Review Article

ISSN 2639-9512

Stem Cell & Regenerative Medicine

Stem Cells as A Possible Treatment for Pediatric Cardiomyopathy

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Received: 25 February 2020; Accepted: 12 March 2020

Citation: John Dinger, Vincent S. Gallicchio. Stem Cells as A Possible Treatment for Pediatric Cardiomyopathy. Stem Cells Regen Med. 2020; 4(1): 1-5.

ABSTRACT

Pediatric cardiomyopathies are a collection of diseases that deal with improper formation of the ventricular myocardium in infants and children. These cardiomyopathies are split into dilated, hypertrophic, restrictive, and left ventricular noncompaction cardiomyopathy; classified by the exact irregularity that is present. This analysis dives into the use of stem cells to help correct the abnormalities that occur. There are currently two methods utilizing stem cells with one being the creation of an in vitro model that replicates the problematic tissue and then using stem cells as a means of replacing the defective cells. The other method is finding animals with or generating animals with cardiomyopathies and then introducing stem cells into the organism. To date, in rat and pig models, mesenchymal stem cells derived from cord blood and bone marrow show immense promise as the results indicate increased cardiac efficiency. A decrease in cardiomyocyte apoptosis, an increase in left ventricular fraction shortening levels, and an increase in cardiac contractile function have been observed in these animal models. Mesenchymal stem cells have shown their massive capabilities in early animal models, however; more studies need to be conducted to transition to the next stage and eventually to human clinical trials. That being said, stem cells appear to be a viable solution to pediatric cardiomyopathies in the future.

Keywords

Stem cells, Pediatric, Cardiomyopathy, Animal model.

Abbreviations

ASCs: Adult stem cells; AD: Autosomal Dominant; AR: Autosomal Recessive; DCM: Dilated Cardiomyopathy; ESCs: Embryonic Stem Cells; FSCs: Fetal Stem Cells; HSCs: Hematopoietic Stem Cells; HCM: Hypertrophic Cardiomyopathy; iPSCs: Induced Pluripotent Stem Cells; LVNC: Left Ventricular Noncompaction Cardiomyopathy; MSCs: Mesenchymal Stem Cells; NSCs: Neural Stem Cells; RCM: Restrictive Cardiomyopathy.

Introduction

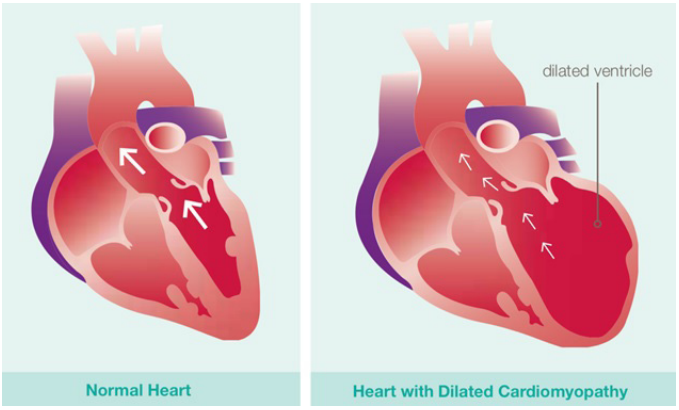
Cardiomyopathies are deformities in the muscle of the heart, more specifically the ventricular myocardium. The ventricular myocardium is the muscular tissue of the lower half of the heart, known as the ventricles, that pumps bloods to the lungs and the rest of the body. Pediatric cardiomyopathies refer to these abnormalities aforementioned above but taking place in infants and children. These diseases have a morbidity of 1.1-1.5 cases every 100,000 people [1]. The etiology of pediatric cardiomyopathies stem from deformities in the coronary artery, a regular or irregular rapid heartbeat known as tachyarrhythmia, being in proximity of certain drugs or poisons, contracting certain infections, or resulting from a separate disease [2]. Heavy metals, such as cobalt or copper, or alcohol abuse are common toxins that can result in cardiomyopathy [3]. Pediatric dilated cardiomyopathy (DCM), one of the four types of cardiomyopathy discussed below, due to infection can be bacterial, viral, or fungal. The pathogens that cause infectious cardiomyopathy can be seen in Table 1. As previously stated, other diseases can play a role in the development of cardiomyopathy, such as hyperthyroidism [4]. The different types of pediatric cardiomyopathy are dilated, left ventricular noncompaction, hypertrophic, and restrictive [2]. These classes of pediatric cardiomyopathies are based on the pathological effects on the anatomy of the heart. That being said, some children may suffer from more than one type of cardiomyopathy.

