Heart Failure in Children
Part I: History, Etiology, and Pathophysiology
Daphne T. Hsu, MD; Gail D. Pearson, MD, ScD

Why is heart failure in children important? If we just consider the number of individuals affected, adult heart failure is clearly a more compelling public health problem. However, the relatively small numbers belie the overall economic and social impact of pediatric heart failure. When a child is admitted to the hospital for heart failure, the costs are considerably higher for children than adults because of the frequent need for surgical or catheter-based intervention. The demands of medical care can fray the family structure and adversely affect parental economic productivity. When a child dies of heart failure, the economic impact is magnified enormously because of the number of potentially productive years lost per death. For these and other reasons, heart failure in children is a serious public health concern.

In addition, growing numbers of children with heart failure are reaching adulthood because of the successful application of medical and surgical heart failure therapies and the improved outcomes of congenital heart surgery. A greater understanding of the pathophysiology of heart failure in childhood may help inform therapeutic strategies once these children become adults. Furthermore, given the recent explosion of research in the impact of cardiac development and childhood may help inform therapeutic strategies once these children become adults. Furthermore, given the recent explosion of research in the impact of cardiac development and structural diseases branch (G.D.P.), national heart, lung, and blood institute, national institutes of health, Bethesda, Md.

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vulnerable children are concerned. In children with heart failure, there are can be significant barriers to the implementation of clinical trials methodology, as illustrated by the fact that the first “large” multicenter randomized trial of a therapeutic agent in children with heart failure was not published until 2007. Shaddy et al\textsuperscript{13} enrolled 161 children and adolescents in this landmark trial comparing 2 dosages of carvedilol to placebo. However, the fact that enrolling 161 children required 26 centers and nearly 5 years illustrates the difficulties with pediatric heart failure research.

Definition and Classification of Heart Failure in Children

Definition

Heart failure was classically viewed as synonymous with left ventricular pump dysfunction, usually progressive, culminating in a common end-stage cardiac phenotype of dilation, thinned walls, and poor contractility.\textsuperscript{14} In recent years, this thinking has been refined and expanded to include further understanding not only of cardiac mechanics, but also of the complex pathways that modulate normal and abnormal cardiac performance.\textsuperscript{15–17} And if the rapidly expanding systems biology of heart failure is not confusing enough, pediatric heart failure encompasses clinical presentations as disparate as an infant presenting with acute decompensated heart failure secondary to idiopathic dilated cardiomyopathy and a teenager presenting with dyspnea in the setting of palliated complex heart disease. These complexities make a “grand unifying theory” of heart failure difficult to achieve in children.

Several groups have tackled the definition problem in the context of adult and pediatric practice guidelines.\textsuperscript{11,18} There is general agreement that heart failure is a progressive clinical syndrome with numerous etiologies and characteristic signs and symptoms, although the causes and clinical presentations may differ considerably among children of different age groups, and between children and adults. There is also agreement that the clinical syndrome is a manifestation of the pathophysiological syndrome of heart failure, which includes complex interplay among circulatory, neurohormonal, and molecular abnormalities. The importance of genetic characteristics in regulation of the cardiovascular system and predisposition to heart failure have been highlighted recently,\textsuperscript{19–21} but these factors have not yet been incorporated into formal definitions.

Extrapolating from these general points, a good working definition of heart failure in children is a progressive clinical and pathophysiological syndrome caused by cardiovascular and noncardiovascular abnormalities that results in characteristic signs and symptoms including edema, respiratory distress, growth failure, and exercise intolerance, and accompanied by circulatory, neurohormonal, and molecular derangements.

