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Pharmacological Interventions to Mitigate Immunodeficiency in Children with Congenital Heart Defects: A Review Article

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Background _ Heart failure (HF) is a multifaceted clinical illness caused by several primary and secondary factors, and it follows similar patterns of disease progression. It is associated with significant rates of mortality, morbidity, and financial burden. Heart failure (HF) in children is mostly caused by the presence of congenital heart disease (CHD), with varying risks depending on the exact type of abnormality. The current management and therapy for heart failure in children are derived on treatment strategies used in adults.

Aim of Work – This review examines the etiology, epidemiology, and clinical presentations of heart failure (HF) in children with congenital heart disease (CHD). Additionally, it highlights the clinical, genetic, and molecular features that are shared or different between pediatric HF and adult HF. The aim of this study is to establish a structure for comprehending the constantly expanding genetic and molecular data within the complex context of comprehensive phenotyping.

Methods – We conducted a comprehensive search of relevant terms in ProQuest, PubMed, Web of Science, Cochrane Library, Embase, and Scopus. We evaluate clinical and translational research investigations on heart failure in congenital heart disease, encompassing the analysis of genetic, transcriptomic, and epigenetic aspects.

Results – The review presents the key findings from the evaluated research, including:

- Etiology and epidemiology of heart failure in children with congenital heart disease
- Clinical presentations and phenotypes of pediatric HF compared to adult HF
- Genetic, transcriptomic, and epigenetic factors contributing to the development and progression of HF in CHD
- Potential biomarkers and therapeutic targets identified through the molecular and genetic studies.

Conclusion – The paper presents unresolved challenges in the field of pediatric heart failure associated with congenital heart disease and provides directions for future research. This review aims to enhance our understanding of the complex interplay between genetic, molecular, and clinical factors in the context of heart failure in children with congenital heart abnormalities

Keywords – Heart Failure, Impaired Ventricular Function, Congenital Heart Defect, Genetic Factors, Pediatric Population.

1. Introduction

The International Society for Heart and Lung Transplantation provides a definition of pediatric heart failure (HF) as a syndrome that occurs due to ventricular dysfunction, volume overload, pressure overload, or a combination of these factors. In pediatric patients, congenital heart disease (CHD) manifests as distinct clinical manifestations, including stunted growth, difficulties in feeding, respiratory distress, limited exercise capacity, and fatigue.

Additionally, CHD is linked to abnormalities in circulatory function, neurohormonal regulation, and molecular processes **[1,2]**. Furthermore, CHD often presents with ventricular dysfunction, as well as volume or pressure overload. Heart failure (HF) in young patients with congenital heart disease (CHD) can be attributed to multiple factors, some of which are similar to the causes of cardiomyopathy. This leads to a combination of unique and common mechanisms that result in ventricular dysfunction and

the clinical presentation of HF (Figure 1). This study specifically examines fundamental, practical, and medical investigations pertaining to heart failure in children with congenital heart disease.
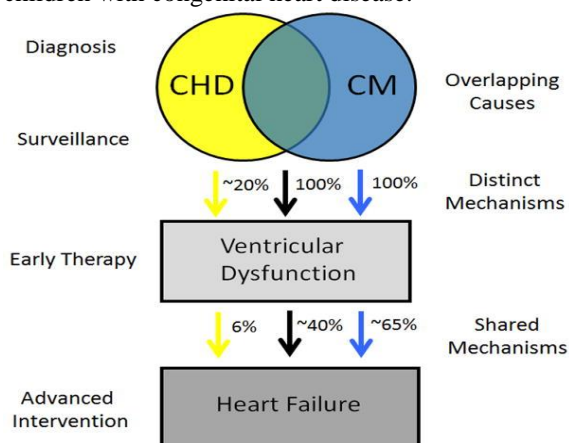

Figure 1. Conceptual framework illustrating the relationship between heart failure, congenital heart disease, and cardiomyopathy.

Diagnosis And Epidemiology

Heart failure (HF) is a complex clinical syndrome that can occur due to any structural or functional problem with the heart that affects its ability to fill or pump blood. The American Heart Association and American College of Cardiology have provided a definition for HF. Diagnosis of HF is primarily based on clinical criteria, and various standardized diagnostic classification systems have been suggested. Pediatric HF involves a wider range of associated symptoms and conditions compared to adult HF, partly due to the different ages at which it can present. HF, as a clinical condition, is further categorized according to its initiation, rapidity, and intensity. The well recognized New York Heart Association Heart Failure Classification is not suitable for children and is believed to be insufficiently sensitive in assessing and measuring the evolution of heart failure severity in children. The Ross Heart Failure Classification was created to evaluate infants with HF, while a modified version was produced to examine children of different age groups. However, both classification systems are not commonly utilized in pediatric treatment [3-5].

