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REVIEW

Heart Failure with Preserved Ejection Fraction in Children

Bibhuti Das[1] · Shriprasad Deshpande[2] · Jyothsna Akam-Venkata[1] · Divya Shakti[1] · William Moskowitz[1] · Steven E. Lipshultz[3]

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Abstract

Diastolic dysfunction (DD) refers to abnormalities in the mechanical function of the left ventricle (LV) during diastole. Severe LVDD can cause symptoms and the signs of heart failure (HF) in the setting of normal or near normal LV systolic function and is referred to as diastolic HF or HF with preserved ejection fraction (HFpEF). Pediatric cardiologists have long speculated HFpEF in children with congenital heart disease and cardiomyopathy. However, understanding the risk factors, clinical course, and validated biomarkers predictive of the outcome of HFpEF in children is challenging due to heterogeneous etiologies and overlapping pathophysiological mechanisms. The natural history of HFpEF varies depending upon the patient's age, sex, race, geographic location, nutritional status, biochemical risk factors, underlying heart disease, and genetic-environmental interaction, among other factors. Pediatric onset HFpEF is often not the same disease as in adults. Advances in the noninvasive evaluation of the LV diastolic function by strain, and strain rate analysis with speckle-tracking echocardiography, tissue Doppler imaging, and cardiac magnetic resonance imaging have increased our understanding of the HFpEF in children. This review addresses HFpEF in children and identifies knowledge gaps in the underlying etiologies, pathogenesis, diagnosis, and management, especially compared to adults with HFpEF.

Keywords HFpEF: Heart failure with preserved ejection fraction · Pediatric · Child · Adolescents · Diastolic heart failure

Introduction

A working definition of heart failure (HF) in children is "a progressive clinical and pathophysiological syndrome caused by cardiovascular and non-cardiovascular 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 [1]." Heart failure can occur with preserved or a reduced left ventricular ejection fraction (LVEF). When a predominant or isolated abnormality in diastolic function accompanies HF symptoms, this clinical syndrome is called diastolic HF or HF with preserved EF (HFpEF). Diastolic dysfunction (DD) is defined as impaired ventricular relaxation and increased ventricle chamber stiffness, which increases cardiac filling pressures, but no overt symptoms of HF.

Diastolic dysfunction includes ventricular twist and deformation (diastolic strain), delay in untwisting, and reduced ventricular suction leading to impairment of early diastolic filling. The ventricular stiffness and impaired diastolic filling raise LV end-diastolic pressure (LVEDP) and left atrial (LA) pressure. Unlike systolic function, assessment of diastolic function in children is challenging because of considerable variability and inconsistency in echocardiographic criteria of DD. Conventionally, Doppler parameters such as mitral valve inflow, pulmonary venous flow, LV systolic-to-diastolic duration ratio, myocardial performance indices, and LA size are used to assess LVDD. However, these conventional noninvasive measures of DD may not be accurate, and the results are poorly correlated with invasive

✉ Bibhuti Das
bdas@umc.edu

[1] Department of Pediatrics, Division of Cardiology, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA

[2] Department of Pediatrics, Children's National Hospital, The George Washington University, Washington, DC, USA

[3] Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Oishei Children's Hospital, Buffalo, NY 14203, USA

hemodynamics [2]. Recently, novel echocardiographic measures of LV stiffness, such as strain, and strain rate analysis by speckle-tracking echocardiography (STE) and tissue Doppler imaging (TDI), are better correlated with gold standard estimates of DD derived from pressure–volume loop analysis in children [3].

It is estimated that more than half of all adults with HF have HFpEF. Pediatric onset HFpEF is often not the same disease as in adults. Pediatric HFpEF has been described in patients with cardiomyopathy, patients with congenital heart disease (CHD), and patients who received cancer therapies, among other conditions [4–10]. The etiologies, risk factors, clinical course, biomarkers, and therapies in children with HFpEF may not only be different from adults but even within children. This review paper aims to describe HFpEF in children and identify knowledge gaps in the underlying etiology, pathogenesis, diagnosis, and management compared to adults with HFpEF.

Epidemiology

In 1983, one of the first papers was published that recognized that many adult patients hospitalized for HF had normal LVEF [11]. In another paper, in 1984, Dougherty et al. reported that in 188 adult patients with HF, the EF was ≥ 45% and coined the term HF with normal systolic function [12]. Then, the Acute Decompensated Heart Failure National Registry (ADHERE) reported that 46% of patients with HF had no impairment or mild systolic dysfunction [13]. It is currently estimated that about 6.2 million Americans over the age of 20 years carry an HF diagnosis, with half a million new diagnoses every year [14]. Estimates suggest that by 2030 the prevalence of HF will increase by 46%. Total medical costs in the US alone may exceed $53 billion, with HFpEF patients expected to outnumber HF with reduced EF (HFrEF) [15].

Epidemiological evidence suggests a latent phase (6 years) in which DD is present and progresses in severity before the symptoms of HF arise in adults [16]. Elevated LV stiffness is associated with diastolic filling abnormalities and exercise intolerance. LA pressures increase further when the LVDD progresses, resulting in pulmonary edema and dyspnea, classical features of left-sided HF. In one population-based study, asymptomatic LVDD was found in 21%, and moderate or severe DD was present in 7% of the general population without any signs of HF [17]. Also, the same study showed that both moderate and severe DD were associated with an increased risk of progression to end-stage HF in adults.

There is limited literature on the epidemiology of HFpEF in children beyond the classic phenotypes of hypertrophic cardiomyopathies (HCM) and restrictive cardiomyopathies (RCM). The difficulties in estimating the prevalence of HFpEF in children are due to heterogeneous etiologies, distinct clinical courses, and different genetic and biomarker profiles. Nevertheless, the recent epidemiological study of Acute Decompensated Heart Failure (ADHF) in children admitted to intensive care units (ICU) across 23 centers in the US showed 6% of 26,294 consecutive ICU admissions had either HFrEF or HFpHF requiring continuous vasoactive or diuretic infusion, respiratory support, or mechanical support [18]. The Pediatric Critical Care Consortium data are a resource to evaluate the prevalence of severe pediatric HFpEF requiring ICU admissions.

