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REVIEW ARTICLE

Pharmacotherapy of Congenital Heart Defects

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Congenital cardiovascular defects account for significant morbidity and mortality in the pediatric population. Complications of congenital heart disease are lesion-dependent and may range from mild heart failure with no cyanosis to severe cyanosis and shock. Pharmacotherapy of congenital heart disease is also lesion-dependent and usage may range from palliative agents (e.g., prostaglandin E_1 for relaxation of aortic stricture) to corrective agents (e.g., indomethacin for closure of the ductus arteriosus). This review will discuss the aberrant pathophysiology and complications associated with specific congenital heart defects, as well as the selection of pharmacological agents used in the management of these defects.

KEYWORDS: congenital heart defects, ductus arteriosus

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INTRODUCTION

Congenital heart defects occur in about 36,000 infants per year.[1] At least 35 types of defects have been identified, with the four most common being ventricular septal defect (VSD; 20% to 25%), atrial septal defect (ASD; 8% to 13%), patent ductus arteriosus (PDA; 6% to 11%, excluding preterm infants),[1] and coarctation of the aorta (5% to 7%).[2] Congenital heart defects may result in a wide variety of complications ranging from mild congestive heart failure to severe hypoxemia and shock. Depending upon the severity of the defect, abnormalities may be diagnosed at birth in some infants, while defects may not be diagnosed in others until adulthood. This article will review the development and maturation of the cardiovascular system, the aberrant pathophysiology and resultant complications of various congenital heart lesions, and treatments for each lesion.

MATURATION OF THE CARDIOVASCULAR SYSTEM

Fetal circulation

Fetal circulation is characterized as a parallel flow system in which blood is shunted away from the right-sided circulation (i.e., right atrium, right ventricle, and pulmonary vasculature) to the left-sided circulation (i.e., left atrium, left ventricle, and systemic vasculature) to form two almost independent pathways through the heart.[2,3] Normally, there are three anatomical shunts (openings or connections) present in the fetal circulation that are not there later in life (Figure 1). These are: 1) the ductus venosus, which connects the umbilical vein to the inferior vena cava in the fetus, 2) the foramen ovale, which is a membranous opening between the right atrium and the left atrium, and 3) the ductus arteriosus, which is a connection between the pulmonary artery and the descending aorta.[2,3]

In utero, the placenta acts as a low pressure oxygenating system for the fetus. Approximately 50% of the oxygenated blood from the placenta goes to the fetal liver. The remaining 50% enters the fetal inferior vena cava via the ductus venosus. About two-thirds of the oxygenated blood from

ABBREVIATIONS: ASD, atrial septal defect; CHF, congestive heart failure; CoA, coarctation of the aorta; NEC, necrotizing enterocolitis; NYHA, New York Heart Association; PDA, patent ductus arteriosus; PGE_1, prostaglandin E_1; PVR pulmonary vascular resistance; RVOT, right ventricular outflow tract; SVR, systemic vascular resistance; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect

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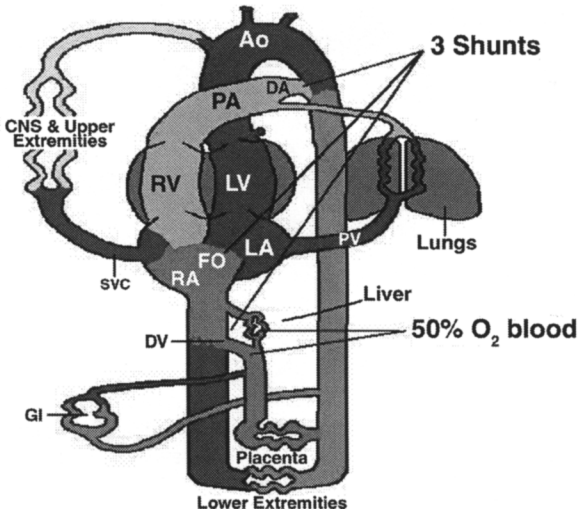

Figure 1. Fetal circulation. RA, right atrium; RV, right ventricle; PA, pulmonary artery; DA, ductus arteriosus; DV, ductus venosus; FO, foramen ovale; LA, left atrium; LV, left ventricle; Ao, aorta; GI, gastrointestinal tract; CNS, central nervous system.

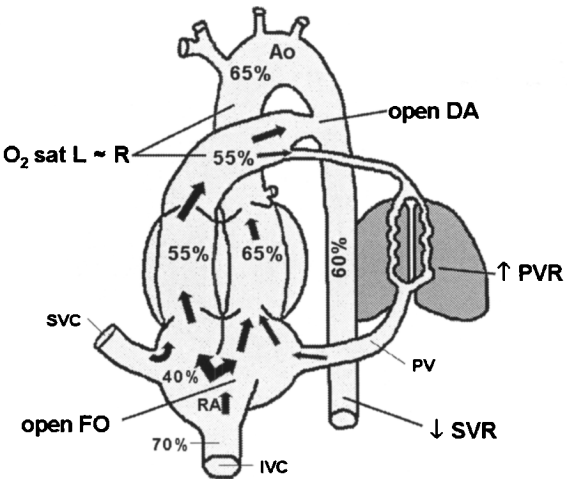

Figure 2. Fetal circulation. Numbers represent oxygen saturation (O_2 sat). Arrows indicate direction of blood flow. L, left-sided circulation; R, right-sided circulation; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; DA, ductus arteriosus; PV, pulmonary vein; FO, foramen ovale; LA, left atrium; LV, left ventricle; Ao, aorta; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

the placenta mixes with most of the desaturated blood from the fetal superior vena cava in the right atrium and enters the right ventricle.[2,3]

Blood entering the right ventricle is ejected into the pulmonary artery. Because of pulmonary vasoconstriction only about 10% of this blood enters the lungs. In order to perfuse the splanchnic vasculature and the placenta, the majority of blood enters the descending aorta through the ductus arteriosus.[2,3]

The remaining one-third of the oxygenated blood from the placenta and the desaturated blood from the lower extremities is shunted across the right atrium through the foramen ovale to the left atrium. Blood then enters the left ventricle and is ejected into the ascending aorta to perfuse the central nervous system, the upper extremities, the myocardium, and the placenta.[2,3]

Figure 2 depicts right-sided and left-sided oxygen saturations *in utero*. Due to the mixing of saturated and desaturated blood through the foramen ovale, the oxygen content of blood in the left ventricle is not much greater than the oxygen content in the right ventricle (65% versus 55%). Additionally, there is high pulmonary vascular resistance (PVR) with low perfusion through the lungs. Systemic vascular resistance (SVR) is low with high perfusion to the periphery.[3]

Transitional circulation

At birth the circulation becomes a circuitous system with cessation of right-to-left shunting of blood, and the lungs begin functioning as the principal oxygenating system. These changes occur for several reasons. Firstly, the low resistance placenta is removed from the systemic circulation causing the ductus venosus to close and the SVR to rise. Secondly, PVR falls due to mechanical expansion of the lungs and increased arterial oxygen content. Right ventricular output to the pulmonary circulation increases dramatically, and flow through the ductus arteriosus becomes left-to-right (from the aorta to the pulmonary artery) until ductal constriction is complete (usually within 96 hours of birth). Left atrial pressure exceeds right atrial pressure due to the higher blood return from the lungs. This leads to a functional closure of the foramen ovale and a further increase in the delivery of blood from the right side of the heart to the pulmonary vasculature.[2,3]

Figure 3 depicts transitional pressures and oxygen saturations. The oxygen content on the left side of the heart is higher than on the right side of the heart (97% versus 67%) due to decreased mixing of highly saturated blood with desaturated blood across the foramen ovale and increased return of highly saturated blood from the lungs to the left atrium.[3]

Mature circulation

The mature circulation is characterized as a circuitous system with no shunting of blood. There is membranous closure of the foramen ovale and