The clinical manifestation of CHD is primarily defined in physiological terms, such as outflow tract obstruction (resulting in increased pressure) or pulmonary overcirculation (resulting in increased volume). Surgical correction is the usual approach for treating CHD, focusing on anatomic rectification. In this context, the term ventricular dysfunction is commonly employed instead of the less specific "HF". Nevertheless, ventricular dysfunction can be linked to either inadequate contractility (systolic dysfunction) or insufficient relaxation (diastolic dysfunction), with or without the observable

symptoms of heart failure. This presents a linguistic obstacle that encompasses both clinical and research endeavors in the fields of pediatric cardiology and cardiothoracic surgery. The situation is further complicated by the substantial difference in practice among different centers [6,7].

Various prominent multi-center organizations, such as the Pediatric Heart Network (PHN), Society of Thoracic Surgeons (STS), Pediatric Cardiomyopathy Registry (PCMR), Pediatric Cardiac Genomics Consortium (PCGC), and National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC), employ different methods to identify heart failure (HF) and categorize its severity. This leads to unintentional discrepancies in the literature, making it challenging to harmonize the findings of different studies. For instance, the PHN, which is the leading multisite network in the field, has employed various methods to categorize cardiac dysfunction or HF in different studies. These methods include comparing function between groups without differentiating dysfunction, using the Ross criteria, or focusing on imaging evidence of dysfunction without addressing HF. Although there are legitimate reasons for these variations in study design, the absence of a standardized approach to ventricular dysfunction and HF complicates the integration of findings from multiple studies [8-10]. The limited population sizes for each individual kind of CHD pose a challenge in making generalizable observations. These data demonstrate that the main problems in the discipline involve addressing differences in practice and establishing standardized methods for phenotyping. However, it is crucial to acknowledge that it is possible to strive for a solution by utilizing the various established networks and consortia to enhance the effectiveness of the data already gathered in these extensive cohorts.

Challenges in accurately determining the frequency and occurrence of juvenile heart failure (HF) might be attributed to the absence of consistent classification methods for both congenital heart disease (CHD) and HF, as well as the wide range of factors causing HF in children with CHD. High frequency (HF) has been a significant public health issue for several decades. In the United States, more than 550,000 new cases are diagnosed each year and the overall prevalence is greater than 6 million individuals [2]. Pediatric HF contributes substantially to the economic impact of this disease as a result of the frequent need for procedure based intervention and the significant morbidity and mortality [9]. Children whose hospitalizations are complicated by HF have over a 20-fold increased risk of death [10-13]. There have been no comprehensive epidemiologic studies addressing HF in the pediatric population in the United States, but two single site studies in Europe indicate that more than half of the pediatric HF cases were in children with CHD

[14,15]. In these studies, there were differences in the rate of HF in their CHD populations, with one study identifying HF in 10.4% of all patients with congenital and acquired heart disease and the other identifying HF in 34%, suggesting differences in study design or HF definitions.14, 15 Within the CHD populations, and the rate of HF was 6.2% and 39%, respectively.

Coronary heart disease (CHD) is the primary etiology of heart failure (HF) in pediatric patients. Heart failure (HF) can arise from various causes, congenital and acquired, related to cardiac and non-cardiac illnesses. In the past, HF was commonly associated with cardiomyopathy in the field of pediatric heart disease. However, it is now recognized that cardiomyopathy is just one of the many factors that can lead to HF. While the percentage of individuals with heart failure (HF) who also have coronary heart disease (CHD) is smaller compared to those with rhythm abnormalities or cardiomyopathy, CHD is a more prevalent condition, resulting in a larger number of HF cases overall. Approximately 60% of occurrences of heart failure (HF) in pediatric patients occurred during the first year of life. However, the death rate was lower in the group with congenital heart disease (CHD) compared to patients with HF caused by other factors, according to these research [14,15]. The variability of HF risk based on the underlying cause begs the fundamental inquiry of whether HF is a uniform disease process across different age groups and triggering factors. Furthermore, it implies the possibility of categorizing risks and tailoring treatment accordingly.

Heart failure (HF) is a frequently occurring health condition observed in adults with congenital heart disease (ACHD), a population that encompasses a wide age range and is affected by various additional factors. However, there is a lack of research specifically focused on pediatric studies in this age group [16]. Heart failure (HF) is observed in around 25% of patients with adult congenital heart disease (ACHD) before the age of 30, and its occurrence becomes more frequent as patients get older. By studying the progression of different types of congenital heart disease (CHD) or specific genetic factors, as well as comparing the similarities and differences between HF in children and adults, we can gain a better understanding of the likelihood of developing HF during childhood diagnosis. Collectively, these results suggest that heart failure (HF) is a significant contributor to illness and death among children and adults with congenital heart disease (ACHD). Furthermore, HF in this group of individuals is diverse in terms of its underlying etiology and outcome. A recent review has examined the challenges arising in the management of the expanding population with adult congenital heart disease (ACHD) [17–20].

