

Cellular Cardiomyoplasty For Myocardial Infarction: a 2014 Evidence-based Update

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ABSTRAK

Infark miokard merupakan salah satu penyebab kematian utama di banyak negara. Oleh karena itu, terapi yang efektif untuk infark miokard sangatlah diperlukan. Saat ini, terapi reperfusi dan pengobatan konvensional merupakan pendekatan utama pada infark miokard. Namun, banyak pasien yang tidak memberikan respons yang baik terhadap terapi ini. Kardiomioplasti seluler merupakan terapi baru dengan menggunakan sel punca untuk perbaikan jantung. Sel punca merupakan terapi yang potensial untuk menyelamatkan sel jantung yang rusak.

Berdasarkan penelitian yang ada, sel punca merupakan pilihan yang potensial untuk infark miokard. Namun, terdapat beberapa tantangan yang perlu dijawab sebelum terapi ini dapat diaplikasikan secara luas. Seiring dengan bertambahnya pengetahuan kita tentang sel punca, maka berbagai pertanyaan yang ada akan terjawab, dan pada akhirnya memberikan solusi terbaik untuk pengobatan penyakit jantung iskemik. Ulasan artikel ini memaparkan berbagai perkembangan terbaru tentang terapi sel punca untuk pasien infark miokard.

Kata kunci: sel punca, kardiomioplasti selular, infark miokard.

ABSTRACT

Myocardial infarction is one of the main cause of mortality in many countries. Therefore, an effective therapy for myocardial infarction is required. Reperfusion and other conventional therapy have been the mainstay therapy for myocardial infarction. However, many patients remain refractory to this therapy. Cellular cardiomyoplasty is considered a novel therapy, in which stem cells are used for cardiac repair. Stem cells are potential therapeutic approach that could be the ultimate solution for salvaging damaged cardiomyocyte.

Based on current studies, stem cells are a promising therapeutic approach for myocardial infarction. However, some challenges need to be answered by future studies before this novel therapy can be widely applied. As we advance our understanding, all questions behind stem cell therapy would finally be revealed, and eventually provide the ultimate solution for ischaemic cardiac repair. This paper provide an overview of the latest progress in stem cell therapy for myocardial infarction.

Key words: stem cells, cellular cardiomyoplasty, myocardial infarction.

INTRODUCTION

Stem cells technology used to be an untouched realm of medicine. Until recently, the robust potential of stem cells were still a mystery, but today, we are constantly getting new information on this particular topic. The prospect of stem cell therapy is so vast, one of which is to treat damaged cardiomyocyte.^{1,2}

Acute myocardial infarction is one of the main causes of mortality and morbidity in many countries. Not only this disease causes a massive socio-economic burden, but also reduces the quality of life for patients who survive the attack.³ Currently, one of the mainstay therapy for myocardial infarction is rapid revascularization to limit ischaemic damage.

Reperfusion and other conventional therapy have undoubtedly saved so many lives, yet there are patients remained refractory to this therapy and left with no other treatment options. In addition to that, many patients who have underwent reperfusion strategy and survived, often left with significant impairment of left ventricular systolic function. One big question remain unanswered. Is there any other treatment option for these patients? Medical therapeutic approach to reduce damaged cardiomyocyte and generate new functioning muscle is the current unmet need.

Stem cells emerge as the novel procedure to restore damaged cardiomyocytes, and this procedure is popularly known as cellular cardiomyoplasty.^{4,5} Many clinical trials have documented the potential use of stem cells to generate viable cardiomyocyte and improve cardiac function.⁶⁻⁷ To date, there are many different types of adult stem cells and progenitor cells used for this procedure, some of which are bone marrow derived stem cells, hematopoietic stem cells, mesenchymal stem cells and so on. Since the advance of stem cells technology is faster than ever before, this review aimed to give an evidence based update on stem cells use for myocardial infarction, what have we achieved so far, and what does the future hold for this breakthrough.

CELLULAR CARDIOMYOPLASTY

Cellular cardiomyoplasty is a cell therapy using stem cells or progenitor cells for myocardial

regeneration. After an ischaemic attack due to occluded coronary vessels, heart muscle usually left damaged and nonfunctioning. However, recent evidence suggested that the cardiac muscle could actually undergo a limited amount of renewal. A prospect of inducing muscle cell to undergo division for cardiomyocyte replacement, or generating new muscle by stem cells are certainly intriguing.^{8,9}

