

# Computed Tomographic Assessment of Coronary Arteries in Patients Undergoing Stem Cell Therapy Following an Acute Myocardial Infarction

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## ABSTRACT

Despite of numerous treatment strategies developed in the last years, ischemic heart disease remains the leading cause of death around the world. Acute myocardial infarction (MI) causes irreversible destruction to the myocardial tissue, which is replaced by fibroblast cells, leading to the formation of a dense, collagenous scar, a non-contractile tissue, and often to heart failure. Stem cell therapy seems to represent the next therapeutic method for the treatment of heart failure caused by myocardial infarction. Several international trials proved the beneficial outcome of the intracoronary infusion of bone marrow-derived stem cells, improving left ventricular systolic function and clinical symptomatology. Many noninvasive imaging procedures are available to evaluate the beneficial properties of stem cell therapy. Most studies have demonstrated the role of multislice computed tomography (MSCT) in evaluating left ventricular parameters such as end-diastolic and end-systolic volumes and ejection fraction, or to quantify myocardial scar tissue. In this review we will discuss the usefulness of MSCT for the assessment of coronary arteries, new tissue regeneration, and evaluation of tissue changes and their functional consequences in subjects undergoing stem cell treatment following MI.

**Keywords:** stem cells, myocardial infarction, computed tomography

## INTRODUCTION

Despite of numerous pharmacological interventions and invasive therapeutic techniques available, ischemic heart disease (IHD) and especially acute myocardial infarction (AMI) represent the leading cause of morbidity and mortality worldwide.<sup>1,2</sup> AMI leads to irreparable destruction of the myocardial tissue, because the heart has a restricted ability to produce new cardiomyocytes. Following myocardial injury, endothelial and fibroblast cells transform into a solid

collagenous scar to sustain the structure of the myocardial wall. However, this scar is inflexible and non-contractile, and frequently leads to the development of heart failure (HF).<sup>3</sup>

Stem cells (SC) have been often suggested as the next therapeutic method for the treatment of HF secondary to AMI.<sup>4</sup> SC have the capacity to differentiate into numerous specific types of cells. SC can be classified into embryonic cells and adult stem cells.<sup>5</sup> Moreover, adult stem cells can be categorized into tissue-specific and bone marrow-derived cells.<sup>6</sup> In cell therapies, the use of autologous bone marrow-derived stem cells seems to be among the most essential elections in clinical use due to ease of obtainment and absence of immune rejection. The intracoronary infusion of SC recruited from the bone marrow in patients following a myocardial infarction has been proved by several international trials to have a beneficial outcome, such as improvement in the left ventricular contractility and symptomatology.<sup>7,8</sup>

Several noninvasive imagistic methods are utilized to explore the therapeutic role of stem cell transplant in pre-clinical and clinical situations. Earlier research has demonstrated that cardiac multislice computed tomography (MSCT) can determine the volume of the left ventricle and the ejection fraction, and can exactly quantify myocardial scar tissue. The aim of this manuscript was to overview the usefulness of MSCT for the assessment of coronary arteries in subjects undergoing stem cell therapy after myocardial infarction.

## STEM CELL EXTRACTION AND TECHNIQUE FOR INTRACORONARY INJECTION

First, all subjects undergo a careful clinical examination including detailed medical history, routine laboratory testing, echocardiography, and electrocardiography. Stem cell extraction is performed with the patient under general anesthesia, at the level of the posterior iliac crest. About 300 to 500 milliliters of bone marrow is collected, and 10 IU/ml of heparin is applied the day before the injection. Using apheresis techniques, a concentrated solution of stem cells can be obtained, which is mixed with a solution of acid citrate dextrose to prevent coagulation. After evaluating the patency of the implanted stents using coronary angiography, the solution containing the SC is injected repetitively in the coronary arteries in small dosages of 2–3 ml. During the injection, a balloon is inflated in the coronary artery, proximal to the site of infusion, for one minute, in order to prevent the washout of the cells.<sup>9</sup>

