

## Lectures Series of Congenital Heart Disease (1) “Cyanotic Congenital Heart Disease”

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### Abstract

The incidence of Congenital heart disease (CHD) is reported around 6 to 8 in every 1000 live births. Depending upon the anatomical defects and physiological changes after birth, various clinical presentations of CHD are expected; some present as very unstable immediately after birth, whereas others do not become symptomatic until after several weeks of life. There are specific physiological principles that determine clinical presentation of CHD including signs and symptoms, onset, and severity. To manage these infants properly, it is imperative to understand the specific underlying pathophysiology caused by the anatomical defects. CHD can present with varying degrees of cyanosis, respiratory distress, congestive heart failure, decreased cardiac output, or even cardiovascular collapse. In this review, a new classification of cyanotic CHD is introduced. Cyanotic CHD is classified into the following four categories based upon the underlying pathophysiology: (1) ductus-dependent pulmonary blood flow, (2) abnormal mixing, (3) parallel circulation, and (4) obstruction of pulmonary venous drainage. Understanding the specific mechanisms of cyanotic CHD will provide us with proper management guidelines for cyanotic babies and will outline the rationale of surgical emergency in certain cases.

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### Introduction

Congenital heart disease (CHD) is reported to occur around 6 to 8 per 1000 live births<sup>[1]</sup>. Conventionally, CHD is categorized as cyanotic or acyanotic based upon the presence or lack of cyanosis. However, the clinical presentation of CHD (signs and symptoms, timing, and severity) is complex and is determined by a combination of anatomical defects. Approximately 15% of all CHD are of cyanotic type<sup>[2]</sup>, and about 30% of these cyanotic lesions are potentially fatal or may become critical conditions without surgery<sup>[3,4]</sup>. The early recognition and diagnosis of CHD is imperative, as a prompt initiation of proper management including prostaglandin E1 (PGE1) infusion and transfer to the Pediatric Congenital Heart Center are crucial for the prognosis and survival of the sick babies with CHD<sup>[5]</sup>. After cardiac anatomy is confirmed by echocardiogram and other imaging modalities, the pathophysiology of the CHD should be correctly understood to initiate proper management for stabilization of these infants.

CHD can present with varying degrees of cyanosis, respiratory distress, congestive heart failure, decreased cardiac output, or even cardiovascular collapse. Some cases may develop into a life-threatening condition unless treated properly. Cyanotic CHD presents with either isolated cyanosis or cyanosis in combination with other abnormal presentations including low systemic cardiac output, pulmonary venous congestion, and systemic venous congestion. Cyanotic CHD consists of a wide clinical spectrum presenting with either decreased or increased pulmonary blood flow<sup>[6,7]</sup>. In this article, a new classification of cyanotic CHD is introduced and classified into four categories based upon underlying pathophysiology. The aim of this classification is to help rationalize proper decision-making based upon understanding of pathophysiology of these cardiac malformations.



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## Physiological Significance of Cyanosis

Physiological definition of cyanosis (central cyanosis) is a bluish color of the skin and mucous membrane caused by reduced hemoglobin (deoxyhemoglobin) level of 5 g/dl or more in a capillary bed, which corresponds to approximately oxygen saturation of 70% in newborn infants. Acute physiological outcome of cyanosis is reduced oxygen delivery to peripheral tissues unless compensated by increased cardiac output and/or elevated hemoglobin level. Persistent unrelieved cyanosis results in tissue hypoxia, increased anaerobic metabolism, metabolic acidosis, and circulatory failure. Although young infants can generally tolerate low oxygen saturation better than older children, young brain tissue is more vulnerable to hypoxic injury<sup>[8]</sup>, which could result in lifelong consequences. Long-term consequences of persistent hypoxia include exercise intolerance and high risk of thromboembolism and stroke due to polycythemia. Acute cyanosis (oxygen saturation < 70%) should be regarded as a life-threatening condition and requires urgent treatment.

There are five different physiological mechanisms that cause cyanosis (summarized in Table 1). The possibility of cyanotic CHD should be considered after ruling out cyanosis from central nervous system (CNS), airway, or lung diseases. Hyperoxia test is useful in differentiating cardiac cause (CHD with right-to-left shunt) from non-cardiac causes in cyanotic neonates<sup>[9]</sup>. Partial pressure of oxygen ( $\text{PO}_2$ ) obtained either by arterial blood gas from right radial artery or transcutaneous oxygen monitor (TCOM) at right arm is to be measured first on room air ( $\text{FiO}_2$  0.21) and then on 100% oxygen ( $\text{FiO}_2$  1.0). On  $\text{FiO}_2$  1.0,  $\text{PaO}_2$  rarely becomes higher than 50 mmHg in cyanotic CHD with PDA-dependent pulmonary blood flow or parallel circulation (see sections 1 and 3 below, respectively), whereas  $\text{PaO}_2$  increases beyond 100 mmHg in non-cardiac conditions.

