

The Concept of Cell Therapy in Advanced Heart Failure: New Reality, Hope or Hype

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ABSTRACT

Chronic heart failure (CHF) is considered as a life-threatening disorder and a leading cause of morbidity and mortality in worldwide. A complex contributing factors including the hypertrophy of ventricles, intracellular organelles dysfunction, structural membrane deteriorations due to oxidative stress, deleterious signaling cascades, that inhibit of endogenous cardioprotective mechanisms and contribute alterations of metabolism, microvascular pathology, apoptosis and necrosis, lead to cardiomyocytes loss, spreading fibrosis, and, in fact, manifestation and advancing CHF. The review summarizes the current challenges and future research directions for concept of regenerative approaches of CHF. While stem cell therapy is currently being considered as a perspective treatment approach for patients with severe and advance CHF, the robust steps for subjects' enrollment are not still evaluated. There are some wide spectrum stem cells (embryonic stem cell, induced pluripotent stem cells, adult stem cells) that are the most promising potential treatments for CHF. Embryonic stem cell types have limited in their development and have not practical evidences of favorable clinical effects in CHF patients. Pluripotent human embryonic stem cells have emerged as an attractive candidate stem cell source for obtaining cardiomyocytes. Juvenile cells possibly represent a more potent alternative, but the impact of patient-related variables on such cell products is unknown. Although isolated stem cell therapy with different types cells has been demonstrated its clinical efficacy and safety, but additional using novel methods of tissue engineering or stimulation of endogenous cardiac repair by pharmacological agents are conceivable for improving prognosis in CHF patients.

INTRODUCTION

Chronic heart failure (CHF) is considered a life-threatening disorder and a leading cause of morbidity and mortality worldwide^[1]. It has been known that CHF is the end-stage of events occurring in multiple cardiovascular diseases, including hypertension, myocardial infarction, myocarditis, cardiomyopathies, genetic mutations, diabetes, and metabolic dysregulation^[2]. A diverse range of the structural, cellular, and molecular disorders due to wide spectrum cardiovascular reasons, that shares common maladaptive changes in the heart, lead to adverse cardiac remodeling and associates with fatal progression of CHF^[3-5]. Indeed, a complex contributing factors including the hypertrophy of ventricles, intracellular organelles dysfunction, structural membrane deteriorations due to oxidative stress, deleterious signaling cascades, that inhibit of endogenous cardio-protective mechanisms and contribute alterations of metabolism, microvascular pathology, apoptosis and necrosis, lead to cardiomyocytes loss, spreading fibrosis, and, in fact, manifestation and advancing CHF^[6-10]. In this setting, cell-based therapy for cardiac repair as a component of contemporary regenerative medicine aimed at improving survival looks promising^[11]. New technologies such as bioengineered, stem-cells transplantation and cells scaffold implantation in situ, have been introduced to different clinical settings, especially for ischemic-induced CHF^[12-14]. Although the delivery of bone marrow-derived stem cells and circulating progenitor cells via the coronary artery, intravenous, the left ventricle (transendocardial) as well as directly into the heart muscle during cardiac bypass surgery (intramyocardial) is being investigated intensively for the treatment of acute myocardial infarction and chronic coronary artery disease^[15], the role of stem-cells approaches in CHF care is still unclear. The review summarizes the current

challenges and future research directions for concept of regenerative approaches of CHF.

CIRCULATING PROGENITOR CELLS IN PATIENTS WITH CHRONIC HEART FAILURE

Clinical studies suggest that the number of circulating progenitor cells presented in CHF patients is related to clinical outcomes or disease severity^[16-18]. It has been found that ischemic cardiomyopathy is associated with selective impairment of progenitor cell function in the bone marrow and in the peripheral blood, which may contribute to an unfavorable left ventricular remodeling process^[19,20]. An exhaustion of hematopoietic stem cells in the bone marrow led to both reduced levels and functional disability of circulating endothelial progenitor cells are suitable for CHF. Therefore, apart from ischemia and pathologic extracellular matrix architecture, CHF may affect stem cell function through circulating disease-related humoral factors. Klose K *et al*^[21] (2013) identified temporarily inhibition of clonality and proliferation of "healthy" juvenile mesenchymal stem cells isolated from CHF patients *in vitro*. According to the authors, possible mechanisms of this effect include production of neurohormones, reactive oxygen species, pro-inflammatory cytokines (interleukins, tumor necrosis factor-alpha), and also angiostatin. These data explain early known phenomenon that associates with capacity of CHF serum to inhibit the initial proliferation of mesenchymal stem cells. Results of our investigations support a hypothesis of the impact of multiple cardiovascular risk factors on disorders of cellular protective mechanisms affected mobilizing endothelial progenitor cells even at early stages of heart diseases^[22]. Thus, deficiency of bone marrow-derived stem cells in circulation may contribute a deterioration of the regeneration of non-haematopoietic organs in CHF and are powerful indicators of cardiovascular risk and CHF-related outcomes. Based on this data, dotation of stem cells aimed improving clinical outcomes in CHF patients was considered as perspective^[23].

