Regenerative Medicine Strategies for Hypoplastic Left Heart Syndrome

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Hypoplastic left heart syndrome (HLHS), the most severe and common form of single ventricle congenital heart lesions, is characterized by hypoplasia of the mitral valve, left ventricle (LV), and all LV outflow structures. While advances in surgical technique and medical management have allowed survival into adulthood, HLHS patients have severe morbidities, decreased quality of life, and a shortened lifespan. The single right ventricle (RV) is especially prone to early failure because of its vulnerability to chronic pressure overload, a mode of failure distinct from ischemic cardiomyopathy encountered in acquired heart disease. As these patients enter early adulthood, an emerging epidemic of RV failure has become evident. Regenerative medicine strategies may help preserve or boost RV function in children and adults with HLHS by promoting angiogenesis and mitigating oxidative stress. Rescuing a RV in decompensated failure may also require the creation of new, functional myocardium. Although considerable hurdles remain before their clinical translation, stem cell therapy and cardiac tissue engineering possess revolutionary potential in the treatment of pediatric and adult patients with HLHS who currently have very limited long-term treatment options.

Keywords: hypoplastic left heart syndrome, stem cells, tissue engineering, heart failure, congenital heart

Introduction

Hypoplastic left heart syndrome: definition, epidemiology, and current clinical management

SINGLE VENTRICLE HEART DISEASE is a spectrum of congenital heart defects defined by hypoplasia of the right ventricle (RV) or left ventricle (LV), leaving only one effective pumping chamber to deliver blood flow to both pulmonary and systemic vasculature. Hypoplastic left heart syndrome (HLHS), the most common form of single ventricle heart disease, is characterized by hypoplasia of the mitral valve, LV, and LV outflow structures, which include the aortic valve, ascending aorta, and aortic arch. In HLHS, blood flow into the aorta is dependent on cardiac output generated by the RV passing through the patent ductus arteriosus, a normal fetal structure that connects the pulmonary artery to the aorta. Without intervention, HLHS is uniformly fatal during infancy either from closure of the patent ductus arteriosus or shock due to exuberant blood flow to the lungs and insufficient blood flow to the body.

While the incidence of HLHS is 0.016–0.036% of all live births, it is responsible for up to 23% of cardiac deaths during the first week of life and 15% of cardiac deaths within the first month of life if left untreated.1–3 Three-stage palliative surgeries have been the mainstay of treatment for infants born with HLHS since the early 1980s, culminating in the total cavopulmonary anastomosis, or the Fontan procedure, performed at 2–3 years of age.4 Upon completion of the Fontan, the arterial and venous circulations are connected in series with the RV providing the lone driving force for systemic blood flow while venous blood drains passively into the lungs.

Results of current clinical management of HLHS

Although advances in surgical technique and medical management have improved survival into adulthood, HLHS patients suffer decreased quality of life and extensive reliance on medical care due to severe morbidities, including chronic RV failure. One third of these patients die by 25 years of age from end-stage RV failure.5–7 This number will undoubtedly increase as more and more patients survive past childhood and represent an emerging epidemic. Heart transplantation remains the only long-term treatment option for HLHS patients with RV failure and is unfortunately far from an optimal treatment due to the shortage of donor organs, need for immunosuppression, and limited lifespan of the allograft.8,9 Thus, there is a dire need for novel approaches to preserve and improve the function of the systemic RV, as emphasized recently in a report from a National Heart, Lung, and Blood Institute Working Group.10
The purpose of this review is to introduce HLHS, highlight the mechanisms of RV failure, and review various regenerative medicine approaches and their rational implementation for treating the failing RV in this important clinical entity.

