



B. Vrtovec, M.D., Ph.D.

STEM CELL THERAPY IN PATIENTS WITH HEART FAILURE

Bojan Vrtovec, M.D., Ph.D.^{a,b}; Gregor Poglajen, M.D., Ph.D.^a; François Haddad, M.D.^b

^aLjubljana University Medical Center, Ljubljana, Slovenia

^bStanford University School of Medicine, Stanford, California

Abstract

Heart failure results from injury to the myocardium from a variety of causes, including ischemic and nonischemic etiologies. Severe heart failure carries a 50% 5-year mortality rate and is responsible for more than one-third of cardiovascular deaths in the United States.¹

Heart failure progression is accompanied by activation of neurohormonal and cytokine systems as well as a series of adaptive changes within the myocardium, collectively referred to as left ventricular remodelling. The unfavorable alterations may be categorized broadly into changes that occur in the cardiac myocytes and changes that occur in the volume and composition of the extracellular matrix.² Since remodelling in heart failure is progressive and eventually becomes detrimental, the majority of treatment strategies are aimed at stopping or reversing this process. Although medical management, cardiac resynchronization therapy, and long-term or destination mechanical circulatory support have been successful in this regard, a considerable number of patients still progress to end-stage heart failure with limited therapeutic options. For these patients, stem cell therapies are being investigated as a safe treatment strategy for decreasing cardiac remodelling on top of conventional medical and device treatment.

Introduction

Stem cells, by definition, are a population of cells capable of differentiating into more specific cells and can provide replacement cells.³ Stem cells are capable of self-renewal — they can make more of themselves in addition to providing daughter cells that go on to differentiate towards specific lineages. Although there is increasing evidence that the heart can renew itself by activation of resident cardiac stem cells, this endogenous capacity for regeneration is insufficient to mediate repair after severe cardiac injury.⁴ Thus, the ability of injured myocardium to recruit extracardiac stem cells after injury would be beneficial to aid in myocardial repair and regeneration. The injured myocardium, via peripheral blood, signals the mobilization of the extracardiac stem cells from the bone marrow into the peripheral circulation. After mobilization, these circulating bone marrow-derived stem cells then follow a trail marked by specific signals, subsequently exit the circulation, and home to injured sites to initiate the cardiac repair process.⁵ However, in the setting of chronic heart failure of both ischemic and nonischemic etiology, the recruitment stimuli are low and not sufficient to significantly decrease cardiac injury. As shown in recent clinical trials, exogenous delivery of stem cells to injured areas of the myocardium may overcome this limitation.

Stem Cell Therapy for Ischemic Heart Failure

Stem Cells and Remodeling in Ischemic Heart Failure

In ischemic heart disease, all three integrated components of the myocardium (myocytes, extracellular matrix, and capillary microcirculation) undergo complex, dynamic, and time-dependent changes.⁶ Remodeling caused by myocardial ischemia has been divided into an early phase (within 72 hours of acute ischemia) and a late phase (after 72 hours). In the early phase, the majority of the remodeling occurs in the infarcted myocardium and peri-

infarct region, potentially resulting in infarct expansion. During this phase, degradation of the extracellular matrix occurs by serine proteases and activated matrix metalloproteases released from neutrophils.^{6,7} During the late phase of remodeling, changes in extracellular matrix lead to alterations in ventricular architecture, and compensatory myocyte hypertrophy may be observed.⁷ Although these changes are beneficial for stabilization of heart function, progressive ventricular dilatation may lead to worsening heart failure.

The aim of antiremodeling therapy in ischemic cardiomyopathy is to prevent, limit, or even reverse adverse structural remodelling and thus interrupt the sequence of progressive left ventricular dilatation/dysfunction and decrease the incidence of ventricular arrhythmias. Unfortunately, while there have been some major advances in medical management of heart failure and in coronary reperfusion strategies for chronic ischemic heart disease and after acute myocardial infarction (MI), prevention and treatment of adverse remodeling in ischemic heart failure still remains a therapeutic challenge.

