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**Stem cells and its heart work**

Bilgimol JC *et al.* Stem cells and its heart work

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**Abstract**

Stem cells are of global excitement for various complications including Heart diseases. It is worth to understand the mechanism or role of stem cells in the treatment of heart failure. Bone marrow derived stem cells are commonly practiced with an aim to improve the function of the heart. Majority of studies has been conducted with acute myocardial infarction and a few has been investigated with the use of stem cells for treating chronic or dilated cardiomyopathy. Heterogeneity in the treated group using stem cells has greatly propounded. Ever increasing demand for any alternative made is of at most priority for cardiomyopathy. Stem cells are of top priority with the current impact that has generated among physicians. However it requires meticulous selection of proper source since redundancy is clearly evident with the present survey. This review focuses on the methods adopted using stem cells for Heart diseases and outcomes that are generated so far with an idea to determine the best therapeutic possibility in order to fulfill the present demand.

**Key words:** Bone marrow stem cells; Mesenchymal stem cells; Induced pluripotent stem; Heart diseases;Progenitor cells; Stem cells

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**Core tip:** Heart diseases are most common all over the world and any form of treatment would be well appreciated to enable successful well-being in the patients. Though there are enormous efforts attempted to handle heart diseases, there has been no propounded evidence so far to utilize a particular source of cell globally. In this regard, if the responses all over the world are collectively segregated to a global database, there may be options to identify the best suitable cell source that provides effective cure.

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**INTRODUCTION**

Diseases related to cardiac have become major cause of death worldwide[1-4]. Common causes of heart failure are ischemia, hypertension, coronary artery disease and idiopathic dilated cardiomyopathy. Up to 40% of patients are predominantly affected by diastolic dysfunction though the left ventricular systolic function is mostly unaffected[5]. There are established medical and surgical procedures available for patients but these standard therapeutic modalities have not been much responsive[1,6,7]. Cardiac risks are also associated with other complications[8-10] which thus gives steady increase in the number of patients looking for an effective treatment option that can sustain their normal wellbeing. There is an urge for alternative therapies that can fulfill the present overwhelming demand[6,11]. Cardiac diseases trigger damage to cardiomyocytes that affects the heart muscles and there is a possibility of scar formation that will overload the blood flow and eventually stretches the cardiac cells. This ultimately leads to heart failure and commonly, deaths[12].

The current situation is therefore mostly favorable for alternative treatment possibilities that can improve the disease considerably with better progress at least with respect to the rate of survival or improvement in quality of life[13-15]. Recent evidences on cell based therapies have suggested improvement in cardiac function and regeneration of the damaged tissue[16]. It is stated that cell therapy has got potentials to do the extremities which standard drugs cannot do by replacing the damaged tissues with healthy tissue. Drugs have been accounted to slower the progression of heart failure but none have shown their potential in reversing the process. However, the physiological perspectives have not shown any clear picture with cell therapies as it is difficult to estimate the cell survival and monitoring *in vivo*[17,18] along with their low engraftment rate[18]. Valid doubts and concerns are raised for the existing use of stem cells for heart diseases and it is elaborated that though regenerative medicine has lots of hopes, results haven’t substantiated their importance in the in-house attempted studies[19]. There are some important factors that need to be considered such as appropriate selection of the cell type, number of cells required and appropriate route of administration that can help regeneration. Route of Injection generally are being performed *via* catheter-guided endocardium, intracoronary, transvenous, and epicardium[20]. Subsequently, the selected cells should have a control over their migration, proliferation and differentiation *ex vivo* and also *in vivo*[21]. Even though the mechanism of action pertaining to cell therapies are not very clear, studies in comparison with routine therapies have shown promising results by significantly improving vessel density, inhibiting apoptosis of myocytes and decreasing in the fibrosis and increasing survival rate even in non-ischemic heart failures[22,23]. There are other reports available with similar strategy to improve the survival of transplanted cardiac progenitor cells[24-27].