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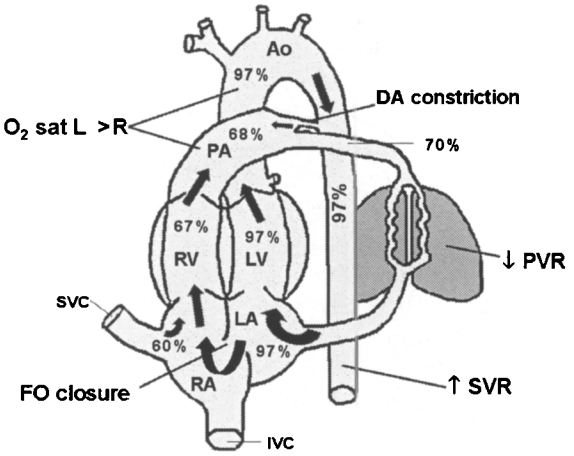

Figure 3. Transitional circulation. Numbers represent oxygen saturation (O_2 sat). Arrows indicate direction of blood flow. L, left-sided circulation; R, right-sided circulation; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; DA, ductus arteriosus; PV, pulmonary vein; FO, foramen ovale; LA, left atrium; LV, left ventricle; Ao, aorta; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

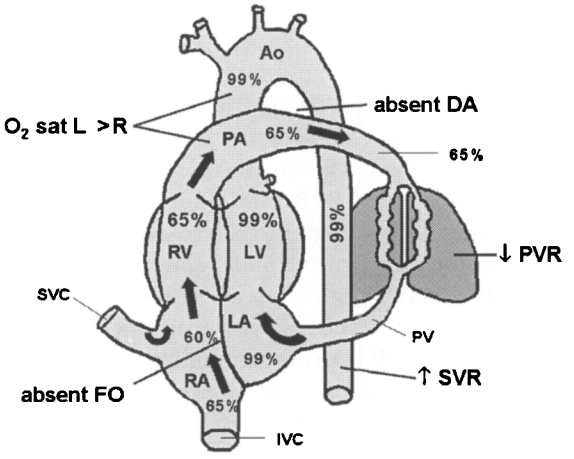

Figure 4. Mature circulation. Numbers represent oxygen saturation (O_2 sat). Arrows indicate direction of blood flow. L, left-sided circulation; R, right-sided circulation; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; DA, ductus arteriosus; PV, pulmonary vein; FO, foramen ovale; LA, left atrium; LV, left ventricle; Ao, aorta; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

permanent destruction of the ductus arteriosus. Oxygen saturations are much higher on the left side of the heart than on the right (99% versus 65%), and PVR is much lower than SVR (Figure 4).[3]

CLASSIFICATION OF CONGENITAL HEART DEFECTS

Congenital heart defects may be broadly categorized as acyanotic or cyanotic lesions. Acyanotic lesions generally maintain adequate or even excessive pulmonary blood flow, but cause compromised systemic blood flow. Blood is oxygenated in the lungs, but the oxygenated blood is not delivered to the tissues efficiently. Cyanotic lesions generally maintain sufficient blood flow to the systemic vasculature, but cause compromised blood flow to the pulmonary vasculature. Blood is delivered to the tissues efficiently, but the blood is not adequately oxygenated.

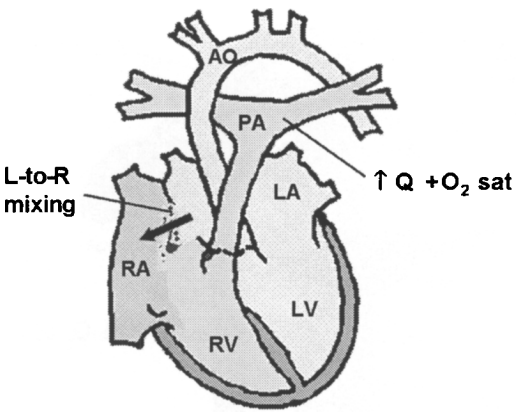

Figure 5. Atrial septal defect. Arrow indicates direction of blood flow through the defect. L, left-sided circulation; R, right-sided circulation; RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AO, aorta; Q, blood flow; O_2 sat, oxygen saturation.

Acyanotic lesions

Acyanotic heart defects may be subclassified as lesions that cause either an increased volume load to the heart or an increased pressure load on the heart. The increased volume load is most commonly caused by left-to-right shunt lesions, while the increased pressure load is usually caused by ventricular outflow obstruction or narrowing of one of the great vessels. Interestingly, the four most common heart defects are all acyanotic lesions.[2]

Atrial septal defect

Atrial septal defect (ASD) is an opening in the membrane that separates the right atrium from the left atrium (Figure 5). Because the right side of the heart pumps against the lower pressure system of the lungs, the pressure in the right atrium is lower than the pressure in the left atrium. This allows blood from the left atrium to enter the right atrium across the ASD, thereby causing a left-to-right shunting of blood.[2,4] Ultimately, blood flow entering the lungs is higher than normal. The

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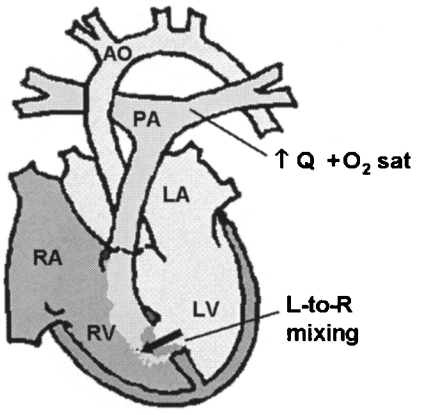

Figure 6. Ventricular septal defect. Arrow indicates direction of blood flow through the defect. L, left-sided circulation; R, right-sided circulation; RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AO, aorta; Q, blood flow; O_2 sat, oxygen saturation.

blood entering the lungs also has a higher oxygen content than normal due to the mixing of highly saturated blood from the left atrium with desaturated blood from the right atrium.[2,4]

Most patients with an ASD are asymptomatic. Diagnosis is generally made when the child is referred to a cardiologist by the primary care physician to evaluate a heart murmur.[2,4] Most patients with ASD do not develop congestive heart failure (CHF) with failure to thrive, unless the ASD is associated with another heart defect.

There are several forms of ASD with ostium secundum being the most common. An ostium secundum defect is present at the fossa ovalis site, which is at the center of the atrial septum. Except for the ostium secundum ASD, other forms of ASD do not spontaneously close.[2,4] These patients will require surgical closure, usually at 2–4 years of age. The risk of death with uncomplicated ASD closure is less than 1% for patients operated on less than 24 years of age.[4,5] Left untreated, ASD can cause right ventricular hypertrophy and heart failure, as well as right atrial enlargement that may lead to arrhythmias.[4]

Ventricular septal defect

A ventricular septal defect (VSD) leads to mixing of highly saturated blood from the left ventricle with desaturated blood from the right ventricle (Figure 6). Similar to an ASD, a VSD causes an increased delivery of saturated blood to the pulmonary bed. The physical signs and symptoms of a VSD will depend upon the size and location of the defect, the PVR, and the degree of left-to-right shunting. For instance, because PVR is still relatively high infants with a VSD may be fairly asymptomatic shortly after birth. High PVR prohibits excessive left-to-right shunting. However as PVR rapidly decreases, shunting increases and signs of CHF (e.g., tachypnea, tachycardia, pallor, and poor feeding) may develop. The goals of treating a VSD are the prevention of failure to thrive, pulmonary vascular obstructive disease with pulmonary hypertension, right and left ventricular dysfunction, and bacterial endocarditis.[2,4]

About 50% to 80% of VSDs are small at birth or begin to spontaneously close. These patients do not develop heart failure or pulmonary hypertension; therefore, they do not require surgical or pharmacological intervention. Infants with moderate to large defects and heart failure are typically treated with digoxin, diuretics, and a calorically dense enteral formula to promote adequate weight gain. If growth failure, pulmonary hypertension, or cardiomegaly with ventricular hypertrophy occur or continue despite pharmacologic intervention, then surgical closure is needed.[2,4] Operative mortality for uncomplicated VSD is generally less than 5%.[4]

