Congenital Heart Defects, Heart Surgeries, Low Cardiac Output Syndrome

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LEARNING OBJECTIVES

1. Distinguish the pathophysiology of common congenital heart defects and lesions compared with normal heart physiology to classify which defects are cyanotic, acyanotic, and/or single ventricle defects.
2. Evaluate which congenital defects benefit from alprostadil.
3. Assess which patient symptomatology would benefit from closure of patients' patent ductus arteriosus and the preferred method for closure on the basis of patient signs, symptoms, and laboratories.
4. Evaluate the pathophysiology and diagnosis for low cardiac output syndrome and the appropriate pharmacologic management.
5. Classify which interventions can be evaluated at the bedside as surrogates of cardiac output.

ABBREVIATIONS IN THIS CHAPTER

ASD	Atrial septal defect
CHD	Congenital heart defect
CHF	Congestive heart failure
CO	Cardiac output
CoA	Coarctation of the aorta
CPB	Cardiopulmonary bypass
CVP	Central venous pressure
DORV	Double outlet right ventricle
HLHS	Hypoplastic left heart syndrome
IAA	Interrupted aortic arch
IM	Interstage mortality
IVH	Intraventricular hemorrhage
LCOS	Low cardiac output syndrome
LV	Left ventricle/ventricular
NEC	Necrotizing enterocolitis
NIRS	Near-infrared spectroscopy
PA	Pulmonary atresia
PDA	Patent ductus arteriosus
PS	Pulmonary stenosis
PVR	Pulmonary vascular resistance
RV	Right ventricle/ventricular
SVR	Systemic vascular resistance
TA	Tricuspid atresia
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect

Table of other common abbreviations.

INTRODUCTION

Congenital heart defects (CHDs) are the most common class of major birth defects, with an incidence of about 8 in 1000 live births (Behrman 2004). Congenital heart defects can affect both heart structure and pulmonary and systemic blood circulation. Around 25% of defects are critical CHDs, which often require earlier surgical intervention and are associated with high morbidity (Botto 2001). To understand the physiology of CHDs, a general understanding of normal cardiac anatomy and physiology is first required. This is best obtained by reviewing the referenced websites and pictures describing the defects and visualizing oxygenated, deoxygenated, and mixed blood.

In utero ultrasonography assists with the prenatal diagnosis of CHD; however, a diagnosis is then made in the immediate postnatal period on the basis of clinical and physical evidence of CHD. It is therefore vital to assess for initial signs, including persistent tachypnea or dyspnea, feeding difficulties, and general irritability. Affected newborns may also have signs of poor perfusion such as blue skin discoloration and cool periphery. Heart murmurs and cardiomegaly on chest radiography further support these findings. Cyanosis (Sao_2 below 95% in a neonate with normal Hgb concentrations) may be confounding because a decreased Sao_2 is more often attributed to pulmonary complications in neonates. An AAP-endorsed screening algorithm for CHD is available online (Kemper 2011).

To differentiate between low oxygenation and poor perfusion, Sao_2 values are measured in limbs, both pre- and post-patent ductus arteriosus (PDA) (typically the upper right arm and foot). If concern for CHD ensues, blood gas monitoring for hypoxemia and diagnostic imaging (chest radiography and echocardiogram [ECHO]) are assessed (Lilly 2016).

Although published data are sparse regarding pharmacotherapy for pediatric patients with CHD, a goal-based approach of optimizing cardiac output (CO) can be applied. This is done throughout managing the patient's defect, both pre- and postoperative, and recognizing and managing low cardiac output syndrome (LCOS) to minimize morbidity and mortality.

Surgical procedures and postoperative care have greatly evolved over the past decade, with significant improvements in survival. Advances that have helped decrease mortality include improvements in prenatal and preoperative evaluation and diagnosis, improvements in anesthetic and intraoperative management, improvements in noninvasive postoperative monitoring, reductions in cardiopulmonary bypass (CPB) time, and avoidance of bypass by advances in interventional cardiology, resulting in more procedures now performed in the catheterization laboratory. The advantages of such interventional cardiology include avoidance of thoracotomy (trauma, scarring, and infection) and LCOS from CPB, which is also associated with acute kidney injury and poor neurologic outcomes. Such interventional procedures are associated with decreased morbidity and mortality with concomitant long-term survival (Kang 2018; Lehenbauer 2018; Gupta 2017; Pappachan 2017; Zampi 2017).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:
- General knowledge of normal cardiac physiology
- General knowledge of hemodynamic differences between neonates and children
- Drug knowledge of doses and the mechanism of actions of pharmacologic agents used to treat LCOS and heart failure

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:
- Marino BS, Tabbutt S, MacLaren G, et al. Cardiopulmonary resuscitation in infants and children with cardiac disease: a scientific statement from the American Heart Association. Circulation 2018;137:e691-e782.
- Kirk R, Dipchand AI, Rosenthal DN, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary [corrected]. J Heart Lung Transplant 2014;33:888-909.

In addition to the postoperative complications listed in Table 1 and Table 2, bleeding, pulmonary hypertension, valve injury, heart block, and residual defects can occur. Patients who require CPB for surgical repair and have postprocedural cardiac failure can transition to extracorporeal membrane oxygenation (ECMO) as a bridge to recovery. In addition, a ventricular assist device can be used as a bridge to transplantation, if warranted.

ACYANOTIC LESIONS

Acyanotic lesions (see Table 1; Figure 1, Figure 2, and Figure 3) usually result in the shunting of oxygenated blood from the left side to the right side of the heart because of a pressure gradient. With these lesions, cyanosis is avoided, but pulmonary over circulation and lack of systemic perfusion prevail. If left untreated, acyanotic lesions can result in right-sided heart failure, for which signs and symptoms include, but are not limited to, poor weight gain, feeding difficulties, diaphoresis, increased heart rate, increased respiratory rate, pulmonary congestion, and liver enlargement (Lilly 2016; Behrman 2004).

PDA CLOSURE AND CYCLOOXYGENASE INHIBITORS

The ductus arteriosus, a short, broad blood vessel that connects the pulmonary artery (PA) to the aorta in fetal circulation, usually closes by postnatal age day 4.3 plus or minus 2 days (Koch 2006); however, it may remain patent. Patent ductus arteriosus accounts for 5%–10% of all congenital heart disease, with 80% of cases presenting in infants weighing less than 1200 g at birth (Liebowitz 2019; Dice 2007). Although a
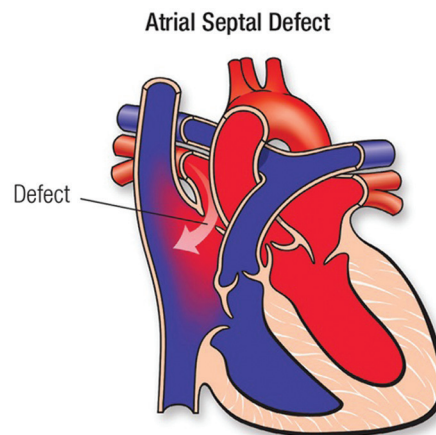

Figure 1. Atrial septal defect (ASD): hole in septum of atria. Blood flow is from higher pressure in the left atrium to the right atrium.

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Table 1. Acyanotic Heart Lesions, Description, Preoperative Treatment, Usual Surgical Repair, Postoperative Complications Summary

Acyanotic Heart Lesions	Description	Incidence/Comments	Preoperative Tx	Usual Surgical Repair	Postoperative Complications
Atrial septal defect	Opening between atria (see Figure 1)	10%–15%. Single defect or may also occur with PS, VSD, PDA, MV, TV prolapse, etc. Defined by size and location within atrial septum	Diuretics	Transcatheter patch repair	Transient postoperative HTN
Ventricular septal defect	Opening between ventricles (see Figure 2)	20%–30% single defect or may also occur with TOF and TGA. Defined by size and location within ventricular septum	Diuretics	Transcatheter patch repair	Transient postoperative HTN
Patent ductus arteriosus	Venous communication between pulmonary artery (PA) and aorta (see Figure 3)	5%–10% of all congenital heart disease. PDA is present in 80% of infants weighing < 1200 g at birth, compared with 40% of infants weighing < 2000 g at birth	Diuretics Pharmacologic closure: COX inhibitors (indomethacin IV, ibuprofen IV, acetaminophen (IV/PO)	If pharmacologic closure ineffective, ductal ligation, coil or plug[a]; stent[a] if needed to keep open	None
Interrupted aortic arch	Complete blockage between ascending and descending aorta	1%, but often occurs with other CHD (VSD, complex with truncus, TGA, DORV, AS) Common with DiGeorge syndrome. Collateral veins may develop to enhance perfusion to systemic circulation	PGE$_1$, CHF treatment	Transcatheter patch or end-to-end anastomosis or	HTN, LCOS
Coarctation of the aorta	Narrowing of the aorta	Single defect or occurs with VSD, AV canal, DORV	PGE$_1$ and CHF treatment	Balloon angioplasty or end-to-end anastomosis	HTN, LCOS
Atrial ventricular canal (AV canal)/ endocardial cushion defect Atrioventricular septal defect	TV and MV defect with resulting ASD and VSD	4%, more common in Down syndrome: 25%	CHF treatment, PPHN treatment	Repair by 4–6 mo of age: Single or double patch, dividing common valve into R and L sides, close the holes. Valve replacement PRN. If unbalanced, will be single ventricle physiology	LCOS, CHF
Pulmonary stenosis	Stenosis: Thickened, narrowed pulmonary valve	10% single or may also occur with ASD or VSD. Primary defect in TOF. Defined by pressure differences: Mild: < 30–40 mm Hg. Moderate: 40–60 mm Hg, Severe: > 60–70 mm Hg. **Critical:** > 90 mm Hg	Diuretics, CHF management	Stenosis: Balloon angioplasty.[a] pulmonary valve, surgical valvotomy (repair) or valvuloplasty patch PRN[a]	LCOS, CHF

(*Continued*)

Table 1. Acyanotic Heart Lesions, Description, Preoperative Treatment, Usual Surgical Repair, Postoperative Complications Summary (*Continued*)

Acyanotic Heart Lesions	Description	Incidence/Comments	Preoperative Tx	Usual Surgical Repair	Postoperative Complications
Aortic valve stenosis	Thickened narrowed aortic valve	0.6% Types: Bicuspid, subvalvular, or supravalvular. Defined by pressure gradients across valve. LV hypertrophy can ensue with severe narrowing	CHF management	Balloon angioplasty aortic valve. Surgical valvotomy (stretch),[a] valve replacement[a]	LCOS, CHF

[a]Catheter laboratory procedures possible: occlusions, valvuloplasty, stents.

AS = aortic valve stenosis; ASD = atrial septal defect; CHD = congenital heart defect; CHF = congestive heart failure; DORV = double outlet right ventricle; HTN = hypertension; IV = intravenous(ly); LCOS = low cardiac output syndrome; LV = left ventricular; MV = mitral valve; PDA = patent ductus arteriosus; PGE = prostaglandin; PPHN = primary pulmonary hypertension; PO = oral(ly); PRN = as needed; PS = pulmonary stenosis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; TV = tricuspid valve; Tx = treatment; VSD = ventricular septal defect.

Information from: Rao PS. Management of congenital heart disease: state of the art. Part I. Acyanotic heart defects. Children (Basel) 2019;6:42. Available at https://doi.org/10.3390/children6030042. Accessed June 30, 2020; C.S. Mott Children's Hospital [homepage on the Internet]. Ann Arbor, MI: University of Michigan C.S. Mott Children's Hospital. Available at https://www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects. Accessed June 24, 2020.

