Chapter

Cardiomyopathies in Children: Genetics, Pathomechanisms and Therapeutic Strategies

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Abstract

Despite great advances in cardiovascular medicine, cardiomyopathies in children still are challenging for pediatricians as well as cardiologists. Pediatric cardiomyopathies can manifest in diverse phenotypes but are often life-threatening and have a poor prognosis. However, many therapeutic options available for adult patients do not apply for children, leaving a very limited portfolio to attenuate disease progression to avoid or postpone heart transplantation. Childhood cardiomyopathies can arise from different etiologies, but genetic defects such as mutations, for example, in sarcomeric proteins, which are pivotal for the contractile function, are common. This leads to the demand to identify new variants found by genetic screening as pathogenic and furthermore to allow a prognosis or risk assessment for related carriers, thus increasing the need to uncover molecular pathomechanisms of such mutations. This chapter aims to highlight the unique characteristics of pediatric cardiomyopathies in contrast to adult forms, including etiology, pathophysiology, genetics, as well as molecular mechanisms. We will also tackle currents options, challenges, and perspectives in diagnosis and treatment of pediatric cardiomyopathies.

Keywords: pediatric cardiomyopathy, mutations, sarcomere, molecular mechanism, genotype-phenotype correlation, calcium sensitivity, fibrosis, inflammation

1. Introduction

Cardiomyopathies (CM) in children occur relatively rarely with an incidence of less than 1.3 in 100,000 children below 10 years of age and are still challenging for pediatricians, cardiologists, and cardiac surgeons [1]. Cardiomyopathies, which by definition are diseases of the heart muscle, are very heterogeneous and include a cluster of different diseases that often cannot be clearly separated from each other. Generally, CMs are classified into dilated (DCM), hypertrophic (HCM), restrictive (RCM), left ventricular non-compaction (LVNC), arrhythmogenic (ACM), and mixed phenotypes. They further may be subdivided into primary, that is, inherited, and secondary diseases (e.g., metabolic disorders or other genetic diseases as muscular dystrophy). In children, often the pathology is very severe with rapid progression. In addition, comorbidities such as diabetes, renal and pulmonary diseases, and obesity may affect the outcome [2]. There is still a vast amount of known pediatric CM cases that are idiopathic, that is, of unknown cause, often because of lack of causal diagnosis. In consequence, this increases the inefficiency of treatments [3]. Since often suitable therapies besides heart transplantation for diagnosed CM types are not available or inefficient, prognosis is poor [4]. Here, we will describe common features of pediatric CMs concerning their etiology, pathophysiology, and molecular mechanisms, thereby underlining the challenges for classification, diagnosis, and treatment. Also, unique features will be covered, as well as current options and perspectives in diagnosis and treatment.

2. Classification of pediatric cardiomyopathies and their clinical characteristics

The classification of cardiomyopathies in general still is a challenging and debated topic due to different approaches used by larger population-based studies and guidelines provided by different cardiologic societies [2]. In many cases, CMs were (and still are) classified mainly by the morphofunctional phenotype of the myocardium, although, more and more often, pathogenetic and genotypic criteria were included. The different classifications lead to inconsistencies in terminology between different published systems such as the AHA, ACC, or ESC guidelines, thus adding to the difficulty to finding common pathophysiological patterns and therapeutic approaches in different cardiomyopathy studies, even more so for the relatively rare pediatric CMs. One attempt to integrate the different disease characteristics in a single system is the MOGE(S) classification [5]. It includes the morphofunctional phenotype (M), organ involvement (O, e.g., isolated to the heart vs. systemic/multi-organ), genetic inheritance pattern (G), and etiological or explicit genetic defects (E). Optionally, the functional status (S) can be included. But, these characteristics still can be applied in different hierarchies. Thus, the widely used current ESC approach implies the morphofunctional phenotype as the highest category and the genetic and pathogenetic characteristics as subcategories, as the phenotype provides the basis for diagnosis and therapeutic management in the first place. Still, the pathogenetics are of great importance for genetic counseling of mutation-carrier families in order to provide long-term risk assessment and, if necessary, regular monitoring of (as yet) seemingly unaffected family members by a cardiologist. Hereinafter, the different CM types will be discussed with regard to their most prominent morphofunctional aspects and their general prevalence in children. An overview on pediatric CM types is given in **Figure 1**.

2.1 Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is by far the most common CM in adults as well as in children (50–70% of all pediatric CM cases), though the prognosis is generally much worse for the latter [6]. In a North American study, 46% of 1426 pediatric DCM patients underwent heart transplantation or died during a 5-year follow-up period [6]. The hallmarks of DCM are dilation of the left ventricle (LV) and systolic dysfunction in absence of a hemodynamic cause (e.g., coronary artery and aorta anomalies, sepsis and ischemia) [7]. In addition to LV dilation, other features such as reduced ventricular wall thickness, mass-to-volume ratio, and mitral regurgitation are

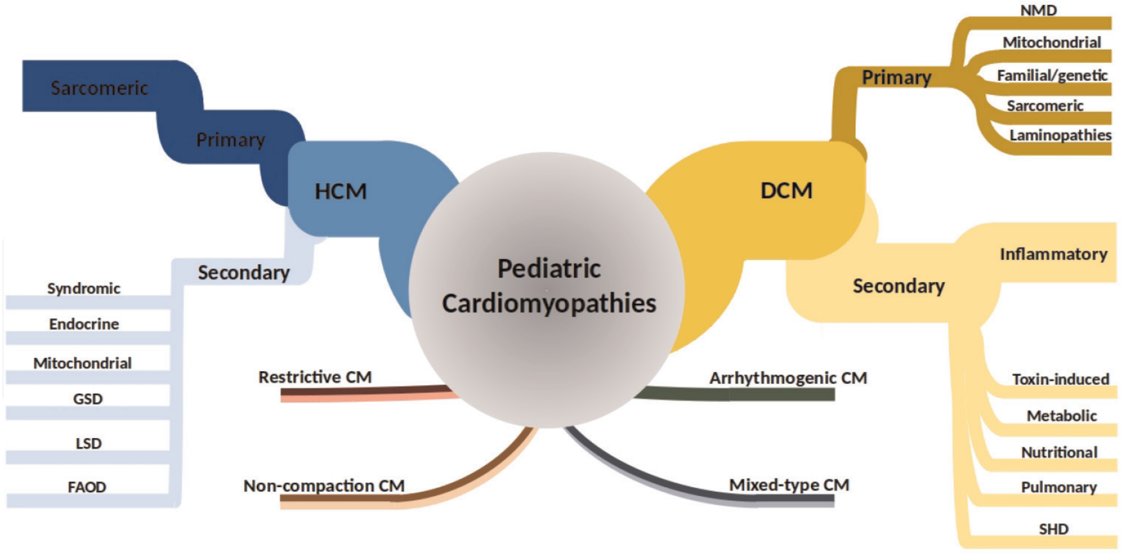

Figure 1.
Overview on pediatric cardiomyopathy (CM) types. The thickness of the branches reflects the relative prevalence in children, except for the rare cardiomyopathies (restrictive, arrhythmogenic, non-compaction, and mixed-type CMs). Here, dual color reflects both primary and secondary etiologies; single-color primary etiology only for arrhythmogenic CM. HCM: Hypertrophic CM; DCM: Dilated CM; NMD: Neuromuscular disorders; GSD: Glycogen storage disorders; LSD: Lysosomal storage disorders; FAOD: Fatty acid oxidation disorders; SHD: Structural heart disease.

observed in the patients. The dilation and decreased contractility can also affect the right ventricle, resulting, for example, in elevated pulmonary pressures and even in pulmonary and peripheral edemas. Again, the phenotype of DCM is highly diverse, ranging from asymptomatic to single or biventricular heart failure, failure to thrive, arrhythmias, and sudden cardiac death. [7] Manifold causes have been described for DCM and encompass primary (genetic and idiopathic) as well as secondary categories. [5, 6] Sometimes, structural heart diseases are associated with DCM, being the end-stage condition of the former, often resulting in the diagnostic “hen and egg” challenge: is the DCM the consequence of the abnormal loading conditions, or are the latter a consequence of an abnormal myocardium? This can often be answered only by successful treatment of the hemodynamic dysfunction (and the subsequent recovery of the myocardium), which is not always possible. The same question applies to DCM associated with pulmonary conditions, which primarily affect the right ventricle.