Maturation of Diastolic Function

Neonatal LVDD is common but often difficult to determine whether it is due to "normal physiology" or "abnormal pathology." Therefore, it is essential to understand the maturation of diastolic LV function from fetal life to adolescence before appreciating DD in children. The neonatal myocardium is immature with impaired function of the sarcoplasmic reticular and T tubular function. Due to the limited ability to increase stroke volume due to reduced contractility, cardiac output depends predominantly on heart rate. Doppler echocardiography demonstrated sequential changes in the human fetal ventricular filling pattern at different gestational ages [19]. Doppler studies in 238 healthy neonates suggested that impaired LV relaxation and early diastolic filling were prevalent at birth, as noted by the reversal of the E to A wave's velocity ratio [20]. The effect of heart rate on early LV filling appears to be negligible and does not account for the observed differences in diastolic function in the first two months of infancy [21]. In preterm infants, the maturation of diastolic function is prolonged and limits tolerance to any preload stressors [22]. Therefore, LVDD on echocardiography is relatively common in preterm infants, primarily due to volume overload from a patent ductus arteriosus in an already immature myocardium, while HFpEF is less frequent.

In a study of 121 echocardiograms in 31 infants, profound changes in diastolic function are reported between one week and one-month post-birth [23]. A study of cardiac growth in healthy children using TDI showed a correlation between changes in diastolic function and age [24, 25]. There are distinct age-dependent changes in myocardial responsiveness, structural changes such as hypertrophy and fibrosis, and systemic inflammation due to different comorbidities that are recognized as pivotal for the differences in severity of HFpEF [26].

Etiology of HFpEF in Children

In general, HFpEF in children is a unique phenotype caused by heterogeneous etiologies such as HCM or RCM, CHD, cancer therapy including radiotherapy and chemotherapy, HIV infection, renal failure, and obesity, among many etiologies. In many situations, there is a thin line between LVDD and HFpEF. For example, childhood cancer survivors who had LVDD with restrictive physiology and limited exercise tolerance due to radiation therapy and/or anthracycline therapy years earlier [27]. Patients are often asymptomatic at rest but develop symptomatic restrictive disease with exercise. Steiner et al. [5] pointed out that these children may have asymptomatic HFpEF early, which clinically manifests in later years. The etiologies of HFpEF in children are summarized in Table 1.

Pediatric HFpEF has heterogeneous and multifactorial elements that come into play (Fig. 1). Factors that can lead to or aggravate HFpEF in adults [28], such as prior CHD surgery, especially after Fontan procedure, valvular diseases, obesity, hypertension, diabetes mellitus, coronary artery disease, metabolic syndrome, severe anemia, chronic kidney disease, radiation or chemotherapy exposures, antiretroviral therapy (ART), and obstructive sleep apnea, are also some of the effectors of DD in children. However, multiple studies have demonstrated substantial differences in patient profiles and risk factors for HFpEF in CHD compared with those with cardiomyopathies and between pediatric and adult patients. Generally, most children with ADHF, either due to cardiomyopathy or CHD, have overlapping systolic dysfunction and DD [29, 30].

Table 1 Etiologies of HFpEF in Children with Common Examples

1. Congenital heart disease
Pressure overload
Example: Aortic stenosis, coarctation of the aorta
Volume overload
Example: Left to right shunts, left-sided regurgitant lesions
Both pressure and volume overload
Example: Fontan for CHD with single ventricle physiology, mixed aortic valve disease
2. Myocardial diseases
Cardiomyopathy
Examples: Hypertrophic and restrictive cardiomyopathies
Endocardial fibroelastosis
Infiltrative/storage cardiomyopathies
Examples: Glycogen and lysosomal storage disorders, amyloidosis, hemochromatosis
Toxic
Example: Chemotherapy-induced cardiac toxicity, exposure to radiation
Inflammation
Example: Inflammatory cardiomyopathy, HIV cardiomyopathy
Ischemic
Examples: Anomalous origin of the coronary artery from the pulmonary artery
3. Arrhythmias
Persistent tachycardia
Dyssynchrony
4. Pericardial diseases
Constrictive pericarditis
5. Systemic diseases
Obesity
Hypertension
Chronic renal disease
Hemolytic anemia
Sepsis
Obstructive sleep apnea
HIV infection
Antiretroviral therapies

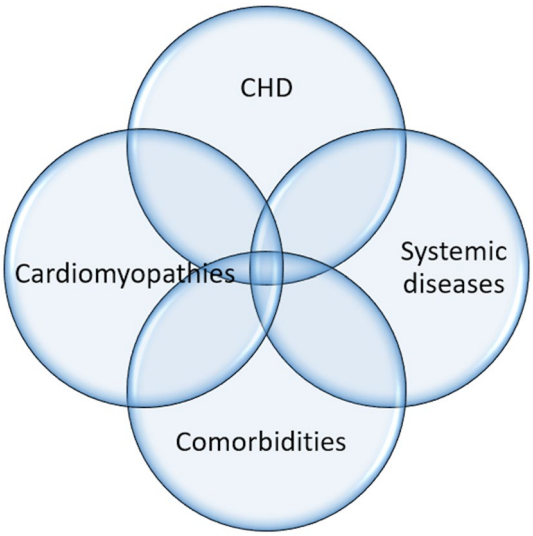

Fig. 1 Venn diagram illustrating the heterogeneity and multifactorial elements in pediatric heart failure with a preserved ejection fraction

Congenital Heart Disease

The top three cardiovascular causes of HFpEF in children are complex CHD (53.4%), simple CHD (15.7%), and cardiomyopathies (7.4%) [31]. The pathophysiological causes of HFpEF in CHD are multifactorial. They involve ventricular fibrosis, intracardiac scarring, valvular abnormalities, arrhythmias, the presence of cyanosis, or pulmonary hypertension. There are five main classes of CHD, which results in diastolic dysfunction: (1) pressure–overload lesions such as aortic stenosis, (2) volume overload such as mitral regurgitation, (3) mixed pressure and volume overloads, such as aortic stenosis and regurgitation, (4) transposition of the great arteries leading to a unique situation in which the right ventricle (RV) is faced with increased afterload and the LV with a much lower pressure than normal, both of which may cause decreased compliance, and (5) single ventricle CHD, especially after Fontan operation.

