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# Pediatric Cardiomyopathies

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/55820>

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## 1. Introduction

### 1.1. Development of the cardiovascular system

The development of the cardiovascular system is an early embryological event. From fertilization, it takes eight weeks for the human heart to develop into its definitive fetal structure. During this period the system develops so it can 1) **supply nutrients and oxygen to the fetus**, and 2) **immediately start functioning after birth**.

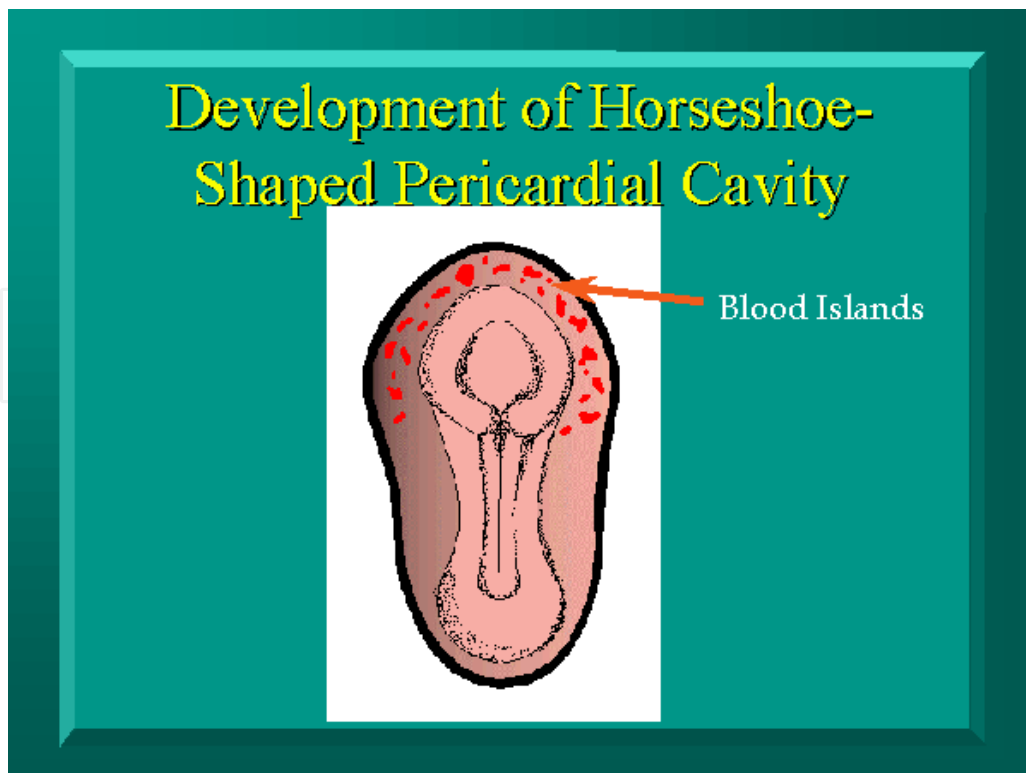
### 1.2. Early development of the circulatory system

#### 1.2.1. Blood islands

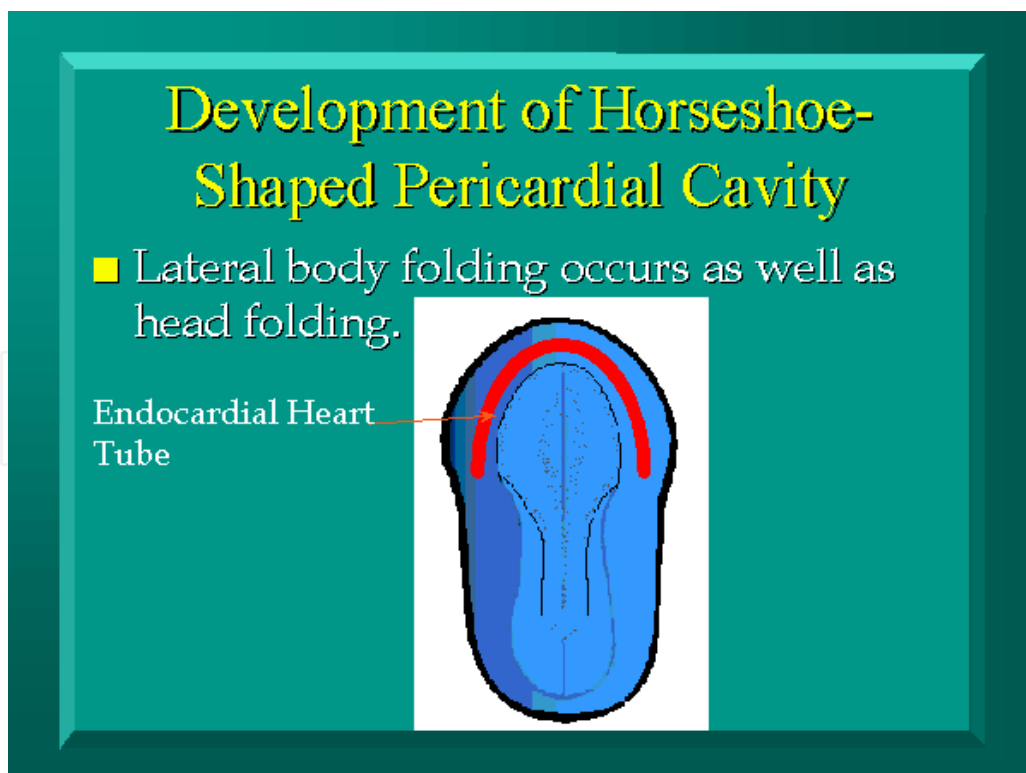
During the third week of gestation angioblastic blood islands of mesoderm (angiogenic clusters) appear in the yolk sac, chorion and body stalk. The innermost cells of these blood islands are hematopoietic cells that give rise to the blood cell lines. The outermost cells give rise to the endothelial cell layer of blood vessels. A series of blood islands eventually coalesce to form blood vessels (fig 1).

#### 1.2.2. Heart tube

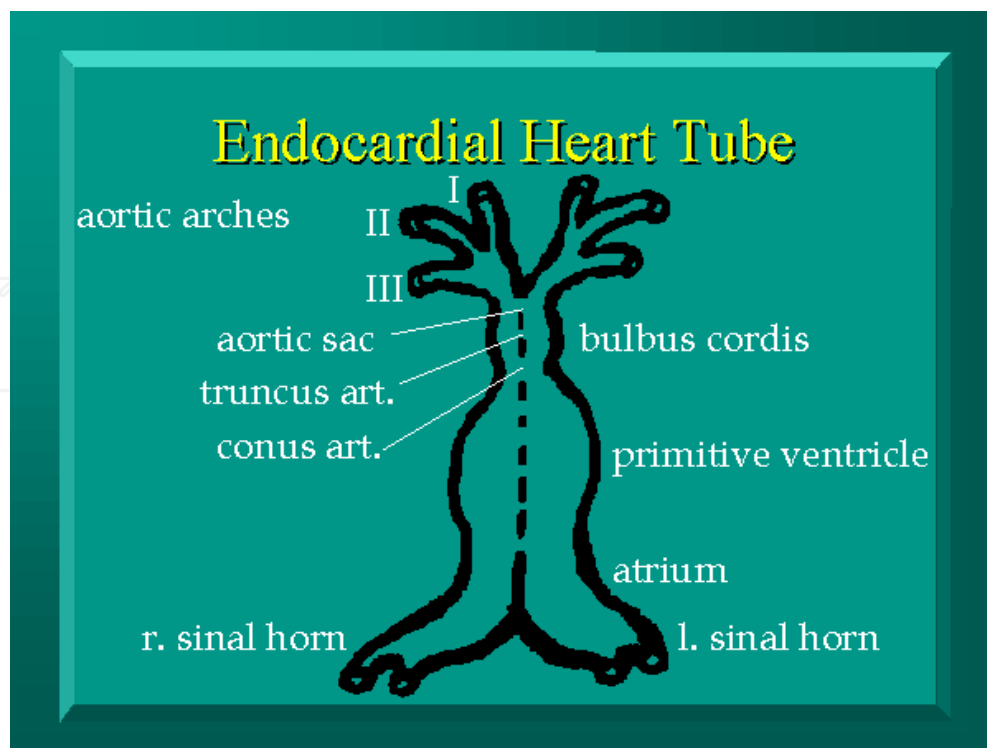
By the middle of the third week of gestation angioblastic blood islands from the splanchnic mesoderm appear and form a plexus of vessels lying deep into the horseshoe-shaped prospective pericardial cavity (fig 2). These small vessels develop into paired endocardial heart tubes. The splanchnic mesoderm proliferates and develops into the myocardial mantle, which gives rise to the myocardium. The epicardium develops from cells that migrate over the myocardial mantle from areas adjacent to the developing heart (fig 3,4).



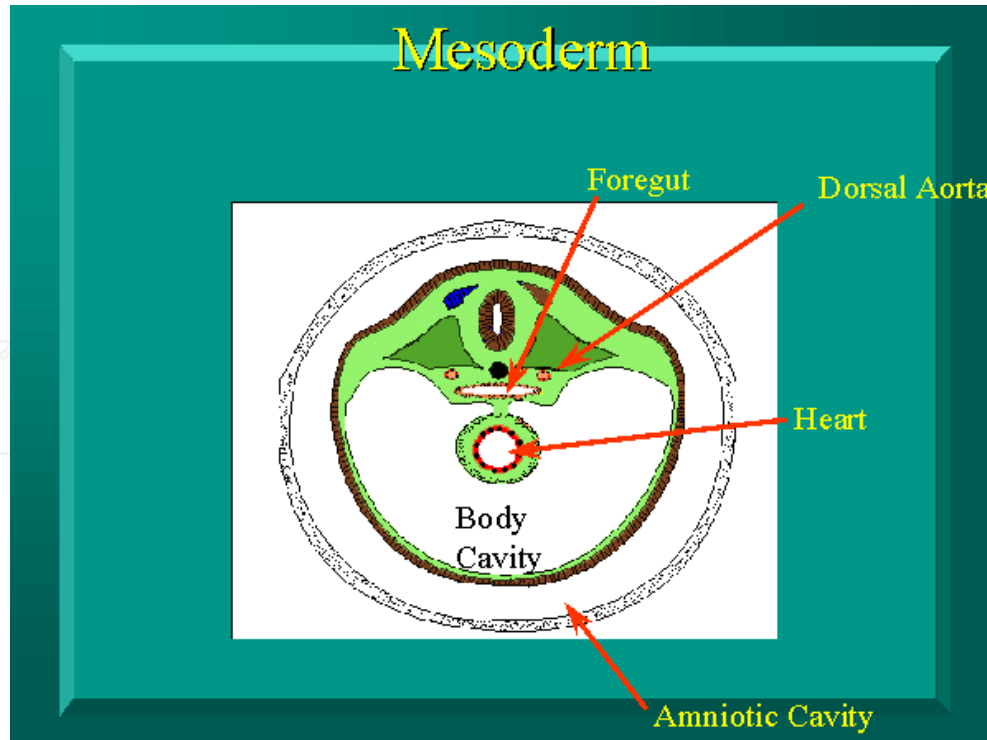
**Figure 1.** Angioblastic blood islands of mesoderm