Primary DCM is difficult to diagnose in absence of identified familial mutations, as all secondary causes have to be excluded first [5]. Thus, patients with de-novo mutations are diagnosed potentially later due to lack of family history. Most cases of idiopathic DCM are considered to have a genetic cause, and there is a growing number of idiopathic DCM cases being reclassified into familial DCM upon further investigation. The estimated occurrence of FDCM is about 30–50% of all DCM cases in children; the 5-year event-free survival rate is 50–60% [6]. The inheritance is autosomal dominant, and the affected genes encompass those encoding for cytoskeletal, sarcomeric, and Z-disk proteins [8]. In addition, DCM is common and a leading cause of mortality in children with neuromuscular disorders (NMDs) such as Duchenne muscular dystrophy, Barth syndrome, myofibrillar myopathies and so on, as well as Emery-Dreyfuss syndrome, caused by a mutation in *LMNA*, the gene encoding for lamin A/C [9, 10]. Primary mitochondrial disorders can also present with a DCM phenotype or develop it over time [11]. Altogether, this underlines the importance of extensive genetic testing of DCM as well as NMD patients.

The distinct feature of secondary DCM (as opposed to primary DCM) is that the underlying causes affect multiple organs and can sometimes be treated, although this is a very broad group of different disorders, accounting for 50–70% of pediatric DCM cases. [6] Also, the phenotype can be very diverse, as well as disease onset and progression. Thus, the common classification criteria here are the dilated morphology and systolic dysfunction in the first place. In case of DCM presentation in very young patients, secondary causes have to be considered in the first place, as primary DCM is expected to be more prevalent in adults. A common type of secondary DCM is the inflammatory DCM, which can be further classified into infectious and non-infectious (e.g., reactions to drugs or toxins, autoimmune diseases etc.) [6]. In children, non-infectious causes are generally rarer than the infectious, with viral myocarditis being the most common cause of inflammatory DCM in children. Especially in cases of viral myocarditis with subsequent DCM, the changes in the morphology of the heart are remarkable, usually starting without significant dilation during the early and acute phase of the infection and remodeling to a dilated phenotype over time. Attributing the myocarditis clearly to a virus can be challenging, though, so that as complete a history and examination as possible should be performed to rule out other causes such as toxin or drug exposure, cancer, metabolic disorders (e.g., thyroid hormone dysregulations, diabetes mellitus), and nutritional disorders/deficiencies [12, 13].

2.2 Hypertrophic cardiomyopathy

The hallmarks of hypertrophic cardiomyopathy (HCM) are a hypertrophied but not dilated ventricle without an underlying hemodynamic cause or physiological hypertrophy and relaxation abnormalities/diastolic dysfunction, whereas the systolic function is usually preserved or even enhanced. Thus, the main diagnostic criterion is the diastolic septal or LV wall thickness, which has to be adjusted for body size in children and is expressed as wall thickness z scores. The wall thickening often presents focally or regionally, so that not the whole ventricle is affected. Nevertheless, the pattern is very diverse, with global biventricular involvement in the most extreme cases. In addition, structural disturbances are common, and mixed phenotypes of HCM with non-compaction and restrictive CM have been described [14, 15]. Similar to other cardiomyopathies, HCM can further be subclassified into primary and secondary forms, with the former being caused by mainly sarcomeric mutations and the latter associated with a multitude of causes, for example, syndromic diseases like Noonan syndrome, lysosomal and glycogen storage diseases (e.g., Anderson-Fabry disease, Pompe and Danon disease), disorders of the fatty acid metabolism, mitochondrial diseases, and hyperinsulinism [2, 16–18]. The latter occurs only in newborn and results from an overproduction of insulin, due to primary causes like pancreatic hyperfunction or to secondary causes like maternal diabetes mellitus. Usually, in these cases, HCM resolves when the underlying hyperinsulinism is treated [2, 14, 19]. In total, HCM accounts for approximately 40% of all pediatric cardiomyopathies and is the second most common CM after DCM in children (**Figure 1**) [20]. The occurrence is ten times higher in children under 1 year of age than in those older than 1 year. In 75% of all HCM cases, idiopathic and genetic/familial HCM are the most common etiologies in children, though it is not clear how many of the idiopathic cases arise from underlying genetic causes that have not been identified yet [21, 22]. Survival in infants with HCM is overall poorer than in older patients, but the prognosis highly depends on etiology and age at diagnosis. For example, inborn errors of metabolism are associated with a very early diagnosis (mean age 6 months) and a 5-year survival rate of only 42%, while for idiopathic non-infantile HCM (age at diagnosis older than 1 year), 94% of children survive 5 years [22]. Thus, early-onset HCM generally has a much worse prognosis, especially in infants with inborn metabolic errors and malformation syndromes, as well as for idiopathic HCM (5-year survival of 82% for early-onset cases vs. 94% for non-infantile cases) [22].

2.3 Restrictive cardiomyopathy

Restrictive cardiomyopathy is in general a rare type of CM, characterized by enhanced ventricular stiffness, abnormal filling patterns, and enlarged atria but absent or very mild hypertrophy or dilation [23]. Thus, the systolic function is nearly normal, while the diastolic function is impaired. The primary diagnostic criterion is the abnormal myocardial stiffness, which is caused by dysfunctions within the myocytes or of the intracellular matrix such as fibrosis, and has to be distinguished from constrictive pericarditis, where the impaired filling results from an abnormal pericardium [24, 25]. As in other cardiomyopathies, the RCM phenotype can vary from asymptomatic to prominent heart failure, pulmonary hypertension, arrhythmias, and sudden death. Causes of RCM can be mutations in sarcomeric and non-sarcomeric genes (primary RCM), as well as infiltration (e.g., amyloidosis), storage disease (e.g., Anderson-Fabry disease), and autoimmune disorders [26]. An important cause of RCM particularly in tropical regions is endomyocardial fibrosis caused by parasitic infections [27]. In children, primary RCM accounts for less than 5% of all CM cases but has the worst outcome [4, 28, 29]. About 66% of the patients present with a pure RCM phenotype and have a 5-year mortality rate of approximately 20% and a 5-year transplantation rate of 58% [28]. In about 50% of children with RCM, pathogenic or likely pathogenic gene variants were found [8].