The progress with cell therapy is reported in Mayo Clinic proceedings as breakthroughs that have reached certain milestones and expectations that are high to prospect towards imminent benefits. The 6 major breakthroughs are summarized as: (1) Safety establishment in intracoronary delivery; (2) possibility with therapeutic regeneration; (3) allogeneic cell therapy; (4) increasing mechanistic insights; (5) sparkling clinical efficacy; and (6) progress to phase 2 and 3 studies[28]. Cell Therapy has shown enormous progress since its application in 1998 and this lightning speed is progressing towards the development of eliminating the underlying cause of Heart failures and handling the control over the damage[29]. Different cell types have been used to heart diseases[30-32]. There are potential benefits underlying with the application of cardiac progenitor cells and induced pluripotent stem cells (iPSCs) for a promising approach to bring true myocardial regeneration[30].

The advent of iPSCs is also under remarkable consideration to model heart disease[33]. Stem cells have been suggested to be promising new therapeutic usage for heart diseases because of their remarkable proliferative and differentiation capacity that can supply specific cell types along with the viable functioning of heart muscles[12]. Evidences have shown that resident cardiac stem cells have got potentials to turn into cardiomyocytes *in vivo*[31]. There are other well-known and commonly available sources of progenitor cells from bone marrow, adipose tissue, and skeletal muscle or cells circulating in blood that are capable of improving myocardial function[11,34].

Though there are waves of research undertaken with stem cells or any cell therapy applications, it requires exploitation with in vitro studies which is of high priority to advance with the strategies to tailor clinical applications and the task is highly challenging[35]. Appropriate selection of patients, informed consent and periodic patient monitoring are important factors to be reviewed by expert panel independent of investigators while opting for clinical trials[36,37]. While manufacturing stem cells, parameters like screening and testing for pathogens have to be carried out with utmost precision. Generation of consistent batches while manufacturing is highly recommended for therapeutic derivative of stem cells and this has to be carried out in aseptic conditions withstanding robust quality programs that qualify regulatory expectations which are suitable for clinical use in patients. It is also necessary to validate the procedures for transplant and confirm the regeneration of infarcted heart[38,39]. Overall, it is expected that the strategies adopted from routine therapies into stem cell-based therapies, have glorious potentials to increase the efficacy of treatment[40]. This review thus focusses on the studies attempted with various alternative therapeutic applications for heart diseases and to suggest the best suitable and effective source that has produced better success rate.

**CURRENT PROGRESS WITH ROUTINE THERAPIES**

Heart disease continues to be the main cause of death though there is a considerable decline in the death rate and advancement in medicine since 1999. Nonetheless, medical care hasn’t been successful in reversing the loss of functional cardiomyocytes[41]. The surgeries being attempted for diagnostic cardiac catheterizations, coronary artery bypass graft procedures, cardiac pacemaker procedures, percutaneous transluminal coronary angioplasty procedures and heart valve procedures are all very expensive since it requires hospitalizations, post-surgical care etc. They consume enormous time to handle the recovery process. Still, the evidences suggest that cardiovascular diseases aren’t prevented though the lethality has been reduced considerably[42]. Presently, the treatment options vastly carried out for cardiovascular function include organ transplantation, surgical reconstruction, and mechanical or usage of artificial devices or administration of metabolically derived products[43]. Benefits have been associated with inotropic therapy, ventricular assist devices and hospice care. Recommendations are given towards the use of Angotensin-converting enzyme (ACE) inhibitors as a first line of treatment in patients with reduced left-ventricular (LV) systolic function with ejection fraction ≤ 35%-40%[44]. For normal ventricular ejection fraction, beta blockers, isosorbide dinitrate plus hydralazine are being considered[45].

At this context, researchers have been encouraged to identify better strategies to image the detection and monitoring of cardiovascular diseases progression. Biotech industries have also been progressing in different scenario with other therapeutic possibilities which with mutual understanding with the pharmaceutical industries and medical specialists, may aim to bring options that provide immediate recovery along with cost effective strategies[3,46]. Interest relies with the targeted delivery of alternatives such as stem and progenitor cell populations that has also kindled the combinatorial use of genes to treat cardiovascular diseases. However, challenge depends on the host environment where it has poorly retained the survival of implanted cells and thus it requires the delivery of cells transfected or transduced *ex vivo* with genes that can enhance resistance to apoptosis in order to provide protection from the stressed microenvironment that can enable the improved function of the engrafted cells to appreciate better therapeutic outcome[47].

