World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v3.i3.93

World J Cardiol 2011 March 26; 3(3): 93-97
ISSN 1949-8462 (online)

REVIEW

Benefit of stem cells and skeletal myoblast cells in dilated cardiomyopathies

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Received: January 15, 2011 Revised: March 2, 2011
Accepted: March 9, 2011
Published online: March 26, 2011

Abstract

Although some authors suggest that there is mitotic division in the heart, most cardiomyocytes do not have the capacity to regenerate after myocardial infarction and when this occurs there is a deterioration of contractile function, and if the area of infarction is extensive ventricular remodeling may occur, leading to the development of heart failure. Cell transplantation into the myocardium with the goal of recovery of cardiac function has been extensively studied in recent years. The effects of cell therapy are based directly on the cell type used and the type of cardiac pathology. For myocardial ischemia in the hibernating myocardium, bone marrow cells have functional benefits, however these results in transmural fibrosis are not evident. In these cases there is a benefit of implantation with skeletal myoblasts, for treating the underlying cause of disease, the loss of cell contractility.

Key words: Cell transplantation; Cardiomyopathy; Skeletal myoblasts; Stem cells

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Guarita-Souza LC, Francisco JC, Simeoni R, Faria-Neto JR, de Carvalho KAT. Benefit of stem cells and skeletal myoblast cells in dilated cardiomyopathies. *World J Cardiol* 2011; 3(3): 93-97 Available from: URL: http://www.wjgnet.com/1949-8462/full/v3/i3/93.htm DOI: http://dx.doi.org/10.4330/wjc.v3.i3.93

INTRODUCTION

Congestive heart failure is the common final pathway for patients with ischemic and non-ischemic cardiomyopathies. Therapeutic options mainly target the consequences of heart failure, such as fluid overload and neurohumoral activation, which are known to have long term deleterious effects[1]. However, improvement in ventricular contractility by restoration of cardiomyocyte contractile capacity has not been an issue until recently[2].

Although some authors have shown evidence of mitotic division of cardiomyocytes, scar formation following myocardial injury leads to remodeling and permanent loss of ventricular contractility[3]. Not surprisingly, attempts to restore ventricular contraction in ischemic cardiomyopathy by cell transplantation have emerged as a feasible therapeutic option.

The beneficial effect of cellular transplantation in the full range of cardiomyopathies remains to be investigated. The most appropriate cell type to be used for each dilated cardiomyopathy will probably vary, since mechanisms of myocardial damage are different. In this article we will first review the characteristics of some of the cells that have been studied as appropriate for transplantation either in ischemic or non-ischemic cardiomyopa-

thies. In addition, we will review some experimental and human studies in different types of non-ischemic dilated cardiomyopathies.

CHARACTERISTICS OF DIFFERENT CELLS

Myoblasts

Skeletal myoblast transplantation has been shown to be effective in many experimental[4-7] and clinical[8] studies. These cells differentiate into viable muscle fibers within the scarred tissue and they seem to be less prone to ischemia compared to cardiomyocytes[9].

In a phase I clinical trial, Hagège *et al*[8] evaluated 10 patients with severe post-infarct ventricular dysfunction who received autologous myoblasts cultured for 16 d after being taken from the thigh. The authors demonstrated a recovery of function in areas previously akinetic and non-viable, but the mechanism of improvement was not completely understood. They hypothesized that it could happen either by a change in cell phenotype, since they expressed slow myosin instead of fast myosin, or simply by colonizing the infarcted area with new contractile cells and avoiding further dysfunction[8]. However, the high incidence of ventricular arrhythmias in patients who received myoblasts was of major concern.

Paradoxically, in the phase Ⅱ randomized, placebo-controlled trial Myoblast Autologous Grafting in Ischemic Cardiomyopathy by the same investigators, there were no statistically significant differences between the treatment and placebo groups in terms of ventricular arrhythmias (all the patients had received an implantable cardioverter-defibrillator). However, the study was ended early after an analysis by an independent data-monitoring board indicated that the trial was unlikely to show that treatment would be superior to placebo in terms of functional improvements in heart regional wall motion or global ventricular function (data presented at the Scientific session of the American Heart Association, Chicago, 2006)[10].