Stem cells are capable to proliferate in the same state (self-renewal) and differentiate into multiple cell lineages. On the other hand, progenitor cells are more specific and have limited differentiation potential. Mechanism on how stem cells work are as follows: firstly, these stem cells need to be extracted from the source (eg. bone marrow), after that these stem cells need to be delivered to the injured area. These cells are implanted in the myocardium, and due to the nature of these cells, they would grow and differentiate/transdifferentiate into cardiomyocyte. To achieve the goal of cardiac repair, these cells should also have the ability to fuse with the surrounding tissues that their harmonious contraction increases the heart contraction. Furthermore, these newly-formed cardiomyocyte should also express the appropriate electromechanical properties required for contraction to yield a synchronous contraction.^{5,10}

Many clinical studies have documented the feasibility and safety of cellular cardiomyoplasty in patients with coronary artery disease.¹⁰⁻¹² There is wide arrays of cell types being used for cellular cardiomyoplasty and the exact efficacy of each cell type is yet to be determined. To date, there are some different types of adult stem cells and progenitor cells used for this procedure, some of which are bone marrow derived stem cells, hematopoietic stem cells, mesenchymal stem cells and many others.¹²⁻¹⁴

POTENTIAL SOURCE AND TYPE OF STEM CELLS

Bone Marrow Derived Stem Cells

Bone marrow derived stem cells (BMCs) are the most widely studied type of stem cells. Orlic et al. first describe the ability of bone marrow cells to regenerate infarcted myocardium in

mouse models. The transplanted cells showed transdifferentiation into cardiomyocyte which eventually lead to improved left ventricular ejection fraction.¹⁵ The three types of stem cells derived from bone marrow are hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs).¹⁵⁻¹⁷

The role of BMCs for acute myocardial infarction has been reported to improve left ventricular ejection fraction (LVEF), both in REPAIR-AMI and BOOST trial.^{18,19} BOOST trial demonstrate an acceleration of LVEF after intracoronary BMCs transfer (ejection fraction increased by 6.7% in the BMCs group as compared to 0.7% in the control group), and significant result was sustained until 18 months.¹⁸ While in REPAIR AMI trial, improvement of LVEF, infarct size and wall thickening of infarcted segments were reported at two years follow up. At two years, the cumulative end point of death, myocardial infarction, or necessity for revascularization was significantly reduced in the BMC group compared with placebo (hazard ratio, 0.58; 95% CI, 0.36 to 0.94; $P=0.025$).^{20,21}

The long term effect of intracoronary stem cell application was also under studied. Strauer BE et al.²² in a study named the STAR-heart, a non-randomized study reported that intracoronary BMCs therapy improves ventricular performance, quality of life and survival in patients with heart failure. BMCs therapy was not associated with any adverse effect during the 5-year. Feng Cao et al.²³ reported long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in eighty-six patients with STEMI that were randomized to receive BMCs or saline. After four years, the improved LVEF was still sustained.²³ Long term benefit of BMC transplantation was further confirmed by the BALANCE study. In this study, intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction was associated with a higher ejection fraction, and a lower mortality at 5-year.²⁴

Skeletal Myoblast

Skeletal muscle has the ability to regenerate under certain circumstances. Skeletal resident

stem cells are usually known as satellite cells, and these cells would differentiate to new myocytes in response to injury. However, whether this ability can be translated to a different condition, as in cardiomyocyte repair, should be further studied.^{25,26}

MAGIC trial, a randomized controlled phase II trial, showed no significant changes in terms of global and regional LV function in skeletal myoblast-treated patients.²⁷ Another study performed by Dib et al.²⁸ showed an increased in LV ejection fraction in the group treated with transepical injection of autologous SMs.²⁸

One downside of using skeletal myoblasts (SMs) is its pro-arrhythmogenic effect. This effect was observed by Meanasche et al.²⁹ One possible mechanism by which SMs may caused cardiac electrical discordance is the failure of SMs to couple electrically with adjacent cardiomyocyte after being transplanted to the heart. This group of transplanted cells with different electrophysiology properties might contributed to the pro-arrhythmogenic effect of SMs.^{30,31} However, according to MAGIC trial there was no significant increased in arrhythmic events in the intervention group, however an increased trend towards arrhythmic events was recorded.²⁷

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are another potential option for cellular cardiomyoplasty. Mesenchymal stem cells can be found in various tissue, such as bone marrow and adipose tissue.³² One interesting mechanism by which MSCs mediate cardiac function improvement is the paracrine effect. MSCs may secrete soluble cytokines and growth factors that would eventually influence adjacent cardiomyocyte.³³

Hare JM et al.³⁴ studied the efficacy of intravenous allogenic human mesenchymal stem cells in patients with myocardial infarction. According to this study, intravenous MSCs were safe as showed by the similar adverse event rates in both intervention and control group. MSCs treated patients also present with a better ejection fraction and improved pulmonary function, as showed by increased forced expiratory volume in 1 second.³⁴ In another study, named The POSEIDON trial, Hare JM et al.³⁴ showed that

transendocardial injection of allogeneic and autologous MSCs without a placebo control were both associated with low rates of treatment-emergent serious adverse effects, including immunologic reactions. The alloimmune reactions in patients receiving allogeneic MSCs for ischemic LV dysfunction were low (3.7%). In summary, MSCs injection favorably affected patient functional capacity, quality of life and LV remodeling.³⁵