Pressure Overload Caused by Left-Sided Lesions

Global and regional deformation of LV occur in response to obstruction of the LV outflow tract (LVOT) [32–35]. The LV remodels and develops hypertrophy. The LV hypertrophy results in delayed and incomplete relaxation of the LV wall, with decreased early diastolic filling with an increased dependence on late diastolic filling. With myocardial tagging cardiac magnetic resonance (CMR), Nagel et al. [32] showed that LV pressure overload was associated with a reduction in basal rotation and an increase in apical rotation of the heart, indicating increased torsion of the LV in severe aortic valve stenosis. It was also shown that diastolic untwisting was delayed and prolonged in patients with aortic valve stenosis. These findings explained the occurrence of DD in patients with left-sided obstructive lesions. Furthermore, the pressure overload by aortic stenosis causes increased interstitial fibrosis and LV stiffness and is related to a worse prognosis [35].

Volume Overload

Children with LV volume overload due to aortic or mitral regurgitation have shown dysfunction of myocardial contractility [36]. LV compliance usually decreases in isolated mitral regurgitation as the LV dilates to accommodate an increased volume. According to Laplace's law, as the ventricular radius increases, myocardial wall tension also increases [37]. Over time, LV myocardial fibrosis occurs, resulting in relaxation impairment and DD.

Mixed Pressure and Volume Overload

Mixed pressure and volume overload can affect compliance, such as mixed aortic valve disease with aortic stenosis and aortic regurgitation. Similar to the effect of mixed aortic valve disease on the LV, RVDD can occur in repaired TOF with residual pulmonary valve stenosis and regurgitation. Right ventricular DD can also occur after surgical repair of tetralogy of Fallot (TOF) at intermediate follow-up [38]. More importantly, clinically asymptomatic patients with repaired TOF showed LV systolic dysfunction and DD and a lower than normal LV mass/volume ratio consistent with a pattern of eccentric LV remodeling [39].

Transposition of Great Arteries

Transposition of the great arteries (TGA) is one of the most common cyanotic CHD in neonates. The pulmonary artery (PA) is connected to the LV, and the aorta is connected to the RV. An arterial switch operation (ASO) is performed in TGA to convert the LV into the systemic ventricle, replacing the RV which was the systemic ventricle during the prenatal period. Therefore, the adaptation of LV and RV after ASO is an interesting issue. A study found impairment of the DD of both LV and RV by TDI and conventional Doppler parameters of DD during the short- to mid-term follow-up of pediatric patients who underwent ASO [40]. LV myocardial stiffening also was observed in adolescents and young adults with TGA after ASO and is associated with impairment of LV deformation and increased myocardial fibrosis leading to DD [41]. Reduced proximal aortic elasticity and aortic root dilatation are present in TGA patients post-ASO and are likely to contribute to LVDD. Also, impaired aortic elasticity is associated with age, suggesting it is useful to follow-up TGA patients for early onset LVDD.

Single Ventricle CHD

In the single ventricle CHD patients, myocardial hypertrophy, fibrosis, and DD often result from multiple, cumulative insults, which may include volume loading, pressure loading, chronic hypoxemia, coronary ischemia, chronic upregulation of the renin–angiotensin–aldosterone system, and chronic underfilling [29, 30, 42–44].

The Fontan patients with DD and normal EF had clinical evidence of decreased exercise tolerance suggestive of early HFpEF [45]. Diastolic dysfunction appears to be a progressive phenomenon in patients with single ventricles, with elevated filling pressures, sometimes already being present in childhood and deteriorating over time. Michel et al. [46] showed that children who have undergone Fontan surgery for hypoplastic left heart syndrome demonstrated progressive impairment of diastolic function at follow-up. Several factors may contribute to this impairment, including chronic deprivation of preload to the single ventricle with insufficient ventricular filling and resultant progressive myocardial stiffness. Alternatively, myocardial fibrosis may be a progressive phenomenon contributing to diastolic dysfunction. Amino-terminal procollagen type III, a surrogate marker of fibrosis, is more prevalent with impaired diastolic function in patients with dilated cardiomyopathy [47–49]. Hypoxemia and volume overload before the Fontan procedure are associated with elevated amino-terminal procollagen type III levels, and pre-Fontan amino-terminal procollagen type III levels correlate significantly with post-Fontan end-diastolic pressures [49].

Cardiomyopathies

Among all types of cardiomyopathies, HCM and RCM are two common causes of DD in children. Left ventricular hypertrophy induces LVDD [50]. Varying degree of DD is common in children with HCM with or without LVOT obstruction. The etiology of DD in HCM is multifactorial. At the molecular level, changes in Ca^{2+} affinity between the various contractile proteins, and at the tissue level, myocyte hypertrophy, myocyte disarray, and endocardial and interstitial fibrosis contribute to DD in HCM patients [51]. On the other hand, DD with normal to near normal systolic performance and little or no increase in end-diastolic or end-systolic dimensions of either RV or LV is the primary abnormality in RCM. The DD in RCM can result from myocardial or endomyocardial disease, the etiologies of which may be known or idiopathic. Diastolic dysfunction that is essentially myocardial can be idiopathic, infiltrative (myocardial interstitium), or within myocardial cells (storage diseases). Diastolic dysfunction that results from endomyocardial disease is typified by endomyocardial fibrosis or the hypereosinophilic syndrome, although carcinoid, metastatic malignancies, radiation, and anthracycline toxicity may be accompanied by endomyocardial restriction [52]. The DD in RCM leads to impaired ventricular filling affecting either or both ventricles and may result in HFpEF.

Heart Transplantation

Diastolic dysfunction is a well-recognized complication early after heart transplantation. After the first few days to months after heart transplantation, the right atrial (RA) pressure and LA pressure are often elevated, reflecting decreased compliance of the transplanted heart. This early diastolic impairment usually improves due to a general reduction of inflammation within the allograft. The incidence of DD gradually decreases within the first year after heart transplantation. Diastolic dysfunction often progresses to HFpEF after a few years of heart transplantation due to coronary microvascular dysfunction, interstitial fibrosis, and increased myocardial stiffness [53–55]. Children with mild cardiac allograft vasculopathy detected by angiography and HFpEF are at increased risk of graft loss or death [55]. Pulmonary capillary wedge pressure (PCWP) measured at rest and after exercise revealed a high prevalence of exercise-induced HFpEF after heart transplantation [56]. Early treatment with sirolimus is associated with improved diastolic function and filling pressures than calcineurin-inhibitor therapy [57]. The exact mechanism of progression from DD to HFpEF in post-transplanted hearts is unknown. Allograft vasculopathy, endothelial dysfunction, low-grade inflammation, epicardial and endocardial fibrosis, chronotropic incompetence, and immunological mechanisms are suggested as possible mechanisms [58].