**ROLE OF ALTERNATIVE MODALITIES IN RESTORATION OF HEART DISEASES**

***Mesenchymal stem cells***

Even after maturation, cardiomyocytes have limited flexibility. The recovery of heart after structural damage is less possible. Mesenchymal stem cell therapy is predicted to be a promising area of research for regenerating damaged cardiac tissues. Mesenchymal stem cells (MSCs) lack both major histocompatibility II and T-cell co-stimulatory signal expressions thus are immune-privileged. When MSCs are delivered systematically they own a unique ability to enter into the specific sites of myocardial damage. There are mechanisms by which MSCs help in cardiac tissue regeneration. Data generated from several studies reveal that MSCs are therapeutically valuable and has a great role to play in cardiac diseases. In future, MSCs could be used for cell-based therapy for cardiac diseases.

MSCs are generally derived from any tissue sources. In the translational research MSCs used are mainly derived from bone marrow. Specifically, for cardiac repair or cardiac disorders the MSCs used are derived from bone marrow[48]. Several studies are carried out to understand the mechanism of action of MSCs in cardiac repair. One of the studies conducted by Yang *et al*[49] demonstrated that a combination of statin along with bone marrow derived MSCs intramyocardial injections improved the efficiency of cardiomyocyte differentiation by 4 fold in a swine model.

Numerous preclinical studies are carried out using large animal models to understand the efficacy of MSC therapy for cardiac diseases. In these studies, stem cells are delivered to the heart *via* peripheral intravenous infusion during the open heart surgery. It can also be administered through catheter-based intracoronary infusion. The studies carried out after delivery of MSCs showed that intramyocardial injection had the highest retention rate of cells[50]. Among all the preclinical studies carried out with MSCs for cardiac diseases, surgical injection was the commonly most used method to deliver MSCs[51-53].

Though there are varieties of sources of MSCs, there has been particular interest in adipose lineage of MSCs which was found to be easily available and successful in several preclinical studies. Several studies were carried out by the administration of adipose derived MSCs for myocardial infarction which were found to be successful[54].

***Hematopoietic stem cells***

Many clinical trials are carried out to improve the function of cardiac recovery. There were several favorable and unfavorable results during the course of time. In many of the studies, bone marrow mononuclear cells were injected. Nevertheless, detailed studies are to be carried out to understand the fate and effects of transplanted cells[55-58]. It is understood that bone marrow contains heterogeneous populations of cells generally hematopoietic stem cells (HSCs) and MSCs[59].

Apart from these, bone marrow also has different progenitors of myeloid and lymphoid lineages. Several studies indicate that both HSCs and MSCs are reported to acquire the phenotype of cardiomyocytes in syngeneic or xenogeneic recipients. Even though various studies were carried out, none of them quantitatively analyzed the regenerative capacity. Nevertheless, there are evidences shown by Norol *et al*[60] in nonhuman primate models that HSCs don’t differentiate into cardiomyocytes or into endothelial cells in the infarcted myocardium. Apparently, the growth factors produced locally doesn’t have any positive effect on the regeneration of myocardium[60]. It is well known that the Hematopoietic stem cells are unique sources of adult stem cells that are easily accessible. It is documented about its evidence of neoangiogenesis to treat ischemic vascular diseases. HSCs subsets are also positive for endothelial precursors that are AC133+ which are considered to be major requirements in patients with ischemic and refractory peripheral vascular or coronary artery diseases[61].

***Endothelial progenitor cells***

Endothelial progenitor cells (EPCs) consist of a heterogeneous group of cells which are originating from multiple precursors within the bone marrow and are present in different stages of endothelial differentiation. The existence of endothelial dysfunction forecast the consequences in patients who suffer with cardiovascular risk factors and persons with coronary artery disease. EPCs possess the ability to home in on sites of vascular injury. Thus EPCs could be easily adopted for therapeutic uses related to angiogenesis. Several studies conducted in CAD patients revealed that they had reduced number of EPCs. They also had reduced number of circulating EPCs[62-65].

Bone marrow derived EPCs will be mobilized to stimulate angiogenesis and will attenuate tissue ischemia for CAD and PAD. Further to this, the clinical trials carried out with different animal models favor the application of EPCs as a potential therapeutic agent in cardio vascular diseases[66,67].

