Aetiology, diagnosis and management of heart failure in infants and children

Lungile Pepeta

Faculty of Health Sciences, Nelson Mandela Metropolitan University, Port Elizabeth, South Africa

Address for correspondence:
Prof. Lungile Pepeta
Executive Dean
Faculty of Health Sciences
Nelson Mandela Metropolitan University
Port Elizabeth
6001
South Africa

Email:
Lungile.Pepeta@nmmu.ac.za

ABSTRACT

Heart failure is due to failure of ventricular filling with failure of ejection of blood from the ventricles. It may present as volume overload with ventricular dysfunction, volume overload with preserved ventricular function, and pressure overload. Causes of heart failure in the paediatric age group include both congenital and acquired heart diseases. Dilated cardiomyopathy remains the most common cause of heart failure in the paediatric population. In this article, epidemiology; pathophysiology; aetiology; clinical presentation; investigations including radiological and laboratory investigations; medical and non-medical management of acute, chronic and end-stage heart failure and prognosis will be reviewed. SAHeart 2017;14:6-15

INTRODUCTION

Heart failure occurs when there is failure of ventricular filling associated with a failure to eject blood from the ventricles. Heart failure may be due to pump dysfunction, volume overload (preload) and pressure overload (afterload).[1]

Causes of heart failure in children differ to causes seen in adults.[2] The most common cause of heart failure in children with a structurally normal heart is cardiomyopathy.[3] Most studies in the management of heart failure, including clinical trials, have been done in adults. Management of children with heart failure is therefore based on adult studies.[2]

EPIDEMIOLOGY

In the United States of America, heart failure accounts for 14 000 admissions annually, and in-hospital mortality ranges between 7 and 11%.[4] The incidence of cardiomyopathy in the US is 1.13 cases/100 000 population.[3] The most common subtype is dilated cardiomyopathy, followed by hypertrophied cardiomyopathy and then restrictive cardiomyopathy. About 40% of paediatric patients with symptomatic cardiomyopathy will be submitted for a cardiac transplant, or succumb within the first 2 years of life.[5]

PATHOPHYSIOLOGY

Heart failure may result from ventricular pump dysfunction, volume overload with preserved pump function, and pressure overload with preserved pump function.[2] Ventricular pump dysfunction may be seen in both acquired and congenital heart disease. In acquired heart disease, this occurs early in childhood, whereas in congenital heart disease, this may occur much later and may be experienced in adulthood (Table. I).[2]

Volume overload can be seen in patients born with congenital heart lesions with left to right shunting. This dysfunction can also be seen in patients with valvular insufficiency.

Pressure overload is seen in patients with congenital heart defects with obstruction to the left ventricular outflow tract.[2] These include discrete sub-aortic stenosis, aortic valve stenosis, supra-valvular aortic stenosis, aortic arch hypoplasia, aortic interruptions of various types and coarctation of the aorta of various types.

AETIOLOGY OF HEART FAILURE IN INFANTS AND CHILDREN

Ventricular dysfunction

Structurally normal heart

Cardiomyopathy

Causes of ventricular dysfunction are presented in Table I.[2]

Myocarditis may present with acute heart failure and is usually caused by a viral insult.[6] It may then progress to chronic heart failure in patients that develop dilated cardiomyopathy as a complication.

Myocardial ischaemia may be due to anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA).[7] This may present with heart failure associated with left ventri-

TABLE 1: Causes of heart failure in infants and children.[2]

Ventricular pump dysfunction
Structurally normal heart
Primary cardiomyopathy
• Dilated
• Hypertrophic
• Restrictive
• Non-compaction
• Arrhythmogenic right ventricular dysplasia (ARVD)
Secondary cardiomyopathy
• Myocarditis
• Myocardial infarction/ischaemia
• Anomalous left coronary artery arising off the pulmonary artery (ALCAPA)
Arrhythmogenic
• Complete heart block with bradycardia
• Supraventricular or ventricular tachycardia
Drug/toxin exposure
• Anthracycline
Noncardiac causes
• Sepsis
• Renal failure
Congenital heart disease
• Complex congenital heart defect with concurrent ventricular dysfunction
• Complex congenital heart defect, surgically corrected with late ventricular dysfunction ("burnt-out" congenital heart disease)
Preserved ventricular pump function
Volume overload (increased preload)
Left-to-right shunting
• Ventricular septal defect
• Patent ductus arteriosus
• Atrial septal defect (rare)
• Aortopulmonary window
• Atrioventricular septal defect
• Single ventricle physiology with unobstructed pulmonary blood flow
Valvular insufficiency
• Aortic regurgitation
• Mitral regurgitation
• Pulmonary regurgitation
Pressure overload (increased afterload)
Left-sided lesions
• Aortic stenosis
• Aortic coarctation
Right-sided lesions
• Pulmonary stenosis