Another interesting source of stem cells is the adipose tissue, namely adipose tissue derived stem cells (ADSCs). The characteristics of ADSCs are generally similar to MSCs, though not identical.³⁶ One study to investigate the safety of ADSCs is the APOLLO trial. In this trial, patients who had undergone the first episode of myocardial infarction, with an ejection fraction of <50%, will be underwent liposuction within 24 hours of percutaneous intervention. ADSCs that were extratcted during liposuction would eventually injected intracoronary to the patient's heart. According to this study, the infarct size was significantly reduced in the treatment arm and was still sustained after 18 months follow up. Perfusion of the infarcted heart, as measured by single photon-emission computed tomography (SPECT), showed significant improvement as well. This study concluded that ADSCs can be safely obtained and administered to the patients.³⁷ Another studies named ADVANCE, still on-going during the preparation of this manuscript, and will provide further information regarding the efficacy of this approach on a larger population, since this study enroll up to 370 patients.

The administration MSC present one particular advantage over the other type of stem cells, that in the case of MSC use, it is possible to use allogenic graft. This fact is due to the lack of various major histocompatibility complex and costimulatory cell-surface antigens in MSCs.³⁸ However negative experience with MSCs use was documented by Fischer UM et al.³⁹ whom aimed to track the journey of stem cells after intravenous infusion. MSCs were labeled using a cell labeling kit. Infrared imaging system was used to identify the presence of labeled cells. According to this study, the majority of

MSCs were trapped inside the lungs following intravenous infusion.³⁹

The negative finding documented by Fischer UM et al. suggested a more cautious intepretation of positive outcome observed in the study by Hare JM et al.³⁵ Some questions remained unanswered, if MSCs indeed trapped in the lung, the explanation of the positive result of intravenous MSCs infusion in the study performed by Hare JM et al.³⁵ Need to elaborate more. If intravenous administration is not compatible with MSCs, the best way to administer MSCs, need to be determined.

Endothelial Progenitor Cells

Endothelial progenitor cells (EPCs) have been linked with neovascularization in ischemic tissue. This interesting finding lead to the use of EPCs for another therapeutic purpose like cellular cardiomyoplasty.⁴⁰ The human peripheral blood-derived EPCs would be a potential approach because those cells can be easily isolated without the need of major surgical intervention.⁴¹

This assumption was later confirmed by Badorff et al.¹⁷ In this study, Badorff et al. reported that EPCs from healthy volunteers and Coronary Artery Disease (CAD) patients can transdifferentiate into functionally active cardiomyocytes when co-cultivated with rat cardiomyocytes.¹⁷ However, this finding was later opposed by Gruh I et al. According to this study, there was no significant evidence of transdifferentiation of human EPCs into cardiomyocyte.⁴²

Whether EPCs possed the ability of transdifferentiation into cardiomyocyte still required further investigation. A preclinical study in rat models by Chang ZT⁴³ showed promising result. This study showed that the administration of peripheral derived EPCs (PB-EPCs) increased cardiac contractility as assessed by echocardiography. PB-EPCs are able to protect cardiomyocytes through increased expression of proteins involved in mediating vascular growth.⁴³

Resident Cardiac Stem Cells

Until recently, we believe that heart is a fully mature organ with no capability of self-renewal. However, the adult heart is not a terminally

differentiated organ, but harbors stem cell with regenerative capacity, namely resident cardiac stem cells (CSCs). Although the origins of CSCs are yet unclear, they can be isolated from heart tissue and expanded *ex vivo* for use as a cell-based therapy. There were many types of CSCs have been described in previous studies, like: epicardium-derived cells, cardiosphere-derived cardiac cells, and cardiac Sca-1+ cells. These resident stem cells have the potential to differentiate into different types of cells like vascular smooth muscle and myocardial cells.⁴⁴⁻⁴⁶

A study in animal model by Oh H et al.⁴⁷ documented the beneficial effect of resident stem cell therapy in terms of reducing infarct size and improving LV function. Given intravenously after ischemia/reperfusion, adult heart-derived cardiac progenitor cells home to injured myocardium and differentiate to myocytes, as shown by the positive result of cardiac specific genes (Nkx2.5). These cells also expressed α -actin, cardiac troponin I and connexin.^{43,47}

Embryonic Stem Cells and Induced Pluripotent Stem Cells (iPS)

