Chapter 11

Optimal Delivery Strategy for Stem Cell Therapy in Patients with Ischemic Heart Disease

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Abstract

Stem cell therapy is a new strategy for patients with ischemic heart disease. However, no consensus exists on the most optimal delivery strategy, but an important factor that determines the success of stem cell therapy is the choice of cell delivery route to the heart. Delivery strategy affects the fate of cells and subsequently influences outcome of procedure. Our review summarizes current approaches for administration of stem cells to the heart. Three most used approaches are intracoronary, intramyocardial, and epicardial injection. They have been widely used for delivery of different types of cells. There are several advantages of these stem cell administration approaches, but stem cell retention and stem cell survival rates are quite low using these methods, which might limit their therapeutic effects. Alternative attempts to improve current stem cell therapy methods are reviewed along with emerging new stem cell delivery approaches. The present chapter displays the current status on stem cell delivery techniques, their efficacy, and clinical success in different trials.

Keywords: stem cell therapy, delivery method, ischemic heart disease, intramyocardial injection

1. Introduction

Regenerative medicine with stem cell therapy has been tested in clinical trials in patients with ischemic heart disease [1]. The aim of this method is to induce growth of new blood vessels in the myocardium or replacement of damaged myocardial cells either directly by differentiation of stem cells or by a paracrine effect of cytokines secreted from the stem cells.

When applied to the heart stem cell therapy, it has several important factors that might influence therapeutic success, including the properties of stem cells and type of the disease that affect the heart of host.

The choice of the delivery methods is also very important because this will affect the retention rate, survival, integration in the host, and functionality of stem cells. Therefore, delivery method influences the subsequent outcome of this new emerging treatment [2].

The aim of this review is to discuss methods of delivery in regenerative stem cell therapy in patients with ischemic heart disease. We will focus on current issues derived from conducted clinical trials and emerging new approaches.

2. Routes to the heart: advantages and disadvantages

Different approaches for delivering cells to the heart were developed and are utilized in preclinical and clinical current studies: intramyocardial (IM), intracoronary (IC), and intravenous (IV) (**Figure 1**) approaches were widely used, but no method currently meets the criteria of a perfect delivery method [3]. A stepwise approach of optimal delivery would consider if the patient needs open chest surgery. Surgical intramyocardial delivery is the most direct but

