Molecular and Cellular Mechanisms in Heart Failure

Ilaria Puggia[1,2], Teisha J. Rowland[1], Shelley D. Miyamoto[3], Gianfranco Sinagra[2], Luisa Mestroni[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, United States; [2]Hospital and University of Trieste, Trieste, Italy; [3]University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO, United States

INTRODUCTION

Heart failure (HF) is classically defined as a "clinical syndrome caused by the inability of the heart to supply blood to the tissues commensurate to the metabolic needs of that tissue" [1,2]. HF results from ventricular dysfunction and volume or pressure overload, alone or in combination, and involves circulatory, neurohormonal, and molecular abnormalities [3]. Clinical presentation and etiology of HF is widely heterogeneous in the pediatric population and also differs greatly between children and adults [4]. Generally, in the pediatric population, the main causes of HF are congenital heart diseases (CHD) and cardiomyopathies. Although CHD is the most common cause of severe HF in the infant population, cardiomyopathies are the most common cause of HF and indication for heart transplantation in older children and adolescents [4], and will be the focus of our discussion in this chapter.

While the etiology of many cardiomyopathies remains unknown (idiopathic), genetic defects (primary forms) or other pathogenic conditions have been implicated. In the primary forms of cardiomyopathy, mutations of genes encoding a variety of structural and functional cellular proteins are involved. In particular, genetic abnormalities of the sarcomere, cytoskeleton, cell membrane proteins, and ion channels have been extensively investigated as causes of cardiomyopathies. Moreover, genetic mutations involving sarcomeric and cytoskeletal proteins may promote the progression of HF through ventricular remodeling, a process resulting from complex and numerous molecular mechanisms including inflammation, oxidative stress, mitochondrial dysfunction, loss of cardiomyocytes, and eventually the fibrotic replacement of myocardial tissue. Understanding the molecular and cellular mechanisms of HF could be exploited in prognostic stratification and clinical management of pediatric patients through identification of biomarkers such as inflammatory mediators or microRNAs (miRNAs). In particular, the expression of specific miRNAs seems to have a role in HF progression in adult populations, and thus miRNAs are currently being investigated as potential therapeutic targets.

Finally, due to a paucity of evidence specific to the pediatric population, treatment of HF in children is primarily based on adult HF guidelines [4]. However, therapies that are known to be effective in adults do not seem to have the same benefit in the pediatric population, and HF outcomes in children have been slow to improve [5]. There are likely many reasons for this differential response to therapy, including the heterogeneous etiologies of HF in children as well as distinctive, age-related molecular and cellular mechanisms of HF. Accordingly, processes involving tissue regeneration and repair after myocardial injury may be different between the young and old. In fact, cardiomyocyte proliferation rate seems to be higher in children than in adults, in whom it is low or absent [6]. This could have important implications in myocardial regenerative therapeutic strategies that are currently under evaluation, which are explored in the final section of this chapter.

GENETICS OF CARDIAC DYSFUNCTION AND HEART FAILURE

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a myocardial disease characterized by dilation and systolic dysfunction of the left ventricle. Right ventricular dilation and dysfunction may also be present [7]. DCM is the most common cause of HF and indication for transplantation in children. According to the North American Pediatric Cardiomyopathy Registry (PCMR), 71% of children with DCM present with congestive HF at diagnosis and the 1- and 5-year rates of death or heart transplantation are 31% and 46%, respectively [8]. There are 0.58 cases of DCM per 100,000 pediatric patients (<18 years old) per year [8], with

more boys being affected than girls (0.66 vs. 0.47 per 100,000) and more infants (<1 year old) affected than older children (>1 year old; 4.40 vs. 0.34 cases per 100,000) [9].

DCM is a complex multifactorial disorder that can derive from genetic causes or could be secondary to myocarditis, valvular disease, tachyarrhythmias, cardiotoxic drugs such as chemotherapy, or vascular or immunologic diseases [10]. Unfortunately there is no known cause for the majority of children with DCM (idiopathic), with only about a third of young DCM patients with an identified cause, 5% of them having a familial form [8]. However, many of the idiopathic cases of DCM may also be due to genetic causes. These DCM cases can be mislabeled as idiopathic due to various factors that make identifying the genetic cause difficult, such as a small family size, poor familial history, high genetic heterogeneity of the disease, and low penetrance of the particular genetic variant [11]. De novo genetic variants, while not "familial," may result in a diagnosis of idiopathic DCM, but ultimately may be disease causing [11].

Pediatric and adult DCM share mutations in genes encoding a variety of proteins of the sarcomere, cytoskeleton, nuclear envelope, sarcolemma, ion channels, and intercellular junctions. While it may seem counterintuitive that mutations in such apparently diverse proteins can result in a similar clinical phenotype (i.e., DCM), this similarity is due to these proteins having shared functions or participating in overlapping or related molecular pathways [12]. Overall, genetic mutations are thought to generate DCM phenotypes through impairment of myocardial cell function in terms of contractility and electrical conduction (the latter of which typically results in arrhythmias). For many relevant genes, a single gene mutation that alters the expression of a relevant contractile protein and modifies myocyte structure has been shown to be sufficient to cause DCM and myocardial failure in human and animal models [13,14].

According to recent studies, the most frequent mutations in DCM are thought to be ones that cause truncations of the titin protein (responsible for 18% and 25% of all idiopathic and familial DCM cases, respectively). Titin is the largest-know human protein and functions as a molecular spring by connecting the Z line and the M line in the sarcomere, providing passive force and elasticity in the contraction process [15]. Sarcomeres consist of long, fibrous proteins that contract and relax, and repeated sections of sarcomeres make up the tubular myofibrils (Fig. 1.1). While truncation mutations of the titin gene (TTN) are thought to cause DCM, the pathogenic role of TTN missense mutations is less clear, although they are likely primarily benign [16].