Table 2. Cyanotic Heart Lesions, Description, Preoperative Treament, Usual Surgical Repair, Postoperative Complications Summary

Cyanotic Lesions: Critical or Severe	Description	Incidence/Comments	Preoperative Tx[a]	Usual Surgical Repair	Postoperative Complications
Transposition of the great arteries	Aorta arises from RV, PA arises from LV (see Figure 4)	5%–7%. Usually occurs with ASD, VSD. May occur with LVOT obstruction, CoA	PGE_1, cardiogenic shock, lactic acidosis, cyanosis	If cyanotic, atrial septostomy (BAS) critical. Arterial switch within first few weeks of life. Occasionally, Mustard or Senning if patient is older or has coronary artery involvement or Rastelli shunt procedure: Conduit from RV to PA	Ischemia of coronary arteries → NTG; LCOS, PHTN, HTN
Tetralogy of Fallot	Four anomalies: (1) PA stenosis, (2) VSD, (3) overriding aorta, and (4) RV hypertrophy (see Figure 5)	10% more common with Down syndrome, DiGeorge syndrome, Infant of Diabetic Mother (IDM)	"Pink tets": watch. "Blue tets": PGE_1, esmolol, phenylephrine	Immediate in severe PS and low Sao_2 to 4–6 mo (usual). BT shunt or PDA stent ± balloon angioplasty of pulmonic valve if immediate or primary repair: VSD closure and enlarge RVOT through infundibular or transannular patch	LCOS, PHTN, HTN

Table 2. Cyanotic Heart Lesions, Description, Preoperative Treament, Usual Surgical Repair, Postoperative Complications Summary (*Continued*)

Cyanotic Lesions: Critical or Severe	Description	Incidence/ Comments	Preoperative Tx[a]	Usual Surgical Repair	Postoperative Complications
Total anomalous pulmonary venous return	Total = All pulmonary veins return to the RA (instead of LA). Partial APVR: Not all veins have abnormal return	< 1% Location: Supra cardiac, intracardiac, and infracardiac. ASD necessary for survival	PGE$_1$, cyanosis. PVO, CHF, PHTN	Re-routing all the PVR to the LA. ASD patch closure	Possible pulmonary venous obstruction (PVO) = higher morbidty/ ortality
Truncus arteriosus	Great arteries do not differentiate into PA and aorta. Instead single conjoined vessel	1%. Usually with VSD. May also occur with abnormal CoA and IAA. One-third of patients have DiGeorge syndrome	PGE$_1$	PA is separated from common artery. Conduit/homograft sewn into RV and other end sewn into PA. Common artery is reconstructed to create new aorta. Truncal valve repaired PRN. VSD closed	CHF, conduit replacement PRN. SBE px
Hypoplastic left heart syndrome[b]	Small or absent LV, PDA, CoA, or hypoplastic aorta (see Figure 6)	< 1% MV small/ not formed, aortic valve small, not formed. Usually with ASD	PGE$_1$	**Three-Stage Repair:** <u>Stage 1</u>: Within 2 wk of age: Norwood/ Sano, includes **BT shunt**, neoaorta, removal of wall between atria	LCOS, CHF, sudden death (4%), may need tx
				<u>Stage 2</u>: 4–6 mo of age: Hemi-Fontan or Glenn. BT shunt removed, RA patched	LCOS, CHF
				<u>Stage 3</u>: 2 yr of age: Fontan. RA patch removed, baffle with fenestration built in RA	LCOS, CHF
Tricuspid atresia[b]	TV does not develop, small RV, severe narrowing or absence of pulmonary valve	<< 1%. Usually occurs with ASD and VSD	PGE$_1$ cyanosis, PHTN, CHF	Repairs: Subaortic and double connected – Tunnel (conduit) repair, connecting LV to aorta and a patch directing LV blood to aorta. Subpulmonary – TGA switch repair. Remote. Fontan or biventricular repair	CHF, LCOS, PHTN

Table 2. Cyanotic Heart Lesions, Description, Preoperative Treament, Usual Surgical Repair, Postoperative Complications Summary (*Continued*)

Cyanotic Lesions: Critical or Severe	Description	Incidence/ Comments	Preoperative Tx[a]	Usual Surgical Repair	Postoperative Complications
Double outlet right ventricle[b]	Aorta connects to RV instead of LV	1%. Usually occurs with VSD. Four types depending on location of VSD. Subaortic, subpulmonary, double committed, non-committed. May also have PS, TGA, PA, CoA, MR	No PGE if VSD, PGE if cyanosis, PHTN, CHF	Repair depending on location of VSD and severity of PA or PS subaortic or double committed: TOF repair. Subpulmonary: Switch repair. Noncommitted: Single ventricle repair: Tunnel (conduit) repair, bidirectional Glenn, modified Fontan	CHF, LCOS, PHTN

[a]CHF tx: Inotropes, diuretics, spironolactone, digoxin. PHTN (mean pulmonary arterial pressure > 25 mm Hg) tx: Inhaled Nitric Oxide, epoprostenol, sildenafil, bosentan.

[b]Single ventricle defects.

BT = Blalock-Taussig; LVOT = left ventricular outflow tract; MR = mitral regurgitation; NTG = nitroglycerin; px = prophylaxis; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow obstruction; SBE = subacute bacterial endocarditis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot.

Information from: C.S. Mott Children's Hospital [homepage on the Internet]. Ann Arbor, MI: University of Michigan C.S. Mott Children's Hospital. Available at https://www.mottchildren.org/conditions-treatments/ped-heart/conditions/. Accessed June 24, 2020; Heart.org. Single Ventricle Defects. Available at https://www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects/single-ventricle-defects. Accessed June 30, 2020, Rao PS. Management of congenital heart disease: state of the art. Part II. Cyanotic heart defects. Children (Basel) 2019;6:54.
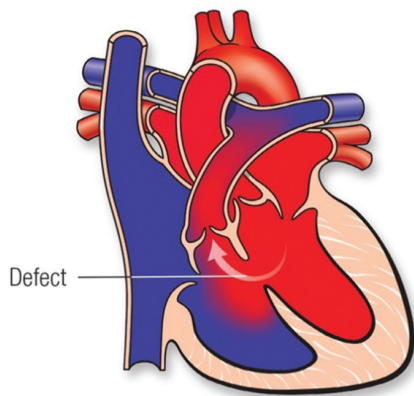

Figure 2. Ventricular septal defect (VSD): hole in septum of ventricle. Blood flow is from higher pressure in the left ventricle to the right ventricle.

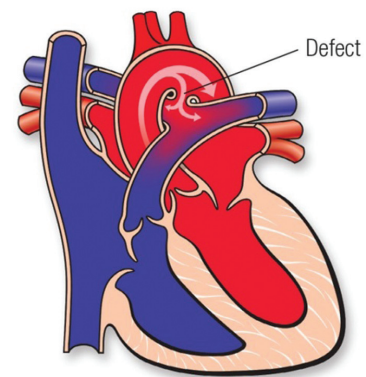Reprinted with permission from: American Heart Association. 2019.

Figure 3. Patent ductus arteriosus: venous communication between the pulmonary artery and the aorta. Blood flow is from the higher pressure aorta to the pulmonary artery.

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small PDA may not cause problems or require treatment, a large PDA can be life threatening (Jain 2015). The initial clinical presentation of a patient with PDA includes a wide pulse pressure, a heart murmur, and pulmonary edema from the shunting of blood back into the lungs. This results in hypoperfusion of the brain and end organs, which, if left untreated, increases the propensity for morbid complications, including metabolic acidosis, intraventricular hemorrhage (IVH), renal dysfunction, and necrotizing enterocolitis (NEC). Neonates may also have several episodes of apnea and increased ventilation requirements/dependence (Jain 2015; Dice 2007). The cycle of shunting of blood through the PDA, back into the lungs, and then back to the left ventricle (LV) can lead to left-sided heart failure.

If suspicion for a PDA ensues after birth, an ECHO should be obtained to confirm the presence and size of a PDA and to rule out other cardiac lesions. If the PDA is small, the patient can be watched and the patient's fluid restricted, with anticipation that the PDA will close naturally. For larger PDAs associated with hemodynamic compromise, pharmacologic therapy with an NSAID – indomethacin or ibuprofen lysine – is standard (Table 3). Indomethacin and ibuprofen lysine inhibit cyclooxygenase isoenzymes (COX-1 and COX-2), thereby blocking the synthesis of prostaglandins from arachidonic acid, resulting in constriction and closure of the PDA. Treatment is usually a 3-day course of either drug; however, a second course of therapy or surgery may be required to close the PDA.

Ibuprofen lysine was FDA approved for the treatment of PDA in 2006 with a potential to cause less renal insufficiency. Ibuprofen lysine is dosed at 10 mg/kg intravenously for the initial dose, followed by two doses of 5 mg/kg at 24 and 48 hours.

The risks of NSAID therapy should be considered at the beginning and throughout treatment. Therapy with NSAIDs has been associated with adverse events such as increased risk of NEC and renal insufficiency (Gulack 2015), given that the loss of prostaglandins results in decreasing renal perfusion. For this reason, NSAIDs may be avoided in light of the presence or risk of acute kidney injury, such as a urinary output less than 1 mL/kg/hour and/or a SCr greater than 1.2–1.5 mg/dL. In addition, the reduction in thromboxane production from COX inhibition decreases platelet aggregation and thus the risk of bleeding. For this reason, NSAIDs should be avoided in the setting of thrombocytopenia (Platelets less than 50,000–100,000/mm^3), in conditions of active bleeding, NEC, and IVH. Neonates of very low birth weight (VLBW) and extremely low birth weight (ELBW) are at higher risk of these complications. In the presence of contraindications to NSAID therapy, other options include intravenous acetaminophen, a PDA coil or plug, or surgical ligation. Surgical ligation mortality is low at 1.8% (Lehenbauer 2018).

The superiority of indomethacin compared with ibuprofen has been debated. Indomethacin has been used since 1970 and ibuprofen lysine since 2006, with the marketed potential to cause less renal insufficiency. One study confirmed this after randomizing 148 infants to either indomethacin or ibuprofen. The study found similar rates of PDA closure between the two groups, but renal dysfunction was significantly increased in patients treated with indomethacin (Van Overmeire 2000). However, in a retrospective study, early treatment with ibuprofen was associated with an increased risk of spontaneous intestinal perforation (Rao 2011).

More recently, acetaminophen has been used for PDA in several small randomized controlled studies. One study included 41 neonates with a median birth weight of 760 g, median gestational age of 25 weeks, and median postnatal age of 15 days who were treated with acetaminophen 15 mg/kg/dose every 6 hours for a median of 7 days. Intravenous therapy was used in neonates receiving less than 100 mL/kg/day of enteral feeds (n=36 [88%]). Twenty-seven neonates (66%) required no further PDA treatment, with ECHO-confirmed PDA closure in 10 neonates (24%) and reduced ductal size in 15 (37%). No adverse effects were attributed to acetaminophen (Luecke 2017). Because long-term outcomes have not been quantified, an 18- to 24-month follow-up is thought to be needed to assess neurologic outcomes after pre- and postnatal exposure to acetaminophen (Ohlsson 2018).

Moderate-quality evidence suggests that acetaminophen is as effective as ibuprofen in closing a PDA. However, low-quality evidence suggests that acetaminophen is as effective as indomethacin in closing a PDA. In a secondary analysis of the multicenter PDA-TOLERATE trial, infants with moderate to large PDAs were randomized 1:1 at 8.1 plus or minus 2.1 days to drug treatment with acetaminophen (n=27), ibuprofen (n=38), indomethacin (n=39), or conservative management (n=98). Conservative management included continuing feedings of up to 130 mL/kg/day beyond day 3 and pharmacologic rescue at 7 or 8 days, or PDA ligation if cardiopulmonary compromise occurred. Drug treatments were assigned by center preference rather than within each center. The PDA closed in 62% of study participants receiving indomethacin, compared