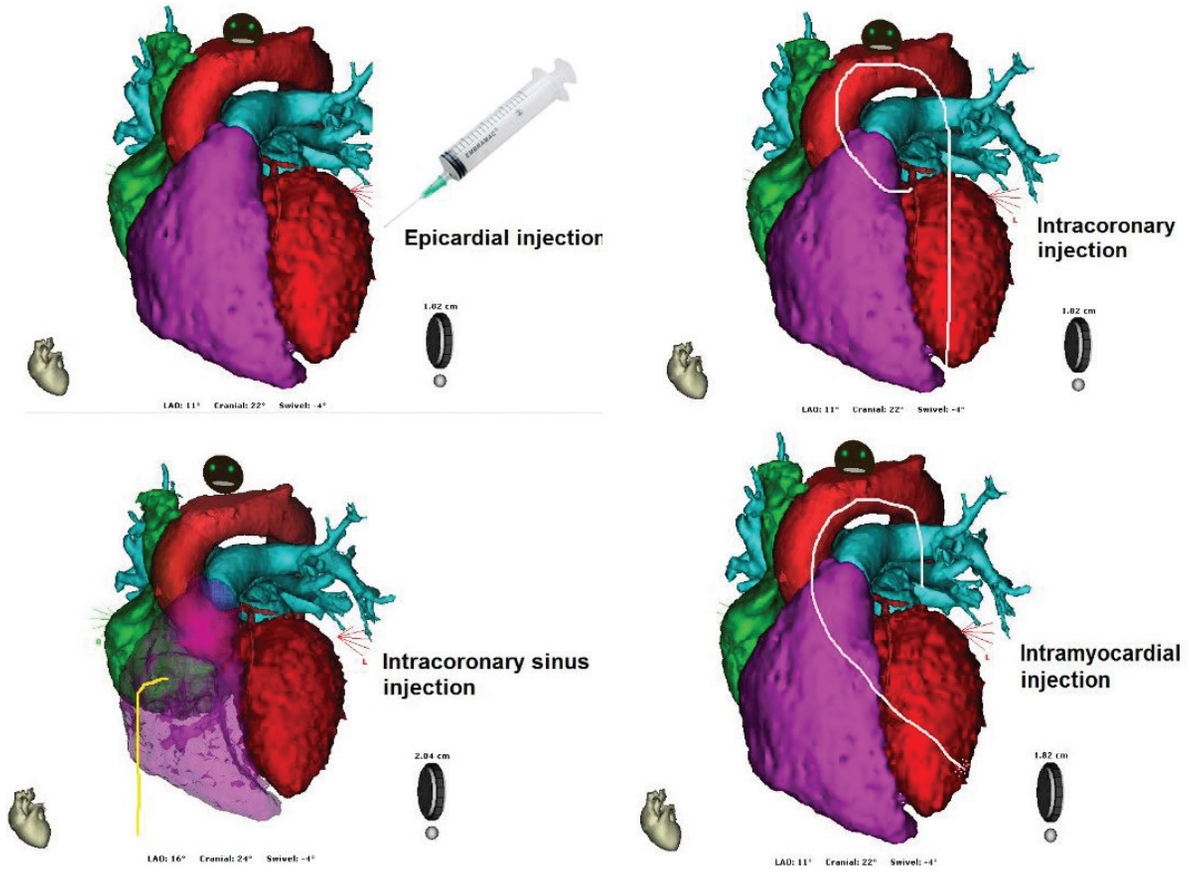

Figure 1. Major routes for delivering stem cells to the heart.

reserved for patients necessitating coronary artery bypass grafting (CABG) with direct thoracotomy. Catheter-based intramyocardial delivery is limited by the technology of catheters and mapping systems. In patients with recent myocardial ischemia and injury due to a significant stenosis or occlusion of a coronary artery, intracoronary artery delivery may not be the optimal route regardless of experimental results with the technique. In this case, intravenous or intracoronary venous injection is preferred.

Each of the techniques has its own advantages and disadvantages. The optimal method is still unclear. Studies have used either intravenous, intracoronary, or intramyocardial injection.

2.1. Chronology of optimal delivery developments

In 2001, the first rodent study with stem cells was published by Orlic et al., showing improvement in the heart function by regeneration [4]. Six months later, the first clinical trial on humans reported positive results for intracoronary injection of bone marrow stem cells after acute myocardial infarction [5].

Starting with the preclinical pioneering work of Orlic et al., intramyocardial and intravenous deliveries of BMC have been shown to improve left ventricular function in ischemic heart disease (**Table 1**).

- The transcoronary catheter-based procedure was first performed by Thompson et al. using a catheter in combination with an intravascular ultrasound imaging and demonstrated in swines that are feasible and safe [6]. Few years later, Siminiak et al. finished the first phase I clinical trial with his method confirming the feasibility and safety of the procedure in humans [7].
- The transendocardial technique was first used in a swine model by Fuchs et al. who demonstrated improvement of the cardiac function [8]. Since then, clinical studies have been published with positive results.
- The first trial of bone marrow stem cells in chronic ischemic cardiomyopathy was performed by Perin et al. [9]. He studied percutaneous transendocardial injection of stem cells and provided encouraging results.
- For the intravenous infusion, the safety and feasibility have been confirmed using a swine model [10] as well as later in a phase I clinical study on humans [11].
- In a swine model of myocardial injury, Vicario et al. [12] and Yokoyama et al. [13] demonstrated that retrograde coronary sinus injection does not produce significant hemodynamic changes and reported presence of autologous bone marrow stem cells in the myocardium.