Embryonic stem cells (ESC) are derived from the blastocyst (inner cell mass) of human embryo prior to implantation. ESCs are pluripotent cells, which means they have the capability to differentiate into any cells, one of which is cardiac myocytes. Due to the source of these cells, there are ethical issues regarding the use of ESC.⁴⁸

The huge potential of ESC comes with a price. The pluripotency of ESC made these cells predisposes to tumor formation including teratomas. Amariglio N et al.⁴⁹ documented the occurrence of a human brain tumour following neural stem cell therapy. A boy with telangiectasia was treated with intracerebellar and intrathecal injection of human fetal neural stem cells. Four years later, he was diagnosed with a multifocal brain tumour. After thorough analysis, the tumor was of nonhost origin, indicating it was derived from the transplanted neural stem cells.⁴⁹ To date, due to the scarcity of studies on ESC and negative experiences of previous studies, the significance of ESC as cell-based therapy for myocardial infarction remains elusive. The above-mentioned limitation would hopefully be elucidated in

future research.

One possible solution to this ethical issue is by reprogramming somatic cells to produce induced pluripotent stem cells. Takahashi and Yamanaka demonstrated the induction of pluripotent stem cells from mouse embryonic or adult fibroblasts by introducing four factors (Oct3/4, Sox2, c-Myc, and Klf4). They reprogrammed murine fibroblast into stem cells with the capacity to form all three germ layers, and the term used for these cells are induced pluripotent stem cells (iPS). The iPS exhibited the morphology and growth properties of ESC and expressed ESC marker genes.^{50,51}

The therapeutic potential of iPS used to be limited into noncardiac diseases, like sickle cell anemia, parkinson's disease and hemophilia A. Nelson TJ et al.⁵² is the first to study the use of iPS in acute myocardial infarction in mice model. The origin of iPS was mouse embryonic fibroblast that was transduced with human stemness factor (Oct3/4, Sox2, c-Myc, and Klf4). The administration of iPS restored postischemic contractile performance, ventricular wall thickness, and electric stability. The tumour predisposition of these cellswas determined in immunocompetent mice, with no tumour development observed, whereas in immunodeficient mice, tumour development was observed, which highlights the importance of immune surveillance to prevent tumour growth.⁵² Induced pluripotent stem cells exhibit a wide arrays of reparative potentials, yet we still need to advance our knowledge in cell programming and cell fate customasization in order to make this approach a safe option for cardiac repair.

Human Umbilical Cord Blood Cells

Human umbilical blood cells (hUCB) contains a large number of non-hematopoietic stem cells which rarely express human leukocyte antigen (HLA) class II antigens, thus reducing the risk of rejection. Many studies have reported the efficacy and safety of hUCB administration in acute myocardial infarction model, with conflicting result.^{53,54}

According to Henning RJ et al.⁵³ hUCB administration reduce infarction size and improve ventricular function in rats without requirements for immunosuppression.⁵³ Similar

positive finding were documented by Kim et al. The study reported improvement in ventricular function after intramyocardial hUCB cell injection in immunosuppressed infarcted pigs.⁵⁵ However, another study done by Moelker et al.⁵⁴ reported contrary result that intracoronary administration of hUCB was not associated with cardiac improvement in the same animal model.⁵⁴

Circulating Blood-derived Progenitor cells

Circulating blood-derived progenitor cells (CPCs) are similar to BMCs, which mainly composed of EPCs. Santoso T et al.⁹ studied the safety and feasibility of combined granulocyte colony stimulating factor (G-CSF) and erythropoietin (EPO) based-stem cell therapy using intracoronary infusion of peripheral blood stem cells in patients with recent anterior myocardial infarction. G-CSF is used to mobilized stem cells to the injured area, inhibits cardiomyocyte apoptosis, promotes neovascularization, and increase the production of nitric oxide. While EPO, that is originally thought to be a hematopoietic hormone only, also may inhibited apoptosis and induced angiogenesis. This phase I study concluded that this procedure is safe and resulted in improved endpoints for LV ejection fraction and cardiac viability.⁹

The comparison between BMCs and CPCs in terms of efficacy and safety, were performed by Assmus B et al.⁵⁶ (TOPCARE-AMI trial). This study reported positive outcome (LV global function) in both arms with no significant difference.⁵⁶ A meta-analysis performed by Wen Y et al.⁵⁷ to determine the effects of CPCs on improvement of cardiac function. According to this metanalysis, the administration of CPCs provide moderate improvements over conventional therapy.⁵⁷

Cardiopoietic Stem Cells

Cardiopoietic stem cells are not a distinct type of stem cells but refer to the novel way of processing stem cells in order to get a lineage specification. Cardiopoietic stem cells are harvested stem cells that are treated with a protein cocktail to replicate natural cues to heart development, before being injected into the patient's heart. The C-CURE trial studied the efficacy of bone marrow derived-mesenchymal

stem cells in chronic heart failure. The isolated mesenchymal stem cells were exposed to a cardiogenic cocktail that trigger expression and nuclear translocation of cardiac transcription factors, before being injected to the patient's heart. After six months follow up, patients in the treatment group significantly improved in terms of LVEF and fitness capacity. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic cell therapy.⁵⁸ Unfortunately, data comparing the efficacy and safety between cardiopoietic stem cells and ordinary stem cells without cocktail-based priming is still lacking.