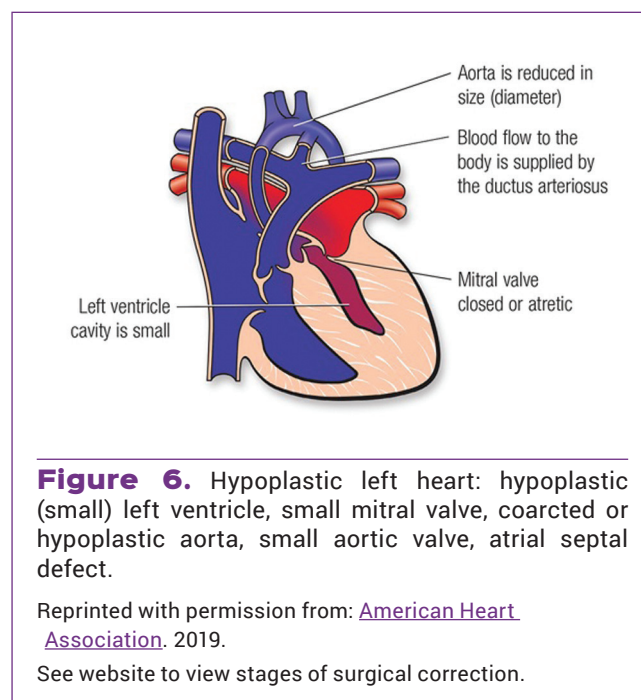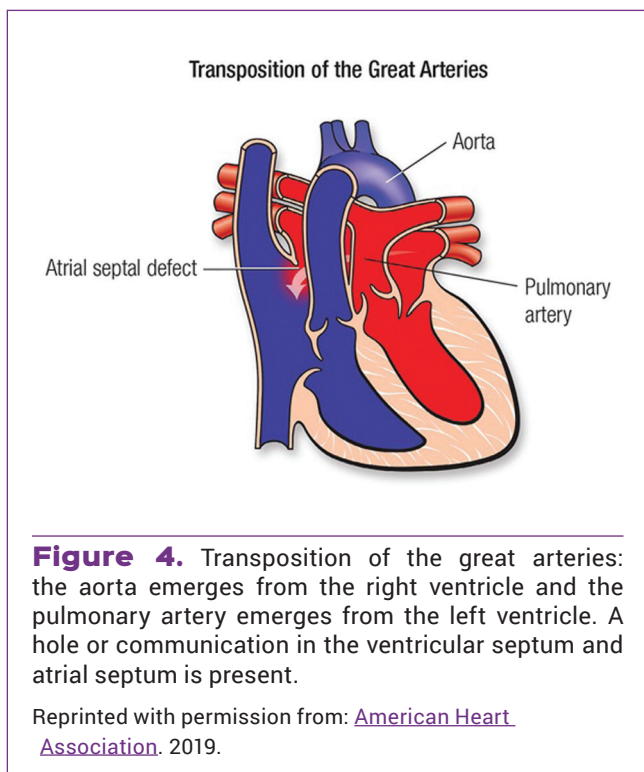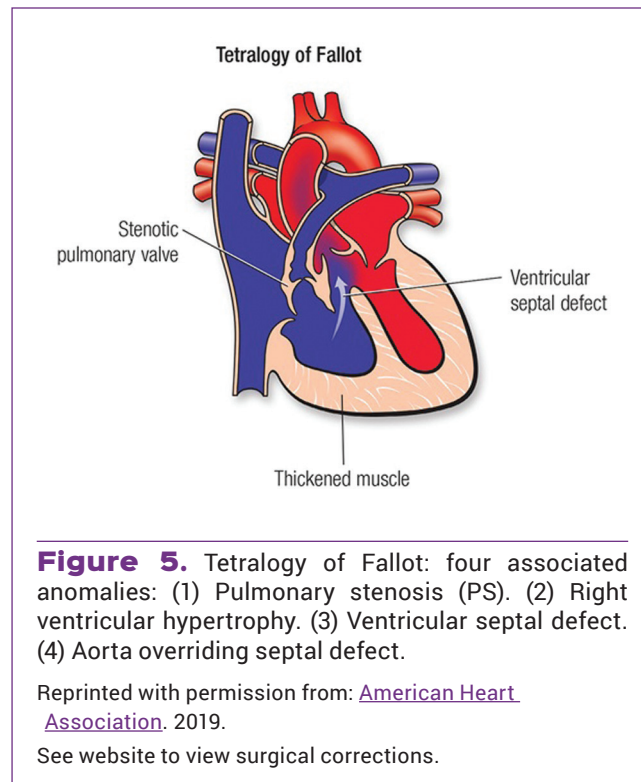| Table 3. Indomethacin Dosing: IV Every 12 hr × 3 Doses			
Age at First Dose	Dose 1 (mg/kg)	Dose 2 (mg/kg)	Dose 3 (mg/kg)
< 2 days	0.2	0.1	0.1
2–7 days	0.2	0.2	0.2
> 7 days	0.2	0.25	0.25

Information from: Lexicomp. Pediatric & Neonatal Dosage Handbook. Hudson, OH: Lexicomp, 2019.

with 20% of participants receiving conservative management (RR 95%; CI, 3.21 [2.05–5.01]); 43% with ibuprofen (RR 95%; CI, 2.03 [1.05–3.91]); and 27% with acetaminophen (RR 95%; CI, 1.33 [0.55–3.24]). Infants with persistent moderate to large PDAs after acetaminophen received indomethacin. The final rate of constriction after acetaminophen plus or minus indomethacin was 60%, similar to the rate in infants receiving indomethacin alone (62%) (Liebowitz 2019). A 2015 Cochrane review of 2190 infants also found no statistical difference in PDA closure between indomethacin and ibuprofen and found more evidence of renal insufficiency and NEC associated with indomethacin (Ohlsson 2018). Although acetaminophen is potentially attractive in patients who have contraindications to NSAIDs, it is less effective.

CYANOTIC LESIONS: ABBREVIATIONS, DESCRIPTIONS, PRE- AND POSTOPERATIVE CONSIDERATIONS, SURGICAL REPAIR

Cyanotic heart lesions (see Table 2; Figure 4, Figure 5, and Figure 6) result in the delivery of deoxygenated or mixed blood to the systemic circulation, resulting in Sao_2 values of 85% or less and often a blue-purple skin discoloration. Such patients may present with signs of hypoxia, including tachypnea, tachycardia or bradycardia, and lethargy, which can escalate with clinical decompensation. Early presentation of a cyanotic lesion is therefore regarded as a medical emergency. Some lesions depend on the PDA (see Figure 3)

to provide blood flow to the systemic circulation or the lungs in the immediate postnatal period. Although the necessity of the ductus is similar in these lesions, each lesion is physiologically different, with tailored treatment strategies to optimize oxygenation and perfusion.

Figure 5. Tetralogy of Fallot: four associated anomalies: (1) Pulmonary stenosis (PS). (2) Right ventricular hypertrophy. (3) Ventricular septal defect. (4) Aorta overriding septal defect.

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See website to view surgical corrections.

Figure 4. Transposition of the great arteries: the aorta emerges from the right ventricle and the pulmonary artery emerges from the left ventricle. A hole or communication in the ventricular septum and atrial septum is present.

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Figure 6. Hypoplastic left heart: hypoplastic (small) left ventricle, small mitral valve, coarcted or hypoplastic aorta, small aortic valve, atrial septal defect.

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See website to view stages of surgical correction.

ALPROSTADIL FOR PDA MAINTENANCE

In utero, circulating prostaglandins maintain the patency of the ductus arteriosus. Postnatally, prostaglandin concentrations wane within hours to days, which results in closure of the PDA. Alprostadil (PGE$_1$) is the primary pharmacologic intervention used to maintain the patency of the ductus arteriosus for ductal-dependent lesions until surgical correction. Alprostadil causes vasodilation through a direct effect on vascular and smooth muscle, resulting in increased pulmonary blood flow and improved oxygenation. For patients with a suspected cyanotic ductal-dependent lesion, initiation of alprostadil is urgent. Alprostadil is initiated at 0.05–0.1 mcg/kg/minute as a continuous intravenous infusion and titrated to a maximum of 0.4 mcg/kg/minute. According to a 1981 study, the effects of alprostadil usually occur within 30 minutes (Freed 1981); however, clinical improvement may take several hours after initiation. In infants with an already closed PDA, reopening may be attempted with a high-dose alprostadil infusion (e.g., 0.4 mcg/kg/minute) (Freed 1981). Once the ductus is confirmed as patent by ECHO, alprostadil should be decreased to the lowest effective dose (usually 0.01–0.02 mcg/kg/minute) to minimize dose-dependent adverse effects (Huang 2013). Reported adverse effects of alprostadil include skin flushing, hypotension, seizure-like activity, jitteriness, temperature elevations, and diarrhea. Prolonged infusions are also associated with hypoglycemia or hypokalemia and hematologic effects, such as platelet dysfunction, thrombocytopenia, and coagulopathies. Apnea has been reported in 5%–10% of patients and may prevail without the ability to decrease the alprostadil dose. In such circumstances, caffeine citrate, a methyl xanthine, can be considered. Usual loading doses of caffeine citrate are 20 mg/kg orally or intravenously with maintenance doses of 5–10 mg/kg/day every 24 hours. A recent study suggested that a loading dose and one or two maintenance doses are sufficient if a patient has had a single apneic event (Higgins 2020). Caffeine has a wide therapeutic index, with an extended half-life elimination of 72–96 hours. Therapeutic drug monitoring is not always warranted; however, it may be useful if apnea persists or if the patient has adverse effects (e.g., arrhythmia, tachycardia, or increased reflux). The therapeutic range of caffeine is 5–20 mcg/mL. Use of aminophylline, also a methylxanthine with a half-life of 24 hours, for alprostadil-induced apnea has also been reported. In a randomized placebo-controlled study of 42 infants, 21 infants received aminophylline as a 6-mg/kg loading dose, followed by a maintenance dose of 2 mg/kg/dose every 8 hours. Patients in the treatment group had a lower incidence of apnea (2 vs. 11) and intubation. This dosing regimen resulted in aminophylline concentrations of 7.6 plus or minus 1.2 mcg/mL with no significant adverse effects. Monitoring of aminophylline remains warranted, with effective concentrations of usually 10 mcg/mL or less (Lim 2003).

SINGLE VENTRICLE DEFECTS

Single ventricle lesions are rare disorders that involve an underdeveloped or nonfunctioning right ventricle (RV) or LV (Box 1). Single ventricle CHDs are associated with the highest morbidity and mortality. In one study, 1-year survival differed between the various categories of functional single ventricle (survival of patients with a balanced lesion was 93.5%). The lowest 1-year survival occurred with hypoplastic left heart syndrome (HLHS) (41.8%); survival was highest with tricuspid atresia (TA) (76.1%). These are ductal-dependent lesions until surgical repair occurs. As hemodynamic changes occur during development, these defects often require multistage surgical procedures (Beroukhim 2015; Fixler 2010). Surgical procedures for repair of single ventricle lesions are associated with higher mortality, especially during the early years of life (Fixler 2010), than biventricular surgical procedures. Patients with single ventricle defects who develop heart cardiopulmonary failure after surgical procedures often require heart transplantation. One study reported an in-hospital mortality of 7%–19% post-Norwood with a discharged home mortality of 2%–12% before stage II palliation (hemi-Fontan or bidirectional Glenn) (Oster 2016).

SINGLE VENTRICLE CONSIDERATIONS/TREATMENTS

Presurgical Pulmonary and Systemic Flow Estimation

Before surgical repair, the patient with single ventricle defects appears lethargic, cyanotic, and tachypneic and has difficulty feeding because of suboptimal pulmonary and system

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Box 1. Examples of Single Ventricle Heart Lesions

- Double Inlet Left Ventricle (DILV)
- Double Outlet Right Ventricle (DORV) with PA
- Hypoplastic Heart Syndrome (HLHS)
- Pulmonary Atresia (PA)
- Tricuspid Atresia (TA)
- Unbalanced Atrioventricular Septal Defects (AVSD)

For a detailed summary of staged single ventricle surgical procedures, see Table 2; C.S. Mott Children's Hospital [homepage on the Internet]. Ann Arbor, MI: University of Michigan C.S. Mott Children's Hospital. Available at https://www.mottchildren.org/conditions-treatments/ped-heart/conditions/. Accessed June 24, 2020; Heart.org. Single Ventricle Defects. Available at https://www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects/single-ventricle-defects. Accessed June 30, 2020.

perfusion. Presurgical medical management requires an accurate assessment and optimization of both systemic and pulmonary blood flow, for which shunt ratios of pulmonary (Qp) versus systemic (Qs) can be calculated (usually by heart ECHO) to help determine medical management. In the normal heart without defects or shunts, the Qp/Qs ratio is 1. In patients with left-to-right shunts, pulmonary flow is greater than systemic flow, resulting in Qp/Qs greater than 1. When Qp is greater than Qs, pulmonary congestion can ensue, which can be managed by diuretics and LV afterload reduction to reduce left-to-right shunting into the pulmonary circulation. Alternatively, in patients with right-to-left shunts, systemic flow is greater than pulmonary flow, resulting in Qp/Qs of less than 1 and thus resulting in cyanosis (Procaccini 2017). Calculation of the Qp/Qs can help determine whether a complete repair with ventricular septal defect (VSD) closure or a staged repair would be more successful in patients with single ventricle defects. Patients with severe pulmonary obstruction usually present with a Qp/Qs ratio of 0.4 or less, for whom a conduit or graft replacement is not viable. Patients with preoperative Qp/Qs ratios greater than 1 usually tolerate a VSD closure because they have appropriate RV systolic pressures, which are associated with positive long-term outcomes after complete repair (O'Byrne 2016; Grosse-Wortmann 2013).

The first procedure of single ventricle palliation is a Norwood procedure, which includes placement of a systemic-to-pulmonary shunt, which can be a Blalock-Taussig (BT) shunt (conduit from right subclavian to PA), a Sano shunt (RV to PA conduit), or a central shunt (conduit from aorta to main PA). Reevaluation of the Qp/Qs ratio is crucial after shunt placement, which dictates the individual pharmacotherapy, with the goal of having the optimal perfusion to both the lungs and the systemic circulation.

Major Aortopulmonary Collateral Arteries

Use of Qp/Qs is especially helpful when determining the medical management and surgical approach with the presence of major aortopulmonary collateral arteries (MAPCAs). Major aortopulmonary collateral arteries develop to supply blood to the lungs when normal pathways are not appropriately developed as an adaptive process for survival. Ideally, surgical correction should occur before MAPCAs form; however, medical management is often required for hemodynamic stabilization before correction. Major aortopulmonary collateral arteries may present at a later age if pulmonary blood flow is gradually reduced during development. In patients with tetralogy of Fallot (TOF) with PA, for example, MAPCAs may present at a later age (older than 1 year, median age 5.9 years). A staged repair would require combining the collaterals using a femoral vein homograft, balloon stenting them to enlarge the MAPCAs, or ligating the collaterals with coils. A complete repair requires a conduit or graft as a replacement for the absent PA with VSD closure (O'Byrne 2016; Procaccini 2017; Grosse-Wortmann 2013).