**Figure 2.** Horseshoe-shaped prospective pericardial cavity

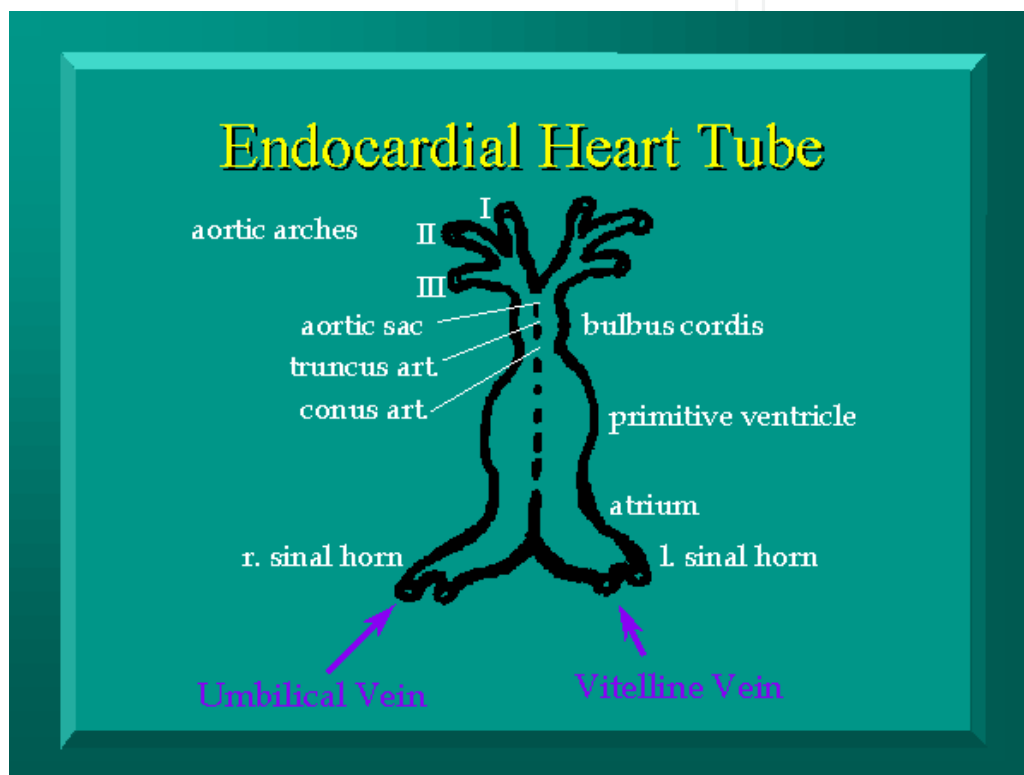


**Figure 3.** Endocardial heart tubes



**Figure 4.** Splanchnic mesoderm

The bilateral endocardial heart tubes continue to develop and connect with a pair of vessels, the dorsal aortae, located on either side of the midline. As the embryo develops, the lateral folding and cephalic growth of the embryo shift the endocardial heart tubes medially, ventrally and caudally. They fuse in the midline as a single endocardial heart tube. The endocardial heart tube is surrounded by the myocardial mantle and between these two layers is the cardiac jelly. The resulting heart tube is kept suspended in the pericardial cavity through the dorsal mesocardium. When the single heart tube is formed, the embryo is in the fourth week of gestation, is about 3 mm in length, has 4 - 12 somites, and the neural tube is beginning to form. The heart now begins to beat (fig 5).

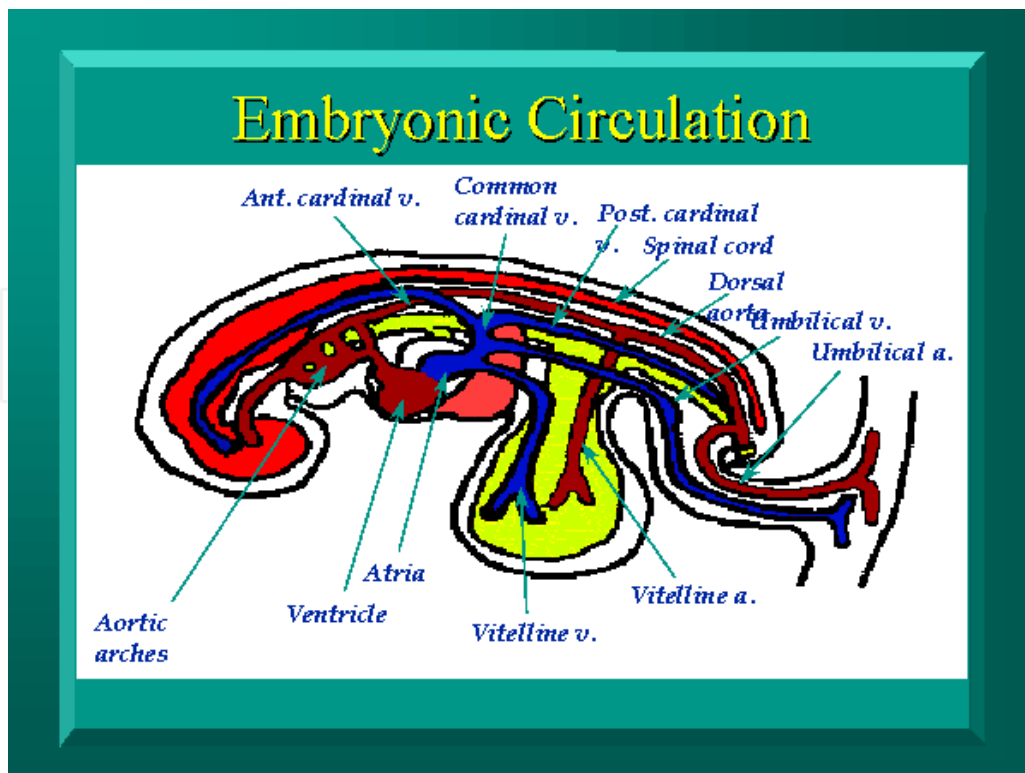


**Figure 5.** Endocardial heart tube

### 1.2.3. Vascular circuits

As the heart begins to beat, three sets of blood islands coalesce to form three vascular circuits. Within the embryo an embryonic circuit forms (fig 6.) It consists of paired dorsal aortae that arise from the endocardial heart tube and break up into capillary networks that supply blood to the developing embryonic tissues. Blood is drained from these tissues by anterior and posterior cardinal veins that drain into common cardinal veins, which in turn drain into the endocardial heart tube.

Two extraembryonic circuits also form. The first is the vitelline (omphalomesenteric, yolk sac) circuit. In this circuit blood from the dorsal aortae drain into vitelline arteries that in turn



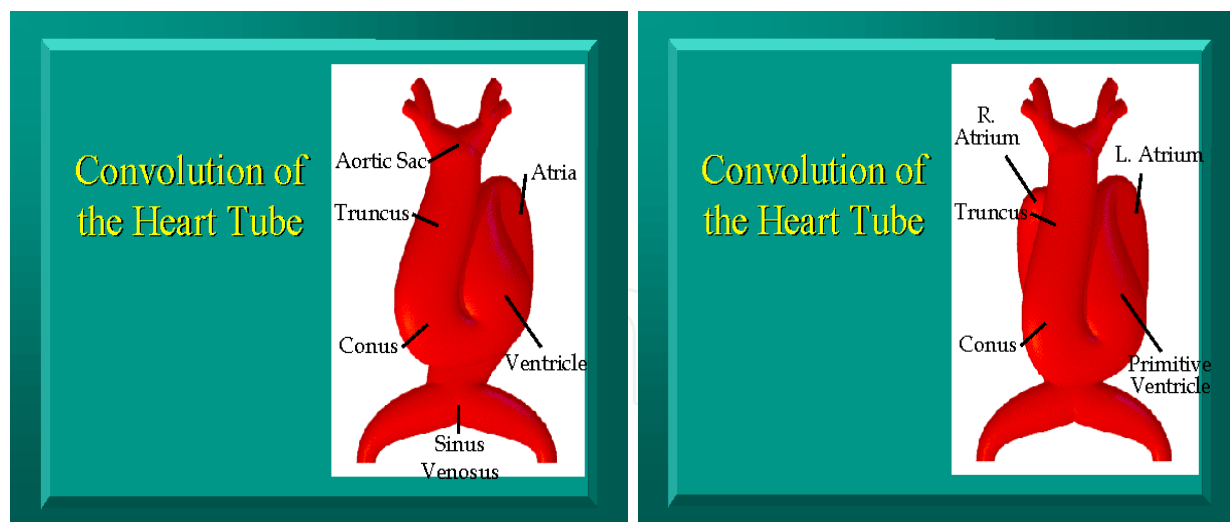
**Figure 6.** Embryonic circuit forms

supply the yolk sac. The blood drains back to the heart tube via paired vitelline veins. The second circuit is the umbilical (allantoic, placental) extraembryonic circuit. In this instance, the dorsal aortae supply blood to umbilical arteries that in turn bring this now unoxygenated blood back to the placenta. Blood from the placenta is carried to the heart tube via umbilical veins.

### 1.3. Formation of the primitive four chambered heart

As the endocardial heart tubes fuse, several bulges and sulci appear. From the cephalic end, the bulges are the bulbus cordis (truncus arteriosus and the conus arteriosus), the primitive ventricle, the primitive atrium and the sinus venosus (fig 7.) The veins connect to the heart tube via the sinus venosus, while the paired dorsal aortae arise from aortic arches that in turn arise from the aortic sac. The aortic sac is at the most cephalic end of the bulbus cordis. The sulci are present as the bulboventricular sulcus, between the bulbus cordis and the ventricle, and the atrioventricular sulcus, between the atrium and the ventricle.

Then, a rapid growth of the heart tube takes place, and the heart begins to convolute. With this convolution the dorsal mesocardium begins to degenerate. During the process of convolution, the first flexure seen is between the bulbus cordis and the ventricle. The bulbo-ventricular loop that is formed shifts this region of the heart to the right and ventrally. The second flexure, the atrioventricular loop, is between the atrium and the ventricle and this region of the heart is shifted to the left and dorsally. As growth continues the atria shift cephalically.



**Figure 7.** Convolution of the Heart Tube

The sinus venosus gradually shifts to the right to empty into the right atrium. The bulbo-ventricular sulcus is represented inside the heart as the bulbo-ventricular flange. The bulbo-ventricular flange and the muscular interventricular septum begin to separate the primitive ventricle (which will become the left ventricle) from the proximal bulbus cordis (which will become the definitive right ventricle). The atria continue to grow, and bulge forward on either side of the bulbus cordis, and shift the bulbus medially. With increased blood flow the bulbo-ventricular flange regresses. Thus, the primitive four-chambered heart is formed and blood flows from the veins to sinus venosus, to atria, to ventricles, to conus, to truncus, to aortic sac, to dorsal aorta.

Now the enlarging liver encroaches upon the developing vitelline and umbilical veins and gradually all the blood will drain to the proximal right vitelline vein. The distal vitelline veins will give rise to the portal system. The left umbilical vein remains and drains into the ductus venosus, a shunt which allows blood to bypass the developing liver.

