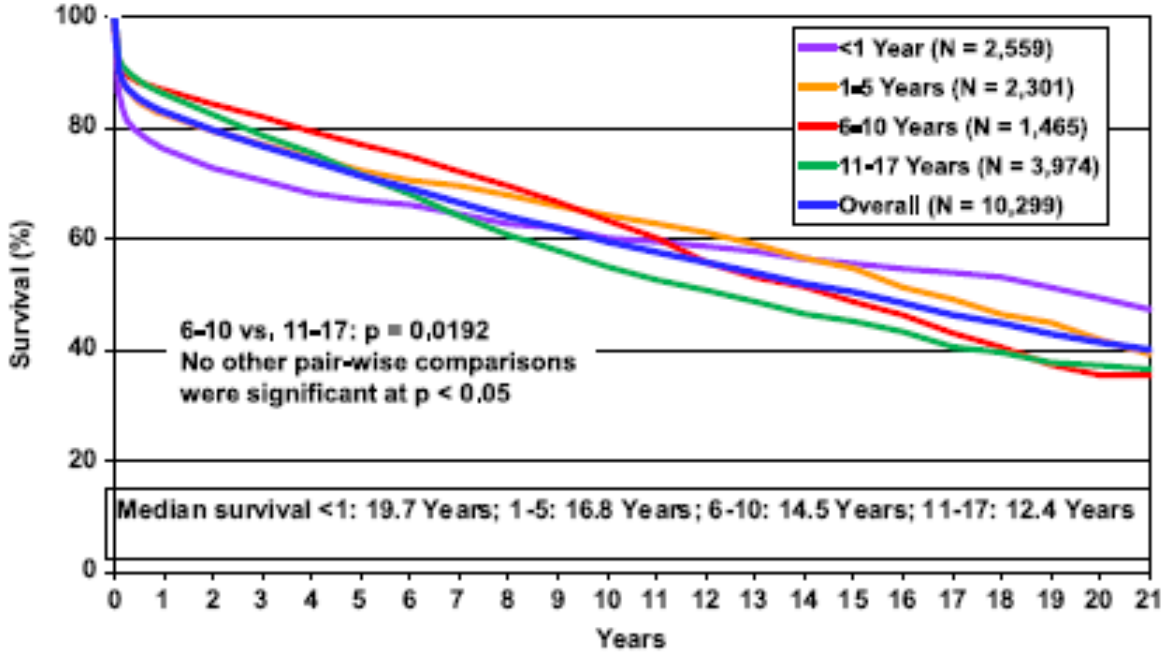


Figure 14 Kaplan-Meier survival for pediatric heart transplant recipients (Transplants: January 1982–June 2011).