Recent data suggest that mutations in sarcomeric genes are linked to both congenital heart disease (CHD) and cardiomyopathy [21]. Mutations in certain protein domains of the MYH7 gene not only cause cardiomyopathy but also contribute to the development of Ebstein anomaly [22]. Intriguingly, the initial description revealed that 6% of a group of patients with Ebstein anomaly, a condition characterized by a defect in tricuspid valve formation and position, had MYH7 mutations. Among these patients, 75% also had left ventricular noncompaction cardiomyopathy (LVNC). The familial MYH7 mutation was detected in persons with various forms of congenital heart disease (CHD) as well as in individuals with isolated left ventricular noncompaction (LVNC), however it was not present in unaffected family members. These cases demonstrate that individuals in the same family who have the same disease-causing mutation can exhibit different levels of severity in terms of coronary heart disease (CHD) and cardiomyopathy. This suggests that there are other factors, such as genetic modifiers, that can impact how the disease manifests itself. LVNC is commonly linked to particular forms of congenital heart disease in a specific group of instances. LVNC is distinguished by irregular and excessive ventricular trabeculation and a myocardium that is thin-walled. Mutations in sarcomeric genes have been linked to the LVNC phenotype [23-25]. However, mutations in developmental signaling pathways, such as the Notch pathway and noncanonical Wnt signaling, which are already known to be associated with CHD, can also cause LVNC in both animal models and humans [26-28]. Considering the crucial role of these signaling pathways in cardiogenesis, further research exploring the common developmental mechanisms that lead to both CHD and cardiomyopathy when these pathways are disrupted is expected to provide valuable insights.

Aside from the MYH7 gene, mutations in other sarcomeric genes can also lead to the development of both congenital heart disease (CHD) and cardiomyopathy [29]. Mutations in the MHY6 gene, which codes for α myosin heavy chain, can lead to hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), familial atrial septal defect, and sick sinus syndrome. Similarly, mutations in the ACTC1 gene, which codes for α cardiac actin, a component of the thin filament of the sarcomere, can cause cardiomyopathy and/or septal defects [30,31]. Mutations in the MYBPC3 and TNNI3 genes have also been observed in individuals with both congenital heart defects (CHD) and cardiomyopathy. Surprisingly, there has not been a comprehensive analysis of sarcomeric gene mutations in the CHD population to determine whether rare variants or common polymorphisms in these genes are associated with ventricular function. The existence of a primary heart muscle illness in patients with CHD and myocardial failure that is disproportionate to their heart defect remains uncertain. It is essential to conduct studies that examine the natural progression

of patients with mutations in sarcomeric genes and CHD in order to evaluate the extent to which left ventricular dysfunction or cardiomyopathy develops in these people [32].

Genetic Syndromes Linked To Congenital Heart Defects (CHD)

The development of the heart is regulated by genetics, and congenital heart disease (CHD) is mainly a genetic disorder. However, teratogens can also cause malformations independently, and maternal factors can contribute to the manifestation of the disease [33,34]. The genetic causes of CHD include abnormalities in chromosomes, genomic disorders, single gene mutations, and multifactorial causes. In general, it is less likely to identify the genetic cause of CHD compared to cardiomyopathy [34-36]. One reason for this is that cardiomyopathy typically demonstrates Mendelian inheritance, following an autosomal dominant pattern. On the other hand, CHD is typically caused by a combination of several genes and environmental factors, making it a complicated condition. This vulnerability to developing a structural defect is influenced by various factors [34,35]. However, syndromic CHD is an exception to this pattern, as it has a greater rate of diagnosis. Genetic disorders frequently exhibit distinct categories of circulatory abnormalities; however there is significant variation in the physical characteristics observed. Furthermore, these cases demonstrate sporadic instances of heart abnormalities not being expressed, a phenomenon that lacks comprehensive understanding. Genetic syndromes have provided valuable insights into finding the specific genes responsible for congenital heart defects (CHD). Studies have shown that knowing the genetic basis of syndromic CHD can help discover significant genes that either cause or influence isolated CHD. This notion holds great significance [37-41].