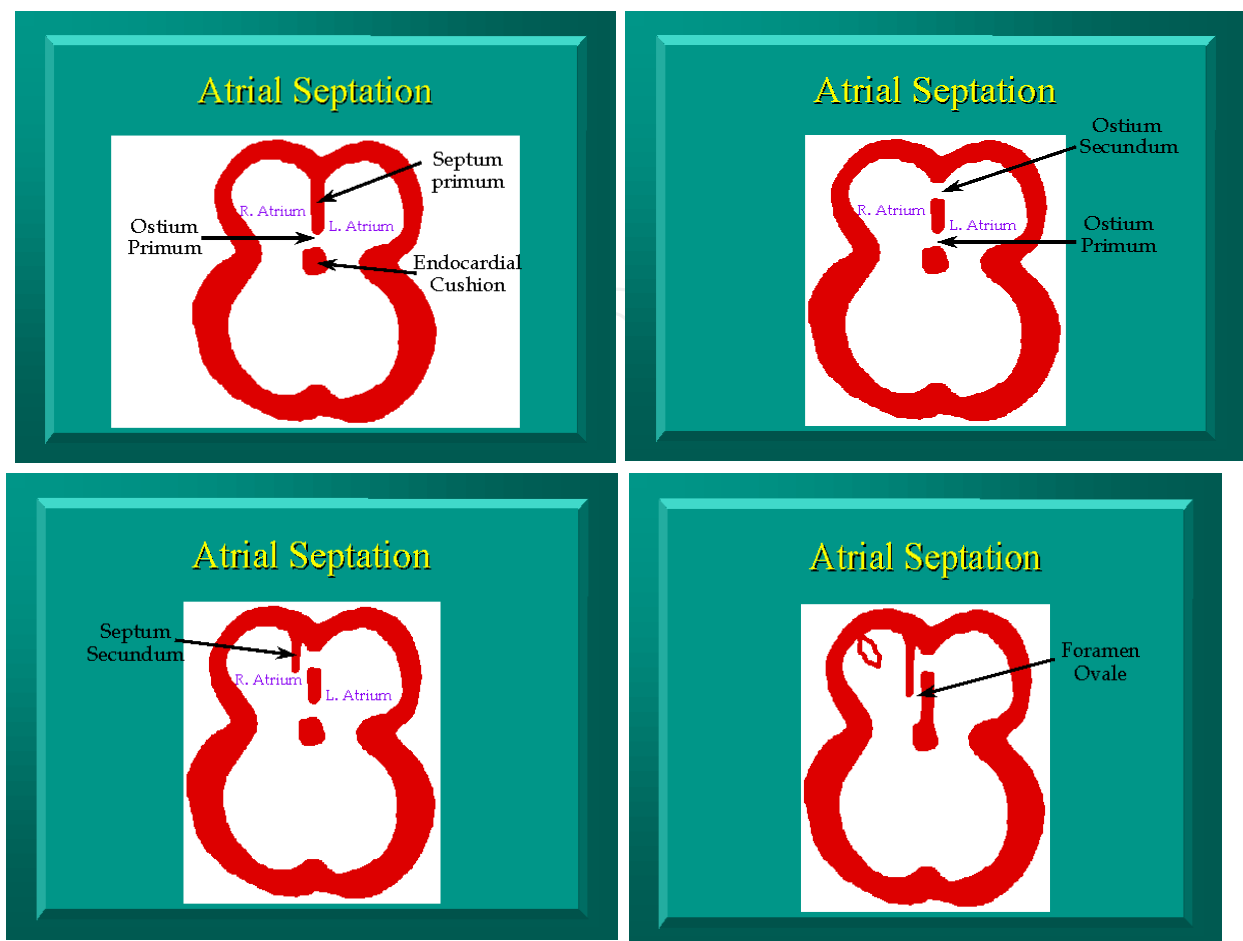
#### 1.4. Septation of the heart

During the second month, the heart begins to septate into two atria, two ventricles, the ascending aorta and the pulmonary trunk.

##### 1.4.1. Atrial septation

Endocardial cushions develop in the dorsal (inferior) and ventral (superior) walls of the heart. These grow toward each other as the cardiac jelly mesenchyme proliferates deep to the endocardium. These cushions fuse and divide the common AV canal into the left and right AV canals.

At the same time there is a developing septum from the dorsocranial atrial wall that grows toward the cushions. This is the septum primum, and the intervening space is called the



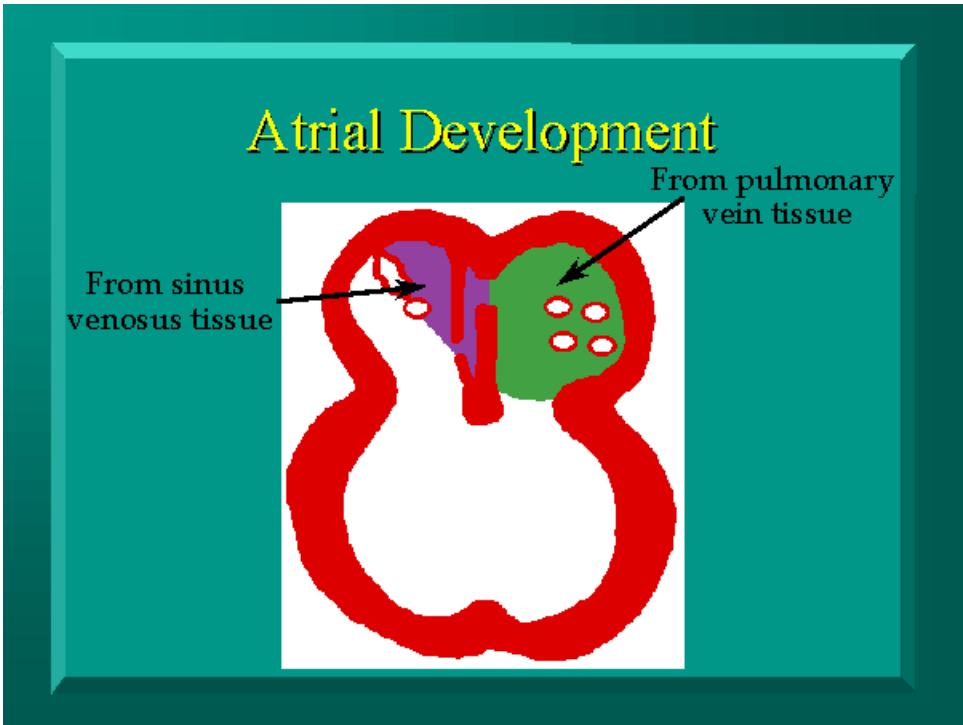
**Figure 8.** Atrial Septation

foramen primum. As the septum reaches the endocardial cushions closing foramen primum, a second opening, foramen secundum appears in septum primum. As foramen secundum enlarges, a second septum, septum secundum forms to the right of septum primum. Septum secundum forms an incomplete partition (lying to the right of foramen secundum) which leaves an opening, the foramen ovale. The remaining portions of septum primum become the valve of foramen ovale (fig 8).

Concurrently, the sinus venosus has shifted to the right as the proximal portions of the left vitelline and umbilical veins are obliterated by the liver. The right sinus venosus becomes incorporated into the right atrium forming the smooth portion of the right atrium. The primitive right atrium is seen in the adult as the rough portion (auricle) of the right atrium. The remainder of the left sinus horn is the coronary sinus and the oblique vein (of Marshall) in the adult heart (fig 9).

On the left side, the primitive atrium is enlarged by the incorporation of tissue from the original, single pulmonary vein and its proximal branches. This incorporated tissue is the adult smooth left atrial wall through which four pulmonary veins empty independently. The trabeculated left atrial appendage originated from the primitive left atrium.

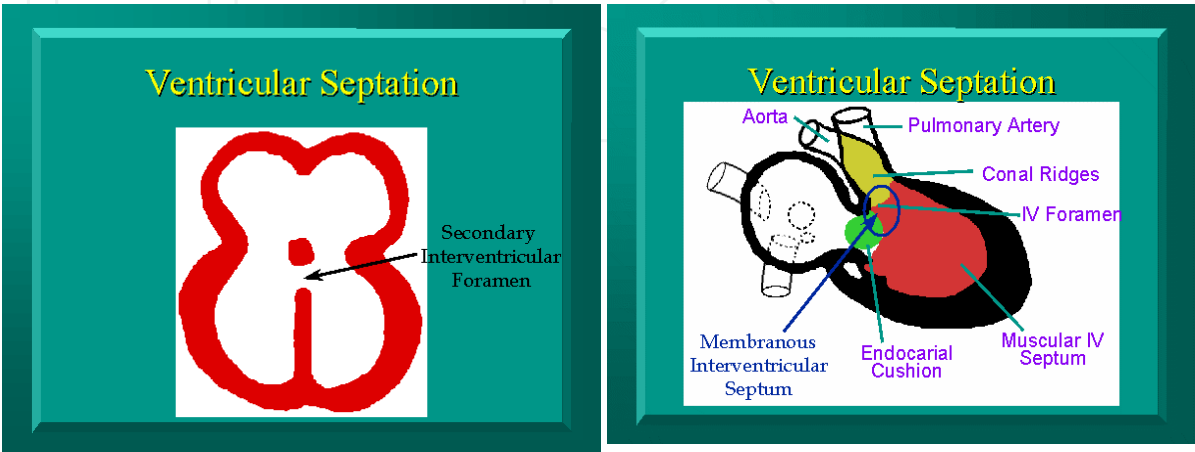




**Figure 9.** Atrial Development

1.4.2. Ventricular septation

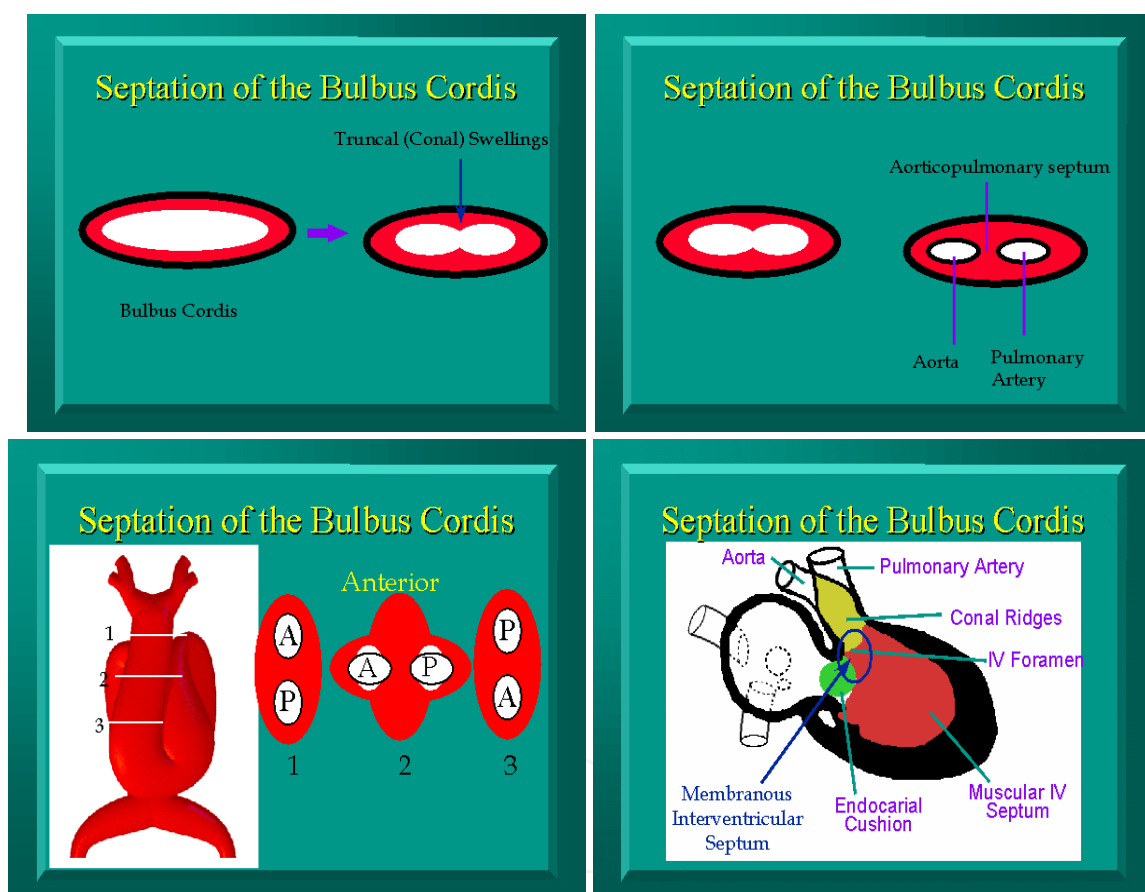
The muscular interventricular septum grows as a ridge of tissue from the caudal heart wall toward the fused endocardial cushions. The remaining opening is the interventricular (IV) foramen. The IV foramen is closed by the conal ridges, outgrowth of the inferior endocardial cushion, the right tubercle, and connective tissue from the muscular interventricular septum. This portion of the I.V. septum is called the membranous part of the interventricular septum (fig 10).



**Figure 10.** Ventricular Septation

### 1.4.3. Septation of the bulbus cordis

Truncal swellings (ridges) appear first as bulges in the truncus on the right superior and the left inferior walls. They enlarge and fuse in the midline to form the truncal (aorticopulmonary) septum. This septum spirals as it develops distally, separating the distal pulmonary artery from the aorta. At the same time, right dorsal and left ventral conal ridges form and fuse in the midline. The conal septum helps dividing the proximal aorta from the pulmonary artery and contributes to the membranous IV septum. The truncal and conal septa fuse to form a 180° spiral and together definitively form the aorta and the pulmonary artery. Cells that contribute to the conal and the truncal septa are in part derived from neural crest cells that migrate into these regions (fig 11).