Infectious Causes	Pathogen
Bacterial	Borrelia burgdorferi, Chlamydia, Corynebacterium diptheria, legionella, Mycobacterium tuberculosis, myoplasma, staphylococcus, Streptococcus A, Streptococcus pneumonia
Fungal	Actinomyces, aspergillus, candida, Cryptococcus helminthic: Echinococcus granulosus, Trichinella spiralis protozoal: Toxoplasma gondii, Trypanosoma cruzi

Viral	Adenoviruses, enteroviruses, herpes simplex virus, varicella-zoster virus, human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, influenza A and B viruses, HIV, parvovirus B19, variola virus, vaccinia virus, mumps virus, measles virus, rubella virus, hepatitis C virus, coronavirus, respiratory syncytial virus

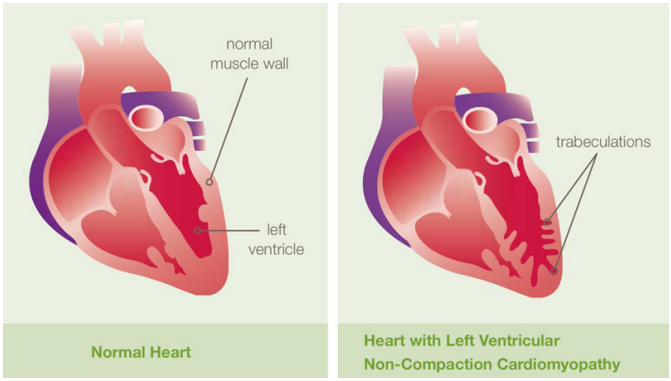
DCM in children results from lower ventricular function. In other words, their heart is not pumping enough blood into the arteries [2]. This reduced function is a result of subpar contraction of the myocardial fibers during systole. Systole is one of the two stages of the heartbeat, the other being diastole. Systole occurs when the heart is contracting and pushing blood into the arteries. Those with DCM cannot pump as much blood into their arteries because the muscle fibers in their hearts are not contracting, or shortening, normally. This can be seen in over 50% of pediatric cardiomyopathies and has an incidence of 0.57 cases for every 100,000 children [2]. As seen above in the structural defects, DCM cannot be taken lightly as the heart is unable to pump enough blood to the body. As a result, pediatric DCM has a mortality of 40% in the two years after it is diagnosed [2]. The anatomy of DCM can be seen in Figure 1.

Figure 1: Anatomical representation of a normal heart compared to a heart with dilated cardiomyopathy. Adapted from 'Dilated Cardiomyopathy (DCM)', n.d., Retrieved from https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/dilated-cardiomyopathy. Copyright 2019 by the Cincinnati Children's Hospital Medical Center [18].



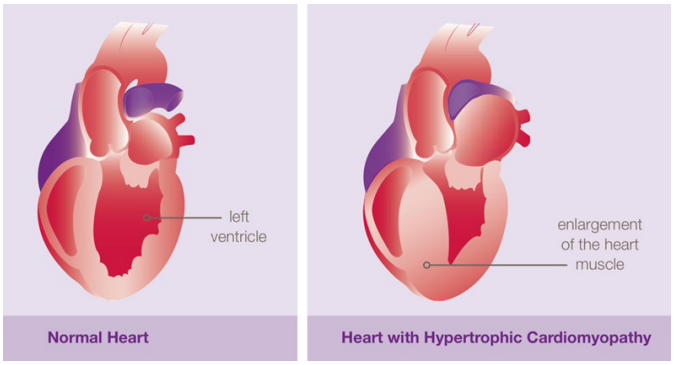
Left ventricular noncompaction cardiomyopathy (LVNC) in children results from columns of muscle in the ventricles of the heart, known as trabeculae carneae, not forming perfectly [2]. This results in the muscle of the wall looking thick, porous, and sponge like. Due to thicker walls, there is less space in the heart that blood can occupy. This, in turn, reduces the amount of blood that can flow through the heart. The anatomy of LVNC can be seen in Figure 2. LVNC has an incidence of 0.12 cases for every 100,000 children aged 0 to 10 years old and 0.81 cases for every 100,000 infants. A mortality of 18% is seen in children with LVNC [2].

