DE GRUYTER OPEN

Journal of Interdisciplinary Medicine

REVIEW

CARDIOLOGY // IMAGING

Magnetic Resonance Imaging of Myocardial Function Following Intracoronary and Intramyocardial Stem Cell Injection

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ARTICLE HISTORY

Received: 29 October, 2016
Accepted: 22 December, 2016

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ABSTRACT

Stem cell-based therapy is a new therapeutic option that can be used in patients with cardiac diseases caused by myocardial injury. Cardiac magnetic resonance imaging (MRI) is a new noninvasive imaging method with an increasingly widespread indication. The aim of this review was to evaluate the role of cardiac MRI in patients with myocardial infarction undergoing stem cell therapy. We studied the role of MRI in the assessment of myocardial viability, stem cell tracking, assessment of cell survival rate, and monitoring of the long-term effects of stem cell therapy. Based on the current knowledge in this field, this noninvasive, in vivo cardiac imaging technique has a large indication in this group of patients and plays an important role in all stages of stem cell therapy, from the indication to the long-term follow-up of patients.

Keywords: stem cells, myocardial infarction, magnetic resonance imaging, noninvasive, in vivo

INTRODUCTION

Acute myocardial infarction (AMI) is the most common cause of mortality and morbidity in Europe.[1] In AMI, heart muscle tissue is regionally destroyed, leading to the appearance of severe heart failure and, in some cases, death. New treatment methods, such as percutaneous coronary angioplasty, cannot always prevent ventricular remodeling following an AMI, which can occur in as many as 60% of the patients.[2] Furthermore, it is estimated that left ventricular ejection fraction (LVEF) is increased by approximately 3% to 4% only after a percutaneous coronary intervention (PCI).[3] Cardiac MRI is a newly established technique that can identify with high accuracy the viability of the myocardial tissue, which influences the treatment management of patients with myocardial infarction.[4] The stem cells can be labeled with different modalities and can be tracked with various imaging techniques such as magnetic resonance imaging (MRI), single

photon emission computed tomography (SPECT), and positron emission tomography (PET).[5,6]

The treatment of myocardial damage caused by acute or chronic myocardial ischemia is limited.[7] In the last decades, radiologists and cardiologists have developed new methods for the treatment of myocardial dysfunction caused by ischemia, and cell replacement therapy is a promising option in this patient population.[8] The cells can be delivered through the coronary arteries, coronary veins, or peripheral veins, the most often used methods in clinical practice being intracoronary, endocardial intra-myocardial, and epicardial intra-myocardial application of stem cells.[9,10] Several different types of cells have been explored, such as embryonic stem cells, mesenchymal stem cells, or cardiac stem cells, each with their own benefits and limitations.[11] Clinical and experimental studies have demonstrated the capacity of stem cells in cardiac repair and regeneration of the injured heart muscle.[12] The majority of reviews in this field deal with the type of stem cells, implantation technique, and the mechanism of action of the implanted cells. This review focuses on the role of MRI-based, noninvasive, in vivo assessment in stem cell therapy and on the outcome of patients following this intervention.