**Figure 11.** Septation of the Bulbus Cordis

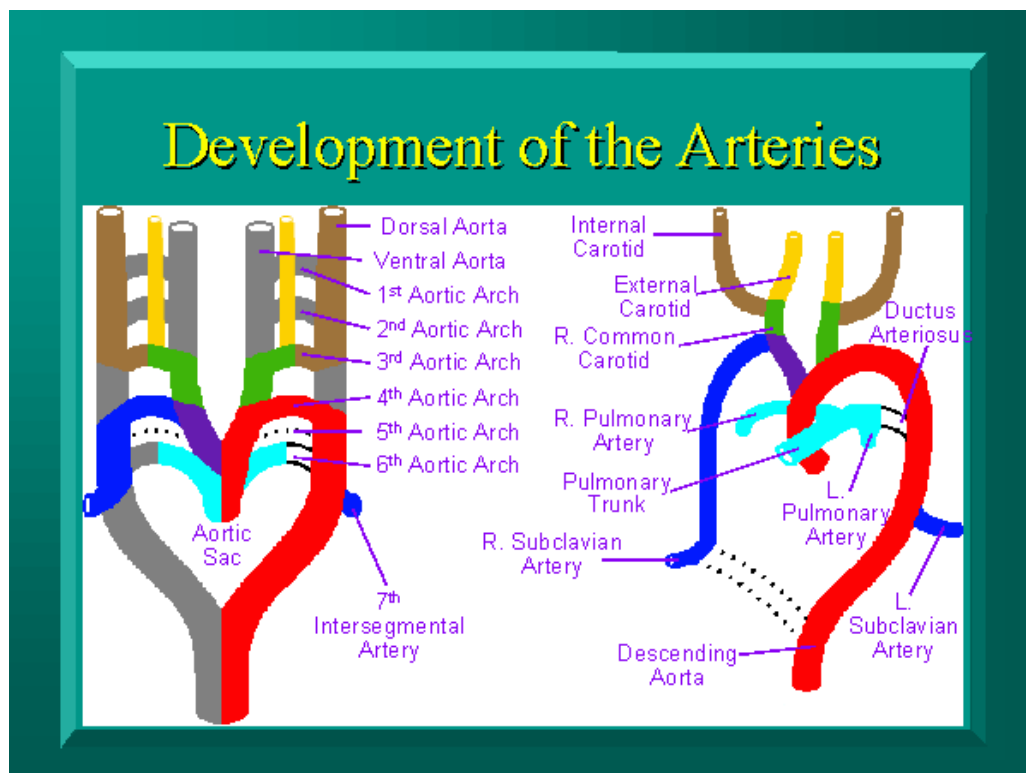
### 1.4.4. Cardiac valve formation

Semilunar valves develop in the aorta and pulmonary artery as localized swellings of endocardial tissue. The atrioventricular valves develop as subendocardial and endocardial tissues and project into the AV canal. These bulges are excavated from the ventricular side and invaded by muscle. Eventually, all the muscle, except that remaining as papillary muscle,

disappear and three cusps of the right AV (tricuspid) valve, and two cusps of the left AV (mitral) valve remain as fibrous structures.

#### 1.4.5. Development of the major arteries

The six pairs of aortic arches, develop in a cephalocaudal direction and interconnect the ventral aortic roots and the dorsal aorta. They are never all present in the developing human heart. Of the six pairs of aortic arches, most of the first, second and fifth arches disappear (fig 12).

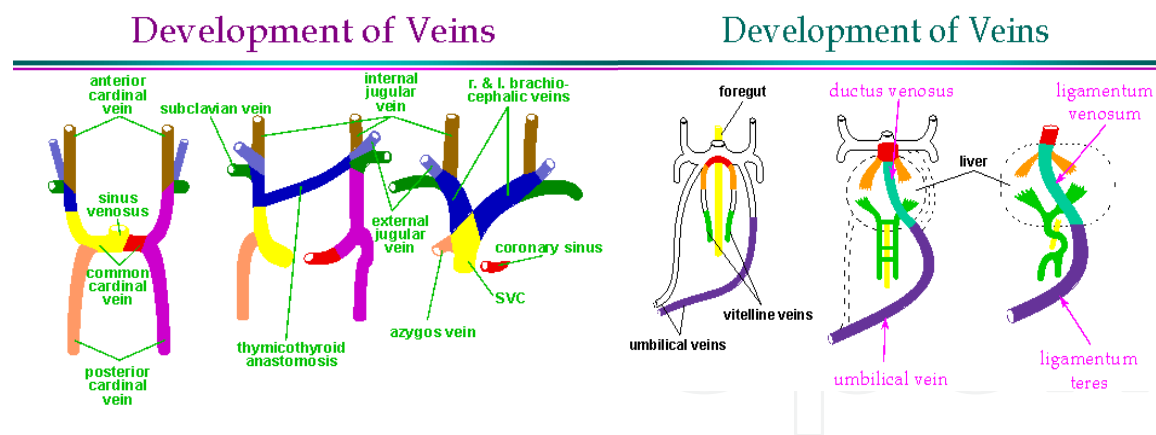


**Figure 12.** Development of the Major Arteries

#### 1.4.6. Development of the veins

The veins develop from the three major vascular circuits. As with the arteries they develop in a cephalocaudal direction and as a consequence the precursors to the veins are never all present at the same time. In addition, as new structures develop the course of veins changes.

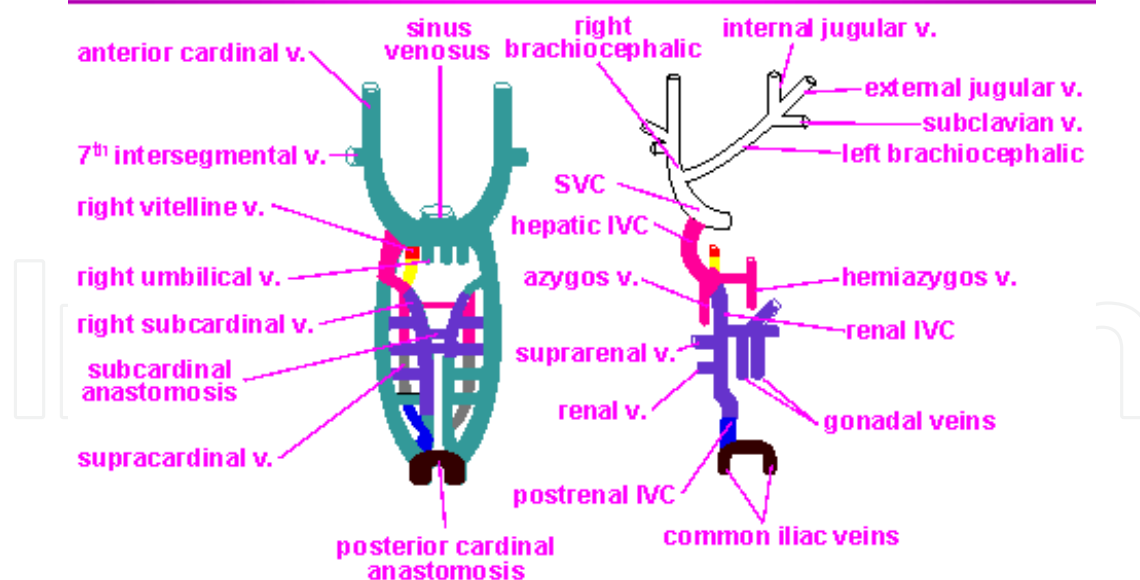
In considering the development of the veins, the veins to the head are derived from the anterior cardinal veins. New channels also develop such as the thymicothyroid anastomoses and the external jugular veins and give rise to veins of the head and neck (fig 13).



**Figure 13.** Development of the Veins

In the trunk, one set of veins develops from the posterior cardinal veins and veins that develop from it later in development, such as the subcardinal, supracardinal, and sacrocardinal veins. These veins will give rise to the inferior vena cava, the renal, adrenal and gonadal veins, as well as the azygos and hemiazygos veins (fig 14).

## Development of Azygos Veins



**Figure 14.** Development of Azygos Veins

The superior mesenteric vein (and perhaps the splenic vein) as well as the veins to the liver develop from the vitelline (omphomesenteric) veins. The ductus venosus develops as a new structure that connects the left umbilical vein with the inferior vena cava (fig 12).

## 2. The cardiomyopathies

Cardiomyopathy is a chronic disease of the heart muscle (myocardium), in which the muscle is abnormally enlarged, thickened, and/or stiffened. The weakened heart muscle loses the ability to pump blood effectively, resulting in irregular heartbeats (arrhythmias) and possibly even heart failure. Cardiomyopathy, a disease of the heart muscle, primarily affects the left ventricle, which is the main pumping chamber of the heart. Usually, cardiomyopathy begins in the heart's lower chambers (the ventricles), but in severe cases can affect the upper chambers, or atria. The disease is often associated with inadequate heart pumping and other heart function abnormalities. Cardiomyopathy is not common but it can be severely disabling or fatal. Most people are only mildly affected by cardiomyopathy and can lead relatively normal lives. However, people who have severe heart failure may need a heart transplant. Cardiomyopathy is a heart condition that not only affects middle-aged and elderly persons, but can also affect infants, children, and adolescents. Cardiomyopathy is classified as either "ischemic" or "nonischemic". All cases related to children and teenagers are considered "nonischemic" cardiomyopathy. Non-ischemic cardiomyopathy predominately involves the heart's abnormal structure and function. It does not involve the hardening of arteries on the heart surface typically associated with ischemic cardiomyopathy. Nonischemic cardiomyopathy can then be broken down into: 1) "primary cardiomyopathy" where the heart is predominately affected and the cause may be due to infectious agents or genetic disorders and 2) "secondary cardiomyopathy" where the heart is affected due to complications from another disease affecting the body (i.e. HIV, cancer, muscular dystrophy or cystic fibrosis). Cardiomyopathy is nondiscriminatory in that it can affect any adult or child at any stage of their life. It is not gender, geographic, race or age specific. It is a particularly rare disease when diagnosed in infants and young children. Cardiomyopathy continues to be the leading reason for heart transplants in children. Pediatric cardiomyopathy is a rare heart condition that affects infants and children. Specifically, cardiomyopathy means disease of the heart muscle (myocardium). Several different types of cardiomyopathy exist and the specific symptoms vary from case to case. In some cases, no symptoms may be present (asymptomatic); in many cases, cardiomyopathy is a progressive condition that may result in an impaired ability of the heart to pump blood; fatigue; heart block; irregular heartbeats (tachycardia); and, potentially, heart failure and sudden cardiac death. There are numerous causes for a complex disease such as cardiomyopathy. For the majority of diagnosed children, the exact cause remains unknown (termed "idiopathic"). In some cases, it may be related to an inherited condition such as a family history of cardiomyopathy or a genetic disorder such as fatty acid oxidation, Barth syndrome, or Noonan syndrome. Cardiomyopathy can also be a consequence of another disease or toxin where other organs are affected. Possible causes include viral infections (Coxsackie B - CVB), auto-immune diseases during pregnancy, the build-up of proteins in the heart muscle (amyloidosis), and an excess of iron in the heart (hemosiderosis). Excessive use of alcohol, contact with certain toxins, complications from AIDS, and the use of some therapeutic drugs (i.e. doxorubicin) to treat cancer can also contribute to the development of the disease.

### 3. Pediatric cardiomyopathies

Pediatric cardiomyopathy is a rare heart condition that affects infants and children. There is a vast amount of literature on adult cardiomyopathy but not all of the information is relevant to children diagnosed with the disease. Unfortunately, there has been little research and focus on pediatric cardiomyopathy over the years. Consequently, the causes are not well understood. Pediatric cardiomyopathy is more likely to be due to genetic factors while lifestyle or environmental factors play a greater role in adult cardiomyopathy.