**Table 1:** Differential Diagnosis of Central Cyanosis

Pathophysiology	Disease	Diagnostic Procedures
1 <b>Alveolar Hypoventilation</b>		
a) CNS	Central apnea (seizures)	CT/MRI, EEG
b) Upper airway	Obstructive apnea Upper airway obstruction	Bronchoscopy, pneumogram Fluoroscopy, bronchoscopy
2 <b>Ventilation-Perfusion (V/Q) Mismatch</b>		
a) Small airway	Asthma, emphysema	CXR, PFT
b) Pulmonary parenchyma	Pneumonia, RDS	CXR, CT, ABG
c) Pulmonary arteries	Pulmonary embolism	D-dimer, ventilation-perfusion scan
3 <b>Diffusion Abnormalities</b>		
a) Cardiac (LV dysfunction)	Pulmonary edema	CXR, echocardiogram, cardiac catheterization
b) Pulmonary	Interstitial pulmonary fibrosis	CXR, PFT, ABG, CT, biopsy
4 <b>Right-Left Shunt</b>		
a) Intracardiac	Cyanotic CHD	CXR, echocardiogram, cardiac catheterization
b) Extracardiac	Pulmonary AVM	Echocardiogram (bubble study), CT angiography
5 <b>Hematological</b>		
a) Polycythemia	Twin-twin transfusion, IDM	CBC
b) Hemoglobin abnormality	Methohemoglobinemia	Hb assay

ABG: arterial blood gas, AVM: atriovenous malformation, CBC: complete blood count, CNS: central nervous system, CXR: chest radiograph, Hb: hemoglobin, IDM: infant of diabetic mother, PFT: pulmonary function test, RDS: respiratory distress syndrome.

## Physiological Sequence during Transition from Fetal to Neonatal Circulation

Immediately after the first cry at birth, three major physiological changes start to outline the transition from fetal to neonatal circulation. The first is the initiation of effective pulmonary circulation. In utero, oxygenation was provided by placenta, and pulmonary circulation is nearly bypassed via either foramen ovale or ductus arteriosus due to very high pulmonary vascular resistance (PVR). After birth, the two independent circuits, systemic and pulmonary circulations, in series, are essential in maintaining life. With an initiation of effective pulmonary circulation immediately after birth, arterial oxygenation significantly increases, and the patent ductus arteriosus (PDA) begins to regress and usually closes within the first 2 days in term neonates, which denotes the second event. Simultaneously, PVR starts to decrease drastically as oxygenation continues to improve. The physiological decline in PVR, the third physiological event, continues to progress and reaches the normal adult level by 2 months after birth. These physiological changes explain the reasons for specific timing and severity of clinical presentation of CHD.

## Underlying Mechanisms of Cyanosis in CHD

After extra-cardiac etiologies of cyanosis (1,2,3 and 5 in Table 1) are ruled out, possible etiology of cyanotic CHD should be investigated<sup>[10]</sup>. History (onset of cyanosis, other associated clinical manifestations, and prenatal history), physical examination (skin color and perfusion, respiratory distress, cardiac findings, and dysmorphic features), chest radiograph (cardiac silhouette, pulmonary vascular markings, and lung fields), ECG (rhythm, P wave axis, QRS axis, delta wave, and chamber hypertrophy), and arterial blood gas (oxygenation, ventilator status, and acid-base balance) are the important markers to determine the underlying pathophysiology, which will be confirmed by echocardiogram in most cases. The basic mechanisms of cyanotic CHD are summarized in Table 2 and including the following: 1) PDA-dependent pulmonary blood flow, 2) abnormal mixing lesions, 3) parallel

circulations, and 4) obstruction of pulmonary venous drainage. These different mechanisms can co-exist in some infants. In the following paragraphs, the pathophysiology of each category is discussed.