Single Ventricle Defects and Digoxin to Decrease Mortality Post-Stage I Repair

Patients with stage I single ventricle defects may have increased morbidity secondary to occult arrhythmias. Digoxin, a cardiac glycoside medication that has historically been used to treat congestive heart failure (CHF) and arrhythmias, has had a resurgence in use in stroke volume defects in patients post-stage I (Brown 2016; Oster 2016). Use of interstage digoxin may increase survival in patients with no history of documented arrhythmia.

Characterizing data from the Pediatric Heart Network Single Ventricle Reconstruction Trial public use data set, a retrospective cohort study measured survival outcomes in patients with single ventricle defects post-Norwood. The data included patient stratification of the specific CHD, as well as the type of systemic-to-pulmonary shunt used, from 15 institutions in North America during 2005–2008. Parametric survival models were used to compare the risk of interstage mortality (IM) post-Norwood between those discharged home on digoxin and those not. Data were adjusted for center volume, ascending aortic diameter, shunt type, and socioeconomic status. Of the 330 infants eligible for this study, 102 (31%) were discharged home on digoxin. Interstage mortality for those receiving digoxin was 2.9%, compared with 12.3% in those who did not receive digoxin, with an adjusted hazard ratio of 3.5 (95% CI, 1.1–11.7; p=0.04) (Oster 2016). The number needed to treat to prevent one death was 11. There were no differences in complications between the two groups during the interstage period. These authors concluded that digoxin used in infants with single ventricle CHD is associated with significantly reduced IM. Typical doses of oral digoxin were 10–15 mcg/kg/day, divided twice daily. These findings were corroborated with (1) a propensity score–adjusted logistic regression with IM and (2) a retrospective cohort analysis of patients discharged on digoxin compared with those not discharged on digoxin. Data were extracted from 50 different surgical centers from June 2008 to July 2013. Patients were matched for surgical site and other established IM risk factors. Of the 544 study patients analyzed, 119 (21.9%) were discharged on digoxin. Logistic regression analysis with propensity score concluded an increased risk of IM in those not discharged on digoxin (OR 8.6; CI, 1.9–38.3) (Brown 2016). Therefore, preliminary data analyses support the use of digoxin in single ventricles to decrease IM, though further studies are needed.

Although digoxin concentrations do not correlate well with efficacy in pediatric patients, therapeutic drug monitoring of digoxin concentration may be warranted in patients with renal dysfunction or with signs and symptoms of toxicity. In infants and children, the half-life of digoxin varies from 18 to 25 hours

with normal renal function; therefore, steady state is usually reached 3 days to 1 week post-initiation. Digoxin trough concentrations are preferred; however, a random concentration at least 6 hours after a dose at steady state can be obtained. Until further studies define specific goal serum concentrations, heart failure goal concentrations of 0.5–2 ng/mL are reasonable for this indication.

OTHER POSTOPERATIVE COMPLICATIONS/THERAPEUTICS

Shunt Venous Thromboembolism

Thrombotic complications can occur in a patient's post-palliative procedures in which foreign material is placed, including the modified Norwood, Fontan, conduit, and valve replacements. Once hemostasis is achieved after palliation, therapy with low-dose heparin or enoxaparin is initiated and continued until the patient can tolerate long-term enteral prophylaxis with aspirin, warfarin, and/or clopidogrel. Aspirin 3–5 mg/kg (max 81 mg) is a well-established and standard venous thromboembolism (VTE) prophylactic modality for systemic-to-pulmonary shunts (BT, Sano, and central shunts). Although the need for VTE prophylaxis is controversial, it is usually provided postoperatively with an unfractionated heparin infusion of 5–15 units/kg/hour before the transition to enteral aspirin (Marino 2018) once enteral administration is feasible. Some centers report using rectal aspirin successfully until patients can be transitioned to enteral aspirin. Treatment is best decided by analyzing all the risk factors for VTE in conjunction with the preferences of the cardiothoracic surgeon and the medical team (Giglia 2016).

A suspected BT shunt thrombotic occlusion (as evidenced by a low Sao_2, acute hypoxemia, and decreased CO) is a medical emergency that should be treated immediately. Medical management includes an unfractionated heparin bolus of 100 units/kg, 100% oxygen, phenylephrine 10 mcg/kg every 5–10 minutes to increase systemic vascular resistance (SVR), inhaled nitric oxide to decrease pulmonary vascular resistance (PVR), and fluids, and/or pressors as needed, depending on clinical sequela (Procaccini 2017). This therapy should be continued until thrombectomy or thrombolysis can be performed in a catheterization laboratory or operating room. Patients with acute hemodynamic compromise refractory to the aforementioned medical management may require ECMO.

Aspirin compared with anticoagulant monotherapy for other procedures, such as the Fontan, remains controversial. In one study, no significant difference was reported between aspirin and heparin/warfarin as primary thromboprophylaxis in the first 2 years after Fontan surgery. The rate of thrombosis of the 111 patients enrolled in the study was suboptimal for both regimens, suggesting alternative approaches should be considered (Monagle 2011; Giglia 2016). Postoperative

thromboprophylaxis indications and recommendations are covered in more detail in the Anticoagulation in the Cardiac Patient chapter.

Peri- and Postoperative Infection Prophylaxis

Postoperative infections in pediatric cardiac surgery are an ongoing clinical challenge, with rates of 1%–20%. Perioperative antibiotics remain the standard for preventing surgical site infections, but selection of antibiotic and duration of treatment remain poorly defined. There are vast differences in practice variation, as indicated by informal surveys. Rates of antibiotic-resistant organisms are increasing steadily around the world (Anand 2017). A more recent study of neonates reviewed the safety of a perioperative antibiotic prophylaxis protocol. Either cefazolin or vancomycin was used pre- and interoperation, and postoperative cefazolin (closed sternum) or vancomycin and gentamicin (open sternum) was used for neonatal cardiac surgery. Surgical site infection rates before and after protocol implementation evaluated compliance with four process measures (appropriate drug, dose, timing, and discontinuation of perioperative antibiotic prophylaxis) for perioperative antibiotic prophylaxis. This study included all cardiac procedures performed on neonates from July 2009 to June 2012 at a single center. An interdisciplinary task force developed a standardized perioperative antibiotic prophylaxis protocol in the fourth quarter of 2010. Surgical site infection rates were compared pre-intervention (July 2009 to December 2010) and post-intervention (January 2011 to June 2012). Compliance with process measures was also compared in the two periods. During the study, 283 cardiac procedures were performed. Surgical site infection rates were similar pre- and post-intervention (6.21 vs. 5.8 per 100 procedures, respectively). Compliance with the four-process measures significantly improved post-intervention. Restricting the duration of perioperative antibiotic prophylaxis after neonatal cardiac surgery to 48 hours in neonates with a closed sternum and to 24 hours after sternal closure was safe did not increase the surgical site infection rate. The study concluded that additional multicenter studies are needed to develop national guidelines for perioperative prophylaxis for this population (Murray 2014).

Chylothorax

Chylothorax, the accumulation of lymphatic fluid or chyle in the pleural space, after cardiothoracic surgery is common because of surgical trauma of the lymphatic system. The primary treatment goal is to stop or decrease the thoracic lymph flow and allow the thoracic duct to heal. Conservative management includes drainage of the pleural space, termination of enteral feeding, and administration of total parenteral nutrition (TPN) and/or supplementation with medium-chain triglyceride–enriched diets. Pharmacists can work with nutritionists to outline a low-fat diet to decrease chyle production and avoid malnutrition in these patients.

When conservative therapies fail, treatment with the somatostatin analog octreotide has been used with mixed results. In a recent review, which included 39 case reports, octreotide was effective in 47% of patients, with a slight but not significant difference between congenital (30 of 57 [52.6%]) and acquired (9 of 27 [33.3%]) chylothorax (p=0.1). Although the octreotide dosage varied widely, the most common dosing used was an initial octreotide dose of 1 mcg/kg/hour and gradually increased up to 10 mcg/kg/hour, depending on therapeutic response. Adverse effects were reported in 12 of 84 patients and included cholestasis, bloody stools, NEC, hyperglycemia, hypotension, pulmonary hypertension, mild abdominal distension, increased liver function tests, and transient hypothyroidism (14.3%) (Bellini 2018). A 2013 study reported that the use of a protocol for high chyle output (greater than 20 mL/kg/day) that included nothing by mouth (NPO) status with parenteral nutrition for 7–10 days and octreotide at 3 mcg/kg/hour resulted in earlier time to diagnosis of chylothorax and decreases in ICU and total hospital lengths of stay; duration of mechanical ventilation; repeat intubations; total days of chest tube(s); central venous line use; and NPO days. If the patient's chyle production did not decrease to 10 mL/hour, the thoracic duct was ligated. Because most treatment data with octreotide are from case studies, further studies are needed (Bellini 2018; Yeh 2013; Panthongviriyakul 2008).

In some case studies, intravenous immunoglobulin has been used to treat chylothorax, given the rationale that the prolonged losses of lymphocytes in chyle decreased the patient's immunologic response to infection (Mohan 1999).

If the earlier treatments fail, more invasive therapies (e.g., thoracic duct ligation, pleuroperitoneal shunts, or chemical pleurodesis) can be considered.

Electrolytes

Electrolyte levels should be monitored frequently in patients undergoing cardiac surgical procedures. Supplementation of potassium and magnesium should be administered in these patients during surgery and in the immediate postoperative period to optimize contractility and avoid arrhythmias and other complications (Polderman 2004).

Intra- and extracellular sodium and potassium concentration gradients are important to maintain normal cardiac conduction.

Potassium concentrations should remain at a goal of 4–4.5 mEq/L to avoid arrhythmias and other postoperative complications. Intermittent potassium chloride doses of 0.5–1 mEq/kg/dose, to a maximum dose of 40 mEq, administered over 2 hours can be administered safely for concentrations below the goal range. Postoperative acidemia causes potassium to shift out of the cells, whereas diuretics and increased aldosterone concentrations post-bypass can deplete serum potassium. Furthermore, postoperative renal function can be compromised because of bypass, especially if the patient requires vasopressors to support blood pressure. A mild hypokalemia can be corrected using aldosterone receptor antagonists such as spironolactone, whereas a more severe hypokalemia should be corrected using intravenous or oral potassium supplements (Lexicomp 2019; Urso 2015; Parham 2006).

Calcium is an important electrolyte for myocardial muscle contraction and ion channel function. The neonatal myocardium is thought to be more dependent on extracellular calcium for optimal function because of low stores of calcium in the sarcoplasmic reticulum. Maintaining ionized calcium greater than 1.2 mmol/L is the goal in the postoperative patient. Calcium can be administered as calcium chloride or calcium gluconate. The preference of salt form tends to be institutionally driven. Historically, calcium chloride was preferred because it was recommended in pediatric advanced life support and results in a greater increase in ionized calcium than in gluconate (Marino 2018). However, calcium gluconate is more soluble in TPN than chloride when considered on a milliequivalent (mEq) basis. Caution needs to be used if dosing is ordered in milligrams of salts rather than milliequivalents. Continuous infusions of calcium chloride at a rate of 5–10 mg/kg/hour (15–30 mg/kg/hour of calcium gluconate = 0.07–0.14 mEq/kg/hour of elemental calcium) increase CO and end-organ perfusion and decrease lactate and vasoactive medication requirements (Averin 2016; Polderman 2004; Salsburey 1992).

Magnesium is an intracellular cation and important cofactor in several enzymatic processes in the body, including mitochondrial function and modulation of cellular potassium permeability, and helps prevent intracellular sodium overload (Polderman 2004). Hypomagnesemia negatively affects calcium uptake and distribution and can cause QRS widening and torsades de pointes (TdP) (Urso 2015). Maintaining magnesium concentrations of 2 mg/dL or greater helps prevent cardiac arrhythmias (including TDP and junctional ectopic tachycardia), hypertension, and coronary vasoconstriction. Intraoperatively, patients may receive magnesium sulfate at a dose of 25–50 mg/kg (maximum 1–2 g) administered into the CPB circuit over 10–20 minutes to avoid hypotension (Young 2012; Polderman 2004). Postoperatively, different strategies are used to maintain magnesium serum concentrations in the normal range. Some institutions continue to administer intermittent infusions like those administered in the operating room as described earlier, whereas others place magnesium sulfate in the maintenance intravenous fluid or TPN to run continuously (around 100 mg/kg = 0.8 mEq/kg/24 hours).