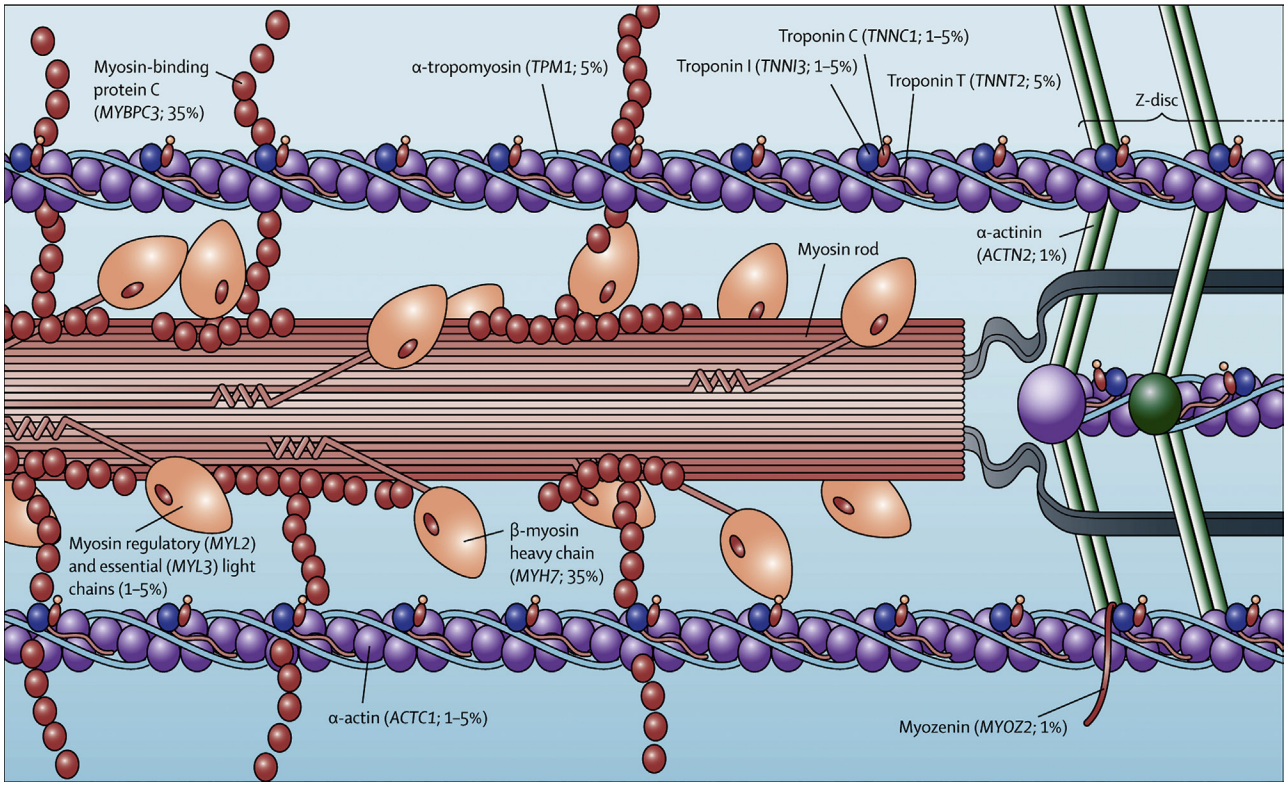

FIGURE 1.1 **Structure of a sarcomere.** Sarcomeres consist of long, fibrous proteins that contract and relax. Mutations in genes encoding the different components of the sarcomere are a frequent cause of dilated cardiomyopathy. *(Reprinted from B.J. Maron, M.S. Maron, Hypertrophic cardiomyopathy, Lancet 381 (9862) (January 19, 2013) 242–255, with permission.)*

Mutations of other genes encoding sarcomeric proteins comprise the next largest group of DCM cases with an identified genetic cause, accounting for 5%–10% of all DCM cases. These sarcomeric genes include the myosin heavy chain 6 (MYH6) and 7 (MYH7), myosin-binding protein C (MYBPC3), α-actin cardiac muscle 1 (ACTC1) and 2 (ACTC2), and α-tropomyosin (TPM1) [11]. DCM-causing sarcomeric mutations typically result in the disruption of a coupling–uncoupling mechanism of the sarcomere that results in a reduction of sarcomere contractility and produces systolic ventricular dysfunction. Recently, studies have shown that mutations in the gene encoding the BCL2-associated athanogene 3 protein (BAG3) are linked to DCM; the BAG3 protein is a cochaperone with antiapoptotic function that is localized to the Z-disc of the striated muscle, and mutations of this gene seem to induce cell apoptosis under metabolic stress. It is estimated that BAG3 mutations are present in 2.8% of Japanese families affected by DCM [17].

Another gene in which mutations can cause DCM is the gene encoding the protein lamin A/C (LMNA); mutations in LMNA are thought to account for 8% of DCM cases and are typically inherited in an autosomal dominant manner [18]. The clinical phenotype of individuals with DCM due to a LMNA variant is characterized by fast or slow arrhythmias, conduction disease, and in some cases variable degrees of skeletal muscle involvement (such as Limb-Girdle Muscular Dystrophy and Emery–Dreifuss Muscular Dystrophy). Association with Familial Partial Lipodystrophy has also been described. Lamins are intermediate filaments that provide strength and stability to the nuclear envelope, which can control the traffic into, and out of, the nucleus, and in this way may regulate the expression of specific genes.

Mutations in genes encoding the cytoskeleton are also known to result in DCM, and in these cases the disease is frequently associated with skeletal myopathy. Specifically, mutations in DES, the gene that encodes the protein desmin, can cause DCM associated with a conduction disorder and myopathy [19]. Mutations in the gene encoding dystrophin (DMD), which connects the cytoskeleton to the extracellular matrix (ECM), can result in an X-linked form of DCM and a skeletal myopathy, specifically Duchenne and Becker muscular dystrophy [20].

Ion channel mutations are associated with DCM frequently with an arrhythmogenic phenotype. Mutations in the gene encoding the sodium channel, voltage-gated, type V α subunit (SCN5A) account for 1.7% of DCM cases and are characterized by an early onset, the presence of conduction disease, and arrhythmias (atrial and ventricular) [21]. Mutations of the phospholamban protein (encoded by the PLN gene), which is involved in regulating the activity of calcium ion pumps (specifically SERCA2a) in cardiac tissue, can lead to DCM through inhibition of these pumps. SERCA2a is an isoform of the cardiac sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) protein (Fig. 1.2). SERCA2 is the SERCA isoform mainly expressed in cardiomyocytes, and it uses ATP to transport Ca^{2+} released during excitation–contraction coupling against the electrochemical gradient [22]. A PLN founder mutation (R14del) is associated with a high risk of ventricular arrhythmias and end-stage HF in late adolescence [23] and can present as an arrhythmogenic right ventricular cardiomyopathy (ARVC) phenotype.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a disease characterized by left ventricular (LV) or septal hypertrophy associated with normal to hyperdynamic systolic function, no dilation of ventricular chambers, and the absence of another cardiac or systemic disease that would cause the hypertrophy [24]. HCM can be classified as being symmetric (involving the LV and septum) or asymmetric (with only septal hypertrophy and normal LV posterior wall thickness). Most individuals who inherit a disease-causing HCM mutation typically present with LV or septal hypertrophy during adolescence, with disease completely manifesting at physical maturity (age ≥17 years). According to the PCMR, the annual incidence of the disease is 0.47 per 100,000 children, making it slightly less common than DCM in the pediatric population [8]. However, HCM is still one of the most frequent causes of life-threatening arrhythmias or sudden death (SD) in young individuals, with an annual mortality rate of 1% [25]. HCM rarely progresses to HF in the pediatric population (with only 13% of pediatric HCM patients developing HF, according to registry data). 8%–9% of infants with HCM have a malformation syndrome (e.g., Noonan, Costello, or Multiple-Lentigines syndrome), a metabolism disorder (e.g., Pompe disease or Danon disease), or a neuromuscular disease [8], which causes additional complications.