Several genetic disorders that have a strong likelihood of causing congenital heart defects (CHD) are also linked to heart failure (HF) and/or cardiomyopathy. Noonan syndrome, a genetic condition inherited in an autosomal dominant manner, is characterized by short stature, cardiac defects, and abnormal physical features. This syndrome is caused by mutations in genes within the RAS/MAPK pathway. Patients with Noonan syndrome may exhibit signs of hypertrophic cardiomyopathy (HCM), congenital heart defects (CHD), or both, with pulmonary valve stenosis being a classic CHD associated with this syndrome. It is important to note that individuals with Noonan syndrome are at a lifelong risk of developing HCM, even if they do not have CHD, and therefore require continuous monitoring of their heart health [42,43]. Additional RASopathies encompass Cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome with multiple lentigenes (NSML; previously known as LEOPARD) syndrome. NSML is mostly attributed to mutations in PTPN11, a protein tyrosine phosphatase 2 that governs the RAS/MAPK cascade. PTPN11 mutations are the primary cause of Noonan syndrome, leading to the constant activation of the protein [44].

Conversely, in NSML, mutations in PTPN11 result in a protein that is unable to function properly as a catalyst. The hyperactivation of the AKT/mTOR pathway causes hypertrophic cardiomyopathy (HCM) in more than 80% of people with Noonan syndrome with multiple lentigines (NSML). An investigation was conducted to examine the efficacy of early treatment with the mTOR inhibitor rapamycin in preventing hypertrophic cardiomyopathy (HCM) using a mouse model of Noonan syndrome with multiple lentigines (NSML). Mice that received treatment in the early stages did not develop hypertrophic cardiomyopathy (HCM), while those treated later showed a reversal of the disease. A recent study reported the first trial of a mTOR inhibitor in an infant with Noonan syndrome with multiple lentigines (NSML) and rapidly progressive HCM. The goal of the trial was to halt the progression of hypertrophy and outflow tract obstruction until the time of transplantation. The decision to try a pathway-specific inhibitor for treatment was based on an understanding of the genetic cause of heart failure in this case [44].

Marfan syndrome (MFS) is a genetic condition that affects the connective tissue due to mutations in a protein called FBN1. Recent studies suggest that a subset of persons with MFS have an increased likelihood of developing heart failure (HF). Genetic alterations in the fibrillin-1 gene result in an increase in TGFβ signaling in people with Marfan syndrome (MFS). The microfibril's structural network regulates the release of signaling molecules that are crucial for morphogenesis and tissue homeostasis [45]. Case reports have documented the occurrence of left ventricular failure or dilated cardiomyopathy (DCM) in patients with Marfan syndrome (MFS), indicating a possible convergence of molecular networks that regulate heart function. The study utilized a mouse model of Marfan syndrome (MFS) to establish that dilated cardiomyopathy (DCM) in mice lacking fibrillin-1 is caused by abnormal mechanosignaling in cardiomyocytes [46,47]. Specifically, the mice exhibited spontaneous elevation of angiotensin II type I receptor signaling and a decrease in focal adhesion kinase activity, despite the absence of aortic or valvular disease. A separate investigation revealed two different characteristics in elderly Marfan mice. One of these characteristics was the enlargement of the left ventricle, which was linked to increased phosphorylation of ERK1/2 and p38 MAPK, as well as higher expression of BNP. This study observed similar variable responses in phenotype to a small group of Marfan syndrome patients who develop dilated cardiomyopathy (DCM). To understand the

heterogeneity in phenotypes, a comprehensive approach that combines genetics, animal models, and patient-oriented research is necessary [48].

The Occurrence Of Heart Failure (HF) In Coronary Heart Disease (CHD) According To Individual's Age

Although genetic factors can help identify children who are at a high risk of having heart failure (HF) due to congenital heart disease (CHD) or cardiomyopathy, this is only the case for a small number of individuals. The evaluation of risk and implementation of surveillance for HF mostly rely on clinical criteria associated with phenotype and presentation. Age has a crucial role in evaluating the clinical characteristics of HF [49]. Fetal heart failure (HF) is marked by reduced fetal movement, pericardial effusion, and ascites. In preterm low birth weight newborns, HF is characterized by acidemia, anemia, and hypoxemia. Tachypnea, tiredness during feedings, and decreased urine output are prevalent indications of heart failure in term newborns. At this age, decompensation tends to occur rapidly, with the newborn transitioning from being asymptomatic to experiencing cardiac shock swiftly. This is partly because the cardiac reserve is reduced at this age. Consequently, typical indications of heart failure, such as edema and abnormal pulses, are less frequent and may not be observed. The timing of heart failure serves as an indication of the underlying structural abnormality [50,51]. For instance, heart failure (HF) in hypoplastic left heart syndrome (HLHS) typically occurs between the third and seventh day after birth, whereas HF in severe coarctation of the aorta tends to develop between the seventh and tenth day. Certain types of congenital heart defects (CHD) may not exhibit heart failure (HF) symptoms until the pulmonary vascular resistance reduces. For example, a big ventricular septal defect (VSD) or an atrioventricular septal defect (AVSD) can lead to HF within a period of 1-3 months. However, certain abnormalities, such an atrial septal defect, may not cause any symptoms until the child reaches 3 to 5 years of age, or may not cause symptoms at all. While certain observations are a result of the basic structure and functioning of the body, it is now widely acknowledged that other factors, such as genetic makeup and environmental influences, also have a role in determining when a disease begins.