Dipchand AI, et al. J Heart Lung Transplant 2013; 32:979-88

Recipient Causes of Death

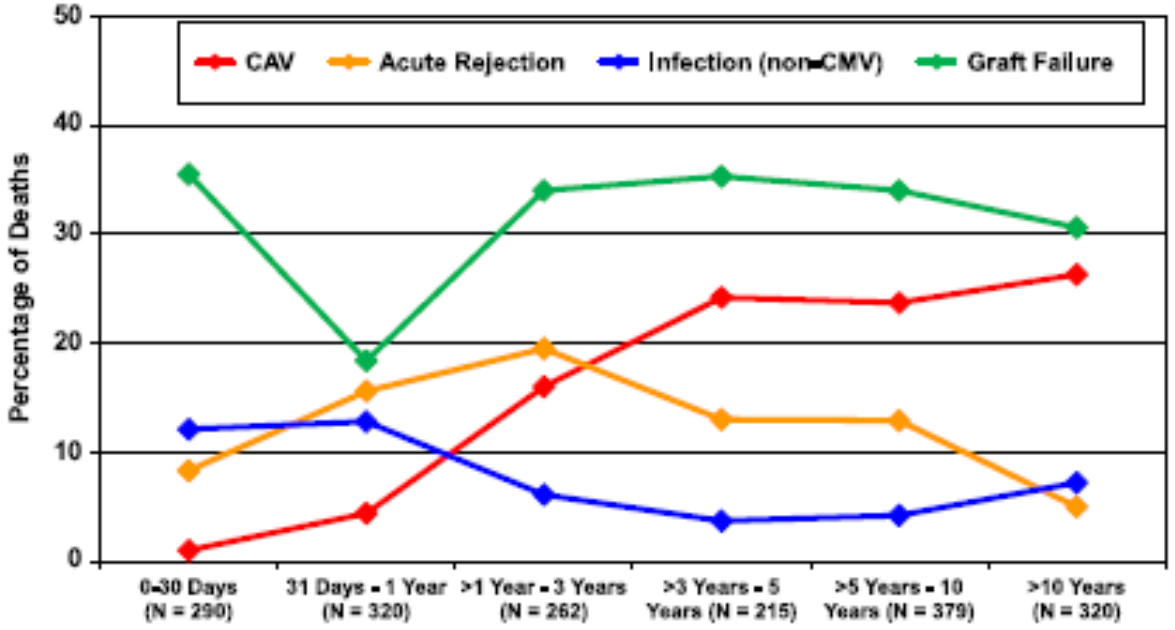


Figure 21 Relative incidence of leading causes of death (Deaths: January 2000–June 2012). CMV, cytomegalovirus.

Dipchand AI, et al. J Heart Lung Transplant 2013; 32:979-88

Preoperative Evaluation of Noncompliant Patient

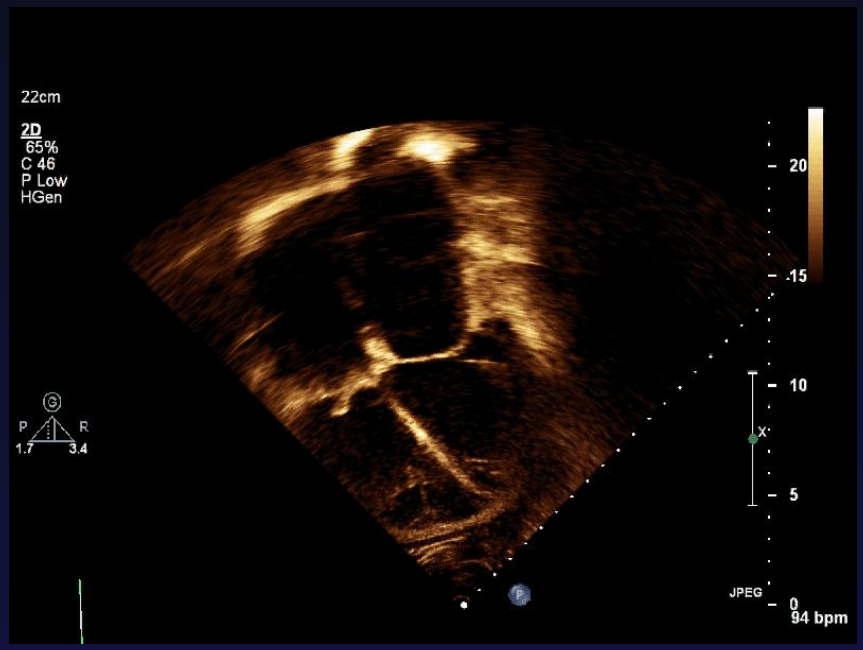
- Complete H&P
- Signs of rejection
  - Tachycardia
  - Tachypnea
  - Lethargy
  - Irritability
  - Fever
  - Hepatomegaly
  - New murmur
  - New-onset arrhythmias

Preoperative Evaluation of Noncompliant Patient

- Laboratory evaluation to determine end organ damage
- Echocardiography
- EKG
- Review of medications, including immunosuppression agents

Echo in Diagnosis of Rejection

- Non-invasive method to diagnose acute rejection?
- Indices of systolic and diastolic dysfunction
- Cath still gold standard



Cardiac Rejection

Type of Rejection	Mechanism	Approx Onset After Transplant
Hyperacute	Preformed Antibodies	Minutes to hours
Acute cellular	T-cell mediated	Anytime (often 1st 3-6 mo)
Acute humoral	Antibodies	Days to weeks
Chronic	Humoral and cellular	After 1st year

Law YM. Curr Opin Cardiol 2008; 22:66-71.