## COMPUTED TOMOGRAPHY FOR THE ASSESSMENT OF STEM CELL THERAPY

Cardiac imaging methods hold a major part in the assessment of innovative therapeutic approaches, including stem cell implantation, and show promising results regarding the exploration of new strategies to treat heart disease. Stem cell therapy has been broadly explored as a possible treatment option for MI and heart failure.<sup>10</sup> Besides the routinely used echocardiography, cardiac magnetic resonance is one of the preferred imaging methods for providing a reliable evaluation of infarct size, ejection fraction, and left ventricular function, which are commonly accepted surrogate endpoints in stem cell clinical trials. The use of cardiac magnetic resonance in clinical situations is restricted in subjects with pacemakers, metal implants, and severe claustrophobia; besides, it is a relatively complex and time-consuming technique.<sup>11–13</sup> Multidetector computed tomography has shown several developments in spatial and temporal resolution and has emerged as a new tomography cardiac imaging modality.<sup>14</sup>

Coronary computed tomography is a widely accepted imaging method for the assessment of ischemic heart diseases, as well as for the evaluation of global cardiac function parameters. Many international trials have evaluated the improvements of left ventricular function, clinical symptomatology, and myocardial scar formation after long-term stem cell therapy in post-myocardial infarction patients.<sup>15,16</sup> This imaging tool is a highly validated and non-invasive technique for the evaluation of coronary atherosclerotic disease.<sup>17,18</sup> MSCT angiography permits a strong qualitative and quantitative evaluation of atherosclerotic lesions. Recently, semi-quantitative plaque-analyzing tools offer a great intra- and inter-observer coronary plaque description and quantification, which have been confirmed by intravascular imaging techniques such as intravascular ultrasound and virtual histology.<sup>19,20</sup>

Coronary artery calcium scoring (CACS) has a major role in evaluating calcified plaque burden, which has a remarkable prognostic accuracy in predicting cardiovascular events in subjects with little to no symptoms and intermediary cardiovascular risk.<sup>21,22</sup> Many studies suggested that total plaque burden assessed by MSCT has a better predictive capacity than separate plaque characteristics. Semi-quantitatively, the overall plaque burden is defined by the sum of segments involved by any atherosclerotic plaque.<sup>23</sup> Automatic plaque quantification, such as lumen and plaque volumes as well as the degree of stenosis analyzed with MSCT angiography, evidenced a very good correlation with virtual histology intravascular ultrasound.<sup>24</sup>

An earlier study conducted by Benedek *et al.* was the first human trial to evaluate the longstanding decrease in the total plaque burden, number of coronary lesions and calcium scores in the treated arteries using multislice-64 computed tomography in the four-year follow-up after stem cell therapy. Using the 17-segment coronary tree model, 306 segments have been scanned and 145 plaques were assessed among the 18 patients. The results showed that total plaque burden was considerably reduced in the vascular segments that had been infused with bone marrow-derived SC compared to the control segments ( $702 \text{ mm}^3$  vs.  $1,465 \text{ mm}^3$ , with a mean value of  $87.75 \pm 12.38 \text{ mm}^3$  vs.  $183.12 \pm 16.78 \text{ mm}^3$ ,  $p < 0.0001$ ). From the 10 plaques that had been infused with SC, only 2 presented significant coronary artery stenosis ( $>50\%$ ). Comparing these 10 plaques with the 21 plaques found in the segments treated with placebo, the average degree of stenosis per artery was  $0.25 \pm 0.46$  in group 1 vs.  $1.0 \pm 0.75$  in group 2 ( $p = 0.03$ ). This result suggests a reduced progression of atherosclerosis in the territories injected with SC.<sup>9</sup>

When evaluating coronary calcium scoring in the segments of both groups, the summation of total CACS was 295 in the SC group and 796 in the control group, with mean values of  $36.87 \pm 12.4/\text{patient}$  vs.  $99.5 \pm 7.82/\text{patient}$  ( $p < 0.0001$ ). It is evident from these results that calcium scores are lower in the coronary segments that had been treated with SC infusion. CACS evaluated on coronary CT angiography is generally considered to be a biomarker that illustrates cardiovascular risk. The remark that SC therapy decreases calcium accumulation in the wall of the coronary arteries offers innovative research hypotheses that address the local effects of SC on the endothelium.<sup>25</sup>