Sepsis

Myocardial dysfunction is seen in patients with sepsis and carries significant mortality compared with those who do not have myocardial dysfunction [59]. Recent studies have demonstrated isolated DD and HFpEF in children with sepsis [60–62]. In children with sepsis-induced DD, this is reported to be an independent risk factor for poor outcomes [63].

Human Immunodeficiency Virus Infection

Cardiomyopathy and subclinical cardiac abnormalities have been reported in children and adolescents infected with the human immunodeficiency virus (HIV) [64, 65]. HIV infection is a primary cause of acquired heart diseases, notably accelerated atherosclerosis, symptomatic HF, and pulmonary arterial hypertension (PH). Cardiac complications often occur in late-stage HIV infections as the prolonged viral infection becomes more relevant with improved

longevity. Thus, multi-agent HIV therapies that help sustain life may also increase the risk of cardiovascular events. In recent years, prospective studies in HIV-positive patients on combined antiretroviral therapy (ART) have reported a higher prevalence of DD, elevated LV mass index, accelerated atherosclerosis, and dysautonomia [66, 67]. Children exposed to ART in utero have subclinical yet significant differences in specific LV diastolic indices. Follow-up with serial echocardiograms is recommended in this population to assess further the potential cardiac toxicity of perinatal exposure to ART [68].

The cardiometabolic abnormalities in HIV-infected children include high rates of unfavorable lipid profiles, insulin resistance, cardiovascular inflammation, vascular stiffness, and the phenotypic features of truncal adiposity and facial/extremity wasting [69]. Children who received ART prenatally may have reduced LV mass, LV dimension, and septal wall thickness *z*-scores and increased LV fractional shortening and contractility up to age two years [70]. Cardiac structure and function were relatively preserved in perinatally HIV-infected children exposed to highly active antiretroviral therapy (HAART) but declined over time when compared to those of similar children from the pre-HAART era [71]. The perinatal exposure to HAART therapies blocks normal cardiac growth resulting in hearts being too small for body surface area as they grow older.

Cancer Therapy

A continuum of changes starting with cardiac biomarker increase, myocardial structural deformation, and asymptomatic LVDD occurs during chemotherapy leading to HF in children and adults [9, 72]. Children treated with doxorubicin had decreased wall thickness relative to somatic growth compared to normal healthy children at a median follow-up of 11.8 years [7]. Cardiac abnormalities are persistent and progressive after doxorubicin therapy. Inadequate ventricular mass with chronic afterload excess was associated with the progressive contractile deficit and possibly reduced cardiac output due to restrictive physiology [73]. Typically, adult number of myocytes is present before the first year of life, and subsequent myocardial growth occurs by increasing the size of the cells. Therefore, damage to or loss of these cardiomyocytes might impair the heart's ability to generate an average adult myocardial mass. During long-term follow-up after completing doxorubicin treatment, a particular pattern of cardiac dysfunction has been noted in children. Early on, doxorubicin-treated children appeared to have dilated-like cardiomyopathy, which seemed to resolve but instead progressed to restrictive-type cardiomyopathy in later years [74]. The progressive restrictive-like cardiomyopathy was persistent because of a progressive fall in LV mass and cavity size that became inadequate for body size. Cardiomyopathy, marked by shrinking myocardial mass and cavity size for body size ("Grinch Syndrome"), appears to be a long-term risk in this population [75].

Myocardial injury induced by chemotherapies in children with malignancy starts with subclinical LVDD and increases cardiac biomarkers before progression to more advanced HFpEF or HFrEF, similar to some adult cancer patients, even though the subsequent course of progressive late cardiotoxicity in survivors may differ [76, 77]. Serum biomarkers of myocardial injury and increased myocardial stress during anthracycline therapy for childhood cancer are associated with abnormal LV structure and function years later as long-term survivors [78]. In pediatric Hodgkin lymphoma patients treated with mediastinal radiation therapy, DD during follow-up resulted in the loss of physical functioning as monitored by the Short-Form 36 quality-of-life instrument [9]. Alehan et al. [79] screened survivors of childhood Hodgkin lymphoma with Doppler echocardiography and confirmed that DD is common after anthracycline therapy, even without radiotherapy. Their findings are even more remarkable when considering that the median dose of doxorubicin was only 150 mg/m^2 and that 69% of patients received < 300 mg/m^2, a cut-off used to designate those at the highest risk for systolic dysfunction. Dexrazoxane, a cardioprotective iron chelator that reduces mitochondrial iron levels in children receiving anthracycline without reducing chemotherapeutic efficacy, is approved for this indication with increasing use based on multiple pediatric clinical studies demonstrating long-term cardioprotection [80, 81]. Pediatric cardio-oncology issues related to cardiac structure and function have been comprehensively reviewed and available in the literature for those interested in details [81–83].

Chronic Renal Failure

Elevated cardiac troponin T levels identify subclinical cardiac damage in patients with chronic renal failure without coronary artery diseases and are associated with depressed LV load-independent contractility [84]. Recently, TDI in 128 patients with chronic kidney disease showed significant LVDD compared to healthy children [85]. Early identification of LVDD in patients with uremia may prevent further progression to HFpEF and reduce cardiovascular morbidity and mortality in this high-risk population [86]. The underlying pathophysiological mechanisms of LVDD are LV hypertrophy with myocardial interstitial fibrosis due to chronic volume overload and uncontrolled hypertension. Several other factors, including secondary hyperparathyroidism, over-activation of the renin-angiotensin-aldosterone system, and inflammation, may influence LVH [87, 88]. LVDD causes an increase in LV filling pressure, which may lead to pulmonary congestion.