Heart failure in HLHS: key vulnerabilities in the pressure-overloaded RV

In the normal heart, the RV pressures are \( \sim 20\% \) of systemic arterial (and LV) blood pressure. In HLHS, the RV is required to generate systemic arterial blood pressures during the patient’s entire lifetime and is, therefore, prone to early failure.\(^5,11,12\) Pressure loading creates increased work and stress for the RV. The normal myocardial response to pressure overload is myocyte hypertrophy accompanied by angiogenesis and increased antioxidant enzyme activity to mitigate damage from increased oxidative stress encountered in this setting.\(^13\) Recent evidence has revealed that the RV is disadvantaged compared with the LV in its molecular adaptation to pressure overload. The angiogenic response in a pressure-overloaded RV is diminished and has been documented in HLHS and pulmonary hypertension.\(^8\,22\) This blunted angiogenic response is believed to lead to an inadequate supply of oxygen and nutrients, thereby causing cardiomyocyte dysfunction. Furthermore, the antioxidant response in the RV is also diminished, thus making the myocardium more susceptible to oxidative injury during pressure loading.\(^13\,23\)

Consistent with these molecular mechanisms is strong clinical evidence that the RV does not adapt well to chronic systemic afterload in HLHS.\(^10,12,26\) Therefore, designing regenerative therapies to preserve RV function in HLHS should target both myocardial angiogenesis and oxidative stress. Furthermore, in HLHS patients with advanced stages of RV failure, irreversible damage from chronic ischemia and oxidative injury result in a reduction in the total number of cardiomyocytes. In this situation, regenerative medicine approaches would need to increase the number of viable cardiomyocytes as well as provide a blood vessel network to support this new myocardium.

Regenerative Medicine Strategies For HLHS

Regenerative medicine approaches to promote myocardial angiogenesis in the pressure-overloaded RV

The normal response to pressure overload is myocyte hypertrophy accompanied by angiogenesis\(^13\) and upregulation of angiogenic signals such as vascular endothelial growth factor A (VEGFA) and angiopoietin-2.\(^39\) Chronic pressure overload leads to a maladaptive diminution or rarefaction of capillary density.\(^30\,32\) Capillary rarefaction causes ischemia and progression to decompensated heart failure.\(^33\,34\) Various clinical conditions such as hypertension, aortic stenosis, and hypertrophic obstructive cardiomyopathy lead to pressure overload of the LV and result in capillary rarefaction.\(^35\,37\) The RV is also pressure overloaded and subject to capillary rarefaction in diseases such as HLHS and pulmonary hypertension.\(^18\,20\) There is strong clinical evidence that the RV does not adapt well to chronic systemic afterload in HLHS, consistent with the progression and sequela of capillary rarefaction.\(^10,12,26\)

Promoting angiogenesis has been shown to prevent LV heart failure in the setting of hypertrophy.\(^38\,39\) A variety of stem cells, including mesenchymal stem cells (MSCs), resident cardiac stem/progenitor cells (CPCs), and endothelial progenitor cells (EPCs), have been demonstrated to stimulate myocardial angiogenesis. Most of these cell therapies have been evaluated for use in LV ischemic heart disease, but are included in our discussion here.

MSCs are believed to reside in the perivascular regions of essentially all tissues and are comprised of a heterogeneous population of plastic adherent cells that do not possess a unique surface marker phenotype.\(^40\) It is well recognized that MSCs are proangiogenic and secrete numerous angiogenic growth factors.\(^41\,49\) Multiple paracrine and juxtacrine mechanisms exist, by which MSCs promote angiogenesis, indicating a complex and regulated process that is superior to the indiscriminate, forced expression of an angiogenic gene such as VEGFA in the myocardium.\(^50\,52\) Therefore, MSC therapy provides an approach to therapeutic angiogenesis that cannot be replicated by other noncell therapy strategies. Furthermore, MSCs have been demonstrated to possess the ability to differentiate into endothelial cells during 3D culture or when exposed to VEGFA or sphingosine-1-phosphate.\(^53\,55\)

