Myocardial Disorders in the Neonate

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Education Gaps

1. Several physiologic changes take place in the myocardium after birth.
2. Knowledge about common primary myocardial disorders that present in the neonatal period has been limited.

Abstract

Myocardial disorders in the neonate could be a significant cause of morbidity and mortality. The neonatal myocardium is immature and undergoes several changes after birth. These include changes in the size of the myocardium, cellular transport of calcium, and utilization for fatty acid and glucose metabolism. Neonatal myocardium relies heavily on the heart rate to improve cardiac output. Myocardial disorders in the neonate can be classified as primary and secondary. Primary myocardial disorders have an inherent abnormality in the cardiac muscle and can be further subclassified based on the morphology and presentation. These include hypertrophic cardiomyopathy, dilated cardiomyopathy, and restrictive cardiomyopathy. Secondary myocardial disorders are usually caused by a systemic disorder that affects the cardiac muscle and function. These include inborn errors of metabolism, neuromuscular disorders, and mitochondrial disorders. The diagnosis and management of cardiomyopathy is very specific to the type of cardiomyopathy or underlying disorders. A team approach, including neonatology, genetics and metabolism, and cardiology and cardiac transplantation, is essential in managing these cases.

Objectives

After completing this article, readers should be able to:

1. Describe myocardial physiology and adaptation in the neonatal period.
2. List the common primary myocardial disorders.
3. Recognize myocardial disorders secondary to other diseases.

AUTHOR DISCLOSURE
Dr. Bansal has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS
- ARVC: arrhythmogenic right ventricular cardiomyopathy
- DCM: dilated cardiomyopathy
- ECG: electrocardiography
- HCM: hypertrophic cardiomyopathy
- IEM: inborn error of metabolism
- LVOT: left ventricular outflow tract
- MRI: magnetic resonance imaging
INTRODUCTION
The neonatal myocardium differs from the adult myocardium structurally as well as functionally. An understanding of the newborn myocardium and its disorders is crucial in the management of newborns. This review provides a summary of the structural and functional differences in the newborn myocardium and describes common myocardial disorders encountered in the neonatal period.

POSTNATAL CHANGES
The newborn myocardium is disorganized in structure and has a lower amount of contractile proteins than the adult mature myocardium. The neonatal myocardium also has decreased cellular transport. Both effects lead to a relatively impaired myocardial function in the neonate. (1) However, the role of the myocardium is similar in the neonate as in the adult: to increase heart rate and/or inotropy to improve cardiac output.

At birth, neonatal myocardial tissue responds to changes in the circulation quite rapidly. Both left ventricular mass and volume increase due to changes in the left and right ventricular workloads. (2) As the pulmonary vascular resistance drops, the right ventricular workload decreases and the left ventricle becomes the dominant ventricle after birth. (3) The number of myocytes increases initially in the first few weeks after birth, and is then followed by the increase in cardiac mass, mostly as a result of hypertrophy of the myocytes. (4)

After birth, the neonatal myocyte changes from a relatively short and round shape into a longer and more slender shape as it matures. (1) The amount of mitochondria in the neonatal myocyte is localized centrally. With maturity, the amount of mitochondria increases and thus, the mature myocardium is able to use long-chain fatty acids rather than carbohydrates as its energy source. (5) In contrast, immature myocardium is more dependent on extracellular calcium for myocardial contraction. Because the neonate has a lower amount of calcium channels compared with later in life, the neonatal myocardium has less functional reserve. (6) The fetal and neonatal myocardium also has a limited ability to respond to an increased afterload, and ventricular compliance is relatively decreased compared with the adult. Thus, a newborn heart is stiffer and requires relatively small volumes to achieve a desired filling pressure.

Myocardial disorders account for only approximately 1% of childhood cardiac disease (7) and can be classified into 2 major groups based on the organ involvement. (8) Primary cardiomyopathies have myocardial involvement as a part of a generalized systemic disorder.