2.4 Left ventricular non-compaction cardiomyopathy

The most distinctive feature of LVNC is a prominent trabeculation of the left ventricle, as diagnosed by cardiac imaging, which can occur isolated and even without any functional disturbances as well as as part of congenital heart disease or together with skeletal muscle and other systemic abnormalities, for example, Barth syndrome [30]. In addition, it has been associated with atrial and ventricular arrhythmias, atrial fibrillation, and conduction defects. A popular hypothesis suggests that LVNC represents a failure of maturation of the myocardium during embryonic development, although there is also evidence of histological differences of LVNC and normal myocardium even in the embryonic state [31]. The fact that excessive trabeculation does not necessarily lead to functional disturbances also gives rise to controversial views on LVNC as unclassified CM or even just a morphological trait not per se associated with dysfunction [32]. LVNC can occur as mixed phenotype together with, for example, HCM, RCM, or DCM, the latter being the most frequent case in children. Similar to the clinical phenotype, the prognosis in patients with LVNC is highly variable, as the presence of other factors than hypertrabeculation appears to be a major factor [33]. Children with isolated LVNC have a 94% 5-year survival rate, while cases with mixed hypertrophic, restrictive, or dilated phenotypes and/or arrhythmias show significantly poorer outcomes [33]. Barth syndrome is a well-characterized inborn metabolic disease associated with LVNC and DCM. In the United Kingdom and France, about half of the infants diagnosed with Barth syndrome died or received a heart transplant

[34, 35]. Among the transplant-free survivors, cardiac function often stabilized or even recovered after 3 years of age. [34, 35]

2.5 Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) encompasses genetic diseases like AVC (arrhythmogenic ventricular CM), channelopathies, and non-genetic pacing-induced CMs. The clinical and pathological hallmarks of AVC are ventricular arrhythmias, palpitations, syncope in connection to physical exercise, cardiac arrest, impaired ventricular systolic function, and replacement of the myocardium by fibrous and/or fatty tissue. In some cases, patients may also present with ventricular tachycardia and/or heart failure (HF). The formerly used term "arrhythmogenic right ventricular (RV) cardiomyopathy" was established because often the disease affects mainly the right ventricle. But, due to an increasing number of reports of biventricular or even isolated LV involvement, the more general term AVC is now recommended. [36, 37] AVC has an estimated incidence of 1:100 to 1:5000 in the general population and is an important cause of sudden cardiac death (SCD) in children and young adults (11% of all SCD cases and 22% of SCD cases in young athletes), male patients being more often and more severely affected than females. [38] The phenotype is highly diverse though, ranging from nearly normal hearts to severe biventricular dysfunction. The fibrofatty replacement of the muscle tissue is often considered to arise from ischaemic damage of the myocardium, often more prominent in the RV. In contrast, in the LV, often only an isolated fibrofatty scar is observed, leading to a higher risk of severe ventricular arrhythmias and SCD. [39] The diagnosis of AVC is based primarily on cMRI imaging- and/or biopsy-based evidence of fibrofatty replacement in the myocardium and electrocardiographic (ECG) abnormalities. As the disease mostly follows an autosomal-dominant inheritance pattern, family history assessment and genetic screening are also indicated. Common AVC mutations affect desmosomal proteins and proteins involved in cell-cell adhesion. Commercial screening panels are available but do not encompass all genes associated with AVC. For adults, the diagnostic criteria were described in the revised Task Force Criteria of the AHA, but they have only limited validity for pediatric patients, as children often may not exhibit all of the features (e.g., prominent fibrofatty replacement), despite being mutation carriers. [40, 41] Instead, in a larger study, a significantly increased occurrence of SCD and resuscitated SCD was found in pediatric patients compared to adults, while sustained tachycardia was observed significantly less often. [42] Furthermore, athletes were overrepresented among the pediatric patients compared to adults, suggesting an association between endurance exercise during adolescence and pediatric-onset AVC. [42]

Channelopathies are inherited arrhythmic diseases typically without structural changes of the heart and myocardium, which is distinctive from, for example, desmosomal, sarcomeric, and cytoskeletal AVC. [43] Channelopathies arise from mutations in genes encoding cardiac ion channels and encompass long- and short-QT syndromes, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and Lenègre disease. [43] Typical phenotypic manifestations are syncopes, cardiac arrest during physical activity, arrhythmias, potentially leading to ventricular fibrillation and SCD. In children, Brugada syndrome has been linked to sudden infant death syndrome. [44] While the heart appears structurally normal, there are prominent changes in the electrocardiographic patterns, which are often characteristic of the specific type of channelopathy, such as prolonged QT intervals in LQTS. Pacing-induced cardiomyopathies arise from ventricular dysfunction caused by tachycardia, arrhythmia, or frequent cardiac ectopy [45]. The phenotype often presents as heart failure symptoms in the presence of tachycardia and ventricular dysfunction or even cardiogenic shock in neonates and infants. Mostly though, the myocardium recovers at least partially after treatment of the underlying arrhythmia [46]. Pacing-induced cardiomyopathy can also occur in children with chronic RV pacing, for example, in cases with atrioventricular block, and develops over time after pacemaker implantation [47]. This type of CM is thought to arise from unwanted abnormal transmission of electric impulses to the LV and can recover after changing to a biventricular pacemaker.

3. Etiology and pathophysiology of pediatric CM

Phenotypes as well as the etiology of pediatric CMs are very heterogeneous. Thus, in inherited CMs, genetic defects may occur in genes encoding proteins of the sarcomere, including the Z-disc proteins, structural proteins (e.g., costameric, desmosomal, cytoskeletal, nucleoskeletal proteins), mitochondrial or Ca^{2+}-handling proteins, signaling proteins such as Ras, or proteins of the Notch signaling pathway, and even mutations in non-coding regions of the genome have been described (see also **Figure 2**). Other causes of pediatric CMs might be inflammation due to viral or bacterial infections and toxins, including chemotherapeutics or neurohormonal or metabolic disorders [48–62]. Inborn errors of metabolism associated with

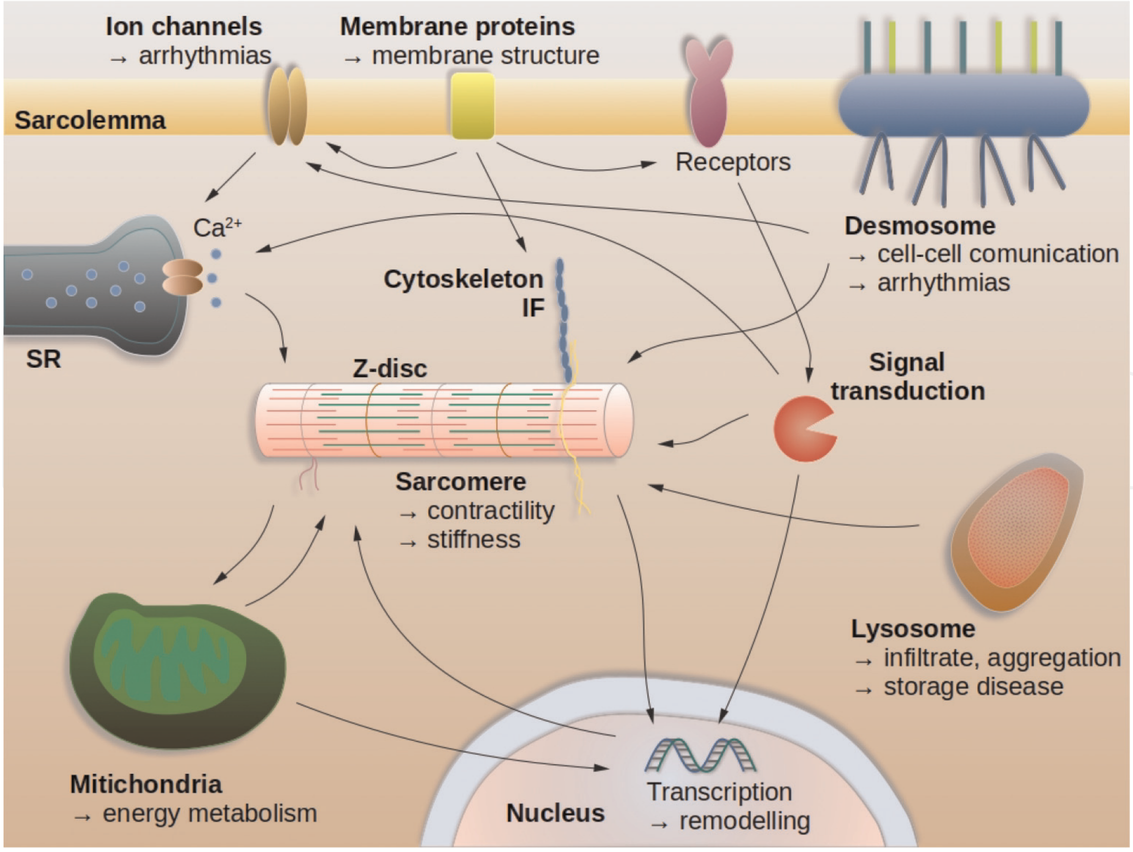

Figure 2.
Cellular compartments affected by genetic mutations causing cardiomyopathy in children. Arrows indicate interactions between different compartments altered in the presence of mutations (e.g., sarcomeric mutations leading to energy depletion and altered transcription). IF: Intermediate filaments.