MSCs are being evaluated as a therapeutic agent for promoting angiogenesis in various ischemic conditions, but have not been specifically evaluated in the setting of RV pressure-overload hypertrophy.\(^56\,64\) The success of MSCs in treating ischemic conditions depends on their inherent proangiogenic characteristics, and thus numerous investigators have sought to enhance the ability of MSCs to promote angiogenesis by augmenting the expression of various angiogenic signals in these cells.\(^55\,70\) However, genetically modified MSCs face extensive and protracted safety and regulatory hurdles before clinical use, and thus the identification of the most potent proangiogenic MSC sources or subtypes is currently preferable for the most direct pathway to clinical translation. Several studies have examined the proangiogenic potency of MSCs isolated from different tissue sources and ages of tissue source. MSCs derived from adipose, bone marrow, myocardium, and skeletal muscle are all equivalent in promoting angiogenesis.\(^71\,72\) MSCs from other clinically relevant sources, such as umbilical cord, placenta, thymus, and sternum have not been comparatively evaluated in their ability to promote angiogenesis.\(^73\,79\) While the influence of MSC tissue source is unclear, it is evident from existing data that MSCs derived from younger, healthy subjects are more potent in promoting angiogenesis.\(^80\,82\) Yet another approach to increasing the proangiogenic potency of MSCs is to precondition them with hypoxia, growth factors, and small molecules.\(^83\,86\) Ultimately, selection and preparation of the ideal proangiogenic MSC therapeutic product will depend upon ease of isolation, availability of neonatal source tissue, ability to expand these cells, and finding an optimal preconditioning approach.

Cardiac stem/progenitor cells, a subset of stem cells that reside within the myocardium, have the potential to differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells. Injection of exogenous CPCs into models of ischemic heart disease has been shown to exert a paracrine effect that promotes angiogenesis, protect existing cardiomyocytes, and stimulate endogenous CPCs to potentially enhance regeneration.\(^87\,91\) Although no experimental evidence exists of whether CPCs can improve angiogenesis in the pressure-overloaded RV, there is some experience that...
these cells may promote angiogenesis in the pressure-overloaded LV. Mice receiving intravenous administration of CPCs after transverse aortic constriction (a model of LV pressure overload) resulted in increased expression of angiogenic growth factors (such as bFGF) and density of CD31+ endothelial cells. Cardiac progenitor cells can be isolated from neonates undergoing open heart surgery; however it is unclear whether clinically relevant amounts of these cells can be harvested for patient therapy. Currently, there is no evidence that CPCs improve angiogenesis in a pressure-overloaded RV.

EPCs belong to a subset of bone marrow-derived cells that are found in the peripheral circulation and aid in endothelial homeostasis as well as angiogenesis. EPCs differentiate into endothelial cells through the activation of an upstream, highly conserved regulator gene named heterochromatin protein 1 alpha (HP1α). Subsequently, a multi-cellular process ensues that initiates sprouting to culminate in angiogenesis. While the complex biology of EPCs has yet to be fully understood, an inverse correlation between the absolute number of EPCs and cardiovascular risk factors and disease has been elucidated. This has been corroborated by preclinical and clinical studies that demonstrate an improvement in LV function with EPC therapy in the setting of ischemic heart disease. The precise role of EPCs in pressure overload-induced RV failure and potential therapy for this distinct entity has yet to be defined, although some evidence exists that endogenous EPCs are mobilized in experimental models of LV pressure overload.

Human umbilical cord blood-derived mononuclear cells (UCBMCs) were recently described to promote angiogenesis in the pressure-overloaded RV in athymic nude mice. Human UCBMCs were injected into the RV 4 weeks after pulmonary artery banding, and animals were euthanized at 8 weeks for histological analysis. Therapy with UCBMCs resulted in a significantly increased RV myocardial capillary density as compared with untreated controls. Recent evidence indicates that culturing UCBMCs for 2 weeks yields a heterogeneous collection of cells that is comprised of EPCs and MSCs, but it is unknown if having this combination of both these cell types yield an additive or synergistic proangiogenic effect.

There is convincing evidence that a variety of stem cells can promote angiogenesis in the heart, although most of these findings were obtained in models of acute myocardial ischemia. Further research is needed to determine the ability of these stem cells to promote angiogenesis in the pressure-overloaded RV. The magnitude of therapeutic effect is likely related to the intrinsic proangiogenic potency, and thus identifying a stem cell with especially potent proangiogenic characteristics is important.

Scaffold therapy for HLHS

Acellular scaffolds are made from synthetic polymers or human or animal extracellular matrix and can be administered in patch form to the appropriate myocardial site and can serve as a platform for endogenous progenitor cell migration and proliferation. Short-term results of both animal models and clinical studies using the FDA-approved porcine small intestinal submucosa (pSIS) demonstrate that the material is suitable for closure of septal defects. However, an inflammatory response with fibrosis is generated without site-specific tissue growth. Moreover, in the pediatric population, pSIS is associated with vessel stenosis and a sub-optimal aortic valve repair.