DELIVERY METHODS

In order to make these stem cells reach the heart, a reliable delivery method need to be employed. The ideal method should be able to safely and efficiently deliver an optimal number of stem cells to the target tissue. Beside the high efficacy, this delivery method should be as minimally invasive as possible for the sake of patients' comfort. There are some delivery methods worthy to know.

Intracoronary Infusion

As the name implies, intracoronary infusion is a process of delivering stem cells through coronary artery, usually through intracoronary catheterization. Stem cells are infused under pressure via a balloon catheter. The balloon was inflated in order to prevent anterograde blood flow that would compromise stem cells delivery. Catheter guided cell transfer has its unique advantage of safety under local anesthesia, and a part of routine cardiac catheterization. The intracoronary method provide a maximum number of cells to the target area, with good blood supply which is crucial for cell survival. Multiple studies have reported the use of intracoronary infusion for stem cells delivery.^{11,19}

Strauer BE et al. and Schächinger V et al. reported improved outcome in acute myocardial patients after BMCs intracoronary infusion. Improved parameters in these studies include LV function and infarct size.^{11,19} Grieve SM et al. reported microvascular obstruction after MSCs delivery through intracoronary route.

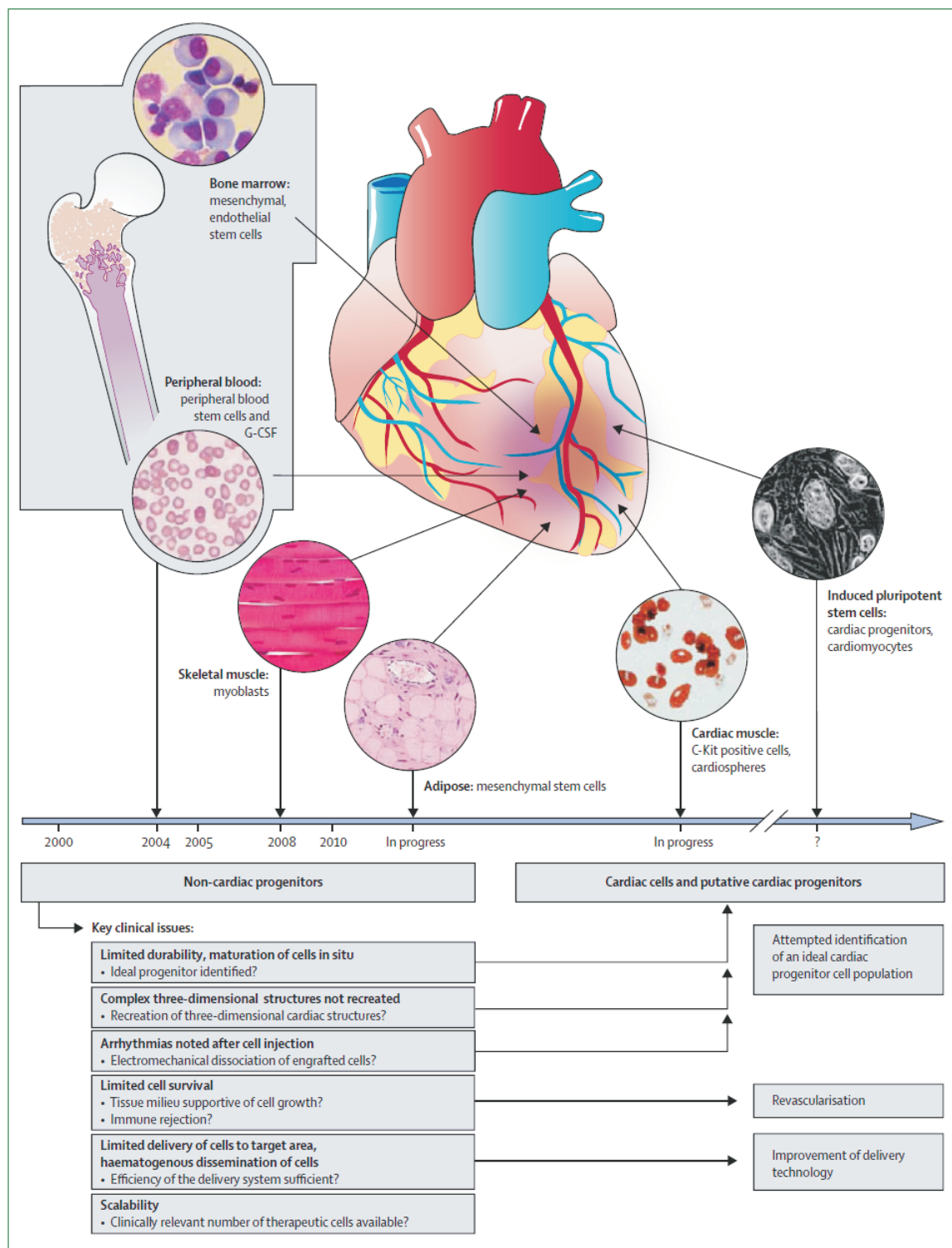


Figure 1. Clinical trials on stem cells over the years. The focus of research shifted from finding non-cardiac progenitors towards finding cardiac cells and putative cardiac progenitors.⁵⁹

As previously discussed, MSCs are large cells that might induce myocardial damage by microvascular obstruction. This finding raise another question of which delivery method is the best for each type of stem cells.⁶⁰

Intravenous Peripheral Infusion

Intravenous stem cells administration is one of the easiest method to be employed. Intravenous administration is possible through homing phenomenon of stem cells to the injured

heart. Homing is a process where cells migrate to the organ of their origin. Homing of bone marrow stem cells to injured myocardium is now also thought to occur after myocardial infarction.^{51,61} This process is believed to be a multistep complex process involving many cytokines and granulocyte colony-stimulating factor (G-CSF), that usually rise more intense in acute settings. Orlic et al¹⁵ studied the potential of BMC mobilized by stem cell factor and G-CSF in mice with infarcted heart. The resulted in the intervention group, was significant decrease of mortality, reduced infarct size and improved ejection fraction.¹⁵