Obesity

Diastolic dysfunction is common in children with obesity or overweight [89, 90]. Obesity adversely affects morbidity and mortality in children with HF [91]. Many overweight children had three or more metabolic syndrome risk factors, indicating that being overweight in early adolescence may put children at risk for adult-onset cardiovascular disease and type 2 diabetes before they become teenagers [92]. Early bariatric surgical intervention not only improves body mass index but, more importantly, also improves cardiovascular and metabolic comorbidities of severe obesity, including HFpEF in adolescents [93]. Studies have also demonstrated LVDD in obstructive sleep apnea in obese and non-obese children and young adults [94, 95]. Obese children and adolescents often have prediabetes, a risk factor for LVDD leading to HFpEF [96–98].

Hemolytic Anemia

LV hypertrophy and LVDD in children with hereditary hemolytic anemia, sickle cell anemia, and thalassemia have been well documented [99, 100]. About one-third of children with sickle cell anemia had TDI evidence of LVDD, which correlated with hemoglobin levels [101]. Adding serial assessments of LV function with TDI may detect early DD, especially in children with severe anemia. In a study by Nanjegowda et al., a higher serum ferritin level (greater than 2076 ng/mL) is associated with an increased incidence of LVDD [102]. Diastolic dysfunction has been reported in children with Kawasaki disease [103], Marfan syndrome [104], juvenile rheumatoid arthritis [105], systemic lupus erythematosus [106], and other rare non-cardiovascular etiologies [107].

Pathophysiology and Mechanism of HFpEF in Children

Pediatric HFpEF is a complex heterogeneous clinical finding for which our pathophysiological understanding is limited. Recently, experimental models of HFpEF have demonstrated an interaction between metabolic stress and chronic inflammation, resulting in alterations in systemic and cardiac immune responses that contribute to HFpEF pathophysiology [108]. There is also evidence of elevated circulating inflammatory biomarkers such as interleukin-1, C-reactive protein, tumor necrosis factor-α, and soluble suppression of tumorigenesis-2 in HFpEF. Inflammatory cells express transforming growth factor β, interferon-γ, Galectin-3, connective tissue growth factor, and ACE, promoting the conversion of fibroblasts to myofibroblasts and collagen deposition [109].

The myocardial response to biochemical stress is different between pediatric and adult HF patients [110]. Differences in pediatric and adult HFrEF are also supported by a lack of adequate response to adult HF therapies [111–114]. Titin is a sarcomere protein and has been recognized as a determinant of myocardial relaxation. Titin is expressed in two isoforms: a smaller, stiffer N2B, and a larger, more compliant N2A. Nagueh et al. found an increase in the N2B:N2A titin isoform ratio compared with healthy controls in children with DCM [115]. This shift to a smaller (N2B) titin isoform can cause myocardial stiffness and DD. Moreover, titin is modulated by phosphorylation. The cGMP-protein kinase (PK) G-dependent pathway has been suggested to play an important role in regulating diastolic relaxation through titin phosphorylation and troponin I phosphorylation [116]. In pre-clinical models, many cardiac myosin-binding protein C mutations increase DD by increasing myofilament Ca^{2+} sensitivity and cross-bridge turnover between actin and myosin filaments [117, 118]. The pathophysiology of pediatric HFpEF depends upon age-related myocardial responsiveness, energy metabolism at the cellular level, the systemic inflammatory response, and the interaction of genes with environmental elements [16].

In children with CHD, remodeling processes in the LV depend upon hemodynamic stressors: pressure overload, volume overload, and pressure and volume overload [119, 120]. There are overlapping changes in the LV in CHD and cardiomyopathies due to hemodynamic overload, including collagen deposition, increased extracellular matrix deposition, myocardial and perivascular fibrosis, activation of the local tissue renin-angiotensin, secretion of pro-inflammatory chemokines, altered neurohormonal response, and increased matrix metalloproteinase activity (including collagenase) [121–123]. In addition, the impairment of sarcoplasmic Ca2 + -ATPase activity is a significant determinant of myocardial stiffness, leading to LVDD and ultimately to HFpEF [124]. The extent of fibrosis differs depending on the physiological age. Understanding these developmental differences in cardiomyocytes' response to injury has important therapeutic implications [125].

In an autopsy study, Perens et al. found that in children with end-stage HF who underwent heart transplantation, the explanted hearts showed interstitial and perivascular fibrosis in most cases [126]. The authors also examined their failed pediatric allografts and found a different pattern of severe epicardial fibrosis and relatively sparing of the myocardium, which could explain the HFpEF with relatively preserved systolic function after heart transplantation.

Masutani et al. reported that children with HFpEF had abnormal systolic and diastolic function at rest, arterial stiffening, and dissociation of ventricular-vascular coupling