cardiomyopathies are nicely summarized by [63]. One of these diseases, the Barth syndrome, is associated with CM in early childhood. Characteristically, the Barth syndrome may induce DCM or LNVC, skeletal muscle myopathy, mitochondrial dysfunction, neutropenia, and growth retardation [64]. According to Neuwald [65], a defect in the *TAZ* gene encoding several tafazzins due to alternative splicing might be causative. The taffazin protein family includes acyltransferases involved in phospholipid formation, indicating that the mitochondrial membranes might be defective, leading to an inefficient oxidative phosphorylation and thus to an inefficient energy production for cardiac performance.

LNVC can be caused not only by systemic diseases such as the Barth syndrome but also by gene defects also described in congenital or arrhythmogenic heart disease and restrictive, hypertrophic, or dilated CM. The affected genes identified include those encoding sarcomeric or cytoskeletal proteins as for example *MYH7* (myosin heavy chain 7), *MYL2,3* (myosin light chain 2,3), *MYBPC3* (cardiac myosin binding protein C), *TTN* (titin), *ACTC1* (cardiac alpha actin), *TPM1* (cardiac tropomyosin), *TNNT2* (cardiac troponin T), *TNNI3* (cardiac troponin I), and *ZASP* (LIM binding domain 3), a Z-disc protein [4, 66–71]. Non-sarcomeric gene defects have also been identified, for example, in *HCN4* (hyperpolarisation activated cyclic nucleotide gated potassium channel 4) coding for an ion channel located in pacemaker cells or in genes encoding intermediate filament proteins such as *LMNA* (Lamin A/C), which is involved in heart development, or *DES*, encoding desmin [72, 73]. A list of affected genes in LNVC and their functions can be found in the National Library of Medicine, Medline PLUS. LNVC is mainly due to developmental failure, and it is associated with increased trabeculation, leading to a sponge-like appearance of the heart chambers. Such a remodeling may result in contractile dysfunction, arrhythmia, and sudden cardiac death. The latter is also characteristic of other CMs such as ACM, HCM, or DCM.

DCM, a systolic disorder, is characterized by dilation of the left ventricle or of both ventricles associated with suppressed contractile function. DCM based on genetic defects seems to form the main cause of pediatric DCM, whereby the vast majority of gene mutations is found in sarcomeric proteins, especially in *MYH7*, *TTN*, *TNNT2*, *TPM1*, *MYBPC3*, *MYL2*, *TNNC1* (Troponin C), and *ACTN2*. Others are found in *LMN, DES, VCL* (Vinculin), *TTR* (transthyretin), *BAG3* (associated with apoptosis), *MT-TS2* (encoding a mitochondrial small RNA), or transcription factor encoding PRDM16 [74–78]. In adult and pediatric DCM, the same genes seem to be affected, though unfortunately, most genetic testings have been performed in adults [79]. Besides the genetic causes, inflammation may lead to DCM, the main non-genetic cause in children. Myocarditis is mainly caused by viral infections and is rather challenging for diagnosis and treatment [80]. In most cases, Coxsackieviruses B and adenovirus infections are the causes of myocarditis in children [81]. Recently, SARS-CoV-2 virus has also been described as a possible cause [82]. Besides viral infections, toxins and chemotherapeutics are also emerging as DCM-inducing agents. Especially anthracyclines, which often are used to treat tumors in children as well as in adults, have been linked to the development of heart failure, DCM, or RCM [83]. The onset of cardiomyopathy in cancer patients varies largely; it may develop within a week or less than one year after starting the treatment, depending on various risk factors (e.g., sex, age, dosage, and subtype of the agent) [84].

Most pediatric HCM cases are due to genetic defects mainly in genes encoding sarcomeric proteins, though diagnosis in respect of etiology remains challenging. The HCM mutations often may also cause other CMs such as DCM, RCM, ARVC, or LNVC, even within the same family, indicating additional factors such as further gene mutations, polymorphisms, or comorbidities. Mutations have been identified in genes encoding thick- and thin-filament proteins, whereby most mutations have been identified in *MYBPC3* and *MYH7*. Frequently, mutations have also been described in *TNNT2, TNNI3,* and *MYL2* or more seldom in *TPM1* and *ACTN*. HCM in children is even more heterogeneous than in adults. There are also several non-sarcomeric causes recently summarized in [85], which may occur alone or in combination with sarcomeric mutations and then modify the severity and prognosis of the disease [86]. These non-sarcomeric causes of HCM in children include rasopathies, a set of diseases with genetic defects encoding proteins of the Ras signaling cascade, for example, the Noonan syndrome. Others are glycogen storage diseases, including Pompe or Danon disease, characterized by glycogen-filled vacuoles within the cardiomyocytes [87]. In lysosomal storage diseases, for example, mucopolysaccharidoses, partially or undigested macromolecules are accumulated due to dysfunctional lysosomal enzymes [88]. In addition, mitochondrial disorders may occur, which mostly affect oxidative phosphorylation and thus energy production. Thus, HCM is often characterized by an energy deficiency probably due to over-contractility, as might also be the case in RCM.

In contrast to HCM, RCM is characterized by restrictive ventricular filling mostly without an increase in wall thickness. The genetic/familial causes of RCM are mainly due to mutations in genes encoding sarcomeric proteins (listed in [4]). Here, mutations in *TNNI3* occur frequently, but mutations have also been identified in genes of cytoskeletal or nuclear envelope proteins, leading to storage diseases (e.g., Danon disease, Friedrich ataxia, etc.) or infiltrative diseases (cardiac amyloidosis, cardiac sarcoidosis). The latter may also develop due to non-genetic causes.

All CM types are associated with an increased risk of developing severe arrhythmias, but they are most prominent in ACM. ACM is a genetically based disease, whereby most studies have concentrated on adult patients, underlining the need for more studies with children under 18 years of age. Histologically, ACM is characterized by the loss of cardiomyocytes being replaced by fibrofatty tissue [42, 89]. As a consequence of the cardiac remodeling, life-threatening arrhythmia and sudden cardiac death can occur. Causes for this familial disease are mutations in genes encoding desmosomal proteins with a deletion mutation in the junctional plakoglobin gene (*JUP*) being the first identified in ACM [90]. It seems that truncation mutations and splice variants in the *PKP2*, encoding plakophilin 2, are the most frequent causes of ACM, together with mutations in *DSP* (desmoplakin), *DSC2* (desmocollin 2), *DSG2* (desmoglein 2), and *JUP* [91]. Less frequently, mutations in *TMEM43* (Transmembrane Protein 43) and *PLN* (phospholamban) have been described.

4. Molecular mechanisms

Molecular mechanisms of CM development—as far as known to date—often are not specific for a distinct CM type. Generally, contractile function is affected via various mechanisms, and involvement of several cell compartments and cardiac remodeling is common (**Figure 2**).