In conclusion, there is still controversy on whether myoblast transplantation is a good option, at least as sole treatment. Potential pitfalls of this strategy are the lack of morphological differentiation into cardiomyocytes and also the absence of an intercalated disc between transplanted cells and the native adult cardiomyocytes, suggesting there may be no synchronicity in contraction between these types of cell.

Bone-marrow stem cells

Adult stem cells are pluripotent[11]. They have the ability to differentiate into specific cells depending on the surrounding tissue and factors. The differentiation capacity of bone marrow cells is not completely understood. Some studies have shown that these cells are able to differentiate into cardiomyocytes[12] but in another study only neoangiogenesis was seen and left ventricular ejection fraction deteriorated similarly in the transplanted and control groups (from 42% ± 5% to 30% ± 4% and from 40% ± 4% to 31% ± 1%, respectively, $P = 0.86$)[13]. In fact, different results have been observed according to the studied model.

In a model of myocardial infarction, Orlic *et al*[14] have demonstrated the beneficial effect of bone marrow cell injection in the border of the infarcted myocardium shortly after coronary ligation. In this tissue, proliferating myocytes and vascular structures were noted. Bone marrow cells were transplanted in an area with viable myocardium, and not scar tissue, and this may explain why they differentiated into cardiomyocytes. In a clinical trial, Wollert *et al*[15] evaluated patients with acute myocardial infarction who, after acute treatment with percutaneous transluminal coronary angioplasty, were randomized to standard clinical treatment alone or standard treatment and bone marrow cell transplantation. Ventricular function significantly improved in patients who received cells, in comparison to those who did not.

In patients with established fibrosis, results are conflicting. Perin *et al*[16] showed that transendocardial injection of autologous mononuclear bone marrow cells in patients with end-stage ischemic heart disease improves perfusion and mechanical function of the injected segments. However, different results were demonstrated by Marzullo[17], who demonstrated by scintigraphy that bone marrow cells can improve perfusion but not contraction. The author evaluated patients with a coronary artery bypass graft who had cells injected in the area of fibrosis. In areas where reperfusion was achieved after grafting, improvement was seen in perfusion and contraction. On the other hand, in areas where cell injection was performed, compared with culture medium only, an improvement in perfusion was seen.

Combined transplantation

The idea of using a combination of skeletal myoblasts and cells derived from the bone marrow is based on the concept of providing angio-muscular regeneration and not only isolated muscular or angiogenic regeneration. Our group has evaluated transplantation of co-cultured myoblasts and mesenchymal stem cells (MSC) in a rat model of myocardial infarction, and it was effective in improving ventricular function, with development of new skeletal muscular fibers and new blood vessels in the region of myocardial fibrosis[18]. Our results with co-culture in Chagasic cardiomyopathy are described in the next section[19].

CELL TRANSPLANTATION IN NON-ISCHEMIC DILATED CARDIOMYOPATHY

Experimental studies

While animal models of ischemia and myocardial infarction can be easily reproduced, models of non-ischemic dilated cardiomyopathy are lacking. In an interesting myocarditis model, where rats are immunized with porcine cardiac myosin resulting in severe heart failure, Nagaya *et al*[20] evaluated the effect of MSC on induction of myogenesis and angiogenesis. They isolated MSC from bone marrow aspirates, cultured them for 5 wk, then injected

cells or vehicle into the myocardium. Some engrafted MSCs were positive for the cardiac markers desmin, cardiac troponin T, and connexin-43, whereas others formed vascular structures and were positive for von Willebrand factor or smooth muscle actin. Compared with the control group, MSC transplantation significantly increased capillary density and ventricular maximum dp/dt, decreased the collagen volume of the myocardium and decreased left ventricular end diastolic pressure. Authors suggested that MSC transplantation improved cardiac function not only by induction of myogenesis and angiogenesis, but also by inhibition of myocardial fibrosis.

