

## **Application of Mesenchymal Stem Cells Therapy in Heart Failure**

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### **Abstract**

Heart failure is a common cardiac disease with high mortality and morbidity rates worldwide, especially for the elderly. At present, medicine and surgery are still the main treatments for heart diseases despite the limited number of suitable organ donors and risks like infection and organ rejection. New therapy with high level of safety and efficacy is therefore highly desirable.

Latest trends in stem cell therapy offer a new hope for treating heart damage. Laboratory and clinical researches on stem cells have revealed the applicability of mesenchymal stem cells (MSC) therapy to treating heart failure by regenerating and repairing injured heart tissue in animal models. MSCs can be classified into two main groups, namely bone marrow-derived Mesenchymal Stem Cell (BM-MSC) and Tissue-derived Mesenchymal stem cell (T-MSC). Every single stem cell has its own therapeutic benefit. The combined effect of different stem cells, however, has demonstrated higher effectiveness in cardiac therapy. This implies an optimal cardiac therapy may involve various stem cell administrations depending on the nature of disease. The results of clinical trials on MSC therapy to regenerate injured hearts are encouraging so far. But the expected survival of regenerated cells is still uncertain. Therefore, the study of developing strategy for risk prevention should be in parallel with MSC trials for standardization of a safe and effective MSC treatment.

Besides, people show much concern on ethical relativism of stem cell therapy as it may violate the principle of the sanctity of human life. Although MSCs do not involve embryo, the researches on MSCs should be conducted in full compliance with legal and ethical requirements set out by the Government, medical councils and research institutions.

**Key words:** Mesenchymal Stem Cells (MSC), Bone Marrow-derived Mesenchymal Stem Cell (BM-MSC) and Tissue-derived Mesenchymal Stem Cell (T-MSC), Diastolic Heart Failure (DHF), Systolic Heart Failure (SHF)

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## Introduction

Heart disease has the highest death rates in many countries.<sup>1-2</sup> In the past, the mortality rate for patients with class IV heart failure (severe) was as high as 50% in one year.<sup>3</sup> According to the latest report on the statistics of heart diseases and strokes from the American Heart Association, there were 5.1 million Americans aged 20 or over who had heart failure from 2007 to 2010. The risk of heart failure, no matter age, race or gender, is keeping an uprising trend. In the report, it is projected that the prevalence of heart failure will increase to 25% in 2030.<sup>4</sup>

The development of new heart-failure therapies is therefore crucial to relieve heart failure and to reduce the mortality of the large population of heart-failure patients.<sup>3</sup> Cardiac stem cell therapy is one of the new therapies to treat heart failure.<sup>5</sup> Although successful human clinical trials and administration methods are still limited, a majority of the clinical trials in animals such as rats and pigs, support stem cell mechanism of action in heart repair.<sup>6-7</sup> This paper will discuss, with emphasis on mesenchymal stem cells, the mechanism of stem cells, routes of administration methods and clinical trials in order to compare their advantages and disadvantages for heart failure treatment.

## Heart Failure

The heart acts as a pump to circulate blood throughout the body to carry oxygen and

nutrients to the organs and muscles while bringing back carbon dioxide and waste materials to the lungs for filtering. Heart failure is a condition when the heart is inadequate to maintain blood flow to cater for the body's demand resulting in dumping of blood in cardiac chambers. Heart failure can be developed into either acute or chronic one.<sup>2</sup> It is caused by the weakening of the heart muscle due to myocardial infarction (MI), hypertension, coronary artery disease, previous heart attack, high blood pressure, diabetes mellitus and sleep apnea. MI, a well-known heart attack, can interrupt the proper blood supply to heart muscles leading to heart cell damage or death. It is a common cause of heart failure.<sup>1-2,4</sup>

Both diastolic heart failure (DHF) and systolic heart failure (SHF) are common clinical syndromes.<sup>2</sup> Left ventricular dysfunction, in particular, is the most popular diagnosed heart failure in which the muscle of left-sided heart loses the ability to contract or relax leading to insufficient blood flow to the body. Right ventricular dysfunction usually occurs after left heart failure. The decrease in pumping effect of the right-sided heart would lead to venous pooling of blood in legs.<sup>2</sup> In fact, heart failure has already aroused public concern owing to its increasing incidence, prevalence, morbidity, and mortality.<sup>3</sup>

## Management of Heart Failure

To maintain a good health without taking medication is the natural way to eliminate

all health problems. Patients with heart diseases may need to modify their lifestyle in order to avoid the situations triggering heart attacks and to lower the likelihood of heart problem progression, thereby to minimize contribution risk for heart failure. A healthier lifestyle includes sufficient rest, regular exercise, healthy diet, giving up smoking and alcohol intake, restriction of salt and fluid intake and healthy living environment. These are non-medical treatment, which can help patients to improve the quality of life.<sup>2,4</sup>

