



**HAL**  
open science

# Pediatric heart failure with preserved ejection fraction, a review

Sophie Quennelle, Damien Bonnet

► **To cite this version:**

Sophie Quennelle, Damien Bonnet. Pediatric heart failure with preserved ejection fraction, a review. *Frontiers in Pediatrics*, 2023, 11, 10.3389/fped.2023.1137853 . hal-04191461

**HAL Id: hal-04191461**

**<https://hal.science/hal-04191461>**

Submitted on 30 Aug 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

## Pediatric Heart Failure with Preserved Ejection Fraction, a review.

1 **Quennelle Sophie<sup>1,2,3</sup>, Bonnet Damien<sup>1,3</sup>**

2 <sup>1</sup>M3C-Necker, Hôpital Universitaire Necker-Enfants malades, Assistance Publique-Hôpitaux de Paris  
3 (AP-HP), Paris, France

4 <sup>2</sup>HeKA Team, Inria-Inserm UMR\_S1138, Paris, France

5 <sup>3</sup> Université de Paris Cité, Paris, France

6 **\* Correspondence:**

7 Corresponding Author

8 sophie.quennelle@aphp.fr

9 **Keywords: Heart failure with preserved ejection fraction<sub>1</sub>, Diastolic heart failure<sub>2</sub>, Pediatric<sub>3</sub>,**  
10 **Child<sub>4</sub>, Cardiomyopathy<sub>5</sub>, Pulmonary hypertension<sub>6</sub>. (Min.5-Max. 8)**

### 11 **List of abbreviation**

12 CMRI: cardiac magnetic resonance imaging

13 CPH: combined postcapillary and precapillary pulmonary

14 FCW: forward compression wave

15 FEW: forward expansion wave

16 DT: mitral E wave deceleration time

17 HCM: hypertrophic cardiomyopathy

18 DCM: dilated cardiomyopathy

19 HFpEF: heart failure with preserved ejection fraction

20 IPH: isolated postcapillary pulmonary hypertension

21 IVRT: isovolumic relaxation time

22 LV: left ventricular

23 LVEDP: left ventricular end diastolic pressure

24 MISC: Multisystem Inflammatory Syndrome in Children

25 NT-proBNP: N-terminal pro-B-type natriuretic peptide

26 PH: pulmonary hypertension

27 PVR: pulmonary vascular resistance

28 RCM: restrictive cardiomyopathy

29 TTE: transthoracic echocardiography

### 30 **Abstract**

31 Diastolic dysfunction refers to a structural or functional abnormality of the left ventricle, resulting in  
32 impaired filling of the heart. Severe diastolic dysfunction can lead to congestive heart failure even  
33 when the left ventricle systolic function is normal. Heart failure with preserved ejection fraction  
34 (HFpEF) accounts for nearly half of the hospitalizations for acute heart failure in the adult population  
35 but the clinical recognition and understanding of HFpEF in children is poor. The condition is  
36 certainly much less frequent than in the adult population but the confirmatory diagnosis of diastolic  
37 dysfunction in children is also challenging. The underlying causes of HFpEF in children are diverse

38 and differ from the main cause in adults. This review addresses the underlying causes and prognostic  
39 factors of HFpEF in children. We describe the pulmonary hypertension profiles associated with this  
40 cardiac condition. We discuss diagnosis difficulties in clinical practice, and we provide a simplified  
41 diagnostic algorithm for HFpEF in children.

## 42 **1 Introduction**

43 Left Ventricular (LV) diastolic function plays an important role in determining the kinetics and  
44 quality of ventricular filling and thereby also the stroke volume. It can be defined as the capacity of  
45 the heart to relax and distend during diastoles leading to fulfilling of the LV chamber up to an  
46 appropriate telediastolic volume. Diastolic dysfunction is defined by the incapacity of the ventricle to  
47 fill in even if the atrial pressure is normal. Diastolic dysfunction might be due to a prolonged  
48 relaxation or/and an increased stiffness of the ventricle (1). The normal functioning of the left  
49 ventricle during diastole involves the relaxation of its walls, allowing for the ventricle to expand and  
50 accommodate incoming blood. This is facilitated by the normal functioning of muscle cells within  
51 the ventricle, which contract during systole and then relax during diastole. However, in diastolic  
52 dysfunction, the relaxation of the ventricular walls is impaired or slowed, resulting in decreased  
53 filling of the left ventricle. At a cellular level, relaxation of the left ventricle during diastole is  
54 enabled by the detachment of actin-myosin cross bridges, which occurs after calcium uptake by the  
55 sarcoplasmic reticulum, leading to a decrease in cellular tension. It is the main protein that's  
56 modulates myocyte stiffness. Additionally, the increased stiffness of the ventricular walls, due to  
57 conditions such as fibrosis or hypertrophy, can also contribute to diastolic dysfunction by limiting the  
58 ventricle's ability to expand and accommodate blood. Chamber stiffness is primarily determined by  
59 the stiffness properties of the sarcomeres, the interstitial space, and LV chamber geometry and wall  
60 thickness (1). Another component that influences LV filling and diastolic pressures is elastic recoil.  
61 Early diastolic recoil, is the ability of the left ventricle to "snap back" into its relaxed state, it  
62 contributes to the quick decrease in LV pressure during isovolumic relaxation time (IVRT). In  
63 diastolic dysfunction, this recoil may be delayed or reduced, further impeding the ventricle's ability  
64 to fill with blood during diastole. Titin plays an important role in LV expansion. It is an elastic  
65 protein that assembles sarcomere unity and acts as an elastic spring that is squeezed during systole  
66 and recoils during diastole (2). Left atrial pressure, is closely related to LV pressure and is used as a  
67 surrogate marker of LV filling pressures. During diastole, when the LV is filling with blood, the  
68 pressure within the LV pressure increases. This increased pressure is then transmitted backwards into  
69 the left atrium, resulting in an increase in left atrial pressure. Therefore, in conditions where LV  
70 diastolic function is impaired, there is an associated increase in LAP, reflecting the elevated filling  
71 pressures within the LV.

72 Today, the commonly used definition is heart failure with a left ventricle ejection fraction  
73 (LVEF) >50% associated with evidence of spontaneous or provokable increased left ventricle (LV)  
74 filling pressures (2). There is a thin line between HFpEF and diastolic dysfunction as patients with  
75 LV diastolic dysfunction are often asymptomatic at rest but experience limitations during exercise.  
76 Clinical presentations of HFpEF rank from acute heart failure to shortness of breath during effort.  
77 While adults are able to describe the onset or worsening of shortness of breath after having  
78 experienced well-tolerated efforts in the past, poor exercise tolerance in a child could be difficult to  
79 identify.