BASIC MECHANISMS OF REALIZING STEM CELLS EFFECT ON LEFT VENTRICULAR FUNCTION AND MYOCARDIAL PERFUSION

Overall, known mechanisms of stem cells therapy include mainly three points: paracrine regulation of cell function, differentiation stem cells into myocardial cell, and improving neovessels. Indeed, early *in vivo* studies dedicated cell effects in CHF animal model were based on results of *in vitro* preclinical investigations and have been supported hypothesis about transplanted myoblasts can secrete multiple cytokines, such as vascular endothelial growth factor and hepatocyte growth factor that maintained electrical and functional capacity of recipient myocardium^[24,25]. In fact, the primary mechanism of action for cell therapy is considered as paracrine effects that include the release of growth factors, cytokines, and chemokines, that inhibit apoptosis and fibrosis, modulate angiogenesis, enhance contractility, and activate endogenous regenerative mechanisms thereby circulation improvement or site-specific stem cells activation, mobilizing and migration^[26]. All mentioned paracrine mechanisms are discussed to play a pivotal role in improving diastolic and systolic function of myocardium^[27]. On the other hand, there is a possibility to speculate around increased cytokines level in recipient myocardium that factually enhances angiogenesis and stem cells recruitment, but can lead to reactivation the tissue damage^[28]. The capability to direct differentiation stem cells into functional

myocardial cell as a concept of regenerative medicine is widely discussed. Despite exciting progress, achieving the optimal benefits has been hampered by the immature nature of these cardiomyocytes. Promising approaches that have begun to be examined in human pluripotent stem cells differentiated into cardiomyocytes include long-term culturing, 3-dimensional tissue engineering, mechanical loading, electric stimulation, modulation of substrate stiffness, and treatment with neurohormonal factors. However, the role of tissue engineering and other methods mentioned above in improving stem cells differentiation is not still understood.

CELL-BASED TECHNOLOGY IN ANIMAL MODELS OF CHF

Currently it is reported about high potential regenerative capability of wide spectrum of cells (skeletal myoblasts, hematopoietic stem cell, mesenchymal stem cells, fibroblast sheets co-cultured with progenitor cells, etc.) transplanted into myocardium to be regenerate cardiomyocytes and restore its function by attenuating cardiac remodeling that is expected to lead to prolonged survival rates^[29-31]. It has been expected that newly formed vessels, undifferentiated cells and few new cardiomyocytes were appeared in recipient myocardium after transplantation stem cells or engrafted myoblasts sheet. Indeed, analysis of histologic findings obtained after myoblast transplantation in early investigations has been revealed greater cellularity, reduced fibrosis and abundant widespread neocapillaries in association with higher numbers of hematopoietic stem cells (c-kit, stem cell antigen 1, and CD34) in the myoblast sheet infarct heart region when compared with intact regions^[29]. Overall, skeletal myoblast implantation has led to improved cardiac function, but studies show formation of skeletal muscle in the heart and a lack of electrical integration with surrounding myocardium^[32]. Therefore, it also needs to consider the possibility of arrhythmias after skeletal myoblast implantation that probably may be due to the imperfection of cell delivery devices.