**Table 2:** Pathophysiology, Onset, Severity, and Management of Cyanotic CHD

	<b>Pathophysiology</b>	<b>Severity</b>	<b>Onset</b>	<b>Management</b>
1	<b>PDA-dependent Pulmonary Blood Flow</b>  Anatomical obstruction of RV outflow tract and obligatory R to L shunt Critical PS, PA, TOF, Ebstein's anomaly	Varies; Mod to Severe	Progressive, Within 2 days	PGE1
2	<b>Abnormal mixing</b>  Mixing of arterial and venous blood at the anatomical defects a) Systemic veins: TAPVC (draining into SVC, coronary sinus, or innominate vein) b) Atria: Common atrium, TAPVC (draining into RA), tricuspid atresia c) Ventricles: Single ventricle with PS (DORV, DILV) d) Great arteries: Truncus arteriosus	Mild, CHF	Insidious	None urgent
3	<b>Parallel Circulation</b>  d-TGA with intact ventricular septum	Severe, Low CO	Usually early	PGE1 + BAS
4	<b>Obstruction of pulmonary venous drainage</b>  a) In TAPVC (infracardiac type, obstruction at the drainage site) b) In HLHS with restrictive PFO	Severe Low CO	Very early	Urgent surgery

BAS: balloon atrial septotomy (septostomy), CHF: congestive heart failure, CO: cardiac output, DILV: double inlet left ventricle, DORV: double outlet right ventricle, d-TGA: d-transposition of the great arteries, HLHS: hypoplastic left heart syndrome, PA: pulmonary atresia, PS: pulmonary stenosis, PFO: patent foramen ovale, SVC: superior vena cava, RA: right atrium, TAPVC: total anomalous pulmonary venous connection.

**1. PDA-dependent pulmonary blood flow:** When the pulmonary blood flow is partly or entirely supplied via PDA, the patients become progressively cyanotic as PDA closes. PDA closure is accompanied by decrease in pulmonary blood flow and simultaneous increase in right-to-left shunt at either the patent foramen ovale (PFO) or ventricular septal defect (VSD). This category of CHD commonly presents when Right Ventricular Outflow Tract (RVOT) is anatomically or functionally obstructed, consisting of critical pulmonary stenosis (PS), pulmonary atresia (PA), tetralogy of Fallot (TOF) with severe PS or RVOT obstruction, or hypoplastic RV. Patients with severe Ebstein's anomaly are included in this category. These infants may be asymptomatic soon after birth but progressively become cyanotic within the first one or two days. The progressiveness and severity of cyanosis are proportional to the degree of anatomical obstruction of the antegrade pulmonary blood flow. Supplemental oxygen may slightly improve the oxygenation. The chest radiograph commonly shows paucity of pulmonary vascular markings. PGE1 infusion is essential for maintaining an open PDA to improve oxygenation by securing pulmonary blood flow. Surgical palliation (Blalock-Taussig shunt) or complete repair can then be performed.

**2. Abnormal mixing lesions:** Abnormal mixing of arterial blood (pulmonary venous blood) and venous blood (systemic venous blood) occurs at multiple different levels including systemic veins (total anomalous pulmonary venous connection or TAPVC to systemic veins), atria (TAPVC to right atrium, common atrium, tricuspid atresia, and Ebstein's anomaly), ventricles (physiological single ventricle), and great vessels (truncus arteriosus). The clinical presentation is usually insidious, and the degree of cyanosis is relatively mild. As these cases are usually not PDA-dependent, PGE1 infusion may not be beneficial unless there is an associated RVOT obstruction. Tricuspid atresia and Ebstein's anomaly may present with a wide clinical spectrum depending upon the associated anomalies and the severity of tricuspid valve deformity, respectively. The severity of cyanosis in tricuspid atresia is determined by restrictiveness of VSD or the degree of pulmonary stenosis. Patients with abnormal mixing at ventricular or great vessel level usually present with congestive heart failure (CHF) within a few weeks after birth in addition to mild cyanosis. The progressive fall in PVR leads to progressive increase in pulmonary blood flow and lessens systemic blood flow due to a shift of circulating blood volume from systemic to pulmonary circulation. These patients may not develop severe cyanosis, and the primary management should be focused on controlling (CHF). Pharmacological therapy with diuretics (furosemide) and digoxin may be started when increased work of breathing and/or poor feeding occur. Surgical intervention with complete biventricular repair or staged single ventricle palliation is indicated.