## 80 **2 Epidemiology**

81 LV diastolic dysfunction has been well studied and described in adults as HFpEF accounts for at least  
82 half the patients diagnosed with heart failure (3). Risk factors in adults include age, obesity,  
83 hypertension, coronary artery disease and diabetes mellitus (4,5). However, comprehensive studies  
84 were conducted on elderly diabetic and hypertensive patients (6–8) and do not reflect diastolic  
85 dysfunction epidemiology and physiopathology in the pediatric population. Indeed, insights on the  
86 epidemiology and causes of HFpEF in children are scarce. There are few studies that evaluated the  
87 LV diastolic function in children (9–11) and diastolic function screening is challenging in routine  
88 pediatric cardiologist’s evaluation (12). As a consequence, HFpEF prevalence in children is unknown  
89 and probably underestimated. Pan and al. (10) reported 421 children suffering from diastolic heart  
90 failure. This large cohort was collected between 2004 to 2014 at the Children’s Hospital of  
91 Chongqing Medical University. Among a series of 3,907 pediatric hospitalizations in a cardiology  
92 department that were retrospectively reviewed, only 18 patients were considered as having HFpEF  
93 (0.5%) (11).

### 94 **3 Physiopathology**

95 HFpEF is a heterogeneous group of diseases characterized by symptoms of heart failure due to  
96 increase in myocardial stiffness. The physiology and cellular mechanism of HFpEF depends on the  
97 cause and involves, among other things, cardiac hypertrophy and fibrosis (13), intrinsic myocardial  
98 dysfunction (14) impaired calcium handling (15), titin stiffening (16), inflammatory state (17), large  
99 and small vessels disease (18).

100 In restrictive cardiomyopathy (RCM), LV wall thickness is more often within normal limits  
101 and for Gewillig the pathophysiology of RCM is related to myocyte abnormality such as myocyte  
102 hypertrophy, enlarged, irregular and hyperchromatic myocyte nuclei (19). Genetic disorders leading  
103 to intracellular accumulation of substances such as Anderson Fabry disease (20), Danon disease (21),  
104 iron overload cardiomyopathy (22) are examples of myocyte induced restrictive physiology.

105 In the study of Lombardi and al. (23), a linear correlation between aortic elasticity and LV  
106 diastolic function was observed, which raises the hypothesis that, just like in the elderly population,  
107 aortic vascular stiffness leads to LV diastolic dysfunction. Indeed, with increased vascular stiffness,  
108 the systolic pulse wave velocity is increased and, thus, the reflected wave returns to the heart earlier,  
109 during late systole increasing late systolic afterload, which affects thick-thin myofilament  
110 interactions and crossbridge dissociation, leading to impaired relaxation.

111 Interstitial myocardial fibrosis also plays a role in the pathogenesis of the LV diastolic  
112 dysfunction as it increases ventricular rigidity and compromise the stretching capability of the  
113 myofibrils (24). Collagen is a key component of the myocardial extracellular environment, and  
114 increased collagen deposition alters myocardium viscoelasticity, impairing relaxation, diastolic  
115 recoil, and passive stiffness (25). Fibrosis is a common endpoint of myocardium pathologic processes  
116 such as chronic ischemic heart disease of myocarditis.

### 117 **4 Etiology**

118 The causes of LV diastolic dysfunction in children differs substantially from the classical risk factors  
119 identified in adults, intrinsic myocytes abnormality seems to be the leading cause of diastolic  
120 dysfunction in children. Primary cardiomyopathies are diseases of the heart muscle in which the  
121 myocardial dysfunction appears in the absence of systemic comorbidities, valvular or congenital  
122 heart disease (26). Hypertrophic, dilated, and restrictive cardiomyopathies are primary  
123 cardiomyopathies that can lead to diastolic dysfunction. There are two major clinical categories of

124 LV diastolic dysfunction in children : congenital, related to a genetic or metabolic disorder and  
125 acquired i.e. secondary to another cause (27). In this review, we choose not to describe transitory  
126 diastolic dysfunction related to congenital heart defect as it almost always resolves after cardiac  
127 surgery.

128 4.1- Congenital: genetic hypertrophic, restrictive cardiomyopathies, inherited infiltrative  
129 cardiomyopathies

130 Dilated cardiomyopathy (DCM) is defined by the presence of a dilated LV with systolic  
131 dysfunction without any hemodynamic, physiological, ischemic or anatomic cause (28). DCM  
132 accounts for around 50% of the pediatric cardiomyopathy cases (26). Patients suffering from DCM  
133 present at first heart failure with reduced ejection fraction, but progression of cell death and extension  
134 of fibrosis of the LV often lead to diastolic dysfunction. Occurrence of diastolic dysfunction with  
135 elevated filling pressures is associated with poor prognosis in these conditions (29).

136 Hypertrophic cardiomyopathy (HCM) is defined by an hypertrophied and non-dilated  
137 ventricle in the absence of a hemodynamic cause of wall thickening, excluding physiological  
138 hypertrophy (secondary to physical activity) and pathological hypertrophy (secondary to aortic  
139 coarctation, aortic valvular stenosis, hypertension) (28). HCM is the second most common pediatric  
140 cardiomyopathy (40% of patients) (26). Diastolic function impairment is common and of variable  
141 severity. Impaired calcium handling, myocyte hypertrophy and disarray, ischemia and fibrosis are the  
142 etiologies of diastolic dysfunction (30).

143 Diastolic dysfunction has been described mainly in children suffering from restrictive  
144 cardiomyopathy, accounting for less than 5% of pediatric cardiomyopathy cases (19,26). Leading  
145 mutations associated with restrictive cardiomyopathy are MYH7, TNNT3, TNNT2, MYL2, and DES  
146 (31). Restrictive cardiomyopathies may also be secondary to systemic diseases including infiltrative  
147 disorder, collagen-vascular diseases (9), neoplastic process (32), thoracic irradiation and  
148 chemotherapy, bone marrow transplantation (26,32,33), and endomyocardial disease with or without  
149 eosinophilia resulting in fibrosis of the endocardium. Left heart obstruction such as coarctation and  
150 aortic stenosis can result in restrictive physiology of the left ventricle that persists after  
151 repair(18,34,35). The common mechanism in these cardiomyopathies is the increasing myocardial  
152 stiffness, which decreases compliance.

153 4.2- Acquired: relaxation abnormalities secondary to cardiac remodeling and fibrosis reducing  
154 relaxation capacity.

155 LV diastolic dysfunction has been described in patients with aortic coarctation or aortic  
156 stenosis (18,23,24,35) even after successful repair. In the study of Moskowitz and al. (35), altered LV  
157 relaxation was found in children with successful coarctation repair and late diastolic filling pressures  
158 were influenced by LV mass suggesting that hypertrophy rather than increased afterload is the  
159 primary determinant of the impaired LV diastolic function.