Patent ductus arteriosus

In utero, the ductus arteriosus shunts blood from the right-sided circulation to the left-sided circulation (from the pulmonary artery to the aorta) due to high PVR and low SVR.[2,6,7] The ductus arteriosus remains patent *in utero* due to low oxygen tension and high levels of circulating prostaglandins. After birth, oxygen saturations rise and circulating prostaglandin concentrations fall leading to muscular constriction of the ductus.[2,6,7] Muscular constriction is complete in approximately 96 hours. Permanent destruction of vessel endothelium with connective tissue, which seals the ductal lumen, is complete in about two weeks for term infants.[7] The ductus remains patent in 1 in 5,000 live births. The incidence jumps to 8 in 1,000 live births for premature infants.[4] When the ductus remains patent, there is increased blood flow from the aorta into the pulmonary artery (i.e., retrograde flow) (Figure 7). This retrograde flow leads to pulmonary overcirculation.[2] The risks associated with a long-standing patent ductus arteriosus (PDA) include bacterial endocarditis, calcification of the ductus, and possibly the development of CHF and pulmonary hypertension.[2,4] Because of the increased retrograde flow into the

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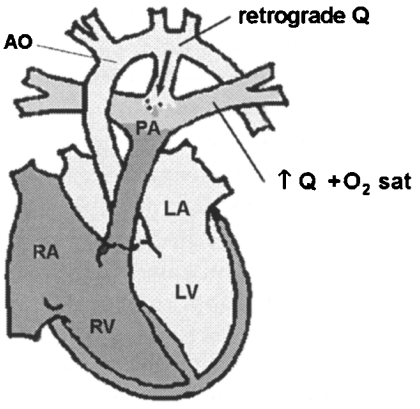

Figure 7. Patent ductus arteriosus. Arrow indicates direction of blood flow through the defect. RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AO, aorta; Q, blood flow; O_2 sat, oxygen saturation.

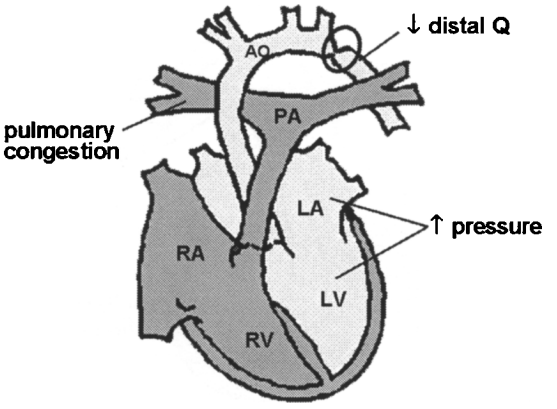

Figure 8. Coarctation of the aorta. RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AO, aorta; Q, blood flow.

lungs from the aorta, left atrial filling pressures are higher. These alterations lead to left-sided heart failure. Increased flow into the lungs also causes pulmonary edema and pulmonary hypertension. Eventually, right-sided failure will occur as the right ventricle continues to pump against higher lung pressures.[6,7] Although the development of CHF in full-term infants usually occurs only when the PDA is large, all PDAs that are apparent by physical examination should be closed regardless of their size due to the risk of bacterial endocarditis.[2,4]

Basic management of heart failure symptoms with agents like digoxin and diuretics may be used until the ductus can be closed.[4] All patients with a PDA should receive endocarditis prophylaxis until the ductus is closed.[4] The ductus may be closed pharmacologically or surgically. Oftentimes, nonsteroidal anti-inflammatory drugs are tried first.[4,6,7] If these agents fail, then the ductus may be closed by surgical ligation or by the insertion of metal coils into the ductus.[4]

Coarctation of the aorta

Coarctation of the aorta (CoA) is a narrowing or constriction of the aorta, usually distal to the left subclavian artery and proximal to the ductus arteriosus, which causes left ventricular outflow obstruction (Figure 8). The most obvious complications of the coarctation are decreased peripheral perfusion, increased left atrial and left ventricular pressure secondary to impedance of blood flow from the aorta, and pulmonary congestion resulting from high left-sided pressures.[2,8]

Clinical presentation depends upon the age of the patient, the severity of the obstruction, and any other related heart defects.[2,8] Since the CoA is generally proximal to the ductus arteriosus, newborns with a PDA maintain some right-to-left shunting of blood through the ductus to the systemic circulation. If the CoA is severe, closure of the ductus in the first weeks of life can lead to life-threatening cardiogenic shock due to poor perfusion.[8] If the obstruction is relatively mild, patients may be asymptomatic. In this case, diagnosis is often not made until upper extremity hypertension and discrepant pulses are noted at a follow-up visit to the pediatrician.[8]

The goals of treating an infant with critical CoA include improvement of peripheral perfusion, correction of metabolic acidosis, and administration of PGE_1 to maintain ductal patency.[2,8] Even if an infant presents with severe CoA after permanent closure of the ductus, or if the ductus does not respond well to intervention, PGE_1 still may play a valuable role in the management of the obstruction.[9] Ductal tissue may extend to the aortic site of the obstruction or may encircle the aorta forming the stricture.[9] If the ductus is no longer able to be reopened, PGE_1 may still relax the area of the narrowing enough to aid distal perfusion until the lesion can be repaired.[9] Repair may be surgical (e.g., end-to-end anastamosis) or may involve balloon angioplasty via cardiac catheterization.[2,5,8] One of the more common problems encountered post-operatively is rebound hypertension. This usually responds well to β-blockers and angiotensin converting enzyme (ACE) inhibitors.[5,8,10]

Pharmacotherapy of acyanotic lesions

Pharmacotherapy of acyanotic lesions is directed towards managing pulmonary volume over-

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Table 1. Cardiovascular activity of selected agents

Agent	Inotropy	Preload	Afterload	References
ACE inhibitors	↔	↓	↓	11,51,77,90
Inamrinone	↑	↔	↓	68,70
Digoxin	↑	↔	↔	19,31
Diuretics	↔	↓	↔	33
Milrinone	↑	↔	↓	73,75
Nitroprusside	↔	↓	↓	11,77,78
Phenylephrine	↔	↔	↑	94
Prazosin	↔	↓	↓	11,77,78,90

↑ = *increased effect;* ↓ = *decreased effect;* ↔ = *no effect.*

load and CHF. Left-to-right shunting of blood into the lungs generally is reduced by closing a PDA (unless there is CoA) and by decreasing the SVR (i.e., afterload). Heart failure is managed primarily by augmenting cardiac output. Cardiac output may be improved by decreasing the filling pressure of the heart (preload), decreasing the systemic pressure against which the heart pumps (afterload), and by enhancing the ability of the heart to pump blood (inotropy).[11] Table 1 summarizes the effect of various cardiovascular agents on heart contractility, preload, and afterload. These agents will be discussed in detail.

PDA closure

Of all the acyanotic lesions, PDA is the only defect in which pharmacotherapy is directed towards correcting the lesion. For other acyanotic lesions, pharmacotherapy is directed towards managing symptoms associated with the defect or with repairing the defect. Although fluid restriction, diuretics, and digoxin may be considered first-line management of symptomatic PDA, the focus of this section will be agents for ductal closure.

Indomethacin. Several prostaglandin inhibitors including indomethacin, aspirin, ibuprofen, and sulindac have been used to close a patent ductus.[12-20] Although ibuprofen may be as effective as indomethacin and associated with fewer renal side effects,[14,18,19] additional large, randomized clinical trials are needed before ibuprofen can be routinely recommended for closure of a PDA. Most clinicians have greater experience using indomethacin for this indication. Unfortunately, serious adverse effects including renal dysfunction, gastrointestinal perforation, and necrotizing enterocolitis (NEC) have been reported following the use of indomethacin.[7,12-15,20] Although PDA may be an independent risk factor for the development of NEC in preterm infants, indomethacin still may exacerbate the problem by disturbing gut perfusion.