Unfortunately, intravenous peripheral infusion comes with some disadvantages. First, only 3% of normal cardiac output will flow per minute through the left ventricle. This low amount of blood would limit the amount of stem cells delivered. Secondly, due to the passing of venous blood in the lung, many cells would trap in lung vasculature that eventually lead to stem cells reduction.⁶⁰ One obvious example is the trapping of big-sized MSCs in lung, as clearly demonstrated by Fischer UM et al.³⁹

Intramyocardial, Transendocardial and Transpericardial Route

As mentioned earlier, the downside of intravenous administration is the passing of the blood in certain organs that would entrapped some of the stem cells. Unlike intravenous route, intramyocardial method is undoubtedly provide direct access to the injured cardiomyocyte bypassing the need for mobilization, homing and any risk of cells entrapment in other organ, thus provide a more effective way to deliver abundant stem cells to the injured area. However, this method comes with its own expense of a more invasive method, not to mention the risk of ventricular perforation in the already damaged cardiomyocyte. Intramyocardial delivery usually performed during an open heart surgery or needle-tipped delivery catheter.^{61,62} Nelson et al.⁵² documented that intramyocardial delivery of iPS originating from reprogrammed fibroblast, yielded progeny that properly engrafted and resulted in restored contractile performance, increased ventricular wall thickness, and electric stability.⁵²

Transendocardial and transpericardial route have been explained in some animal studies.⁶³ One particular advantage of this method is the visualization and the chance of administering stem cells directly to the target area. Perin EC et al.²¹ elaborate the transendocardial BMCs administration in patients with ischemic heart disease. The injection catheter advanced into the left ventricle through the aortic valve, then the catheter tip is placed against the endocardial surface and this procedure is finalized with needle extension into the myocardium to deliver the BMCs. This study concluded that transendocardial route was a safe way to transfer BMCs and resulted in improved ejection fraction and global left ventricular function.²¹

STUDIES USING STEM CELLS IN MYOCARDIAL INFARCTION

Many studies have been carried out to investigate the efficacy and safety of stem cell therapy in patients with myocardial infarction. Each of these studies investigated different kind of stem cells with different delivery methods. The ultimate goal of these studies is to answer whether stem cell therapy could be a feasible therapeutic approach for patients with myocardial infarction. The result of these studies were not always positive, even some of the studies did not document any beneficial effect of stem cell therapy. However, this conflicting result need to be interpreted with caution due to the different study method, different type of stem cells used, and different delivery methods employed. **Table 1** summarize some studies on stem cells therapy for myocardial infarction, that have been performed.