160 Some extrinsic factors have also been described in children such as inflammatory diseases :  
161 acute myocarditis (36), Kawasaki shock syndrome (37), and more recently Multisystem  
162 Inflammatory Syndrome in Children (MISC) due to severe acute respiratory syndrome coronavirus 2  
163 (SARS-CoV-2) (38). Graft rejection is also a cause of LV diastolic dysfunction in pediatric heart  
164 recipients (39,40). Myocardial edema secondary to the inflammation causes the impaired ventricular  
165 compliance.

166 Transient LV diastolic dysfunction can be observed in acute contexts such as tachycardia,  
167 during the early post-operative period or during sepsis. It is important to note that at birth (during the  
168 first 7 days / the first two months for preterms) the diastolic properties of the LV are significantly  
169 impaired without pathological significance.

170 As for adults, renal insufficiency (41–44) and obesity are risk factors for diastolic dysfunction  
171 (45,46). Restrictive physiology of the left ventricle has also been described in infants of mothers with  
172 gestational diabetes (47–49). Other acquired conditions include deposition diseases that reduce  
173 ventricular compliance (e.g.: iron infiltration) (22).

## 174 **5 Clinical presentation**

175 In some cases, diastolic dysfunction may not cause any symptoms and may only be suspected during  
176 a routine echocardiography. In other cases, it can cause symptoms such as shortness of breath,  
177 atypical asthma, and syncope. The clinical signs that may suggest the presence of diastolic  
178 dysfunction include increased jugular venous pressure, hepatomegaly, oedema and ascites (19). Lack  
179 of appetite, fatigue and infection susceptibility are markers of heart failure exacerbation.  
180 Electrocardiogram (EKG) findings are generally not specific for diastolic dysfunction. Electric signs  
181 of left atrial enlargement, biatrial hypertrophy, abnormal Q wave or pseudoinfarct pattern,  
182 repolarization abnormalities such as the T wave notched or biphasic can be noted (19). Chest X-ray  
183 can show pulmonary venous congestion, and, depending on the underlying cardiac condition,  
184 cardiomegaly (19). These symptoms are not specific and may be related to left ventricular systolic  
185 dysfunction which makes the diagnosis even more difficult.

## 186 **6 Pulmonary hypertension**

187 Group 2 pulmonary hypertension includes PH associated with left heart disease including HFpEF,  
188 heart failure with reduce ejection fraction, valvular heart diseases and congenital heart diseases.  
189 Despite similar hemodynamic profiles, there are significant disparities between these patients' groups  
190 in terms of comorbidities and clinical phenotypes (50). The hemodynamic definition of group 2 PH  
191 was proposed during the 6th World Symposium on PH as a mean pulmonary artery pressure of > 20  
192 mm Hg and a pulmonary artery wedge pressure of > 15 mm Hg (51). HFpEF associated with PH can  
193 be subdivided into isolated postcapillary pulmonary hypertension (IPH) and combined postcapillary  
194 and precapillary pulmonary hypertension (CPH). The diagnosis is based on the pulmonary vascular  
195 resistance (PVR) measurement during RHC: < 3 Wood units (WU) for IPH or  $\geq 3$  WU for CPH. This  
196 distinction is crucial since it influences therapeutic strategies (52). The pathophysiologic mechanisms  
197 in HFpEF associated with PH have been well described in adults. Abnormal relaxation and increased  
198 stiffness of the LV lead to an increase in LV and left atrial pressure (53). Left atrial elevated  
199 pressures expose the lung pulmonary veins to elevation in pressure (54) and cause the stress failure of  
200 the alveolar-capillary junction resulting in pulmonary edema and inflammation. Inflammatory  
201 mediators increase endothelin-1 depression and decrease nitric oxide and natriuretic peptide activity.  
202 The fibroblast proliferation is activated and leads to the occlusion of the lumen and thickening of the  
203 alveolar septa (55). This structural remodeling associated with lung edema compresses small lung  
204 arterioles and induces precapillary PH. Thus, with progress of the diastolic disease PH can evolve  
205 from a postcapillary to a combined PH (pre and postcapillary). The pulmonary hemodynamic profiles  
206 in HFpEF have received little attention but the development of PH with elevated pulmonary vascular  
207 resistance in HFpEF is recognized as an important contributor to morbidity and mortality. PH  
208 profiles has not yet been studied in pediatrics HFpEF patients but PH has been well described in  
209 children suffering from RCM as a relevant proportion of them developed CPH unresponsive to

210 vasodilator testing and precluding them from orthotopic heart transplantation (56). Up to half of the  
211 RCM children have PH at diagnosis (57) it is a factor of poor prognosis and therapeutic solution are  
212 scares (58).

## 213 **7 Diagnostic**

214 The clinical recognition and understanding of heart failure with preserved ejection fraction in  
215 children is poor. This might be because it is a rare condition but also because the diagnosis of  
216 diastolic dysfunction in children is difficult in clinical practice. The symptoms may be subtle and can  
217 vary depending on the severity of the condition. The consensual definition of HFpEF is the presence  
218 of signs and symptoms of heart failure, a LV ejection fraction >50% associated with evidence of  
219 spontaneous or provokable increased LV filling pressure (3).

220 The gold standard to characterize LV relaxation is cardiac catheterization. A high-fidelity  
221 catheter placed into the LV measure simultaneously LV volumes and pressure. The LV pressure-  
222 volume loops reflects the filling and contractile properties of the ventricle (5). The commonly  
223 measured parameters are (1) Time constant of relaxation ( $\tau$  or  $\tau$ ) that reflects the rate of decline of  
224 LV pressure during the isovolumic relaxation period (IVRT). Normal duration of  $\tau$  is 30-40ms (1).  
225 (2) Pulmonary capillary wedge pressure (PCWP) is the pressure measured in the pulmonary artery  
226 during diastole, which reflects the pressure in the left atrium and left ventricle. (3) Left ventricular  
227 end-diastolic pressure (LVEDP) is the pressure measured directly within the left ventricle at the end  
228 of diastole. Also, rapid saline loading during RHC can be used to assess the response of the LV and  
229 further elucidate the pathophysiology of heart failure (59). Indeed, an increase in PCWP in response  
230 to an increased afterload may suggest that diastolic dysfunction is related to increased ventricular  
231 stiffness.