Indomethacin generally is administered intravenously in three doses ranging from 0.1 to 0.25 mg/kg based upon postnatal age.[16] The doses may be given at 12 hour intervals provided urine output is $\geq$ 1 mL/kg/hr. If the urine output is $\geq$ 0.6 to $<$ 1 mL/kg/hr the dose should be given at 24 hour intervals. When the urine output falls below 0.6 mL/kg/hr indomethacin should be withheld.[16] Initial closure rates, recurrence rates, and the incidence of adverse effects with this short, larger dose course of indomethacin have been compared to a long, smaller dose course of indomethacin.[12,15,20] Kumar et al found a higher initial response rate and a lower recurrence rate when indomethacin was given in six doses of 0.1 mg/kg at 24-hour intervals.[15] In contrast, when Tammela and colleagues compared the traditional three-dose regimen with a seven-dose regimen of 0.1 mg/kg at 24-hour intervals, there was a higher primary closure rate with the three-dose regimen.[12] In this study, the sustained closure rates were no different between the dosing regimens, but the need for surgical ligation was still lower in the three-dose group.[12] In a more recent clinical trial comparing the conventional regimen with a six-dose regimen of 0.1 mg/kg at 24-hour intervals, there were no statistical differences in primary closure rate or the number of infants requiring a second indomethacin course or surgical ligation.[20] There was a higher incidence of transient oliguria with the conventional regimen, but a five-fold higher incidence of NEC with the prolonged, low-dose regimen. Overall, there does not appear to be any advantage to using the prolonged, low-dose regimen versus conventional dosing.

Important monitoring parameters for indomethacin include blood urea nitrogen, serum creatinine, and urine output as measures of renal function; guaiac-positive stools, enlarging ventricles, and thrombocytopenia as measures of bleeding complications; and dilated bowel as a sign of NEC.[6,7] For babies already at risk for these adverse events, clinicians will usually opt for surgical closure versus a trial of indomethacin.

Pre-operative therapy

Symptoms of CHF and pulmonary overcirculation are managed pre-operatively with agents like digoxin, diuretics, and ACE inhibitors. Prostaglandin E_1 is also used pre-operatively to maintain ductal patency for left ventricular out-

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flow obstructive lesions like severe CoA.

Digoxin. There is considerable controversy regarding the use of digoxin to manage heart failure associated with acyanotic heart lesions.[21-23] The literature currently lacks adequate double-blind, placebo-controlled trials evaluating digoxin's ability to improve contractility and clinical symptoms in infants with heart failure. Unless there is a documented decrease in left ventricular function, it is unlikely that digoxin offers benefit in the management of left-to-right shunt lesions.

Standard maintenance doses of digoxin for heart failure are 5 mcg/kg/day for preterm infants, 8 to 10 mcg/kg/day for full-term newborns less than two months of age, 10 to 12 mcg/kg/day for infants less than two years of age, and 8 to 10 mcg/kg/day for children greater than two years of age.[24] It is recommended that the maintenance dose be divided and given twice daily; however, the drug's half-life is sufficiently prolonged in infants and children (20 to 40 hours) to allow digoxin to be administered once daily without causing a large fluctuation in peak-to-trough concentrations.[25,26] At least two clinical trials confirm that once daily dosing is as effective as twice daily dosing, maintains adequate serum concentrations throughout the dosing interval, and does not produce peak serum concentrations that are above the upper end of the reference range.[25,26]

Digoxin is approximately 60 to 75% eliminated via the kidney, primarily by glomerular filtration and tubular secretion.[27-29] As tubular function matures during the first three months of life, the renal clearance rapidly increases.[27] According to Halkin et al the average renal clerance of digoxin doubles from 32 ± 7 mL/min/1.73 m^2 for one-week-old infants to 65.6 ± 30 mL/min/1.73 m^2 for infants three months of age.[30] Renal clearance for children 12 months of age modestly increases to 87.7 ± 43 mL/min/1.73m^2. Since digoxin is primarily eliminated by the kidney, doses should be adjusted for renal dysfunction according to the equations listed in Table 2.

Adverse effects of digoxin range from gastrointestinal difficulties, including vomiting and loss of appetite, to bradycardia and atrioventricular block.[24,27,31] Visual disturbances (e.g., the "green halo" effect) may be an early sign of toxicity; however, these signs are rarely appreciated in infants and young children.[24,27,31]

Because there is a poor correlation between serum digoxin concentration and pharmacodynamic effects (i.e., efficacy or toxicity) the monitoring of serum digoxin concentrations remains controversial.[27,30,31] Serum concentration often must be repeated due to inappropriate collection (i.e., the sample is collected within 4 to 6 hours after dosing), thus adding to the cost of therapy. The interpretation of serum concentrations may be further complicated by the presence of digoxin-like immunoreactive substances (DLIS).[27] DLIS cross-reacted with many assays producing falsely elevated serum digoxin concentrations. Today, most immunoassays have minimal cross-reactivity, so that DLIS may contribute only 0.1 to 0.4 ng/mL to the actual serum digoxin concentration.[32]

Table 2. Renal adjustment of digoxin[29]

$RF = ClCr_{pt}/ClCr_{nl}$
$CL_{pt} = CL_{nl} \bullet [1 - fe \bullet (1 - RF)]$
$D_{0,pt} = D_{0,nl} \bullet CL_{pt}/ CL_{nl}$

RF, renal function; $ClCr_{pt}$, creatinine clearance of patient; $ClCr_{nl}$, normal creatinine clearance; CL_{pt}, renally adjusted drug clearance; CL_{nl}, normal drug clearance; fe, fraction eliminated as unchanged drug in urine; $D_{0,pt}$, renally adjusted dosing rate; $D_{0,nl}$, normal dosing rate.

Furosemide. Furosemide is a loop diuretic that may be used to decrease preload in an effort to improve cardiac output.[33] More often it is used to decrease pulmonary edema that results from a left-to-right shunt or heart failure. Doses of 1 to 2 mg/kg may be given orally or intravenously at 6 to 24-hour intervals.[33] A continuous infusion of furosemide (2.4 to 10 mg/kg/day) has been used to manage postoperative cardiovascular surgery infants.[34-37] Continuous infusions may produce a more controlled diuresis with less fluid shifts and subsequent hemodynamic compromise.[35-37] Intratracheal instillation of furosemide 0.5 mg/kg (using 10 mg/mL solution) has been shown to decrease pulmonary edema without causing a large diuresis.[38] This route may be beneficial to patients who are intravascularly depleted but still have significant pulmonary edema.

The main adverse effects of furosemide are electrolyte wasting, contractional hypochloremic metabolic alkalosis, ototoxicity, and nephrocalcinosis resulting from chronic calciuria.[33] Patients receiving furosemide should be assessed for signs and symptoms of dehydration and should have serum electrolytes monitored.

Spironolactone. The aldosterone antagonist, spironolactone, is categorized as a weak diuretic. In patients requiring chronic diuresis, it is usually coupled with a thiazide diuretic for its potassium-sparing properties. It may also be useful in

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managing the hyperaldosteronism associated with CHF.[39] Spironolactone doses of 1 to 3 mg/kg/day may be administered orally every 12 to 24 hours.[39,40] The main adverse effects include hyperkalemia, metabolic acidosis, and gastrointestinal complaints (e.g., nausea, vomiting, and diarrhea).[39,40] Serum electrolytes and renal function should be monitored with therapy.