**3. Parallel circulations:** D-Loop transposition of the great arteries (d-TGA) with intact ventricular septum (IVS) can present with severe and progressive cyanosis immediately after birth, but the severity of clinical presentation may vary depending upon the degree of interatrial mixing. In d-TGA with IVS, the two circuits are totally parallel or separated, and the mixing takes place primarily at PFO and, to some extent, PDA. Direction of blood flow across PDA is predominantly aorta (left) to pulmonary artery (right) as PVR continues to fall. This induces a blood volume shift from systemic circulation to pulmonary circulation. Without sufficient size of PFO that allows fully saturated blood flow from LA to RA into systemic circulation, PGE1 sometimes may reduce systemic cardiac output and even worsen the oxygenation by increasing pulmonary edema. Patients with restrictive PFO almost always require

emergency balloon atrial septostomy (BAS) to improve oxygenation and systemic blood flow. Thus, early recognition of d-TGA and prompt transfer of these patients to a Pediatric Congenital Heart Center is mandatory. In addition to early and severe cyanosis refractory to supplemental oxygen and a peculiar “egg-shaped heart” on chest radiograph, the presence of differential cyanosis (oxygen saturation is higher in lower extremities than in upper extremities) is helpful in making the diagnosis. However, the clinical presentation of d-TGA with IVS is diverse, and these patients may not always have a typical presentation. Arterial switch operation with coronary transfer is a standard surgical procedure performed with low mortality and morbidity during the newborn period in all Pediatric Congenital Heart Centers except for rare exceptions<sup>[11]</sup>.

**4. Obstruction of pulmonary venous drainage:** Isolated pulmonary venous obstruction can occur alone, but it is commonly associated with TAPVC. Hypoplastic left heart syndrome (HLHS) with restrictive PFO may show similar physiology. When complicated by pulmonary venous obstruction, the clinical presentation is early and progressive with severe cyanosis and low cardiac output. These conditions are frequently refractory to maximum medical management including PGE1 infusion and ventilator support. Chest radiograph shows severe pulmonary edema or total “white-out” of lungs, resembling severe hyaline membrane disease. This CHD condition is an emergency upon diagnosis and requires immediate surgical intervention. Early recognition and prompt transfer for surgery is essential for recovery and survival. Congenital pulmonary venous obstruction may require repeated surgical interventions<sup>[12]</sup>.

In CHD, cyanosis may be associated with respiratory distress secondary to pulmonary venous congestion, CHF, and low cardiac output status (Table 3). Although not included in this classification, PDA-dependent systemic circulation, including HLHS, critical coarctation of aorta, and interrupted aortic arch (IAA), may present with cyanosis due to right-to-left shunt across PDA. As their principal presentation is a decreased systemic perfusion, these conditions will be discussed elsewhere. Chest radiograph may indicate the degree of intracardiac shunt (cardiomegaly), the increase or decrease in pulmonary blood flow (pulmonary vascular markings), and the degree of pulmonary venous congestion. ECG findings are relatively nonspecific in making an anatomical diagnosis, but they may reflect abnormal underlying hemodynamic status such as ventricular volume or pressure overload (Table 4). This new classification would be helpful in understanding pathophysiology of variable clinical presentation of cyanotic CHD. Some cyanotic CHD can be classified into one of the above four categories, whereas others may be identified as a combination of more than one categories. For example, TAPVC (infracardiac type) consists of abnormal mixing and pulmonary venous obstruction, and d-TGA with intact ventricular septum and restrictive PFO is identified by a combination of parallel circulation and pulmonary venous obstruction. Tricuspid atresia with restrictive VSD or PS has both abnormal mixing and PDA-dependent pulmonary blood flow. With these four categories, most cases of existing cyanotic CHD can be addressed from the pathophysiological standpoint.

**Table 3:** Signs & Symptoms, Timings, and Severity of Cyanotic CHD

Signs & Symptoms Onset	Cyanosis (mild)	Cyanosis (mod to severe)	Cyanosis (severe) + Resp distress with Low CO	Cyanosis (mild to mod) with CHF
<b>Immediately after birth Initiation of pulmonary circulation</b>	Truncus arteriosus DORV without PS DILV without PS d-TGA with large VSD TAPVC	d-TGA/IVS Epstein with severe TR	d-TGA/IVS with restrictive PFO TAPVC with PVO HLHS with restrictive PFO	
<b>Within 1 to 2 days Closure of PDA</b>		PA, Critical PS TOF with severe PS or PA Tricuspid atresia with PS	d-TGA/IVS with PGE1	
<b>Within 6 to 8 weeks Fall in PVR</b>	TOF with mod PS TAPVC without PVO Common atrium			Truncus arteriosus DORV without PS DILV without PS d-TGA with large VSD Tricuspid atresia without PS

CHF: congestive heart failure, CO: cardiac output, DILV: double inlet left ventricle, DORV: double outlet right ventricle, d-TGA: d-transposition of the great arteries, HLHS: hypoplastic left heart syndrome, IVS: intact ventricular septum, PA: pulmonary atresia, PDA: patent ductus arteriosus, PFO: patent foramen ovale, PGE1: prostaglandin E1, PS: pulmonary stenosis, PVO: pulmonary venous obstruction, PVR: pulmonary vascular resistance, VSD: ventricular septal defect, TOF: tetralogy of Fallot, TAPVC: total anomalous pulmonary venous connection.