Modified from: Hsu DT, Pearson GD. Heart failure in children: Part I: History, etiology, and pathophysiology. Circ Heart Fail 2009;2:63-70.

cular dysfunction as the pulmonary pressures decrease post-delivery.

Arrhythmias

Neonatal complete heart block due to either congenital heart disease or maternal autoimmune disease may lead to heart failure if the junctional escape rhythm is not adequate enough to provide for the body's needs.[8,9] Atrial arrhythmias, like supraventricular tachycardias or junctional or ventricular arrhythmias, may cause ventricular dysfunction.[10]

Toxic drugs may cause ventricular dysfunction or failure. In paediatrics, this is often due to chemotherapy, in particular anthracyclines.[11]

Sepsis may cause ventricular dysfunction that results in heart failure due to release of cardiotoxic cytokines.[12]

Complex congenital heart disease may degenerate into ventricular dysfunction with heart failure before or following surgical intervention, presenting with "burnt-out" myocardium.[13] This may occur quite early or much later in the management of these patients with single ventricle aberrations.

Volume overload

Conditions associated with volume overload and preserved ventricular function include ventricular septal defects, patent ductus arteriosus, atrioventricular septal defects, aorto-pulmonary window, single ventricle with unobstructed pulmonary blood flow and rarely atrial septal defects.[2] Volume overload becomes more pronounced in the first 6 - 8 weeks after delivery as a result of a physiologic decline in pulmonary artery pressures. At this stage, patients may present for the first time with heart failure.

Valve incompetence may lead to volume overload. This would include mitral, aortic and pulmonary valve incompetence. Pulmonary valve incompetence is usually seen in patients with tetralogy of Fallot following repair.[14]

Pressure overload

Conditions causing ventricular outflow obstruction result in pressure overload. It is usually severe outflow obstruction that presents with acute heart failure in infancy.

Moderate or severe outflow obstruction may also cause heart failure from chronically elevated filling pressures. The obstructive lesions associated with heart failure include aortic valve stenosis, coarctation of the aorta and pulmonary valve stenosis, amongst others.[2] Systemic hyper-tension may also lead to pressure overload.[15]

CLASSIFICATION OF HEART FAILURE

Heart failure can be classified according to its natural progression or stage following exposure to a risk factor or based on severity of clinical progression.[16-21] Heart failure staging in infants and children is presented in Table II.[16]

Classification of heart failure severity may include the New York Heart Association (NYHA) classification which is applicable only to adults and adolescents[17] (Table III); the Ross Classification which is applicable to children of all ages and

TABLE II: Paediatric heart failure staging and recommended therapy.[16]

Stage	Definition	Example	Therapy
A	Increased risk of developing heart failure, but preserved cardiac function and chamber size.	Exposure to cardiotoxic drugs, family history of hereditary cardiomyopathy, congenital single ventricle, l-transposition of the great arteries.	None
B	Abnormalcardiac morphology or function, with no past or present symptoms of heart failure.	Aortic regurgitation with dilated left ventricle, history of anthracycline exposure with left ventricular systolic dysfunction.	Angiotensin converting enzyme inhibitors for patients with systemic ventricular dysfunction.
C	Structural or functional heart disease, and past or current symptoms of heart failure.	Cardiomyopathy or congenital heart defect with ventricular pump dysfunction.	Angiotensin converting enzyme inhibitors, mineralocorticoid receptor antagonists and beta blockers for remodeling reversal; low dose digoxin and diuretics for symptom control.
D	End-stage heart failure requiring specialised interventions.	Marked symptoms at rest despite maximal medical therapy.	Intravenous diuretics and/or inotropes, positive pressure ventilation, mechanical circulatory support, heart trans-plantation.