Clinical experience with acellular scaffolds suggests that the scaffolds do not regenerate site-specific tissue. Furthermore, they stimulate very little regenerative response for the myocardium, which limits their use as sole therapy. An alternative approach to promote regeneration is to combine acellular scaffolds with stem cell therapy. The scaffolds can serve as a delivery vehicle for stem cells and also prime the stem cells for angiogenesis and regeneration. When pSIS is seeded with either MSCs or CPCs, the stem cells proliferate and differentiate to display early cardiogenic profile. Another approach that is currently being investigated is to convert the extracellular matrix scaffolds into a hydrogel that can be directly injected, with or without stem cells, into the ischemic myocardium. Other types of hydrogels have also been described and have been supplemented with stromal cell-derived factor 1α (SDF1α), angiogenic peptides, and other instructive growth factors to promote angiogenesis. Preclinical evaluation of acellular scaffolds and injectable hydrogels in small and large animal models of ischemic heart disease has demonstrated efficacy and promotion of angiogenesis. They have not been evaluated in an RV pressure-overload model of heart failure, so its relevance to HLHS is unknown.

Regenerative medicine approaches to alleviate oxidative stress in the pressure-overloaded RV

Although there are no studies specifically evaluating the utility of regenerative medicine approaches to mitigate oxidative injury in the pressure-overloaded RV, there is strong experimental evidence which demonstrates that a variety of stem cells can provide antioxidative benefit. Endogenous mechanisms to mitigate damage from oxidative stress are largely dependent on antioxidant enzymes. The enzyme superoxide dismutase (SOD) is important in its role as part of an antioxidative defense mechanism in all cells. It catalyzes the dismutation of the damaging superoxide (O2−) free radical into less damaging H2O2. There are three isoforms of SOD: SOD1, 2, and 3. SOD1 is located in the cytosol and uses copper and zinc. SOD2 is located in the mitochondria and uses manganese. SOD3 is secreted into the extracellular space and uses copper and zinc. Extracellular SOD3 has been demonstrated to blunt tissue damage and inflammation. Because it is secreted, SOD3 is a potential mediator of the antioxidative property observed in stem cells.

Yang et al. determined that EPCs secrete unidentified soluble factors that protect endothelial cells against oxidative stress, thereby increasing survival and cellular function. Bone marrow-derived EPCs have also been demonstrated to have therapeutic effects in a dilated cardiomyopathy model in rats with streptozotocin-induced diabetes, and that these beneficial effects are associated with increased expression of SOD2 and decreased apoptosis and fibrosis. Qiu et al. determined that EPCs protect against cerebral ischemia–reperfusion injury in rats, and this therapeutic effect was associated with increased total SOD activity, increased levels of...
the nonenzymatic scavenger, glutathione, and decreased apoptosis in the affected areas.124

MSCs have been shown to possess antioxidative effects, which are mediated by extracellular SOD3. DeSantiago et al. determined that mouse bone marrow MSCs protect mouse ventricular cardiomyocytes from ischemia–reperfusion injury 

in vitro by secretion of SOD3, which can reduce the levels of damaging reactive oxygen species (ROS).125 Arslan et al. determined that exosomes secreted by MSCs possess antioxidative properties in a murine model of cardiac ischemia–reperfusion injury.126 These investigators found that only intact exosomes could improve cardiac function, reduce oxidative stress, and restore bioenergetics after myocardial ischemia–reperfusion injury.

Forced expression of SOD3 in bone marrow-derived MSCs may lead to enhanced therapeutic effects.127 Bone marrow MSCs infected with adenovirus-containing SOD3 had a significantly higher survival after transplantation and could provide sustained SOD3 production. This enhanced SOD3 expression was accompanied with a reduction of myocardial infarction-induced oxidative stress, improvement of cardiac function, reduction of fibrosis, and apoptosis after myocardial infarction in rodents. In vitro, bone marrow MSCs expressing SOD3 attenuated cardiomyocyte apoptosis and ROS production and enhanced cardiomyocyte proliferation after hypoxia/serum deprivation.