Lesion type is an additional characteristic that is beneficial for risk stratification in the context of heart failure. High frequency in patients with coronary heart disease (CHD) is commonly associated with simultaneous pressure or volume overload. Hence, newborns with certain forms of congenital heart disease (CHD) would invariably encounter heart failure (HF) if not treated surgically. Examples include critical aortic stenosis, which causes excessive pressure on the heart, and Ebstein anomaly with severe tricuspid regurgitation, which leads to an excessive volume of blood flowing back into the heart. Genetic factors and environmental triggers are involved in the intricate process that leads to heart failure. Therefore, it is crucial to detect the occurrence of newly developed ventricular dysfunction in order to implement early therapeutic techniques. Typically, children older than one year have superior overall health and a larger ability to withstand stress on the heart compared to adults. They may maintain a stable condition for longer periods of time, but are prone to quickly transitioning to acute heart failure. The prevalence of ventricular dysfunction or heart failure at the time of diagnosis varies across different kinds of congenital heart disease (CHD). For instance, the presence of pulmonary insufficiency in a patient who has had surgical repair for tetralogy of Fallot (TOF) may or may not result in ventricular dysfunction and heart failure (HF), and the capacity to forecast these occurrences is restricted. Greater rates of HF at the time of diagnosis are associated with an increased likelihood of developing HF later in life. Implementing coordinated strategies that target specific lesions may improve the effectiveness of surveillance algorithms for HF [16].

Metabolic, Molecular, And Neurohormonal Variables Alter HF

The majority of our knowledge regarding HF is derived from research conducted on adult individuals. The metabolic, molecular, and neurohormonal abnormalities that arise in HF have been extensively discussed in recent reviews, including a previous Compendium issue on HF [52]. For detailed information on these intricate topics, readers are directed to refer to that source. These findings have also been applied to the pediatric population. HF exhibits molecular-level changes, including variations in transcription, translation, and epigenetics. These changes are a result of the heart's adaptive and compensating processes as it tries to meet its functional requirements (Figure 2). In both adult and juvenile cases of heart failure (HF), the gradual decline in the functioning of the heart muscle results in the heart's inability to meet the body's needs. This can be understood as a mismatch between the amount of blood the heart can give and the amount of blood the body requires. The concept of energy deprivation is suggested as a unifying factor that causes cardiac contractile failure. This often occurs due to a series of events in which reduced oxygen and substrate availability lead to adaptive responses such as excessive neuroendocrine activity, activation of signaling pathways, remodeling of the extracellular matrix (ECM), and changes in mechanical load, among other factors. Although these adaptive mechanisms initially stabilize the contractile function, they can ultimately lead to further deterioration due to a vicious cycle marked by an increased imbalance between supply and demand. As metabolic remodeling transitions from adaptation to

maladaptation, the failing heart gradually loses its ability to function efficiently [53-55].
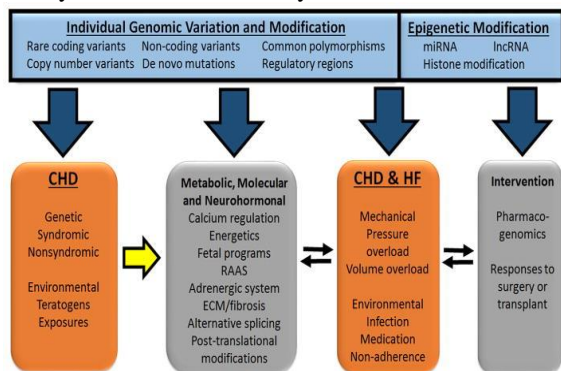

Figure 2. Diagram illustrating the relationships between causative, predisposing, and contributory factors that lead to the development of congenital heart disease and heart failure