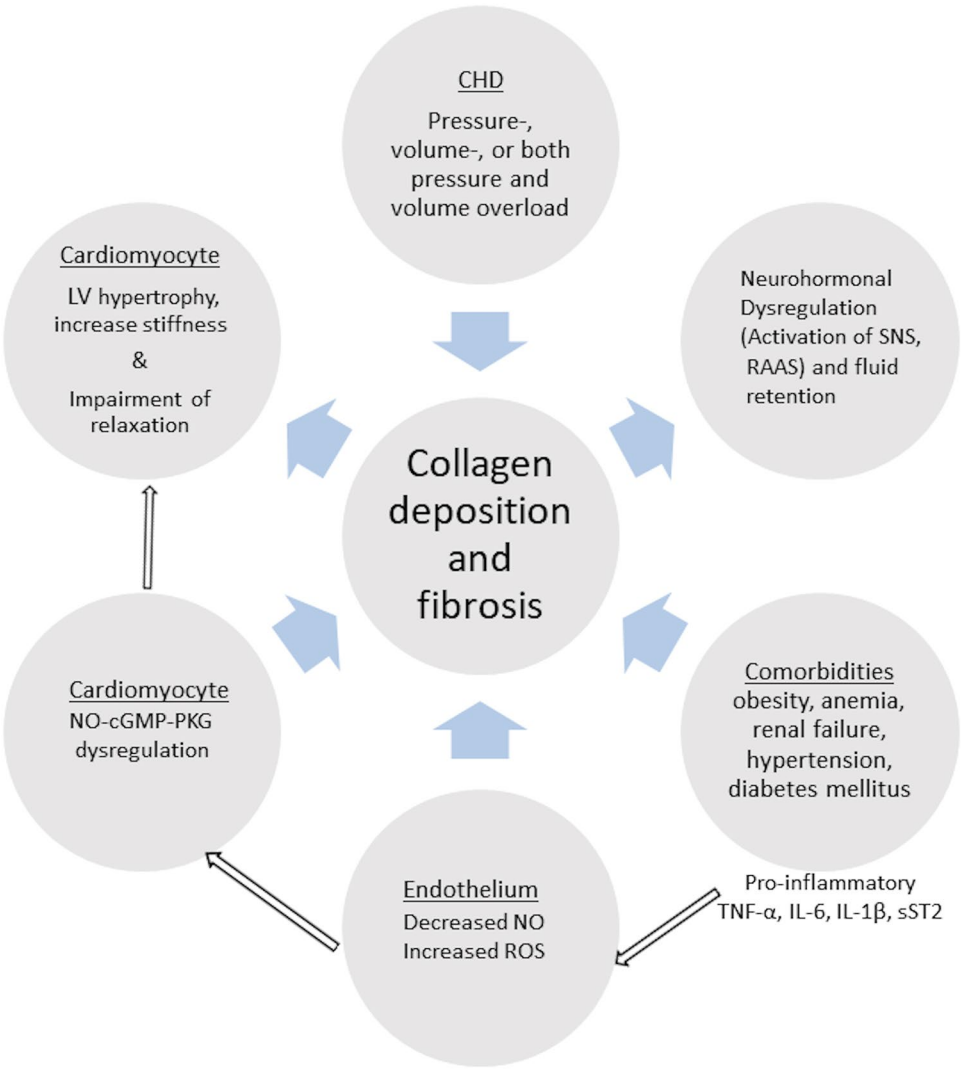

Fig. 2 Pathophysiology of HFpEF in children (TNF-α = tumor necrosis factor-α; IL-6 = interleukin-6; IL-1β = interleukin-1β; sST2 = soluble ST2 (receptor for IL-1 and 33); NO = nitric oxide; ROS = reactive oxygen species; cGMP = cyclic guanosine monophosphate; PKG = protein kinase G; SNS = sympathetic nervous system; RAAS = renin–angiotensin–aldosterone system)

at baseline long before the development of HF [127]. In addition, they had limited diastolic reserve capacity in response to enhanced preload and inotropic, lusitropic, and ventricular–arterial coupling responses to beta-adrenergic stimulation. Furthermore, children with HFpEF also had an abnormal coronary supply/demand balance, associated with ventricular diastolic stiffening and poor beta-adrenergic responsiveness. These findings in children support shared overlapping pathways in the pathogenesis of HFpEF in both children and adults [128, 129]. Pathophysiologic mechanisms that contribute to the development of HFpEF in both children and adults include systemic inflammation, endothelial dysfunction, decreased nitric oxide production, increased reactive oxygen species, increased sensitivity of the myocardium to Ca^{2+}, cardiomyocyte hypertrophy, and ultimately deposition of interstitial and perivascular collagen deposition leading to fibrosis [42, 121]. These shared pathophysiological processes speculated to develop HFpEF in children are summarized in Fig. 2.

In HFpEF, concentric remodeling and increased stiffness of the LV lead to an increase in LA pressure to maintain the gradient of transmitral pressure that allows LV filling. The elevated LA pressure, in turn, causes passive PH. In addition, increased LA pressure leads to alveolar capillary stress failure and vascular remodeling, further increasing pulmonary vascular resistance and a mixed type of pre- and post-capillary PH. Compared to patients with pure passive PH (i.e., caused by isolated LA hypertension or post-capillary PH). HFpEF patients are at increased risk of death due to structural remodeling in the lung vasculature that may not be reversible after the management of LVDD alone. Patients with HFpEF and pulmonary vascular disease display unique pathophysiology. The inability to enhance RV ejection increases right heart enlargement and LV underfilling, even though LV filling pressure is elevated. Even among patients with HFpEF who display normal pulmonary vascular resistance at rest, there is inadequate pulmonary vasodilation during exercise in HFpEF. This is associated

with adverse clinical outcomes and impairment in RV functional reserve. The development of RV dysfunction identifies patients with HFpEF with a markedly increased risk of death [130]. The RV is dilated in response to chronic pressure overload, functional tricuspid incompetence, and further RV dilation progression, ultimately resulting in RV failure.

Diagnosis of HFpEF in Children

Making a diagnosis of HFpEF in children remains a challenge. The diagnosis of HFpEF requires history, clinical symptoms, signs of HF, and evidence of DD with normal or mildly reduced LVEF. It is also important to exclude other medical conditions like lung diseases and PH, which may mimic HFpEF. Elevated natriuretic peptides support, but normal levels do not exclude a diagnosis of HFpEF. Pediatric and adult dilated cardiomyopathy patients display distinct biomarker profiles, and pediatric-specific biomarkers may be more useful in future [131].

Cardiac Catheterization

Cardiac catheterization measurements of elevated PCWP, which reflects LV filling pressure, can diagnose HFpEF at rest but may be more apparent after an intravenous fluid challenge. In the early stages of LVDD, mildly elevated LVEDP is the only abnormality noted. With tachycardia and/or increased LV afterload with intravenous Dobutamine, mean PCWP and LA pressure increase becomes more prominent, providing the basis for the diastolic stress test. Changes in PCWP, an indirect estimate of LV diastolic pressure, during exercise can be assessed by right heart catheterization through the right internal jugular vein. Right heart catheterization is also useful to differentiate between pre-, post-, and mixed-type PH. Hemodynamics including mean PA pressure, diastolic PA pressure, pulmonary vascular resistance, and vasodilator testing are crucial for the management of PH associated with HFpEF.

Left heart catheterization measures the time constant, tau (τ), representing the LV relaxation delay. When the log of the diastolic pressure is plotted as a time function, τ is equal to the inverse of the slope of this linear relationship. When $\tau > 48$ ms, it reflects significant LVDD. Thus, τ is considered the best index for evaluating LV relaxation [132]. However, performing a cardiac catheterization is an invasive procedure, and serial cardiac catheterization is not suitable for clinical surveillance for HFpEF in children.