THE ROLE OF MRI IN STEM CELL THERAPY

The assessment of myocardial viability with MRI

MRI is a technique that provides excellent spatial and moderate temporal resolution for imaging cardiac function and anatomy. This noninvasive method allows a detailed delimitation of cardiac tissue from the surrounding soft tissues.[13] Cardiac MRI is capable to assess the scar burden, coronary perfusion, and contractile reserve of the myocardium with high sensitivity and specificity.[14–16] MRI, using gadolinium-diethylenetriamine pentaacetic acid contrast agents, is able to identify the infarcted area of the myocardium, by visualizing excess accumulation of gadolinium in this area.[17,18] Another major indication of MRI after MI is for recognizing the potentially viable myocardial tissue in the infarcted area, and to distinguish the recent MI from the fibrosis of an old infarction.[19] Dash *et al*. demonstrated that the LGE and Mn uptake are capable to define the peri-infarct zone.[20] Several studies demonstrated the importance of delayed-enhancement MRI (DE-MRI) in the early detection of inviable myocardial tissue after MI.[21,22] In 1999, Kim *et al*. were the first who demonstrated that DE-MRI performed before coronary revascularization, can predict the functional improvement of the myocardium.[23] Lowie *et al*. also considered that DE-MRI is extremely useful for the differentiation of potentially reversible ventricular dysfunction from irreversible dysfunction.[24] Romeo *et al*. presented that DE-MRI has the highest sensitivity of 95% with a specificity of 51%, a positive prediction value of 69%, and a negative prediction value of 90% for predicting regional wall motion improvement after intervention.[25] Cwajg *et al*. demonstrated that myocardium thinning is not equal with the absence of viability, as in some cases the thinned regions can improve after revascularization.[26] Shah *et al*. studied 1,055 patients with coronary artery disease in whom they performed DE-MRI and found that 201 (19%) patients had regional wall thinning. Limited scar burden was present in 18% of thinned regions. In these cases, they noticed a significant improvement of contractility and resolution of wall thinning after revascularization.[27] Tadamura *et al*. demonstrated in their cohort trial on 29 patients that DE-MRI and PET/SPECT are equally effective in determining myocardial viability.[28] Furthermore, several studies demonstrated the superiority of DE-MRI to dobutamine stress echocardiography in patients with arrhythmias.[29]

Stem cell tracking with CMRI

In addition to the previously described applications, magnetic resonance is able to track the injected stem cells using novel contrast agents, following the direct and indirect labeling of the injected stem cells.[30] MRI contrast agents commonly used for the direct labeling of stem cells are represented by two main categories. The first group includes contrast agents based on gadolinium and manganese, such as manganese chloride ($MnCl_2$) and gadolinium chelating agents (Gd-DTPA).[31,32] These agents offer mainly T1-positive contrast effects. The second major group consists of paramagnetic and super paramagnetic contrast agents based on iron oxide nanoparticles that have strong T2/T2*-negative effects.[33,34] The cardiac MRI detection of labeled stem cells is affected by MRI sequence, intracellular iron distribution, magnetic field intensity, spatial resolution, and surrounding tissue heterogeneity.[35] The use of paramagnetic/superparamagnetic iron oxide particles in stem cell tracing has been demonstrated to be associated with a high sensitivity and specificity.[30] The indirect labeling of stem cells with MRI reporter gene is highly valuable in long-term studies of labeled cell differentiation, migration, survival, and proliferation in vivo.[36] Reporter genes can be divided into two major groups based on their reporter mechanism.[37] The

genes in the first group lead to overproduction of intracellular enzymes such as β-galactosidase, creatinine kinase, tyrosinase, cytosine deaminase, and arginine kinase.[38] The second group is characterized by overexpression of iron-regulatory elements such as ferritin and/or the transferrin.[39] Naumova *et al*. found that overexpression of ferritin heavy chain did not affect cell proliferation or viability, and neither did modify the expression of surface markers of multi-potency and cardiac lineage.[39,40] Moriel Vandsburger considered in his review that MR reporter gene imaging is a very useful technique that can promote stem cell therapy in patients with ischemic heart disease.[41] Lu *et al*. also considered that with the help of this new imaging technology, stem cell therapy will play a major role in the treatment of myocardial infarction.[30]

The assessment of cell survival and differentiation using MRI

The new in vivo imaging techniques have revealed that the majority of stem cells die shortly after transplantation.[42] Chen *et al*. found that myocardial engraftment of cells is less than 10% within 48 hours and is not influenced by the number of injected cells, delivery route, or the type of cells.[6] An important problem of all cell-labeling techniques is that the presence of the label in the area of interest is not equal with the survival of the cell. The label can persist after the death of the injected cell in inflammatory cells or in free form in the myocardium. David and Sosnovik considered that special imaging methods are needed to evaluate the survivor rate of stem cells after implantation.[43] For this purpose, MR-detectable and PET-detectable probes are used such as stem cells labeled with reporter genes. These methods are feasible, but the genetic manipulation and injection of cells is expensive and still difficult to achieve. In 2006, Cao *et al*. presented the first study regarding the role of stably express of fluorescence, bioluminescence, and PET reporter genes in the visualization of embryonic stem cell survival, migration, and proliferation after cardiac delivery.[44] Several researchers demonstrated that macrophages containing labeling agents released by dead labeled stem cells can persist in the myocardium for up to 5 weeks,[45,46] and can be confused with living cells, being interpreted as robust cell survival. These studies used stem cells labeled with ferumoxides, and the cells were genetically modified to overexpress β-galactosidase. After three weeks, they performed an MRI and identified the presence of iron in the myocardium. At the same time, X-gal stain could not identify any surviving β-galactosidase–positive cells.[47] Partlow *et al*. affirmed that functional magnetic resonance imaging (F-MRI) is capable of identifying cells labeled with perfluorocarbon particles. This method has a high sensibility and specificity in the determination of living cells, with reduced false-positive results.[48]