Modified from: Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: Practice guidelines for management of heart failure in children. The Journal of Heart and Lung Transplantation. 2004 Dec 1; 23(12):1313-33.

TABLE III: The New York Heart Association classification of heart failure.[17]

Class	NYHA Functional Classification
I	Patients with cardiac disease without resulting limitations of physical activity.
II	Patients with cardiac disease resulting in slight limitation of physical activity.
III	Patients with cardiac disease resulting in marked limitation of physical activity.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest.

Modified from: Hurst JW, Morris DC, Alexander RW. The use of the New York Heart Association's classification of cardiovascular disease as part of the patient's complete Problem List. Clinical Cardiology. 1999 Jun 1;22(6):385-90.

based on a history of feeding intolerance, growth problems, exercise intolerance and physical signs of heart failure.[18-20] Classification of heart failure in the paediatric population may also include The New York University Paediatric Heart Failure Index.[21] Like the NYHA classification, the Ross classification of severity of heart failure in children and infants has 4 classes as follows:

Class I: Asymptomatic.

Class II: Mild tachypnea or diaphoresis with feeding in infants. Dyspnea on exertion in older children.

Class III: Marked tachypnea or diaphoresis with feeding in infants.

Prolonged feeding times with growth failure.

Marked dyspnea on exertion in older children.

Class IV: Symptoms like tachypnea, retractions, grunting, or diaphoresis at rest.

Diagnosis

Signs and symptoms of heart failure are a reflection of the inability of the heart to produce adequate cardiac output.

History

Symptoms of heart failure are different at different age groups, as follows:[22]

Infants: This age group commonly presents with tachypnea and diaphoresis during feeds, decreased amount of feeds, irritability, easy fatigability and poor weight gain.

Young Children: In this group, the symptoms may simulate common childhood illnesses like gastroenteritis, reflux, asthma or even behavioral problems. These may be abdominal pain, nausea, vomiting, poor appetite, failure to thrive, easy fatigability and recurrent or chronic cough with wheezing.

Older Children: This age group may present with both cardiac-specific and cardiac non-specific symptoms such as exercise intolerance, anorexia, abdominal pain, wheezing, dyspnea, oedema, palpitations, chest pain or syncope.

Physical examination

The physical findings depend on severity of heart failure and its complications like pulmonary congestion.

The clinical signs may include the following:[23]

- Tachycardia
- Hypotension
- Poor peripheral perfusion due to reduced cardiac output.
- A thrill that may be heard in congenital heart lesions or a heave with a displaced apex may be detected in cardiomyopathies.
- Gallop rhythm due to either pump failure, volume overload or both.

- Pulmonary oedema, manifesting as respiratory distress and other features of respiratory distress like grunting and nasal flaring in infants, retractions and use of accessory muscles, wheezing or rales (in older children).
- Features of systemic congestion, which include hepatomegaly, jugular venous distension (not generally observed in infants and young children) and peripheral oedema.
- Features suggestive of aetiology of heart failure, which include: proximal hypertension in coarctation of the aorta, cardiac murmurs seen in congenital heart defects with left to right shunting, cardiomyopathies or regurgitant valves.

INVESTIGATIONS

The diagnosis of heart failure requires radiological and laboratory studies.

Chest Roentgenogram

The chest X-ray assists in the diagnosis of cardiomegaly, pulmonary oedema, and in monitoring clinical improvement whilst the patient is on heart failure medication.

In left to right shunts, cardiomegaly suggests a moderate to large lesion, volume overload with, or without, dysfunction and atrial and/or ventricular enlargement. Cardiomegaly may also be noted in dilated cardiomyopathy more than myocarditis.

Right ventricular dilation may be seen in patients with pulmonary hypertension and Arrhythmogenic Right Ventricular Hyperplasia. Restrictive cardiomyopathy may present with features in keeping with bi-atrial enlargement.