Most HCM cases are idiopathic or have an underlying genetic cause (the latter of which comprises almost 50% of cases) [26]. The genetic transmission of the disease is usually autosomal dominant, but maternally inherited mitochondrial patterns of transmission have also been reported [26]. As in DCM, sarcomeric gene mutations are a significant cause of HCM, consisting of 60% of HCM cases with a genetic etiology [27]. They include mutations in MYH6, MYH7, MYBPC3, TPM1, ACTC1, ACTC2, TTN, myosin essential light chain (MLC17), myosin light chain kinase (MYLK), and troponin T type 2 (TNNT2). Mutations in genes encoding nonsarcomeric proteins within the z-disc (e.g., LBD3) and calcium handling control mechanisms (e.g., PLN) can result in a similar HCM phenotype [28]. It is possible particularly for a young individual in an affected family who is positive for an HCM-causing variant to have a normal phenotype, demonstrating a lack of full penetrance.

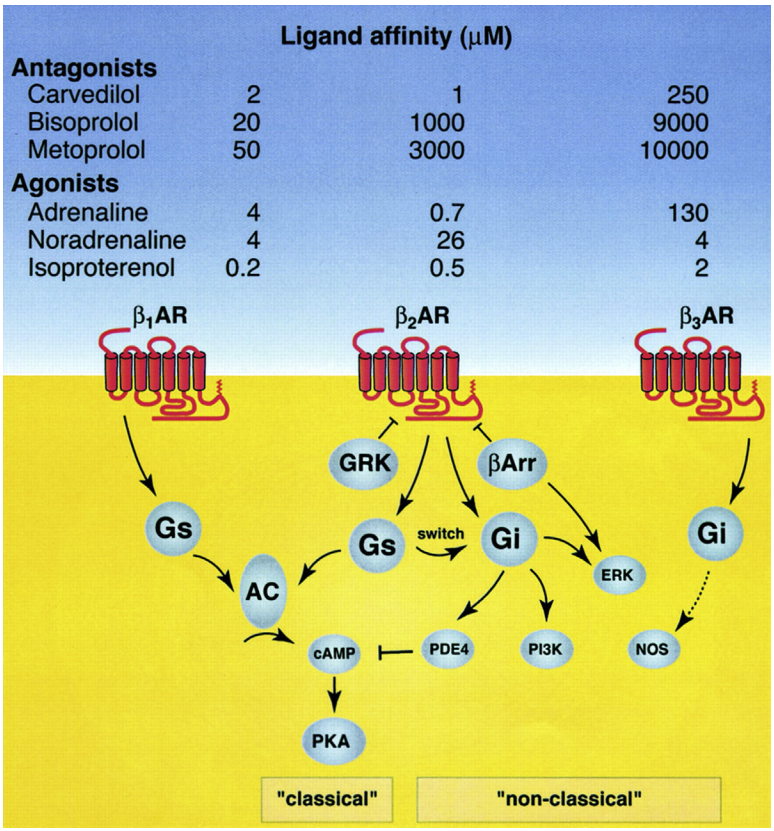

FIGURE 1.2 **β-adrenergic activation.** β1-adrenergic receptors (AR) are the main contributors to the cardiac contractility, β2 are the predominant subtype in most vascular and bronchial smooth cells, while β3 are present in adipose tissue. In the heart, adrenergic agonists bind β1-AR, stimulating the production of cAMP thought G stimulatory protein, and activating PKA. *AC*, adenylyl cyclase; *β Arr*, β-arrestin; *cAMP*, cyclic adenosine monophosphate; *ERK*, extracellular-signal receptor kinase; *Gi*, G inhibitory protein; *GRK*; G protein-coupled receptor kinase; *GS*, G stimulatory protein; *NOS*, nitric oxide synthase; *PDE*, phosphodiesterase; *PI3K*, phosphatidylinositol 3-kinase; *PKA*, protein kinase A. *(Reprinted from M.J. Lohse,* S. Engelhardt, T. Eschenhagen. *What is the role of β-adrenergic signaling in heart failure? Circ. Res. 93 (10) (October 23, 2003) 896–906, with permission.)*

Notably, HCM can be characterized by an obstructive or a nonobstructive phenotype. It is well known that the presence of LV obstruction increases the risk of HF progression by fourfold (compared to patients without obstruction). The likely underlying mechanism of HF in these patients is the chronic elevation of LV pressure secondary to the obstruction, which progressively leads to increased wall stress, myocardial ischemia, and consequent fibrosis. In this case, stiffness of the LV produces a variable degree of diastolic dysfunction, which causes congestive HF symptoms [29]. In nonobstructive HCM disease with a small ventricular cavity, diastolic dysfunction can also occur with even mild or moderate hypertrophy and preserved LV systolic function. Uncontrolled atrial fibrillation can result in progression of HF, especially in presence of obstructive disease. Finally, in the end stage of HCM disease, systolic LV dysfunction may develop and the ventricular chamber can remodel and dilate over time. Mice expressing mutant myosin heavy chains are characterized by a development of hypertrophy and then a late ventricular dilation and decompensation [30]. In human HCM-end-stage hearts, LV dilation and wall thinning are often seen. This is thought to be due to fibrosis that replaces myocardial tissue, especially in the LV septum and free wall [31,32]. A recurrent and silent myocardial ischemia may lead to this scarring and a consequent loss of contractile function [32] (this is further explored later in this chapter in the section "Inflammatory Signaling and Fibrosis").

Left Ventricular Noncompaction

Left ventricular noncompaction (LVNC) is a cardiomyopathy characterized by hypertrabeculation of the LV. According to PCMR registry data, 4.8% of children with a cardiomyopathy specifically have LVNC [33]. LVNC is thought to represent an arrest in the normal process of myocardial compaction, at the end of myocardial morphogenensis [7]. In particular, the NOTCH signaling pathway (a crucial pathway involved in several differentiation processes including cardiac embryonic

development) seems to be affected. This results in a persistence of deep trabeculations and intratrabecular recesses resembling the right ventricular morphology [34].