Treatment of Acute Rejection

- Steroid pulse therapy
- Intensifying immunosuppression
- Plasma exchange
- IVIg administration
- Hemodynamic support
  - Milrinone
  - Diuretics

The Case

- Patient sent to ICU
  - Steroid therapy
  - IV Milrinone
- Several days later, her echo demonstrates improved ventricular function with EF of 30%
- She is “better”
- Very anxious



Now how would you approach anesthetizing this child?

A. MAC with nasal cannula/face mask oxygen
B. General anesthesia with endotracheal tube
C. General anesthesia with LMA
D. I still refuse to touch this child

Obesity and Anesthesia

Table 5. Comparison of Perioperative Respiratory Adverse Events between Obese and Nonobese Children

	Nonobese	Obese	OR (95% CI)
Difficult mask ventilation	34 (2.1)	24 (8.7)	4.5 (2.6–7.7)*
Coughing—major	74 (4.3)	21 (7.1)	2.0 (1.4–2.8)†
Breath holding—major	27 (1.6)	5 (1.7)	1.1 (0.4–2.9)
Airway obstruction—major	193 (11.2)	55 (18.9)	1.8 (1.3–2.6)*
Laryngospasm	75 (4.3)	14 (4.8)	1.1 (0.6–1.9)
Bronchospasm	34 (2.0)	18 (6.1)	3.3 (1.8–5.8)*
Oxygen desaturation—major	155 (9.1)	48 (16.8)	1.8 (1.4–2.5)*
Overall airway event‡	1,027 (59.3)	213 (72.4)	1.8 (1.4–2.4)*
Critical airway event§	435 (25.1)	117 (39.8)	1.9 (1.5–2.5)*
Minutes to incision	23.3 ± 16.9	25.7 ± 19.6†	
Minutes to arousal	28.8 ± 31.8	20 ± 65.3*	
PACU duration of stay	107 ± 57.0	102.9 ± 59	
Discharge disposition			
Home	1,280 (74.3)	211 (72.3)	0.9 (0.7–1.2)
General care	393 (22.8)	71 (24.3)	1.1 (0.8–1.5)
Intensive/moderate care	50 (2.9)	10 (3.4)	1.1 (0.6–2.3)
Unanticipated hospital admission	38 (2.2)	4 (1.4)	0.6 (0.2–1.7)

Data are presented as n (%) or mean ± SD.

* $P = 0.001$. † $P < 0.05$. ‡ At least one respiratory event at any time point. § At least one major respiratory event at any time point.

CI = confidence interval; OR = odds ratio; PACU = postoperative anesthesia care unit.

Tait AR, et al. Anesthesiology 2008; 108:375-80.

Obesity and Anesthesia

- No studies on choice of ETT or LMA in obese children compared to normal weight children

- No study comparing use of LMA vs. ETT in children with OSA

Schwengel D, et al. Anesth Anal 2009; 109:60-75.
Mortensen A, et al. Ped Anesth 2011; 21:623-29.

The Panel's Opinion

Summary

- Cardiac cath involves complex patients undergoing risky procedures
- Practitioners need to be familiar with environment and its unique challenges
- Evaluate cardiac transplant patient for signs of rejection
- Transplant patients often have multiple comorbidities which affect the anesthetic

Cyanotic Congenital Heart Disease (CCHD):
Focus on Long-Standing Hypoxemia, Secondary Erythrocytosis and Coagulation.

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The anesthetic management of patients with cyanotic congenital heart disease (CCHD) relies on the clear understanding of the underlying anatomic defect and the physiologic implications of long-term hypoxemia on every organ system. Hematologic and hemostatic abnormalities have been recognized in patients with CCHD since the 1950's (1). Reduced tissue oxygenation, from arterial hypoxemia, stimulates erythropoietin production from the kidney resulting in *secondary erythrocytosis*. There are two distinct forms of secondary erythrocytosis based on erythrocyte indices and hyperviscosity symptoms (2,3):

Compensated erythrocytosis:

> Patients with established equilibrium at an elevated hematocrit level to hypoxemia. Hyperviscosity symptoms are absent in these patients and iron stores are replete.