Classification

Part of defining heart failure is defining a spectrum of severity. The well-established New York Heart Association (NYHA) Heart Failure Classification\textsuperscript{22} is not applicable to most of the pediatric population. The Ross Heart Failure Classification\textsuperscript{23} was developed to provide a global assessment of heart failure severity in infants, and has subsequently been modified to apply to all pediatric ages. The modified Ross Classification incorporates feeding difficulties, growth problems, and symptoms of exercise intolerance into a numeric score comparable with the NYHA classification for adults (Table 1). More recently, Connolly et al\textsuperscript{24} developed the New York University Pediatric Heart Failure Index for children and adolescents, which yields a weighted score based on physiological indicators and medical therapy. Scores range from 0 (no heart failure) to 30 (severe heart failure). When these classifications were compared in a population of children undergoing surgery for rheumatic valve disease, the Pediatric Heart Failure Index correlated with electrocardiographic, echocardiographic, and biochemical markers better than the Ross and NYHA scoring systems.\textsuperscript{25} None of these measures has been validated as surrogate clinical end points in large numbers of children or patients with congenital heart disease, but neurohormonal activation and deteriorating clinical status have been shown to correlate with increasing class.\textsuperscript{26–28}

Causes and Occurrence of Heart Failure in Children

The causes of heart failure in children differ substantially from those found in the adult population, and comprise

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cardiac and noncardiac causes. The main cardiac causes of heart failure in children are listed in Table 2. Today, with the near-disappearance of rheumatic fever, the most common cause of pediatric heart failure in the United States is structural congenital heart disease. Cardiomyopathies are the most common cause of heart failure in children with a structurally normal heart.

Heart failure signs and symptoms can be the initial presentation of congenital heart disease, such as with left ventricular outflow tract obstructive lesions (e.g., critical AS in newborns) or systemic right ventricular systolic dysfunction (e.g., congenitally corrected L-transposition in older children). The heart failure syndrome may occur transiently in the postoperative period following cardiopulmonary bypass during corrective congenital heart surgery, or may develop and become chronic late after surgical repair or palliation. Examples of late sequelae include right heart failure due to residual right ventricular outflow tract obstruction or volume overload from pulmonary insufficiency following repair of tetralogy of Fallot (TOF), and systemic ventricular dysfunction or elevated venous pressures in single ventricle physiology, leading to low cardiac output.

In the absence of a national database for pediatric heart disease, there are no comprehensive data on the incidence of the pediatric heart failure syndrome in the United States. However, several European and 2 US studies provide some general information. The largest study, using 2 large databases encompassing ≈50% of US pediatric (age <19 years) hospital discharges, identified 5610 children in a single year, using a comprehensive set of ICD-9 heart failure codes. Congenital heart disease or cardiac surgery accounted for 61% of cases, and for 82% of cases of heart failure in infants. In contrast, in adults, fewer than 1% of heart failure discharges were due to congenital heart disease.

Two studies of heart failure in children, each covering 10 years, have been reported recently from European tertiary care facilities. Children with heart failure represented 10% to 33% of all cardiac admissions. Slightly more than half of the pediatric heart failure cases reported in both studies were due to congenital heart disease, although the incidence of heart failure in children with congenital heart disease was only 6% to 24%. This reflects the fact that congenital heart disease is considerably more common than other causes of heart failure. In contrast, 65% to 80% of children with cardiomyopathies had heart failure, but this represents only 5% to 19% of total pediatric heart failure cases. The majority of heart failure cases (58% to 70%) occurred in the first year of life, with congenital heart disease disproportionately represented compared to older ages.

Primary cardiomyopathies are the principal cause of heart failure signs and symptoms in children with a structurally normal heart. Three studies provide population-based data on heart failure in children with primary myopathies. The most recent one collected data from all pediatric cardiac centers in the United Kingdom and Ireland during 2003 on children less than 16 years old. The incidence of new onset heart failure was 0.87 per 100,000 population less than 16 years of age, with the highest incidence occurring in the first year of life. More than half of the cases were due to dilated cardiomyopathy. The NHLBI-funded Pediatric Cardiomyopathy Registry, in a prospective, population-based data set from 1996 to 1999 in 2 geographic regions of the United States, reported that 58% of all children with cardiomyopathy were given therapy for heart failure, with 83% of those with dilated cardiomyopathy receiving such therapy. A population-based Australian study published simultaneously found a similarly high incidence of heart failure in children with dilated cardiomyopathy, reporting heart failure as the presenting symptom in 90%. The incidence of heart failure differs dramatically among the morphological types of cardiomyopathy, with data from the Pediatric Cardiomyopathy Registry and the Australian cohort demonstrating a much lower incidence of heart failure in children with hypertrophic cardiomyopathy (7.5% to 20%).