LVNC can be associated with a normal LV size and normal systolic and diastolic function [35]. However, in some cases, underlying arrhythmias are present. LVNC can also occur in association with LV systolic dilation and dysfunction, and when this happens the cardiomyopathy mimics DCM in terms of signs and symptoms, but in young children the outcome is worse than for those with DCM [7]. LVNC can be associated with LV thickening, usually with asymmetric septal hypertrophy, diastolic dysfunction, and hypercontractile systolic function [36]. Other forms of LVNC, such as those with a restrictive phenotype, are rare. LVNC can also be associated with CHD. Similarly to other cardiomyopathy forms, LVNC is known to have genetic causes; several mutations have been identified that are associated with this disease. The first mutation described was in the X-linked gene TAZ (which encodes for tafazzin) and resulted in Barth syndrome (see also "Mitochondrial Dysfunction" section) [37]. Mutations in the Z-line protein-encoding gene LDB3, in the sarcomere genes (MYH7, ACTC, TNNT2, MYBPC3, TPM1, and TNNI3), in LMNA, in dystrophin, in SCN5A, and in DSP have all been reported to have associations with LVNC [38–44].

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is a rare cardiomyopathy, with prevalence in the general population estimated to range from 1 in 1000 to 1 in 5000 [45]. In the PCMR, 5% of pediatric patients are affected by ARVC [8]. This cardiomyopathy is usually diagnosed between 20 and 40 years of age, and rarely in individuals younger than 10 years old. Criteria for ARVC diagnosis are well established [46], with it being characterized by a fibro-fatty replacement progressing from the right ventricular epicardium to ultimately becoming transmural. This gradual fibro-fatty replacement interferes with electric impulse conduction, leading to ventricular arrhythmias that often have LV involvement [45]. Among children and young adults it is important to suspect this disease in the presence of recurrent ventricular arrhythmias and a suggestive family history of ARVC or SD. While SD in young asymptomatic ARVC gene carriers may be the first sign of disease, HF mimicking DCM is a less common presentation in the pediatric population [45].

On a molecular and cellular level, ARVC is thought to be caused by defects in cellular adhesion due to mutations in desmosomal genes, including plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and plakoglobin (JUP). Recently, mutations in TTN have also been identified in some ARVC families [47]. In this particular case, a recent study demonstrated that carriers of TTN mutations have a greater risk for supraventricular arrhythmias and conduction disease but a better prognosis than ARVC patients who are desmosomal gene mutation carriers [48]. Mutations in genes that do not encode for demosomal proteins, such as RYR2 and TGFB, have additionally been found to be associated with ARVC [49,50]. Interestingly, PLN (also associated with DCM, as discussed above) and TMEM43 gene variants have also been found to be associated with ARVC, with a TMEM43 missense mutation having been identified as a "founder" ARVC variant observed in populations of the Newfoundland islands and affecting both adults and children [51].

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is very rare in childhood, with typically only 5% of pediatric cardiomyopathy patients being affected, based on data from the PCMR [8]. Prognosis for these pediatric patients is often poor, and heart transplantation is usually required. In the adult population, etiologies of RCM can include amyloidosis, sarcoidosis, hemosiderosis, glycogenoses, endomyocardial fibroelastosis, scleroderma, and therapeutic radiation. In children, this disease is often idiopathic, but can also be familial. An important cause of pediatric cases of RCM is mutations in sarcomeric genes [52]. Rarely RCM is caused by an accumulation of mutated desmin proteins in the cardiomyocytes and, in these cases, it is associated with atrioventricular block [53]. Recently, it was demonstrated that mutations in TTN can also cause this disease [54]. HF develops due to a restrictive ventricular physiology and increased filling pressure. The affected heart is characterized by marked atrial enlargement, normal or reduced ventricular diastolic volumes, normal ventricular wall thickness, and (usually) preserved LV ejection fraction [10].

MOLECULAR MECHANISMS OF HEART FAILURE

Ventricular Remodeling

Ventricular remodeling is the process resulting in a modification of structure and function of the heart after an injury of the myocardium that can lead to HF (Table 1.1). This condition is promoted by changes in energetic metabolism,

TABLE 1.1 Some of the Most Important Mechanisms of Ventricular Remodeling in Heart Failure

Mechanisms	Mediators
Genetic mechanism	Cytoskeletal gene mutations
	Sarcomeric gene mutations
	Signaling gene mutations
	Reactivation of "fetal program"
	Posttranslational mRNA modifications
Compensatory mechanisms	β-adrenergic pathway
	Renin–angiotensin–aldosterone system
Inflammatory signaling	Oxidative stress
	Fibrosis
Mitochondrial dysfunction	Reduced energy supply

excitation–contraction coupling, Ca^{2+} handling, contractile proteins or their regulatory elements, or cytoskeleton components [55]. Potentially, changes in the expression of the genes responsible for all of these functions are present in the failing heart and promote the remodeling process [56].

In HF, typically, the primary response is hypertrophic growth of the myocytes in an effort to reduce wall stress of the ventricle in the presence of a pressure or volume overload [55]. A pressure overload could be the consequence of left-sided obstruction, such as in obstructive HCM, severe congenital aortic or subaortic stenosis, aortic coarctation, or hypertensive disorders [4]. In cases with pressure overload, an increase in LV wall thickness due to the parallel assembly of sarcomeres and the growth of the cross-sectional area of cardiomyocytes with a normal chamber volume (i.e., concentric remodeling) occurs [57].

A ventricular volume overload is due to left–right ventricular shunting and atrioventricular or semilunar valve regurgitations [4]. Ventricular volume overload is specifically characterized by the in series array of sarcomeres and longitudinal cardiomyocyte growth. This provokes eccentric hypertrophy with an increase in chamber volume. If stress is prolonged, this leads to a decompensation phase of the failing heart. According to La Place law, the increase of ventricular volume associated with a reduction of thickness promotes wall stress, one of the major determinants of myocardial oxygen consumption. This leads to a shift toward anaerobic glycolytic metabolism, which alters the subcellular ion flux, and contributes to cardiomyocyte dysfunction and consequently to the development of HF [56].

Pathophysiological changes are accompanied by reactivation of fetal gene expression programs (which are normally postnatally downregulated) and repression of the expression of several adult genes. The induction of fetal genes provokes an increase in expression of MYH7, ACTA1, B-type natriuretic peptide, and atrial natriuretic peptide and a decrease in MYH6 and SERCA2. While this gene expression pattern is most well described in adult HF, the decrease of MYH6 was demonstrated to occur in pediatric DCM as well [58]. As a consequence of these gene expression alterations, the quality and bioenergetic yield of contractile proteins and their functions becomes reduced [56,59].

Lastly, cardiomyocyte function is modulated by the β-adrenergic pathway with its inotropic and chromotropic effects. In HF, β-adrenergic stimulation is attenuated because of multiple changes at the signaling level, specifically of G proteins and adenylyl cyclase; this is discussed in further detail in the following section. Finally, at the same time, reduction in parasympathetic drive occurs [60].