Thiazides. The thiazide diuretics are usually employed for chronic diuresis, as they generally cause less adverse effects than the loop diuretics. Hydrochlorothiazide doses of 2 to 4 mg/kg/day divided every 12 to 24 hours may be given orally to patients $\leq$ 6 months of age, while a dose of 2 mg/kg/day divided every 12 hours may be given to patients $>$ 6 months of age.[40] Oral chlorothiazide 20 to 40 mg/kg/day divided every 12 hours or intravenous chlorothiazide 2 to 8 mg/kg/day divided every 12 hours may be administered to infants $\leq$ 6 months of age.[40] For children $>$ 6 months, oral doses of chlorothiazide are 20 mg/kg/day divided every 12 hours, and intravenous doses are 4 mg/kg/day.[40]

Adverse effects of thiazide diuretics include hypokalemia, hyperglycemia, metabolic alkalosis, hyperlipidemia, gastrointestinal complaints, pancreatitis, and hepatic cholestasis.[40] Serum chemistries, triglycerides, and renal function should be monitored during therapy.

Angiotensin converting enzyme inhibitors. These agents primarily are used to lower SVR in an effort to decrease left-to-right shunting.[41-46] They are also useful for managing rebound hypertension with CoA.[5,8,10] Of the angiotensin converting enzyme inhibitors, published experience in children is greatest with captopril and enalapril. Initial doses of captopril for infants and children are generally 0.25 to 0.75 mg/kg/day divided every 6 to 8 hours.[40,46,47] Doses are gradually increased by 0.5 mg/kg/day to a maximum of 6 mg/kg/day based upon clinical response.[40,46] Preterm neonates may be particularly susceptible to the hypotensive effects of captopril.[48,49] Because of the high risk for compromised renal and cerebral blood flow in this population, starting doses should be reduced to 0.01 to 0.05 mg/kg given every 8 to 12 hours.[48,49]

The main advantage enalapril may have over captopril is the longer duration of action.[42,44,50] Enalapril may be given once daily to infants and children at a dose of 0.1 mg/kg with titration to 0.5 mg/kg/day.[40,42,51] Similar to captopril, enalapril may cause excessive hypotension in preterm infants.[52,53] Initial doses should be lowered to 0.01 mg/kg with gradual titration until blood pressure is under adequate control.[52] Additionally, the active form of enalapril, enalaprilat, may be given intravenously. Intravenous doses of 0.01 mg/kg may be given to infants and children every 8 to 24 hours,[40,41] while doses of 0.005 to 0.01 mg/kg may be given to preterm infants.[53]

Hypotension, chronic renal insufficiency, acute renal failure, hyperkalemia, neutropenia, rash, angioedema, and cough have all been reported as side effects of captopril and enalapril.[10,46,47,54] Monitoring blood pressure, renal function indices, serum potassium, and white blood cell count are indicated when therapy is initiated with ACE inhibitors.

Propranolol. Beta-blocking agents traditionally are avoided in patients with congestive heart failure due to their potential negative inotropic effect. However, recent evidence suggests that clinical signs of heart failure are well correlated with high catecholamine activity and that symptoms of heart failure may actually improve by deactivating the neurohumoral system with β-blockers.[55,56] Buchhorn et al noted a reduction in heart failure symptoms in infants with large left-to-right shunt lesions after beginning therapy with low-dose propranolol.[55,56] According to the authors, it is important to initiate propranolol with low doses and to titrate slowly based on clinical response. A single 1 mg oral dose of propranolol may be given at the start of therapy. If this is tolerated, oral dosing may be continued at 1 mg/kg/day in three divided doses. Dosing should be titrated by 1 mg every three days up to 2 mg/kg/day.

Two of the most notable adverse effects of β-blockers are hypotension and bradycardia, therefore, heart rate and blood pressure should be monitored closely during therapy. Patients must also be followed for signs of decreasing cardiac index and worsening heart failure, although these problems did not occur in infants receiving propranolol on a prolonged titration regimen.[55,56]

Carvedilol. Carvedilol is a nonselective β-blocker with additional vasodilating properties due to α-blockade. Carvedilol has been shown to improve signs and symptoms of CHF in pediatric patients with congenital heart lesions or dilated cardiomyopathy when added to standard therapy with digoxin, diuretics, and ACE inhibitors.[57-59] Bruns and colleagues retrospectively evaluated pe-

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diatric heart failure patients at six centers who received carvedilol as adjunctive therapy.[57] Average starting doses were low at 0.16 mg/kg/day divided twice daily with slow titration over several weeks to an average maintenance dose of 0.92 mg/kg/day divided twice daily. Eighty percent of patients achieved a final dose between 0.6 and 1.5 mg/kg/day with an average titration period of 11.3 weeks. Sixty-seven percent of patients showed an improvement in modified New York Heart Association (NYHA) class. For those patients with morphologic left ventricle as their systemic ventricle, there was a statistically significant improvement in shortening fraction from 16.2% to 19.0%. Hypotension, dizziness, and headache were the most common side effects associated with carvedilol. In a randomized, double-blind, placebo-controlled study, pediatric heart failure patients awaiting heart or heart/lung transplantation received carvedilol 0.01 mg/kg/day with slow titration to 0.2 mg/kg/day or placebo.[58] Therapy was maintained for at least six months. Of the ten patients randomized to the carvedilol group, one patient underwent heart transplantation and three patients died. The six patients receiving carvedilol for six months had a statistically significant improvement in left ventricular ejection fraction, with five of the patients showing an improvement in NYHA class (NYHA I = 4 patients, NYHA II = 1 patient). Of the seven patients receiving placebo, two patients underwent heart transplantation and one patient died. In the remaining four patients, there was no statistically significant improvement in left ventricular ejection fraction, and all patients were NYHA IV. Läer et al enrolled pediatric heart failure patients in a prospective, open label trial of carvedilol as an adjunct to standard therapy with digoxin, diuretics, and ACE inhibitors.[59] Carvedilol was initiated at 0.18 mg/kg/day divided twice daily. Doses were increased twice at two-week intervals (0.36 and 0.7 mg/kg/day) as tolerated, up to a maximum of 50 mg/day. The target dose of 0.7 mg/kg/day was continued for an additional six months. Of the 15 patients enrolled, drug was discontinued prematurely in one patient due to serious infection, in one patient due to VSD repair, and in one patient who underwent heart transplantation. Overall, signs and symptoms of CHF improved as evidenced by a significant increase in ventricular ejection fraction (36% versus 54%) and decrease in modified Ross Score (5 ± 2 versus 3 ± 3). The pharmacokinetics of carvedilol were determined and compared to values obtained from healthy adult volunteers. Pharmacokinetic parameters showed age-dependency with a significantly shorter elimination half-life and lower systemic carvedilol exposure in young children as compared to adults. The authors concluded that thrice daily dosing with higher target doses may be necessary in young children to optimize the therapeutic response.

Prostaglandin E_1. PGE_1 is primarily used to maintain ductal patency in ductal dependent congenital heart lesions.[2,60] These are lesions that rely upon the ductal connection for adequate blood flow to the systemic circulation (e.g., critical aortic stenosis) or for adequate blood flow to the pulmonary circulation (e.g., tetralogy of Fallot (TOF) with severe subpulmonic stenosis). PGE_1 also may be used to relax a CoA, as some aortic strictures are formed by bands of ductal tissue.[9] Finally, PGE_1 may be beneficial in the treatment of pulmonary hypertension resulting from large left-to-right shunt lesions due to its ability to relax the pulmonary vasculature.[61]

PGE_1 is traditionally administered as a 0.05 to 0.1 mcg/kg/min continuous infusion with tapering to the lowest effective dose.[60] According to Kramer et al a low dose infusion of 0.005 to 0.04 mcg/kg/min maintains ductal patency as effectively as the large dose infusion with less adverse effects.[62] In contrast, Singh and colleagues report a similar incidence of complications for both large and small dose regimens.[63] At a minimum, infusions that use less total drug may offer a cost advantage.

Numerous side effects can occur with PGE_1 therapy (Table 3). Some of the more notable adverse effects are hypotension, bradycardia, fever, seizure-like activity, and apnea.[60,62,63] Gastric distension, gastric outlet obstruction, and NEC are also associated with intravenous PGE_1.[60,64-66] Prolonged infusions may lead to bone changes such as pseudowidening of the cranial sutures, underossification of the skull cap, and periostitis.[67] The smallest dose of PGE_1 that will maintain ductal patency should be used to limit these complications. Withdrawal of PGE_1 is usually not an option if complications arise, since it is a life-saving agent. Earlier surgical intervention is generally considered at this point.