2.1.1. Intravenous delivery

The systemic route of delivery is simple, not so invasive, but retention to the heart of stem cells is very low. Higher rates of retention were seen with mesenchymal cells because of their homing capacity. This route needs to be associated with methods of enhancing homing to the

Clinical trial	Administration	Reference
2002 TOPCARE-AMI	Intracoronary	[14]
2004 Perin et al.	Intracoronary	[47]
2004 BOOST	Intracoronary	[16]
2004 Chen et al.	Intracoronary	[38]
2004 Siminiak et al.	Epicardial	[48]
2005 Katritsis et al.	Intracoronary	[36]
2005 Erbs et al.	Intracoronary	[49]
2006 REPAIR-AMI	Intracoronary	[50]
2006 Assmus et al.	Intracoronary	[51]
2006 ASTAMI	Intracoronary	[19]
2006 Chen et al.	Intracoronary	[39]
2006 Fuchs et al.	Intracoronary	[34, 35]
2006 Beeres et al.	Intracoronary	[52]
2006 Hendrikx	Epicardial	[53]
2006 Kang et al.	Intracoronary	[54]
2007 Losordo et al.	i.m.	[30]
2007 Katritsis et al.	Intracoronary	[36]
2007 Mohyeddin-Bonab et al.	i.m.	[55]
2007 Beeres et al.	Intracoronary	[56]
2007 Ahmadi et al.	i.m.	[57]
2008 Diederichsen et al.	Intracoronary	[58]
2008 FINCELL	Intracoronary	[59]
2008 Menasche et al.	Epicardial	[60]
2008 HEBE	Intracoronary	[61]
2008 Beeres et al.	Intracoronary	[62]
2009 Hare et al.	i.v.	[11]
2009 Van Ramshorst et al.	i.m.	[63]
2009 BALANCE	Intracoronary	[64]
2009 MYSTAR	Intracoronary/i.m.	[65]
2009 REGENT	Intracoronary	[66]
2010 Kastrup et al.	i.m.	
2010 Strauer et al.	Intracoronary	[67]
2011 Yerebakan et al.	Epicardial	[68]

Clinical trial	Administration	Reference
2011 Williams et al.	i.m.	[69]
2011 Perin et al.	i.m.	[70]
2011 Povsic et al.	i.m.	[71]
2011 Duckers et al.	i.m..	[72]
2011 Hirsch et al. HEBE	Intracoronary	[73]
2011 Roncali et al. BONAMI	Intracoronary	[74]
2011 Traverse et al. Late TIME	Intracoronary	[75]
2011 Quyyumi	Intracoronary	[76]
2011 Tuma	Retrograde coronary	[45]
2011 Moreira	Retrograde coronary	[46]
2012 Makkar et al. CADUCEUS	Intracoronary	[77]
2013 Bolli et al. SCIPIO	Intracoronary	[78]
2013 Vrtovec	Intracoronary	[79]
2013 Huang	Intracoronary	[80]
2013 Kurbonov et al.	Intracoronary	[81]
2013 Forcillo et al	Via CABG + i.m.	[82]
2014 Assmann et al.	Via CABG+epicardial	[83]
2014 Nasseri et al	i.m.	[84]
2014 Brickwedel et al.	Via CABG	[85]
2014 Hong	Intracoronary + retrograde coronary sinus	[86]
2015 Hao	Intracoronary	[87]
2015 Chang	Intracoronary	[88]
2015 Gao	Intracoronary	[89]
2015 Fiarresga	Intracoronary	[90]
2015 Helseth	Intracoronary	[91]
2015 Eirin	Intrarenal	[92]
2015 Lee	Intracoronary	[93]
2016 Tseliou	Intracoronary	[94]
2017 Xiao	Intracoronary	[95]

i.m., intramyocardial.

Table 1. Cell delivery in studies and publications on myocardial infarction and chronic ischemic heart failure.

ischemic tissue because most of the stem cells show localization in other tissues with only a small part of injected cells engrafted at the level of the heart [14–17]. This method may be limited to acute myocardial infarction and not be suitable for chronic ischemic heart disease because it relies on physiologic homing signals present few days after an acute myocardial infarction.