Echocardiography

Echocardiography is the primary testing modality for diagnosing LVDD in children. Based on the conventional pulsed Doppler study of the mitral inflow, there are four phases of diastole: Phase1: isovolumic relaxation, Phase 2: Rapid passive filling (E wave), Phase 3: Slow filling and mild stasis, and Phase 4: Active filling (A wave) due to atrial contraction. According to the 2016 American Society of Echocardiography (ASE) guidelines for adults, four variables are obtained to assess LVDD: E′ velocity, E/E′ ratio, LA volume indexed to body surface area, and tricuspid regurgitation peak velocity [133]. The 2016 ASE criteria have simplified the echocardiographic assessment of diastolic function and reduced inconclusive diagnoses [134]. However, the adult echocardiographic guidelines are yet to be validated in children with cardiomyopathy and CHD [135, 136].

Tissue Doppler Imaging

The LV diastolic function is better determined by TDI evaluating the longitudinal movement at the mitral, tricuspid, and septal annulus levels, calculating early (E') and late diastolic (A') velocities, respectively. Normal TDI parameters for children are available for comparison [25]. TDI-Based myocardial deformation imaging evaluate LV stiffness and LVDD in children with CHD. Lateral E:E'/end-diastolic volume (EDV) appeared to correlate well with LVEDP obtained by simultaneous cardiac catheterization in pediatric patients after Fontan Surgery [137]. TDI has also been proven to be helpful in children with dilated cardiomyopathy to predict cardiac events [138, 139], characterize LV diastolic function in LV non-compaction cardiomyopathy in children [140, 141], estimate filling pressures in HCM and RCM in both children and adults [142–145], and to distinguish RCM from constrictive pericarditis in children and adults [146, 147].

Speckle Tracking Echocardiography

In adult patients, two-dimensional STE has been applied to assess LA function, and LA strain (LAS) has recently been proposed as a novel technique to be used in clinical practice [147–149]. Strain imaging aims to provide a high-resolution, real-time measure of LV contractility and relaxation in children with normal loading conditions [150–152]. Strain imaging can be used to distinguish between restrictive cardiomyopathy and constrictive pericarditis [153], as well as helping to distinguish the athletic heart from HCM [154]. The three-dimensional STE has proven to be a relatively accurate and efficient method for assessing early abnormalities in LV systolic deformation (peak LV global longitudinal, circumferential, and radial strain); abnormalities in strain analysis are known to predict adverse outcomes in HFpEF [155, 156]. Diastolic strain and strain rates measured by STE are reduced in adult patients with HFpEF [157]. The STE

imaging has also been shown to correlate with invasively measured pressure–volume loops, which might achieve an accurate diagnosis [157, 158]. Some data are available on LAS in children to be helpful for the assessment of LV filling pressures and LVDD [159, 160]. All components of the LAS decline modestly with age. Ghelani et al. have reported normative data for 3-dimensional echocardiography-derived LAS, which may be very useful in comparing LAS obtained in children with HFpEF [161].

Cardiac Magnetic Resonance (CMR) Imaging

CMR imaging is the modality of choice in diagnosing and following up cardiomyopathy patients. Myocardial tissue characterization enables the evaluation of the presence and extent of myocardial fibrosis [162, 163]. After administration of intravenous gadolinium-based contrast, late gadolinium enhancement (LGE) is the gold standard noninvasive tool for detecting focal areas of fibrosis and myocardial disarray. The LGE may not detect diffuse myocardial fibrosis. Parametric tissue mapping with myocardial T1 relaxation time and extracellular volume evaluation helps detect diffuse fibrosis even in the absence of focal LGE [162].

The abnormalities in LGE, T1 relaxation times, and extracellular volume are vital findings in differentiating HCM from athlete's heart or hypertensive heart disease [163]. In asymptomatic or mildly symptomatic HCM patients, the presence of LGE was associated with ventricular arrhythmia detected on Holter monitoring [164]. With better visualization, CMR can assess additional phenotypic features such as septal hypertrophy, apical hypertrophy, sigmoidal and reverse curve HCM, involvement of specific LV segments, involvement of papillary muscles, presence of myocardial crypts, aneurysm, presence of dynamic LVOT obstruction and LA dilation. CMR is also the gold standard in assessing LA and LV volumes, biventricular function, and LV myocardial mass [165]. Specifically, maximum wall thickness, focal or diffuse fibrosis, LVOT obstruction, and LV mass are markers for risk stratification in HCM. Quantification of LGE (% of myocardial mass involved) provides additional prognostic values. Every 10% increase in LGE was associated with a 36% relative risk for sudden cardiac death. CMR evidence of myocardial fibrosis with T1 imaging in Fontan patients relates to DD, increased liver stiffness, and elevated circulating fibrosis biomarkers [42]. The CMR with T2* imaging is helpful as a noninvasive diagnostic tool for quantifying myocardial iron overload in children with hemochromatosis [166]. Hence, multimodality imaging such as echocardiography and CMR provides important information to assess the etiology of HFpEF.

Chronic hypoxemia, altered loading conditions, and genetic predisposition have been linked to diffuse myocardial fibrosis in CHD [167]. The application of CMR is crucial in evaluating DD in children with CHD, such as TOF [168], single ventricle physiology with systemic RV [169], after Fontan [170], and congenital aortic valve stenosis [171]. While the pediatric CMR community is moving toward implementing parametric mapping, challenges remain, the most important being the lack of standardization in pediatric parametric mapping. However, the Society of CMR has published a consensus recommendation in its 2020 update on reporting results of parametric mapping in clinical practice [172].

Treatment of HFpEF in Children

The treatment for HFpEF in children is extrapolated from adult clinical trials and is predominantly used for symptomatic relief. Diuretics are commonly used to relieve congestion in HFpEF. Large clinical trials testing neurohormonal inhibition failed to reach positive outcomes in children [107–109]. Theoretically, an ideal drug should facilitate myocardial relaxation and improve ventricular compliance. The drug should relieve congestion, increase cardiac output, improve quality of life, and decrease hospitalization and cardiac-related events, including death or heart transplantation. However, currently, there is no such ideal pharmacological agent available.