In 2001, Orlic et al. showed that bone marrow-derived stem cells can lead to a regenerative response in a mouse model of MI. This study brought considerable interest in the field of myocardial regeneration for ischemic heart failure.⁸ Numerous animal studies have confirmed the initial promising results, showing that stem cell transplantation in ischemic myocardium may indeed reduce myocardial scar burden, improve ventricular function, increase myocardial perfusion, and even affect left ventricular geometry.⁹⁻¹² Initially, beneficial effects of stem cell therapy on reverse myocardial remodelling were attributed to de novo myocardiogenesis. Although this was shown to occur in some animal studies, it was not confirmed uniformly.

Today, it is believed that stem cells exert their beneficial effect

on ischemic myocardium mainly through neovascularization and paracrine effects.¹³ It has been shown that stem cells inhibit synthesis of proinflammatory cytokines (TNF alpha, IL-6) and promote expression of anti-inflammatory cytokines (IL-10).¹⁴⁻¹⁶ The proinflammatory cytokines TNF alpha and IL-6 have a direct cytotoxic effect on cardiomyocytes, can inhibit cardiac contractile function, and have been shown to induce apoptosis of cardiomyocytes. They also act as chemoattracting agents, promoting the chemotaxis of inflammatory cells into the myocardium.¹⁴⁻¹⁶ Furthermore, stem cells have been shown to improve cardiac function through regulation of fibroblast proliferation and downregulation of types I and III collagen synthesis.¹⁷

Clinical Effects of Stem Cell Therapy in Ischemic Heart Failure

The first clinical trial evaluating the effects of stem cell therapy on ischemic heart failure was reported in 2002. In 2006, three large randomized clinical trials (ASTAMI, REPAIR-AMI, and TOPCARE-CHD) were published.¹⁸⁻²⁰ Although results on the beneficial effects of stem cells on myocardial function from these first trials were somewhat conflicting, further clinical trials (BOOST, STAR-HEART, SCIPPIO, CADUCEUS, REGENT, FocusHF, and others) suggest the beneficial effects of stem cells on the function and remodeling of ischemic myocardium (Table 1).²¹⁻²⁵

In the Focus-HF trial, Perin et al. were able to demonstrate that intramyocardial transplantation of autologous bone marrow mononuclear cells in patients with ischemic heart failure improved quality of life and exercise capacity.²⁶ They attributed these beneficial effects of stem cells to improved perfusion of the ischemic myocardium. Similarly, Losordo et al. showed that intramyocardial application of CD34+ stem cells in patients with refractory angina significantly reduced frequency and duration of anginal episodes.²⁷ Furthermore, the SCIPPIO trial showed that intracoronary infusion of cardiac stem cells in patients with ischemic heart failure who had suffered an acute MI resulted in a reduction of infarct size and improved left ventricular function.²⁵ However, this trial was done on patients who underwent prior coronary artery bypass grafting, and there is a possibility that at least some beneficial effects that were attributed to stem cell treatment were in fact the result of improved coronary perfusion

due to revascularization. The largest randomized clinical trial on stem cells and chronic ischemic heart failure to date was STAR-HEART, done by Strauer et al. in 2010.²¹ They were able to show that intracoronary infusion of CD34+/CD133+ stem cells improved myocardial function and patients' exercise capacity. Importantly, they were also able to demonstrate the persistence of these beneficial effects 5 years after the procedure. Furthermore, they showed the 5-year survival of patients who received stem cells was significantly better than that of controls (96% vs. 84%, $P < 0.01$).

The results of clinical trials in ischemic heart failure are difficult to compare since stem cell types, their amount, and delivery routes were different. Based on available preclinical and clinical data, however, it seems that bone marrow stem cells (CD34+, mesenchymal stem cells) delivered intramyocardially yielded the best results. Although a significant step forward was made in stem cell therapy for ischemic heart failure, several important questions regarding stem cell type, delivery method, amount of cells to be transplanted, and, above all, timing of stem cell transplantation in patients with ischemic heart disease remain unanswered and represent a focus of future research in this field.