LOW CARDIAC OUTPUT SYNDROME

Low cardiac output syndrome affects up to 25% of neonates and young children post-cardiac surgery. Low cardiac output syndrome has been defined as inadequate oxygen delivery

secondary to decreased CO and increased metabolic demand. Specific guidelines on the safe and effective use of drugs for LCOS in children are often lacking; therefore, use of cardiovascular drugs in children is commonly derived from findings in adult trials. Neonates with congenital heart disease may appear hemodynamically stable after the operation and then suddenly have catastrophic decompensation. This is secondary to reperfusion injury and a systemic inflammatory response post-CPB. Low cardiac output syndrome has been reported as a cardiac index of less than 2 L/minute/m^2 postoperatively and is a predictor of acute cardiac death (Hoffman 2003); however, outcomes vary for each CHD and surgical procedure. One study reported that 25% of neonates with transposition of the great arteries (TGA) who underwent an arterial switch operation had a decline in cardiac index to 2 L/minute/m^2, typically occurring 6–18 hours after surgery (40% reduction from baseline) (Hoffman 2003). The reduction in CO greatly decreases the body's ability to transport oxygenated blood to the tissues (Chandler 2016). As a result, SVR increases to maintain blood pressure and perfusion to vital organs. Therefore, the goal of pharmacologic therapy is to maintain CO by optimizing preload, with increasing inotropy, and decreasing SVR postoperatively. An understanding of monitoring a patient post-cardiac surgery is paramount because it helps the clinician provide the safest and most effective pharmacotherapy.

Physical Assessment/Monitoring

Because direct measurement of CO is often unavailable, the physical examination may be paramount. Skin temperature should be warm with normal and even color. A patient with adequate CO will have a capillary refill below 3 seconds with normal blood pressure for age. Blood pressure depends on SVR and tends to move in the opposite direction of CO secondary to sympathetic reflexes. Low blood pressure can be an ominous late sign of LCOS. The patient should have a strong pulse and have normal sinus rhythm and heart rates for age on auscultation. Tachycardia that is often secondary to pain, agitation, or temperature aberrations or that is compensatory because of decreased CO will increase oxygen demand while decreasing tissue perfusion. Bradycardia diminishes tissue perfusion and can be an ominous sign for impending cardiac arrest. Finally, decreases in CO reduce renal blood flow and glomerular filtration, which manifest as decreased urinary output. Urinary output should be greater than 2 mL/kg/hour in neonates and infants and greater than 0.5 mL/kg/hour in older children and adults (Marion 2018; Hoffman 2003; Wessel 2001).

Postoperative patients require many catheters for monitoring, including peripheral, arterial, central venous, transthoracic (left and right atrial), and PA lines. In addition, central venous pressure (CVP) catheters are required because they are important in assessing preload. Placement of vascular access is imperative for the surveillance of hemodynamic parameters, CVP as a marker of preload, electrolytes, and blood gases, all of which are approached with different pharmacotherapies. Frequent monitoring of blood gases is important to evaluate acid-base status and correct base deficits. Normal acid-base balance is essential for optimal cardiac function, given that alkalosis is a vasodilator and acidosis is a vasoconstrictor (Hoffman 2013). Serum lactate concentrations should also be monitored because an increase in lactate indicates poor organ perfusion, which can lead to tissue oxygen debt. An elevated initial lactate concentration greater than 6 mmol/L (54 mg/dL) and/or an increase in lactate concentration of 0.75 mmol/L/hour (6.75 mg/dL/hr) or more were associated with a poor outcome (Charpie 2000). Appropriate ventilator management and administration of sodium bicarbonate or acetate in these patients can help normalize serum lactate.

In addition, patients with CHD must adequately be monitored with pulse oximetry to ensure that goal Sao$_2$ values are met. Patients with TGA and arch abnormalities should be monitored with pre- and post-ductal pulse oximetry. Cerebral and somatic near-infrared spectroscopy (NIRS) monitoring is a noninvasive technology used as a surrogate for perfusion to the brain and systemic circulation. Near-infrared spectroscopy involves placing cutaneous sensors on the forehead (cerebral perfusion) and on the flank region of the abdomen (kidney perfusion). Infrared light is used to detect changes in regional Sao$_2$. The NIRS values correlate with mixed venous oxygen saturation (Svo$_2$), which is another marker of systemic perfusion. Svo$_2$ is the percentage of oxygen bound to hemoglobin in blood returning to the right side of the heart. This reflects the amount of oxygen "left over" or returned to the heart after the tissues in the systemic circulation extract what is needed. The normal value of Svo$_2$ is 65%–75% (Marino 2018; Hoffman 2013; Ghanayem 2011; van Beest 2011; Tweddell 2007). One benefit of NIRS and Svo$_2$ monitoring is that values are often predictive of hemodynamic instability. Decreased Svo$_2$ or NIRS measures less than 50 are early signs of low CO and can occur before the changes in vital signs (Sivarajan 2011; Chakravarti 2009), allowing the clinician to make proactive (as opposed to reactive) interventions to prevent hemodynamic compromise.
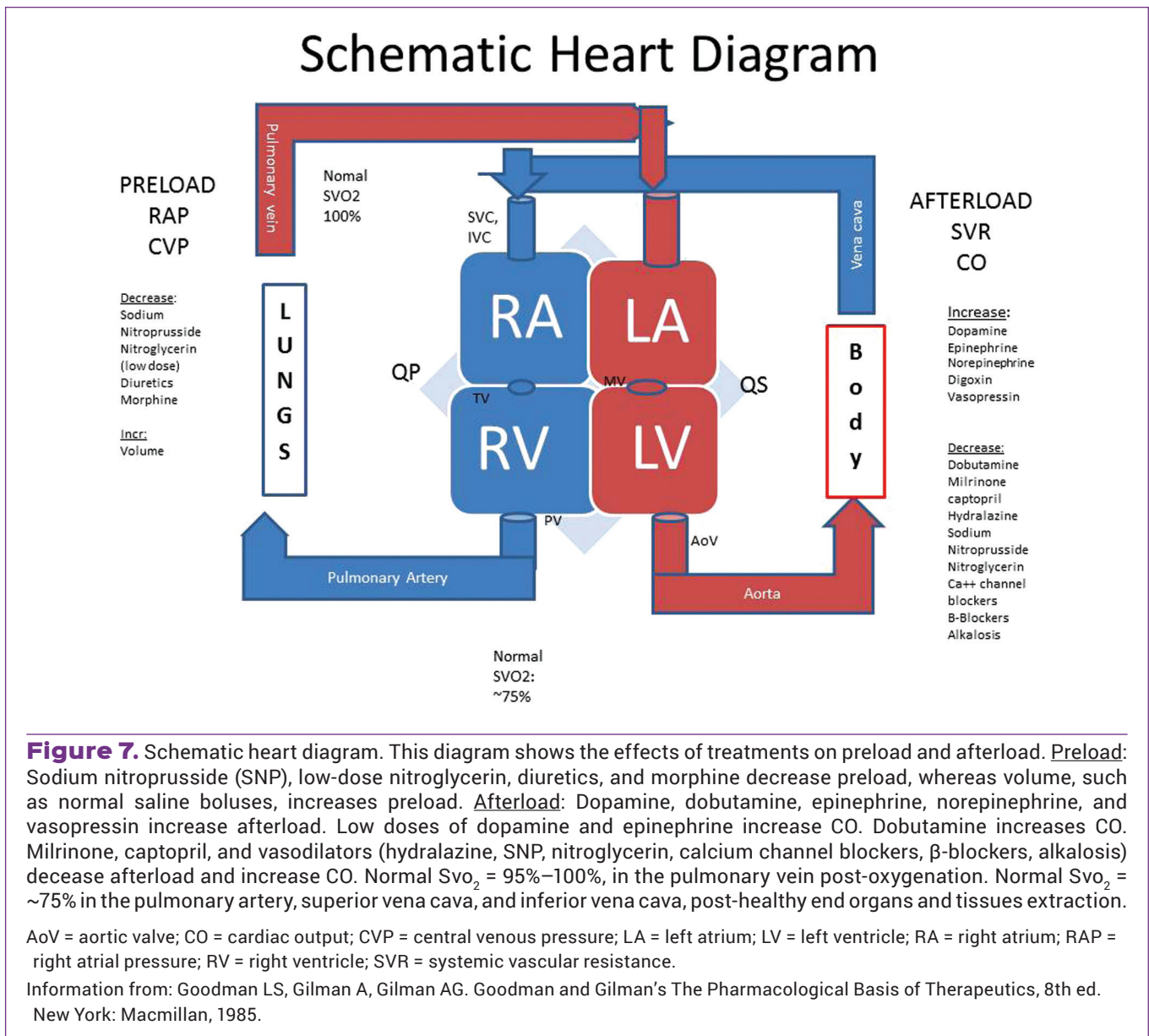
CARDIAC OUTPUT

The equation to calculate cardiac output (CO) is heart rate (HR) × stroke volume (SV). Heart rate and rhythm contribute to CO. Bradycardia decreases CO by decreasing the frequency of the contraction, thereby decreasing the blood ejected per minute. Tachycardia decreases CO by not allowing complete ventricular filling, thereby decreasing stroke volume. Cardiac arrhythmias are discussed more completely in another chapter.

Stroke volume is the amount of blood ejected from a ventricle (LV) every contraction, which depends on preload, afterload, and contractility.

PRELOAD

Preload is the compliance of the ventricles and the volume that distends the ventricle during diastole (Figure 7). Preload is primarily monitored and assessed by measuring CVP or right atrial pressure from a central venous catheter. If there is too little preload, the ventricle does not fill adequately; if there is too much stretch, the ventricle will lose function over time. Preload can be managed with extracorporeal ultrafiltration if more aggressive fluid removal is warranted. Modified ultrafiltration is now routinely used in the operating room, before cessation of CPB and transfer to the ICU. This practice often mitigates the degree of diuretic needed post-surgery. Ultrafiltration, however, should not replace diuretics for the initial treatment of acute decompensated heart failure (Shin 2009).

In addition to ultrafiltration, preload optimization is usually managed by balancing volume and diuresis. Preload can easily be exceeded in neonates, infants, and children whose ventricles are less compliant and is exacerbated after cardiac surgery. Fluid overload can be a primary pathophysiologic mechanism in both LCOS and heart failure. Although the possible negative effects of diuretic therapy have been controversial, such as decreased intra-arterial volume with neuroendocrine hyperactivation (through the renin-angiotensin-aldosterone system), diuretics decrease the symptoms of vascular congestion, such as dyspnea and edema. The three main classes of diuretics are loop diuretics, thiazide diuretics, and mineralocorticoid receptor antagonists.

Figure 7. Schematic heart diagram. This diagram shows the effects of treatments on preload and afterload. Preload: Sodium nitroprusside (SNP), low-dose nitroglycerin, diuretics, and morphine decrease preload, whereas volume, such as normal saline boluses, increases preload. Afterload: Dopamine, dobutamine, epinephrine, norepinephrine, and vasopressin increase afterload. Low doses of dopamine and epinephrine increase CO. Dobutamine increases CO. Milrinone, captopril, and vasodilators (hydralazine, SNP, nitroglycerin, calcium channel blockers, β-blockers, alkalosis) decease afterload and increase CO. Normal Svo_2 = 95%–100%, in the pulmonary vein post-oxygenation. Normal Svo_2 = ~75% in the pulmonary artery, superior vena cava, and inferior vena cava, post-healthy end organs and tissues extraction.

AoV = aortic valve; CO = cardiac output; CVP = central venous pressure; LA = left atrium; LV = left ventricle; RA = right atrium; RAP = right atrial pressure; RV = right ventricle; SVR = systemic vascular resistance.

Information from: Goodman LS, Gilman A, Gilman AG. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. New York: Macmillan, 1985.

Loop Diuretics

Loop diuretics inhibit sodium and chloride reabsorption in the thick ascending limb of the loop of Henle and have the most potent natriuretic effect. Loop diuretics also cause depletion of potassium, calcium, and magnesium. Furosemide is the most commonly used loop diuretic. Bumetanide (40 times more potent than furosemide, enterally) and torsemide (2 times more potent than furosemide, enterally) are other loop diuretics that are used less commonly and reserved for more severe or resistant fluid overload. A final loop diuretic used by some centers in patients with sulfa allergies is ethacrynic acid. Ethacrynic acid is about 25% less potent than furosemide when given enterally, and the intravenous formulation (as of now) is of high expense. Acute adverse effects of loop diuretics include electrolyte abnormalities (e.g., hyponatremia, hypochloremia, hypokalemia), hypotension, and renal insufficiency. Continuous infusions of loop diuretics can result in less hemodynamic and electrolyte variations and less fluctuation in urinary output and can achieve greater urinary output than equivalent intermittent dosing. Overuse of loop diuretics can cause metabolic alkalosis, requiring chloride replacement, usually with ammonium chloride and/or arginine hydrochloride (Pacifici 2012). Long-term loop diuretic therapy can lead to nephrocalcinosis and ototoxicity, usually with high intravenous doses. Secondary to increased calcium excretion, an increased risk of bone fractures has also been reported (Kim 2017; McCallister 2015; Miller 2014; Pacifici 2012).

Thiazide Diuretics

The primary role of thiazide and thiazide-like diuretics in LCOS is to provide synergy with loop diuretics through sequential inhibition of solute reabsorption (or sequential nephron blockade) at the distal convoluted tubule. This may also decrease the dose requirement or frequency of loop diuretics (Yancy 2013; Jentzer 2010).