2.1.2. Intracoronary delivery

An attractive method is intracoronary infusion because it can disseminate relatively uniformly cells to the entire region infused [18]. It is also widely available, less invasive than intramyocardial method, and it is used in numerous clinical trials [14–22]. Intracoronary infusion implies a percutaneous approach typically through the femoral artery with a standard balloon catheter. The catheter used for delivery infuses cells to the myocardial regions in which blood supply is preserved. For injection, balloon occlusion is needed in order to reduce the washout into the systemic circulation and increase adhesion of cells and transmigration of the infused cells to the myocardium [19–24].

One reason to use this method is the familiarity between interventional cardiologists. The method is less invasive than injection directly in the myocardium and requires the equipment standardly found in a catheterization laboratory. The method enables a relatively homogeneous dissemination of stem cells to the target area.

The disadvantage of this method is that some adult stem cells such as autologous cardiosphere-derived cells [25] or mesenchymal stem cells (MSCs) [26, 27], produced microvascular occlusion after intracoronary delivery, raising concerns over the use of this method delivery in patients with ischemic heart disease. Actually, the diameter of autologous cardiosphere-derived cells and mesenchymal stem cells is around 20 μm, which could exceed the diameter of some arterioles [28]. The great majority of clinical studies use this approach to inject smaller cells such as bone marrow mononuclear cells. Another disadvantage could be the poor retention rate following intracoronary injection. This is caused by the loss of a high proportion of stem cells in the systemic circulation during several minutes.

2.1.3. Intramyocardial-transendocardial injection

Transendocardial injection is performed percutaneously and is less invasive than epicardial injection [29, 30] but more invasive than intracoronary injection. The access is made by puncture of the femoral artery or vein (transseptal approach) and then the catheter is passed in the left ventricle. An electroanatomical map of the left ventricle is realized in order to navigate inside the cavity and position the injection catheter to specific areas (**Figure 2**).

Electroanatomical mapping system permits left ventricular mapping and guides injection to the border zone between healthy and necrosed endocardium [26, 31–35]. Intramyocardial injection of bone marrow-derived stem cells and also angiogenic genes has been reported to be safe in terms of arrhythmia or death [26, 30–35]. On the other hand, intramyocardial injection of skeletal myoblasts has been shown to have a pro-arrhythmogenic effect [26, 31–35].

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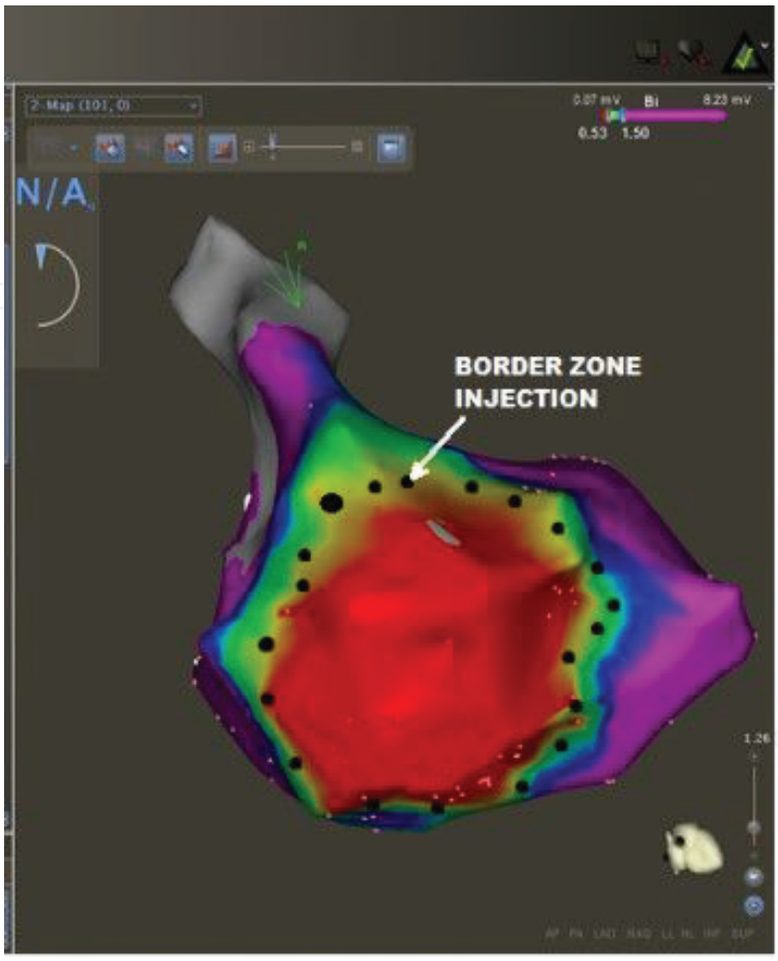