In rare cases, pediatric cardiomyopathy may be a symptom of a larger genetic disorder that may not be immediately detected. For example, when an infant or young child is diagnosed with dilated cardiomyopathy, a rare genetic heart disease called Barth Syndrome or a mitochondrial defect (i.e. Kearns-Sayre syndrome) may be the cause. Similarly, a child with severe hypertrophic cardiomyopathy may actually have Noonan Syndrome, Pompe disease (type II glycogen storage disease), a fatty acid oxidation disorder, or mitochondrial HCM. It is therefore important for any diagnosed child to be properly evaluated for other suspected genetic disorders. A thorough evaluation remains a complicated and expensive process due to the large number of rare genetic causes, the broad range of symptoms and the existence of many specialized biochemical, enzymatic and genetic tests. Verifying a diagnosis may require getting additional blood, urine or tissue tests and consulting other specialists such as a neurologist and geneticist.

Cardiomyopathy in children may also present differently from diagnosed teenagers or adult. It is considered unusual when an infant or a child is diagnosed with symptoms at such a young age. Typically, symptoms are not apparent until the late teens or adult years when most patients are diagnosed. With hypertrophic cardiomyopathy, the disease commonly develops in association with growth and is detected when a child progresses through puberty. Even in genetically affected family members, a child that carries the muted gene from birth may appear to have a normal heart and be asymptomatic until puberty.

A diagnosis at a young age usually, but not always, signifies a serious heart condition that requires aggressive treatment. The concern lies in the uncertainty of how the heart muscle will respond with each additional growth spurt. With some older children, the condition may stabilize over time with the aid of certain medications or surgery. In severe cases, small children may experience progressive symptoms quickly leading to heart failure. This presentation contrasts with most diagnosed adults who may only have minor symptoms without serious limitations or major problems for years. Aside from differences in the cause and manifestation, cardiomyopathy may also progress differently in children than adults. When children are diagnosed at an early age, the prognosis may be poor depending on the form of cardiomyopathy and the stage of the disease. For example, dilated cardiomyopathy can progress quite rapidly when diagnosed in young children. Up to 40% of diagnosed children with dilated cardiomyopathy fail medical management within the first year of diagnosis and of those that survive many have permanently impaired heart function. Children diagnosed with hypertrophic cardiomyopathy seem to fare better but the outcome is highly variable. Mortality and heart transplant rates of childhood cardiomyopathies are much higher than in adults due to the



rarity and uncertainty of the disease. Less than optimal outcomes may be attributed to the more fragile state of infants and young children or it may be a function of the disease's advanced progression associated with another genetic disorder. Another unfortunate reason is that cardiomyopathy is not usually detected until the end stage when obvious symptoms of heart failure are apparent. Cardiomyopathy can be easily missed in routine check-ups when there are no obvious symptoms (i.e. heart murmur) or when there is no reason for diagnostic testing (i.e. no family history of the disease).

### 3.1. What causes cardiomyopathy?

Although pediatric cardiomyopathy is one of the leading causes of cardiac death in children, an explanation for why it occurs remains unknown. Most cases are familial conditions that are genetically transmitted, but the disease can also be acquired during childhood. The most common cause for acquired cardiomyopathy is myocarditis, a viral infection that weakens the heart muscle. Other causes for acquired cardiomyopathy include: 1) cardiovascular conditions (i.e. Kawasaki disease, congenital heart defect, hypertension, cardiac transplantation or surgery), 2) infectious or inflammatory diseases, 3) immunologic diseases (i.e. HIV), 4) obesity or dietary deficiencies, 5) toxin reactions (i.e. drug, alcohol, radiation exposure), 6) connective tissue and autoimmune diseases, 7) endocrine diseases and 8) pregnancy related complications. Persistent rhythm problems or problems of the coronary arteries, either congenital or acquired, can also lead to a weakening of the heart.

It is being increasingly recognized that certain genetic mutations are the primary cause for pediatric cardiomyopathy. Mutations are defects in the DNA spiral, the protein structure of many genes. The abnormalities in DNA involve a displacement in the sequence of one or more of the amino acids that make up a gene protein. The disease is either inherited through one parent who is a carrier (autosomal dominant transmission with a 50% chance of recurrence) or through both parents who each contribute a defective gene (autosomal recessive transmission with a 25% chance of recurrence). Cardiomyopathy can also be inherited by maternal transmission (X-linked). Research continues to focus on identifying the specific genes that cause cardiomyopathy and better understanding how these genetic abnormalities contribute to the disease. However, it is a complex process with multiple diverse genes producing extremely variable outcomes. Many children with hypertrophic cardiomyopathy (50-60%) and to a lesser degree with dilated cardiomyopathy (20-30%) have a family history of the disease. Recent advancements in genetic research show that hypertrophic cardiomyopathy involves defects in the sarcomere genes and can be inherited in an autosomal dominant manner. Dilated cardiomyopathy involves defects in the cytoskeleton genes and can be inherited autosomal dominant, autosomal recessive or X-linked. In some cases, cardiomyopathy can be related to another inherited metabolic or congenital muscle disorder such as Noonan syndrome, Pompe disease, fatty acid oxidation defect or Barth syndrome. Most often, symptoms of these disorders present early in life. Although there is a long list of possible causes for cardiomyopathy, few of them are directly treatable and most therapy is aimed at treating the secondary effects on the heart.

According to the Pediatric Cardiomyopathy Registry, cardiomyopathies can be grouped into five categories based on the specific genetic cause of the disease:

- myocarditis and other viral infections (27%),
- familial inherited cardiomyopathies (24%),
- neuromuscular disorders associated with cardiomyopathy (22%),
- metabolic disorders (16%),
- malformation syndromes associated with cardiomyopathy (10%).

### **3.2. Myocarditis and other viral infections**

This is a leading cause in children with cardiomyopathy and is more commonly associated with DCM. It is caused by viral infections that cause the body's immune system to malfunction damaging/inflaming the heart muscle tissue while attacking the invading virus. At this point, it is unknown whether certain children have a certain genetic makeup that may make them more susceptible to contracting myocarditis.

### **3.3. Familial inherited cardiomyopathies**

Isolated familial cardiomyopathy is considered when the child does not show features of metabolic or muscular disorders, and there is a known family history of cardiomyopathy. In affected families with HCM, ARVD, DCM, and RM, the condition is predominately inherited in an autosomal dominant manner where an affected parent has a 50% chance of passing the defective gene to his/her offspring. In rare cases, ARVC, DCM and HCM can be inherited through autosomal recessive or maternal transmission where unaffected parent(s) have a 25% chance of an affected child with each pregnancy.

Although the genetic defect is the same in all members of an individual family, there are variable outcomes and severity of the disease in different family members. The disease's manifestation can range from minimal abnormality and no symptoms to severe complications within the same family. In some families it may appear that the mutated gene skips a generation but in reality the defective gene may not have expressed itself fully in a particular family member, and therefore echocardiograms may appear normal.

#### *3.3.1. Neuromuscular disorders associated with cardiomyopathy*

Neuromuscular diseases associated with cardiomyopathy include those that affect the nerve or skeletal muscles. These include muscular dystrophies (i.e. Duchenne and Becker), congenital myopathies, metabolic myopathies, and ataxias (i.e. Friedreich Ataxia). Common symptoms are decreased muscle tone, weakness beginning after infancy, loss of motor control, decreased muscle relaxation and decreased muscle bulk. Almost all of the neuromuscular diseases associated with cardiomyopathy have a genetic basis.



### 3.3.2. Metabolic disorders

Inborn errors of metabolism consist of numerous infiltrative storage diseases, abnormal energy production, biochemical deficiencies and disorders related to toxic substances accumulating in the heart. This category also includes mitochondrial abnormalities (i.e. MELAS, MERRF, respiratory chain diseases, mitochondrial myopathies), fatty acid oxidation defects (carnitine deficiency, VCHAD, LCHAD, LCAD, MCAD), Pompe disease and Barth syndrome. When the demand for energy exceeds what the body can supply (i.e. during illness, physical stress or decreased oral intake), patients with impaired energy metabolism are unable to maintain their body's biochemical stability. This may lead to low blood sugar, excessive acidity in the blood and/or high ammonia levels that put additional strain on the heart. Metabolic disorders are inherited by autosomal recessive transmission (each parent contributes a defective gene) or X-linked transmission (mother contributes defective gene). Usually patients appear to be physically normal in early childhood but as the body's energy production continues to be impaired, toxic substances may accumulate throughout the body leading to multiple organ failure. Common symptoms include muscle weakness, decreased muscle tone, growth retardation, developmental delays, failure to thrive, constant vomiting and lethargy. In critical states, the child may exhibit stroke like symptoms, seizures, have low blood sugar, and be unable to use the body's fuel correctly.

In contrast, patients with storage diseases such as Pompe, Cori, and Andersen disease cannot break down glycogen, the storage form of sugar. These syndromes are characterized by problems with growth, brain dysfunction, decreased muscle tone, muscle weakness, and symptoms of heart failure.

### 3.3.3. Malformation syndromes associated with cardiomyopathy

Malformation syndromes are characterized by minor and major physical abnormalities with distinctive facial features. It is caused by genetic mutations through autosomal dominant, autosomal recessive, or X-linked recessive inheritance. It can also be caused by a chromosomal defect where a specific chromosome is deleted or duplicated. Noonan syndrome is the most common form associated with pediatric cardiomyopathy. Common symptoms include short stature, webbed neck, wide set eyes, low set ears and extra skin folds.

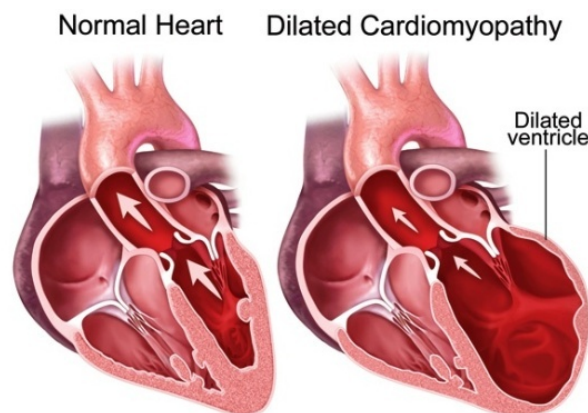
## 3.4. Forms of cardiomyopathy

There are four main types of nonischemic cardiomyopathy that are recognized by the World Health Organization: dilated (DCM), hypertrophic (HCM), restrictive (RCM) and arrhythmogenic right ventricular (ARVC). Each form is determined by the nature of muscle damage. With some patients, cardiomyopathy may be classified as more than one type or may change from one type to another over time. According to the pediatric cardiomyopathy survey, dilated cardiomyopathy is the most common (58%), followed by hypertrophic cardiomyopathy (30%) and a few cases of restrictive cardiomyopathy (5%) and arrhythmogenic right ventricular cardiomyopathy (5%). Although not formally categorized by the World Health Organization, left ventricular non-compaction cardiomyopathy (LVNC) is increasingly being recognized.

With each type of cardiomyopathy, symptoms and reactions to pharmaceutical or surgical therapies may vary widely among patients.

## 4. Dilated cardiomyopathy

Dilated or congestive cardiomyopathy (DCM) is diagnosed when the heart is enlarged (dilated) and the pumping chambers contract poorly (usually left side worse than right). A diagram and echocardiogram comparing a normal heart and a heart with DCM (fig. 15)



**Figure 15.** A normal heart is shown on the left compared to a heart with dilated cardiomyopathy on the right.

This condition is the most common form of cardiomyopathy and accounts for approximately 55–60% of all childhood cardiomyopathies. It can have both genetic and infectious/environmental causes. It is more commonly diagnosed in younger children with the average age at diagnosis being 2 years. Dilated cardiomyopathy can be familial (genetic), and it is estimated that 20–30% of children with DCM have a relative with the disease, although they may not have been diagnosed or have symptoms.