Compensatory Mechanisms of Heart Failure

In the development of HF, the role of compensatory mechanisms is crucial. It is well known that the activation of the adrenergic nervous system and renin–angiotensin–aldosterone system (RAAS) contributes to, or is responsible for, the progression of HF. Based on this fact, clinical HF trials in adults have demonstrated the usefulness of angiotensin converting enzyme inhibitors [61–65], angiotensin receptor blockers [66,67], aldosterone receptor antagonist [68,69], and beta blockers [70–73].

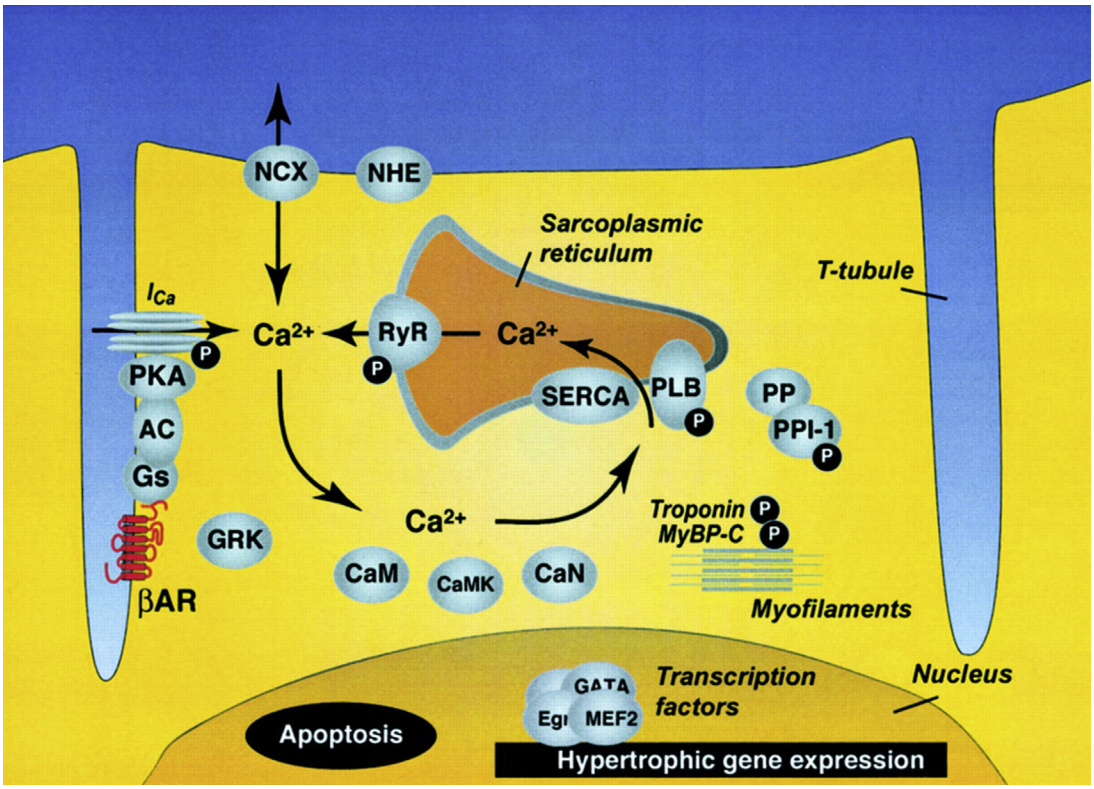

FIGURE 1.3 **Ca^{2+} cycling in cardiomyocytes.** PKA activity affects the cardiac excitation–contraction coupling thought phosphorylation, by increasing intracellular Ca^{2+}, its reuptake in sarcoplasmic reticulum, and the Ca^{+} sensitivity of myofilaments. *AC*, adenylyl cyclase; *AR*, adrenergic receptor; *CaM*, calmodulin; *CaMK*, calmodulin-dependent kinase; *CaN*, calcineurin; *GRK*, G protein-coupled receptor kinase; *GS*, G stimulatory protein; *NCX*, sodium–calcium exchanger; *NHE*, sodium–proton exchanger; *PKA*, protein kinase A; *PLB*, phospholamban; *PP*, protein phosphatase; *RyR*, ryanodine receptor; *SERCA*, sarcoplasmic reticulum calcium ATPase. *(Reprinted from M.J. Lohse, What is the role of β-adrenergic signaling in heart failure? Circ. Res. 93 (10) (October 23, 2003) 896–906, with permission.)*

When a myocardial insult causes systolic dysfunction, β-adrenergic activation (through the β-1 and β-2 receptors) increases heart rate and contractility acutely. The Frank–Starling mechanism is activated in a few hours (by a volume expansion that increases the stroke volume), and cardiac myocyte hypertrophy increases the number of contractile elements in days to 1 week [56]. At the cellular level, the β-adrenergic signaling pathway initially results in increased levels of cyclic adenosine monophosphate (cAMP) through the activation of adenylyl cyclases via stimulatory G proteins. Increased cAMP levels lead to activation of protein kinase A, which phosphorylate several proteins, such as L-type calcium channels, PLN, troponin I, ryanodine receptors, MYBPC3, and protein phosphatase inhibitor-1. This results in impacted myocardial contractility: the phosphorylation of L-type calcium channels increases the Ca^{2+} flux, while the phosphorylation of PLN and SERCA increases the reuptake of Ca^{2+} into the sarcoplasmic reticulum, and MYBPC3 and troponin I phosphorylation modulates the myofilament Ca^{2+} sensitivity. These compensatory adjustments can lead to a stable condition for some days or even months, but they create damage over the long term; chronic stimulation of the β-adrenergic system results in downregulation and desensitization of the β1-adrenergic receptor, resulting in decreased cAMP, dephosphorylation of phospholamban, and repression of SERCA2A activity (Fig. 1.3) [56].

Many differences between adult and pediatric HF populations in terms of myocellular mechanisms (on examination of explanted hearts) have been reported (for a recent review, see Miyamoto et al.) [58]. As one such example [74,75], in adult HF the PLN protein is dephosphorylated, likely through elevated phosphatase activity, resulting in decreased Ca^{2+} reuptake in the sarcoplasmic reticulum. However, PLN phosphorylation has been demonstrated to be unchanged in pediatric HF. The pediatric population is also characterized by downregulation of both the β-1 and β-2 adrenergic receptors, whereas in adult HF the β-2 adrenergic receptor maintains its expression. Therefore, age-related differences in these compensatory mechanisms likely contribute to the different responses to HF therapy between adults and children. For example, a recent randomized controlled trial of carvedilol in pediatric HF patients showed an absence of improvement in long-term mortality, even though this therapy has been shown to be effective in adult patients [76]. While there likely are subsets of pediatric patients that respond to

adult-based therapies such as carvedilol, the heterogeneity of pediatric HF and differential age-related adaptations make direct extrapolation of adult HF data challenging. On the other hand, the use of phosphodiesterase 3 inhibitors (PDE3i) in pediatric DCM patients with HF demonstrates an improvement of HF symptoms without an increase in SD and life-threatening arrhythmias, both of which are seen in adults treated with PDE3i [77]. This beneficial treatment response in children may be due to augmented cAMP expression with PDE3i treatment and preserved phospholamban phosphorylation unique to the pediatric failing heart [78]. The unique myocellular changes in pediatric HF continue to be under investigation.