Extrapolating from these studies, with full recognition of their limitations for this purpose, we estimate that heart failure caused by congenital heart disease and cardiomyopathy affects ≈12 000 to 35 000 children below age 19 in the United States each year.
Pathophysiology

Developmental Considerations
The heart is the first organ to develop and become functional in the embryo. Bilateral collections of cardiogenic cells coalesce in the midline to form the heart tube, which is then covered with myocardium and begins to beat at ≈3 weeks of gestation in the human. The heart then undergoes a complex process of looping, septation, and valve formation, accompanied by coronary artery and conduction system development, resulting in a fully-formed heart at ≈10 weeks of gestation.

Although the heart may now resemble an adult heart, the physiology is considerably different. The ventricles pump in parallel rather than in series, with the left ventricle (LV) pumping to the head and upper body, and the right ventricle (RV) pumping to the ductus arteriosus, lower body, and placenta. One implication of the parallel circulation is that in cases of obstruction to or impairment of one ventricle, the other ventricle can compensate.

The fetal myocardium continues to develop during fetal life and for a short time after birth. Myocyte numbers increase through cell division until ≈6 months postnatally. The fetal myocyte is smaller than its adult counterpart, with fewer myofibrils and mitochondria. There is less intracellular calcium, and greater dependence on trans-sarcolemmal calcium flux. In addition, specific fetal and neonatal forms of structural proteins such as titin and troponin I have been identified. The net result of these factors is myocardial stiffness, which limits preload reserve, and less contractile reserve than in the adult heart. Thus, the principal means of increasing fetal and neonatal cardiac output is through increased heart rate.

Data from several animal models demonstrate that myocardial contractility matures during the postnatal period, mediated by changes in signal transduction and calcium homeostasis. In the fetal and newborn heart, for example, stimulation of the β-adrenergic receptor-adenylyl cyclase-cAMP pathway has less effect on contractility than in adult myocardium. Similarly, the contractile response to phosphodiesterase inhibition is generally less robust than in the adult heart. However, there is some evidence that contractility can be increased in newborn myocardium. Forskolin, which directly stimulates cAMP generation, increased contractility in newborn rabbit myocardium significantly, and to a greater degree than in juvenile or adult myocardium. In another set of experiments, isoproterenol, a β-adrenergic agonist, increased contractility in newborn rabbit myocardium, but the effect was much less than in adult myocardium. However, when a nonselective phosphodiesterase inhibitor was combined with isoproterenol, newborn myocardial contractility was significantly enhanced, with no additive effect seen on adult myocardium. The difference between the effect of selective and nonselective phosphodiesterase inhibitors on newborn myocardium has been attributed in part to developmental changes in phosphodiesterase enzymes. These findings, if present in human myocardium, have clear implications for therapeutic approaches to pediatric heart failure.

As a result of the compensatory features of the parallel circulation, most congenital cardiac malformations are well-tolerated in utero. However, because of fetal myocardial physiology, heart failure in the fetus can occur in the presence of elevated venous pressure caused by tachyarrhythmias, cardiomyopathy, significant atrioventricular valve regurgitation, obstructed foramen ovale, restrictive patent ductus arteriosus, or high-output states such as twin–twin transfusion syndrome.

Congenital Heart Disease
The pathophysiology or heart failure caused by structural malformations has much in common with adult heart failure, but there are also significant differences related to etiology and age at presentation.

Volume Overload
Significant left-to-right shunting can cause congestive heart failure symptoms despite normal systolic ventricular function. The most common example is a large ventricular septal defect. After birth, as fetal myocytes attain adult form, muscle fiber length increases and ventricular compliance improves. This means that the LV can contract more forcefully to maintain systemic cardiac output compensating for the increased shunting of blood from the left to the RV during systole that occurs as pulmonary vascular resistance falls in the first 3 months of life.

The appearance of heart failure symptoms coincides with this transition from the fetal to the neonatal circulation. The increased pulmonary blood flow, coupled with the greater permeability of the neonatal pulmonary vasculature, causes pulmonary edema, leading to tachypnea. Tachypnea and the increased left ventricular work impose a metabolic “tax” that is difficult for the infant to pay. Feeding requires caloric expenditure because of the work of sucking, and is further compromised because tachypnea interrupts feeding.