These results indicate that EPCs and MSCs do possess the ability to neutralize oxidative stress, and that they may provide benefit in mitigating oxidative injury in the pressure-overloaded RV. Stem cells with forced or intrinsically high expression of SOD3 may effectively preserve RV function in HLHS and thus deserve further investigation.

Regenerative medicine approaches to creating new myocardium

Perhaps one of the boldest and most exciting regenerative medicine approaches to heart failure is the possibility of creating functional heart tissue patches or ventricles 

in vitro for implantation in patients. Enlarging the LV with engineered heart tissue (EHT) has even been proposed for patients with HLHS.128 However, to create a useable LV would require more than adding myocardium to increase LV volume. It would necessitate the creation of a mitral valve, aortic valve, and ascending aorta. Hence creating functional heart valves, myocardium, and larger arteries.

However, leaving palliated patients with their single ventricle (Fontan) physiology and improving the contractile function of the pressure-overloaded RV would be clinically feasible and perhaps more achievable from a tissue engineering standpoint. EHT would be of benefit in HLHS patients with advanced stages of RV failure and ideally augment cardiac output immediately upon implantation. To fabricate EHT that would accomplish this feat, a large number of contractile human ventricular cardiomyocytes organized in a compact arrangement and supplied by a dense, perfused vascular network is required.

With embryonic stem cells, the advent of induced pluripotent stem cells (iPSCs), and further molecular insights into heart development, derivation of large numbers of human cardiomyocytes is now possible.129 One of the key remaining challenges on this front is creating and arranging pure ventricular-type cardiomyocytes, and then arranging these millions to billions of cardiomyocytes, along with fibroblasts, smooth muscle cells, and endothelial cells into the compact, organized fashion seen in native myocardium. Such a construct would require a mature and perfused vasculature to provide the obligatory flow of nutrients and oxygen to supply the cardiomyocytes, especially those deep to the surface of the construct beyond the oxygen diffusion distance.130,131 A functioning, perfused microcirculation is paramount, without which central necrosis is observed in tissues greater than 100 μm in thickness.132 The vascularization problem is one of the most important bottlenecks in the field of tissue engineering as it is otherwise not possible to create adequately sized, functional replacement tissues.

The vasculature of EHT must be multiscale and multiphenotype to properly distribute energy and mass flow to parenchymal cardiomyocytes. As in the architecture of the native terminal vascular bed, the engineered vascular network must contain a perfused artery (≥24 mm diameter), arterioles (10–200 μm), capillaries (4–10 μm), venules (10–200 μm), and a draining vein (≥4 mm) to optimally accomplish their function. The artery and vein must also be at least several millimeters in diameter to make surgical anastomosis to the patient’s native vascular network possible.

Most research thus far has focused on the creation of microvasculature in EHT. Most 

in vitro approaches have incorporated the coculture of cardiomyocytes and endothelial cells with EPCs, fibroblasts, or MSCs.133–135 The density of the engineered microvasculature in these EHT constructs are generally at least one order of magnitude less than the capillary density present in native myocardium (5000/mm²). Thus, the thickness of constructs is currently still constrained because the relatively sparse engineered microvasculature lacks perfusion and, therefore, the EHT construct thickness is limited by oxygen diffusion limitations.

There have been recent descriptions of methods to perfuse engineered macro- and microvasculature. Since their seminal description of the perfusion–decellularization method of rat hearts to obtain scaffolds that were then seeded with neonatal rat cardiomyocytes, the group led by Ott has recently followed up with a study of decellularizing human hearts and reseeding with cardiomyocytes derived from human iPSCs.136,137 In this method, the scaffold for the native multiscale vascular network is also left intact, and thus can be used to perfuse seeded cardiomyocytes. Furthermore, these investigators have seeded endothelial cells into this perfusable vascular network in an attempt to recreate a living vasculature.136 The ultimate success of this strategy to create a vascularized heart tissue (or even entire hearts) is still unclear as the resistance of the endothelial cell-seeded vascular network to the development of thrombosis has not been rigorously studied.

Another ingenious approach that partially borrows from the multiscale vascular bed of native tissue was recently described by Sekine et al.138 A pedicle tissue flap based off the femoral vessels of the rat was used as a perfusable tissue bed and serially applied cardiomyocyte cell sheets were then juxtaposed to this perfused vascular bed to generate a thick, vascularized, and perfused EHT construct. This approach
appears to have great potential, but has yet to be applied to human-derived tissues and EHT.