**Table 4:** Chest Radiograph and ECG Findings

Categories	Underlying Hemodynamic Abnormalities	CXR	ECG
1 <b>PDA-dependent pulmonary blood flow</b>	<b>Decreased pulmonary blood flow</b> RVPO: Critical PS, TOF, PA RV hypoplasia: PA, Epstein's anomaly	↓ PVM “Boot-shaped” heart in TOF (25%)	RVH (not in RV hypoplasia) RAH LVH in RV hypoplasia
2 <b>Abnormal mixing</b>	<b>Ventricular volume overload</b> LVVO: Truncus, tricuspid atresia RVVO: TAPVC, common atrium <b>Congestive heart failure</b>	↑ Cardiac silhouette ↑ PVM “Snowman sign” in Supracardiac TAPVC	LVH or RVH or BVH
3 <b>Parallel circulation</b>	Two separate circulation with limited mixing at PFO and PDA Increased pulmonary blood flow	↑ PVM “Egg-on-its-side” shaped heart in d-TGA	RVH or BVH
4 <b>Obstruction of pulmonary venous drainage</b>	<b>Pulmonary venous congestion</b> <b>RV pressure overload</b>	Pulmonary venous congestion Small heart size with severe pulmonary venous obstruction	RVH, RAH, RAD

BVH: biventricular hypertrophy, CXR: chest radiograph, d-TGA: d-transposition of the great arteries, LVH: left ventricular hypertrophy, LVVO: left ventricular volume overload, PDA: patent ductus arteriosus, PFO: patent foramen ovale, PA: pulmonary atresia, PVM: pulmonary vascular markings, RAD: right axis deviation, RAH: right atrial hypertrophy, RVH: right ventricular hypertrophy, RVPO: RV pressure overload, RVVO: right ventricular volume overload, TAPVC: total anomalous pulmonary venous connection, TOF: tetralogy of Fallot.

Factors other than the above four categories influence the prognosis of cyanotic CHD. For example, the prognosis of Ebstein's anomaly is not solely determined by the degree of cyanosis but more by the degree of tricuspid regurgitation and CHF. The prognosis of pulmonary atresia with intact ventricular septum is determined not by the severity of cyanosis but rather by RV morphology (hypoplastic vs normoblastic RV) and the presence of RV-dependent coronary circulation. These two types of CHD have higher mortality than other types of CHD. Other important aspects to consider are prematurity, low birth weight, initial patient presentation, type of operation, early postoperative complications, and associated non-cardiac issues (chromosomal abnormalities, genetic abnormalities, Pierre-Robin sequence, VACTREL association, etc)<sup>[13-15]</sup>.

## Summary

For infants presenting with cyanosis, the first step is to rule out extracardiac cause of cyanosis; CNS, airway, and pulmonary diseases with thorough history and physical, chest radiograph, and arterial blood gas measurements (Table 1). Infants who fail a hyperoxia test should be suspected to have cyanotic CHD. PGE1 infusion is always justified for severe and progressive cyanosis even before a specific cardiac diagnosis is made. Some cases of cyanotic CHD do not respond to PGE1 unless pulmonary blood flow is dependent upon PDA (Category 1). The initiation of PGE1 may not be helpful in those patients with d-TGA/IVS with restrictive PFO and TAPVR with pulmonary venous obstruction (Categories 3 and 4). These conditions require emergency intervention either by cardiac catheterization (BAS) or surgery. Understanding the baseline pathophysiology of cyanotic CHD in combination with ongoing dynamic physiological changes after birth is thus of utmost importance in caring for infants with cyanotic CHD.

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<ul style="list-style-type: none"> <li>• Signs &amp; Symptom Onset</li> </ul>	<ul style="list-style-type: none"> <li>• Cyanosis (mild)</li> <li>• Cyanosis (mod to severe)</li> <li>• Cyanosis (severe) + Resp distress</li> <li>• with Low CO</li> </ul>