232 Because of its invasive nature, technical complexity, and cost, heart catheterization is  
233 impractical for the routine evaluation of the LV filling pressures that are almost always estimated by  
234 transthoracic echocardiography (TTE). The H2FPEF (60) and the HFA-PEFF diagnostic algorithm  
235 (61) have been proposed to evaluate LV filling pressure in adults but precise thresholds are missing  
236 in the pediatric population (12). Indeed, in children, tachycardia and pediatric particularities make  
237 Doppler measurements challenging and adults cut-off values for these various parameters are  
238 inappropriate (62). Former studies attempted to determine specific TTE parameters to facilitate LV  
239 End Diastolic Pressure (LVEDP) estimation (63,64). Dragulescu and al. found that the mitral E wave  
240 deceleration time (DT) ( $153\pm 23$ ms in control patient vs.  $97\pm 27$ ms in RCM patients) and the mitral  
241 lateral peak early diastolic tissue velocity (normal if > 11cm/s) were the most discriminating  
242 parameters (12). Peak late diastolic mitral velocities (A) vary significantly throughout childhood, this  
243 impacts the peak early to late diastolic filling velocity (E/A) ratio and this parameter should not be  
244 considered without taking into account the patient's age (65). In contrast, the isovolumic relaxation  
245 time appeared stable with age which makes it an excellent parameter in children. Sasaki and al.  
246 compared the echocardiographic findings of 9 RCM patients with 27 controls and concluded that the  
247 left atrial size distinguished patients with and without diastolic dysfunction with the least overlap as  
248 the indexed left atrial area was significantly larger in RCM group: median 22.8 cm<sup>2</sup>/m<sup>2</sup> (range 16.9–  
249 28.6) versus 10.3 cm<sup>2</sup>/m<sup>2</sup> (range 8.3–12.3) in the control group (66). By providing quantitative  
250 analysis of LV longitudinal function speckle tracking-derived global longitudinal strain (GLS) is  
251 accurate in early detection of subclinical alterations in LV longitudinal function (63). There is not  
252 clear threshold for normal GLS in children (64). In the study of McAree and al. (67), it appears that  
253 patients suffering from MISC presented a lower mean GLS than controls (- 20.4 ( $\pm 2.8$ ) vs -22.0  
254 ( $\pm 1.9$ )).

255 The B-type natriuretic peptide (BNP) and its pro-hormone NT-proBNP (N-terminal pro-B-  
256 type natriuretic peptide) is produced by the ventricles in response to increased pressure or volume  
257 loads. It is typically released when the myocytes are stretched or under stress (68) NT-proBNP levels  
258 can be elevated in children with left ventricular diastolic dysfunction because the increased pressure  
259 or volume in the heart leads to the release of NT-proBNP. Higher levels of NT-proBNP can therefore  
260 be a marker of diastolic dysfunction and may be used to help diagnose this condition. However, NT-  
261 proBNP levels are dependent on age and, to a lesser extent, on gender in the pediatric population. In  
262 the review of Nir and al. (69), the data from four studies which included patients who had NT-  
263 proBNP dosage for other reasons than heart failure was concatenated, taking the 95th percentile as  
264 the upper limit for normal. They proposed the normal NT-proBNP threshold for age (reported in  
265 Table 1). Inspired by H2FPEF (60) and the HFA-PEFF diagnostic algorithm (61) that is used in  
266 adults, we propose a stepwise diagnosis approach that is a compilation of published criteria (Table 1).  
267 Another pertinent biomarker is aldosterone, indeed, in the study of Masutani and al. (11) the  
268 aldosterone/BNP ratio was markedly higher in HFpEF patients than in HFrEF patients ( $38\pm 63$  vs.  
269  $1.7\pm 1.9$ ,  $P<0.05$ , Figure 1A) and “ROC curve analysis showed that an aldosterone/BNP ratio of 10.3  
270 or higher best predicted HFpEF (area under the curve [AUC]=0.89), with a sensitivity of 0.67 and  
271 specificity of 1.0.”

272

273 Cardiac magnetic resonance imaging (CMRI) is a non-invasive imaging modality that can  
274 provide valuable information about the structure and function of the heart. By providing details about  
275 myocardial phenotype such as the localization of the myocardial hypertrophy (septal or apical) in  
276 HCM or the specific myocardial composition such as the presence fibrosis, edema, fat, iron overload  
277 (by T2\* imaging) in patients with hemochromatosis (70) CMRI is helpful to access the etiology of  
278 HFpEF. CMRI allows myocardial tissue characterization and fibrosis extension which makes it the  
279 modality of choice in diagnosing and following up cardiomyopathies. Indeed, the administration of  
280 intravenous gadolinium based contrast is the gold standard to locate and quantify the extension of the  
281 myocardial fibrosis (71). In the absence of focal LGE, T1 relaxation times and extracellular volume  
282 evaluation confirm the diagnosis of diffuse fibrosis (72). The extend of myocardial fibrosis estimated  
283 by late gadolinium enhancement (LGE) significantly correlates with the degree of diastolic  
284 dysfunction (25). Quantification of fibrosis, maximum wall thickness, and LV mass are markers of  
285 risk for sudden cardiac death that can be obtained by CMRI. Another important feature of CMRI is  
286 its ability to provide information on blood flow patterns in the heart. The analysis of LV filling  
287 velocity and volume flow, of the volumetric assessment of LV and of left atrium makes CMRI an  
288 highly accurate and reproducible noninvasive technique for the assessment of diastolic function (73).  
289 The wave intensity represents the energy flux per unit area that is carried by waves traveling in the  
290 cardiovascular network and derived from CMRI flow data (74). There are two main wave patterns  
291 during systole: the forward compression wave at systolic ejection (FCW) and the forward expansion  
292 wave (FEW) at end systole. The FCW/FEW ratio was significantly lower in patients suffering from  
293 HFpEF as peak FCW was lower in patients with LV diastolic dysfunction. CMRI is helpful in  
294 assessing graft function in pediatric heart transplant recipient (75).

## 295 **8 Clinical course and outcomes**

296 The clinical course of children with diastolic dysfunction varies depending on the underlying cardiac  
297 condition. Global prognosis of HFpEF in children is uncertain especially since this term refers to a  
298 heterogeneous group of patients. There is limited literature on the prognosis of HFpEF in children  
299 beyond the phenotypes of HCM and RCM. No well-defined predictors exist for determining survival



300 after diagnosis but it appears that RCM prognosis is grim due to the risk of sudden death and  
301 progression of pulmonary hypertension leading to early transplantation (76), younger age at  
302 diagnosis, repeated admissions for heart failure, diuretic use and isolated RCM phenotype are risk  
303 factors for death (76,77). In the NHLBI Pediatric Cardiomyopathy Registry, children with RCM who  
304 had congestive heart failure and a lower fractional shortening Z score at diagnosis had the worst  
305 prognosis. The occurrence of LV diastolic dysfunction in patients with dilated cardiomyopathy is a  
306 marker of poor prognosis (29,78) but there are no specific studies in children. Masutani and al. (11)  
307 compared the clinical course of 18 children suffering from HFpEF to 22 children suffering from HF  
308 with reduced EF (HFrEF) and observed that the heart failure mortality rate was significantly lower in  
309 the HFpEF than in the HFrEF patients (22% vs. 41%). Future works should focus on patients with  
310 isolated left ventricular diastolic dysfunction (and preserved ejection fraction) to define the pertinent  
311 predictor of outcome.