Figure 2: Anatomical representation of a normal heart compared to a heart with noncompaction cardiomyopathy. Adapted from 'Left Ventricular Non-Compaction Cardiomyopathy (LVNC)', n.d., Retrieved from https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/left-ventricular-non-compaction-cardiomyopathy. Copyright 2019 by the Cincinnati Children's Hospital Medical Center [19].



Hypertrophic cardiomyopathy (HCM) in children is due to the myocardium being unusually thick [2]. The thicker the heart muscle, the more laborious is it to pump blood throughout the body. This is seen in 42% of cases. The anatomy of HCM can be seen in Figure 3. HCM has an incidence of 0.47 for every 100,000 children. Although death is rare in older children with HCM, infants have a two-year mortality of 30% [2].

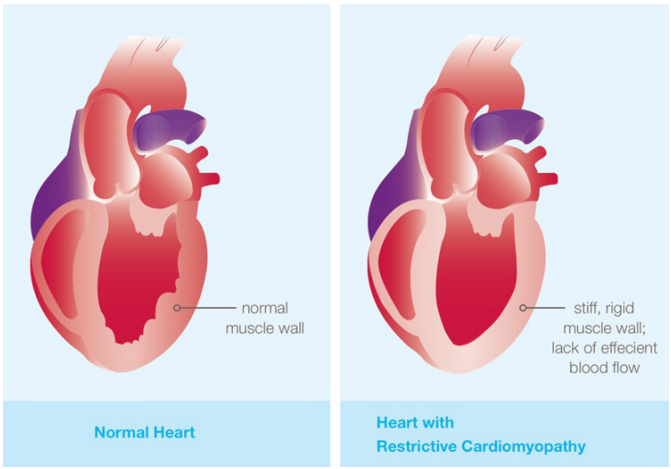
Figure 3: Anatomical representation of a normal heart compared to a heart with hypertrophic cardiomyopathy. Adapted from 'Hypertrophic Cardiomyopathy (HCM)', n.d., Retrieved from https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/hypertrophic-cardiomyopathy. Copyright 2019 by the Cincinnati Children's Hospital Medical Center [20].



Restrictive cardiomyopathy (RCM) is due to debilitated myocardium in the ventricles of the heart, only seen in 4.5% of pediatric cardiomyopathies [2]. This causes the ventricles to become too rigid and cannot pump blood as efficiently or effectively. Some diuretics are used to monitor and lower the blood pressure to remove some of the workload for the heart, but the amount is controlled severely. The anatomy of RCM can be seen in Figure 4. This final class of cardiomyopathies is the rarest form and has an incidence of 0.03-0.04 cases per 100,000 children [2]. Although RCM has an extremely low incidence in children, it has a tremendously high mortality. It is infrequent that no medical intervention is necessary as between 66-100% of children with RCM undergo heart transplantation or die [5].

Figure 4: Anatomical representation of a normal heart compared to a heart with restrictive cardiomyopathy. Adapted from 'Restrictive

Cardiomyopathy (RCM)', n.d., Retrieved from https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/restrictive-cardiomyopathy. Copyright 2019 by the Cincinnati Children's Hospital Medical Center [21].



The genetics of the pediatric cardiomyopathies is extremely diverse and complicated. As expected, the four different classes of pediatric cardiomyopathies can be caused by a myriad of mutations in the genome. Scientists have discovered hundreds of mutations in hundreds of genes that lead to the cardiomyopathies. As seen in Table 2, there are several genes that can cause the same cardiomyopathy and there are also genes that can cause multiple different types of cardiomyopathies. These genetic mutations are autosomal dominant (AD), autosomal recessive (AR), or X-linked. The distinction between autosomal dominant and autosomal recessive is found in the number of copies of the mutation is/are present. In autosomal recessive mutations, both copies of the mutated gene are present, while in autosomal dominant it is only one. Mutations that are X-linked refer to the chromosome, X chromosome, that the mutation is located [6].