Post-operative therapy

Diuretics, ACE inhibitors, and β-blockers are

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Table 3. Adverse effects of prostaglandin E_1

Cardiovascular	Edema Hypotension Bradycardia Flushing
Central Nervous System	Fever Seizure-like activity Jitteriness Lethargy
Respiratory	Apnea Tachypnea
Metabolic	Hypocalcemia Hypoglycemia
Infectious	Sepsis
Gastrointestinal	NEC Gastric distension Gastric outlet obstruction
Hematologic	DIC Thrombocytopenia Hemorrhage
Bone	Periostitis
Renal	Dysfunction

used in the immediate post-operative period. Additional post-operative agents include inamrinone, milrinone, and sodium nitroprusside. Prostacyclin, sildenafil, and bosentan also have potential application in the post-operative management of pulmonary hypertension.

Inamrinone. Inamrinone acts as a positive inotrope to improve systolic function.[68,69] It also acts as a vasodilator in both the pulmonary and systemic vascular beds.[69,70] One advantage the drug may have over other vasodilators is the ability to preferentially relax the pulmonary vasculature in patients with pulmonary hypertension without causing excessive systemic hypotension.[70]

There are several published pharmacokinetic analyses of inamrinone in infants and children.[69,71,72] These studies suggest that a total loading dose of 3 to 5 mg/kg divided into 2 to 4 doses, usually given 15 minutes apart, will produce "therapeutic" inamrinone serum concentrations without the development of excessive hypotension. The loading dose is followed by a continuous infusion of 3 to 5 mcg/kg/min in neonates. The infusion is then titrated to desired effect (up to 10 mcg/kg/min in infants older than one month of age).

Thrombocytopenia may occur in up to 50% of patients receiving inamrinone.[72] Hypotension, dysrhythmias, and hepatotoxicity may also occur.[40,68,69,71] Consequently, platelets, blood pressure, heart rate, electrocardiogram, and liver function tests should be followed during inamrinone therapy.

Milrinone. Milrinone is a derivative of inamrinone, but is about 15 times more potent.[73] It is used as an inotrope and vasodilator and has been shown to reduce the risk of developing low cardiac output syndrome when used prophylactically in the post-operative period.[74] In contrast to inamrinone, loading doses of 50 mcg/kg usually are given as one infusion over 5 to 15 minutes without the development of undue hypotension.[73,75,76] Loading doses are followed by infusions of 0.5 to 0.75 mcg/kg/min with titration based upon clinical response.[73,75,76] Unlike inamrinone, milrinone is eliminated primarily by the kidneys.[73] Smaller doses may be required in patients with significantly compromised renal function.

Thrombocytopenia may not occur as often with milrinone as with inamrinone[73,75]; however, the risk increases with the duration of the infusion.[76] Dysrhythmias and hypotension have also been observed with milrinone therapy.[76] Monitoring parameters during milrinone infusion are similar to those for inamrinone, with the exception of liver function tests.

Sodium nitroprusside. Sodium nitroprusside is a potent vasodilator that acts on both the venous and arteriolar beds leading to decreased preload, afterload, and PVR.[11,61,77,78] These effects make sodium nitroprusside useful in managing low cardiac output syndrome and pulmonary hypertension.[11] Starting doses of sodium nitroprusside infusion are 0.5 mcg/kg/min with titration to desired response.[11,77,78] Average doses are approximately 3 mcg/kg/min with a maximum of 10 mcg/kg/min.[77]

The most common side effects of sodium nitroprusside are hypotension and cyanide toxicity.[11,77-79] A nitroprusside molecule contains five cyanide groups.[79] When the drug is metabolized, cyanide is released. Most of the cyanide is conjugated with thiosulfate in the liver to form thiocyanate.[11,77-79] Thiocyanate is then excreted in the urine.[11,77,79] In the presence of hepatic and/or renal dysfunction, cyanide and/or thiocyanate may accumulate and lead to toxicity.[11,77-79] Cyanide concentrations greater than 2 mg/L may be toxic,[11,78] and greater than 3 mg/L may be lethal.[40] Toxic thiocyanate concentrations range from 50 to 100 mg/L;[11,77,78] 200 mg/L may be lethal.[11] Large-dose or prolonged sodium nitroprusside

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infusions may also lead to accumulation and toxicity.[11,77,78] Typical symptoms of toxicity include tachycardia, tachypnea, vomiting, lactic acidosis, and mental status changes (e.g., coma).[11,77-79]

Beyond limiting the dose and duration of sodium nitroprusside infusions, cyanide toxicity may be reduced by co-infusing sodium thiosulfate.[11,80] Sodium thiosulfate provides additional sulfhydryl groups for the conversion of cyanide to thiocyanate; however, thiocyanate accumulation is still a risk especially with any component of renal dysfunction. The extemporaneous preparation of intravenous sodium thiosulfate 1000 mg mixed with sodium nitroprusside 100 mg is stable for seven days if protected from light.[80] Vitamin B_{12a}, or hydroxycobalamin, has also been used to neutralize sodium nitroprusside.[11,79] The cyanide ions released from nitroprusside interact with the hydroxycobalamin to form cyanocobalamin, or vitamin B_{12}, which is excreted in the urine. A major disadvantage of using vitamin B_{12a} is the large volume required to deliver the agent. It requires 24 mg of hydroxycobalamin to neutralize 1 mg of sodium nitroprusside, and the commercially available solution is $\leq$ 1 mg/mL.[11,79] Hydroxycobalamin also must be ordered directly from the manufacturer on a patient-specific basis, so it may not be available to treat toxicity in a timely fashion.

Pulmonary hypertension

Pulmonary hypertension in the post-operative period may occur secondary to residual left-to-right shunting or to cardiopulmonary bypass.[81] While inhaled nitric oxide is the preferred agent for selective pulmonary vasodilation in this setting, several other pharmacologic agents have been studied as adjunctive therapy.

Prostacyclin. Prostacyclin is a potent vasodilator that also inhibits platelet aggregation and vascular smooth muscle proliferation. It has been shown to improve pulmonary vascular hemodynamics, cardiac output, and survival in patients with primary pulmonary hypertension.[82-84] Less is known about the benefit of continuous infusion prostacyclin for managing pulmonary hypertension associated with congenital heart defects and left-to-right shunting. Rosenzweig and colleagues published the results of a long-term evaluation of prostacyclin in 20 patients with pulmonary hypertension and congenital heart defects who failed conventional therapy.[85] Patients received prostacyclin continuously via a portable infusion pump for at least one year. Initial doses ranged from 2 to 14 ng/kg/min and were increased until patients reached a clinical plateau. Thereafter, doses were increased to alleviate symptoms of pulmonary hypertension (e.g., exercise intolerance). Sixteen patients showed significant improvement in cardiac index, pulmonary vascular resistance, and pulmonary artery pressure. Nineteen patients showed significant improvement in NYHA class. The authors concluded that chronic prostacyclin improves hemodynamic parameters and quality of life in patients with pulmonary hypertension and associated congenital heart defects who fail conventional therapy.

Important considerations for prostacyclin therapy include the frequency of drug-related side effects (e.g., jaw pain, rash, arthralgias, nausea, vomiting), complications of prolonged central venous access (e.g., infection), and complications of the drug delivery system (e.g., pump malfunction).[85] Other considerations include severe rebound hypertension with interruption of therapy and expense.