Monitoring the long-term effect of stem cell transplantation

It has been proposed that the new in vivo imaging techniques have an important role in understanding the mechanisms of pathological remodeling and attenuation after stem cell therapy.[42] In the majority of cases the implanted stem cells lead to a decrease of myocardium fibrosis and thereby to an improvement of LV dilatation and of the diastolic and systolic function of the heart.[49] Left anterior descending artery infarction, a higher number of implanted cells (≥107), chronic occlusion, and cell injection at least 1 week after myocardial infarction are predictors of improvement in LVEF after stem cell implantation.[50] Studies most often follow-up patients 1 year after intervention. Jay *et al*. followed 95 patients in whom CMRI was performed in the 6th and 12th months. They found that LV function increased in the infarct and border zones between baseline and 6 months in both the placebo and the bone marrow cell (BMC) group, but they did not see any increase between months 6 and 12.[51] Konstantinos *et al*. reported in 2014 the complete 6-month and partial 12-month results of the CADUCEUS trial. In this study, they used MRI to determine LV scar mass, LV viable myocardial mass, global function, LV volumes, regional function, and scar size. They found that intracoronary administration of autologous cardiosphere-derived cells (CDC) did not raise significant safety concerns.[52] Several meta-analyses showed that intracoronary BMC infusion in myocardial infarction patients has moderate positive results on the recovery of LV function.[53,54] In a meta-analysis that included six trials, BMC therapy led to a modest but statistically significant improvement of LV function in patients after myocardial infarction.[55] In several studies the ejection fraction (EF) is used as a marker of LV function improvement. While the early trials of stem cell therapy used echocardiography to determine the EF of the heart, recent trials replaced echocardiography with MRI for this application.[43,56]

CONCLUSION

Stem cell therapy is a new therapeutic option for cases of heart failure caused by myocardial ischemia after acute myocardial infarction. Cardiac MRI plays an important

role in the therapeutic management of these patients, being capable to identify and to distinguish the scarred, nonviable myocardium from the viable one. Cardiac MRI is considered nowadays a gold standard technique because it is capable to distinguish with high sensitivity and specificity between these two types of myocardial tissue. Compared with other noninvasive imaging techniques, cardiac MRI is capable to provide high definition images of the anatomical and functional character of the heart in real time, without the need for any radiation. Therefore, this noninvasive imaging technique plays an important role in the evaluation of cardiac stem cell therapy. Cardiac MRI is also able to track the directly or indirectly labeled stem cells after injection, regardless of the implantation method. Data from the literature demonstrated that this is a safe method, it has a high sensitivity in short-term follow-up, and it can identify with high accuracy the location of injected stem cells. Stem cell labeling with reporter genes represents a new method which is yet under investigation, and which can have an important role in long-time follow-up and the determination of cell viability and differentiation after infusion.

Cardiac MRI can play an important role in all the stages of stem cell therapy, from indication to long-term follow-up of patients; however, further studies are needed to demonstrate the real advantages of this noninvasive imaging technique in this group of patients.

CONFLICT OF INTEREST

Nothing to declare.

ACKNOWLEDGEMENT

This research was supported via the research grant no. 103545/2016, contract number 43/05.09.2016, entitled "High performance multimodal MRI/CT imaging-platform, for applications in computational medicine, nanoparticles and hybrid imaging for the research of atherothrombotic disorders – CARDIO IMAGE" financed by the Romanian Ministry of European Funds, the Romanian Government and the European Union.

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