Decompensated erythrocytosis:

> Patients with ongoing erythrocytosis noted by increase erythropoietin secretion without improvement in tissue oxygen concentration. Increase in erythrocyte mass continues despite harmful effects. Iron deficiency may be present and hyperviscosity symptoms are moderate to severe.

In the presence of decompensated erythrocytosis, erythropoietin titters are elevated despite the increase in blood red cell mass. As a consequence, negative iron balance and iron deficient erythropoiesis occurs. The resultant erythrocytes are microcytic and less deformable in the microcirculation than their normocytic equals. This change in the viscoelastic properties of the erythrocyte may affect blood viscosity and tissue oxygenation.

Secondary Erythocytosis and its effect on the coagulation system:

Thrombocytopenia is commonly cited as the primary abnormality present in these patients. Platelet count and hematocrit levels tend to be inversely related (4). The larger the right-to left shunt, the lower the systemic arterial saturation, the higher the hematocrit, and the lower the platelet counts. Other mechanisms considered responsible are shortened platelet survival (<80 hours), deficient von Willebrand multimers, decreased prothrombin levels, and more recently there is evidence suggesting that right-to-left shunts deliver whole megakaryocytes into the systemic arterial circulation, bypassing the lungs where megakaryocytes cytoplasm is fragmented into platelets, thus reducing platelet production (4). However, there is dispute about the platelets being the primary cause of hemostatic abnormalities in CCHD. Recent studies have demonstrated ***impaired fibrinogen function*** based on the magnitude of fibrinogen contribution to the clot strength on the Thromboelastogram - TEGFF (functional fibrinogen assay). Despite, a low platelet count, platelet function does not seem to be severely affected, as earlier assumed, and fibrinogen function seems to be impaired (5,6).
Low grade ***disseminated intravascular coagulation (DIC)*** has also been implicated. The resultant hyperviscosity derived from increased red cell and vascular stasis predisposes the patient for intravascular deposition of fibrin and platelet thrombi, leading to consumption coagulopathy. Other common disorders encountered in patients with secondary erythrocytosis are ***deficiency of coagulation factors II, V, VII, IX and X*** and a state of ***accelerated fibrinolysis*** (7).

Based on the altered coagulation profile described above, consideration should be given to perioperative strategies that might lessen the risk of postoperative bleeding in patients with long-standing hypoxemia.

Strategies:

Preoperative coagulation screening (PT, aPTT, AT, and Baseline TEG)

The detection of abnormalities and its correction will likely minimize the risk of thrombosis or bleeding in the perioperative period.

Isovolemic Phlebotomy / Intraoperative autologous blood donation

Current indications include: (a) moderate to severe hyperviscosity symptoms due to secondary erythrocytosis. and (b) preoperative phlebotomy for autologous blood donation if the hematocrit level is above 65%. Acute red cell volume reduction or perhaps more accurately, intraoperative autologous donation (IAD), may prove beneficial in the patient with CCHD.

Viscosity of blood is inversely related to shear rate. In fact shear rate is the main determinant of blood viscosity at any given location in the circulation. Hence, in the microcirculation where the flow rates are relatively low, shear rate is reduced, and viscosity greatly increased, potentially affecting tissue oxygenation. Moderate and linear increments in viscosity occur as hematocrit rises up to 45%. The rise in viscosity is exponential as hematocrit increases above 50%, especially in areas of low shear rate. Viscosity is also negatively influenced by temperature, having a greater impact at higher hematocrit levels.

Advantages of hemodilution and/or decrease in red cell mass might include: decreased blood viscosity, improved regional blood flow, improved oxygen delivery to tissues, improved cerebral blood flow, improved blood flow at lower perfusion pressures (lower shear rate) during hypothermia and improved coagulation profile and less postoperative bleeding in patients with CCHD.

To date, there are no studies defining the optimal "higher" level of hematocrit for hypothermic cardiopulmonary bypass in patients with decompensated erythocytosis, but, allowing enough hemodilution or acute red cell reduction for a hematocrit < 50% seems rational.