The Control Of Cardiac Metabolism Affects The Progression Of Heart Failure

HF is characterized by a metabolic state where energy expenditure is inefficient. The heart utilizes fatty acids and glucose as energy sources, with a preference for the former as the primary substrate. Mitochondrial dysfunction is a prominent feature of HF and is both a contributing factor and a result of abnormal energy production. Some of the outcomes of mitochondrial dysfunction include reduced breakdown of fatty acids, heightened DNA damage and programmed cell death, and changes in the amounts of calcium within mitochondria. During the prenatal period, the heart primarily relies on glucose as its main source of energy. After birth, there is a shift from a low oxygen environment in the womb to a high oxygen environment. This transition is accompanied by a change from anaerobic glycolysis to fatty acid oxidation and oxidative phosphorylation for ATP production, which is a more efficient way of generating energy. This change in how the body uses substances is also accompanied by an increase in the number of mitochondria and is an important period of transition. Infants who have rare inborn errors of metabolism, such as fatty acid oxidation abnormalities or mitochondrial disorders, often go through a period of cardiac decompensation during this transition [56-58].

There are significant variations in the way nuclear encoded mitochondrial genes are expressed during development, indicating the presence of stage-specific regulation of mitochondrial biogenesis. However, the particular time frame in which this occurs in humans has not been clearly determined. Mouse models have shown that there is a significant increase in the production of new mitochondria in the heart muscle during the period immediately before and after birth. Eliminating transcription factors that are crucial for this metabolic shift, such as TFAM or

PGC-1 isoforms, leads to an increase in the expression of glycolytic genes and causes neonatal heart failure that progresses rapidly and ends in fatality. It is worth noting that recent evidence suggests that the shift from a low oxygen to a high oxygen environment after birth causes damage to mitochondria, leading to a halt in cell cycle progression and withdrawal from the cell cycle. On the other hand, hypoxic cardiomyocytes maintain a fetal or neonatal phenotype, which is characterized by smaller size, fewer mitochondria, less evidence of oxidative damage, mononucleation, and most importantly, increased ability to proliferate. These findings have important implications for strategies in cardiac regeneration and addressing the energy needs in heart failure [59-61].

Clinical Research On Pediatric Ventricular Dysfunction And Heart Failure

Heart failure (HF) has undergone thorough examination in adults, but its assessment in children has just lately commenced. In order to evaluate the present state of clinical research in this field, we conducted a search on the clinical trials website (www.clinicaltrials.gov) and found that 1.3% of the ongoing HF studies that are presently accepting participants involve children with CHD (n = 29). There are still unresolved doubts over whether HF is the same disease in children. However, the limited sample size and the presence of heterogeneity provide challenges in finding answers. Here are some instances of clinical trials conducted on the SV population, which has been extensively researched in recent years. A constraint of existing studies is the challenge in comparing findings across several trials. For instance, the PCGC has not provided any information about the occurrence of ventricular dysfunction or heart failure as a separate or modifying characteristic, and the NPC-QIC has only examined cases that are moderately abnormal or more [62,63]. A significant overall requirement is to utilize existing groups of individuals by merging them together to enable studies that can address both primary and secondary inquiries. Implementing a learning health system, like the NPC-QIC, could enhance the outcomes of trials conducted with existing groups of patients. This approach has demonstrated notable improvements in patient participation, which is often a challenge in pediatric heart disease trials. Clinical trials that utilize learning health systems have the potential to enhance results through quality improvement initiatives and expedite the dissemination of findings. Collaborations with non-profit organizations can support this kind of research by sharing the financial burden and, more significantly, by mobilizing patients and coordinating their combined knowledge to discover and promote patient-centered research issues that are relevant to clinical practice [64,65].

Patients with coronary heart disease (CHD) who have complicated abnormalities are more likely

to experience heart failure (HF) as a complication. Functional single ventricle heart defects contribute significantly to the morbidity and mortality in congenital heart disease (CHD). The mortality rate in the first year of life for these defects ranges from 10% to 35%. Furthermore, the management of these patients is associated with a substantial economic burden and high resource requirements. The PHN has conducted clinical research that has documented comprehensive clinical results in this patient population [66].

The prognostic indicators for unfavorable outcome in functional SV defects are determined by the specific form of congenital heart disease (CHD) and the complications that arise during the stages palliative procedures. While the surgical procedure for SV lesions is generally the same, the genetic factors responsible for these lesions vary, and specific genetic syndromes are associated with a more unfavorable prognosis. The PHN SV Reconstruction Trial has yielded data regarding the outcomes in this specific group of patients [6, 67-69]. In the initial comparison between the Blalock-Taussig and right ventricle-pulmonary artery shunt types for SV, the transplant-free survival rate at 12 months was 74% and 64% respectively, with no statistically significant differences observed at 3 years [6,68]. The mortality rate with stage I palliation (Norwood procedure) ranges from 7% to 19%, while the mortality rate between stage I and stage II palliation ranges from 4% to 15%.