Gene	Location	Means of Inheritance	DCM	LVNC	HCM	RCM
ACTC1	Sarcomere	AD	X	X	X	X
TNNC1	Sarcomere	AD	X		X	
TNNI3	Sarcomere	AD, AR	X		X	X
TNNT2	Sarcomere	AD	X	X	X	X
TPM1	Sarcomere	AD	X	X	X	
MYBPC3	Sarcomere	AD	X	X	X	X
MYH7	Sarcomere	AD	X	X	X	X
MYL2	Sarcomere	AD			X	
MYL3	Sarcomere	AD, AR			X	X
ACTN2	Z-disc	AD	X	X	X	
CSRP3	Z-disc	AD	X		X	
LDB3	Z-disc	AD	X	X		
MYOZ2	Z-disc	AD			X	
TCAP	Z-disc	AD, AR	X		X	
TTN	Z-disc	AD	X		X	
DSC2	Desmosome	AD, AR				
DSG2	Desmosome	AD	X			
DSP	Desmosome	AD, AR	X			
JUP	Desmosome	AD, AR				
PKP2	Desmosome	AD				
VCL	Cytoskeleton	AD	X		X	
DES	Intermediate Filament	AD, AR	X			
EMD	Nuclear Membrane	X-Linked	X			
LMNA	Nuclear Membrane	AD, AR	X		X	X
SYNE1	Nuclear Membrane	AD	X			
SYNE2	Nuclear Membrane	AD	X			
CAV3	Plasma Membrane	AD, AR			X	
SGCD	Plasma Membrane	AD, AR	X			

Table 2: Known Genes Responsible for All Types of Pediatric Cardiomyopathies.

Current Standard Treatment

The current standard of care for children with cardiomyopathy depends on which type or types they are suffering from. Treatments for pediatric DCM include therapies to combat the symptoms, physical implantations such as pacemakers or defibrillators, or a heart transplant. Children with DCM have a very low life expectancy. Unfortunately, DCM in children has a mortality of 30% within a year of being diagnosed [7]. Treatments for LVNC typically included drugs for anticoagulation, but any treatment is influenced by the level of systolic functionality. Of the patients with LVNC, 18% died or received heart transplant surgery [2]. Known treatments for HCM include beta blockers and calcium channel blockers to reduce the blood pressure and workload of the heart, disopyramide to regulate heartbeat, septal myomectomy in an attempt to remove excess muscle tissue, or obtaining an implantable cardioverter defibrillator. This device monitors for any abnormal heartbeats and is able to send a shock to the heart in order to reset it. Upon diagnosis, children have a 97% 5-year survival. Most deaths occur as infants, below 1 year, and between 8-17 years [2]. Finally, for RCM, anticoagulations and anti-arrhythmics are also given to oversee any abnormalities in blood pressure or heart rate, respectively. There is also the option of an implantable cardioverter defibrillator or heart transplant. After diagnosis, the 5-year survival is 68% [1].

Stem Cells

Most of the offered treatments aforementioned treat the symptoms of cardiomyopathies or they attempt to govern the heart so that it does not have to work as hard. These treatments do not tackle the problem of fixing the reduced ventricular function. One possible solution that is becoming more and more popular, due to an increase in knowledge on their capabilities, is the use of stem cells. Stem cells are categorized by origin and potency, or their maximum ability to differentiate. In terms of potency, stem cells can be totipotent, pluripotent, or multipotent. Totipotent stem cells are able to differentiate into any cell type, including placental structures. These stem cells are totipotent until the blastocyst

is formed. Upon formation of the blastocyst, the stem cells are considered pluripotent as they are able to differentiate into any of the three germ layers but cannot give rise to placental structures [8]. Finally, after continued maturation, stem cells become multipotent. Multipotent stem cells can differentiate into a finite number of cell types, but these cell types must be related to one another.

As aforementioned, stem cells can be categorized by their origin as well. Stem cells can be embryonic stem cells (ESCs), fetal stem cells (FSCs), adult stem cells (ASCs), or induced pluripotent stem cells (iPSCs). The last group of stem cells, the iPSCs, do not necessarily originate from one portion of the body, but are adult cells that have undergone manipulation to inherit the capabilities of ESCs [8].

The previously mentioned blastocyst is one of the stages of development that consists of an inner cell mass on the inside of a hollow ball of cells known as the trophoblast. The inner cell mass later gives rise to the organism itself. The inner cell mass is where ESCs originate and due to the early nature of their development, they are pluripotent. Fetal tissue provides an additional source of stem cells known as FSCs. These stem cells like originate from fetal blood or bone marrow, but can also come from additional tissue, such as the liver or kidney [9]. FSCs are multipotent but, depending on the tissue they were derived from, they can differentiate into multiple types of cells. This also applies to ASCs, which are derived from multiple tissue locations in the body and are also multipotent. The tissue in which stem cells are derived from, in terms of both FSCs and ASCs, determines which type it will be. These stem cells can be hematopoietic, mesenchymal, endothelial, epithelial, or neural stem cells [8].