When medical treatments are inevitable, pharmacological drugs are the first choice for the treatment of chronic heart failure (CHF). At the early stage of CHF, angiotensin converting enzyme inhibitors (ACEI), beta-blockers, diuretics, and aspirin are commonly used. Digoxin and vasodilators are usually for patients with moderate to severe heart failures.<sup>2</sup>

Surgery or heart transplant are always necessary when the patients' conditions are so severe that their hearts can no longer be controlled by drug treatments. Surgical therapies of implanting medical devices like cardiac resynchronization therapy (CRT), defibrillator therapy and left/right ventricular assist device (LVAD & RVAD) have proved symptomatic improvement and sudden death prevention, but may have side effects such as bleeding, thrombosis, infection and device malfunction. Besides, percutaneous coronary intervention (PCI) and bypass surgery are effective operations

for patients having acute myocardial infarction (AMI) caused by thrombus formation.<sup>2,5</sup> Cardiac transplant would be the last resort for patients with final stage heart failure or severe coronary artery disease. Unfortunately, the limitation of favorable organ donors is an irresolvable problem and patients may not be able to wait for a suitable donor heart. Also, there may be risks of infection, sepsis and organ rejection after heart transplantation.<sup>5</sup>

Although medical technologies advance, most therapies or treatments to major heart diseases, such as ischemic heart disease and congestive heart failure, are focused on postponing the progression of the disease. Meanwhile, organ transplantation is the only cure to chronic diseases. New therapy with high level of safety and efficacy is highly desirable.<sup>5</sup>

While medicine and surgery are still the main treatment for diseases, stem cell therapy has become a new trend in treating different kinds of diseases such as hematopoiesis, heart damage, brain damage and cancer.<sup>5</sup> Recently, stem cell therapy to regenerate injured heart is gaining public attention. Studies on stem cells indicated that the results of clinical trials or animal models have proved the applicability of stem cell therapy to treating heart failure and highlighted some recommendations to improve devices and methods for increasing the effectiveness to reduce death rate.

## **Application of Stem Cells Therapy in Heart Failure**

Stem cells are unspecialized cells capable of developing into various types of cells in the body through cell division. They can renew themselves to become tissue-specific or organ-specific cells such as myocardial tissue. Thus stem cells can be regarded as an internal repair system for regenerating damaged tissues, which offer the potential for treating diseases such as regeneration of injured heart.<sup>5,8</sup>

A lot of laboratory and clinic researches have been done in investigating cardiac stem cell therapy. In general, stem cells can be divided into two main groups, namely embryonic stem cells and adult (non-embryonic) stem cells. Adult stem cells can be further classified into human adult bone-marrow derived cells, skeletal myoblasts, mesenchymal stem cells, cardiac stem cells, endothelial progenitor cells and other cells such as fibroblasts.<sup>8</sup> Differentiation of both groups of stem cell into cardiomyocytes (CMC), vascular smooth muscle cells (VSMC), and endothelial cells (EC) would be important for treating cardiovascular disease.<sup>5</sup> The major difference between embryonic and adult stem cells is that embryonic stem cells can be developed more easily into all cell types of the body, while adult stem cells are limited to differentiate into certain cell types from their original cells. However, it is believed that tissues derived from the patient's own adult stem cells are less likely

to immune rejection.<sup>6</sup> In fact, studies revealed that reparative stem cells extracted from patients have shown innate efficacy.<sup>9</sup> Therefore the paper is focused on adult stem cells, particularly mesenchymal stem cell (MSC), owing to fact that MSC therapy has been tested to be successfully in treating damaged heart tissue in heart failure.<sup>10</sup>

## **Mesenchymal Stem Cells**

Mesenchymal stem cells (MSCs) are multipotent stem cells which can be classified into two main groups, bone marrow-derived Mesenchymal Stem Cell (BM-MSC) and Tissue-derived Mesenchymal stem cell (T-MSC). BM-MSC can be found in bone marrow while T-MSC can be found in non-marrow tissues, such as adipose tissues, fat, organ, muscles, umbilical cord blood and placenta.<sup>5,11</sup> MSC is a possible and probable therapeutic agent for regenerating and repairing injured hearts. There are investigations in animal models which have proven MSCs' ability to differentiate into cardiomyocytes and vasculature cells, as well as to improve the performance of ventricles, induce reverse remodeling and reduce scar size.<sup>12</sup> Unlike to what was believed, hearts have self-renewal capacity. MSC is a potential cell source to differentiate into cardiac lineage in both in vitro and in vivo environment.<sup>13</sup> Although there are MSC-based treatments available, the clinical application of MSC is still in the preliminary stage and is limited to use autologous stem cell.