Atrioventricular and semilunar valve regurgitation are also important causes of heart failure because of volume overload in children, particularly in the presence of congenital heart defects such as Ebstein’s anomaly, atrioventricular septal defect, or TOF. The severity of heart failure that occurs with valvar regurgitation can be exacerbated by underlying abnormalities in ventricular structure and function that are present in unrepaired and repaired congenital heart defects. Neonates with Ebstein’s anomaly can present with heart failure that is the result of severe tricuspid regurgitation, abnormal right and left ventricular geometry, and hypoxia because of right-to-left atrial shunting. In a patient with atrioventricular septal defect and cleft mitral valve, mitral regurgitation can be an important cause of acute heart failure in the neonate and chronic heart failure after surgical repair. The common approach to surgical relief of severe pulmonary stenosis in TOF includes patch augmentation of the right ventricular outflow tract and resection of pulmonary valve tissue. The effects of long-standing pulmonary insufficiency on right ventricular and tricuspid valve function are increasingly recognized as an important cause of heart failure in adult TOF patients.

Elevations of the neurohormonal and inflammatory mediators that characterize adult heart failure such as renin, aldosterone, norepinephrine, brain natriuretic peptide (BNP), N-terminal prohormone BNP, and tumor necrosis factor-α...
receptor have been demonstrated in children with volume overload lesions.54–56 Activation of these and other factors may help explain symptoms previously ascribed solely to hemodynamic alterations.

Pressure Overload

The most common LV pressure overload lesion is congenital AS. AS exhibits a spectrum of obstruction, and can cause heart failure symptoms at the severe end of the spectrum, even in fetal life. Studies in a fetal sheep model of AS show LV myocardial hypertrophy through myocyte hyperplasia, and decreased LV cavity size.57 Although LV output is decreased, combined ventricular output usually is normal because of the ability of the RV to compensate independently in the parallel fetal circulation. In extreme cases, subendocardial ischemia and severe myocardial dysfunction can occur, leading to hydrops fetalis.

After birth, with the transition from the parallel to the series circulation, the RV can no longer compensate for the LV to sustain cardiac output, peripheral perfusion becomes inadequate, and metabolic acidemia ensues. Ongoing subendocardial ischemia may lead to further LV dilation and dysfunction, and ultimately, cardiogenic shock. Depending on the severity, cardiac dysfunction can include increased LV end-diastolic volume and filling pressure, increased LV mass, increased wall stress, ventricular dilation and remodeling to a more spherical shape, and left atrial hypertension. These findings may be exacerbated by the immature myocyte configuration and Ca++-handling found in fetal and newborn hearts. The newborn response to severe AS is an acute model of the progressive remodeling that occurs over months to years in adult heart failure due to AS.

We have found no published data on neurohormonal activation in severe AS in childhood. If the data on adults apply to children, it is likely that BNP levels will be increased, triggered by both increased LV systolic load and diastolic stretch load.58 Further, tracking BNP levels, as a reflection of wall stress, may be able to predict transition from a compensated to an uncompensated state.59

Complex Malformations

About one third of congenital heart disease consists of complex malformations that contribute disproportionately to the occurrence of heart failure. A detailed review of the pathophysiology of heart failure in the myriad of conditions in this category is beyond the scope of this article, but a few general topics will be discussed.

Complex malformations often combine volume and pressure overload characteristics, and both systemic and pulmonary circulations can be affected. Cyanosis is often present, with attendant risk of subendocardial ischemia contributing to impaired ventricular performance. The molecular abnormalities, often in transcription factors, that lead to congenital structural abnormalities have also been associated with abnormal myocardial performance and arrhythmias, which can increase the likelihood of heart failure.60

A major difference between adult and pediatric heart disease is that in pediatrics, much of the pathology is due to an abnormal RV, either due to congenital heart disease or pulmonary hypertension. The latter will not be discussed here. During embryonic development, the RV and LV develop from different but overlapping molecular programs and biomechanical forces. Fetal circulation is RV-dominant, with the RV contributing about two third of cardiac output. After birth, this circulation transitions to an LV-dominant pattern. The prolate ellipsoid structure that represents normal LV geometry is well-designed to support the systemic circulation. The normal RV is tripartite, consisting of an inflow portion, a body, and an outflow portion. This design is intended to support a low-pressure circulation, and is not well suited to systemic levels of afterload.