Hematopoietic stem cells (HSCs) are responsible for giving rise to all types of cellular components found in the blood, a process known as hematopoiesis. They have the ability to become oxygen carrying erythrocytes, clot controlling platelets, and every leukocyte that makes up the immune system. HSCs first manifest in the fetal embryo until hematopoiesis shifts to the fetal bone marrow where it stays for the duration of the organism's life [10].

Mesenchymal stem cells (MSCs) have the ability to differentiate into mesodermal tissue with a possibility of differentiating into non-mesodermal tissue. MSCs have been identified from bone marrow, adipose tissue, synovial tissue, lung tissue, umbilical cord blood, and peripheral blood in humans. MSCs have also been derived from almost every tissue in adult mice, which proposes the possibility that MSCs have the capability to be isolated from all adult tissue types [11]. Due to their high potential, MSCs are a highly researched topic today and provide a lot of promise going forward.

Endothelial stem cells are a category branched off of FSCs and have the ability to give rise to bone marrow and placental cells, but more information remains at large due to their complex nature. This is also the case for epithelial stem cells. Epithelial stem cells come from FSCs and can differentiate into liver and pancreatic cells, but also have limited available information [8].

Neural stem cells (NSCs) are multipotent stem cells that are located in the nervous system. As seen above, fetal and adult stem cells give rise to several tissue types and have a function of replacing injured or dead cells, NSCs, however, do not have an undeviating function. It has been shown that NSCs can give rise to neurons and these neurons can be placed in former neural circuits, however; there is evidence that NSCs can give rise to other cells in the nervous system other than neurons [12]. This leaves the field of NSCs open for immense amounts of research and possibility.

Discussion

Mesenchymal Stem Cells

Mesenchymal stem cells that originate from the human umbilical cord show immense promise because of their ability to differentiate into all three germ layers [13]. In a recent study, a DCM model was generated in male rats. This experiment divided the rats into three groups; a control group, a group that was injected intravenously with 106 human umbilical cord mesenchymal stem cells, and a vehicle group that was given the same volume solution but with no stem cells. It was found that the DCM rats injected with only the serum and no stem cells had elevated myocardial fibrosis. On the other hand, rats given the human umbilical cord mesenchymal stem cells suppressed this increase seen in the vehicle group [14]. In almost an identical study a few years earlier, male rats were used to see if human umbilical cord mesenchymal stem cells could mitigate myocarditis, a disease caused by inflammation of the heart wall. A reduction of cardiomyocyte apoptosis and inflammatory cells was observed post injection of the human umbilical cord mesenchymal stem cells [15].

Although the disease studied was myocarditis and not cardiomyopathy, it shows great potential that human umbilical cord mesenchymal stem cells have on heart tissue. In an additional study, Sprague-Dawley rats were injected with doxorubicin to create a DCM model. Two groups of rats were established; one being injected with a serum of human umbilical cord mesenchymal stem cells in limb skeletal muscles and the other being a control group injected with a blank serum. The rats injected with the stem cells showed notable refinement in cardiac function as left ventricular ejection fraction and left ventricular fraction shortening levels improved significantly [16].

Mesenchymal stem cells that do not come from the umbilical cord can also originate from the bone marrow. A study was conducted to determine if bone marrow mesenchymal stem cells treated with 5-azacytidine or double intravenous infusion would amplify their capabilities as a therapy for DCM. The cells were split into four groups; Groups 1 and 2 received no pretreatment; Groups 3 and 4 received pretreatment with 5-azacytidine; and Groups 2 and 4 were carried out via double infusion. The pretreatment of 5-azacytidine caused no enhancement on their productiveness. On the other hand, the groups that were carried out via double intravenous infusion, Groups 2 and 4, showed significant results.

Double intravenous bone marrow mesenchymal stem cell infusion resulted in lower brain natriuretic peptide levels and an increase in cardiac contractile function [17]. This provides great promise that human umbilical cord and bone marrow mesenchymal stem cells are capable of sequestering disease related pathologies in animal models.