Three meta-analysis on the efficacy of BMCs therapy for myocardial infarction have been published. In a meta-analysis by Delewi R et al, intracoronary BMCs infusion is associated with improvement of LV function and remodelling in patients after ST-segment elevation myocardial infarction. The benefit in terms of LVEF improvement was more pronounced in patients with a worse baseline LVEF (LVEF cut off: 40%) and younger age (age cut off: 55 years).⁶⁸ In a second meta-analysis by Clifford DM et al.⁶⁹ which include

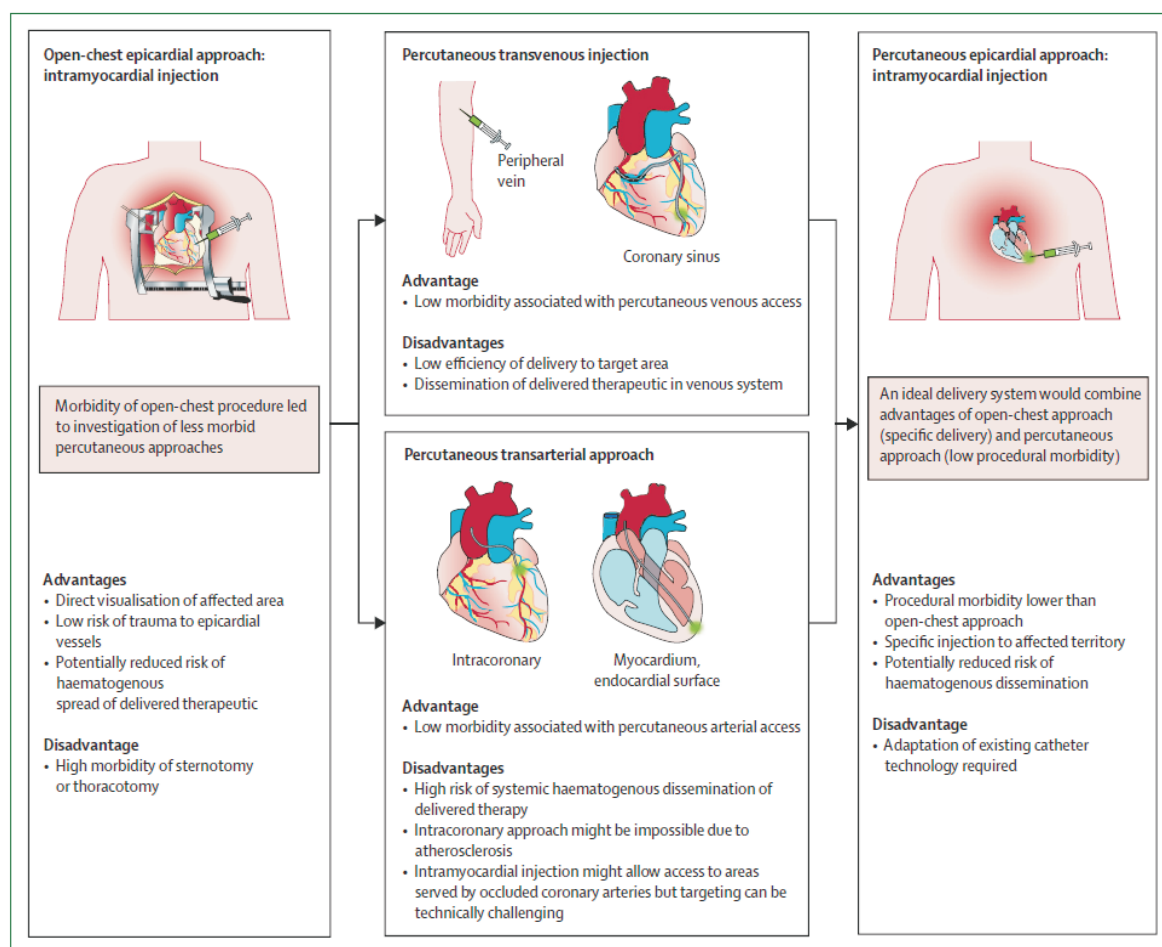


Figure 2. Delivery methods for cellular cardiomyoplasty with their advantages and disadvantages.⁵⁹

thirty-three RCTs, there was no significant difference in hard end point like mortality and morbidity in the BMCs treated group. However global heart function, as represented by LVEF and infarct size, was improved significantly and was sustained long term (12 to 61 months) in the BMCs group.⁶⁹ The third meta-analysis by Long C et al.⁷⁰ further confirmed the beneficial effect of intracoronary BMCs in patients with acute myocardial infarction. According to this meta-analysis, BMCs therapy significantly improved LVEF, while mildly but not significantly reduced left ventricular end-systolic volume and left ventricular end-diastolic volume.⁷⁰ These three meta-analysis synonymously agree that BMCs therapy is beneficial in terms of improved heart function and reduced infarct size.