Inflammatory Signaling and Fibrosis

Fibrosis is a determinant of HF outcome, and addressing it using effective antifibrotic therapies in adult HF is crucial for improving patient prognosis. There is a knowledge gap regarding the pathogenesis of fibrosis in children with HF, but pathways of stress-induced fibrosis are thought to be similar in pediatric and adult hearts [79]. Cardiac fibrosis is caused by an irregular deposition of ECM proteins in the cardiac interstitium. The fibroblasts that are central to this process are derived from the differentiation of epicardial cells through endothelial–mesenchymal transformation, which is a process that can be reactivated in adult hearts during stress (e.g., pressure overload) [80] or similarly in pediatric hearts with HCM [81]. Other cells contribute to cardiac fibrosis, including monocytes/macrophages, lymphocytes, mast cells, vascular cells, and cardiomyocytes.

Inflammatory cytokines and chemokines, reactive oxygen species (ROS), matrix metalloproteinases (MMPs), and growth factors (e.g., TGFβ and PDGF) are some of the main fibrosis mediators [82]. Fibrosis can be stimulated by long-term activation of the RAAS. Specifically in the RAAS, angiotensin II (AT II) induces increased levels of aldosterone, which promotes LV remodeling and dysfunction [83,84]. Fibrosis can also be caused by an imbalance between MMPs (which are a family of zinc-dependent enzymes involved in the degradation of the ECM) and their inhibitors, with irregular upregulation of the inhibitors, which can occur during pressure overload. On the other hand, in volume overload (i.e., valvular regurgitation), an overexpression of MMPs occurs [85].

Fibrosis contributes to both diastolic and systolic LV dysfunction, interfering with myocardial excitation–contraction coupling [86]. Initially, fibrosis is associated with an increase in stiffness and a consequent diastolic dysfunction. Over time, the prolonged degradation of the ECM caused by increased levels of MMPs leads to ventricular dilation and an impairment of the systolic function [87]. The generation of fibrotic tissue is also known to alter the electrical conduction of that tissue and creates reentry circuits that promote arrhythmogenesis [88]. Several cardiac diseases are characterized by fibrotic ventricular remodeling. Typically, loss of cell is followed by fibrosis that replaces myocardium with a collagen-based scar [89].

A cardiac condition in which fibrosis plays an important role is HCM. Related to the fibrotic process, elevated collagen accumulation is a hallmark of diastolic impairment in HCM [90]. Moreover, a high level of MMP-2 seems to be related to LV remodeling and a worse prognosis in HCM [91]. Collagen breakdown products and collagen turnover enzymes have also been found to be elevated in HCM patients' family members with pathogenic sarcomere mutations, even in the absence of septal hypertrophy and fibrosis, on clinical examination and MRI imaging. This suggests that increased degradation of collagen, indicating a prefibrotic state, could be present before clinical evidence reveals the presence of pathogenesis [92]. The trigger for increased myocardial fibrosis in this disease is unclear, but it seems to be related to sarcomere mutations and other pathological alterations, such as ischemia secondary to small vessel coronary disease. In fact, hypoxia is another stimuli of the fibrotic process. Studies have shown that increased expression levels of hypoxia-inducible factor 1-α in children with a positive HCM genotype is related to a more severe LV hypertrophy and diastolic dysfunction, and less freedom from surgical myectomy [81]. Finally, a lower oxygen supply in terms of fewer capillaries has been observed in many forms of human adaptive cardiomyopathies, including end-stage DCM. Oxygen deficiency provokes a degeneration of cardiomyocytes, a metabolic imbalance, and interstitial fibrosis [93].

Inflammation and Oxidative Stress in Heart Failure

Inflammation is not well studied in pediatric HF; here we will primarily explore what is known about inflammation in HF in adults, since the process is significantly better characterized.

Inflammation has a primary role in response to cardiac injuries (i.e., ischemia, virus) and secondarily in ventricular remodeling. Notably, tissue damage (e.g., a cardiac injury) can induce an innate immune system response through toll-like receptors, which activate nuclear factor kappa B (NF-κB) transcription factors. Whereas NF-κB activation is known to serve a cardioprotective role in the relatively short-term events of acute hypoxia and reperfusion (i.e., myocardial infarction (MI)) [94], long-term activation (such as caused by long-term cardiac damage) can promote HF through a chronic release of proinflammatory cytokines (i.e., cell signaling proteins) and chemokines (i.e., small cytokines) [95].

The RAAS and sympathetic nervous system are thought to also contribute to the production of cytokines in HF through catecholamines and neurohormonal activation of NF-κB [96]. Chemokines recruit leukocytes to the damaged myocardium; neutrophils and macrophages not only remove the dead cells but also produce other cytokines that promote a local inflammatory response. Cytokines such as tumor necrosis factor-alpha (TNFα) and interleukin 6 (IL-6) are known to directly cause decreases in myocardial contractility and induce myocyte hypertrophy, collagen deposition, and fibrosis [97]. In the same way, IL-1β promotes inflammation, myocardial collagen deposition, and cardiomyocyte apoptosis [98]. Moreover, a high level of circulating inflammatory biomarkers are found in adult HF patients and are associated with a negative prognosis; these include TNFα, the soluble TNFα receptor, and IL-6 [99–101]. On the other hand, high circulating levels of neutrophil gelatinase-associated lipocalin (NGAL) (which is upregulated via various proinflammatory stimuli, including TNFs) [102] are associated with a high negative prognostic value in patients with HF. NGAL levels are also known to be increased in young HF patients [103]. Therefore, stimuli that lead to chronic inflammation are important to analyze when determining if ventricular remodeling is occurring and remain an intriguing therapeutic target.

HF progression is promoted by the loss of cardiomyocytes through apoptosis (i.e., programmed cell death), which can involve regulation of downstream inflammation pathways. Studies have shown that apoptosis rates in patients with end-stage DCM are higher than in nonfailing control hearts. Classically, the apoptosis process is initiated by the activation of cell surface death receptors (i.e., Fas/FasL) that promote the caspase cascade, the latter of which can be critically important for regulating inflammation [104].