Sildenafil. Sildenafil is an oral selective phosphodiesterase type 5 inhibitor that causes smooth muscle vasodilation by inhibiting breakdown of cyclic guanosine monophospate. It may be a useful treatment option for reducing pulmonary vascular resistance when used alone or in combination with nitric oxide. Unfortunately there is little published information supporting the use of sildenafil in children. There are two published case reports in children with congenital heart defects and secondary pulmonary hypertension.[86,87] In the first report, a nine-month-old infant with mitral stenosis developed pulmonary hypertension after valve replacement.[86] Despite nitric oxide, he continued to have recurrent pulmonary hypertensive crises with interventions (e.g., endotracheal suctioning). Four days postoperatively, he was started on sildenafil 0.3 mg/kg every 4 hours. He had no further pulmonary hypertensive events, allowing nitric oxide to be weaned slowly. No adverse effects on heart rate, systemic blood pressure, or oxygen saturation were noted during sildenafil therapy. No rebound pulmonary hypertension was seen after sildenafil discontinuation.

Carroll and Dhillon described their experience using sildenafil to manage pulmonary hypertension in three children.[87] Congenital heart disease was the most likely cause of pul-

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monary hypertension in a 7-year-old patient. He was administered a test dose of 0.5 mg/kg sildenafil, followed by 1 mg/kg every 6 hours. As the dose was gradually increased to 2 mg/kg every 6 hours, there was a linear increase in his exercise tolerance. He continued to show benefit from the drug for at least nine months after the start of therapy. No adverse effects were associated with sildenafil in this patient.

Bosentan. Bosentan is an oral antagonist of endothelin receptors. Endothelin is a potent vasoconstrictor, and levels of endothelin have been correlated with severity of pulmonary hypertension in pediatric patients.[88] Published experience of bosentan use in children is limited to one open-label, noncontrolled study.[89] This trial evaluated the pharmacokinetics, efficacy, and safety of single- and multiple-dose bosentan in pediatric patients with primary or secondary pulmonary hypertension. Nineteen patients were enrolled in the study, with nine of the patients having pulmonary hypertension related to congenital heart defects. Six patients were receiving concomitant prostacyclin infusions. Patients were assigned to one of three dosing regimens based on body weight: > 40 kg, initial dose 62.5 mg twice daily, target dose 125 mg twice daily; 20 to 40 kg, initial dose 31.25 mg twice daily, target dose 62.5 mg twice daily; 10 to 20 kg, initial dose 31.25 mg daily, target dose 31.25 mg twice daily. Initial doses were maintained for four weeks, then the dose was increased to the target dose and continued for an additional eight weeks.

Pediatric bosentan exposures were similar to values reported for adults. Pulmonary arterial pressure and pulmonary vascular resistance index were significantly improved after 12 weeks of therapy. Cardiac index was also improved, but this value did not reach statistical significance. When patients receiving bosentan with prostacylin were compared to patients receiving bosentan alone, there was no statistically significant difference between the groups for any of the hemodynamic parameters. The most frequently reported side effects of the drug were flushing, headache, and elevation of liver transaminases. No symptomatic hypotension or clinically relevant changes in electrocardiographic variables, pulse rate, or other laboratory values were observed. The authors concluded that the pharmacokinetic, safety, and efficacy profiles of bosentan were similar for pediatric and adult patients.

Chronic therapy

Diuretics, digoxin, ACE inhibitors, and β-blockers are used in the chronic management of congenital heart defects, as well as pre- and post-operatively. Another agent that may be used beyond the immediate post-operative period is prazosin.

Prazosin. Prazosin is a selective α_1-blocking agent that may be thought of as an oral form of nitroprusside.[77,78] It reduces both preload and afterload, and is useful for treating low cardiac output syndrome.[77,78,90] Therapy usually is initiated with 5 mcg/kg for the first dose, then 20 to 25 mcg/kg every 6 to 12 hours.[40,78] Doses are increased as needed up to 50 mcg/kg.[77] Despite a relatively short half-life of 2.5 to 4 hours, 12-hour dosing intervals are usually sufficient, since prazosin's duration of action is 12 hours for most patients.[11,77]

The most notable adverse effect of prazosin is the "first dose phenomenon" in which severe orthostatic hypotension may occur 30 to 90 minutes after the initial dose.[11,77,78] In older children that are ambulating, this effect can be limited by giving the first dose at bedtime. Although controversial, the benefit of using prazosin for heart failure may be limited by tachyphylaxis with chronic use.[11,77,78]

Cyanotic lesions

Cyanotic heart lesions may be subdivided into lesions that maintain blood flow to the lungs and those with compromised lung blood flow.[2] In the first type of lesion, infants become cyanotic because oxygenated blood is flowing into the lungs and not to the rest of the body. Even though pulmonary blood flow is relatively unrestricted, the tissues remain hypoxic. Transposition of the great arteries (TGA) illustrates this type of lesion. Cyanosis can also develop when a heart defect causes decreased pulmonary blood flow and inadequate oxygenation of blood that is delivered to tissues. TOF is an example of this type of lesion.

Transposition of the great arteries

The most common cardiac cause of cyanosis in neonates is TGA (Figure 9).[91] In this type of lesion, as the name implies, the aorta is connected to the right ventricle instead of the left ventricle. The pulmonary artery usually is connected to the left ventricle instead of the right ventricle, although it may not always form the outflow tract for the left ventricle due to variations of TGA (e.g., double-outlet right ventricle or pulmonary atre-

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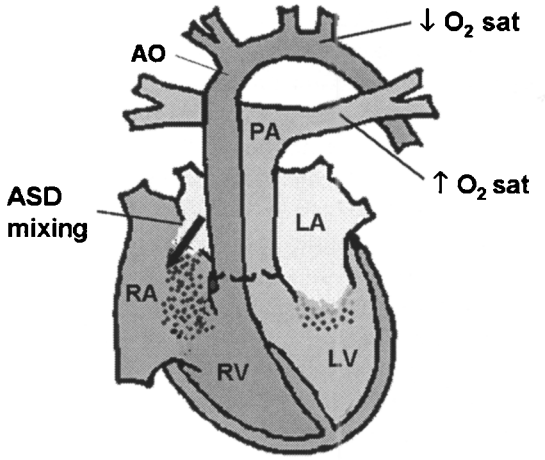

Figure 9. Transposition of the great arteries. RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AO, aorta; O_2 sat, oxygen saturation; ASD, atrial septal defect. Arrow indicates direction of blood flow through the ASD.

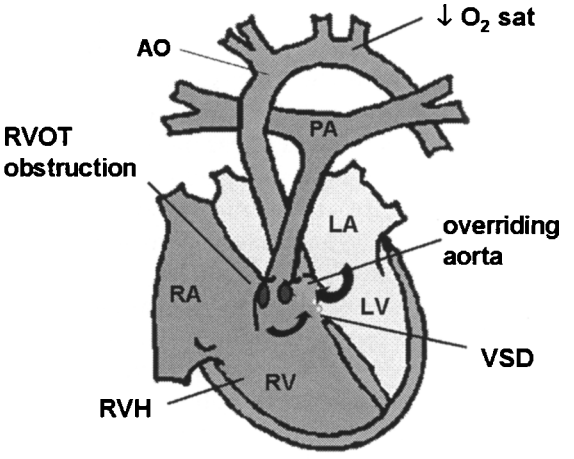

Figure 10. Tetralogy of Fallot. RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AO, aorta; O_2 sat, oxygen saturation; VSD, ventricular septal defect; RVH, righ10t ventricular hypertrophy; RVOT, right ventricular outflow tract. Arrows indicate direction of blood flow through the VSD.

sia).[91] Desaturated blood from the body enters the right atrium, the right ventricle, and the aorta to be pumped back into the systemic circulation without being oxygenated in the lungs. Likewise, saturated blood flows in a closed, parallel circuit from the left atrium to the left ventricle to the pulmonary artery to be pumped into the lungs without entering the systemic circulation to oxygenate tissues. Ultimately, the oxygen saturation in the pulmonary artery is greater than the oxygen saturation in the aorta.[2,91]