4.1 Sarcomeric dysfunction

The smallest contractile unit of cross-striated muscles is the sarcomere. It is bordered by the Z-discs from which thin and elastic filaments reach out to the center of the sarcomere (M-Line). The thick filaments emanate bidirectionally from the M-line. Cardiac thin filaments are mainly composed of filamentous cardiac actin, cardiac tropomyosin (cTpm), and the cardiac heterotrimeric troponin complex composed of the tropomyosin-binding subunit (cTnT), the inhibitory subunit (cTnI), and the calcium-binding subunit (cTnC). Cardiac thick filaments are composed of cardiac myosin containing the essential and regulatory myosin light chains (MyLC) and heavy chains (MyHC) and cardiac myosin-binding protein C (cMyBPC), linking thick, thin, and elastic filaments. This implies that MyBPC coordinates the action of the filaments in contraction and relaxation processes. The elastic filament is formed by the giant protein titin. Ca^{2+}-binding to cTnC triggers contraction by enabling actin-myosin interaction and the power stroke (for review, see [92]). In addition, the contraction can be fine-tuned by reversible phosphorylation of many sarcomeric proteins, for example, titin, myosin-binding protein C, myosin light chains, cTnT, cTnI, cTpm, and also Z-disc proteins [93, 94].

CM-inducing mutations may occur in genes encoding filament proteins as well as proteins of the Z-disc. They may lead to single amino acid replacements or loss of a single or several amino acids. As a result, the mutations may alter the very sensitive interplay between the components of the sarcomere and/or protein dynamics and thereby induce contractile dysfunction (for review, see [4]). Furthermore, interactions of sarcomeric proteins with associated proteins might be altered, affecting signaling and thereby protein transcription, metabolism, inflammation, oxidation, cell death, protein degradation, fibrosis, cell–cell communication, Ca^{2+} homeostasis, and so on [95–97].

The intracellular Ca^{2+}- concentration is pivotal for the muscles' contractile function. At submicromolar concentrations, the cardiac muscle is at rest. It contracts upon an up to 100-fold increase in intracellular Ca^{2+}- concentration following a nervous impulse and opening of the voltage-gated L-type Ca-channels, which are located in the T-tubules of cardiomyocytes. The resultant Ca^{2+} inward current triggers the opening of the ryanodine receptors, the Ca^{2+}- channels within the membrane of the sarcoplasmatic reticulum (SR). Thereby, Ca^{2+} is released from the SR Ca^{2+}- stores, which leads to a massive increase in intracellular Ca^{2+}- concentration and to Ca^{2+}-binding to cTnC. This finally enables the power-generating interaction of myosin and actin, leading to contraction. On the other hand, relaxation occurs when Ca^{2+} is dissociated from cTnC. The released Ca^{2+} is then pumped back into the SR via the SR Calcium ATPase (SERCA), into the extracellular space via NCX (Na^{+}-Ca^{2+}-exchanger) and plasma membrane Ca^{2+} ATPases, and into mitochondria [98]. These complex procedure makes clear that alterations in the regulation of intracellular Ca^{2+}-concentrations lead to contractile dysfunction and thus to myocardial diseases. Besides mutations in genes of proteins involved in calcium fluxes (for review, see [99]), mutations in sarcomeric protein genes affect the calcium response of sarcomeric proteins and/or the calcium-binding affinity of the sarcomeres' Ca^{2+}-sensor, cTnC. On a simplified level, it is thought that DCM mutations decrease the calcium sensitivity of the actin-myosin interaction, thereby reducing the contractile capacity, which makes DCM a systolic disorder. Though, in pediatric end-stage DCM, cardiomyocytes exhibit an increased calcium sensitivity [100]. The authors assumed that this is caused by a substantial decrease in cTnI phosphorylation, which however cannot be the main reason, since in adult DCM, cTnI phosphorylation is also reduced (see below). In HCM and RCM, often the Ca^{2+}- sensitivity of the actin-myosin interaction is increased (at least in adults), leading to faster relaxation and re-contraction. Since intracellular Ca^{2+} is increased also due to an increased phosphorylation of Ca^{2+} channels, relaxation is impaired. Increased intracellular Ca^{2+}- concentration leads to hypercontractility, causing energy deficiency and increased production of reactive oxygen species (ROS) due to increased oxidative phosphorylation [101]. Posttranslational modifications and increased ROS might contribute to the development of arrhythmias. ROS induce oxidation of proteins, for example, of the calcium calmodulin kinase (CaMKII), which upon oxidation of methionine residues within the autophosphorylation domain is constantly active, because it cannot be inactivated via dephosphorylation and Ca^{2+}- CaM (calmodulin) dissociation [102, 103]. CaMKII regulates several proteins including those involved in calcium fluxes. Its activation increases intracellular Ca^{2+} levels due to increased open probabilities of Ca^{2+} channels as the L-type Ca^{2+} channel or the Ryanodine receptor. This might contribute to the remodeling of T-tubules further affecting EC coupling and Ca^{2+} homeostasis (for review see [92]).

However, calcium regulation might not only be impaired directly by mutations but also disturb the intermolecular interaction between the components of the sarcomere [104, 105]. Additionally, calcium responses might be affected by cross bridge kinetics or phosphorylation of myosin-binding protein C and cardiac TnI [106]. In pediatric and in adult DCM, cAMP-dependent protein kinase (PKA)-dependent hypophosphorylation of cTnI and MyBPC has been described, leading to a reduced stress response. Furthermore, maximal force and passive force were reduced. Hereby, reduced myofiber densities as proposed by [107] might contribute to the impaired force production. The reduced myofiber density seems not to be caused by an impaired protein quality control system [107]. The underlying mechanism is still unknown.

Most mutations, preferentially truncations leading to adult DCM, have been identified in titin. Controversial study results have been obtained with pediatric DCM. *TTN* and *MYH7* mutations were identified as predominant in a cohort of 106 pediatric patients [74]. In another study analyzing 36 patients, only one *TTN* mutation, a truncation (p.Arg33703*), was identified in a 16-year-old male DCM patient [108]. Mutations occur most frequently in A-band N2Ba/N2B-titin and thus may induce structural and contractile dysfunctions [109]. In A-band titin, interaction sites for myosin and myosin-binding protein C are distributed in a regular pattern [110]. This implies that in the case of A-band titin sequence alterations or truncations, its interaction with myosin and/or myosin-binding protein C might be impaired.

The location of mutations within *MYH7* - another frequent target for pathogenic mutations - seems to determine the DCM type according to Khan et al. [74]. They found that mostly single amino acid replacements in ß-Myosin heavy chain (MYH7) in the range of amino acids 1–600 lead to mixed DCM, a DCM–LNVC phenotype, whereas mutations in the C-terminal part from amino acid 600 lead to pure DCM [74]. The C-terminal rod of myosin heavy chain interacts with other myosin rods, which is essential to build up the thick filament. Myosin consists of 2 heavy chains, with the rod region forming a supercoil. The N-terminal part of each myosin heavy chain consists of a lever arm, a converter region with binding regions for the myosin light chains, and the globular motor domain containing the ATPase domain and actin binding domain. Mutations in the motor domain may affect ATPase activity via altered ATP-binding affinities and/or ATP hydrolysis rate and/or dissociation of the hydrolysis products ADP and P_i. Furthermore, it may impair the interaction of the motor domain with actin. Thus, most DCM mutations seem to weaken the affinity for actin. Furthermore, in contrast to MYH7 HCM mutants, in case of DCM, less force is produced due to a lower occupancy of the force generating state and a reduced ATPase velocity [111]. They predict that less ATP is used to hold a specific force.