Stem Cell Therapy for Nonischemic Heart Failure

Stem Cells and Remodelling in Nonischemic Heart Failure

One-third of heart failure patients have a diagnosis of dilated cardiomyopathy (DCM).²⁸ DCM is thought to result from various pathogenic mechanisms including genetic factors, mechanical stress, and intoxication. However, about two-thirds of DCM patients show evidence of a myocardial viral genomic persistence, indicating that inflammation may be the most prevalent cause for DCM development.²⁹ The progression to DCM may be caused by the direct adverse effects of the pathogen upon the myocardial tissue or by activation of autoreactive lymphocytes via molecular mimicry, which leads to unfavorable changes in ventricular myocytes and extracellular matrix. Changes in cardiac myocytes after viral infections result from direct infection-dependent injury and by infection-induced autoimmune response.

Besides their potential effects on cardiac myocyte regeneration, stem cells could improve cardiac function in DCM through potential paracrine effects, which include: (1) secretion of factors that attenuate apoptosis of endogenous cardiomyocytes and endothelial cells;³⁰ (2) promotion of angiogenesis; (3) activation

Study	No. of patients	Baseline LVEF (%)	Follow-up (months)	Cell type	Cell dose	Delivery route	Outcome
ASTAMI ¹⁹ (2006)	100	46	6	BMC	8, 7x10 ⁶	IC	No effect
REPAIR-AMI ¹⁸ (2006)	204	48	12	BMC	2, 4x10 ⁸	IC	LVEF increased 2.5%
TOPCARE-CHD ²⁰ (2006)	121	40	12	BMC	214x10 ⁶	IC	LVEF increased 1.8%
BOOST ²² (2009)	60	51	6	BMC	2, 5x10 ⁹	IC	LVEF increased 6.7%
STAR-heart ²¹ (2010)	391	33	60	BMC	6, 6x10 ⁷	IC	LVEF increased 6.2%
FocusHF ²⁶ (2011)	30	37	6	BM-MNC	484x10 ⁶	IM	No effect on LVEF, scar reduction
SCIPPIO ²⁵ (2011)	14	30	4	CSC	1x10 ⁶	IC	LVEF increased 8.2%
CADUCEUS ²⁴ (2012)	25	39	6	CDC	12, 5x10 ⁶ 25x10 ⁶	IC	No effect on LVEF, scar reduction

Table 1. Prospective randomized trials of stem cell therapy in ischemic heart failure. BMC: bone marrow stem cells; BM-MNC: bone marrow mononuclear cells; CSC: cardiac stem cells; CDC: cardiosphere derived cells; LVEF: left ventricular ejection fraction.

Study	No. of patients	Baseline LVEF (%)	Follow-up (months)	Cell type	Cell dose	Delivery route	Outcome
Bocchi et al. ⁴³ (2008)	22	21%	15	BMC	not specified	IC	LVEF increase 8.8%
Seth et al. ⁴² (2010)	85	23%	36	BMC	168x106	IC	LVEF increased 5.9%
Vrtovec et al. ⁴ (2011)	55	26%	12	Autologous CD34+	123x106	IC	LVEF increased 4.6%

Table 2. Prospective randomized trials of stem cell therapy in nonischemic heart failure. LVEF: left ventricular ejection fraction; IC: intracoronary; BMC: bone-marrow cells; NS: not significant.

of resident cardiac stem cells;³¹ or (4) supplying large amounts of anti-inflammatory factors.³² Alternatively, stem cell transplantation may neutralize circulating autoantibodies that are present in DCM via similar mechanisms that are thought to be responsible for the effects of CD34+ cell transplantation in the treatment of severe autoimmune diseases, such as therapy-resistant rheumatoid arthritis and multiple sclerosis.³³ According to this postulate, stem cells might be able to limit the overactivated immune response in DCM by tolerization of autoreactive T and B cells.³⁴

In addition to alterations in myocytes and cytoskeletal proteins, patients with DCM also have defective vascularization and impaired vasculogenesis and angiogenesis.³⁵ Although the exact underlying mechanisms remain to be defined, they appear to be related to impaired survival of endothelial cells due to increased expression of VE-cadherin/beta-catenin.³⁶ Thus, together with perivascular fibrosis around intramyocardial blood vessels, these findings may partly account for disease progression in DCM. Studies in animal models suggest that implantation of hematopoietic stem cells improves angiogenesis, arteriogenesis, tissue perfusion, and left ventricular function.³⁷ In patients with ischemic heart disease, the neovascularization results in decreased apoptosis of hypertrophied myocytes in the peri-infarct region, long-term salvage and survival of viable myocardium, reduction in collagen deposition, and sustained improvement in cardiac function.³⁸ Based on similar mechanisms, delivery of CD34+ stem cells could improve tissue perfusion and left ventricular function in patients with DCM.