PRIMARY CARDIOMYOPATHY
The clinical disease process of primary cardiomyopathies predominantly involves the myocardium. Primary cardiomyopathy can be further divided into 3 groups: genetic, mixed, and acquired (Table). Not all of these disorders manifest in the neonatal period but most of them are diagnosed in the neonatal period because of a family history of a similar disorder. The types seen in the neonatal period are usually the most severe.

**TABLE. Causes of Primary Cardiomyopathy**

1. Genetic
   a. Hypertrophic cardiomyopathy
   b. Arrhythmogenic right ventricular cardiomyopathy
   c. Left ventricular noncompaction cardiomyopathy
   d. Glycogen storage disorders
      i. PRKAG2
      ii. Danon cardiomyopathy
   e. Conduction defects
   f. Mitochondrial myopathies
   g. Ion channel disorders
      i. Long QT syndrome
      ii. Brugada syndrome
      iii. Short QT syndrome
      iv. Catecholaminergic polymorphic ventricular tachycardia
      v. Asian sudden unexplained nocturnal death syndrome

2. Mixed
   a. Dilated cardiomyopathy
   b. Restrictive cardiomyopathy

3. Acquired
   a. Inflammatory (myocarditis)
   b. Stress-provoked (“tako-tsubo”)
   c. Peripartum
   d. Tachycardia-induced
   e. Infant of insulin-dependent diabetic mother
   f. Ischemia/hypoxia
Genetic

Hypertrophic Cardiomyopathy. Idiopathic hypertrophic cardiomyopathy (HCM) is caused by mutations of the cardiac contractile proteins, most commonly β-myosin heavy chain and myosin-binding protein C. (8) In patients with HCM, the cardiac mass and wall thickness are increased and generally affect the left ventricle. A murmur is usually the presenting feature. (9) Affected infants can have various clinical findings, including marked congestive heart failure and cardiomegaly on chest radiography. Electrocardiography (ECG) shows left ventricular hypertrophy with ST-T changes (Fig 1). Echocardiography (Fig 2) usually confirms the diagnosis in the absence of other reasons for ventricular hypertrophy such as maternal diabetes, steroid exposure, or neonatal hypertension. Cardiac magnetic resonance imaging (MRI) can demonstrate myocardial fibrosis and scarring.

The goal of management for patients with HCM is symptomatic relief and prolonging survival. β-Blockers are the most commonly used agents for the purpose of decreasing gradients in acute settings. (10)(11) These agents help to reduce left ventricular outflow gradients by decreasing contractility, wall tension, and myocardial oxygen demand. At the author’s institution, propranolol 2 mg/kg per day is used in 3 divided doses. The dose can be titrated based on symptoms, heart rate, blood pressure, and response. In neonates with left ventricular outflow tract (LVOT) obstruction, caution is required when using vasodilators or positive inotropic agents because of the risk of increasing the LVOT gradient. Diuretics are generally counterproductive as they decrease the patient’s overall volume, and thus decrease the ventricular cavity.

In general, the prognosis of neonatal HCM is poor, especially if the neonate has congestive heart failure. (9) Patients with inborn errors of metabolism (IEM) and malformation syndrome usually have a poorer prognosis than those with idiopathic infantile HCM, with mean 5-year survival rates of 41%, 74%, and 82%, respectively. (12) HCM secondary to disorders such as hypertension, steroid use, and maternal diabetes have a very good prognosis, with a reversal of the cardiomyopathy with conservative management or treatment of the underlying disorder.

Arrhythmogenic Right Ventricular Cardiomyopathy. This type usually involves the right ventricle with loss of myocytes and fatty or fibroblast tissue replacement. Arrhythmogenic right ventricular cardiomyopathy (ARVC) has a broad clinical spectrum, but most patients present with ventricular tachyarrhythmias. It rarely presents during infancy. ARVC typically has an autosomal dominant pattern of inheritance and the diagnosis is usually based on family history, characteristic findings on ECG, and cardiac MRI.