Another mechanism involved in ventricular dysfunction is oxidative stress. ROS have been reported to be present in myocardial tissues undergoing HF [105–107]. Aldosterone, produced by the RAAS, stimulates ROS production [108]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is an enzymatic complex that is also known to be a major source of ROS and is thought to have increased enzymatic activity in failing hearts (compared to nonfailing controls) [109] and plays a role in cardiac hypertrophy [110]. NADPH oxidase is activated by AT II, noradrenaline, TNFα, and increased mechanical forces. All these factors are involved in pathophysiology of HF as mentioned above. Finally, increased ROS production contributes to endothelial dysfunction [111] and LV remodeling and dysfunction [112], likely due to a reduction of endothelial nitric oxide synthase-derived nitric oxide (NO). Overall, there are multiple ways in which increased ROS production negatively impacts cardiac remodeling and HF, and a better understanding of these molecular mechanisms, especially in the pediatric population, may improve therapeutic approaches.

Mitochondrial Dysfunction

Augmentation of cardiac output required under times of increased metabolic demand requires mitochondria to be able to rapidly supply energy when needed [113]. The amount of energy, or cellular ATP, demanded by the cardiac tissue varies depending on the effort expended, but, for example, during times of high workload, turnover rate of the cardiac ATP pool can be as fast as 2 s [114,115], making the efficient function of the mitochondria essential for cardiac function. Because of the crucial role of mitochondria, cardiomyopathy is present in an estimated 20%–40% of these individuals [116], and consequently screening for cardiomyopathy has become a standard part of management for people with mitochondrial diseases (which may consist of at least 1 in 5000 live births [117]). Estimated frequencies of mitochondrial cardiomyopathies in pediatric patients are similar, affecting approximately 17%–40% of those with a mitochondrial disease [117–119], and mortality has been reported to be significantly higher in these children than in ones with mitochondrial disease but without cardiomyopathy (71% vs. 26%) [118]. While mitochondrial cardiomyopathies are genetically and phenotypically heterogeneous, in both pediatric and adult patients, HCM has been reported to be the most common cardiomyopathy form, although DCM and LVNC have also been found (comprising 58%, 29%, and 13%, respectively, of the cardiac group in one study of 113 pediatric patients) [116,119]. Some studies suggest that if candidates are selected carefully (i.e., mitochondrial disease isolated primarily to the heart), cardiac transplantation is a feasible treatment strategy [117]. The rest of this section will discuss the more common attributes of pediatric mitochondrial cardiomyopathies; for a recent and thorough review discussing mitochondrial cardiomyopathies in both children and adults see Brunel-Guitton et al. [116].

Barth syndrome is a rare X-linked genetic mitochondrial disease caused by mutations in the gene TAZ, which encodes Tafazzin, a mitochondrial enzyme involved in remodeling cardiolipin. Cardiolipin is a phospholipid primarily found in the inner mitochondrial membrane and is essential for ideal mitochondrial function by maintaining electron flux of the mitochondrial electron transport chain [116,120]. Cardiomyopathy in individuals with Barth syndrome nearly always appears before age 5, and the majority of Barth syndrome patients (73%) present with cardiomyopathy [121]. LVNC and DCM are the cardiomyopathies most commonly associated with this syndrome, while HCM is less common but has been reported [116,121].

Patients also have an increased risk of ventricular arrhythmia and sudden cardiac death. While there is often a significant cardiac component, part of the challenge of diagnosing Barth syndrome is its multisystem and variable nature; in addition to being characterized by cardiomyopathy, affected individuals can also possess skeletal myopathy, neutropenia, growth delay, and increased urinary excretion of 3-methylglutaconic acid [116,121]. Similar to Barth syndrome, a small number of other mitochondrial disorders have characteristic 3-methylglutaconic aciduria, with significant and consistent increases in excretion of 3-methylglutaconic acid in urine (40 to >1000 mmol/mol creatinine) [116,122]. This group includes cardiomyopathies (specifically early onset DCM or LVNC) caused by mutations in the gene encoding the DNAJC19 protein, which resides in the inner mitochondrial membrane, where it is a chaperone protein likely involved in protein import [116,123]. Additionally, it has been reported that pediatric patients with idiopathic DCM have significantly lower expression levels of cardiolipin and dysregulation of enzymes involved in cardiolipin biosynthesis and remodeling [120].

Other mitochondrial diseases that have characteristic cardiomyopathy in the pediatric population include mitochondrial fatty acid β-oxidation defects (FAODs) [116]. Fatty acids are an essential energy source for myocardium, and FAODs can cause a substantial decrease in fatty acid utilization that leads to cardiomyopathy by disrupting different, but interrelated, molecular mechanisms in ways that are not yet fully understood [116]. Clinical presentations of FAODs are variable, with the most severe forms being highly associated with neonatal death [124]. Neonatal presentations most frequently are characterized by cardiac features (22%–47% of cases; specifically cardiomyopathy or arrhythmias associated with SD) [125,126] or liver defects (92%; specifically hepatomegaly) [125], among other symptoms. FAOD presentations can be later-onset, although these are more likely to be myopathic in nature [116].

MicroRNAs

miRNAs (miRs) are relatively short (approximately 22 nucleotides long), single-stranded noncoding RNAs that can bind the complementary 3′ untranslated regions of target messenger RNA (mRNA) to repress gene translation [127]. Changes in the expression of specific miRNAs have been found to take place during heart disease progression; for example, decreased expression of miR-133 has been found to correlate with cardiac hypertrophy [128]. Significant similarities have also been found between the miRNA expression pattern in human failing hearts and fetal cardiac tissue, suggesting that reactivation of fetal miRNAs may contribute to altered gene expression in HF [129]. Such findings have implicated the involvement of miRNAs in heart disease progression, and consequently cardiac-related miRNA applications being pursued include both their use as biomarkers and as therapeutics [127,130,131]. However, while such a therapeutic approach may be advantageous compared to conventional drug molecules because there may be lessened or absent target desensitization (which is a problem with many classical drugs), therapeutic miRNAs potentially have many off-target effects as miRNAs target several mRNAs simultaneously [132]. That said, preclinical animal models are being tested for miRNA-based heart disease therapies, although no therapies have yet begun testing in human clinical trials [127].

Investigations into the potential role of miRNAs in pediatric cardiomyopathies have been limited and warrant more attention due to differences in clinical manifestations and treatment responses between adult and pediatric patients. Our investigations in a pediatric population found that the myocardial miRNA expression profiles of pediatric HF patients (with DCM) share little overlap with the profiles of adult patients with DCM, and such differences may contribute to age-specific differences in response to HF therapies such as PDE3i [133]. We later investigated the circulating miRNA expression profile of pediatric DCM patients to determine if circulating miRNAs could be used as biomarkers to predict patient outcomes [131]; while the 5-year rate of death or transplantation for children with DCM is devastatingly high (40%–60%), a small percentage of pediatric DCM patients recover ventricular function (15%–35%) [9,134,135]. While larger prospective investigations are needed, this study demonstrated that the expression of certain circulating miRNAs could predict recovery of heart function in pediatric subjects with severe DCM. Our study revealed a limited number of miRNAs that were significantly differentially expressed in patients who recovered compared to ones who were transplanted or died (specifically, two miRNAs were upregulated [miR-155 and miR-636] and two were downregulated [miR-646 and miR-639]) [131]. It is unclear whether any of these miRNAs contribute to ventricular function recovery; indeed, an area requiring much further investigation is correlating such descriptive studies of miRNA expression differences with miRNA regulatory mechanisms and outcomes on a molecular level.