Genetic abnormalities have been found to be independent risk factors, indicating that some of the variation in the occurrence and severity of heart failure can be attributed to genetic factors. In patients with Fontan circulation, where the venous return bypasses the systemic ventricle and goes directly to the pulmonary artery, there are several medical problems such as growth issues, compromised blood flow leading to bluish discoloration, blockages in the pathways and valve dysfunction, irregular heart rhythms, and fluid accumulation in the lungs or abdomen. Fontan circulation leads to progressive dysfunction in multiple organ systems, and when Fontan failure occurs, a heart transplant is necessary. Ongoing studies are being conducted to investigate the survival rates of various forms of SV malformations, such as hypoplastic left heart syndrome (HLHS) compared to tricuspid atresia. Given the intricate circumstances, it is challenging to separate the root cause and consequences of ventricular dysfunction and heart failure. However, the potential value of this understanding is significant. For instance, the capacity to categorize patients into high-risk or low-risk groups for myocardial dysfunction could result in more customized strategies and protocols for monitoring patients and providing medical intervention [69-71].

The structural and morphological characteristics of the ventricle also play a significant role in determining the outcome. The recreational vehicle does not effectively adjust to the requirements of the systemic ventricle. Prior research has demonstrated that a minimum of 50% of patients with congenital heart defects (CHDs) in which the right ventricle (RV) serves as the systemic ventricle, such as l-TGA (congenitally corrected transposition of great arteries) and HLHS, experience RV dysfunction [72]. Furthermore, there is a 15% occurrence of death or heart transplantation in early adulthood due to myocardial dysfunction. Studies analyzing gene expression have revealed that the right ventricle's inability to respond to chronic pressure overload is linked to its failure to exhibit the gene expression pattern typically seen in the left ventricle, involving genes related to angiotensin, adrenergic receptors, G-proteins, cytoskeletal and contractile components [73-75]. Just as variations in sarcomeric genes may account for a portion of heart failure or predisposition to heart failure in congenital heart disease cases, it is plausible that genetic variations in these pathways make certain individuals more susceptible to myocardial dysfunction when combined with congenital heart disease (Figure 1).

Therefore, genetic differences that may not have an impact on the general population might significantly increase the likelihood of negative outcomes or provide protection in individuals with congenital heart disease. This level of genetic variation remains unexplored. Although expression analyses have not been conducted in SV patients, it is reasonable to hypothesize that the maladaptive responses observed in the RV due to pressure overload would be comparable in the case of chronic volume overload. Therefore, those with left ventricular systolic dysfunction have historically exhibited higher rates of survival compared to those with right ventricular systolic dysfunction. Gaining a more comprehensive understanding of the developmental and genetic factors underlying these variations and their transition to heart failure is crucial. This knowledge will not only shed light on the extent to which pressure and volume overload contribute to the condition, but also yield valuable data for the development of innovative treatments.

Stem cell therapy is now being studied in clinical studies to assess its effectiveness in treating structural heart disorders including hypoplastic left heart syndrome (HLHS). In 2015, the method of injecting mononuclear cells generated from umbilical cord blood directly into the coronary artery or administering cardiosphere-derived cells (CDC) directly into the coronary artery was effectively employed in patients with hypoplastic left heart syndrome (HLHS). During the 36-month follow-up, the right ventricular ejection fraction showed sustained improvement in patients who received CDC infusion [76,77]. Ongoing clinical trials are exploring the use of progenitor cell types, such as allogenic mesenchymal stem cells, bone marrow derived cells,

c-kit+ cells, or umbilical cord cells, which have demonstrated reliable and safe outcomes in previous studies. While there is hope that stem cell therapy could bring substantial benefits to managing pediatric patients, there is still much to be discovered about the specific requirements of different cell types, the optimal timing of administration, the long-term effects on cardiac health, and the underlying mechanisms of action. Additionally, induced pluripotent stem cells offer another avenue for studying and modeling disease processes specific to individual patients [78].

Medical Treatment And Pharmacogenomics

Treatment for heart failure in patients with congenital heart disease is mostly derived from studies conducted on adults with ischemic heart failure. There is insufficient data to substantiate the usage of this in youngsters. For instance, a recent study on valsartan, a medication that blocks angiotensin II receptors, was conducted on patients with a systemic RV. However, the trial did not demonstrate any positive impact on the main outcome of RV ejection fraction. Similarly, a randomized trial on enalapril in infants with SV did not result in any changes in the severity of heart failure or improvements in growth or ventricular function. These findings collectively indicate that pediatric heart failure may have distinct causes and/or additional factors that contribute to it, necessitating the development of novel and diverse treatment approaches [67].