## 312 **9 Treatment**

313 It is important for children with left ventricular diastolic dysfunction to receive timely and  
314 appropriate treatment to help prevent any long-term complications. To date, there is no  
315 pharmaceutical drug facilitating myocardial relaxation or improving ventricular compliance. Also,  
316 pharmaceutical treatment for HFpEF in children is extrapolated from adult clinical trials. Lifestyle  
317 management in children includes fighting against obesity and poor diet, blood pressure control and  
318 physical activity. Medical management strategies include diuretics to relieve symptoms of congestive  
319 heart failure. In adults' patients, the precise monitoring of the pulmonary pressures through a device,  
320 the CardioMEMS Heart Sensor, allows for efficient diuretic titration and has proven its benefit in  
321 reducing hospitalization for heart failure in patients suffering from HFpEF (79,80). Beta Blockers  
322 may be useful as they increase diastolic duration by slowing down the heart rate (81). Spironolactone  
323 appears to improve prognosis in obese and diabetic adult patients suffering from HFpEF (15,82) but  
324 these results are not transferable to pediatric patients. Angiotensin-converting enzyme inhibitors and  
325 sartans are prescribed with the intention to treat and prevent both systolic and diastolic dysfunction in  
326 the case of cardiomyopathies and after aortic coarctation repair but there is no evidence of efficacy of  
327 this treatment on the diastolic function. Empagliflozin and sacubitril/valsartan (83) have shown  
328 promising results in adults but data on children are not available yet. To date, no therapeutic trial has  
329 shown any benefit in treating patients suffering from HFpEF associated with PH with pulmonary  
330 arterial hypertension-approved therapies (84). In patients suffering from post-capillary PH and heart  
331 failure symptoms, the atrial flow regulator, an interatrial shunt device that recently became available  
332 proved to be efficient on symptoms and secure including in the pediatric population (85–87).

## 333 **10 Conclusion**

334 HFpEF is a rare and probably under-diagnosed condition in children. It can be caused by a variety of  
335 underlying conditions. Clinical presentation is not specific, and the diagnosis may be difficult. We  
336 proposed a diagnosis algorithm easy to use in clinical practice. Prognosis depends on the cause, but  
337 the appearance of associated hypertension marks a turning point in the evolution of the disease.  
338 Specific treatments are limited.

339

340 **11 Table**

Signs and symptoms of heart failure	Dyspnea, fatigue, low exercise tolerance, lack of appetite, infection susceptibility
Suggestive TTE parameters	LVEF > 50% No other cause of heart failure (absence of shunt or valvular disease) DT < 100ms TRIV < 90ms E' < 11cm/s LE enlargement > 15cm <sup>2</sup> /m <sup>2</sup> Low GLS
Elevated NT pro-BNP levels (by age)	0-2 days > 12000 pg/mL 3-11 days > 6000 pg/mL 1 month - 1 year > 650 pg/mL 1-2 years > 400 pg/mL 2-6 years > 300 pg/mL 6-18 years > 160 pg/mL (69)
Therapeutic testing	Symptoms improved by diuretics
Right heart catheterization	LVEDP > 15mmHg. If doubtful, a rapid saline loading test may sensitive the RHC

341 **Table 1.** Stepwise diagnosis approach for HFpEF in children 198

342 LVEF: left ventricular ejection fraction; DT: mitral E wave deceleration time; IVRT: isovolumic 199  
343 relaxation time; E' sep: peak early diastolic tissue velocity at medial mitral annulus; LAVi: left atrial  
344 200 volume indexed to body surface area; LVEDP: Left ventricular end diastolic pressure; RHC:  
345 right 201 heart catheterization.

346 **12 Conflict of Interest**

347 The authors declare that the research was conducted in the absence of any commercial or financial  
348 relationships that could be construed as a potential conflict of interest.

349 **13 Author Contributions**

350 Sophie Quennelle: analysis and interpretation of the literature, writing original draft.  
351 Damien Bonnet: supervision, critical revision, validation of the final version of the manuscript.

352 **14 References**

- 353 1. Nagueh SF. Left Ventricular Diastolic Function. *JACC: Cardiovascular Imaging*. 2020  
354 Jan;13(1):228–44.
- 355 2. Fukuda N, Terui T, Ishiwata S, Kurihara S. Titin-based regulations of diastolic and systolic  
356 functions of mammalian cardiac muscle. *Journal of Molecular and Cellular Cardiology*. 2010 May  
357 1;48(5):876–81.
- 358 3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022  
359 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American  
360 College of Cardiology/American Heart Association Joint Committee on Clinical Practice  
361 Guidelines. *Circulation*. 2022 May 3;145(18).
- 362 4. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection  
363 fraction. *Nat Rev Cardiol*. 2017 Oct;14(10):591–602.
- 364 5. Nagueh SF. Heart failure with preserved ejection fraction: insights into diagnosis and  
365 pathophysiology. *Cardiovasc Res*. 2021 Mar 21;117(4):999–1014.
- 366 6. Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection  
367 fraction. *Nat Rev Cardiol*. 2021 Jun;18(6):400–23.
- 368 7. Gevaert AB, Boen JRA, Segers VF, Van Craenenbroeck EM. Heart Failure With Preserved  
369 Ejection Fraction: A Review of Cardiac and Noncardiac Pathophysiology. *Front Physiol*. 2019  
370 May 29;10:638.
- 371 8. Arques S, Quennelle F, Roux E. Accuracy of peak mitral e-wave velocity in the diagnosis of  
372 heart failure with preserved ejection fraction in older patients with acute dyspnea. *Annales de*  
373 *Cardiologie et d'Angéiologie*. 2021 Nov;70(5):281–5.
- 374 9. Das BB, Taylor AL, Yetman AT. Left Ventricular Diastolic Dysfunction in Children and Young  
375 Adults with Marfan Syndrome. *Pediatr Cardiol*. 2006 Apr;27(2):256–8.
- 376 10. Pan B, Hu D, Sun H, Lv T, Xu W, Tian J. Pediatric Diastolic Heart Failure: Clinical Features  
377 Description of 421 Cases. *Frontiers in Pediatrics*. 2022;10.
- 378 11. Masutani S, Saiki H, Kurishima C, Ishido H, Tamura M, Senzaki H. Heart Failure With Preserved  
379 Ejection Fraction in Children: – Hormonal Imbalance Between Aldosterone and Brain Natriuretic  
380 Peptide –. *Circ J*. 2013;77(9):2375–82.
- 381 12. Dragulescu A, Mertens L, Friedberg MK. Interpretation of Left Ventricular Diastolic Dysfunction  
382 in Children With Cardiomyopathy by Echocardiography: Problems and Limitations. *Circ:*  
383 *Cardiovascular Imaging*. 2013 Mar;6(2):254–61.
- 384 13. Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy.  
385 *Nat Rev Cardiol*. 2018 Jul;15(7):387–407.
- 386 14. Rapezzi C, Aimo A, Barison A, Emdin M, Porcari A, Linhart A, et al. Restrictive cardiomyopathy:  
387 definition and diagnosis. *Eur Heart J*. 2022 Oct 21;43(45):4679–93.
- 388 15. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Clinical Phenogroups in  
389 Heart Failure With Preserved Ejection Fraction. *JACC: Heart Failure*. 2020 Mar;8(3):172–84.