Commonly used thiazide diuretics are chlorothiazide, hydrochlorothiazide, and metolazone (a thiazide-like diuretic). Thiazides tend to have a flat dose-response curve and may produce ineffective diuresis without loop diuretics in patients with renal insufficiency (e.g., CrCl less than 30 mL/min/1.73 m^2. Thiazide diuretics induce calcium reabsorption and are therefore used as treatment of nephrocalcinosis secondary to loop diuretics. Thiazide diuretics also mitigate bone degradation. This is especially critical in patients with DiGeorge syndrome, who often have CHD (Lilly 2016).

Survival outcomes when using thiazide diuretics in conjunction with loop diuretics remain controversial. Mortality rates from heart failure in patients who received high-dose loop diuretics were compared with those in patients who received synergistic thiazide diuretic added from a multicenter study. Of 13,898 admissions, 1048 (7.5%) used adjuvant metolazone, which was associated with hyponatremia, hypokalemia, worsening renal function, and increased mortality (p<0.05). High-dose loop diuretics were associated with hypokalemia and hyponatremia (p<0.002), but only worsening renal function retained significance (p<0.001). High-dose loop diuretics were not associated with reduced survival. The authors of this study suggested that until randomized control trial data prove otherwise, titration of loop diuretics is preferred to routine early addition of thiazide-type diuretics when diuresis is inadequate (Brisco-Bacik 2018). However, in practice, either strategy can be used.

In a descriptive, retrospective study, 97 patients younger than 1 year who received metolazone in the cardiac ICU were reviewed. The participants received an initial metolazone dose of 0.27 plus or minus 0.1 mg/kg/day, which was increased to a maximum dose of 0.43 mg/kg/day together with other diuretics, including furosemide (87.6%), spironolactone (58.8%), acetazolamide (11.3%), bumetanide (7.2%), and ethacrynic acid (1%). These authors concluded that metolazone increased urinary output in a select group of patients (Wise 2018). If augmentation of urinary output is desired in the ICU patient who cannot take oral medications, intravenous chlorothiazide can be considered at 5–20 mg/kg/day divided into two to four doses, though this has not been well studied in pediatric patients (Moffett 2007).

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone) decrease sodium reabsorption and potassium excretion in the collecting ducts of kidneys. The overall diuretic effect is weak; however, mineralocorticoid receptor antagonists mitigate the risk of hyponatremia and hypokalemia with loop and thiazide diuretics and the need for electrolyte supplementation. In addition, mineralocorticoid receptor antagonists improve the long-term prognosis in patients with symptomatic heart failure, which is thought to be secondary to a cardiac remodeling effect from aldosterone antagonism. Both spironolactone and eplerenone reduce mortality in adults with heart failure when added to standard therapy (Pitt 2014, 1999). This effect is independent of their diuretic effect and is mediated by inhibition of myocardial fibrosis formation, an important component of LV remodeling. In a randomized trial of 42 boys with cardiomyopathy secondary to Duchenne muscular dystrophy, adding eplerenone to angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker therapy attenuated the decline in LV systolic function. Adverse effects of mineralocorticoid receptor antagonists include hyperkalemia (with both drugs) and gynecomastia (with spironolactone) (Brisco-Bacik 2018; Wise 2018; Kirk 2014; Pitt 2014, 1999; Witte 1986; Hobbins 1981).

Carbonic Anhydrase Inhibitors

Concomitant use of carbonic anhydrase inhibitors, such as acetazolamide, with loop diuretics decreases bicarbonate and increases chloride (reduces loss of chloride in the urine)

Table 4. Diuretic Comparison Chart[a]

Diuretic	Action Site	Renal Blood Flow	Na Excretion (%)	Cl⁻ Excretion	K⁺ Excretion	HCO₃⁻ Excretion	H₂PO₄⁻ Excretion	CA²⁺ Excretion	Mg²⁺ Excretion
Loop (Bumex/Lasix)	Loop, ascending	↑	20−25	↑↑ ↑	↑↑	↑	↑	↑↑	↑↑
Acetazolamide	Proximal tube	↓	3−5	0	↑↑ ↑	↑↑ ↑	↑↑	0↑	0↑
Thiazides	Distal segment	0	5−8	↑↑	↑↑	↑↑	↑	↓	↑
Metolazone	Distal segment	0	5−8	↑↑	↑	0	↑	0	↑
Spironolactone	Distal segment	0	2−3	↑	↓	0	0	↑	↑
Mannitol[b]	Proximal tube	↑	NA	↑	↑	0	↑	↑	↑

[a]This table compares diuretics by the site of action of each diuretic, the effect on renal blood flow and the percent sodium (Na⁺) excretion relative excretion of electrolyte, with the number of arrows indicating more excretion of electrolytes, compared to the other diuretics, including chloride (Cl⁻), potassium (K⁺), bicarbonate (HCO₃⁻), phosphate (H₂PO₄⁻), calcium (CA²⁺), magnesium (Mg²⁺).

[b]% Na⁺ excretion by mannitol was not available (NA).

Information from: Goodman LS, Gilman A, Gilman AG. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. New York: Macmillan, 1985; Lexicomp. Pediatric & Neonatal Dosage Handbook. Hudson, OH: Lexicomp, 2019.

in the blood. Hypochloremic (contraction) metabolic alkalosis (pH 7.45 or greater, bicarbonate greater than 30 mmol/L, and base excess greater than 5 mmol/L) is common in pediatric cardiac patients postoperatively receiving high-dose loop diuretic therapy. In a retrospective, observational study of 58 pediatric cardiac patients, acetazolamide dosed at a median dose of 8.7 (5−10) mg/kg/day orally divided twice daily with a maximum dose of 20 mg/kg/day decreased metabolic alkalosis and serum bicarbonate in patients with metabolic alkalosis. Treatment with acetazolamide was maintained over 4 days (range 3−6) and was associated with decreased serum bicarbonate and Pco₂ while significantly increasing urinary output. The study cautioned about the need to monitor for overcorrection and metabolic acidosis, suggesting that limiting treatment to 2 days could be reasonable (Lopez 2016). Acetazolamide has also been used intravenously for this indication in this population. One study reported on 28 patients who developed hypochloremic metabolic alkalosis from long-term loop diuretics and were treated with intravenous acetazolamide. These patients had lower serum bicarbonate, acid-base excess values, and increased chloride values. The study showed no change in urinary output (Moffett 2007). Table 4 compares diuretics by class, site of action, percent sodium excretion, relevance to site of action, and effect on other electrolytes, including chloride, potassium, bicarbonate, calcium, and magnesium.

CONTRACTILITY

Sympathomimetic Agents

Contractility is the force or strength of muscle contraction and is affected by myocardial oxygen supply, acidosis, electrolyte imbalance, intracellular calcium, and circulating or endogenous catecholamines. Inotropic agents such as dobutamine, isoproterenol, dopamine, and epinephrine are important in managing LCOS.

Dobutamine is primarily a β_1-adrenergic agonist with weak β_2 and α_1 activity. Dobutamine can be used for patients with LCOS with dilated cardiomyopathy or after cardiac transplantation, but its use has diminished after the introduction of milrinone. Similar to dobutamine, isoproterenol is a potent β_1- and β_2-receptor agonist, which is useful in the denervated heart post-cardiac transplantation (Yusuf 1987).

Dopamine is a sympathomimetic amine that directly stimulates β_1, α_1, and dopaminergic receptors. Dopamine is a precursor to norepinephrine; hence, dopamine administration increases norepinephrine release. Dopamine results in afferent arteriole and coronary vasodilation at lower doses; however, it provides inotropic and chronotropic affects with moderate dosing. Dopamine has reported use for LCOS after pediatric heart surgery, including after stage I Norwood palliation (Roeleveld 2018). However, high-dose dopamine causes vasoconstriction and is not typically used in the cardiac

population because of further increases in SVR and increased oxygen consumption (Marino 2018).

Epinephrine at lower doses is an effective inotrope and chronotrope secondary to β-agonist activity; however, at higher doses, epinephrine agonizes α-receptors in the periphery, resulting in vasoconstriction. Epinephrine should be used judiciously at lower doses in LCOS because even moderate doses increase myocardial oxygen consumption and, in bolus doses, cause vasoconstriction that can limit blood flow to end organs. Epinephrine is also arrhythmogenic (ventricular ectopy of fibrillation) when used in an irritable myocardium (Perondi 2004). The goal of therapy is to use the lowest effective dose, including in cardiac arrest management. A pre-arrest, small epinephrine dose can be used in patients postoperative CPB for hypotension or persistent bradycardia with a pulse and/or in patients with an at-risk myocardium to prevent cardiac arrest and allow time to treat an acute reversible problem (e.g., draining of pericardial effusion, opening the sternum, revascularizing a shunt). These small doses are 1/10th the usual bolus doses of epinephrine (1 mcg/kg/dose) (Marino 2018). In a prospective, randomized, double-blind, controlled trial of pediatric patients comparing high-dose (0.1 mg/kg/dose) with standard-dose (0.01 mg/kg/dose) epinephrine for in-hospital cardiac arrest, high-dose epinephrine was associated with worse 24-hour survival (Perondi 2004).

Milrinone is a phosphodiesterase type 3 inhibitor and the preferred drug for decompensated heart failure and LCOS prevention and treatment at most institutions. Milrinone is an inodilator, increasing contractility and reducing afterload. Milrinone is also a lusitropic agent, which enhances cardiac relaxation and helps decrease myocardial oxygen consumption and optimize preload. Milrinone also decreases PVR, rendering it a potential option for pulmonary hypertension (Chang 1995). Milrinone can be initiated with a loading dose of 50 mcg/kg infused over 15–60 minutes, though this may be omitted in the setting of hypotension or risk of hypotension (Soliman 2018; Bailey 1999). Milrinone is administered as a continuous infusion at doses of 0.25–1 mcg/kg/minute. In a randomized, double-blind, placebo-controlled trial of pediatric patients post-cardiac surgery, children treated with a

high-dose milrinone infusion (0.75 mcg/kg/minute) were at a lower risk of LCOS (Hoffman 2003). However, neonates and preterm infants may become hypotensive with higher doses and should be treated with the lowest effective dose. Other adverse effects to monitor include hypokalemia, thrombocytopenia, and bronchospasm.

Preference of inotropic agent to treat LCOS is institution-specific; however, milrinone, dobutamine, dopamine, and epinephrine have been the most studied and tend to be preferred. A 2015 Cochrane review concluded that evidence is insufficient regarding the effectiveness of perioperative milrinone in preventing death or LCOS in children undergoing surgery for congenital heart disease, compared with placebo. The review also concluded that no differences have been shown in reducing the risk of LCOS or death between milrinone and other inodilators, such as dobutamine, in the immediate postoperative period. This review is limited because of the few studies included. A recent randomized study of pediatric patients undergoing a Fontan procedure showed that initiating milrinone before bypass with no loading dose at 0.5 mcg/kg/minute, rather than postoperatively, facilitated weaning from CPB, decreased CVP and serum lactate concentrations, and decreased the need for postoperative pharmacologic support. In addition, milrinone increased CO and arterial oxygen saturation (Soliman 2018). Another study surveyed European hospitals and summarized the treatment preferences according to indication. In treating LCOS with elevated SVR, milrinone was used by 34% and epinephrine by 24%. In treating LCOS with low SVR, dopamine was used by 20%, epinephrine by 29%, and norepinephrine by 24% of responding hospitals. In treating LCOS with elevated PVR, milrinone was used by 17%, inhaled nitric oxide by 20%, and prostacyclin derivatives by 22% (Vogt 2011). Overall, milrinone, epinephrine, dopamine, and dobutamine were used in over 50% of the reported drug regimens for LCOS (Vogt 2011). Another survey and systematic review on preferences of inotropes for LCOS surveyed 197 members of the Pediatric Cardiac Intensive Care Society. Ninety-eight members (50%) responded, representing 62 international centers. Milrinone was routinely used perioperatively by 97% of respondents, vasopressin by 44%, epinephrine by 43%, dopamine by 36%, and dobutamine by 11%. This survey and review showed that despite the lack of sufficient evidence, milrinone is used by most caregivers after congenital heart surgery (Roeleveld 2018). Vasoconstrictors should routinely be avoided in LCOS, except in the presence of a concomitant low SVR or significant hypotension sacrificing perfusion (Marino 2018) with use of inotropic agents. Hypotension with poor perfusion can present in the setting of postoperative sepsis or adrenal insufficiency, for which vasoconstrictors may temporarily be needed. Norepinephrine is a potent α-agonist with minor β_1 and β_2 effects. Norepinephrine can augment coronary blood flow by increasing systemic diastolic pressure at the expense of increased systemic afterload. Alternatively, phenylephrine

is a pure α-agonist that causes arterial vasoconstriction and increases blood pressure. Phenylephrine maintains arterial diastolic pressure and coronary blood flow, which is important for patients with myocardial ischemia (Tanaka 2003); however, phenylephrine is associated with a potential for reflex bradycardia. In addition, a phenylephrine bolus of 10 mcg/kg/dose is a treatment modality for hypercyanotic crisis or a "tet" spell in patients with unrepaired TOF. A phenylephrine bolus is also useful for the treatment of low SVR caused by vasodilator medications.