Besides MYH7, the gene of cardiac MyBPC is the main target for pediatric and adult cardiomyopathies, whereby mutations in the cardiac MyBPC predominantly lead to HCM and, typically for HCM, are associated with hypercontractility. According to Toepfer et al. [112], mutations in *MYBPC3*, which result in either truncations or single amino acid replacements, affect the dynamics of myosin conformations and the super-relaxed state of myosin. cMyBPC interacts with myosin at several sites (rod, lever arm) and with titin, actin, and troponin and is thought to regulate the number of force-producing myosin motor domains. When phosphorylated, at submaximal Ca^{2+}- levels, it promotes the actin-myosin interaction [113]. Mutations in *MYBPC3* or in genes of interacting proteins might impair the interplay between these proteins and thereby the regulation of contraction. Hereby, an impaired interaction of different proteins with cardiac troponin might also play a role, though the role of the MyBPC-cardiac troponin interaction as well as of its interaction with titin remains to be elucidated [104, 114]. Two fascinating studies revealed that MyBPC regulates sarcomeric contractile oscillations, which might be based on its interplay with all sarcomeric partners [115, 116].

Mutations in the cardiac actin gene are relatively rare and mostly are associated with the development of HCM and DCM. They seem to affect the interaction with myosin heads and/or tropomyosin or troponin [117]. Interactions with MyBPC or actin-associated proteins regulating formation and length of the actin filament have not been considered yet. A nice overview of these proteins and their role is given in the review by Ehler [118]. The first hint that filament formation/structure could be impaired by pathogenic mutations in the cardiac actin gene comes from [119]. They showed that different mutations incorporate differently into the actin filament and destabilize the filaments. A destabilization of actin filaments has also been described by Hassoun et al. [114], and pediatric RCM mutations in *TNNI3* have been demonstrated to largely affect the integrity of reconstituted thin filament structure [104].

Other targets for pathogenic mutations are the genes of the three subunits of the troponin complex: cTnC, cTnI, and cTnT. They are associated mostly with HCM and DCM. However, *TNNI3* mutations frequently result in RCM [4]. They affect Ca^{2+}-sensitivity via impaired intra- and intermolecular interactions as well as via impaired posttranslational modifications. Hypercontractility-induced increase in ROS leads to oxidation of not only lipids, nucleic acids, or protein kinases but also sarcomeric proteins. It has been shown by Budde et al. [120] that oxidation of cardiac troponin I and cardiac MyBPC reduced phosphorylation by PKA and PKC and thereby contributed to the impairment of force production. The effects could be reversed fully by using antioxidants and partly by supplementing PKA. Also, specific oxidations of actin or titin have been associated with development of heart diseases [121, 122].

4.2 Cardiac remodeling

Enhanced ROS production leading to oxidative stress contributes to cardiac remodeling as fibrosis, another hallmark of cardiomyopathies, which leads to further contractile dysfunction via increased stiffness of the ventricular walls and also contributes to arrhythmia. Fibrosis occurs due to the activation of fibroblasts via stimulation of pro-fibrotic factors as TGF-ß, PDGF (platelet-derived growth factor), or cytokines and increased production and deposition of collagen I and III as well as cross-linking of the extracellular matrix (ECM). According to Li et al. [123], TGF-ß increases the expression of SerpinE2/nexin-1, leading to increased collagen deposition. Fibrosis as well as hypertrophic growth have been described to be linked also to ERK1/2, JNK, and p38 pathways. Furthermore, there seems to be an association between fibrosis, oxidative stress, and inflammation (for review see [124]). Even in young children, fibrosis could be observed, though the pathways in children have not been investigated. But there might be differences in signaling between children and adults [125]. Thus, in the case of DCM, a study revealed that children show much less interstitial and perivascular fibrosis than adult patients [126]. Furthermore, it seems that genes leading to an inflammatory response in DCM are expressed in adult but not pediatric patients. Also, differences between young children and adults in receptor physiology have been described. These aberrances will have consequences for the therapy of pediatric heart diseases [127].

Fibrous and/or fibrofatty infiltration leading to life-threatening arrhythmia is a hallmark of ACM, which is caused by genetic defects [128]. Genes modified include those encoding mostly desmosomal proteins (e.g., placophilin 2) and rarely junctional proteins as catenins, cytoskeletal proteins as TMEM43, and so on [129]. The molecular mechanisms of ACM development especially in children are not quite understood. ACM is strongly correlated to cardiomyocyte loss, which might be due to a stimulated apoptosis, since defects in desmosomal or junctional proteins lead to reduced cell adhesion and impaired sarcolemmal structure [130]. Apoptosis might be triggered by stimulated hippo pathways and fibrosis via WNT inhibition and TGF-ß pathways [129]. Fibrosis (together with deposits of protein aggregates, amyloidosis, glycogen storage defects), probably due to an impaired protein control system, might also be the causative for the stiffness observed especially with RCM [4]. Increased myocardial stiffness, however, is also observed in other heart diseases than RCM, as in heart failure with preserved rejection fraction, LNVC, and HCM. Increased myocardial stiffness leads to a reduced filling of the heart chambers with blood. Besides fibrosis and protein aggregates, the microtubular network, that is, microtubule density and its cross-linking with intermediate filaments, also contributes to the myocardial elasticity [131]. In addition, sarcomeric titin is a major player in myocardial stiffness. The ratio of the isoforms N2Ba and N2B is decisive [132]. But posttranslational modifications such as changes in titin phosphorylation also contribute to the alterations in stiffness [132–136].

For HCM and RCM but not ACM, another hallmark is the myocyte disarray, which according to Garcia-Canadilla et al. [137] in case of HCM mutations occurs very early, even before birth, indicating a developmental impairment at least in mice. In addition, cardiomyocyte disarray might contribute to arrhythmia associated with HCM/RCM. Molecular mechanisms leading to myocyte disarray are not known. In [138], a cell-to-cell imbalance in the expression of mutant proteins was described, which might lead to arrhythmias, myocyte disarray, and fibrosis.

Epigenetic modulations play a role in all cardiomyopathies. Thus, in HCM, hypertrophic growth is mediated by stimulating the expression of sarcomeric proteins. Hereby, a reprogramming occurs; fetal instead of adult proteins are expressed in adult HCM patients. In newborn CM patients, there might be a different mechanism, since some cardiac-specific genes such as *TNNI3* are expressed within the first year of life and gradually replace the fetal skeletal muscle isoform. In hypertrophic growth and reprogramming, calicneurin and the transcription factors NFAT, GATA4, NFkappaB, and MEF2 play a central role, nicely summarized by Dirkx et al. [139]. NFAT also regulates the expression of micro RNAs (miRNAs), which regulate mRNAs. In hypertrophy, miR23 is induced by targeting MURF1 and FOXO3a, both involved in cardiac remodeling [140, 141]. Epigenetic studies are largely missing in infant cardiomyopathy patients, and investigations are urgently needed. One of the few studies is [142], investigating miRNA profiles in children with heart failure. They found 17 miRNAs that were either not regulated (miR-130b, miR-204, miR-331-3p, miR-188-5p, miR-1281, miR-572, miR-765, miR-223, miR-125a-3p, and miR-1268) or antithetically regulated (miR-638, miR-7, miR-132, and miR-146a) in adult heart failure. Several of these miRs regulate genes, such as SMAD4, which are involved in the transition of hypertrophy to heart failure. In DCM, altered DNA methylation patterns and histone modifications and altered miR and lncRNA (long noncoding RNA) regulation have been identified in adult CM patients, but again, investigations in children are missing [143].

5. Diagnosis of cardiomyopathy in children

Considering the substantial risk of developmental disorders, disabilities, and mortality of children with cardiomyopathies, early detection, accurate classification, and treatment of cardiomyopathies in children are imperative [144–146]. Nevertheless, there is a gap in knowledge and a lack of consensus in the diagnostic approach, definition, and classification of cardiomyopathies in children [2]. Thus, the American Heart Association, in their latest publication, provided some suggestions in the form of a scientific statement instead of a clinical practice guideline. In this statement, a classification system for cardiomyopathy based on a hierarchy incorporating the required elements of the MOGE(S) classification was suggested. Manifestations of cardiomyopathy in children can range from a sole histopathological variation in cardiac tissue to congestive heart failure or sudden death [147–149]. The clinical presentation of patients with cardiomyopathy can resemble those with heart failure with reduced ejection fraction, including dyspnea on exertion, fluid retention and edema, lethargy, orthopnea, presyncope, syncope, and paroxysmal nocturnal dyspnea [26, 32]. Nevertheless, clinicians should be attentive to the rare types of cardiomyopathies such as LVNC or arrhythmogenic right ventricular (RV) dysplasia [37, 150]. Considering the variety of manifestations of cardiomyopathy, taking a thorough history of the patient and other family members as well as general physical examination concerning not only cardiac disorders but also possible extracardiac abnormalities, that is, Noonan syndrome, are essential for choosing the most relevant diagnostic modalities [2].