- 390 16. Zile MR, Baicu CF, Ikonomidis J, Stroud RE, Nietert PJ, Bradshaw AD, et al. Myocardial  
391 Stiffness in Patients with Heart Failure and a Preserved Ejection Fraction: Contributions of  
392 Collagen and Titin. *Circulation*. 2015 Apr 7;131(14):1247–59.
- 393 17. Murdoch CE. Endothelial NADPH Oxidase-2 Promotes Interstitial Cardiac Fibrosis and Diastolic  
394 Dysfunction Through Proinflammatory Effects and Endothelial-Mesenchymal Transition.  
395 2014;63(24):8.
- 396 18. Dusenbery SM, Jerosch-Herold M, Rickers C, Colan SD, Geva T, Newburger JW, et al.  
397 Myocardial Extracellular Remodeling Is Associated With Ventricular Diastolic Dysfunction in  
398 Children and Young Adults With Congenital Aortic Stenosis. *Journal of the American College of*  
399 *Cardiology*. 2014 May;63(17):1778–85.
- 400 19. Gewillig M, Mertens L, Moerman P, Dumoulin M. Idiopathic restrictive cardiomyopathy in  
401 childhood: A diastolic disorder characterized by delayed relaxation. *European Heart Journal*.  
402 1996 Sep 1;17(9):1413–20.
- 403 20. Zarate YA, Hopkin RJ. Lysosomal Storage Disease 3 Fabry's disease. 2008;372.
- 404 21. Yang Z, McMahon CJ, Smith LR, Bersola J, Adesina AM, Breinholt JP, et al. Danon Disease as  
405 an Underrecognized Cause of Hypertrophic Cardiomyopathy in Children. *Circulation*. 2005 Sep  
406 13;112(11):1612–7.
- 407 22. Murphy CJ, Oudit GY. Iron-Overload Cardiomyopathy: Pathophysiology, Diagnosis, and  
408 Treatment. *Journal of Cardiac Failure*. 2010 Nov 1;16(11):888–900.
- 409 23. Lombardi KC, Northrup V, McNamara RL, Sugeng L, Weismann CG. Aortic Stiffness and Left  
410 Ventricular Diastolic Function in Children Following Early Repair of Aortic Coarctation. *The*  
411 *American Journal of Cardiology*. 2013 Dec;112(11):1828–33.
- 412 24. Florianczyk T, Werner B. Assessment of left ventricular diastolic function in children after  
413 successful repair of aortic coarctation. *Clin Res Cardiol*. 2011 Jun;100(6):493–9.
- 414 25. Moreo A, Ambrosio G, De Chiara B, Pu M, Tran T, Mauri F, et al. Influence of Myocardial  
415 Fibrosis on Left Ventricular Diastolic Function: Non-Invasive Assessment by CMR and ECHO.  
416 *Circ Cardiovasc Imaging*. 2009 Nov 1;2(6):437–43.
- 417 26. Choudhry S, Puri K, Denfield SW. An Update on Pediatric Cardiomyopathy. *Curr Treat Options*  
418 *Cardio Med*. 2019 Aug;21(8):36.
- 419 27. D. Knudson J, G. Cabrera A. The Pathophysiology of Heart Failure in Children: The Basics.  
420 *CCR*. 2016 Apr 4;12(2):99–103.
- 421 28. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, et al.  
422 Cardiomyopathy in Children: Classification and Diagnosis: A Scientific Statement From the  
423 American Heart Association. *Circulation [Internet]*. 2019 Jul 2 [cited 2023 Mar 16];140(1).  
424 Available from: <https://www.ahajournals.org/doi/10.1161/CIR.0000000000000682>
- 425 29. Reichart D, Magnussen C, Zeller T, Blankenberg S. Dilated cardiomyopathy: from epidemiologic  
426 to genetic phenotypes: A translational review of current literature. *J Intern Med*. 2019  
427 Oct;286(4):362–72.
- 428 30. Menon SC, Eidem BW, Dearani JA, Ommen SR, Ackerman MJ, Miller D. Diastolic Dysfunction  
429 and Its Histopathological Correlation in Obstructive Hypertrophic Cardiomyopathy in Children

- 430 and Adolescents. *Journal of the American Society of Echocardiography*. 2009 Dec;22(12):1327–  
431 34.
- 432 31. Hershberger RE. Genetic evaluation of cardiomyopathy: a clinical practice resource of the  
433 American College of Medical Genetics and Genomics (ACMG). *GENETICS in MEDICINE*.  
434 2018;20(9):11.
- 435 32. Minotti G, Reggiardo G, Camilli M, Salvatorelli E, Menna P. From Cardiac Anthracycline  
436 Accumulation to Real-Life Risk for Early Diastolic Dysfunction. *JACC: CardioOncology*. 2022  
437 Mar;4(1):139–40.
- 438 33. Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late  
439 anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. *Heart*. 2004  
440 Oct;90(10):1214–6.
- 441 34. Tede NH, Child JS. DIASTOLIC DYSFUNCTION IN PATIENTS WITH CONGENITAL HEART  
442 DISEASE. *Cardiology Clinics*. 2000 Aug;18(3):491–9.
- 443 35. Moskowitz WB, Schieken RM, Mosteller M, Bossano R. Altered systolic and diastolic function in  
444 children after “successful” repair of coarctation of the aorta. *American Heart Journal*. 1990  
445 Jul;120(1):103–9.
- 446 36. Shin JH, Choi HJ. Heart Failure with Preserved Ejection Fraction in Children without Congenital  
447 Heart Disease. *J Cardiovasc Dis Diagn [Internet]*. 2018 [cited 2022 Aug 21];s2. Available from:  
448 [https://www.omicsonline.org/open-access/heart-failure-with-preserved-ejection-fraction-in-](https://www.omicsonline.org/open-access/heart-failure-with-preserved-ejection-fraction-in-children-without-congenital-heart-disease-2329-9517-S2-004-98349.html)  
449 [children-without-congenital-heart-disease-2329-9517-S2-004-98349.html](https://www.omicsonline.org/open-access/heart-failure-with-preserved-ejection-fraction-in-children-without-congenital-heart-disease-2329-9517-S2-004-98349.html)
- 450 37. Selamet Tierney ES, Newburger JW, Graham D, Baker A, Fulton DR, Colan SD. Diastolic  
451 function in children with Kawasaki Disease. *International Journal of Cardiology*. 2011  
452 May;148(3):309–12.
- 453 38. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al.  
454 Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With  
455 COVID-19 in the United States. *Journal of the American College of Cardiology*. 2020  
456 Oct;76(17):1947–61.
- 457 39. Putzer GJB, Cooper D, Keehn C, Asante-Korang A, Boucek MM, Boucek RJ. An improved  
458 echocardiographic rejection-surveillance strategy following pediatric heart transplantation. *The*  
459 *Journal of Heart and Lung Transplantation*. 2000 Dec;19(12):1166–74.
- 460 40. Asante-Korang A, Fickey M, Boucek MM, Boucek RJ. Diastolic performance assessed by tissue  
461 Doppler after pediatric heart transplantation. *The Journal of Heart and Lung Transplantation*.  
462 2004 Jul;23(7):865–72.
- 463 41. Ten Harkel ADJ, Cransberg K, Van Osch-Gevers M, Nauta J. Diastolic dysfunction in paediatric  
464 patients on peritoneal dialysis and after renal transplantation. *Nephrology Dialysis*  
465 *Transplantation*. 2009 Jun 1;24(6):1987–91.
- 466 42. Schoenmaker NJ, Kuipers IM, van der Lee JH, Tromp WF, van Dyck M, Gewillig M, et al.  
467 Diastolic dysfunction measured by tissue Doppler imaging in children with end-stage renal  
468 disease: a report of the RICH-Q study. *Cardiol Young*. 2014 Apr;24(2):236–44.
- 469 43. Mitsnefes MM. Cardiovascular Disease in Children with Chronic Kidney Disease. *J Am Soc*  
470 *Nephrol*. 2012 Apr;23(4):578–85.