Electrocardiogram

The electrocardiogram (ECG) may show sinus tachycardia, a feature of heart failure (reduced cardiac output).[24] Varying degrees of heart block may be observed in rheumatic heart disease, systemic lupus erythematosus and Lyme disease.

Features of atrial enlargement (restrictive cardiomyopathy) and atrial enlargement associated with ventricular enlargement can be seen in dilated and hypertrophied cardiomyopathies, and in significant left to right shunts. Ventricular enlargement may be diagnosed based on QRS Axis deviation together with voltage criteria.

Decreased voltage amplitude can be seen in pericardial oedema, muscle oedema and some forms of myocarditis. T wave changes and ST elevation or depression can be noted in various forms of cardiomyopathy and myocarditis.

A deep q wave in inferior and lateral leads (I, aVL, and V5 - V6) with ST segment and T wave changes is a classic finding in infants with anomalous left coronary arising from the pulmonary artery (ALCAPA).[25]

Echocardiography

This is a fundamental diagnostic tool to ascertain whether the heart is structurally normal, whether there is a congenital heart disease, and whether the heart is enlarged with or without ventricular (pump) dysfunction. In a patient with congenital heart disease, the echocardiogram may further define cardiac anatomy, arterial and venous connections, presence and amount of shunting, presence and amount of valvular stenosis and regurgitation, atrial and ventricular size, diastolic function, estimation of right ventricular and pulmonary artery pressures.

The use of echocardiogram in establishing the cause of heart failure and assessing the clinical status of the patient is illustrated in the following examples:

- Demonstration of the origin of coronary arteries from the aortic root and diagnosis of anomalous origin of the left coronary artery from pulmonary artery (ALCAPA).[26] The affected infants often have severe left ventricular dysfunction and mitral regurgitation at presentation, the latter due to papillary muscle infarction. Reversal of colour flow in the left coronary artery is highly suggestive of the diagnosis.
- Diagnosis of non-compaction cardiomyopathy, which is a rare type of cardiomyopathy, and derives its name from the echocardiographic appearance of left ventricular endocardial surface which, instead of being smooth, has deep trabeculations and multiple deep inter-trabecular recesses communicating with the ventricular cavity.[27]
- In patients with myocarditis and dilated cardiomyopathy, echocardiogram may provide accurate assessment of left ventricular dilation, mass and function. Left atrial and ventricular size may be helpful in determining chronicity, as their dilation and ventricular wall-thinning usually suggest long-standing dilated cardiomyopathy rather than acute myocarditis.[24]

Magnetic resonance imaging (MRI)

The information from echocardiography may be inadequate. Cardiac MRI provides accurate and detailed information about cardiac anatomy, ventricular function, myocardial inflammation (in myocarditis), and infiltration by fat and fibrous tissue.[28-30] It is particularly helpful in distinguishing restrictive cardiomyopathy from constrictive pericarditis.

Cardiac catheterisation

Cardiac catheterisation may be indicated for haemodynamic studies in patients with congenital heart lesions needing surgery, or those in need of heart transplant. A combination of cardiac catheterisation and myocardial biopsy is the gold standard in tissue diagnosis of myocardial disease. Angiography may be indicated in the diagnosis of congenital coronary abnormalities.

Laboratory investigations

Initial laboratory investigations

Complete blood count: The presence of anemia may contribute to heart failure in a predisposed patient (e.g. severe ventricular septal defect) or exacerbate the severity of failure in a patient with preexisting heart failure. In addition, an elevated white blood cell count may be indicative of infection, which

may also contribute to heart failure or be seen in patients with septic shock (who may present with similar symptoms to those of patients with heart failure).[24]

Urea and electrolytes: Serum electrolytes, blood urea nitrogen and creatinine may be indicated to check for hyponatremia which is seen in patients with severe heart failure.[16] Renal impairment may be a contributing factor for heart failure or may exacerbate preexisting failure.

Baseline electrolytes are needed prior to initiating therapy with diuretics or angiotensin-converting enzyme inhibitors to avoid potential side effects of these drugs.

Liver function tests: The activity of liver enzymes can be elevated due to liver congestion as a result of heart failure.