MYOCARDIAL REGENERATIVE STRATEGIES

The field of cardiac regenerative medicine has been rapidly growing but has also frequently become an area of considerable controversy, primarily due to lack of reproducibility of findings and methodological heterogeneity. Because HF progression involves a loss of cardiomyocytes thought to be the underlying cause of the HF itself, and no current therapy targets this loss, there is great interest in improving the human heart's limited regenerative abilities [136–138]. (MI also results in a loss of cardiomyocytes, with estimations of more than a billion cells lost from a single MI event [138].) Such interest has led

to thousands of patients being enrolled in various clinical trials using stem cells to treat cardiac diseases over the past two decades [139]. Here we will discuss relevant studies investigating cardiomyocytes, cardiac progenitor cells (CPCs), bone marrow-derived stem cells (BMSCs), and pluripotent stem cells, while highlighting relevant pediatric findings.

While studies in neonatal mice and lower vertebrates, such as newts and zebrafish, have revealed these other organisms to have clear regenerative abilities [140–143], the situation has been more uncertain in humans due to the great difficulty of accurately assessing the regenerative capabilities of the human heart and isolating specific cell populations for study. Cardiomyocytes themselves, although they have relatively low renewal rates (estimated to be less than 1%–2% per year), are thought to be the major endogenous cardiac source of new cardiomyocytes in the adult human heart [136,144]. Children may have higher renewal rates, with potentially a 3.5-fold increase in cardiomyocyte numbers between birth and age 20 [6,79]. However, these renewal rates are still much debated, and many questions surrounding these cells remain to be answered before they could be efficiently utilized in regenerative therapies, including whether new cardiomyocytes are in fact generated from existing ones or CPCs, how injury may alter renewal rates, and how to promote cardiomyocyte cytokinesis (the cytoplasmic division of the cell; a process these cells resist undergoing) [136,138].

CPCs, which are Lin^- c-kit^+ cells residing in the heart itself, have been pursued for their regenerative abilities since their discovery in 2003 but are controversial due to mixed findings of their regenerative abilities, making it currently unclear whether these cells are true stem cells that can replenish lost cardiomyocyte populations or they only have regenerative abilities in rare situations (the latter seems more likely based on murine studies) [136]. Other endogenous cell types have also been explored for their cardiac regenerative potential, but due to challenges in isolating these cells in significant numbers, they are difficult to study. CPCs have been used in two small-scale clinical trials that demonstrated safety but were not large enough to prove potential benefits or functional improvement [136]. For a thorough, recent review on cardiac progenitors and early heart development, including signaling pathways and transcription factors involved, see Bulatovic et al. [138].

Although endogenous cardiomyocytes and CPCs likely have some regenerative properties, current cardiac regenerative strategies primarily utilize exogenously added cells—mostly BMSCs—or the addition of molecular factors. BMSCs (which are a type of multipotent, mesenchymal stem cell) originally captured much interest and promise due to a 2001 study showing significant cardiac regeneration in rodents using these cell types [145]. Specifically, this study reported that at 9 days post infarction an injection of Lin^- c-kit^+ BMSCs into the injured myocardial site resulted in regeneration of 68% of the injured area [145]. However, several studies following this one failed to reproduce such positive findings [136,146–148]. Many clinical trials have utilized cellular injections (of autologous or allogeneic BMSCs cells or autologous myocardial tissues [139,149–151]) with similarly mixed results and discrepancies, some retractions of data, and a shared problem being that survival has not been clearly assessed as a primary end point [136,139,152,153]. For a thorough review of 47 recent clinical trials using BMSCs, see Ikebe and Suzuki [154], and for a detailed methodological comparison between a few select clinical trials, see Rosen et al. Such studies and trials have also not utilized standard stratification schemes for age, making it difficult to determine the effect of age on outcomes [139]. However, it is still thought that BMSCs donated from younger patients may be more effective than cells donated from older patients, and younger patients undergoing cellular therapies (and other strategies aimed at stimulating myocardial regeneration) may receive greater benefit than older patients [79,139,149,155–158]. Improved, evidence-based international and regulated standards, following good medical practice code, for the isolation, expansion, and application of donor BMSCs is needed before such therapies can become widely adopted practices [154].

The exact mechanism underlying any potential beneficial effects of injecting BMSCs is unclear; low cell retention rate is a frequent problem, with the injected cells not appearing to substantially remain in the cardiac tissue, nor do these cells appear to significantly transdifferentiate into cardiomyocytes [139]. Currently, it is thought that potential benefits may be caused by the release of paracrine factors and/or recruitment of CPCs, but this effect may not be BMSC-specific, as injections of other cell types have been shown to have similar beneficial effects [139]. If endogenous CPCs are recruited, these cellular therapies may be more effective in younger recipients than older ones, as it is thought younger individuals may have CPCs more capable of healing and repairing tissue [139]. Small improvements in cardiomyocyte production in adult animal models have also been caused by modifying certain transcription factors, altering miRNA expression, and administering recombinant proteins, such as neuregulin1 [79]. Neuregulin1 has undergone clinical testing and so far demonstrated safety in adult patients with chronic HF [159]; if successful at demonstrating functional improvement, it may be possible to use this approach in pediatric HF patients.

While there are multiple ongoing clinical trials using human pluripotent stem cells (both embryonic stem cells [hESCs] and induced pluripotent stem cells [iPSCs]), none yet are aimed at treating a cardiovascular-related disease [139], although robust protocols have been recently developed to differentiate hESCs and iPSCs into cardiomyocytes and other cardiac-related cell types [79,160]. These protocols have been used with patient-derived iPSCs to generate patient-based models of cardiomyopathies and other cardiac conditions, such as long QT syndrome and Danon disease [161–165]. Such models hold great potential for screening of therapeutic drugs, development of treatment strategies, and correction of disease-causing genetic variants, although many hurdles remain to be overcome before such cells can be therapeutically used; for a recent thorough review of these challenges, see Martins et al. [166].

CONCLUSION

The molecular and cellular mechanisms of HF in the pediatric population are still poorly understood, and there is an evolving body of literature demonstrating important differences compared to the adult. Understanding the specific mechanisms involved in the pediatric failing heart is essential for the development of novel targeted therapeutic strategies. Therefore, ongoing focused study specific to children is essential to improve outcomes for this challenging population of patients.

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