Clinical Effects of Stem Cell Therapy in Nonischemic Heart Failure

Based on preclinical evidence, it appears that patients with nonischemic heart failure may represent a good target population for stem cell therapy. In these patients, bone-marrow stem-cell functional capacity has shown to be significantly less impaired compared to patients with ischemic heart failure or healthy controls.³⁹ Furthermore, patients with dilated cardiomyopathy also have higher numbers of circulating progenitor cells compared to patients with ischemic heart disease,⁴⁰ suggesting that they may represent a better patient population for stem cell therapy.

To date, there have been very few trials investigating the effects of stem cell therapy in dilated cardiomyopathy (Table 2). In the TOPCARE-DCM trial, such therapy resulted in significant improvement in left ventricular ejection fraction, regional hypokinesia, and N-terminal brain natriuretic peptide (NT-proBNP) at 1 year.⁴¹ In accordance with these findings, the ABCD trial demonstrated an improvement in ejection fraction and quality of life during a mean follow-up of 4 years.⁴² Similarly, evaluations after the first month in patients with end-stage nonischemic heart failure who received bone-marrow stem cell infusions showed improvements in ejection fraction, peak VO_2 , NYHA functional class, and quality of life.⁴³ In a pilot randomized study, our team of

researchers from Ljubljana University Medical Center, Stanford University School of Medicine, and the Methodist DeBakey Heart & Vascular Center found that intracoronary bone-marrow stem cell transplantation could indeed lead to improved ventricular remodeling, better exercise tolerance, and potentially improved survival in these patients.⁴⁴

Based on these results, we have performed a prospective, randomized trial investigating long-term effects of CD34+ stem cell therapy in patients with nonischemic DCM.⁴⁵ Of 110 patients with DCM, 55 were randomized to CD34+ cell transplantation (SC group) and 55 patients did not receive stem cell therapy (Controls). In the SC group, peripheral blood CD34+ cells were mobilized by granulocyte-colony stimulating factor and collected via apheresis. Patients underwent myocardial scintigraphy, and CD34+ cells were injected in the coronary artery supplying the segments with reduced viability. At 5 years, stem cell therapy was associated with an increase in LVEF (from $24.3 \pm 6.5\%$ to $30.0 \pm 5.1\%$; $P = 0.02$), an increase in 6-minute walk distance (from 344 ± 90 m to 477 ± 130 m; $P < 0.001$), and a decrease in NT-proBNP (from 2322 ± 1234 pg/mL to 1011 ± 893 pg/mL; $P < 0.01$). During follow-up, 27 (25%) patients died, and 9 (8%) underwent heart transplantation. Of the 27 deaths, 13 were attributed to pump failure and 14 to sudden cardiac death. Total mortality was lower in patients receiving SC therapy (8/55, 14%) than in Controls (19/55, 35%) ($P = 0.01$). The same was true of the pump failure (3/55 vs. 10/55, $P = 0.03$) but not of the sudden cardiac death (5/55 vs. 9/55, $P = 0.39$). Thus, it appears that intracoronary stem cell transplantation is associated with improved ventricular remodeling, better exercise tolerance, and improved long-term survival in patients with chronic heart failure due to nonischemic dilated cardiomyopathy.

Conclusions

Stem cell therapy appears to be a safe treatment modality in patients with chronic heart failure. In addition to the optimized medical and device therapies, the available data suggest that stem cell therapy is associated with long-term improvement in cardiac function and exercise tolerance and a decrease in NT-proBNP, which may translate into improved outcomes for this patient cohort. Further studies are needed to better define the underlying mechanisms, improve stem cell homing, and further improve the outcome of patients with chronic heart failure, and large randomized trials are needed to validate the early findings.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Funding/Support: The authors have no funding disclosures.

Keywords: stem cells, heart failure, ischemic heart disease, dilated cardiomyopathy

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