Figure 2. Intramyocardial injection at the border zone between healthy myocardium and dense necrosis. The border zone is probably hibernating but viable myocardium.

In a comparative study [26], intramyocardial technique was compared to intravenous delivery and intracoronary method. Intramyocardial injection of MSCs was better than intracoronarian delivery in terms of blood flow to the myocardium. In dogs and also in pigs micro-infarctions were seen probably due to cell micro-thrombi which created obstruction to the blood flow when injected through intracoronary path. In humans, this complication was not seen [36–39].

One disadvantage of intramyocardial injection is the formation of islet-like clusters of stem cells at this level. *Another disadvantage of intramyocardial injection is association with a higher risk of ventricular arrhythmias than with other methods of deliver* [26].

2.1.4. Intramyocardial-transepicardial injection

Epicardial injection is performed using a needle-syringe system under direct visualization of the operated heart. This method is the most used in preclinical research using animal models.

The intramyocardial delivery of stem cells can be achieved by direct injection after open thoracotomy (sternotomy or left thoracotomy). Most of the time this method is used in conjunction

with cardiac surgery such as coronary artery bypass grafting (CABG) or left ventricular assist device (LVAD) [40–42]. Myocardial retention rates have been similar to those of a transendocardial approach [1, 3, 43]. The advantage is that in some types of necrosis: intramyocardial, epicardial, or combined, targeted tissue can be reached only through a direct epicardial access.

Other options not so invasive like open chest thoracotomy have been tried: minimally invasive lateral thoracotomy using thoracoscopic injection to the epicardium and minimally invasive subxifoidian technique using robotic devices [44].

2.1.5. Intracoronary sinus injection

Another technique to inject stem cells to the heart of animals or humans [45–47] is through the coronary sinus or tributary veins. The percutaneous approach is made through the femoral vein. With the use of a catheter that passes in the right atrium, one can cannulate the coronary sinus and access the middle cardiac vein, the great cardiac vein, or other tributaries of the coronary sinus. For injection, balloon occlusion is needed in order to reduce the washout into the systemic circulation. Comparing with the intracoronary injection, this method has the advantage of lower risk of coronary embolism and injection can be made even in areas with low arterial supply.

3. Electroanatomical mapping using the NOGA system

Intramyocardial injection is the method by which stem cell suspension is directly injected in the myocardium using a needle. This method needs electroanatomical mapping in order to identify the zone of necrosis. Intramyocardial injection enables stem cells to be targeted into this localized area. In patients with new or old myocardial infarction, stem cells are usually injected at the border zone of the infarct with the healthy tissue. This area has a relatively good blood supply to ensure stem cell survival compared to the infarcted area with no blood flow. Intramyocardial injection permits to target zones even with low blood flow. Intracoronary injection instead requires a normal flow through a coronary artery. Intramyocardial injection enables cells to be delivered to areas with a limited vascularity. Because this method has no risk of coronary embolism, larger cells can be used, like skeletal myoblasts, mesenchymal stem cells, and others.