Summary and Conclusions

When it comes to pathologies of the heart, any deviation from the normal tissue has the potential to be catastrophic. Pediatric cardiomyopathy follows suit and can be devastating for families to have to go through complications with their child in its first months. As seen above, stem cells provide hope for a possible treatment for all types of pediatric cardiomyopathies. The animal models that are being done show immense amounts of potential and monumental results have been noted. In rats with cardiomyopathies, researchers are observing changes in myocardium contractile function and several other optimistic results. The mesenchymal stem cells that are being used in these models appear to be the most effective type of stem cell. Going forward, human clinical trials need to be the next stage. Stem cells are showing their vast capabilities and a treatment for pediatric cardiomyopathies appears to be right around the corner. There have been publications within the last year that describe other pediatric diseases engaging in clinical trials. Going a step further, these diseases involve the pediatric heart. There are nine active clinical trials that are using cell-based therapy for myocardial regeneration in univentricular hearts. Of those nine trials, four of them are using stem cells as their cell-based therapy and one of them has already entered Phase III [22]. Active clinical trials testing for the use of stem cells in different pediatric heart diseases suggests that stem cells should be used in clinical trials to combat the pediatric cardiomyopathies. This is a promising time in the world of medicine and these clinical trials should be expected to take off very soon.

References

1. Choudhry S, Puri K, Denfield S W. An Update on Pediatric Cardiomyopathy. Curr Treat Options Cardiovasc Med. 2019; 21: 36.
2. Lee TM, Hsu DT, Kantor P, et al. Pediatric Cardiomyopathies. Circulation research. 2017; 121: 855-873.
3. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in Children: Classification and Diagnosis. A Scientific Statement From the American Heart Association. Circulation. 2019; 139: e9-e68.
4. Lipshultz SE, Cochran TR, Briston DA, et al. Pediatric cardiomyopathies: causes, epidemiology, clinical course, preventive strategies and therapies. Future cardiology. 2013; 9: 817–848.
5. Lipshultz SE, Cochran TR, Briston DA, et al. Pediatric cardiomyopathies: causes, epidemiology, clinical course, preventive strategies and therapies. Future cardiology. 2013; 9: 817–848.
6. https://www.ncbi.nlm.nih.gov/books/NBK115561/
7. Michel-Behnke I, Pavo I, Recla S, et al. Regenerative therapies in young hearts with structural or congenital heart disease. Translational pediatrics. 2019; 8: 140–150.
8. Nawab, K, Bhere D, Bommarito A, et al. Stem Cell Therapies: A Way to Promising Cures. Cureus, 2019; 11: e5712.
9. O'Donoghue K, Fisk N M. Fetal stem cells. Best Practice & Reseach Clinical Obstetrics & Gynaecology. 2004; 18: 853-875.
10. Ng A P, Alexander W S. Haematopoietic stem cells: past, present and future. Cell death discovery. 2017; 3: 17002.
11. Williams A R, Hare J M. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. Circulation research. 2011; 109: 923–940.
12. Ma D K, Bonaguidi M A, Ming G L. Adult neural stem cells in the mammalian central nervous system. Cell research. 2009; 19: 672–682.
13. Ding D C, Chang Y H, Shyu WC, et al. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. Cell Transplant. 2015; 24: 339-47.
14. Zhang C, Zhou Y, Lai X, et al. Human Umbilical Cord Mesenchymal Stem Cells Alleviate Myocardial Endothelial-Mesenchymal Transition in a Rat Dilated Cardiomyopathy Model. Transplant Proc. 2019; 51: 936-941.
15. Zhang C, Zhou G, Cai C, et al. Human umbilical cord mesenchymal stem cells alleviate acute myocarditis by modulating endoplasmic reticulum stress and extracellular signal regulated 1/2-mediated apoptosis. Molecular medicine reports. 2017; 15: 3515–3520.
16. Mao C, Hou X, Wang B, et al. Intramuscular injection of human umbilical cord-derived mesenchymal stem cells improves cardiac function in dilated cardiomyopathy rats. Stem cell research & therapy. 2017; 8: 18.
17. Yang S, Piao J, Jin L, et al. Does pretreatment of bone marrow mesenchymal stem cells with 5-azacytidine or double intravenous infusion improve their therapeutic potential for dilated cardiomyopathy?. Medical science monitor basic research. 2013; 19: 20–31.
18. https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/dilated-cardiomyopathy
19. https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/left-ventricular-non-compaction-cardiomyopathy.
20. https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/hypertrophic-cardiomyopathy.
21. https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/restrictive-cardiomyopathy
22. Michel-Behnke I, Pavo I, Recla S, et al. Regenerative therapies in young hearts with structural or congenital heart disease. Translational pediatrics. 2019; 8: 140-150.