Usage of EPC capture stent is also in practice. EPC capture stent is a device which uses the ability of bone marrow derived EPCs to repair damaged arterial segments. This instrument is manufactured in such a way that the surface of EPC antibody contains a covalently coupled polysaccharide intermediate coating with anti-human CD34 antibody and it is attached to a stainless steel stent. Once the stent is placed, the circulating EPCS will be attracted to CD34 antibodies and will direct to differentiate into mature endothelial cells to form functional endothelium layer[68].

There are several studies ongoing to understand the effects of pharmacotherapies of EPCs in cardiac patients. EPC behavior and mechanisms are also elucidated in several studies conducted in patients with CVD, CAD, HF and PAD. There are several promising studies showing that EPCs could be used as a novel therapy for CVDs[69]. However, there are several limitations using EPCs due to its paucity of circulating cells. The efficacy of the treatment using EPCs can be obtained by increasing the cell number by concentrating and transplanting or by functional improvement using *ex vivo* augmentation.

***Induced pluripotent stem cells***

Usage of induced pluripotent stem cells (iPSCs) emerged as a novel therapy for the treatment of cardiac diseases. It has also attracted much attention and is considered to be the promising cell source for patient specific cell therapy[70]. Major advantage of iPSCs are that the clinically relevant number of cells could be generated easily when compared to adult stem cells also it is at a less risk of immune rejection when compared to embryonic stem cells[71].

iPSCs are generally engendered from adult somatic tissues with precise reprogramming. Studies prove that iPSCs have a lot of similarities between human embryonic stem cells especially in terms of morphology, proliferation, feeder dependence, surface markers, gene expression, epigenetic status, promoter activities, telomerase activities *etc*.[72]. The study was conducted on mouse model of myocardial infarction (MI). Human iPSCs were induced into mouse model with MI. The results disclose that mouse had regenerated myocardium, smooth muscles and endothelial tissue, restoring post ischaemic contractility performance and electric stability[73]. Even though, several studies and clinical trials are carried out to understand the efficacy of iPSCs in cardiac repair, when it comes to gene therapy the integration of viral vectors in the genome remains unanswered. These viral vectors in the genome might result in promoting malignancy, apart from that, these virus-encoded genes can act as oncogenes. Thus, the clinical application of iPSC derived cardiomyocytes appears to be a distant possibility at present. But the advent of different study models will resolve the issues in the future.

***Bone marrow mononuclear cells***

Though lots of cell types have been attempted, there has been promising outcomes with crude extracts of bone marrow derived cells. Utilization of such resources not only minimizes time may also be useful in reducing the cost of expenses of application[74]. Recent studies with heart diseases using the Bone marrow derived mononuclear cells (BMMNCs) have been able to improve left ventricular function, increased the myocardial perfusion, but hasn’t produced any significant change in the scar tissue[75,76]. A double blind study attempted with a total of 16 patients after previous placebo injection has portraited the improvement in angina symptoms and myocardial perfusion with the infusion of bone marrow mononuclear cells in chronic myocardial ischemia patients[77]. However, Heeschen *et al*[78], have shown that the application of BMMNCs to Ischemic Cardiomyopathy patients when injected, has profoundly reduced the neovascularization and thus limited its therapeutic potential for cell therapy. But the reduced neovascularization is mostly reported to be impaired with aging that plays a major effect over the aged BMMNCs and the population doesn’t affect the revitalization of neovascularization with the host with the transplantation of young BMMNCs[79]. Although the results have been more commented, scientists overall aren’t in favor of using BMMNCs because of the small number of undifferentiated cells that are unlikely to be effective[74].

***Genetically modified cells***

Genetic modifications of stem cells will result in its enhanced efficacy. Genetically modified stem cells can be utilized for different diseases. Number of diseases can be treated now with it. Various strategies like pre-treatment with growth differentiation factors or cytokines, pre-conditioning like hypoxia and genetic modifications to over express anti-death signals.are developed. It was Mangi *et al*[80] who first genetically modified MSCs to over express Akt which is resistant to apoptosis in vitro and *in vivo*. They proved that there was drastic improvement in cardiac function in an MI rodent model[80]. Further work on this showed that Akt-transduction stimulate MSCs to produce paracrine factors which is advantageous to infarcted heart post-engraftment[81,82]. In another experiment transfected MSCs with bFGF showed an increased survival and cytoprotection in hypoxic condition[83] (Figure 1).