CHALLENGES AND THE FUTURE

We have just entered the new era of stem cell therapy. When advanced therapy like primary PCI and thrombolytic showed more limited beneficial for patients with myocardial infarction, the concept of cell-based therapy is definitely appealing. This new approach could be the answer that have been waited for sometime.

As we have discussed previously, there are many issues on stem cell therapy that need to be addressed in future studies. Firstly, what is considered to be the best stem cells to replace cardiomyocyte. Secondly, the right delivery method of these stem cells need to be determined. Whether different type of stem cells required certain delivery methods also need to be further elucidated. Another question is the right timing

Table 1. Summary of landmark trials on stem cells

No	Stem cell source	Study (year)	Population (Number of patients)	Delivery method	Length of Follow up	Outcome
1.	BMCs	BOOST trial (2006) ¹⁸	AMI patients (60 patients)	Intracoronary	18 months	- Significant increase of LVEF in the BMC group after 6 months. - This effect is not sustained after 18 months
		REPAIR-AMI (2006) ¹⁹	AMI patients (187 patients)	Intracoronary	1 year	- Significant increase of LVEF in the BMC group after 4 months. - At 1 year, BMC group was associated with a reduction in the prespecified combined clinical end point of death, recurrent MI or revascularization
		FOCUS-CCTRN (2012) ²¹	CHF patients (92 patients)	Transendocardial	6 months	- Significant increase in LVEF in the treatment group ($2.7 \pm 5.2\%$; $P = 0.030$; 95% CI, 0.27 to 5.07). - No positive effect observed in LVESV and SPECT defect size
		STAR-HEART (2010) ²²	CHF patients (391 patients)	Intracoronary	5 years	Intracoronary BMC therapy improves ventricular performance, quality of life and survival in patients with heart failure. No side effects were observed
		Ramshorst JV et al (2011) ⁶⁴	CMI patients (50 patients)	Intramyocardial	3 months	Significant increase in LVEF in the BMC group ($52 \pm 5\%$ versus $51 \pm 7\%$, $P=0.001$).
		TIME trial (2012) ⁶⁵	AMI patients (120 patients)	Intracoronary	6 months	No significant difference in LVEF or global LV function between both arms
2.	MSCs	Hare JM et al (2009) ³⁴	AMI patients (53 patients)	Intravenous	6 months	The MSCs treated group demonstrated significant improved LVEF, and global symptom score, as compared to that in the placebo group.
3.	CSCs	SCPIO trial (2011) ¹⁴	Patients with ischemic cardiomyopathy (23 patients)	Intracoronary	1 year	- The initial result showed significant improvement in terms of LVEF and quality of life in the treatment group. - No CSCs related adverse effect observed.
		CADUCEUS (2012) ⁶⁶	AMI patients (31 patients)	Intracoronary	6 months	No increase in EF over control at 6 months follow up.
4.	SMs	MAGIC trial (2004) ²⁷	Myocardial infarction patients (127 patients)	Intracoronary	6 months	- The SM treated group demonstrated increased cardiac function as showed by increase LVEF. - Patients receiving G-CSF alone experienced instant restenosis
		MARVEL-1 trial (2011) ⁶⁷	Heart failure patients with chronic infarction (23 patients)	Transendocardial	6 months	This study is prematurely halted due to financial issue. However, a completed-analysis reported favorable outcome in the SMs treated group, in terms of the distance during 6 minute walk. No difference in LVEF, wall motion and LV dimension observed in both arms.
5.	CPCs	TOPCARE-AMI (2002) ⁵⁶	AMI patients (20 patients)	Intracoronary	4 months	The CPCs treated group showed significant increased global LVEF, improved regional wall motion and reduced end systolic LV volume.

Abbreviation: BMCs: bone marrow derived stem cells; MSCs: mesenchymal stem cells; CSCs: resident cardiac stem cells; SMs: skeletal myoblast; CPCs: circulating blood-derived progenitor cells; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MVO2; G-CSF: granulocyte colony stimulating factor

of delivery (acute, sub acute or chronic), whether it contributes to the fate of stem cells. Fourth, the concentration of stem cells, dose-effect relationship and safety of stem cell therapy need to be further investigated. One particular topic in regard to stem cell safety is the tumorigenicity of ESC. We need to disentangle a way to reprogram these cells so they can differentiate into functional cells, but lack the ability to form tumours. Finally, novel diagnostic tools are required to detect and evaluate stem cells therapy. Future studies would hopefully provide solid proof on hard end-points (eg. mortality), instead of surrogate markers like LVEF or infarct size.

CONCLUSION

Tremendous progresses were made in cell-based therapy, and future advances would further lead us to a new solution for ischaemic heart disease. Stem cells own robust potential in medicine, one of which is to replace damaged cardiomyocyte. More evidents are needed in advance to widely use of this modality.

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