The assessment of atheromatous lesions in the coronary arteries using multislice computed tomography angiography, 4 years following SC infusion in post-myocardial infarction subjects suggests that SC infusion has a beneficial influence on the atherosclerotic process, demonstrated by an important decrease in the plaque volume and count, as well as calcium scoring in coronary segments treated with SC.<sup>9</sup>

Previous studies demonstrated that besides the main role of MSCT in the assessment of coronary arteries, it can be used to evaluate left ventricle global functions and quantify myocardial scar tissue after intracoronary stem cell therapy. Karl *et al.* showed on animal models the use of MSCT in determining end-systolic and end-diastolic left ventricle volumes, ejection fraction, and estimation of infarct extension by quantifying myocardial scar tissue after bone marrow-derived stem cell therapy. MSCT demonstrated a diminution of infarct size from  $14.3 \pm 1.2\%$  to  $10.3 \pm 1.5\%$  ( $p = 0.005$ ) of left ventricle mass in animals

randomized to SC therapy, with a significant difference between placebo and the SC-treated group. Left ventricle ejection fraction assessment showed a similar significant increase at 24 weeks in the SC-treated group from  $32.6 \pm 2.2\%$  to  $36.9 \pm 2.7\%$  ( $p = 0.003$ ) and a decrease in the placebo group from  $33.3 \pm 1.4\%$  to  $29.1 \pm 1.5\%$  ( $p = 0.01$ ). Left ventricular end-systolic and end-diastolic volumes presented identical results.<sup>26</sup>

Infarct size, LV end-diastolic volumes, and ejection fraction analyzed by MSCT were comparable with those analyzed by cardiac magnetic resonance acquisitions ( $r = 0.7$ ,  $r = 0.82$ , and  $r = 0.902$  respectively,  $p < 0.001$ ). These results reported in animal experiments proved the use of MSCT in preclinical and clinical research as a noninvasive imagistic procedure for assessing the therapeutic role of innovative myocardial treatment methods.<sup>26–28</sup>

Another study by Luciano *et al.* showed that MSCT angiography offers important details about the change in scar morphology and tissue characteristics after SC therapy in large animal models. MSCT evidenced the presence of a border of tissue at the endocardial stratum within the first week, if the density of myocardial infarction scar and of this tissue were similar to that of distant myocardium ( $130.9 \pm 31.6 \text{ HU}$ ). This rim increased in thickness in the viable subendocardial tissue in the SC-treated group from  $1.02 \pm 0.16 \text{ mm}$  to  $2.02 \pm 0.28 \text{ mm}$  ( $p = 0.028$ ) over an 8-week interval. There was a clear delineation between tissue densities of viable myocardial tissue and infarction scar. The histological interpretation revealed that this rim of tissue at the endocardial region of the infarcted area encompasses heart myocytes that are smaller than normal cardiomyocytes located in a distant territory from the infarcted zone. These results exclude myocyte hypertrophy as a reason of increased thickness in the subendocardial rim and suggest renewal of the myocardial fibers in this area.<sup>13,29,30</sup>

## CONCLUSIONS

Advanced techniques allow more precise analysis of the favorable outcome of stem cell therapy by using cardiac magnetic resonance, positron emission tomography or multislice computed tomography. The assessment of coronary wall structure and atheromatous plaque morphology by MSCT after long-term follow-up in post-myocardial infarction subjects treated with stem cells indicates that SC therapy has a beneficial influence on the atherosclerotic process. Clinical studies prove the use of MSCT as a prominent noninvasive imaging method for the evaluation of plaque count, plaque volumes and calcifications in coronary segments treated with novel therapeutic meth-

ods. Many animal experimental studies highlight the value of MSCT, not only in the evaluation of coronary arteries, but also in clarifying the mechanism underlying new tissue regenerative therapies.

## CONFLICT OF INTEREST

Nothing to declare.

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