**CHALLENGES TOWARDS FUTURE DEVELOPMENT**

It is clearly understood that there are underlying challenges for the identification of well-deserved type of regenerative therapy. Majority of cell types are under clinical trials but the results have been heterogeneous. Cause has been predicted to be poor survival, proliferation, engraftment and differentiation of engrafted cells. Ultimately, the objective is to increase the functional ability of stem cell before and after transplantation[4,84]. The concern thus lies with the knowledge on structural and functional characteristics of stem cell-derived cardiomyocytes, its capability to integrate with host tissue[85,86]. Concerns need to be imparted for appropriate selection of patients with clear understanding about the variability of disease condition. Prospective outcomes have to be confirmed with the anatomical and histological examinations with the studied number of patients in order to analyze significant observations[87]. With the prevailing methods for achieving an alternative approach to deal with heart diseases, the approach that would in future be available for the treatment is believed to possess, more effective delivery methods; growth and storage methods[17].

Researchers are working on to effective management of the challenges for the utilization of stem cell therapy wherein, newer strategies are being adopted for the combination of cells with bioengineering techniques that may improve the efficacy considerably[88]. However, approaches dealt with the utilization of Epicardium-derived cells (EPDCs) and cardiomyocyte progenitor cells have synergistically shown better impact in cardiac function which is believed to be because of complementary paracrine actions[89]. Whatever the sources have been utilized or approached for such as the Embryonic stem cells (ESCs), induced pluripotent stem cells, adult stem cell lineages, bone marrow derived stem cells, or Mesenchymal stem cells, it is widely acceptable that there is enormous hope underlying the usage of stem cell therapy to be clinically viable alternative for heart diseases[90] and the direction that the researchers are progressing is believed to be perfect which requires clear understanding and revival of the attempted trails to progress with newer ideas and accomplish the ultimate goal.

Challenges are still prevailing for the application of cell therapy to the patient. Considering the complications in delivery of the stem cells to the patient, three factors are to be taken into consideration. First and foremost the type and nature of injury, secondly, timing of the therapy and thirdly, the ability of the cells to engraft the host myocardium[82]. There is a huge dilemma regarding the best time for stem cell delivery to patients. Several studies carried out in this field prove that early time points will be ideal for stem cell transplantation[91].Choosing of best stem cell type also play a crucial role in transplantation and engraftment ability to host myocardium. Recent studies conducted reports that transplanted cells are vulnerable to hostile ischemic environment. Thus it will tend to disappear in a few days[92]. Several investigations are going on to improve the microenvironment, engraftment followed by survival.

**CONCLUSION**

Even though the mechanism of action for all these stem cell based therapies are not well established, it still remains a promising field of research. However, major obstacle in this arena is the poor viability of implanted stem cells for cardiac repair. The strategies reviewed here are for the augmentation and development of appropriate approaches for the treatment of cardiac disorders. Attempts performed using specific kind of cell type by any organization is claimed to provide efficient results in comparison to the other. This has created disputes in pursuing cell types that can generate positive outcomes and thus has deliberately given poor understanding amongst the physicians. Involvement of cell therapy possibilities has therefore anonymously diminished though it is under immediate purview. Future challenges pertaining to the application hence depend on the clear validation of the cell therapy with respect to source, mode of application, dosage and expected outcome. Reciprocation of these results is vital in order to pursue the technology.

Ethical constraints are also major hurdles to circumvent the use of alternative strategies which needs to be clearly framed considering the benefits that medical arena would acquire. Adult stem cells in this regard, has proven safety and generated decent outcomes. We suggest that, instead of exploiting research knowledge to fewer more decades, concentration towards the ultimate requirement is very important. The studies generated so far with various alternative treatment modalities for heart diseases worldwide can be collectively segregated in a common database and significance with the available data can be generated to find the best and viable source of approach that proves effective for heart diseases. In case of any discrepancy with the results, the reciprocation of the data can be attempted in order to obtain a solution.

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**Figure 1 Illustration to show the requirement of a database for identifying alternative cure of cell therapy for heart diseases.**