The current system for intramyocardial delivery is the NOGA® XP Cardiac Navigation System (Biologics Delivery Systems Group of Cordis Corporation, a Johnson & Johnson Company). This system is able to perform electromechanical mapping of both left ventricle and right ventricle. Electromechanical mapping permits clear delineation of the targeted area and precise deployment of the therapeutic product [3]. This delivery method has proved to be feasible in the presence of chronic ischemic heart disease and acute myocardial infarction (within 10 days after infarction). The system incorporates an injection catheter and the real-time reconstruction of the heart's endocardial surface in three dimensions using collection of points with spatial, electrophysiologic, and mechanical information.

By this, a left ventricular endocardial map is obtained with electromechanical information that characterizes the underlying tissue and permits to navigate into the heart. This real map helps to precisely localize the injection catheter at the level of necrosis, border zone of necrosis or healthy tissue. The map is constructed by acquiring multiple points at different locations in the left ventricle from base to apex, from inferior to anterior, and from septal to lateral. These anatomical points with electrical value are gated to a surface electrocardiogram. Ultra-low magnetic fields are generated by the system using a triangular magnetic pad placed under the patient and other three patches positioned on the thorax of the patient. Each point sample contains electrical information about local activity such as unipolar voltage and local contractility such as linear local shortening. The resulting tridimensional map of the left ventricle gives information about electromechanical properties of the myocardium and is able to distinguish between ischemic areas (which have low lineal local shortening and preserved unipolar voltage) from infarcted areas (low linear local shortening and low unipolar voltage) [1].

3.1. Transfemoral approach with the NOGA system

Most of the studies using NOGA tridimensional system for intramyocardial delivery used the conventional right femoral approach in order to reach the endocardium. However there are cases with tortuous, angled right iliac artery, it implies difficulty in advancing the mapping catheter to the left ventricle and manipulating it inside the cavity. When the right femoral artery cannot be used, then left artery can be tried, and in case of failure, other arteries (like radial) or veins (femoral vein with transseptal approach) can be accessed.

3.2. Transradial approach with the NOGA system

The NOGA mapping system was designed for the transfemoral approach. This precludes its use in patients who have peripheral vascular disease with intense calcified and tortuous iliac or femoral arteries. Because NOGA catheters are advanced into the LV without using a guidewire, manipulation can be difficult inside the heart especially when arteries are tortuous and do not permit free rotation and angulation of the catheter. Manipulation can be even more challenging when using a stiffer injection catheter. Although there has been no formal recommendation concerning alternative approaches in patients with peripheral arterial tortuosity, there are reports showing a benefit of using radial artery or femoral vein and transseptal approach in this category of patients. In the case of tortuous iliac or femoral arteries, the brachial access could be taken in order to avoid procedural complications.

4. Perspectives for 2017–2020

To date, there are still many unanswered questions regarding delivery methods in stem cell therapy. Some of these questions will be answered in the ongoing trials. Larger double-blinded placebo-controlled clinical trials are needed to elucidate whether it is trans-aortic or transseptal approach. It is the best method to reach different zones of endocardial necrosis. In

cases of intramyocardial or epicardial necrosis, epicardial approach should be compared with endocardial one. Brachial can be an option for patients who have peripheral vascular disease with impossible femoral approach. Novel biomedical *engineering* is used in several emerging technologies for delivering stem cells to the heart. These include transplantation of stem cells as tissue-engineered constructs [80]. All these delivery options will permit a more individual and personalized stem cell treatment strategy in patients with ischemic heart disease.

5. Conclusions

There are several methods of cell delivery to the heart. However, none of these are perfect for every type of ischemic disease or every stem cell type. Advantages and disadvantages of each technique will help in tailoring the treatment protocol for every individual patient and will aid in planning future clinical trials. Combining these techniques (e.g. intracoronary artery + intracoronary sinus injection) could reduce washout and increase adhesion to the necrosed area. Emerging new approaches need to be also developed for the future of clinical success using stem cell therapy administered for ischemic heart disease.

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