Additional blood tests

Creatinine kinase and Troponin

These are markers of myocardial injury. Elevated Troponin C among children presenting with left ventricular dysfunction may suggest acute myocarditis rather than dilated cardiomyopathy.[31]

Inflammatory markers

Elevated C-reactive protein and erythrocyte sedimentation rate (ESR) may be elevated in myocarditis and may help in differentiating this from dilated cardiomyopathy.[24]

Genetic testing

About 30% of cardiomyopathies may be due to a genetic cause (especially hypertrophied obstructive cardiomyopathy). All patients with cardiomyopathy need a clinical geneticist review and directed testing for a genetic cause.[32]

Brain Natriuretic Peptide (BNP) and N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP)

BNP and NT-proBNP derive from pro-BNP which is produced by the dilated atria.

Whilst BNP and NT-proBNP have been widely studied in adults with heart failure, the role of these markers has not been elucidated in the paediatric age group. This is due to the fact that the paediatric cardiac myocardium reacts differently to heart failure compared to the adult myocardium. Also, there are no standard norms and values that have been determined in paediatrics.

However, BNP and NT-proBNP levels have been shown:

- to correlate with the presence and amount of shunting through a patent ductus arteriosus in premature babies.[33]
- to discriminate serious cardiovascular causes from non-cardiac causes in newborns admitted with respiratory distress to an intensive care unit early after birth.[34]
- to discriminate children with heart failure from those with primary pulmonary disease among those presenting with respiratory distress.[35]
- to discriminate children with and without a significant cardiovascular disease among those referred to a cardiologist.[36]
- to discriminate serious from non-serious disease among children with newly diagnosed cardiac disease.[37]

Also, BNP and NT-proBNP levels are higher in children with newly diagnosed heart failure or those with acute exacerbations of chronic heart failure; higher BNP levels predict poor prognosis; improved BNP levels suggest improved ventricular function; following complex heart surgery, BNP is predictive of heart failure and BNP might be helpful as a marker of anthracycline induced myocardial toxicity.[38-43]

Other studies

Anti-streptolysin O-titre and antinuclear antibody are indicated for rheumatic fever and lupus. Further investigations may include thyroid function tests, carnitine levels and organic acids in patients with cardiomyopathy. Blood and Urine studies may also be indicated to determine infectious causes of cardiomyopathy.

MANAGEMENT

Overview

Heart failure is very common, with numerous studies on its management including randomised clinical trials performed in adults, rather than in children (as mentioned earlier). Management of heart failure in children is therefore extrapolated from adult studies. The management plan is directed or depends on etiology and stage of heart failure.[16,44] In patients with volume overload and preserved ventricular function (e.g. large ventricular septal defect, atrioventricular septal defect or regurgitant aortic or mitral valves), the management modality is either cardiac catheterisation or surgical intervention.[44] In patients with pressure overload but preserved ventricular function (e.g. aortic valve stenosis or hypertrophic cardiomyopathy), the management approach is cardiac or surgical intervention as well. Medical therapy can be given for symptomatic relief whilst patients await definitive therapy. In patients with ventricular pump dysfunction, with either structurally normal hearts or with congenital heart disease, the drug choice depends on severity. Diuretics, aldosterone antagonists, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), digoxin and beta blockers (carvedilol) are used routinely in the treatment of heart failure in children.[16] In patients with advanced heart failure that is refractory to medical therapy, positive pressure ventilation, inotropic support, mechanical circulatory support and heart transplantation may be indicated. Other therapies are directed at reducing risk or to treat complications like thromboembolism, arrhythmias and ventricular dyssynchrony.

Non-pharmacologic therapy may also include stem cell transplantation, optimisation of nutrition and exercise rehabilitation.[16]

Pharmacologic therapies

Diuretics, digoxin, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs) are effective in symptomatic relief of heart failure. Beta-blockers, ACEIs, ARBs and mineralocorticoid receptor antagonists (MRAs) or aldosterone antagonists have been shown to prolong patient survival. ACEIs, ARBs, beta-blockers and aldosterone antagonists have been shown to improve left ventricular function, reverse left ventricular dilation and remodeling. Additional drug therapy for chronic heart failure may include Nesiritide, and more novel drugs like angiotensin receptor blocker and neprilysin inhibitors (ARNIs) and Ivabradine.[45-48]

Intravenous inotropes and diuretics may be given in patients with acute decompensated heart failure or end-stage heart failure awaiting heart transplant.