In a similar model of dilated cardiomyopathy, Werner *et al*[21] investigated the effect of spleen-derived endothelial progenitor cells injected by the femoral vein. These cells reduced the myocardial damage induced by experimental myocarditis and resulted in improvement in cardiac performance as shown by echocardiography. This late finding was consistent with a thicker left ventricular wall compared with the control group as demonstrated by histopathology. Another interesting finding was that endothelial progenitor cells from rats with dilated cardiomyopathy were compromised in their ability to bind immobilized fibronectin, cultured endothelial cells and cardiomyocytes as compared with progenitor cells from healthy rats, suggesting a whole dysfunctional state.

Working with CHF147 Syrian hamsters, a strain characterized by a δ-sarcoglycan deficiency that phenotypically features the human setting of primary dilated cardiomyopathy, Pouly *et al*[22] transplanted autologous tibial myoblasts and found an increment of 26% in fractional area change of transplanted hamsters compared with a reduction of 6% in control animals (fractional area change is an echo parameter commonly applied to evaluate ventricular function in murine models of heart failure). Engrafted myotubes were detected by immunohistochemestry in all myoblast transplanted hearts, suggesting that the functional benefits of myoblast transplantation seen in ischemic cardiomyopathies might also extend to non-ischemic cardiomyopathies.

As Chagasic cardiomyopathy caused by the hemoflagellate protozoa *Trypanosoma cruzi* infection has been one of the leading causes of heart disease in Latin America for decades, animal models of this disease have been developed to better evaluate new therapeutic options. Nevertheless, studies of cell transplantation in these experimental models are still lacking. In a mouse model, Soares *et al*[23] demonstrated that bone marrow cells injected intravenously migrated to the heart and caused a significant reduction in inflammatory infiltrates and in interstitial fibrosis. Cell therapy induced massive apoptosis of myocardial inflammatory cells. The effect was the same when injected bone marrow cells were obtained from normal or infected mice. Because ventricular function was not assessed, it remains to be proved whether these beneficial histological effects with mononuclear cells transplantation is translated into ventricular function improvement in models of Chagas disease.

Also in a rat model of Chagas disease, our group has evaluated the transplantation of co-cultured skeletal myoblasts and mesenchymal cells derived from bone marrow. As previously described, we had successfully tested this approach in a rat model of myocardial infarction. Because physiopathology in Chagas disease resembles the findings in chronic ischemic cardiomyopathy, with fibrosis and ischemia, we hypothesized that simultaneous transplantation of co-cultured MSC and skeletal myoblasts could be an effective approach in this disease.

To develop the rat model, we infected Wistar rats with with trypomastigotes (infective form of *Trypanosoma cruzi*) and after 8 mo the animals which developed dilated cardiomyopathy (left ventricular ejection fraction < 37%) were included in the study. Autologous skeletal myoblasts were isolated from muscle biopsy, and MSC from bone marrow aspirates were co-cultured *in vitro* for 14 d. Rats were randomly assigned to receive subepicardial injection of co-culture of skeletal myoblast and MSC or culture medium as control. Cells were injected into the anterior and lateral left ventricular wall. One month after the procedure, the ejection fraction remained unchanged in the control group (36.7% ± 3.6% to 37.4% ± 6.7%, P = 0.7684) but was enhanced in the treated group (30.1% ± 5.7% to 51.8% ± 6.6%, P < 0.0001). We also found a reduced left ventricular end diastolic and systolic volumes in those rats receiving the cells. No change was observed in the control group. Histological analysis of the control group demonstrated a high degree of fibrosis, a feature of Chagas disease. In the treated group, skeletal muscle cells, with myotubular characteristics, endothelial cells, and formation of new vessels were identified in the epicardium where cells were transplanted. The musculoskeletal origin was confirmed by positive fast myosin immunostaining in the treated group. In conclusion, the combined cellular transplantation with myoblasts and MSC is functionally effective in the model of Chagas disease ventricular dysfunction.