### 4.1. Signs and symptoms of DCM

Dilated cardiomyopathy can appear along a spectrum of no symptoms, subtle symptoms or, in the more severe cases, congestive heart failure (CHF), which occurs when the heart is unable to pump blood well enough to meet the body tissue needs for oxygen and nutrients. When only subtle symptoms exist, infants and young children are sometimes diagnosed with a viral upper respiratory tract infection or recurrent “pneumonia” without realizing that a heart problem is the basis for these symptoms. Older children and adolescents are less likely to be diagnosed with viral syndromes and more likely to present with decreased exercise capacity or easy fatigability. With CHF, babies and young children will usually have more noticeable clinical changes such as irritability, failure to thrive (poor gain weight), increased sweating especially with activities, pale color, faster breathing and/or wheezing. In older children, congestive heart failure can manifest as difficulty breathing and/or coughing, pale color, decreased urine output

and swelling, excessive sweating, and fatigue with minimal activities. Until the diagnosis is made in many children, chronic coughing and wheezing, particularly during activities, can be misinterpreted as asthma. Some patients with DCM caused by viral myocarditis (weakened, enlarged heart muscle usually due to a viral infection) can have a rapid increase in the number and severity of CHF symptoms such that within 24–48 hours the child can become very ill requiring emergency hospitalization, and occasionally, advanced life support. Symptoms due to heart rhythm problems (or arrhythmias, which means irregular, fast or slow heart rates) can also be either the first symptom or a symptom that appears after other symptoms have led to a diagnosis of DCM. Symptoms of rhythm problems include palpitations (feeling of funny or fast heart beats), syncope (fainting), seizures (convulsions), or even sudden cardiac arrest (heart stops beating effectively requiring resuscitation). These symptoms can occur at any age and with any stage of cardiomyopathy, even if other more severe symptoms of congestive heart failure have not yet appeared.

#### 4.2. Diagnosis of DCM

Once there is clinical suspicion based on the patient history and physical exam, the diagnosis of DCM is primarily based on echocardiography. With this test, will be using ultrasound beams to evaluate the heart looking for dilated chambers and decreased pump function. Along with the echocardiogram, there are other tests that will likely be done to confirm the diagnosis or provide clues as to the cause. A chest X-ray will show the heart size and can be used as a reference to follow increases in heart size that may occur over time. An electrocardiogram, or EKG, records the electrical conduction through the heart and is used to look for evidence of thickened or enlarged chambers as well as abnormal heart beats that can occur in children with this diagnosis. To more completely evaluate for the presence or absence of these abnormal heart rhythms, which may effect treatment, your doctor may also order a Holter monitor which records heart beats over a 24–48 hour period. A treadmill test can also be useful in some children (beyond age 5–7 years) who can cooperate with this study. This exercise test is used to assess the energy reserve child's heart and, in cases when children do not respond adequately to medicines, this test may also help predict the need for heart transplantation. Depending on child's age, a battery of blood tests may be done in order to identify treatable causes for the cardiomyopathy. This may include testing for certain viral infections such as adenovirus and the Coxsackie viruses as they have been associated with DCM especially in younger children. In many cases, no cause is discovered, and the cardiomyopathy may be referred to as "idiopathic" (cause unknown). Many heart failure specialists believe this "idiopathic" form of the cardiomyopathy is genetic. While genetic screening has not yet become a standard procedure, some physicians may send blood to molecular testing labs located in a few centers around the country so that limited genetic testing can be performed looking for possible mutations currently known to cause dilated cardiomyopathy. evaluation, usually with echo, of other family members is recommended to rule out presence of this disease in other close relatives (parents, siblings).

Finally, in more advanced cases of DCM, cardiac catheterization may be performed. During this procedure, a catheter (thin plastic tube) will be slowly advanced through an artery or vein

into the heart (while watching its course on a TV monitor) so that pressures within the heart chambers can be measured. A cardiac biopsy, which involves removing tiny pieces of heart muscle for inspection under the microscope, may be performed to help distinguish between infectious and genetic causes.

#### 4.3. Current treatment

Currently, there are no therapies that can “cure” DCM; however, many treatments are available that can improve symptoms and decrease risk in children with DCM. The choice of a specific therapy depends on the clinical condition of the child, the risk of dangerous events and the ability of the child to tolerate the therapy. In the following sections, current medical and non-medical therapies for DCM are summarized.

#### 4.4. Medical therapy

The majority of children with DCM have signs and symptoms of heart failure. The most common types of medications used to treat heart failure include diuretics, inotropic agents, afterload reducing agents and beta-blockers.

**Diuretics**, sometimes called “water pills,” reduce excess fluid in the lungs or other organs by increasing urine production. The loss of excess fluid reduces the workload of the heart, reduces swelling and helps children breathe more easily. Diuretics can be given either orally or intravenously. Common diuretics include furosemide, spironolactone, bumetanide and metolazone. Common side effects of diuretics include dehydration and abnormalities in the blood chemistries (particularly potassium loss).

**Inotropic Agents** are used to help the heart contract more effectively. Inotropic medications and are most commonly used intravenously to support children who have severe heart failure and are not stable enough to be home. Common types of inotropic medications include:

- Digoxin (taken by mouth): improves the contraction of the heart. Side effects include low heart rate, and, with high blood levels, vomiting and abnormal heart rhythm.
- Dobutamine, dopamine, epinephrine, norepinephrine (intravenous medications given in the hospital): medications that increase blood pressure and the strength of heart contractions. Side effects include increased heart rate, arrhythmias and for some, constriction of the arteries.
- Vasopressin (intravenous medication): increases blood pressure and improves blood flow to the kidneys. Side effects include excessive constriction of the arteries and low sodium.
- Milrinone (intravenous medication): improves heart contraction and decreases the work of the heart by relaxing the arteries. Side effects include low blood pressure, arrhythmias and headaches.

**Afterload Reducing Agents** reduce the work of the heart by relaxing the arteries and allowing the blood to flow more easily to the body. Common afterload reducing medications include:

- Angiotensin converting enzyme inhibitors (ACE inhibitors): captopril, enalapril, lisinopril, monopril (taken by mouth). Side effects include low blood pressure, low white blood cell count, high potassium levels and kidney or liver abnormalities.
- Angiotensin I Blocker: Losartan (taken by mouth). Side effects include diarrhea, muscle cramps and dizziness.
- Milrinone is an inotropic agent (see above) that also relaxes the arteries.

**Beta-blockers** slow the heartbeat and reduce the work needed for contraction of the heart muscle. Slowing down the heart rate can help to keep a weakened heart from overworking. In some cases, beta-blockers allow an enlarged heart to become more normal in size. Common beta-blockers (taken by mouth) include carvedilol, metoprolol, propranolol and atenolol. Side effects include dizziness, low heart rate, low blood pressure, and, in some cases, fluid retention, fatigue, impaired school performance and depression. In addition to improving the symptoms of heart failure, ACE inhibitors and beta-blockers have been shown to return the heart size toward normal and lessen the number of deaths and hospitalizations in adult patients with dilated cardiomyopathy without symptoms. An ACE inhibitor is recommended in children with dilated cardiomyopathy even in the absence of symptoms. Currently, no firm recommendations are available for beta-blockers in children.

#### 4.5. Anticoagulation medications

In children with a heart that does not contract well, there is a risk of blood clots forming inside the heart possibly leading to a stroke. Anticoagulation medications, also known as blood thinners are often used in these situations. The choice of anticoagulation drug depends on how likely it is that a blood clot will form. Less strong anticoagulation medications include aspirin and dipyridamole. Stronger anticoagulation drugs are warfarin, heparin, and enoxaparin; these drugs require careful monitoring with regular blood testing. While variable, common side effects of anti-coagulants include excessive bruising or bleeding from otherwise minor skin injuries, interaction with other medications and, for warfarin, fluctuations in anticoagulation blood levels caused by changes in daily dietary intake.

#### 4.6. Anti-arrhythmia medications

In some DCM patients, especially those with very dilated and poorly contractile ventricles, there may be a higher risk of an abnormal, life-threatening heart rhythm (ventricular tachycardia), and medications are used to prevent or control this abnormal rhythm which then keeps the heart beating in a regular pattern. Common anti-arrhythmia medications include: amiodarone, procainamide and lidocaine. General side effects may include slower heart rate, lower blood pressure, GI upset (nausea/constipation), headache, depressed mood, difficulties concentrating, dizziness, and skin rash among others. Consult your cardiologist for drug-specific side effects once a particular anti-arrhythmic medicine has been prescribed.



## 4.7. Pacing therapies for DCM

### 4.7.1. Pacemakers

Pacemakers are small, battery-operated devices that are placed under the skin of the chest or abdomen and attached to electrical wires (leads) which are threaded to the heart. Depending on which type of pacemaker is used, these leads are attached to muscle tissue either on the inside or outside of the heart. The devices monitor the heartbeat and help maintain a regular rhythm in children who are prone to have abnormal heartbeats. In some patients with DCM, the heart rate can become too slow either due to abnormally slow conduction of impulses through the heart or as a side effect of medications. In those instances, a “back-up” pacemaker can be implanted to help maintain an appropriate heart rate. Conversely, as mentioned above, patients with DCM can develop abnormally fast, life-threatening arrhythmias (ventricular tachycardia and/or fibrillation). Implantable cardioverter defibrillators (ICDs) can be used in those children to convert these arrhythmias to a normal rhythm. Finally, a bi-ventricular pacing system has recently become part of the standard therapy in adults with end-stage heart failure associated with DCM, and this treatment modality is currently being evaluated in children.

### 4.7.2. Implantable Cardioverter Defibrillator (ICD)

ICDs are designed to prevent sudden death from a serious arrhythmia known as ventricular tachycardia or fibrillation. An ICD constantly monitors heart rate, and when ventricular tachycardia or fibrillation is detected, the ICD delivers a shock to the heart that restores normal rhythm. ICDs are used in patients with hypertrophic cardiomyopathy who are felt to be at high risk for a sudden death and in children with dilated cardiomyopathy who have serious ventricular arrhythmias.

### 4.7.3. Biventricular pacemaker

In recent promising studies in adult patients with dilated cardiomyopathy, a special pacemaker that can pace both the right and left ventricles has been designed. This system, which has to be specially timed, allows the two ventricles to contract together and improves the synchrony of contraction between the walls of the left ventricle. Study results have shown that, when added to other medical treatments, this mode of pacing has helped some patients live longer with fewer hospitalizations and, in some cases, has decreased the need for transplantation. At the time of this publication, use of bi-ventricular pacing in children is in the early stages of development. It is not yet known which children may benefit most from this form of pacing or the best way to implant the system.

## 4.8. Surgical options for DCM

No surgery has been effective in improving the heart function in dilated cardiomyopathy. In a few patients with a severely dilated left ventricle and a very leaky (regurgitant) mitral valve, surgery to repair or replace the mitral valve may help the heart function improve temporarily.

Heart transplantation is the only effective surgery offered for patients with DCM who have severe heart failure that does not respond to medications or other treatments.

#### 4.9. Cardiac assist devices (Mechanical hearts)

Cardiac assist devices are machines that do the work of the heart using a mechanical pump to deliver blood to the body. Cardiac assist devices are implanted when all other therapies have failed and the heart failure is severe. They improve blood flow to the body and allow other organs to recover from the stress of heart failure. These devices are typically used as bridges to transplantation. That is, they are used to support a child either until the heart function has recovered enough to effectively circulate blood through the body or until a suitable donor organ can be found. In pediatric patients, they are designed as a temporary means of support and cannot be used as a permanent alternative to the child's own heart or a transplanted heart. Potential complications of cardiac assist devices include infection, blood clots, stroke and mechanical problems with the devices themselves. There are a variety of cardiac assist devices available. The type of cardiac assist device that is used for an individual child depends on body size and also the type of assist support needed.