Concomitant heart lesions that allow some oxygenated blood from the lungs to mix with deoxygenated blood from the tissues are crucial to survival. For example, the ductus arteriosus plays a very important role in maintaining a connection between the systemic and pulmonary circulations. Neonates may become severely cyanotic within minutes of birth as the ductus slowly begins to constrict, unless a sufficiently large ASD exists. Maintenance of the ductus with PGE_1 is essential until an ASD can be enlarged or created by balloon atrial septostomy, or until surgical correction of the lesion by arterial or atrial switch can be performed.[2,5,91] Reparative cardiac interventions do not decrease the patient's long-term risk for bacterial endocarditis; therefore, antimicrobial prophylaxis for bacteremia-producing procedures will remain necessary.[92]

Tetralogy of Fallot

TOF is a classic example of a cyanotic heart defect with decreased pulmonary blood flow. Tetralogy typically consists of the following four anomalies: VSD, overriding aorta (the aortic root arises from the VSD), right ventricular hypertrophy, and right ventricular outflow tract (RVOT) obstruction (Figure 10).[2,93] Since the pulmonary artery obstruction is typically muscular, the symptoms of cyanosis can be highly variable depending upon the degree of constriction at the subpulmonic level. This is in contrast to those patients with concomitant pulmonary stenosis or an absent pulmonary artery, in which pulmonary blood flow may be continuously compromised. The degree of right-to-left shunting across the VSD is dependent upon the severity of the pulmonary obstruction and the SVR, since blood moves in the direction of the lowest pressure.[93]

The severity of the pulmonary obstruction determines the onset of symptoms, the degree of cyanosis, and the degree of right ventricular hypertrophy.[2,93] Neonates with severe RVOT obstruction typically develop cyanosis within minutes of birth. For these infants, maintaining pulmonary blood flow through the ductus arteriosus is crucial to preventing circulatory arrest.[2,93] Infants with mild to moderate RVOT obstruction typically remain acyanotic, except for intermittent episodes of subpulmonic spasm known as hypercyanotic spells or "tet" spells.[2] These patients are categorized as having "pink" TOF. Infants with "pink" TOF may actually develop heart failure due to overcirculation of the lungs from increased left-to-right shunting of blood across the VSD. This

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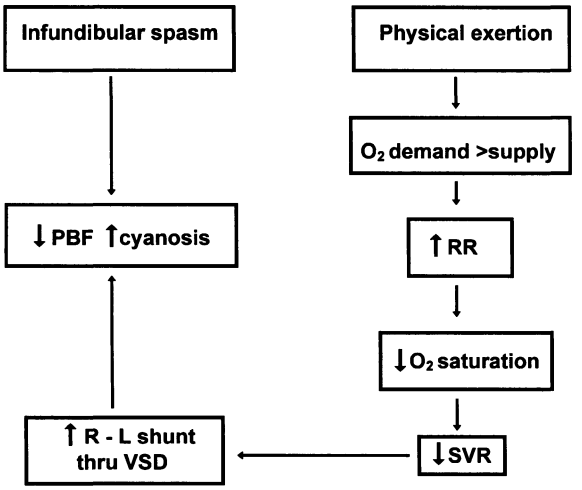

Figure 11. Pathway for the development of a hypercyanotic crisis. PBF, pulmonary blood flow; R, right-sided circulation; L, left-sided circulation; VSD, ventricular septal defect; O_2, oxygen; RR, respiratory rate; SVR, systemic vascular resistance.

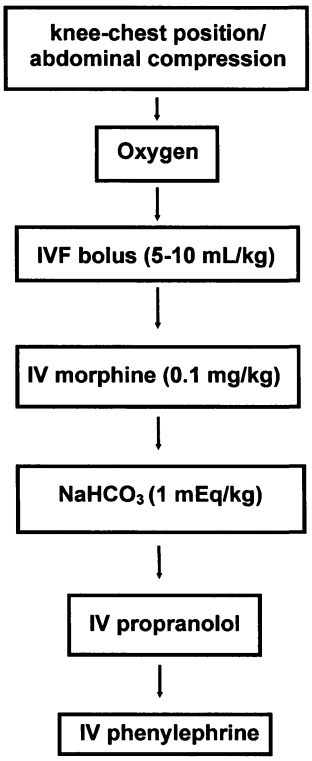

Figure 12. Pathway for the management of a hypercyanotic crisis. IVF, intravenous fluid bolus; IV, intravenous; $NaHCO_3$, sodium bicarbonate.

occurs because blood moves away from the higher systemic pressure of the left ventricle to the lower pressure of the right ventricle and enters the pulmonary artery relatively unimpeded. As infants with "pink" TOF get older, hypercyanotic crises typically increase in frequency.[2]

Infants with severe RVOT obstruction will need emergent PGE_1 infusion to maintain a PDA for adequate pulmonary blood flow. These patients will be maintained on PGE_1 until a palliative systemic-pulmonary shunt can be surgically placed. This shunt is simply a connection between the aorta and pulmonary artery that acts similarly to a permanent ductus. The systemic-pulmonary shunt is used to maintain adequate oxygen saturations until the infant is old enough to have full repair of the tetralogy. Infants with mild to moderate RVOT obstruction often are medically managed for hypercyanotic spells until they are old enough to have primary repair.[2] Patients with TOF have a high risk of developing bacterial endocarditis even after surgical intervention. It will remain necessary for these patients to receive antimicrobial prophylaxis prior to bacteremia-producing procedures.[92]

Hypercyanotic crises

There are several mechanisms that may be involved in the development of a hypercyanotic spell (Figure 11). Hypercyanosis may develop when an infundibular spasm causes decreased pulmonary blood flow. A spasm in the subpulmonic region can occur due to numerous stresses (e.g., agitation from receiving a vaccination). Most often, hypercyanotic crises are caused by physical exertion, which leads to an oxygen demand that exceeds the oxygen supply. This causes tachypnea and relative hypoxemia.[2,94] The body's natural response to improve oxygen delivery to the tissues is vasodilation, which causes the SVR to fall. The lower SVR leads to a greater shunting of blood from the pulmonary circulation to the systemic circulation (i.e., right-to-left) through the VSD. Shunting of blood away from the lungs results in severe cyanosis.

Both non-pharmacological and pharmacological measures are used to abort hypercyanotic spells (Figure 12). Management begins with the simple maneuver of placing the infant or child in a knee-to-chest position.[2,94] The purpose of this maneuver is to increase SVR so that right-to-left shunting through the VSD will decrease. The knee-to-chest position may be difficult to maintain in infants; therefore, an adult-sized blood pressure cuff wrapped around the abdomen may serve the same purpose.[94] Supplemental oxygen should be used to relieve hypoxemia, and modest fluid boluses

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also may be used to increase SVR.[2,94]

Morphine may be beneficial for two reasons. Firstly, morphine may sedate the child and blunt the tachypnea. This effect may be particularly important if the spell started because the child was upset or crying. Secondly, morphine may decrease infundibular tone to help relieve the spasm. Propranolol is usually effective in decreasing infundibular contractility as well. It may be given intravenously at 0.1 to 0.25 mg/kg every 15 minutes as needed to treat hypercyanotic spells. It may also be given orally at 1 to 2 mg/kg every 6 hours for chronic prophylaxis of spells until palliative or corrective surgery.[40] If the hypercyanotic spell remains refractory to these measures, phenylephrine may be tried.[94] Phenylephrine increases SVR through stimulation of a_1 receptors in the vasculature. Intravenous doses of 5 to 10 mcg/kg every 15 minutes as needed are given initially.[94] If prolonged therapy is required, the drug is given as a continuous infusion of 2 to 5 mcg/kg/min.[94] Unfortunately, phenylephrine can cause severe peripheral vasoconstriction leading to poor perfusion of the extremities. For this reason, the agent should be reserved for those patients who have not responded to more benign measures.

SUMMARY

Numerous pharmacological agents are used in the pre-operative, post-operative, and chronic management of congenital heart lesions. With the exception of indomethacin for PDA closure, these agents are generally used for palliation of CHF symptoms or as a bridge to surgical intervention. Many of these drugs are associated with serious adverse effects; therefore, patients must be closely monitored for adverse drug events as well as worsening of their underlying disease.

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