Cellular transplantation has also been evaluated in a model of doxorubicin-induced cardiomyopathy. Ishida *et al*[24] performed the study in rats that randomly received bone marrow mononuclear cells, saline or no injection but a sham operation. After 4 wk of cells delivery through thoracotomy, ventricular function and diameters were evaluated by echocardiography. Systolic left ventricular diameter was smaller and fractional shortening was larger in the transplanted group. Beneficial effects of cellular transplantation were confirmed by Langendorff apparatus that revealed greater peak systolic pressure and lower end diastolic pressure in hearts from the transplant group.

Human studies

Experience with cellular transplantation in non-ischemic cardiomyopathies is still in a very preliminary phase, and bone marrow cells have been widely used for this. Lago *et al*[25], performed the transplantation of bone marrow stem cells into 8 patients with non-ischemic cardiomyopathy, deploying cells directly into coronary arteries. The

ejection fraction significantly increased from 18.3 ± 7 to 26.4% ± 10% ($P < 0.005$) and left ventricular diastolic diameter showed a non significant decrease. Symptoms were significantly improved, as demonstrated by a reduction on functional class (NYHA) from 2.5 ± 0.8 to 1.4 ± 0.5 ($P < 0.001$). Another important issue addressed in this study was safety of the procedure: no mortality or major complications were observed.

Other studies have evaluated different routes for cell transplantation. Ghodsizad *et al*[26] reported the case of a 58-year-old man with end stage non-ischemic cardiomyopathy who received bone marrow cells by the transepimyocardial route through a minimally invasive surgery approach. Six months after the procedure, echocardiography and cardiac magnetic resonance showed improvement of left ventricular contractility. By a similar approach, mini anterior-left thoracotomy, Kalil *et al*[27] transplanted mononuclear cells into the myocardium of 8 patients with dilated idiopathic cardiomyopathy. Evaluation of cardiac performance was performed by magnetic resonance before, 4, 6 and 8 mo after transplantation. Despite an improvement in the first 4 mo, the ejection fraction returned to basal values after 8 mo, suggesting only a transient beneficial effect.

Cellular transplantation has also been tested in patients with Chagas disease. This may be an interesting option for those patients with more advanced stages, particularly when heart transplantation seems to be the only option. It is worth recalling that heart transplantation has some peculiar implications in Chagas disease. First, most patients affected by the disease live in poor areas in developing countries, where the cost of heart transplantation is high and may be unaffordable. Second, immunosuppression treatment may reactivate Chagas infection compromising short-term and long-term prognosis[28].

Vilas-Boas *et al*[29] studied 28 class Ⅲ and Ⅳ patients with Chagas disease, all receiving optimized clinical treatment. Mononuclear bone marrow cells were delivered by intracoronary injection. After 60 d of transplantation there was an increase in ejection fraction (20.1% ± 6.8% to 23% ± 9%, $P = 0.02$), NYHA class (3.1 ± 0.3 to 1.8 ± 0.5, $P < 0.0001$) and distance walked in 6 min, with no augmentation in the incidence of ventricular tachycardia. Their data demonstrated that injection of bone marrow mononuclear cells is feasible and may be effective in patients with heart failure resulting from Chagas disease.

Paracrine effects

In some situations after cell transplantation, there is a clinical improvement in patients, but without confirmation in laboratory tests. Lionetti *et al*[30] support the hypothesis that autocrine and paracrine mechanisms mediated by factors released by resident cardiac cells could play a key role in the repair of heart failure. Such signals may influence the function of cardiac stem cells through various mechanisms, among which the most studied are the survival of cardiomyocytes and angiogenesis. It is knwon that chemical, mechanical or genetic activation of cardiac cells can release peptides to protect tissues against ischemic injury.

CONCLUSION

Despite recent efforts described in this review, the real benefit of cellular transplantation in heart failure, especially caused by non-ischemic cardiomyopathies, is still far from being determined. Considering the experience of the last few years, we believe that different cardiomyopathies will benefit from different cell types. As myocardial perfusion is preserved in most non-ischemic cardyomyopathies, we believe that, in this group, myoblast transplantation may be an interesting and physiological approach by providing new and effective muscle fibers. However, this is just a hypothesis waiting to be tested.

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