Vasopressin is a hormone that works on vasopressin (V_1 and V_2) receptors in blood vessels. Vasopressin causes peripheral vasoconstriction, increasing SVR and mean arterial blood pressure without a direct cardiac effect, though it can decrease heart rate and CO. Vasopressin can be used to increase blood pressure in place of α-agonists, to decrease myocardial oxygen demand and risk of arrhythmias (Roeleveld 2018; Hoffman 2003). Caution should be acknowledged on the potential for fluid retention with vasopressin; however, this can be beneficial in patients with suboptimal preload. Data analyses support the use of a vasopressin in persistent hypotension after pediatric heart surgery. A prospective observational study noted significant variability in plasma arginine vasopressin concentrations after surgery for CHD, but low concentrations were not associated with poor hemodynamics or inotropic score, which supports its potential usefulness (Mastropietro 2010). One study showed improved hemodynamics and a decreased inotropic score with administration of a vasopressin after an arterial switch or Norwood in 19 neonates using 0.3 milliunits/kg/minute initiated in the operating room compared with 18 neonates who did not receive early vasopressin. Mean fluid resuscitation in the first 24 hours was significantly lower in the vasopressin group than in the standard group (182 ± 61 mL/kg vs. 223 ± 53 mL/kg, p=0.03). The vasopressin group also reached median net negative cumulative fluid balance sooner (55 hours: interquartile range [IQR] 45, 74 vs. 76 hours: IQR 69, 92; p=0.02); however, sodium concentrations in the first 48 hours were lower in the vasopressin group (132 vs. 137 mmol/L, p=0.01). Median maximum inotrope scores in the first 24 hours were significantly lower in the vasopressin group (9: IQR 5, 12.5 vs. 16.5: IQR 10.3, 22.1; p=0.02). There was a nonsignificant trend toward shorter duration of mechanical ventilation and cardiovascular ICU length of stay in the vasopressin group. The authors concluded that a low-dose vasopressin infusion initiated in the operating room after complex neonatal cardiac surgery is associated with decreased fluid resuscitation and catecholamine requirements in the first 24 postoperative hours (Alten 2012).

Table 5 summarizes the effects of sympathomimetic agents and other agents commonly used to support patients with LCOS. See the table for further explanation per agent.

Table 5. Sympathomimetic/Others: Review Chart: Pharmacologic Actions of Sympathomimetics/Others[a]

Drug	Dosing	Agonist Activity[b]			Vascular Effects[b]					Cardiac Effects[b]		
		Alpha	Beta-1	Beta-2	BP	SVR	PVR	BBF	RBF	HR	CO	Coronary Perfusion
Epinephrine	0.005–1 mcg/kg/min	XXXX	XXX	XX	↑	↓↑	↑	↑	↓	↑↑	↑↑↑	↑
Norepinephrine	0.05–1 mcg/kg/min	XXXX	XX	0	↑	↑	↓	↓	↓	↓	0↑↓	↑
Phenylephrine	0.1–0.5 mcg/kg/min	XXXXX	0	0	↑	↑↑	↑	↓	↓	↓	↓	↑
Dopamine	2–20 mcg//kg/min	XX	XX	XX	0↑	↓	0↑	↑	↑	0↑	↑	↑
Dobutamine	2–20 mcg/kg/min	0	XX	XX	0	↓	↓	–	0↑	0↑	↑	↑
Isoproterenol	0.05–2 mcg/kg/min	0	XXX	XXXX	↓	↓	↓	↓	↓	↑↑↑	↑↑↑	↓
Milrinone	0.25–0.75 mcg/kg/min	Phosphodiesterase type 3 inhibitor			0↓	↓	↓	0	0	0	↑	0
Fenoldopam	0.2–0.8 mcg/kg/min	Dopamine-1 receptor agonist			↓	0	↓	0	↑	↓↕	0	0
Vasopressin	0.3–2.0 mU/kg/min	None – V_1 and V_2 receptors, pituitary, kidneys			↑	↑	–	–	0↓	0↓	↑	↑

[a]This table summarizes the effects of sympathomimetic agents and other agents commonly used to support patients with LCOS. Number of X's per agent reflects their relative agonist activity. Zeros or dashes mean no action. Number of arrows per agent represent increased relative effects. Agonist actions and effects are dose dependent (i.e. low to moderate doses of sympathomimetics, such as epinephrine at doses less than 0.1 mcg/kg/min or dopamine 2-10 mcg/kg/min), β-1-adrenergic effects predominate, causing increased contractility and heart rate, which increase cardiac output, but may cause decreased blood pressure from the β-2 agonist activity. High doses of epinephrine >0.1 mcg/kg/min or dopamine >10 mcg/kg/min, causes alpha mediated vasoconstriction and raises systemic blood pressure, PVR and SVR. Phenylephrine, which has predominant alpha adrenergic activity, increases SVR and decreases cardiac output. Since milrinone is a phosphodiesterase type 3 inhibitor, it does not support blood pressure, but decreases pulmonary vascular resistance and effectively increases contractility and perfusion to the kidneys. Vasopressin stimulates V_1 and V_2 receptors, increasing blood pressure, systemic vascular resistance (decreases renal blood flow/perfusion) and increases cardiac output without increasing heart rate. Most agents increase coronary perfusion unless noted otherwise.

[b]Dose-dependent.

BBF = brain blood flow; BP = blood pressure; CO = cardiac output; HR = heart rate; PVR = pulmonary vascular resistance; RBF = renal blood flow; SVR = systemic vascular resistance.

Information from: Goodman LS, Gilman A, Gilman AG. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. New York: Macmillan, 1985.

AFTERLOAD

Vasodilators

Afterload is the pressure at which a ventricle must pump to eject blood. In a structurally normal heart, the afterload of the RV is the PVR, and the afterload of the LV is the SVR. Systemic vascular resistance equals mean blood pressure minus right atrial pressure divided by CO (SVR = MBP − RAP/CO). Afterload is evaluated by indirect methods of assessing CO, including serum lactate, urinary output, and peripheral perfusion (i.e., core vs. peripheral temperature, capillary refill time). Poor perfusion to the kidneys stimulates the renin-angiotensin system, increasing SVR and causing decreased end-organ perfusion. Excessive increases in SVR secondary to poor perfusion cause hypertension and increase the risk of heart failure, IVH, and mortality. Pharmacologic agents that reduce SVR include sodium nitroprusside, nitroglycerin, nicardipine, and milrinone.

Sodium nitroprusside is a potent direct-acting vasodilator that reduces afterload, and concomitantly preload, from a

lower end-diastolic volume before contraction. Nitroprusside use has declined in recent years because of the potential for cyanide/thiocyanate toxicity, methemoglobinemia, and tachyphylaxis with higher doses and long-term use (doses of 4 mcg/kg/minute or greater for 3 days or for more than 24 hours in patients with renal dysfunction). Patients at risk of cyanide toxicity because of elevated or prolonged exposure or underlying hepatic impairment may benefit from the addition of sodium thiosulfate to improve the metabolism of nitroprusside to thiocyanate. Those who develop methemoglobinemia should be treated with blood transfusion and/or methylene blue. Successful and contemporary use of lower doses of 0.2–2 mcg/kg/minute results in desired reduction of blood pressure without these toxicities (Davis 2015).

Nitroglycerin is a potent smooth muscle relaxant and vasodilator that plays a specific role in cardiac surgery. Nitroglycerin has been used to reduce afterload in pediatric patients post-cardiac surgery and in cardiogenic shock. Given its potency and affinity for the coronary arteries, however, nitroglycerin remains paramount for surgical procedures involving coronary manipulation. An example is the arterial switch operation, which is the surgical procedure of choice for neonates with TGA. The operation involves transection of both coronary arteries from the transposed aorta, followed by mobilization and reanastomosis to the neoaorta. Furthermore, CPB increases endothelin-1 and endogenous norepinephrine, both increasing coronary vasoconstriction postoperatively. Low-dose nitroglycerin (0.25 mcg/kg/minute) reverses the coronary artery vasoconstriction/vasospasm induced by endothelin-1 and may therefore be beneficial in postoperative management (McGowan 1995). For this reason, the European Task Force recommends an immediate postoperative ECG to look for ST-segment elevations and the administration of nitroglycerin emergently for evidence of ischemia (Sarris 2017; Oskarsson 2002). Therefore, nitroglycerin is an optimal vasodilator for patients requiring afterload reduction post-cardiac surgery involving coronary artery manipulation.

Although well established in older children and adults, use of calcium channel blockers has been avoided in children younger than 1 year. This general avoidance stems from concerns of safety and efficacy in the setting of sarcoplasmic reticulum development, as well as from concerns for myocardial depression resulting from a lower density of myocardial calcium channels. Infants appear to have an increased sensitivity to changes in extracellular calcium and calcium channel blockade.

As vasodilators, dihydropyridine calcium channel blockers such as amlodipine, nifedipine, and nicardipine are useful post-cardiac surgery. These agents have no effect on the sinus or atrial node in slowing conduction compared with non-dihydropyridines (verapamil, diltiazem). Given that the infantile heart heavily depends on myocardial calcium influx for contractility, clinical use of verapamil in infants is associated with clinical deterioration with life-threatening bradycardia, severe hypotension, and cardiovascular collapse (Epstein 1985; Radford 1983).

Nicardipine blocks calcium influx after depolarization across myocardial and smooth muscle cells and has an ideal ICU pharmacokinetic profile with both rapid onset (50% of maximum effect within 45 minutes) and a short half-life of 30 minutes. Nicardipine, currently the only intravenous dihydropyridine calcium channel antagonist in the United States, reduces myocardial oxygen consumption compared with other calcium channel blockers. These effects are a function of selectivity to l-type calcium channels that predominate within vascular smooth muscle, limiting the effects on the potentially underdeveloped myocardium (Sarris 2017). Nicardipine has been studied with positive outcomes for the treatment of hypertension in neonates (Gouyon 1997). In addition, other investigators performed a retrospective review in 68 pediatric cardiac postoperative patients requiring blood pressure management with nicardipine. The patients were separated into two groups: infants younger than 6 months (group 1: n=33 [48%]) and infants older than 6 months (group 2: n=35 [52%]). During the study, patients received nicardipine after cardiac surgical procedures at a dose of 0.5–1 mcg/kg/minute, initiated at a mean of 6.6 plus or minus 13.1 hours postoperatively in group 1 and 5.4 plus or minus 7.8 hours in group 2. A total of nine patients (13%) from both groups had clinically significant hypotension necessitating dosing titration (nonsignificant difference between groups). No other major adverse events occurred after nicardipine administration. These authors concluded that nicardipine is well tolerated after cardiac surgical procedures in children irrespective of age or underlying pathology and should be considered safe in children of all ages for control of hypertension after cardiac surgical procedures (Stone 2018).

TRANSITIONING TO ENTERAL MEDICATIONS AND DISCHARGE

Many patients require continued afterload reduction for persistent hypertension, valvular regurgitation, and/or mitigation of CHF. This is usually achieved with diuretics, digoxin, ACE inhibitors, and/or β-blockers. The addition of mineralocorticoid receptor antagonists should also be considered because of their cardiac remodeling activity.

Captopril and enalapril are orally active ACE inhibitors that are widely used in pediatric patients with CHDs. The effects of ACE inhibitors on the renin-angiotensin-aldosterone system in pediatric patients are similar to those in adults (Castro Díez 2019; Momma 2006), and ACE inhibitors lower SVR and left-sided pressures without significantly affecting PVR. However, ACE inhibitors can decrease left-to-right shunting of blood in infants with large VSDs and concomitant pulmonary hypertension. In addition, ACE inhibitors induce a small increase in LV ejection fraction and systemic blood flow in children

with LV dysfunction, mitral regurgitation, and aortic regurgitation. Common adverse effects of ACE inhibitors in pediatric patients include hypotension and renal injury. These adverse effects usually occur within 5 days after starting therapy or after a dose increase, during which the risk is increased in the setting of hypovolemia and/or hyponatremia, which is present post-cardiac surgery with use of diuretics, ultrafiltration, and other afterload-reducing agents. It is therefore warranted to be conservative with dosing upon initiation, to titrate judiciously, and to monitor blood pressure until a therapeutic dose is achieved. It is also recommended to omit or reduce diuretic doses 24 hours before initiating ACE inhibitors (Momma 2006). Captopril dosing is 0.3–6 mg/kg/day, usually divided every 8 hours in children. Enalapril is administered orally, once or twice a day, and daily doses are 0.1–0.5 mg/kg/day. Systolic blood pressure (SBP) should be assessed immediately before the next scheduled dose and 2 and 4 hours after a dose of captopril and 4 and 8 hours after a dose of enalapril, given its delayed peak and longer half-life, especially in neonates. Captopril is therefore usually favored to enalapril for initiation of therapy and in patients younger than 1 year.