Pharmacogenomics refers to the correlation between genetic characteristics and the way drugs affect the body. Individual differences in how people respond to drugs can result in treatment not working well (e.g., in cases of ultrarapid metabolizers) or causing negative reactions (in cases of poor metabolizers). Although there have been many pharmacogenomic clinical trials conducted in adults with heart failure (HF), there have been very few studies conducted in individuals with congenital heart disease (CHD). These studies face specific challenges, such as the variability in the underlying causes of CHD (genetic variability), the diversity in the types of CHDs and their treatments (phenotypic variability), small sample sizes, frequent changes in dosing as individuals age, and changes in drug responsiveness with age. Moreover, there is considerable diversity in the treatment and handling of these patients at various locations, resulting in difficulties for research conducted across many sites [79].

So far, the only research conducted on heart failure (HF) or ventricular remodeling in congenital heart disease (CHD) was carried out by Mital et al. [7]. They used a combined approach to study the effects of five specific genetic variations (single nucleotide polymorphisms or SNPs) in genes related to the renin-angiotensin-aldosterone system (RAAS) as part of the PHN SV Reconstruction Trial. The study findings indicated a correlation between the RAAS genotype and the lack of reverse remodeling following surgery. However, it is crucial to note that this study had limitations, including a relatively small sample size and a bias towards patients who survived beyond stage I palliation. In 2014, it was discovered that the same RAAS SNP is linked to a higher risk of tachyarrhythmia after CHD surgery, with an odds ratio of 1.6 and a 95% confidence interval of 1.1-2.3 (P=.02) [80]. This provides initial evidence for the potential usefulness of pharmacogenetics in the CHD population, but larger studies with more participants are needed to confirm these findings. In order to achieve individual risk stratification and personalized care, it is crucial that we accomplish three main tasks. Firstly, we need to accurately determine the primary causes of coronary heart disease (CHD). Secondly, we must identify secondary genetic factors that either make individuals more susceptible to or provide protection against myocardial dysfunction in the presence of CHD and environmental/mechanical stressors. Lastly, we need to choose the most suitable medical treatment based on the predicted pharmacogenomic response. The clinical phenotype and result are ultimately determined by the combinatorial interaction of primary, secondary, and tertiary genetic effects in a multifactorial manner.

Conclusion

Pediatric heart failure is a medical condition that occurs when the heart is unable to meet the demands placed on it. While adults with HF share certain metabolic and molecular characteristics with children, there are differences in the underlying causes, presentations, and illness courses between the two groups, as depicted in Figure 3. Therefore, a crucial inquiry arises as to whether heart failure (HF) in children is identical to the illness process observed in adults. What evidence supports the use of conventional heart failure therapy in young patients with congenital heart disease? Are conventional HF prognostic tools effective in these patients? What is the impact of variations in the myocardium during infancy and early childhood on the management and treatment methods? Further investigation is required to arrange the current data and utilize established groups of individuals to address these inquiries.

Examining outcomes in subgroups of large cohorts with CHD is essential for comprehending the shared clinical symptoms and biological attributes of patients whose ventricular dysfunction does not improve or advances to HF. Preliminary evidence suggests that the myocardium has unique molecular characteristics depending on age and location, specifically the right ventricle (RV) versus the left ventricle (LV). Moreover, the myocardium's susceptibility to medicine is subject to variation depending on age. Further examination of these disparities is necessary to categorize the level of risk and tailor treatment accordingly. Stem cell treatment

shows significant potential as an innovative method for treating heart failure in congenital heart disease. However, it is imperative to do fundamental, translational, and clinical research in order to comprehend its use. Further study on the common developmental mechanisms underlying both congenital heart disease (CHD) and cardiomyopathy is expected to provide valuable insights into the genetic and epigenetic pathways that contribute to an increased vulnerability to heart failure (HF).

Various research methodologies have been employed to study HF, and the research community is in a favorable position to utilize these resources effectively. The amount of basic research in HF is significant, and while it is not the main focus of this study, there is a definite requirement for more animal models of HF in CHD. The advancements in genetic and genomic techniques are happening quickly; nevertheless, in order to achieve better treatment strategies, it is necessary to establish standardized biorepositories that integrate consistent data collection methods. Additional research conducted in multiple centers is required to have a more comprehensive understanding of the disease in those specific groups. Enhancing the focus on integrating the many components of HF can expedite the discovery of new treatment opportunities (Figure 2). In the end, employing diverse and integrated research methods will enhance healthcare by enabling the categorization of risks based on factors such as age, lesion, and/or underlying cause, and will result in the development of more effective protocols for medical intervention and therapy.

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