Left Ventricle Noncompaction Cardiomyopathy. This type is characterized by a spongy appearance of the left ventricular myocardium on echocardiography (Fig 3). Noncompaction usually involves the apical portion of the left ventricle with deep intratrabecular recesses (Fig 3) communicating with the ventricular cavity; this results from an

Figure 1. Electrocardiogram showing left ventricular hypertrophy in a patient with hypertrophic cardiomyopathy.
arrest in normal cardiac embryogenesis. (13) Left ventricle noncompaction cardiomyopathy may be an isolated abnormality or associated with other congenital heart diseases such as LVOT abnormalities, Ebstein anomaly, and tetralogy of Fallot. (14) The diagnosis is usually made with 2-dimensional echocardiography or cardiac MRI. Presentation in the neonatal period is usually associated with poor prognosis, leading to death or a need for transplantation early in life.

Conduction System Diseases. As depicted in the Table, there are various conduction system abnormalities and ion channel disorders that are classified as cardiomyopathies. Although classified in this way, the myocardium is usually normal in these disorders. These disorders are characterized by ECG changes and arrhythmias. Cardiac function could be affected secondary to an arrhythmia. Several specific genes have been connected to these disorders.

Mixed Dilated Cardiomyopathy. Dilated cardiomyopathy (DCM) is more common than HCM or restrictive cardiomyopathy. (15) The prevalence is about 1 in 2,500 in the general population and it is the most frequent cause of heart transplantation. DCM can result from a primary abnormality in the cardiac myocyte or can be secondary to a wide range of other disorders such as myocarditis. Other secondary causes include autoimmune and systemic disorders, pheochromocytoma, neuromuscular disorders, and mitochondrial, endocrine, and nutritional disorders. About 20% to 35% of DCM cases are familial. (8) Inheritance is heterogeneous, with most cases being autosomal dominant.

Patients with DCM usually present at a later age and rarely in the neonatal period. This disorder is characterized by ventricular enlargement and decreased systolic function; affected patients present with symptoms of low cardiac output such as pallor, irritability, and diaphoresis. (7) Physical findings include tachypnea, tachycardia, narrow pulse pressure, and hepatomegaly. ECG shows flattening of the T wave with possible depression of the ST segments. Cardiomegaly is evident on chest radiography. Echocardiography is diagnostic. Cardiac MRI is often helpful in identifying myocardial fibrosis and scarring but may be difficult to interpret in neonates with increased heart rates. Management includes treatment of heart failure. In contrast to HCM, vasodilators, diuretics, and inotropes are useful in the management of DCM. If management is unsuccessful, patients can develop severe heart failure, arrhythmias, or sudden death.

Restrictive Cardiomyopathy. This is an extremely rare condition in which the ventricular cavities are small and diastolic function is impaired, involving both but predominantly the left ventricle. (7) The systolic function is normal, at least initially. It is very rare in neonates. Affected neonates present with signs and symptoms of congestive heart failure. ECG often shows conduction abnormalities and evidence of ischemia at higher heart rates. Echocardiography shows normal or small ventricles with dilation of both atria. Restrictive cardiomyopathy should be differentiated from constrictive pericarditis as affected patients could have
similar presentations. The prognosis is poor. Survival without transplantation was reported at 39% in 1 center with children of all ages. (16)

Acquired Cardiomyopathy
Myocarditis. Myocarditis is the most common form of acquired cardiomyopathy in neonates. It is caused by acute or chronic inflammation of the myocardium as a result of a wide variety of toxins or infections. The most common infectious agent is viral (eg, Coxsackie virus, adenovirus, parvovirus, human immunodeficiency virus). Other infectious causes include bacterial, fungal, and parasitic. Most of these infections are encountered outside the neonatal period. Endocardial fibroelastosis is a type of cardiomyopathy that can be caused by an intrauterine infection with the mumps virus. (17) The clinical presentation of myocarditis is similar to that of dilated cardiomyopathy.