- 471 44. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, et al. Impaired left  
472 ventricular diastolic function in children with chronic renal failure. *Kidney International*. 2004 Apr  
473 1;65(4):1461–6.
- 474 45. Bartkowiak J, Spitzer E, Kurmann R, Zürcher F, Krähenmann P, Garcia-Ruiz V, et al. The  
475 impact of obesity on left ventricular hypertrophy and diastolic dysfunction in children and  
476 adolescents. *Sci Rep*. 2021 Dec;11(1):13022.
- 477 46. Saiedi SAE, Mira MF, Sharaf SA, Musaddar MMA, Kaffas RMHE, AbdelMassih AF, et al. Left  
478 ventricular diastolic dysfunction without left ventricular hypertrophy in obese children and  
479 adolescents: a Tissue Doppler Imaging and Cardiac Troponin I Study. *Cardiology in the Young*.  
480 2018 Jan;28(1):76–84.
- 481 47. Kozák-Bárány A, Jokinen E, Kero P, Tuominen J, Rönnemaa T, Välimäki I. Impaired left  
482 ventricular diastolic function in newborn infants of mothers with pregestational or gestational  
483 diabetes with good glycemic control. *Early Human Development*. 2004 Apr 1;77(1):13–22.
- 484 48. Mehta S, Nuamah I, Kalhan S. Altered Diastolic Function in Asymptomatic Infants of Mothers  
485 With Gestational Diabetes. *Diabetes*. 1991 Dec 1;40(Supplement\_2):56–60.
- 486 49. Zablah JE, Gruber D, Stoffels G, Cabezas EG, Hayes DA. Subclinical Decrease in Myocardial  
487 Function in Asymptomatic Infants of Diabetic Mothers: A Tissue Doppler Study. *Pediatr Cardiol*.  
488 2017 Apr 1;38(4):801–6.
- 489 50. Guazzi M, Ghio S, Adir Y. Pulmonary Hypertension in HFpEF and HFrEF: JACC Review Topic  
490 of the Week. *J Am Coll Cardiol*. 2020 Sep 1;76(9):1102–11.
- 491 51. Galiè N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on  
492 Pulmonary Hypertension. *European Respiratory Journal [Internet]*. 2019 Jan 1 [cited 2022 Dec  
493 26];53(1). Available from: <https://erj.ersjournals.com/content/53/1/1802148>
- 494 52. Inampudi C, Silverman D, Simon MA, Leary PJ, Sharma K, Houston BA, et al. Pulmonary  
495 Hypertension in the Context of Heart Failure With Preserved Ejection Fraction. *Chest*. 2021  
496 Dec;160(6):2232–46.
- 497 53. Røe ÅT, Aronsen JM, Skårdal K, Hamdani N, Linke WA, Danielsen HE, et al. Increased passive  
498 stiffness promotes diastolic dysfunction despite improved Ca<sup>2+</sup> handling during left ventricular  
499 concentric hypertrophy. *Cardiovascular Research*. 2017 Aug 1;113(10):1161–72.
- 500 54. Inciardi RM, Rossi A, Bergamini C, Benfari G, Maffei C, Greco C, et al. Mitral regurgitation, left  
501 atrial structural and functional remodelling and the effect on pulmonary haemodynamics.  
502 *European Journal of Heart Failure*. 2020;22(3):499–506.
- 503 55. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, et al. The  
504 neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction.  
505 *European Heart Journal*. 2019 Dec 1;40(45):3707–17.
- 506 56. Ditaranto R, Caponetti AG, Ferrara V, Parisi V, Minnucci M, Chiti C, et al. Pediatric Restrictive  
507 Cardiomyopathies. *Front Pediatr*. 2022 Jan 25;9:745365.
- 508 57. Weller RJ, Weintraub R, Addonizio LJ, Chrisant MRK, Gersony WM, Hsu DT. Outcome of  
509 idiopathic restrictive cardiomyopathy in children. *Am J Cardiol*. 2002 Sep 1;90(5):501–6.