What's old?

Diuretics

Diuretics are preload reducers.

They include loop diuretics, thiazides and mineralocorticoid receptor antagonists.[49-54]

Different types of diuretics, their mechanism of action, their short and long term effects and their common side effects are presented in Table IV.

In addition, loop diuretics have a shorter duration of action than thiazides. Although they act synergistically, combined use of these diuretics may potentiate adverse effects.[55]

MRAs also inhibit left ventricular remodeling by inhibiting myocardial fibrosis.[54]

Digoxin

The mechanism of action of digoxin is by inhibiting sodium-potassium ATPase and increasing intracellular calcium (positive inotropic effect). Digoxin slows atrial conduction as well, thereby resulting in a negative chronotropic effect.[56]

It is indicated for treatment of patients with stage C heart failure because of its physiologic benefit and symptom relief. It is no longer necessary to give high and frequent loading doses of digoxin ("digitalising") as the effects of digoxin are realised with smaller doses (through levels on 0.5 - 1ng/mL). Digoxin use has not been shown to reduce mortality though.[57]

Digoxin is not indicated in patients with asymptomatic left ventricular dysfunction, as it has not been shown to improve morbidity and mortality in such patients. Digoxin has been shown not to effect improvement of heart failure in paediatric patients with left to right shunts and preserved systolic function.[50] Common side effects of digoxin include arrhythmias, digitalis toxicity, particularly in patients with renal impairment or if used with amiodarone.

Angiotensin converting enzyme inhibitors

Heart failure leads to activation of the renin-angiotensin-aldosterone system (RAAS) and increased sympathetic tone. ACEIs inhibit RAAS by inhibiting the formation of angiotensin II, a potent vasoconstrictor that also promotes myocyte hypertrophy, fibrosis and aldosterone secretion. Thus, ACEIs benefit patients in heart failure first by reducing afterload, improving cardiac output and, on chronic use, by mediating reversal of left ventricular remodeling.[16]

ACEIs improve survival and slow progression of heart failure. Based on current evidence from adult trials and paediatric studies, ACEIs are used in children with ventricular pump dysfunction (stage B or C heart failure). Blood pressure and renal function should be closely monitored, especially if ACEIs are prescribed in neonates.[58]

TABLE IV: Diuretic classes, with their mechanisms of action, short and long term effects and common adverse effects.[49-54]

Diuretic class	Mechanism of action	Effects	Common adverse effects
Loop diuretics • Furosemide • Bumetanide • Torasemide	Inhibit sodium and water re-absorption in the thick ascending loop of Henle.	Decongestion, improve exercise capacity, reduce mortality, reduce risk of hospitalisation.	Hypokalemia, metabolic alkalosis, renal insufficiency, nephrocalcinosis and ototoxicity (with chronic use).
Thiazides • Hydrochlo-thiazide • Bendroflu-methiazide • Metolazone Indapamide	Inhibit reabsorption of sodium and chloride ions in the distal convoluted tubules of kidneys.	Decongestion, improve exercise capacity, reduce mortality, reduce risk of hospitalisation.	Hypokalaemia, hyponatraemia, nocturia.
Mineral-ocorticoid Receptor Antagonists • Spirono-lactone • Eplerenone • Amiloride • Triamterene	Block aldosterone receptor with decrease in sodium reabsorption and potassium excretion (potassium-sparring) in the collecting ducts of the kidneys.	Decongestion, reduction in hopitalisations and mortality.	Hyperkalaemia, gynaecomastia.

Beta blockers

The beta blockers counteract the maladaptive effects of chronic sympathetic activation of the myocardium.[59-62] In adults, they improve patient survival, reverse left ventricular remodeling and decrease myocardial fibrosis. The only trial of beta blockers in children showed no benefit of therapy but the trial was underpowered and studied a heterogenous population.[80]

They are indicated for use in the treatment of stage C heart failure. Beta blockers are usually added to an established regimen of diuretics, digoxin and ACEIs. Side effects usually include dizziness, fatigue, hypotension, bradycardia, bronchospasm and hypoglycemia.