Maternal Diabetes. Infants of diabetic mothers may have a transient hypertrophic cardiomyopathy with spontaneous regression during the first 6 months of age when insulin levels normalize. (18) It is a complication in 25% to 30% of infants born to women with gestational or prepregnancy diabetes. The ventricular septum is preferentially affected but both the right and left ventricle free walls may also be involved. (19)

Ischemia/Hypoxia. Neonatal myocardial infarction is rare, with a few case reports in the literature. (20) (21) Neonates can have a good recovery with interventions such as extracorporeal membrane oxygenation or catheter interventions. (22) (23)

Birth asphyxia is associated with several cardiovascular changes. Ongoing severe asphyxia is associated with significantly reduced ventricular output and stroke volume. (24) The cause of eventual myocardial dysfunction is multifactorial, including low heart rate associated with asphyxia, acidosis, and ischemic myocardial injury. (25) (26) AFFECTED newborns have an increased troponin level, which has been associated with myocardial damage. (27) Clinical management of cardiac dysfunction relies on maintaining adequate perfusion to organs by maintaining blood pressure and cardiac contractility.

SECONDARY CARDIOMYOPATHY
The myocardial involvement in these disorders is secondary to various multisystem disorders. The frequency and severity of the myocardial involvement varies significantly among these diseases. Some of these disorders are very uncommon, and even then the involvement might not be seen in the neonatal period. IEMs are among the most common causes of secondary cardiomyopathy.

Inborn Errors of Metabolism
Approximately 5% to 26% of infants and children with cardiomyopathy have an IEM. (28) In some cases, the cardiomyopathy dominates the clinical presentation and is the major cause of death. More than 40 disorders are known to cause IEM cardiomyopathy, including fatty acid oxidation defects, organic acidemias, amino acid disorders, glycogen storage diseases, and congenital disorders of glycosylation as well as peroxisomal, mitochondrial, and lysosomal storage disorders. (29) Most of these present in infancy or early childhood with multiorgan dysfunction. Many of these disorders are treatable by targeting the underlying pathophysiology of the disease. Some of the cardiomyopathies could also be reversed by treating the underlying disorder.

IEMs cause cardiomyopathy through various mechanisms. (29) The first is deposition or infiltration of a substrate within the myocyte. These deposits involve large macromolecules such as triglycerides, glycogen, and lysosomal substrates. This has a mechanical effect on the myocyte function. A second mechanism is impaired energy production within the myocyte. These include oxidative phosphorylation defects. A third mechanism is production of toxic metabolites such as organic acidemias.

Each IEM is associated with a specific type of cardiomyopathy, usually DCM or HCM. Of the HCMs caused by IEMs, 50% are due to glycogen storage diseases, of which Pompe disease is the most common. (15) Infants with Pompe disease present with hypotonia, muscle weakness, an enlarged tongue, and congestive heart failure. ECG shows tall QRS waves and short PR intervals. Chest radiography demonstrates cardiomegaly while echocardiography shows severe left ventricular hypertrophy with or without LVOT obstruction. In the pediatric cardiomyopathy registry, fatty acid oxidation defects and oxidative phosphorylation defects comprise 25% of IEM-related cardiomyopathies, with most leading to DCM.

Most cardiomyopathies caused by IEMs present during infancy or early childhood. Cardiomyopathy may be the dominant clinical presentation. An extensive evaluation often reveals signs of multisystem involvement, including physical findings (coarse facial features, cloudy corneas or cataracts, and hepatosplenomegaly), neurologic abnormalities, skeletal myopathy, and skeletal abnormalities. (29) Early diagnosis is key to management of these disorders. Management is aimed at correction of the underlying metabolic disorder.