Lifestyle factors such as poor diet, obesity, lack of physical activity, smoking, heavy alcohol consumption, and increased emotional stress likely contributes for development of the HFpEF in the younger age group [173]. Physical inactivity and poor cardiopulmonary fitness are modifiable risk factors. Exercise training and rehabilitation have been proven helpful in both HFpEF and HFrEF. Treatment of HFpEF must include lifestyle changes and management of comorbidites such as hypertension, diabetes, obesity, chronic renal failure, anemia, and chronic obstructive pulmonary diseases. The noncardiac comorbidities cause a chronic systemic inflammatory response and increase oxidative stress, are major factors that promote the development of HFpEF pathologies.

In children who receive cancer therapy, it is crucial to identify patients at high risk of cardiotoxicity. Early detection of systolic dysfunction or DD after initiation of cancer therapy with the use of newer echocardiographic modalities and use of cardioprotectives such as dexrazoxane in high-risk cancer patients will help minimize cardiac dysfunction. Oncology patients should be referred to cardiology for evluation and treatment for cardiac dysfunction before, during and after chemotherapy.

While most HFpEF treatment predominantly blocks neuroendocrine activation, newer therapies target inflammation

and oxidative stress pathways and may be more effective in the future.

Pharmacologic Therapy

Diuretics are commonly used to relieve congestion in HFpEF. Betablockers are helpful by decreasing heart rate, and increasing diastolic duration and reducing myocardial oxygen consumption in patients with HFpEF [174]. Milrinone is a phosphodiesterase-3 inhibitor, that increaes cAMP, enhances myocardial contractility, promotes myocardial relaxation and increases cardiac output. Prophylactic intravenous use of high-dose milrinone after cardiac surgery in children significantly reduced the prevalence of low cardiac output syndrome [175]. Angiotensin-converting enzyme inhibitors [176], angiotensin receptor blockers [177], and calcium channel blockers [177–180] are only of limited use for symptomatic relief in pediatric HFpEF. However, spironolactone may be effective in HFpEF treatment [180–184]. The beneficial effect of spironolactone may be due to the afterload reducing impact, changes in serum electrolytes (potassium-sparing effect), reduction in LV mass, and the anti-fibrotic action on the myocardium. New therapies have been developed to interfere with the mediator pathways of HFpEF at the cellular and molecular level, including soluble guanylate cyclase modulators and angiotensin receptor-neprilysin inhibitors (ARNI) [185, 186]. ARNI is highly beneficial in treating adult HFrEF patients, but the PARAGON-HF trial revealed that it does not significantly lower the rate of total hospitalizations for HF and death from cardiovascular diseases in HFpEF patients [187]. A new class of sodium glucose transporter protein 2 (SGLT2) inhibitor drugs is beneficial in various trials in adults across the HF spectrum, including HFpEF [188].

Surgical Therapy

In pediatric patients with CHD, acquired, and congenital myopathies presenting with HF, the treatment should be directed at the underlying etiology and precipitant causes and individualize the therapeutic approach. For those with valvular diseases causing volume overload, such as in TOF, early intervention, including pulmonary valve replacement, may be beneficial. A similar strategy should be used for chronic aortic or mitral regurgitation associated with LV dysfunction. Pediatric patients with LVOT obstructive lesions causing LV hypertrophy and dysfunction would benefit from surgical or interventional catheterization relief of the mechanical obstruction. Restrictive cardiomyopathy is usually progressive and may need earlier consideration for cardiac transplantation. Patients with HCM may benefit from the ease of relief of outflow obstruction through pharmacological or surgical interventions and automated internal cardioverter placement to prevent sudden death due to cardiac arrhythmias. Constrictive pericarditis is a form of HFpEF as a fibrotic, thickened, and adherent pericardium restricts the diastolic filling of the heart. The symmetrical constricting effect of the pericardium results in elevation and equilibrium of diastolic pressures in all four cardiac chambers. Surgical resection of the pericardium results in hemodynamic and symptomatic improvement in patients with constrictive pericarditis. The role of left ventricular assist devices (LVAD) is limited in pediatric patients with HFpEF [189, 190]. Prior studies in children reported that when LVAD was used in HF patients due to HCM or RCM, their mortality rate was comparable to those with dilated or ischemic cardiomyopathy [191]. However, complications including right heart failure, prolonged inotropic use, and central venous catheter infections are more common in patients with RCM and HCM treated with LVAD [191, 192].

While LVAD implantation is technically feasible in patients with severe restrictive physiology and HFpEF, it requires additional thoughts for patient selection, cannulation strategy, and monitoring for PH and RV failure. Patients may also have a small LV cavity in HCM and RCM, raising concern for inflow obstruction and suction events with typical LV apex cannulation [193]. Also, in the HCM and RCM patients, apical cannulation may not be ideal due to contraction around the inflow cannula compromising flow. Alternatively, atrial cannulation may be considered. This strategy also avoids ventriculotomy and cardiopulmonary bypass [194].

Conclusions

The increase in LVEDP represents the final common pathway to HF in children, either due to HFpEF or HFrEF. However, importantly, there may be a rapid progression of PH and RV failure with HFpEF. For this reason, the evaluation of LV diastolic function in children is an important first stage in diagnosis, monitoring of therapy, and prognosis in HFpEF. Echocardiography is the primary tool to assess LVDD. However, heterogeneity of pediatric patient diagnoses, age at presentation, and anatomy of CHD require pediatric-specific DD criteria for early diagnosis of HFpEF in children. To better define pediatric HFpEF, pediatric cardiologists should use CMR imaging modalities and novel echocardiographic parameters, including STE, TDI, and LAS, that may reliably predict prognosis and avoid those twin traps of either overtreatment or therapeutic nihilism. There is a need for research to organize multicenter studies to standardize the newer echocardiographic modalities and CMR imaging criteria to diagnose pediatric HFpEF. In conclusion, a significant understanding of the basic mechanisms of pediatric LVDD and therapies for adults with HFpEF

exists. Clinical trials evaluating adult HFpEF therapies in children are needed to establish their safety and efficacy. Until then, diuretics remain as mainstay of therapy for symptomatic treatment reducing symptoms of congestion in children with HFpEF.

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Declarations

Conflict of interest The authors declare no competing interests.

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