It is recommended that beta-blockers are discontinued in patients with decompensated heart failure (stage D).

Angiotensin II receptor blockers

The ARBs also inhibit RAAS, like ACEIs, by inhibiting the angiotensin II receptor. ARBs are usually reserved for patients unable to tolerate ACEIs due to cough or angioedema. There is limited use of ARBs in the paediatric age group.

Nesiritide

Nesiritide, which is a recombinant Brain Natriuretic Peptide, reduces preload and after load by diuresis, natriuresis, and arterial and veno-dilation, suppression of the renin-angiotensin-aldosterone system (RAAS), thereby improving cardiac output without a direct inotropic effect on the myocardium.[45] Its mechanism of action is via activation of cyclic Guanalyl Monophosphate (c-GMP). The most common side effect is hypotension. Nesiritide is not recommended in acute decompensated heart failure.

Pulmonary vasodilators

Sildenafil: Sildenafil is a phosphodiesterase type 5 inhibitor.[63]

Its use in patients with heart failure is associated with improved left ventricular function, functional capacity, and quality of life in adults with systolic left ventricular dysfunction and secondary pulmonary hypertension.

It has also been shown to improve symptoms of heart failure in 13 children with failing Fontan physiology.[64] Sildenafil use in the treatment of heart failure with ventricular dysfunction remains under investigation.

Drug therapy for advanced heart failure

Inotropes: Inotropes are used for acute exacerbation of heart failure in patients awaiting heart transplant. Their effects are mediated through higher intracellular cyclic adenylate monophosphate (cAMP) levels, either by increased production (catecholamines) or by decreased degradation (phosphodiesterase III inhibition).[65,66]

Inotropes in use include milrinone used in combination with dobutamine or dopamine.

Milrinone is the preferred choice for inotropic support as it improves contractility and reduces after load. It has been given on outpatient basis for patients awaiting transplant.[67]

Non-pharmacologic therapies

Positive pressure ventilation

Ventilation is indicated for advanced heart failure.[68] Noninvasive positive pressure ventilation like continuous positive airway pressure or biphasic positive airway pressure assists in reducing pulmonary oedema and alveolar recruitment. They also reduce left ventricular preload and after load in adults. There are no studies in children that have looked at using these modes of ventilation in patients with advanced heart failure.

Heart transplantation

This is usually recommended for end-stage heart failure that is refractory to medical therapy (stage D).[69] It may be considered in patients with less severe heart failure (stage C) if it is associated with severe limitation of activity, significant growth failure, intractable arrhythmias or restrictive CMO.

Survival in paediatric heart transplant recipients at 1, 5, and 10 years after heart transplantation is approximately 90%, 80% and 60%, respectively.[70]

Early referral to a paediatric heart failure and transplant centre should be considered to optimise medical therapy and the timing of listing for the heart transplant.

Decision to pursue transplantation should be based upon the expected survival with medical therapy, quality of life, alternative options for treatment, and estimation of survival post-transplantation.

Nutrition

Malnutrition is seen in 25% of patients with CMO. Nutritional status correlates positively and independently with survival.[71]

Daily calorie intake of greater than 120kcal/kg for optimal growth is recommended, as there are increased metabolic demands in patients with heart failure. Salt and fluid intake to be discouraged.

Exercise rehabilitation

Cardiovascular rehabilitation shows promising results. However, there is limited data in children.[72]

What's new?

Angiotensin Receptor blocker and Neprilysin Inhibitors (ARNIs)

LCZ696 is a first-in-class of ARNIs. LCZ696 results in systemic exposure to AHU377, a neprilysin inhibitor pro-drug, and valsartan, an ARB.[46] AHU377 is then rapidly metabolised by non-specific esterases to the active neprilysin inhibitor LBQ657. LCZ696 causes dose-dependent increases in ANP, plasma and urinary cGMP, plasma renin activity, and angiotensin II, which

are effects that are consistent with activation of the NPR-A receptor and blockade of the angiotensin II type 1 receptor. In adult studies, ARNIs have been shown to reduce mortality and eliminate side effects associated with ACEIs like angioedema and hold much promise for the treatment of chronic heart failure.[46,47] There are no published paediatric data available for this drug but a study in children is underway.