The mechanism of contraction in the RV is complex and consists of 3 distinct phases. Normally, the RV inflow and RV outflow tracts contract sequentially. The last phase of RV contraction is dependent on normal LV contraction, transduced through the interventricular septum. In comparison with the square- or rectangular-shaped LV pressure–volume loop, that RV pressure–volume loop is triangular, without a distinct isovolumic contraction or relaxation phase.61 Finally, right coronary artery flow, which perfuses the RV free wall and the lower one third of the interventricular septum, normally occurs in systole as well as diastole.

RV myocytes appear to be structurally identical to those found in the LV, which suggests that the differences in contraction compared to the LV are due to the shape of the RV and myocardial organization. There is recent evidence, however, that gene expression patterns are different in the RV and the LV, which may affect function. In 18 children with RV or LV obstructive lesions undergoing surgery, gene expression was measured in resected ventricular tissue, and differential gene expression was identified in 17 genes. Genes that affect angiotensin and β-adrenergic receptor signaling showed lower expression in the RV than the LV, whereas genes that contribute to maladaptive signaling showed higher expression in the RV.62

In complex congenital heart disease, RV function can be affected in several ways. For example, in hypoplastic right heart syndromes, the 3 parts of the RV do not form normally or may be missing entirely. There may be defects in the interventricular septum, or abnormal LV function, which adversely affect the third phase of normal RV contraction through its interdependence on normal septal function. Volume overload of the RV can arise through significant pulmonary or tricuspid valve insufficiency. The ensuing RV dilation has historically been viewed as benign, but in recent years much attention has focused on assessing markers of the transition of compensatory dilation to decompensated dilation.

The RV can experience increased afterload if there is right ventricular outflow obstruction at the subpulmonary, pulmonary, or supravalvular level, or if it is serving as the systemic ventricle. In this case, the RV usually can adapt if the increased afterload is present at birth when the ventricle is still relatively hypertrophied, but once the RV assumes a mature, thin-walled configuration, it cannot always mount a hypertrophic response. The RV is able to support the systemic circulation for many years, as attested to by the number of adults now surviving with congenital heart disease, but function often deteriorates over time.
There have been limited reports of neurohormonal biomarkers in right-sided congenital heart disease in children. In unrepaired TOF in infants, BNP is normal, despite the obligate RV hypertrophy, but in repaired TOF with RV dilation because of pulmonary insufficiency, BNP levels are elevated. The role of neurohormonal activation in right-sided failure remains to be elucidated.

The other group of complex malformations that will be discussed is those with single ventricle physiology, in which the ventricular morphology (left, right, indeterminate, or unbalanced) results in a single functional pumping chamber. At birth, the presentation depends on the morphology, but can range from well-tolerated cyanosis to decompensated heart failure and cardiogenic shock. The pathophysiological factors associated with heart failure in the newborn period are unobstructed pulmonary blood flow, obstruction to systemic flow, obstruction to pulmonary venous return, insufficiency of the atrioventricular valve(s), myocardial abnormalities or dysfunction, and coronary hyperperfusion. These factors can occur individually or in various combinations in single ventricle physiology.

The current surgical strategy for most functional single ventricles consists of 2- or 3-staged procedures, culminating in the Fontan procedure which separates the systemic and pulmonary circulations. The single ventricle pumps to the systemic circulation; pulmonary flow is accomplished passively through surgical connection of the superior and inferior vena cavae directly to the pulmonary arteries. The functional single ventricle heart is volume-loaded because of the need to supply the pulmonary and systemic circulations, until the creation of the cavo-pulmonary anastomosis at ~6 months of age. This volume load is associated with elevated BNP levels before the surgery; afterward, they return to normal.

After the Fontan procedure, diastolic filling properties often remain abnormal for some time, if not indefinitely. Ventricular function may depend on morphology, with single LVs better able to pump to the systemic circulation than single RVs. The single RV has a lower mass-volume ratio which creates a relative increase in wall stress and may portend poorer performance of the single RV. Furthermore, the single RV does not have the functional benefit of the interdependence with the LV and interventricular septum that the RV has in 2-ventricle physiology. Finally, the prevalence of conduction and rhythm abnormalities is relatively high in patients who have undergone the Fontan procedure, and these can further compromise cardiac function.