- 510 58. Schlein J, Riebandt J, Laufer G, Zimpfer D. Reversal of pulmonary hypertension in paediatric  
511 patients with restrictive cardiomyopathy. *Interactive CardioVascular and Thoracic Surgery*. 2021  
512 Oct 29;33(5):834–6.
- 513 59. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, et al. Hemodynamic  
514 Responses to Rapid Saline Loading: The Impact of Age, Sex, and Heart Failure. *Circulation*.  
515 2013 Jan 1;127(1):55–62.
- 516 60. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based  
517 Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction.  
518 *Circulation*. 2018 Aug 28;138(9):861–70.
- 519 61. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart  
520 failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus  
521 recommendation from the Heart Failure Association (HFA) of the European Society of  
522 Cardiology (ESC). *Eur Heart J*. 2019 Oct 21;40(40):3297–317.
- 523 62. Recher M, Botte A, Baudelet JB, Leteurtre S, Godart F. Évaluation de la fonction diastolique du  
524 ventricule gauche en réanimation pédiatrique : quelles indications, quels paramètres mesurer ?  
525 Levy B, Voicu S, editors. *Méd Intensive Réa*. 2019 Mar;28(2):144–56.
- 526 63. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and  
527 evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics:  
528 ASE/EAE consensus statement on methodology and indications endorsed by the Japanese  
529 Society of Echocardiography. *J Am Soc Echocardiogr*. 2011 Mar;24(3):277–313.
- 530 64. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of  
531 adult transthoracic echocardiography reporting in agreement with recent chamber quantification,  
532 diastolic function, and heart valve disease recommendations: an expert consensus document of  
533 the European Association of Cardiovascular Imaging. *European Heart Journal - Cardiovascular*  
534 *Imaging*. 2017 Dec 1;18(12):1301–10.
- 535 65. Eidem BW, McMahon CJ, Cohen RR, Wu J, Finkelshteyn I, Kovalchin JP, et al. Impact of  
536 cardiac growth on doppler tissue imaging velocities: a study in healthy children. *Journal of the*  
537 *American Society of Echocardiography*. 2004 Mar;17(3):212–21.
- 538 66. Sasaki N, Garcia M, Ko HH, Sharma S, Parness IA, Srivastava S. Applicability of Published  
539 Guidelines for Assessment of Left Ventricular Diastolic Function in Adults to Children with  
540 Restrictive Cardiomyopathy: An Observational Study. *Pediatr Cardiol*. 2015 Feb;36(2):386–92.
- 541 67. McAree D, Hauck A, Arzu J, Carr M, Acevedo J, Patel AB, et al. Clinical Predictors of Subacute  
542 Myocardial Dysfunction in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated  
543 with COVID-19. *Pediatr Cardiol [Internet]*. 2022 Oct 19 [cited 2022 Oct 28]; Available from:  
544 <https://link.springer.com/10.1007/s00246-022-03021-9>
- 545 68. Cowie MR, Mendez GF. BNP and congestive heart failure. *Prog Cardiovasc Dis*.  
546 2002;44(4):293–321.
- 547 69. Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, et al. NT-Pro-B-type Natriuretic  
548 Peptide in Infants and Children: Reference Values Based on Combined Data from Four Studies.  
549 *Pediatr Cardiol*. 2009 Jan 1;30(1):3–8.
- 550 70. Treibel TA, White SK, Moon JC. Myocardial Tissue Characterization: Histological and  
551 Pathophysiological Correlation. *Curr Cardiovasc Imaging Rep*. 2014 Mar;7(3):9254.

- 552 71. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical  
553 recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2\* and  
554 extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic  
555 Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging  
556 (EACVI). *J Cardiovasc Magn Reson*. 2017 Dec;19(1):75.
- 557 72. Rao S, Tseng SY, Pednekar A, Siddiqui S, Kocaoglu M, Fares M, et al. Myocardial Parametric  
558 Mapping by Cardiac Magnetic Resonance Imaging in Pediatric Cardiology and Congenital Heart  
559 Disease. *Circ: Cardiovascular Imaging [Internet]*. 2022 Jan [cited 2023 Mar 18];15(1). Available  
560 from: <https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.120.012242>
- 561 73. Paelinck BP, Lamb HJ, Bax JJ, Van der Wall EE, de Roos A. Assessment of diastolic function  
562 by cardiovascular magnetic resonance. *American Heart Journal*. 2002 Aug 1;144(2):198–205.
- 563 74. Ntsinjana HN, Chung R, Ciliberti P, Muthurangu V, Schievano S, Marek J, et al. Utility of  
564 Cardiovascular Magnetic Resonance-Derived Wave Intensity Analysis As a Marker of  
565 Ventricular Function in Children with Heart Failure and Normal Ejection Fraction. *Front Pediatr*.  
566 2017 Apr 3;5:65.
- 567 75. Belay W, Godown J, Chan KC, Bearl DW, George-Durrett K, Slaughter JC, et al. Cardiac  
568 magnetic resonance diastolic indices correlate with ventricular filling pressures in pediatric heart  
569 transplant recipients. *Pediatr Transplant*. 2022 Jun 10;e14332.
- 570 76. Webber SA, Lipshultz SE, Sleeper LA, Lu M, Wilkinson JD, Addonizio LJ, et al. Outcomes of  
571 Restrictive Cardiomyopathy in Childhood and the Influence of Phenotype: A Report From the  
572 Pediatric Cardiomyopathy Registry. *Circulation*. 2012 Sep 4;126(10):1237–44.
- 573 77. Wittekind SG, Ryan TD, Gao Z, Zafar F, Czosek RJ, Chin CW, et al. Contemporary Outcomes of  
574 Pediatric Restrictive Cardiomyopathy: A Single-Center Experience. *Pediatr Cardiol*. 2019  
575 Apr;40(4):694–704.
- 576 78. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB. Prognostic value of a doppler  
577 index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. *The*  
578 *American Journal of Cardiology*. 1998 Nov;82(9):1071–6.
- 579 79. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, et al. Wireless  
580 pulmonary artery pressure monitoring guides management to reduce decompensation in heart  
581 failure with preserved ejection fraction. *Circulation: Heart Failure*. 2014;7(6):935–44.
- 582 80. Heywood JT, Jermyn R, Shavelle D, Abraham WT, Bhimaraj A, Bhatt K, et al. Impact of  
583 Practice-Based Management of Pulmonary Artery Pressures in 2000 Patients Implanted with the  
584 CardioMEMS Sensor. *Circulation*. 2017;135(16):1509–17.
- 585 81. Rai P, Okhominia VI, Kang G, Akil N, Towbin JA, Hankins JS, et al. The effects of cardio-  
586 selective beta blockade on diastolic dysfunction in children with sickle cell disease. *haematol*  
587 [Internet]. 2022 Oct 6 [cited 2022 Oct 10]; Available from:  
588 <https://haematologica.org/article/view/haematol.2022.281428>
- 589 82. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for  
590 Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2014 Apr 10;370(15):1383–92.
- 591 83. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and  
592 Preserved Ejection Fraction: EMPEROR-Preserved Trial [Internet]. [cited 2022 Jul 6]. Available  
593 from: <https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.121.056824>



- 594 84. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, et al. Pulmonary  
595 hypertension due to left heart disease. *European Respiratory Journal* [Internet]. 2019 Jan 1  
596 [cited 2022 Dec 26];53(1). Available from: <https://erj.ersjournals.com/content/53/1/1801897>
- 597 85. Paitazoglou C, Bergmann MW, Özdemir R, Pfister R, Bartunek J, Kilic T, et al. One-year results  
598 of the first-in-man study investigating the Atrial Flow Regulator for left atrial shunting in  
599 symptomatic heart failure patients: the PRELIEVE study. *European Journal of Heart Failure*.  
600 2021;23(5):800–10.
- 601 86. Paitazoglou C, Bergmann MW. The atrial flow regulator: current overview on technique and first  
602 experience. *Ther Adv Cardiovasc Dis*. 2020 Sep 24;14:1753944720919577.
- 603 87. Hansmann G, Sabiniewicz A, Sabiniewicz R. Atrial Flow Regulator for Postcapillary Pulmonary  
604 Hypertension. *JACC Case Rep*. 2022 May 31;4(14):878–84.
- 605