5.1 Laboratory parameters and biomarkers

A few biomarkers are used in the routine clinical approach to children with cardiomyopathies, which to some extent is due to the lack of reliable evidence. A high cardiac troponin concentration in serum can support a diagnosis of myocarditis considering that other causes of ischemia (e.g., acute coronary syndrome and acute myocardial strain such as that induced by pulmonary embolism or recreational drug use) are uncommon in children. Given that natriuretic peptides have been reported in a study on adult patients to be markedly higher in patients with RCM, N-terminal pro-B-type natriuretic peptide may offer supportive evidence for RCM versus constrictive pericarditis [151]. However, studies are warranted to verify their applicability in children. Thus, for example, fibrotic pathways seem to vary age–dependently.

According to Woulfe et al. [152], fibrotic pathways in children (<18 years) were less active than in adults, though here again many more studies are needed [126, 153, 154]. A study of Miyamoto et al. [155] showed that the ß1: ß2 adrenoreceptor ratio differed significantly in pediatric HF patients from the one in adult patients. cAMP levels were commonly decreased in both adult and pediatric HF but were significantly higher in HF children than in HF adults. In addition, gene expressions of BNP, Cx43, and PP1ß and PP2A were regulated antithetically, indicating that signaling is differentially regulated in children and adults. However, it is already difficult to determine a normal BNP level since it alters with age of the children probably due to the maturation process of the heart from fetal to adult including alterations in gene expression and metabolism [156]. This development largely takes place within the first year after birth.

Several biological roles of miRNAs have been identified so far in cardiac development and diseases [157]. Accordingly, emerging studies have revealed the potential utility of miRNAs as biomarkers for the detection of DCM, myocarditis, and the evaluation of heart failure in children [158–160]. The study of Jiao et al. [159] reported an area under the curve (AUC) of up to 0.992, suggesting that these circulating miRNAs may be useful for DCM detection and diagnosis in children. Nevertheless, the studies evaluating the diagnostic role of miRNA in cardiomyopathy in children are sparse. Furthermore, the study of Miyamoto et al. [158] emphasized the inapplicability of employing an adult miRNA profile as a circulating biomarker for pediatric patients, highlighting the significance of developing a signature of circulating miRNAs in this population. Moreover, there are not many miRNAs that are consistent among studies. Therefore, further studies are warranted to find common miRNAs to be accepted as validated biomolecules in the diagnostics of cardiomyopathies.

5.2 Genetic testing

Considering that genetic causes play a major role in pediatric cardiomyopathies, genetic tests are indicated in most cases, not only for better classification but also for determining the cause and screening other family members. Autosomal-dominant inheritance is the most common mode of inheritance in familial isolated cardiomyopathy diagnosed in childhood, but X-linked inheritance and autosomal-recessive inheritance are also reported less frequently [18, 20]. Children with HCM and those with an affected first-degree relative have the highest likelihood of inheritance of a disease-causing mutation among those with isolated cardiomyopathy. Furthermore, HCM that develops in childhood is more likely to be caused by multiple disease-causing mutations compared with HCM that emerges in adulthood [161]. Therefore, it is advised to take into account a broad panel rather than targeted genetic testing when HCM manifests throughout childhood [161]. Thus, whole exome or even whole genome screening should be the gold standard to detect pathogenic or likely pathogenic mutations [162, 163]. Moreover, because the signs of syndromes may be missed at the initial presentation, particularly in infants or critically ill children, a comprehensive genetic examination is helpful. Nevertheless, comprehensive genetic counseling and a thorough family pedigree are essential for understanding the scope and implications of genetic testing. When a child with cardiomyopathy is confirmed to have a pathogenic mutation known to be related to cardiomyopathy, cascade genetic testing of family members is typically advised [2]. Notably, there are various limitations of genetic testing in children. A negative or nondiagnostic test result does not rule out the diagnosis of cardiomyopathy or the possibility that the cardiomyopathy may have a hereditary etiology. Moreover, adult data is the only source of information for commercial panels that may not be applicable to children [2].

5.3 Functional and structural assessment

Assessment of myocardial structural, valvular or coronary artery abnormalities, and cardiac functions by means of proper imaging techniques is considered the cornerstone for the diagnosis and classification of cardiomyopathies.

Electrocardiography and electrophysiology are essential in the diagnosis of some types of pediatric cardiomyopathies, such as ACM. Slow intraventricular conduction in electrophysiology examinations is typically detected in ACM, and most often, right bundle-branch block with right precordial repolarization variations can be detected in electrocardiography. Scar or delayed conduction can be evaluated in 3D using an emerging approach for the diagnosis of ACM called electroanatomic mapping [164–166].

Echocardiography, which is often the initial imaging modality in cardiomyopathy evaluation, provides an overview of structural parameters including chamber dimensions, volumes, wall dimensions, assessment of cardiac functional features such as Doppler traces of ventricular contractility (dP/dt), systolic-to-diastolic ratio, as well as tissue Doppler imaging and extents of myocardial deformation (strain and strain rate) [167]. Notably, no absolute values are attainable as the cutoff point for morphological parameters obtained from echocardiography in children, such as LV end-systolic dimension (LVESD), LV end-diastolic volume, and LV end-diastolic dimension (LVEDD), and they all should be interpreted regarding the z scores adjusted for patient size [168–170]. These parameters are essential to the classification of morphological types. A high LVEDD or LV end-diastolic volume, besides low LV functional parameters, is marker of a dilated, hypokinetic type. Increased wall thickness proposes HCM. Measuring the thickness-to-dimension ratio can aid in distinguishing between idiopathic DCM and myocarditis [2]. However, it is not easy to determine deviations from normal LV morphology, as somatic growth has to be taken into account while monitoring the progression, for example, of HCM or DCM [171]. Thus, performing an accurate assessment by echocardiography in children can be difficult. Specifically, evaluation of diastolic function in children has low interobserver consistency, and the results are not properly associated with invasive haemodynamic investigations; thus, it may not be able to accurately discriminate between cardiomyopathy phenotypes [172, 173].

Cardiac magnetic resonance imaging (cMRI) offers great advantages over echocardiography for the diagnosis and assessment of cardiomyopathies and transcends some limitations of echocardiography in children. Determination of structural features including chamber dimensions, wall thicknesses, and ventricular mass as well as functional parameters including flow rates, shunts, and regional wall motion abnormalities using cMRI can aid in the diagnosis and accurate classification of the cardiomyopathy [174, 175]. Furthermore, assessment of the presence and pattern of fibrosis in tissue with late gadolinium enhancement and also the determination of edema and hyperemia in cMRI are some exceptional properties of cMRI that aid in the noninvasive investigation of patients with cardiomyopathy (e.g., to distinguish the different types of HCM or to discriminate DCM versus myocarditis) [176]. The information acquired from cMRI can also help determine the possible causes of cardiomyopathies (e.g., cardiomyopathies secondary to iron overload). Strain parameters and RV morphology and physiology, which are important in diagnosing and classifying cardiomyopathies, can be evaluated more accurately with cMRI than with echocardiography.

