Intracoronary Stem Cell Delivery to the Right Ventricle: A Preclinical Study

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Clinical protocols for stem cell-based therapies are currently under development for patients with hypoplastic left heart syndrome. An ideal cell delivery method should have minimal safety risks and provide a wide distribution of cells to the nonischemic right ventricle (RV). However, the optimal strategy for stem cell delivery to the RV has yet to be explored in a preclinical model, necessary for a hypoplastic left heart syndrome trial. Human c-kit⁺ cardiac stem cells (CSCs) were delivered to healthy Yorkshire swine through the proximal right coronary artery with a stop and reflow technique. The effect of premedication with antiarrhythmic (AA) medications in this model was retrospectively reviewed, with the primary outcome of survival 2 hours after infusion. A group underwent CSC delivery to the RV without prophylactic AA medication (no AA, n = 7), whereas the second group was premedicated with a loading dose and intravenous infusion of amiodarone and lidocaine (AA, n = 13). Cardiac biopsies were obtained from each chamber to ascertain the biodistribution of CSCs. Survival was significantly greater in the prophylactic AA group compared with the group without AA (13/13 [100%] vs 1/7 [14.3%], P < 0.0001). Cardiac arrest during balloon inflation was the cause of death in each of the nonmedicated animals. In the premedicated group, 9 (69.2%) pigs experienced transient ST segment changes in the precordial leads during CSC delivery, which resolved spontaneously. Most c-kit⁺ CSCs were distributed to lateral segments of the RV free wall, consistent with the anatomical course of the right coronary artery (lateral RV, 19.2 ± 1.5 CSCs/field of view vs medial RV, 10.4 ± 1.3 CSCs/field of view, P < 0.0001). Few c-kit⁺ CSCs were identified in the right atrium, septum, or left ventricle. Prophylactic infusion of AA enhances survival in swine undergoing intracoronary delivery of human c-kit⁺ CSCs to the RV. Additionally, intracoronary delivery results in a limited biodistribution of c-kit⁺ CSCs within the RV. Human clinical protocols can be optimized by requiring infusion of AA medications before cell delivery.

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INTRODUCTION

Hypoplastic left heart syndrome (HLHS) is one of the most complex and high-risk lesions in congenital heart disease (CHD), with 1- and 5-year transplant-free survival rates as low as 64%-74% and 50%-65%, respectively.1,3 Therapeutic options are currently limited to staged palliation or heart transplantation, each of which carries substantial risks to long-term survival and quality of life.5,7 Although the attrition in HLHS is multifactorial, systemic RV dysfunction is a known contributor to morbidity and mortality.5,7 Interventions with
the potential to boost systemic RV performance in HLHS patients are, therefore, being explored with great interest.

Stem cell therapy has been tested extensively in adults with ischemic heart disease, but only recently applied as an adjunct to staged palliation for patients with HLHS. Resident cardiac stem cells (CSCs)—identified by the surface marker, c-kit—exist within mammalian myocardium and represent a compartment of undifferentiated, multipotent cells. C-kit+ CSCs have been shown reproducibly in animal models and early-phase clinical trials to ameliorate postischemic ventricular dysfunction and scar formation. A preparation of CDCs (cardiosphere-derived CSCs) was recently administered to patients with HLHS in a phase I clinical trial, which showed safety and preliminary efficacy to improve RV function relative to standard treatment. Meanwhile, other stem cell preparations are currently being evaluated in other ongoing or planned early-phase trials for patients with HLHS. Although the exact mechanism has yet to be defined, accumulating evidence suggests a paracrine-based mechanism that mediates neovascularization, reduced fibrosis, and enhanced contractility. In particular, pediatric patients may stand to realize the greatest benefit from a cell-based therapy, as the developing myocardium is hypothesized to be more responsive to biological cues directed by transplanted cardiac progenitor cells.

A fundamental translational question that remains to be answered relates to the optimal route of stem cell administration in very young patients with HLHS. An ideal cell delivery method in this population would (1) pose minimal safety risks to the systemic RV and (2) provide wide distribution of cells to the RV myocardium. In existing animal studies and recent clinical trials, as well as ongoing and planned trials, intracoronary or “transcoronary” infusion using the stop-reflow technique has been the prevailing delivery method of CSCs. Despite potential safety risks, clinical experience with intracoronary delivery of CSCs in adults with ischemic cardiomyopathy has overall been safe. However, procedural outcomes from experience in adults may not translate to a pediatric population of patients with single ventricle physiology. The stop-reflow technique—which has been used in all previous, ongoing, or planned clinical trials with intracoronary delivery—involves serial balloon inflations during cell infusion with temporary occlusion of the target coronary vessel. In infants with complex CHD, such a delivery strategy poses serious safety risks and technical challenges. First, global delivery of cells to the RV myocardium is required, rather than to a focal territory of ischemic or infarcted myocardium, necessitating balloon inflation and cell delivery in a proximal epicardial coronary artery. Second, the RV in patients with HLHS may be dysfunctional and is exposed to a number of physiological stressors, including abnormal loading conditions, dysrhythmias, and alterations in coronary blood flow, which together predispose the RV to risk of infarction or life-threatening dysrhythmias with repeated cycles of coronary occlusion and reperfusion. Finally, recognized risks with the use of an intraluminal balloon under pressure include endothelial damage, coronary artery dissection, or perforation. Despite the seriousness of these risks, no study has been performed to date that addresses these issues in a model clinically relevant to pediatric patients with non-ischemic RV dysfunction.

To evaluate the safety and biodistribution of a stem cell product delivered to the RV, a swine model was used to examine catheter-based intracoronary delivery of human c-kit+ CSCs. The delivery technique used in this model was similar to the approach described in adult trials using intracoronary delivery of CSCs as well as a recently published phase I trial for patients with HLHS. The objectives of this study were 2-fold: (1) to retrospectively review our initial experience with this model, with a specific focus on the effect of prophylactic antiarrhythmic (AA) medications on survival when administered before intracoronary CSC delivery to the RV and (2) to assess the biodistribution of CSCs within the RV and other cardiac chambers using this technique.

MATERIALS AND METHODS

Study Design

This study was approved by the University of Maryland School of Medicine Institutional Review Board for use of all human cardiac tissue biopsies. All animals received care in compliance with federal and institutional guidelines with approval from our Institutional Animal Care and Use Committee and following the 1996 Guide for the Care and Use of Laboratory Animals.

This study was a retrospective review of outcomes using intracoronary delivery of CSCs to the RV of healthy Yorkshire swine with the primary endpoint being survival of CSC infusion. A secondary endpoint was the myocardial biodistribution of c-kit+ CSCs to the RV, septum, left ventricle (LV), and other cardiac structures after CSC delivery. Swine that survived the CSC infusion were monitored for 2 hours then euthanized. Retained CSCs were identified by dual
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