The transplantations of other types of cell sheets have been also used effectively to improve cardiac performance and stopped remodeling^[33]. Some methods were based on creating a thick-layered sheet *in vivo* with further transfer into myocardium aimed potential cardiac tissue regeneration. Miyahara Y *et al*^[34] reported that cultured adipose tissue-derived mesenchymal stem cells after transplantation into post-infarcted scarred myocardium increased anterior wall thickness and new vessel formation, accompanied by a low incidence of differentiation of the implanted cells to cardiomyocytes. Authors concluded that mesenchymal stem cell sheet acted through paracrine pathways to trigger angiogenesis. Based on previously data Ale A *et al*^[35] have been predisposed that cell-based therapy approaches using bone marrow derived c-kit(+) pluripotent cells may attenuate apoptosis following ischemic injury. They studied apoptosis in wild-type Kit(+/+) , c-kit mutant Kit(W)/Kit(W-v) and Kit(W)/Kit(W-v) mice after cell therapy with bone-marrow derived c-kit(+) cells after ischemia-reperfusion injury. Analysis of obtained result have revealed increased cardiomyocyte apoptosis in Kit(W)/Kit(W-v) mice and shows that c-kit(+) cardioprotective cells are able to attenuate post-MI apoptosis and rescue mice from progressive CHF. In small study Rigol M *et al*^[36] (2014) have been analyzed the immune response and the histological and functional effects of allogeneic allogeneic adipose tissue-derived mesenchymal stem cells (ATMSCs) in a porcine model of re-perfused acute myocardial infarction and determine the effect of administration timing. Authors found that delivery of ATMSCs after reperfusion compared with that performed

at 7 days was more effective in increasing: vascular density ($P<0.01$), T lymphocytes ($P<0.05$) and expression of vascular endothelial growth factor ($P<0.01$). Allogeneic ATMSC-based therapy did not change left ventricular ejection fraction but generated alloantibodies. Investigators concluded that administration of ATMSCs immediately after reperfusion is more effective in increasing VEGF expression and neovascularization.

Kobayashi H *et al*^[37] used fibroblast sheets co-cultured with endothelial progenitor cells for transplantation in myocardium in experimental model and confirmed that these constructs can improve damaged heart function via continuous cytokine secretion. Hobo K *et al*^[38] successfully transferred co-cultured fibroblasts and human smooth muscle cells to accelerate the secretion of pro-angiogenic factors aimed neovascularization. Other perspectives were related with transplantation of kit-positive cells and stem cells antigen-1-positive cells, which are able to differentiate into cardiomyocytes *in vivo* and improve of cardiac function^[39]. It has been found that an administration of such types of cells by adding to endothelial progenitor cells will be intriguing therapeutic strategy for ischemic cardiomyopathy, but improving CHF treatment remained a problem^[40]. New modalities for therapeutic angiogenesis and tissue regeneration are required, probably, creation of novel magnetic nanoparticle-based tissue engineering technology^[41]. There is date highlighted that extracellular vesicles released by mesenchymal stem cells have higher angiogenesis-promoting activity when compared with traditional recruited stem-cells^[42]. Functional efficacy of bone marrow stems cells that are composed by mononuclear stem cells, which contain hematopoietic stem cells with precursors of endothelial cells and mesenchymal stem cells, became controversial^[43,44]. Hens, while most of mentioned above regenerative strategies have shown a great potential in experimental studies, the translation into a clinical setting met some limitations and obstacles.

ADVANTAGES OF STEM-CELL IMPLEMENTATION IN CHF

While stem cell therapy is currently being considered as a perspective treatment approach for patients with severe and advance CHF, the robust steps for subjects' enrollment are not still evaluated. There are some wide spectrum stem cells (embryonic stem cell, induced pluripotent stem cells, adult stem cells) that are the most promising potential treatments for CHF^[28,45]. Embryonic stem cell types have limited in their development and have not practical evidences of favorable clinical effects in CHF patients in long-term period^[28,46,47]. However, pluripotent human embryonic stem cells have emerged as an attractive candidate stem cell source for obtaining cardiomyocytes^[48]. Clinical cardiac cell therapy using autologous somatic stem cells is restricted by age and disease-associated impairment of stem cell function^[48,49]. Juvenile cells possibly represent a more potent alternative, but the impact of patient-related variables on such cell products is unknown^[50,51]. Currently understanding has been shown that stem cell therapy is as minimum clinically safe and well tolerated, probably moderate effective in humans, and, unfortunately, bone marrow-derived stem cells do not differentiate into cardiomyocytes or new blood vessels after transplantation in myocardium^[28,50,51]. However, initial clinical trials have focused on the use of bone marrow cells to promote myocardial regeneration in ischemic heart disease and have very mixed results, with no clear signs of clinically meaningful functional improvement^[52]. Different cell-types, including bone marrow-derived mononuclear cells, bone marrow-derived mesenchymal stem cells,