#### 4.10. Heart transplantation

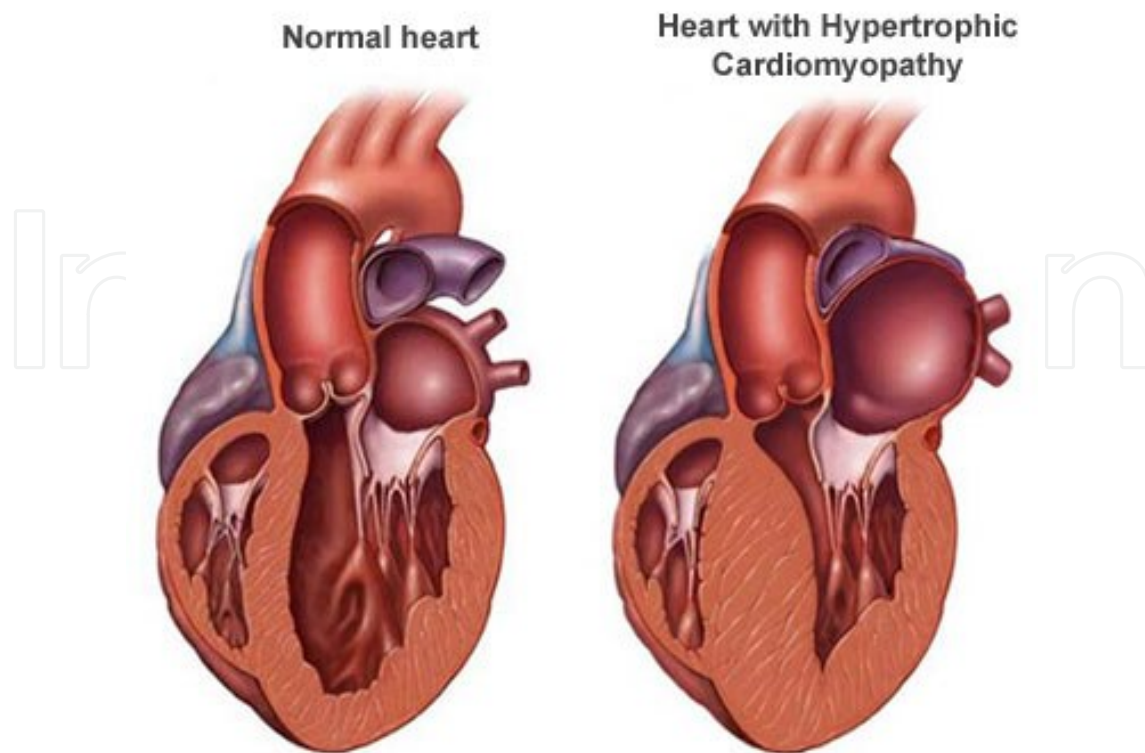
Dilated cardiomyopathy is one of the leading reasons for heart transplantation in children. Heart transplant is only considered in children who have such serious heart disease that there are no other medications or support devices available to sustain the child. A heart transplant offers the child with DCM the chance to return to a normal lifestyle.

While a donor heart can cure the symptoms of heart failure and greatly improve survival, it is a major operation with considerable risks and long-term complications. Once a transplant is done, other concerns arise, such as infection, organ rejection, coronary artery disease, and the side effects of medications.

### 5. Hypertrophic cardiomyopathy

Most often diagnosed during infancy or adolescence, hypertrophic cardiomyopathy (HCM) is the second most common form of heart muscle disease, is usually genetically transmitted, and comprises about 35–40% of cardiomyopathies in children. A diagram and echocardiogram comparing a normal heart and a heart with HCM (fig.16).

“Hypertrophic” refers to an abnormal growth of muscle fibers in the heart. In HCM, the thick heart muscle is stiff, making it difficult for the heart to relax and for blood to fill the heart chambers. While the heart squeezes normally, the limited filling prevents the heart from pumping enough blood, especially during exercise. Although HCM can involve both lower chambers, it usually affects the main pumping chamber (left ventricle) with thickening of the septum (wall separating the pumping chambers), posterior wall or both. With hypertrophic obstructive cardiomyopathy (HOCM), the muscle thickening restricts the flow of blood out of



**Figure 16.** A normal heart is shown on the left compared to a heart with a hypertrophic cardiomyopathy on the right.

the heart. Often, leakage of the mitral valve causes the blood in the lower chamber (left ventricle) to leak back into the upper chamber (left atrium). In less than 10% of patients, the disease may progress to a point where the heart muscle thins and the left ventricle dilates resulting in reduced heart function similar to that seen in DCM. HCM is most often diagnosed during infancy or adolescence. Gene defects can be familial, and it is estimated that 50–60% of children with HCM have a relative with the disease, although they may not have been diagnosed or have symptoms.

### 5.1. Signs and symptoms of HCM

There is tremendous variation in how HCM presents and progresses. While some children have no or mild symptoms, others may have more severe symptoms including heart failure. Some patients develop abnormal heart rhythms (arrhythmias) that may put them at increased risk for sudden cardiac death. Children under 1 year of age often have symptoms of congestive heart failure whereas older children may be symptom free and, therefore, may be unaware that HCM is present. Onset of symptoms often coincides with the rapid growth and development of late childhood and early adolescence. The strenuous exercise of competitive sports has also been known to make symptoms of HCM more apparent. Disease severity and symptoms are related to the extent and location of the hypertrophy and whether there is obstruction to blood leaving the heart or valve leakage from the left-sided pumping chamber



back into the left atrium above. The first sign of HCM may be a murmur, although this is usually absent in the non-obstructive form of HCM. Symptoms in children with HCM can include dyspnea (shortness of breath during exercise), angina (chest pain), presyncope (lightheadedness or dizziness), syncope (fainting), exercise intolerance or palpitations/arrhythmias (irregular heartbeats). Symptoms in infants may be more difficult to detect but include difficulty breathing, poor growth, excessive sweating (diaphoresis) or crying and agitation during feeding thought to be due to chest pain. Children with severe HCM may have symptoms of heart failure such as difficulty breathing, swelling around the eyes and legs (edema), tiredness or weakness, coughing, abdominal pain and vomiting. Mild symptoms of heart failure can also resemble asthma. Children with HCM may also develop an abnormal heartbeat (arrhythmia), either beating too fast (tachycardia) or too slow (bradycardia). Symptoms resulting from rhythm problems can appear without a child having congestive heart failure or other more obvious symptoms of HCM. The risk of sudden death from arrhythmia is higher with this form of cardiomyopathy compared with other forms of pediatric myopathy especially among adolescent patients. Finally, in some cases of HCM (especially those with extreme wall thickness), the disease evolves towards progressive wall thinning and LV chamber dilation until the heart appears to have all the features of DCM. In these cases, a family history of HCM, a prior echocardiogram that showed HCM or a cardiac biopsy may help differentiate between the two.

## 5.2. Diagnosis of HCM

Once suspected, the diagnosis of hypertrophic cardiomyopathy is established with an echocardiogram (or ultrasound of the heart) looking for abnormally thick walls predominantly in the left pumping chamber (left ventricle). In addition, the extent of obstruction or muscular narrowing through the outlet of the left ventricle to the aorta (main vessel which carries blood to the body) will be assessed. This diagnosis can only be made after other potential causes of abnormal wall thickening (i.e., aortic valve stenosis, coarctation of the aorta, high blood pressure, etc.) are eliminated either by physical exam or echocardiogram. An electrocardiogram, or EKG, which records the electrical impulses sent through the heart, may show evidence of thickened pumping chambers. Many cardiologists will order a Holter monitor to record your child's heartbeats over a 24–48 hour period. This will allow your physician to check for abnormal, and sometimes life-threatening, heart rhythms, which can occur more often in children with HCM. To further estimate child's risk for developing these abnormal heart rhythms, some cardiologists may ask, in children old enough to cooperate, to perform an exercise treadmill test. Since the cause of this form of cardiomyopathy varies and depends on child's age, additional laboratory testing may be requested. In some cases, an accumulation of abnormal proteins or sugars (glycogen) may occur in the heart causing the increased wall thicknesses. In others, genetic mutations or abnormalities in the mitochondria (powerhouses of the cells) produce this effect. Genetic testing is available for some but not all forms of HCM. In the next decade, as more genetic bases for HCM are identified, genetic testing may become a routine part of the HCM evaluation.

### 5.3. Current treatment for HCM

Currently, there are no therapies that can “cure” HCM; however, many treatments are available that can improve symptoms and potentially decrease risk in children with HCM. The choice of a specific therapy depends on the clinical condition of the child, the risk of dangerous events and the ability of the child to tolerate the therapy. In the following sections, treatments for HCM are summarized.

### 5.4. Medical therapies

Medications are used to treat children with HCM who have symptoms such as difficulty breathing, chest pain, decreased activity tolerance or fatigue and generally include beta-blocking and calcium channel-blocking medicines. Beta-blocking medications are used to slow the heartbeat and allow the heart to fill more completely when the thick muscle in the ventricular septum narrows the outflow of blood from the heart. These medications can cause excessive slowing of the heart rate, low blood pressure, dizziness, and in some cases, fluid retention, fatigue, impaired school performance and depression. Calcium channel blockers improve the filling of the heart by reducing the stiffness of the heart muscle, and are used in patients with chest pain or breathlessness. Side effects can include excessive slowing of the heart rate and lower blood pressure. Common calcium channel blockers are verapamil and diltiazem. Diuretics, which must be used with caution in this disease, are used to decrease fluid accumulation (when present) from the lungs in children with severe hypertrophic cardiomyopathy. In the case of HCM which has progressed into a myopathy with DCM features (occurs relatively infrequently as a later stage of HCM - see previous discussion of HCM), therapies used to treat HCM will no longer be effective, and standard medicines for the treatment of DCM will be substituted.

### 5.5. Pacing therapies for HCM

#### 5.5.1. Implantable Cardioverter Defibrillator (ICD)

ICDs are designed to prevent sudden death from a serious arrhythmia known as ventricular tachycardia or fibrillation. An ICD constantly monitors heart rate, and when ventricular tachycardia or fibrillation is detected, the ICD delivers a shock to the heart that restores normal rhythm. ICDs are used in patients with hypertrophic cardiomyopathy who are felt to be at high risk for a sudden death or have documented serious ventricular arrhythmias.

### 5.6. Surgery for HCM

Septal myomectomy is a surgery that is performed in patients with hypertrophic cardiomyopathy when symptoms of heart failure have developed because the thickened muscle of the septum (the wall dividing the two sides of the heart) has narrowed (obstructed) the blood flow out of the heart, and medical therapy has not been effective. The surgery involves removing the muscle that has obstructed the blood flow. While septal myomectomy is effective in

controlling symptoms, it does not stop hypertrophy from progressing, nor does it treat the life-threatening abnormal rhythms associated with HCM.

### 5.7. Heart transplantation

Currently, transplantation for HCM is not routinely performed. Two exceptions include medically refractory ventricular arrhythmias, and HCM which has developed features of DCM not responsive to standard DCM therapy. A heart transplant will offer that child the chance to return to a normal lifestyle. While a donor heart can cure the symptoms of heart failure and greatly improve survival, it is a major operation with considerable risks and long-term complications. Once a transplant is done, other concerns arise, such as infection, organ rejection, coronary artery disease, and the side effects of medications.

## 6. Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a rare form of heart muscle disease that is characterized by restrictive filling of the ventricles. In this disease the contractile function (squeeze) of the heart and wall thicknesses are usually normal, but the relaxation or filling phase of the heart is very abnormal. This occurs because the heart muscle is stiff and poorly compliant and does not allow the ventricular chambers to fill with blood normally. This inability to relax and fill with blood results in a “back up” of blood into the atria (top chambers of the heart), lungs and body causing the symptoms and signs of heart failure(fig.17).



**Figure 17.** Restrictive Cardiomyopathy (RCM)

Within the broad category of cardiomyopathy, RCM is the least common in children, accounting for 2.5–5% of the diagnosed cardiomyopathies. The average age at diagnosis is 5 to 6 years. RCM appears to affect girls somewhat more often than boys. There is a family history of cardiomyopathy in approximately 30% of cases. In most cases the cause of the disease is unknown (idiopathic), although a genetic cause is suspected in most cases of pediatric RCM.

### 6.1. Signs and symptoms of RCM

In children the first symptoms of RCM often seem related to problems other than the heart. The most common symptoms at first may appear to be lung related. Children with RCM frequently have a history of “repeated lung infections” or “asthma.” In these cases, referral to a cardiologist eventually occurs when a large heart is seen on chest x-ray. The second most common reason for referral is an abnormal physical finding during a doctor’s examination. Children who have ascites (fluid in the abdomen), hepatomegaly (enlarged liver) and edema (fluid causing puffy looking feet, legs, hands or face) are often sent to see a gastroenterologist first. Referral to a cardiologist is made when additional cardiac signs or symptoms occur, a chest x-ray is found to be abnormal or no specific gastrointestinal cause is found for the edema or enlarged liver. When the first sign of the disease is an abnormal heart sound, or signs of heart failure are recognized, then earlier referral to a cardiologist occurs. In approximately 10% of cases, fainting is the first symptom causing concern. Unfortunately, sudden death has been the initial presentation in some patients.