Ivabradine

Ivabradine works by selectively blocking the sinus node, thereby reducing the heart rate.[48] This has resulted in improved morbidity and mortality in patients suffering from chronic heart failure. This mode of therapy warrants consideration in symptomatic patients (New York Heart Association functional class II - IV) in sinus rhythm, with left ventricular ejection fraction of ≤35%, and a heart rate ≥70b/min despite optimal treatment with a beta-blocker, ACEI, ARB, and a mineralocorticoid receptor antagonist.[73] Ivabradine has been shown to improve clinical outcomes and quality of life and to reduce the risk of death from heart failure or cardiovascular causes. Ivabradine has also been shown to be well tolerated and safe, even at maximal recommended doses. At this stage, experience in this therapy remains limited to adult patients.

Mechanical circulatory support

Mechanical circulatory support (MCS) includes extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) and may be indicated in patients with decompensated heart failure with low cardiac output syndrome that is unresponsive to medical therapy.[74]

It may be used as a bridge to recovery following acute decompensation as seen in myocarditis or post-cardiac surgery (ECMO), or as a bridge to transplant: (ECMO to VAD). The International Society of Heart and Lung Transplant (ISHLT), reported that 25% of children received MCS before heart transplant.

ECMO was instituted in patients with post-cardiotomy shock following cardiac surgery and acute myocarditis with a 38 - 45% survival rate. Mechanical circulatory support should be used as long term therapy, particularly in countries where there is no heart transplant programme.

Stem cell transplant

Stem cell transplantation is a newer modality of treatment of heart failure due to myocardial dysfunction. The therapy has been shown to promote cardiac regeneration by potentially replacing diseased tissue, enhancing endogenous cellular repair and by improving cardiac function.[75]

The stem cells that have been widely studied are bone marrow-derived mononuclear stem cells (BMMSCs) and mesenchymal stem cells (MMCs).[75] A meta-analysis of 50 Clinical Trials (in adults) reported that BMMCs improved left ventricular function and survival in recipients.

In paediatrics, the studies are limited to case series, with mixed results. There are no clinical trials reporting use of stem cells in children.

MANAGING COMPLICATIONS OF HEART FAILURE

What's old?

Thromboembolism

In patients with heart failure and moderate ventricular dysfunction, Acyl Salicylic Acid (Aspirin) is recommended and in children with severe ventricular dysfunction, Warfarin or Enoxaparin may be used.[76] In children with restrictive CMO with atrial dilation, Aspirin is recommended.

Arrhythmias

These may present as the underlying cause of ventricular dysfunction. Ablation therapy has a role in patients who might have chronic atrial tachyarrhythmias.[44] Implantable cardioverter defibrillatory (ICD) therapy may be used in a select group of patients at risk for sudden cardiac death due to ventricular tachycardia (VT) and/or ventricular fibrillation. The indications for ICD placement include aborted sudden cardiac death, unexplained syncope, and recurrent, sustained VTs.

What's new?

Ventricular dyssynchrony

Intraventricular conduction delay or left bundle branch block (LBBB) may worsen heart failure by causing ventricular dyssynchrony. Cardiac resynchronisation therapy (CRT) uses biventricular pacing to minimise ventricular dyssynchrony in patients with heart failure with prolonged QRS duration (LBBB).[77]

In the paediatric population, there is limited data. One retrospective, multicentre analysis of 103 children and young adults with congenital heart disease and prolonged QRS duration showed that CRT was associated with improvement of ventricular ejection fraction from 26 - 40%.[78]

Prognosis

The outcome in heart failure in children depends on the underlying cause, severity or stage of heart failure and whether the stage is reversible or not. In the 1980s, 1 year mortality rates were 20 - 30%, reaching 40% by 5 years in the first world.[79] This has changed due to active transplant programmes. Heart transplant remains unavailable in the developing countries resulting in high heart failure related mortality.

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