According to investigation, stem cells cultured by different environmental cues may differentiate and proliferate into various types of cells. However, the precision of the mechanism for cardiac repair remains equivocal.<sup>8</sup> New hypothesis suggests that the implanted MSC will secrete soluble growth factors to promote cardiac repair, as well as to prevent and reverse remodeling of injured heart.<sup>14</sup>

### **Mechanisms of Repairing Action**

The underlying mechanism of repairing action by MSC for cardiac repair is still arguable.<sup>8</sup> It is believed that cardiac regeneration is achieved through various pathways. In the past, scientists inferred that the transplanted stem cells would differentiate directly into cardiac/ventricular cells. However, this inference has been superseded by a recent hypothesis which proposes that transplanted stem cells would secrete a wide array of soluble growth factors that promote blood vessel formation and stimulate the host cardiac stem cells in vivo to repair the damaged tissue.<sup>14</sup>

After injection of MSC in infarcted heart, growth factors, cytokines and other molecules are secreted to trigger the paracrine mechanism and response to injury. Paracrine activity may function as signal messenger in triggering cardiac therapy.<sup>15</sup> They coordinate and mediate the innate immune system to limit local inflammation and regulate restoring function of cardiac chamber to improve cardiac contraction,

promote angiogenesis for growth of new blood vascular on heart muscle, as well as regenerate damaged heart muscle.<sup>16</sup> Besides, paracrine activity may also alter the extracellular matrix, which can help reduce scar size and avoid scar extension in vivo.<sup>16</sup>

Paracrine activity after MSC transplantation may inhibit pro-inflammatory cytokine secretion but increase anti-inflammatory cytokine production. This is because pro-inflammatory cytokines would suppress cardiac contractile function and induce apoptosis of cardiomyocyte, resulting in boosting ventricular remodelling. Anti-inflammatory cytokine, on the contrary, would inhibit inflammatory response to limit myocardial apoptosis.<sup>17</sup>

Vascular endothelial growth factor (VEGF) can help to reconstruct the myocardial vascular network by increasing the permeability of capillary wall to promote endothelial cell proliferation and migration. Eventually, capillary growth around infarcted area is achievable (Kinnaird et al., 2004). Besides, MSC transplantation induces paracrine anti-fibrotic effects to improve cardiac fibrosis through regulation of cardiac fibroblasts proliferation and transcriptional downregulation of types I and III collagen syntheses.<sup>15</sup>

### **Routes of Administration**

There are several strategies currently used for MSC delivery into patients with heart failure in cardiac therapy. The stem cells can

be injected to the affected areas through coronary arteries/veins, or peripheral veins.<sup>18</sup> It can also be injected to myocardium directly using open-heart surgical administration to open chest and perform surgery on heart muscle, or catheter-based Intramyocardial administration<sup>19</sup> to slowly advance a catheter (a long, thin, flexible hollow tube) into arteries/veins of the heart through a small incision made to the affected area for stem cells injection.

Transepical injection, or direct surgical intramyocardial injection, is to inject stem cells into infarcted heart from outside. It can be done during coronary artery bypass surgery or via lateral minithoracotomy.<sup>8</sup> This is the most direct approach to deliver stem cells accurately and precisely to the infarcted site through direct observation to identify location. However, it is the most invasive and risky method as open-heart surgery would be required.<sup>20</sup>

Transendocardial injection is to inject stem cells into the inner wall of infarcted heart using a catheter.<sup>12</sup> It is one of the catheter-based Intramyocardial administrations commonly used for patients with chronic heart failure to ischemic heart disease. It has the advantage of being less invasive, but requires sophisticated imaging modalities to guide for a correct delivery of stem cells to the infarcted site.<sup>20</sup>

Intracoronary injection, another kind of catheter-based Intramyocardial

administration, is to inject stem cells directly into arteries of the heart using a balloon-like catheter that prevents backflow of cells and increases retention of cells to the affected region.<sup>21</sup> It is the most common route of administration for MI. The approach is considered cost effective, feasible and safe. The limitation of this method, however, is the difficult cell delivery to the right coronary territory and the possibility of blocking small vessels or blood flow reduction to heart.<sup>22</sup>

Intravenous injection is to inject stem cells by way of a vein. It is the simplest and least invasive delivery route of administration commonly used for patients with AMI. Despite the high degree of feasibility and safety, it has low delivery efficiency and is likely to trap in non-cardiac tissue.<sup>18</sup>

The above delivery routes have common problems including retention of stem cells in site and entrapment of stem cells in other organs. To overcome these problems, new routes of administration such as tissue engineered scaffolds and sheets loaded with stem cells are under development.<sup>20</sup>