The Fontan procedure is often well-tolerated for many years, but as increasing numbers of these patients survive to adulthood, the prevalence of so-called Fontan failure is also increasing. There are few studies of neurohormonal activation in the Fontan population. The largest study is from the NHLBI-funded Pediatric Heart Network Fontan Study, in which BNP levels were assessed on 510 children and adolescents who had undergone the Fontan procedure. Although there was considerable variation in BNP levels, the mean concentration in this largely asymptomatic population was similar to individuals without congenital heart disease. In those with markers of adverse ventricular performance, however, BNP levels were elevated.

Primary Cardiomyopathy
Although congenital heart disease is the most common cause of pediatric heart failure, the population at greatest risk of heart failure is children with cardiomyopathy, most notably is dilated cardiomyopathy (DCM). Hypertrophic cardiomyopathy does occur in children, but it rarely progresses to heart failure in childhood, and restrictive and arrhythmogenic right ventricular cardiomyopathies are extremely rare in children.

There are many causes of DCM in children, as in adults, but we will focus here on primary dilated cardiomyopathy, caused by a genetic abnormality of sarcomeric, cytoskeletal, or cell membrane proteins, or of ion channels. The common pathophysiological process leading to heart failure in primary DCM in children is similar to that in adults: impairment in the ability of the myocardium to generate force as a result of altered structure. In a Swedish study of 26 children, 6 of whom had heart failure due to DCM, BNP was significantly elevated in the DCM group. Further, the levels in the DCM group, which had severe LV dilation (mean z-score, 5.88), were significantly higher than in the ventricular septal defect volume-overload group, which had mild to moderate LV dilation (mean z-score, 3.0).

Other Conditions
The list of other cardiac (and noncardiac) conditions that can give rise to heart failure in children is lengthy, and the reader is referred to 2 recent textbooks on the topic for additional details. Two are mentioned here because of their relevance for adult cardiology. Cardiac ischemia is relatively rare in children, but can arise in the setting of congenital coronary artery abnormalities, such as anomalous left coronary artery from the pulmonary artery; in patients who have had palliative surgery that requires reconstruction of or near the coronary arteries, such as the Ross procedure and the arterial switch operation; or in cases of left ventricular hypertrophy and obstruction to coronary flow, such as AS. Ischemia and resultant reperfusion injury occurs during surgical repair of congenital heart disease, and may be cumulative in conditions where multiple surgical procedures are required.

Although the pediatric myocardium is more tolerant of tachycardia than that of the adult, rhythm and conduction disturbances can lead to heart failure in children. Congenital complete heart block may be well-tolerated in utero, but can also give rise to sufficient dysfunction to cause hydrops and intrauterine demise. After birth, progression to heart failure depends on the ventricular rate and the speed of diagnosis and intervention. Children with congenital complete heart block who are pacemaker dependent are also at risk of subsequent pacemaker-mediated cardiomyopathy. The most common childhood tachyarrhythmia is supraventricular tachycardia, which often presents in the first few months of life. Most often, this is diagnosed and treated before heart failure symptoms can occur, but occasionally, such as in permanent junctional reciprocating tachycardia and ectopic atrial tachycardia, there is significant LV dysfunction.

Summary
Since the earliest characterization of the signs and symptoms of venous congestion in a child with a ventricular septal
defect, it has been recognized that the causes of heart failure in children are multifactorial and not limited to the presence of left ventricular dysfunction. Heart failure in children results from etiologies as diverse as volume overload, pressure overload, cyanosis, primary myocardial disease of either or both ventricles, metabolic abnormalities, and genetic mutations. Mechanistic insights into the pathophysiology of heart failure in children, coupled with a molecular understanding of cardiac development, have the potential to identify new therapeutic targets for the treatment of all patients with heart failure.

The absence of accurate disease-specific incidence and outcome data are an impediment to research on pediatric heart failure. The European experience illustrates the potential contributions of systematic national databases for pediatric care in general and pediatric heart disease in particular.

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