Perfused engineered vascular networks that do not rely on living or decellularized tissues have been generated with microfluidics technology and 3D bioprinting. These are interesting, “bottom up” engineering approaches to developing perfusable vasculature since they do not require the presence of native vasculature. The microfluidics approach also utilizes the self-organizing ability of human endothelial cells and yields perfusable capillary networks onto which cardiomyocytes can be seeded to yield in vitro models of heart tissue. Expanding this approach to include the generation and incorporation of larger (surgically-implantable) vessels has yet to be described. Dai’s group described the use of 3D bioprinting to create millimeter scale endothelial cell-lined channels in collagen hydrogels, which were also seeded with endothelial cells. They generated two perfusable endothelial cell-lined bioprinted channels connected by a capillary network formed from self-organizing endothelial cells between these two channels, resulting in a multiscale, perfusable vascular network. Although vascular communication between the two perfusable larger channels was not demonstrated and cardiomyocytes were not included as parenchymal cells in this engineered vascular network, this is a promising approach to developing EHT with a multiscale, perfusable vascular network.

**Stem cell therapy clinical trials for HLHS**

The discovery of cardiomyocyte apoptosis in physiologic states implies that the creation of new cardiomyocytes is necessary to maintain homeostasis. This regenerative process may be mediated by CPCs. While children have a greater quantity of CPCs, the absolute number is not sufficient to correct the anatomic derangements seen in HLHS. However, these limited cells can be harvested, differentiated, amplified, and potentially used clinically. The precise identification of CPCs has evaded the field. For example, these resident cardiac stem cells can be defined by a surface marker (such as c-kit) or can be defined by its method of derivation, as in the case for cardiosphere-derived cells, a more heterogeneous population of cells. The phase I clinical trials SCIPIO and CADUCEUS utilized CPCs as treatment for adult-onset, acquired ischemic cardiomyopathy, and resulted of these trials demonstrated improved LV function and decreased fibrosis.

In HLHS patients, the phase I clinical trial TICAP, investigated the use of autologous CPCs, obtained either at the second or third-stage procedure, delivered into the coronary arteries. There were no complications or tumor formation reported within 36 months of CPC administration. Moreover, a clinical improvement of RV ejection fraction and a reduction in brain natriuretic peptide, a biomarker for heart failure, was seen. Currently, a Phase II clinical trial is underway and will examine the effects of CPCs on RV ejection fraction and myocardial fibrosis in more detail.

Initial use of bone marrow-derived stem cells in the pediatric population with end-stage heart failure was first described through case reports performed for management of dilated cardiomyopathy and RV failure in HLHS. These initial descriptions reported modest improvement in ventricular function and heart failure symptoms based on New York Heart Association classification. However, the benefits were short lived. Moreover, the patients were concurrently treated with sildenafil and erythropoietin, two drugs known to mobilize progenitor cells, as potential confounders in the perceived effects. Recently, Burkhart et al. reported on the safety of intramyocardial injection of autologous umbilical blood-derived cells during the second palliative procedure of a patient with HLHS. Confounding factors such as deviations in medical and surgical treatment made it difficult to attribute the clinical benefits to stem cell therapy alone. Regardless, these case reports highlight the potential benefit of stem cell therapy in pediatric heart disease, although more research is needed to optimize stem cell therapy for those with HLHS.

**Conclusions**

Improvement in the treatment of HLHS has increased survival of some children into adulthood. Nevertheless, the high morbidity and mortality associated with HLHS remains unsatisfactory with an emerging epidemic of RV failure in these patients with no available alternative treatment options. This challenging clinical scenario presents as an ideal situation where regenerative medicine approaches can be applied. Promising preclinical and early clinical evidence suggest that stem cell therapy may be able to preserve the function of the pressure-overloaded RV. Initial case reports and subsequent clinical trials highlight the potential benefits of regenerative medicine in patients with HLHS, while reminding us of the challenges that remain to be conquered. Consequently, further research is required to develop and establish regenerative medicine therapies in the armamentarium of the clinical treatment of HLHS.

**Disclosure Statement**

No competing financial interests exist.

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