Neuromuscular/Neurologic Disorders
Many neuromuscular disorders can have associated cardiomyopathies but it is unusual for cardiomyopathy to be the...
presenting symptom. (30) Duchenne and Becker muscular dystrophies are among the most common myopathies associated with cardiomyopathy. The heart is usually affected later in life and affected infants usually are asymptomatic.

Myotonic dystrophy is the most common form of muscular dystrophy. The clinical presentation depends on the form of the disease: congenital, infantile, juvenile, or adult-onset. The severity depends on the number of CTG repeats, with the most severe disease developing in patients with more than 1,000 repeats. (30) The congenital form presents with decreased movements in fetal life, hypotonia, and respiratory failure. Cardiac involvement appears in the second decade of life. Cardiovascular symptoms in these disorders are not overt because of the low level of physical activity.

Mitochondrial Disorders
Mitochondrial disorders are a heterogeneous group of multisystem diseases secondary to mutations in nuclear or mitochondrial DNA. These can be diagnosed at any age depending on the severity of the disease. Cardiac manifestations could include HCM or DCM. (31) Cardiac involvement is typical of certain abnormalities.

Kearns-Sayre syndrome is a mitochondrial myopathy consisting of ptosis, ophthalmoplegia, and retinal pigmentation; affected patients are predisposed to atrioventricular conduction abnormalities.

Patients with myoclonic epilepsy with ragged red fibers or mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes could develop HCM or DCM.

The most common infantile mitochondrial disorder is Leigh syndrome, a progressive neurodegenerative disorder. (31) This syndrome is characterized by gliosis, demyelination, capillary necrosis, and necrosis in the brain. Cardiac involvement could be in the form of HCM and conduction defects such as Wolff-Parkinson-White syndrome.

Sengers syndrome presents with congenital cataracts, HCM, mitochondrial myopathy, and lactic acidosis. Affected patients can present with a severe neonatal form that causes infantile death or a more benign form with longer survival. The cause of death is usually HCM.

Barth syndrome is an X-linked genetic disorder characterized by cardiomyopathy, intermittent neutropenia, muscular weakness, and 3-methyl-glutamic acidauria. It is caused by mutation in the tafazzin (TAZ) gene. Affected patients have a high mortality rate during infancy as a result of cardiac dysfunction.

DIAGNOSIS AND MANAGEMENT
The evaluation of patients with a cardiomyopathy is methodical, and involves evaluation by multiple specialties including neonatology, cardiology, metabolism, and genetics. Psychological and family support should be available, because quite often these patients have an underlying systemic or genetic disorder that requires extensive counseling and guidance. The cardiac transplant team should be involved when providers suspect a possible cardiomyopathy. If relevant, a muscle or myocardial biopsy can help to identify the underlying neuromuscular disorder. Management of secondary cardiomyopathies often involves correction of the underlying metabolic or genetic disorders. The role of immunoglobulin administration in neonatal myocarditis is uncertain. Cardiac failure is often managed symptomatically with the use of diuretics, afterload-reducing agents in infants with DCM, and β-blockers in patients with HCM.

CONCLUSION
Myocardial disorders in the neonatal period are not uncommon and may have a heterogeneous presentation. Patients with a primary cardiomyopathy usually do not present during the neonatal period. If symptoms are present, the condition is usually associated with a poor prognosis. Patients with a secondary cardiomyopathy may present in the neonatal period, depending on the severity of the underlying defect.

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- Know the anatomy and pathophysiology (including genetics) of an infant with a condition affecting myocardial performance.
- Recognize the clinical features in an infant with a condition affecting myocardial performance.
- Recognize the laboratory, imaging, and other diagnostic features of an infant with a condition affecting myocardial performance.
- Formulate a differential diagnosis of an infant with a condition affecting myocardial performance.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for an infant with a condition affecting myocardial performance.
References


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*NeoReviews* 2018;19:e403  
DOI: 10.1542/neo.19-7-e403

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DOI: 10.1542/neo.19-7-e403

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