### 6.2. Diagnosis of RCM

Restrictive cardiomyopathy is among the rarest of childhood cardiomyopathies. Its diagnosis is difficult to establish early in the clinical course due to the lack of symptoms. Therefore, in many cases, this diagnosis is made only after presentation with symptoms such as decreased exercise tolerance, new heart sound (gallop), syncope (passing out) or chest pain with exercise. Once suspected, there are certain tests that can help confirm this diagnosis. An electrocardiogram, or EKG, which records the electrical conduction through the heart, can be very helpful. This can show abnormally large electrical forces from enlargement of the atria (upper chambers) of the heart. An echocardiogram, or ultrasound of the heart, can provide additional clues to help make this diagnosis. Generally, in children with RCM, the echocardiogram shows marked enlargement of the atria (upper chambers), normal sized ventricles (lower chambers) and normal heart function. In more advanced disease states, pulmonary artery pressure (blood pressure in the lungs) will be increased and can often be estimated during the echocardiogram. Cardiac catheterization is usually the next procedure done to confirm the diagnosis. During this procedure, a catheter (thin plastic tube) will be slowly advanced through an artery or vein into the heart (while watching its course on a TV monitor) so that pressures within the heart chambers can be measured. These measurements often show significantly elevated pressures during the relaxation period of the heart (when it fills with blood before the next beat) and varying degrees of increased pulmonary artery pressure (which can confirm the echo estimates) in the absence of any other structural heart disease. In very rare cases, based on clinical symptoms and prior laboratory evaluation, a cardiac biopsy may



be performed. This involves removing tiny pieces of heart muscle for inspection under the microscope to search for potential causes of this condition (such as amyloidosis or sarcoidosis, which are common causes of RCM in adults but rarely in pediatric patients). Finally, since childhood RCM is often genetic and in many cases will be inherited, once this diagnosis is established, your doctor will likely request that parents, siblings of the patient and sometimes other close relatives be screened with an echocardiogram to rule out the presence of this disease in other family members.

### **6.3. Current treatment**

Currently, there are no therapies that can “cure” RCM; however, some treatments are available that can improve symptoms in children with RCM. The choice of a specific therapy depends on the clinical condition of the child, the risk of dangerous events and the ability of the child to tolerate the therapy.

### **6.4. Medical therapies to treat RCM and associated heart failure**

Some children with RCM have signs and symptoms of heart failure due to the abnormal relaxation properties of the heart muscle. The most common types of medications used to treat heart failure under these circumstances include diuretics, beta-blockers and occasionally afterload reducing agents.

Diuretics, sometimes called “water pills,” reduce excess fluid in the lungs or other organs by increasing urine production. Diuretics can be given either orally or intravenously. Common diuretics include furosemide, spironolactone, bumetanide and metolazone. Common side effects of diuretics include dehydration and abnormalities in the blood chemistries (particularly potassium loss). In patients with RCM, diuretics must be used very carefully and given only in doses to treat extra lung and abdominal fluid without inducing excessive fluid loss as this may cause symptomatically low blood pressure.

Beta-blockers slow the heartbeat and increase the relaxation time of the heart. This may allow the heart to fill better with blood before each heart beat and decrease some of the symptoms created by the stiff pumping chambers. Common beta-blockers (taken by mouth) include carvedilol, metoprolol, propranolol and atenolol. Side effects include dizziness, low heart rate, low blood pressure, and, in some cases, fluid retention, fatigue, impaired school performance and depression.

### **6.5. Anticoagulation medications**

In children with a heart that does not relax well, there is a risk of blood clots forming inside the heart possibly leading to a stroke. Anticoagulation medications, also known as blood thinners, are often used in these situations. The choice of anticoagulation drug depends on how likely it is that a blood clot will form. Less strong anticoagulation medications include aspirin and dipyridamole. Stronger anticoagulation drugs are warfarin, heparin, and enoxaparin; these drugs require careful monitoring with regular blood testing. While variable, common side effects of anticoagulants include excessive bruising

or bleeding from otherwise minor skin injuries, interaction with other medications and, for warfarin, fluctuations in anticoagulation blood levels caused by changes in daily dietary intake. Information regarding which food groups can significantly affect warfarin levels can be obtained from your cardiologist.

### **6.6. Surgery for restrictive cardiomyopathy**

No surgery has been effective in improving the heart function in restrictive cardiomyopathy. Heart transplantation is the only effective surgery offered for patients with RCM, particularly those who already have symptoms at the time of diagnosis or in whom reactive pulmonary hypertension exists.

### **6.7. Heart transplantation**

Since there are no proven effective therapies for children with RCM, transplantation is the only known intervention for this disease. This is especially true in cases where evaluation has demonstrated the presence of pulmonary hypertension, which can be fatal if not treated. For children with RCM, heart transplantation can address both the abnormal heart function as well as associated pulmonary hypertension. A heart transplant offers the child with RCM the chance to return to a normal lifestyle. While a donor heart can cure the symptoms of heart failure and greatly improve survival, it is a major operation with considerable risks and long-term complications. Once a transplant is done, other concerns arise, such as infection, organ rejection, coronary artery disease, and the side effects of medications.

## **7. Miscellaneous (Rare) cardiomyopathies**

There are other forms of cardiomyopathy which comprise only a very small percentage of the total (~2–3%) number of cardiomyopathies in children. These cardiomyopathies may have overlapping features with any of the previous types described and include arrhythmogenic right ventricular dysplasia (ARVD), mitochondrial and left ventricular non-compaction cardiomyopathies (LVNC). Patients with ARVD have dilated, poorly functioning right ventricles which have fatty deposits within the walls and are at risk for abnormally fast, life-threatening heart rhythms (ventricular tachycardia). This myopathy can be diagnosed (usually due to the abnormal rhythms) either in early infancy or later in adolescence/adulthood by echocardiogram or MRI, and its prognosis depends, in part, on the age at presentation. Mitochondrial myopathies are rare and often present early in life. Hearts in the affected patients are often thick-walled (hypertrophic), although dilated hearts with poor function can also occur with this type of myopathy. This cardiomyopathy is caused by abnormalities in the mitochondria of the cells, which are small structures within each cell responsible for generating the energy the cell uses for its normal activities. These cardiomyopathies are often associated with other muscle, liver, neurologic and/or developmental abnormalities and are usually genetically passed from an affected mother to her children. Finally, left ventricular non-compaction (LVNC) cardiomyopathy is characterized by deep trabeculations (or crevices)

within muscle of the left ventricular walls. These hearts may have features of both dilated and/or hypertrophic cardiomyopathy. Conditions associated with LVNC include mitochondrial and metabolic disorders as well as systemic (whole body) processes such as Barth syndrome. Barth syndrome has a constellation of abnormalities including cyclic neutropenia or periodic fluctuations in the white blood cell count (which may not be apparent in early infancy), hypotonia (weak muscles) and LVNC cardiomyopathy. Barth syndrome has recently been linked to an abnormality in the X-chromosome and is passed from mother to son.

### **7.1. Symptoms of ARVD, mitochondrial and LVNC cardiomyopathies**

Symptoms (the problems noted by the child and/or family) and signs (the problems detected by your physician) of cardiomyopathy in children are dependent on several factors including the type, cause and severity of the specific cardiomyopathy, the age when the problems started, and the effects of treatment. Since patients with ARVD generally have symptoms consistent with DCM, and patients with mitochondrial or LVNC cardiomyopathies can have symptoms seen with either HCM or DCM, families are encouraged to review the relevant sections written for dilated and hypertrophic cardiomyopathies within this brochure to become familiar with the pertinent symptoms for each of these cardiomyopathy types.

### **7.2. Diagnosis of ARVD, mitochondrial and LVNC cardiomyopathies**

As with presenting symptoms, the clinical diagnosis of these rare forms of cardiomyopathy will depend on the features of the specific cardiomyopathy. That is, the diagnostic criteria in a child with ARVD will generally follow that of DCM while the mitochondrial and LVNC myopathies will follow that of either DCM or HCM depending on the clinical manifestations of the myopathy. In addition to what is discussed in the diagnostic sections written for the dilated and hypertrophic forms of cardiomyopathy found elsewhere in this brochure, the following comments highlight a few details specific for the diagnosis of each of these rare cardiomyopathies.

The diagnosis of ARVD can be difficult especially in children given its low incidence. However, opposed to the usual form of DCM, which involves the left ventricle to a greater extent, ARVD typically involves the right ventricle preferentially and often times, the clinical suspicion for ARVD can be further explored with MRI (Magnetic Resonance Imaging) which, in many cases, can differentiate fatty deposits from muscle tissue within the wall of the right ventricle that are commonly seen with this disease. The diagnosis can usually be confirmed with visualization of significant fatty deposition within the right ventricular walls (where muscle should be) from biopsy specimens obtained during cardiac catheterization.

Patients with mitochondrial cardiomyopathy often have other associated medical problems such as hearing or vision problems, skeletal muscle weakness in the arm and leg muscles and/or central nervous system issues including learning problems, developmental delay or loss of developmental milestones. Once suspected, in addition to the cardiac assessment (for DCM or HCM) outlined elsewhere in this brochure, a muscle biopsy performed to evaluate both structure and function of the mitochondria can help verify this diagnosis. A cardiac biopsy is

generally not useful because the volume of muscle tissue necessary to perform the mitochondrial analyses can only be safely obtained from arm or leg muscles.

The diagnosis of LVNC can often be strongly suspected when deep crevices or trabeculations are noted with the walls of the left ventricle during an echocardiogram. Very few other cardiac diagnoses have these specific findings. Genetic testing may become more available in the near future to assess identified causes of LVNC especially among male children and those suspected of having Barth syndrome (see following discussion on the G4.5 mutation testing).

### **7.3. Current treatment**

Currently, there are no therapies that can “cure” cardiomyopathy; however, many treatments are available that can improve symptoms and decrease risk in children with cardiomyopathy. The choice of a specific therapy depends on the type of cardiomyopathy, the clinical condition of the child, the risk of dangerous events and the ability of the child to tolerate the therapy.

## **8. Living with cardiomyopathy**

The diagnosis of cardiomyopathy affects many areas of a child’s life. The following sections outline the general approaches to living with cardiomyopathy. It is important that specific recommendations are developed by the team caring for the child with cardiomyopathy

## **9. Diet**

All children with cardiomyopathy should follow a healthy diet. Certain types of cardiomyopathy are associated with an inability to digest certain types of food, and in these cases, a special diet is developed in consultation with metabolic specialists. In children with the dilated subtype of cardiomyopathy and heart failure, a low salt diet is recommended to avoid fluid retention. Some children with heart failure may not grow well. In these cases, a diet that increases calories is recommended. Children who are taking some medications may have low levels of magnesium or potassium and a diet that has a higher amount of one or both of these two electrolytes may be recommended. Some children with severe heart failure can retain extra body fluid, and it may be necessary to limit the amount that a child can drink to prevent fluid from accumulating in the lungs.

## **10. Long term prognosis**

The long-term outlook of pediatric cardiomyopathy continues to be unpredictable because it occurs with such a wide spectrum of severity and outcome. Even if a child has a family history of the disease, the degree to which he or she is affected can vary considerably from his/her



parents or siblings. The overall prognosis for a child also depends on the type of cardiomyopathy and the stage the disease is first diagnosed. Although there is no cure for the disease, symptoms and complications can be managed and controlled with regular monitoring. Some children will stabilize with treatment and lead a relatively normal life with few physical activity restrictions. Other children with a more serious form of cardiomyopathy may face more limitations, need specialized care and encounter minor developmental delays. Occasionally children with certain types of cardiomyopathy do improve, but the majority do not show any recovery in heart function. For the most severe cases, a heart transplant may be necessary. Children diagnosed with DCM or RCM are more likely to require a transplant; it is less common with HCM. Post transplant survival continues to improve with two year survival rates at 80 percent and ten-year survival rates near 60 percent. Longer-term survival remains to be determined but is expected to improve with more medical progress and research.

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