Cardiac computed tomography (CT) and cardiac catheterization are rarely considered for the diagnosis and evaluation of pediatric cardiomyopathies. Cardiac catheterization can be helpful for haemodynamic assessment, performing endomyocardial biopsy, and surgical interventions in patients with amenable lesions [177]. In general, morphological evaluation of the heart in children and infants by imaging techniques as well as cardiac catheterization can be challenging due to the requirement of specialized training and equipment. The availability of both specialized medical professionals as well as equipment still is a major obstacle worldwide to improve the quality of care for patients with pediatric cardiomyopathies.

6. Treatment of pediatric cardiomyopathy

Pediatric cardiomyopathy is treated according to the distinct symptoms that each patient presents [15]. Various factors, including the specific type of cardiomyopathy, the disease's progression at the time of diagnosis, the patient's age, any coexisting medical conditions, the patient's tolerance for particular medications, and other factors, may affect the specific therapeutic procedures and interventions [15]. The therapeutic approach for pediatric cardiomyopathy options may include staged therapy for heart failure, lifestyle modifications, nutrition and strenuous physical activity restrictions, patient and parent education, implanted cardioverter-defibrillator installation, and, in refractory situations, consideration of heart transplantation [178, 179]. A multidisciplinary team of healthcare professionals, including pediatricians, pediatric cardiologists, hematologists, surgeons who specialize in pediatric cardiothoracic surgery, physical therapists, occupational therapists, and/or other healthcare professionals, may be needed to provide this type of treatment [179]. It is crucial to consider that medications and surgical methods for treating cardiomyopathy have mostly been tried and evaluated in adults. Thus, as also stated in a review by Loss et al. [180], pediatric management in general follows the guidelines for adult HF treatment. This is due to the lack of clinical trials with children, which are especially challenging due to difficulties in recruiting an adequate number of probands, high costs, and so on.

6.1 Noninvasive treatment

The usefulness of drugs developed mainly for adults in treating pediatric cardiomyopathy is only dimly documented. There are some studies showing that utilization of medicals as well as signaling differ in children and in adult heart failure patients. In the study of Pan et al. [156], diastolic diseases in children were treated with ACE-inhibitors (angiotensin-converting enzyme), ß-blockers, digitalis, calcium channel blockers, dopamine, and diuretics. In children with diastolic diseases but not CM, the medical treatment was largely successful and improved cardiac function. However, children with CM did not improve. Though, in this study, only few children with CM were included. However, the results underline the observation that medical treatments prescribed for adult patients with CM may not be proper for children with CM. For review on possible medical treatments in pediatric RCM, see [29]. Another nice review on HF drug therapies highlighting the gaps for pediatric HF management is by Das et al. [181].

Thus, to ascertain the long-term safety and efficacy of such medicines in the pediatric population, more studies are required. Some ongoing studies evaluate emerging methods for treatment of pediatric cardiomyopathies such as reducing mitochondrial oxidative stress by MitoQ (mitoquinol mesylate) for DCM, oral Ifetroban for Duchenne muscular dystrophy cardiomyopathy and DCM, or gene therapy for male patients with Danon disease [182–184]. Nonetheless, more investigations are required to determine the optimal therapy approaches for cardiomyopathies in children.

6.2 Minimally invasive and invasive treatments

Altarabsheh et al. evaluated the early and late results of children (<21 years) who underwent transaortic septal myectomy for obstructive HCM [185]. Although the results of this study supported the safety and efficiency of this approach, technical challenges are reported to be augmented in children due to limited exposure during the procedure and subsequently increased risk of suboptimal removal of obstructive muscle, iatrogenic injuries to aortic/mitral valves or papillary muscles, and aneurysm formation in ventricular apex due to excessive muscular resection. Some alternative approaches are also introduced in adult patients such as radiofrequency catheter ablation (RFCA) and alcohol septal ablation, but limited or no data are available for children with HCM [186–188]. There are also ongoing studies evaluating novel methods like intracoronary transplantation of stem cells in pediatric CM [189, 190]. Additionally, surgery in adults is also considered in cases with complex LV morphologic abnormalities, such as papillary muscle anomalies, aberrant intraventricular muscle bundles, intrinsic mitral valve disease (requiring repair or replacement), and associated CAD that necessitates bypass grafting [191].

Cardiac resynchronization therapy (with or without implantable cardioverter-defibrillator) is also available as another option for pediatric and adult patients with DCM with ventricular conduction delay. The goal of this treatment is to enhance heart function by reducing the delay in activation of the left ventricular free wall, which is frequently observed in patients with left ventricular systolic dysfunction. The treatment has been demonstrated to enhance survival in this group, restore coordination and relaxation of the heart chambers, and cause favorable cardiac remodeling. However, using the current suggested criteria, up to a third of patients do not see any therapeutic improvement [192]. Furthermore, recommendations about electrical device therapies for children with DCM are mainly adopted from those for adults but based on considerably less evidence [193].

Despite these promising approaches, often heart transplantation remains as the only treatment option for pediatric CM. The main problem is that waiting for a suitable heart often takes a long time, which the children do not have to survive. The mortality of children while on transplant wait-list might be as high as 17–30% and even higher for infants, due to the general shortage of donor hearts and the high refusal rate due to poor quality (80%) [194, 195]. Also here, a lack of consensus between different centers and listing programs leads to prominent differences in the potential outcomes. Thus, the waiting time has to be bridged by a mechanical circulatory support or total artificial heart, which is suboptimal especially for newborns and infants, due to the limited availability of suitable devices and the adverse effects on the following heart transplantation due to, for example, adhesions. Alternatively, an allograft transplantation can be tried, although here the same problems as the donor heart availability and utilization apply [196]. After transplantation, the problem of immunosuppression arises, bearing the risk of infections or developing cancer. Thus, at Duke University hospital, recently a newborn who in addition to heart failure had a T-cell deficiency has been successfully transplanted a heart together with thymus for the first time in spring 2022. In general, the posttransplant survival rates in children are highly variable and largely depend on comorbidities, general clinical status, the use of mechanical support devices, and, as a major factor, disease progression due to wait-list time.

7. Conclusion and future perspectives

Although pediatric cardiomyopathies share many aspects with CMs in adults, there is rising evidence of unique features that have implications for diagnosis and treatment. First of all, a standard guideline for the classification of CM by the scientific society is desperately needed, as a mutual approach is required for developing protocols and reporting the findings. Age-based scales for diagnostic parameters for distinguishing between normal and abnormal conditions have to be established and adjusted for children.

Furthermore, we need to increase awareness of the medical community to avoid using the same CM therapeutic protocols of adults for children when their experimental evidence did not include children or excluded them. In the future, besides genetic testing (whole exome or whole genome), family analysis and analysis of specific biomarkers and investigation of molecular mechanisms in children will further support diagnosis and treatment design. In addition, large well-conceived trials are needed to increase the efficacy of medical treatments in children. Not only physical/mental effects but also developmental effects of therapeutic practices have to be investigated in long-term cohort studies.

Specifically optimized, mechanical circulatory supports for small children have to be developed that will reduce the deaths while awaiting heart transplantation. The assessment of donor heart suitability needs to be improved and standardized to reduce transplantation wait-list time. Also, increased allograft utilization may contribute to improved survival rates until transplantation, together with modified postoperative care and monitoring optimized for pediatric patients.

An interesting, though controversial, topic in the future might be xenotransplantation, considering the increasing demands for pediatric heart transplantation and advances in tissue engineering and genetic modification of, for example, animal donors. Though ethically highly debated, a survey of congenital heart surgeons revealed a generally high acceptance (80–88%) of xenotransplantation [197].

Acknowledgements

Part of this work was kindly supported by the Boehringer Ingelheim Fonds (S.-R. Sadat-Ebrahimi).

Conflict of interest

The authors declare no conflict of interest.

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