mobilized CD34+ cells, and more recently cardiac-derived c-kit+ stem cells and cardiosphere-derived cells, have been evaluated for further transplantation in myocardium in ischemic CHF patients^[53]. In contrast to experimental models of heart disease, cell-based therapy in humans has brought about only moderate improvements in heart function and there is very little evidence of de novo formation of cardiomyocytes^[51]. Probably, this mismatch between animal experiments and human clinical trials may be explained by age and disease-related impairment of stem cell function in CHF patients, as well as types of cells, which were enrolled for further transplantation^[47,52]. Recent clinical studies have been revealed advantages of cardiac committed cells (resident cardiac progenitor cells or primed cardiogenic mesenchymal stem cells)^[54]. It has been expected that microRNA-based promotion of cardiomyocytes proliferation can improve an efficacy of cardiac repair after stem cell transplantation^[55]. Overall, transplantation of cardiomyogenic cells generated by induced pluripotent stem cells and genetic reprogramming of dividing non myocytes into cardiomyocytes might be constitute attractive new regenerative strategy in CHF care. It is needed to take into consideration that cellular treatment for CHF may be not suitable for emergency situations. Recent therapeutic approaches of regenerative therapy of CHF involve bone marrow-derived mononuclear cells and mesenchymal stem cells, adipose tissue-derived stem cells, cardiac-derived stem cells and cell combinations. Sadat K *et al*^[56] performed a meta-analysis to examine the association between administration of bone marrow mononuclear stem cells (BMMSCs) and LV functional recovery myocardial infarction. Meta-analysis included data from 32 trials comprising information on 1,300 patients in the treatment arm and 1,006 patients in the control arm. BMMSCs therapy was associated with a significant increase in LV ejection fraction by $4.6\% \pm 0.7\%$ ($P<0.001$) (control-adjusted increase of $2.8\% \pm 0.9\%$, $P=0.001$), and a significant decrease in perfusion defect size by $9.5\% \pm 1.4\%$ ($P<0.001$) (control-adjusted decrease of $3.8\% \pm 1.2\%$, $P=0.002$). The effect of BMMSCs therapy was similar whether the cells were administered via intra-coronary or intra-myocardial routes and was not influenced by baseline ejection fraction or perfusion defect size.

LIMITATION OF CELL THERAPY

Serious adverse effects were found in majority patient populations after myoblast cell therapy. However, results of MAGIC trial have been shown trend without significant difference in ventricular arrhythmias or major cardiac adverse events between myoblast-treated patients and placebo group at 6-month follow-up period^[57]. Overall, possible arrhythmogenic effect of myoblast transplantation is wide considered problem affected clinical perspective of the patients with CHF^[58,59]. Probably, the main cause of appearing of arrhythmogenic effect was percutaneous procedure that is required for myoblast transplantations performing. Speculation around it affected also design of catheter system used^[60,61]. However, the risk of sudden deaths due to arrhythmia consists for all patients with CHF who were underwent skeletal myoblast transplantation procedure^[62-64]. Potential fatal complication in patients with left ventricular dysfunction treated bone marrow mononuclear cell therapy, included mesenchymal stem cell and progenitor endothelial stem cell populations are not described^[65,66]. However, more clinical studies are needed to be overcome the speculation surrounding this issue.

THE FUTURE PERSPECTIVES

The new direction for clinical trials includes the use of stem cells

capable of cardiac lineage, such as endogenous cardiac stem cells and bone marrow derived stem cells, previously prepared with new engineering technology^[67]. Because several cytokines mobilize progenitor cells from the bone marrow or are involved in the homing of mobilized cells to ischemic tissue, parallel using of growth factors or cytokines, such as fibroblast growth factor and vascular endothelial growth factor, as expected, may increase clinical efficacy of procedure^[68].

In conclusion, stem cell therapy for ischemic heart failure is very promising approach that have very powerful regenerative potential. Although isolated stem cell therapy with different types cells has been demonstrated its clinical efficacy and safety, but additional using novel methods of tissue engineering or stimulation of endogenous cardiac repair by pharmacological agents are conceivable for improving prognosis in CHF patients.

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