Therapeutic trials of ACE inhibitors have been reported in children with heart failure, including myocardial dysfunction, left-to-right shunts (e.g., large VSD or pulmonary hypertension), and aortic or mitral regurgitation and in patients after a Fontan procedure (Castro Díez 2019; Schranz 2016). The results of a multicenter randomized trial comparing the impact of enalapril administration with placebo in infants with single ventricle physiology in the first year of life showed that enalapril did not improve somatic growth, ventricular function, or heart failure severity. These findings do not support routine enalapril use in this population. No difference in serious cardiac events occurred in either group (Hsu 2010).

β-Blockers are beneficial and even lifesaving in adults with CHF and are therefore part of the standard treatment guidelines. For children, β-blockers are not routinely used; however, similar benefits can be expected. Dosing may also have to be specifically adapted for different age groups. Investigators in the CHF-PRO-INFANT trial, a prospective, randomized, open multicenter trial that compared infants treated with digoxin and diuretics (n=510) with 10 infants receiving additional β-blocker therapy, found that, after 17 days, infants treated with β-blockers (propranolol 1.6 mg/kg/day) improved significantly with respect to Ross heart failure score (3.3 vs. 8.3, p=0.002). Furthermore, those treated with β-blockers had lower renin concentrations (338 vs. 704 mU/L, p=0.008) and lower mean heart rates on Holter ECG (118 vs. 142 beats/minute, p=0.001). The authors concluded that propranolol in addition to digoxin with diuretics can reduce clinical symptoms of heart failure in infants with congenital heart disease who have increased neurohormonal activation (Buchhorn 2001). However, only a few patients received propranolol. A Cochrane review also concluded that data are insufficient to recommend or discourage β-blocker use in children with CHF. Currently available data analyses suggest that children with heart failure benefit from β-blocker therapy. Further research is needed to establish guidelines for therapy (Alabed 2016).

CONCLUSION

It is critically important to evaluate patients with CHD completely and to provide them with appropriate supportive care before surgery as well as postoperatively. In addition to the topics we covered in this chapter, pharmacists must be prepared to frequently evaluate and reevaluate a patient's therapy in the postoperative period because changes can occur quickly. Postoperative complications include changes in cardiac function, including arrhythmias (which can be common in the first 48 hours postoperatively), and changing fluid needs (requiring re-concentration of intravenous medications). Pharmacists must pay attention to acid-base status and to monitor for decreases in renal function in order to discern which medications will require dose adjustments. This becomes even more complex if the patient requires continuous renal replacement therapy to manage fluid balance and/or ECMO, which also affects medication dosing secondary to adherence of medications to the ECMO circuit, changes in volume of distribution of medications, and changes in medication clearance. In addition, signs and symptoms of infection must be recognized and decisions made whether to use prophylactic antibiotics. If a patient has sepsis or symptoms of infective endocarditis, antibiotic choice and treatment duration are important. Each patient must be evaluated for adequate pain control. Optimal nutrition with TPN, depending on the patient's fluid balance needs in the acute phase of recovery, is important for healing and for achieving growth that is as normal as possible. Finally, the patient must be transitioned to appropriate oral medications, doses, and frequencies, with plans for future monitoring to optimize therapy.

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Practice Points

Many challenges face clinical pharmacists in optimizing pharmacotherapy for patients with CHDs and in pharmacologic therapy pre- and postoperatively. Studies of pediatric patients are limited compared with those of adult patients with cardiac pathophysiology. Understanding CHD lesions, pathophysiology, hemodynamics, and pediatric pharmacology is necessary to optimize therapeutic outcomes.

- Of importance, clinical pharmacists should understand that alprostadil must be initiated emergently for cyanotic heart defects as well as for select acyanotic defects (arch abnormalities).
- Various pharmacologic agents are used to close PDAs. Clinical pharmacists should understand the potential contraindications to using NSAIDs in neonates with VLBW (less than 1500 g) compared with pharmacologic treatments for larger infants.
- Digoxin is an important pharmacologic treatment to decrease interstage 1 mortality in patients with single ventricle defects.
- Patients with BT shunts require anticoagulation or antiplatelet therapy postoperatively.
- Milrinone and epinephrine are the most common medications used for LCOS; however, clinical pharmacists need to understand the importance of monitoring therapy and the surrogates of CO and perfusion, such as NIRS, right atrial pressure, urinary output, blood pressure, and dose-dependent effects of pharmacologic agents on hemodynamics, including preload, afterload, contractility, heart rate, and blood pressure that require transition to or addition of other sympathomimetics or vasodilators.
- Clinical pharmacists should understand the importance of maintaining physiologic concentrations of calcium, potassium, and magnesium for optimal cardiac function.
- Clinical pharmacists need to understand which oral pharmacologic agents the patient may require for discharge.

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Self-Assessment Questions

1. According to Freed's 1981 study, which one of the following patients with heart lesions would benefit most from alprostadil to keep the patent ductus arteriosus (PDA) open?

    A. Patient with acyanotic lesions.
    B. Patient with cyanotic lesions.
    C. Patient with either cyanotic lesions or acyanotic heart lesions (including interrupted aortic arch [IAA] and coarctation of the aorta [CoA]).
    D. Patient with single ventricle lesions post-stage I repair.

Questions 2 and 3 pertain to the following case.

A.B. is a newborn boy (weight 3 kg) 2 hours old with circumoral cyanosis. His Sao_2 is 75%.

2. Which one of the following best characterizes A.B.'s as-yet undiagnosed heart lesion?

    A. Atrial septal defect (ASD).
    B. Transposition of the great arteries (TGA).
    C. Ventricular septal defect (VSD).
    D. PDA.

3. Alprostadil 0.05 mcg/kg/minute is initiated for A.B. Which one of the following adverse effects is most important to monitor for in A.B.?

    A. Flushing of the skin.
    B. Hyperkalemia.
    C. Hypertension.
    D. Apnea.

Questions 4 and 5 pertain to the following case.

C.D., a newborn boy (weight 3.5 kg), was discharged home; however, his mother brings him to his pediatrician a few weeks post-discharge, concerned that he has been fussy. When questioned further, his mother reports that he is not finishing his feeds and is sweating. The pediatrician also finds that C.D. has a high respiratory rate and a heart murmur.

4. Which one of the following would best characterize C.D.'s as-yet undiagnosed heart lesion?

    A. Acyanotic lesion.
    B. Cyanotic lesion.
    C. Single ventricle.
    D. Normal heart with respiratory distress.

5. C.D. is found to have a VSD. Which one of the following is best to recommend to avoid cardiopulmonary bypass (CPB) in C.D.?

    A. Valvulotomy.
    B. Patch closure.
    C. Transcatheter closure.
    D. Stent.

Questions 6 and 7 pertain to the following case.

B.B. is a preterm 2-day-old boy (weight 1.9 kg) who was advancing on nasogastric tube feeds and doing well until he had increased Fio_2 (fraction of inspired oxygen) requirements to maintain goal Sao_2 values greater than 95%. Chest radiography reveals a large heart. An ECHO reveals a PDA with left-to-right shift.

6. Which one of the following pharmacologic agents/doses is best to recommend to close the PDA in B.B., assuming normal renal and hematopoietic parameters?

    A. Indomethacin 0.2 mg/kg/dose intravenously every 12 hours × 3 doses.
    B. Ibuprofen 10 mg/kg/dose intravenously every 24 hours × 3 doses.
    C. Acetaminophen 15 mg/kg/dose every 6 hours.
    D. Alprostadil 0.05 mcg/kg/minute.

7. Which laboratory values and other goal patient values would most justify a second treatment with COX-1 and COX-2 inhibitors in B.B.?

    A. SCr less than 1.2 mg/dL, urinary output 1 mL/kg/hour or greater, CBC with Plt greater than 50,000/mm^3.
    B. SCr less than 1.2 mg/dL, urinary output 1 mL/kg/hour or greater, CBC with Plt greater than 100,000/mm^3, good bowel sounds, no intraventricular hemorrhage (IVH).
    C. SCr less than 2 mg/dL, urinary output 1 mL/kg/hour or less, BUN less than 10 mg/dL, CBC with Plt greater than 50,000/mm^3, good bowel sounds, no IVH.
    D. SCr less than 2 mg/dL, urinary output greater than 2 mL/kg/hour, BUN less than 10 mg/dL, CBC with Plt greater than 50,000/mm^3, acid-base, good bowel sounds, no IVH.

Questions 8–15 pertain to the following case.

E.F. is an infant (weight 3.5 kg) with a diagnosis of hypoplastic left heart syndrome (HLHS) and CoA after first-stage Norwood correction; E.F. had an elevated SBP to 90 mm Hg with an elevated central venous pressure (CVP) of 12 cm H_2O.

8. Which one of the following therapies is best to recommend for E.F.?

    A. Fluid bolus of 10 mL/kg × 1.
    B. Epinephrine.
    C. Sodium bicarbonate 1 mEq/kg × 1.
    D. Sodium nitroprusside.

9. Post-Norwood, E.F. has diminished cardiac output (CO), as evidenced by decreased urinary output less than 2 mL/kg/hour, capillary refill of 3 seconds, and decreased brain/kidney near-infrared spectroscopy (NIRS) of 50 with normal blood pressure and heart rate. Which one of the following would most decrease E.F.'s afterload and increase CO?

    A. Furosemide 1 mg/kg/dose every 12 hours.
    B. Milrinone 0.5 mcg/kg/minute.
    C. Nicardipine 0.5 mcg/kg/minute.
    D. Epinephrine 0.01 mcg/kg/minute.

10. About 12 hours post operation, E.F. has the following vital signs and laboratory values: Qp/Qs ratio decreasing less than 0.7/1, Sao$_2$ 70% right atrial pressure, urinary output less than 2 mL/kg/hour, decreasing NIRS brain/kidney from the mid-50s to the mid-40s, and decrease in SBP from 75 mm Hg to 60 mm Hg. Extremities are cool on examination with capillary refill of 4 seconds. Ionized calcium is 1.2 mmol/L and serum magnesium is 2 mg/dL. Which one of the following best assesses what is occurring clinically and the best treatment option for E.F.?

    A. This is common in children post-cardiac surgery, and there is nothing to do but wait it out.
    B. The patient has low cardiac output syndrome (LCOS). Initiate epinephrine at 0.02 mcg/kg/minute and titrate every 2 minutes to a maximum of 0.1 mcg/kg/minute to meet blood pressure goals and increase CO.
    C. The patient has LCOS. Increase sodium nitroprusside to 2 mcg/kg/minute.
    D. The patient has LCOS. Initiate dobutamine at 5 mcg/kg/minute and increase every 5 minutes.

11. After the earlier intervention, E.F. continues to have low blood pressure values and no improvement in NIRS. The patient's SBP is 60 mm Hg and mean blood pressure is 30 mm Hg. Which one of the following is the best treatment for E.F.?

    A. Add vasopressin at 0.3 milliunits/kg/minute; titrate every 5 minutes to 2 milliunits/kg/minute.
    B. Add nicardipine at 0.5 mcg/kg/minute; titrate every 5 minutes to a maximum of 2 mcg/kg/minute.
    C. Initiate bumetanide at 0.02 mg/kg/hour and continue to monitor.
    D. Initiate sodium nitroprusside at 0.2 mcg/kg/minute; titrate by 0.2 mcg/kg/minute to a maximum of 2 mcg/kg/minute every 5 minutes for afterload reduction.

12. Postoperatively, E.F. has milky fluid in the thoracic duct. Which one of the following treatment courses for chylothorax is best to decrease ICU time, intubation time, and length of stay for E.F.?

    A. NPO, TPN × 2 weeks, medium-chain triglyceride oil, octreotide at 10 mcg/kg/hour.
    B. NPO, TPN × 7 days, octreotide at 3 mcg/kg/hour.
    C. NPO, TPN × 7 days, octreotide at 3 mcg/kg/hour, intravenous immunoglobulin.
    D. NPO with immediate thoracic duct ligation.

13. Which one of the following medications would most decrease E.F.'s risk of interstage mortality (IM)?

    A. Propranolol.
    B. Digoxin.
    C. Aspirin.
    D. Enalapril.

14. E.F.'s condition is now stable, and he can be transitioned to oral medications consistent with his continued need of afterload, preload reduction, and his stage of repair. These medications include: captopril, spironolactone, and digoxin. Which one of the following is the best counseling point to share with E.F.'s parents regarding spironolactone?

    A. Spironolactone may cause hypokalemia; make sure you get electrolytes monitored.
    B. Spironolactone may cause fluid retention; make sure you notify your cardiologist.
    C. Spironolactone may cause enlarged breasts; make sure you notify your cardiologist.
    D. Spironolactone may cause unwanted hair growth; make sure you notify your cardiologist.

15. In addition to captopril, spironolactone and digoxin, which one of the following additional medications is best for E.F. upon discharge?

    A. Low-dose aspirin.
    B. Magnesium supplements.
    C. Hydrochlorothiazide.
    D. Potassium supplements.