### **Comparison of Bone Marrow-Derived MSC and Tissue-Derived MSC**

Numerous studies have been conducted for comparing the effect of BM-MSC and T-MSC transplantation on cardiac/ventricular regeneration. In a recent study on animal model with ischaemic heart failure, rats with left coronary artery

occlusion and reperfusion were divided into groups for intramyocardial injection of BM-MSC and T-MSC cells. The result showed that rats with BM-MSC transplantation have greater improvement in left ventricular function with reduced histological scar size.<sup>1</sup> The use of animal model as pre-clinical trial is usually the starting step to a reliable prediction of clinical trial on patients. In fact, studies have illustrated that the characteristics and functionality of human MSCs and animal MSCs, such as rats and pigs, are comparable.<sup>6-7</sup>

Clinical trials demonstrated that administration of MSC, no matter BM-MSC or T-MSC, in infarct are safe and effective with good functional cardiac recovery and reduction in cell death.<sup>8,10</sup> A recent article provided an overview on various stem cell therapies on heart diseases. It is opined that there is no optimal stem cell for treating heart disease exclusively. Nevertheless, clinical results reviewed that BM-MSC would be a more promising and useful clinical approach for heart failure.<sup>8</sup>

Although every single stem cell has its own therapeutic benefit, the combined effect of different stem cells can enhance cardiac therapy.<sup>23</sup> Experiment demonstrated that the biological interactions between human cardiac stem cells and BM-MSCs, for instance, have exhibited greater therapeutic response to reduce infarct size as compared to either stem cell alone.<sup>23</sup> This implies an adequate cardiac therapy may involve

various stem cell administrations depending on the nature of disease.

### **Advantages and Limitations**

About ten years ago, about 70 patients with AMI were enrolled into a study to receive intracoronary injection of BM-MSC or standard saline. Results have shown that implantation of cultured BM-MSC can improve the left ventricular function significantly due to the fact that BM-MSC is able to adhere and infiltrate into the small distal infarct zone along the vessel wall.<sup>11</sup> Many studies have also demonstrated cardiac/ventricular regeneration with improved cardiac/ventricular function after MSC transplantation due to its ability of adhesion on injured areas and possibility of allogeneic grafting.<sup>18</sup> It is also found that MSC is less likely to stimulate immune rejection when autologous MSCs are adopted for transplantation.<sup>6</sup>

Although clinic trials have proved the function of MSC therapy on muscular repair of cardiac tissues with reduced inflammation, there is a long list of uncertainty if applied to humans such as the possibility of long-term complications, the survival of regenerated cells, the immune response, the side effects, the safety and the efficacy of MSC therapy. Besides, the stability of MSC therapy may vary with different sources, culture conditions, dosages and delivery methods.<sup>1,8</sup> For example, prolonged MSC expansion in vitro may induce the risk of chromosomal instability and malignant

transformation.<sup>24</sup> Furthermore, the possibility of MSC differentiation into unwanted mesenchymal lineage would make the matter worse.<sup>25</sup> Therefore, the study of developing strategy for risk prevention should be in parallel with MSC trials for standardization of MSC treatment. This is why MSC therapy is still not widely applied clinically.

### **Ethics**

The ethical relativism of stem cell therapy is still in heated debate, especially embryonic stem cells which have aroused public concern as it may violate the principle of the sanctity of human life.<sup>26</sup> Although MSCs are adult stem cells which do not involve embryo, the researches on MSCs should strictly comply with the rules and regulations set out by the Government and should follow guidance from medical councils and research institutions to make sure stem cell researches are conducted legally and ethically.<sup>26</sup> There is no experiment carried out in this study. However, the experimental procedures or research results from the articles quoted were approved by the relevant institutional bodies such as Interactive CardioVascular and Thoracic Surgery and Animal Ethics Committee and the people involved in the studies like patients and donors who were volunteers.<sup>1,27</sup>

### **Conclusion with Future approach**

Results of clinical trials have shown that the

MSC therapy to regenerate injured heart in patients with heart failure is encouraging. But still, the expected survival of regenerated cells, as well as the safety and efficacy of MSC therapy, is uncertain. In fact, the optimal cell type, dosage and delivery method for treating heart disease are still unknown. But it is believed that different forms of heart disease may need different stem cells or combined stem cells treatment. Further investigation should be taken in areas such as stem cell manipulation, MSC differentiation and regeneration of cardiac tissue in order to improve the mechanism of heart repair by MSC. Nevertheless, stem cell technology is already a biological breakthrough with great potential in applying in cardiac repair. In view of limited donated organs to replace destroyed organs, it is expected that stem cells can be further explored to become an appropriate therapeutic tool and a renewable source of replacement cells complying with both medical and ethical standards in the near future.

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