Heparin – Protamine management strategy

The coagulation alterations of patients with secondary erythrocytosis are complex and highly variable, as noted above. Heparin exerts its anticoagulant effect by binding to the enzyme inhibitor antithrombin III(AT). The activated AT then inactivates thrombin and other proteases involved in blood clotting, most notably, factor Xa. The immaturity of the hemostatic system in infants and the presence of chronic ongoing factor consumption may prevent adequate anticoagulation during CPB due to inherent deficiencies in antithrombin (AT) as well as other coagulation proteins. Thus, a more thorough heparin management is warranted.

The activated clotting time (ACT) is widely used to monitor anticoagulation adequacy, however, there is evidence that ACT is a poor indicator of proper anticoagulation in pediatrics. The use of patient specific heparin dose response and heparin concentration has proven to be more effective in suppressing thrombin generation during CPB than conventional weight based heparin dosing and monitoring (8). In addition, basing the protamine reversal dose on automated heparin/protamine titration will produce a smaller dose than predicted on the initial heparin bolus and last ACT, and avoid the anticoagulant effect of excessive protamine. This strategy is likely to benefit the CCHD population.

Antifibrinolytics

Both lysine analogues (ε–aminocaproic acid and tranexamic acid) exert their antifibrynolytic effect by competitively binding to lysine receptors on plasminogen, thus rendering it incapable of binding to the lysine residue on fibrin and by inhibiting the proteolytic action of plasmin. Another drug in this category is Aprotinin, a nonspecific serine protease inhibitor with antifibrinolytic effects recently withdrawn from clinical practice due to the rise of serious concerns about safety. As mentioned above, patients with long standing hypoxemia have ongoing accelerated primary fibrinolysis and likely to benefit from antifibrinolytic therapy during surgical repair using CPB.

Evidence suggests that aminocaproic acid and tranexamic acid are equally effective in reducing postoperative blood loss, as well as blood and blood product requirements in children with CCHD (9, 10). However, the literature on the topic is confounded by differences in dosage and regimens schemes for each drug, making it difficult to interpret the data. Despite this, there is increasing

evidence to suggest less postoperative bleeding and fewer transfusions with the use of lysine-analogues during complex pediatric and adult cardiac surgery, as part of a cohesive blood conservation strategy, including patients with CCHD.

Intraoperative coagulation and anticoagulation monitoring

Conventional coagulation analysis, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) warrant special handling in patients with severe secondary polycythemia. These analysis are performed in plasma alone (decreased % of the whole blood sample) and do not reflect the interaction with other cellular elements in blood, e.i. platelets. In addition, these laboratory studies take time to process and adequate clinical response in the immediate post bypass is not always a realistic option.

Intraoperative ACT monitoring is widely used to monitor anticoagulation on CPB in the pediatric and adult population. However, concerns about adequacy exist in the pediatric population as stated above. There is evidence of continued thrombin generation during CPB despite a standard heparin dose and an acceptable ACT (11). This thrombin and plasmin generation is associated with bleeding, thrombosis, and organ dysfunction post operatively. Heparin dose response and heparin concentration has been associated with improved clinical outcomes, significant reduction in thrombin generation, reduced bleeding and reduce need for blood transfusion. (12,13)

Another valuable monitoring technology is the Thromboelastography (TEG). It can be used in the preoperative, intraoperative and postoperative period to define the dynamic effects of cyanosis and CPB on the hemostatic system. By modifying the TEG with tissue factor, this speeds the reaction time and allows this test to become a real point-of-care coagulation monitor in the operating room for assessing post-CPB coagulopathies in children (14). Other modifications of the TEG add further information. Reactants such as heparinase will neutralize any effect of heparin and comparison to unmodified TEG will identify inadequate heparin reversal. The functional fibrinogen assay (TEGFF) will reflect the contribution of fibrinogen and platelet (derived from MA), on the clot strength (5). All components of clot formation and lysis can be identified and interpreted from the TEG The use of this technology should provide a more targeted blood product transfusion strategy in this high-risk population.

In summary, patients with long-standing hypoxemia have complex and sometimes severe alterations in their whole blood viscosity and coagulation profile. Understanding the physiology, pathophysiology and available strategies to lessen the risk of post operative bleeding or thrombosis, is warranted when carrying for these patients.

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