

How to predict recovery after cell therapy in post-MI patients?

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Abstract

Cell replacement therapy has been intensively investigated as a new tool in patients with ischaemic heart disease (IHD) and in particular in those treated by reperfusion therapy in the acute phase of myocardial infarction (MI). Cardiac cell transfer and cytokine mobilisation have been originally proposed with the goal of myocardial regeneration and the emphasis has been focused on anti-remodelling effect of this therapeutic approach. Initial phase 1 studies have indicated feasibility, safety and improved functional left ventricular (LV) recovery after stem cell transplantation in patients treated by reperfusion therapy in the acute phase. More recently, results of several prospective, placebo controlled trials have been published with discrepant findings.

Several approaches have been proposed for the early detection of patients at risk for post-MI LV remodelling. We discuss in this article the possibilities of screening of post-MI patients for cell therapy for cardiac repair as well as problems with the choice of parameters to be analysed for the assessment of the efficacy of cell therapy in this subset of patients.

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Introduction

Heart failure has become a very important problem in western countries with the number of patients presenting with its symptoms increasing exponentially. The large majority of patients with heart failure have the ischaemic heart disease as the underlying pathology¹. The occurrence of MI is associated with 10-fold greater risk of developing heart failure compared with a normal population². In patients surviving an acute MI, the development of clinical signs of heart failure is frequently preceded by an asymptomatic period of left ventricular enlargement. This dynamic process, called left ventricular remodelling, is observed in relatively important proportion of patients despite state-of-the-art therapy including early reperfusion, angiotensin-converting enzyme-inhibitors (ACE-I) or angiotensin receptors blockers, beta-blockers and statins^{3,4}.

Transfer of autologous bone marrow-derived or circulating progenitor cells might reinforce LV function recovery. More than truly regenerative potential, the possible anti-remodelling effect of this therapeutic approach has been recently brought up⁵. Potential positive effects on left ventricular remodelling include paracrine anti-apoptotic effects of transferred cells, enhanced neo-angiogenesis, and survival of hibernating myocardium with limitation of infarct expansion. Phase 1 studies have indicated improvement in global and regional left ventricular function⁶⁻⁸. More recently, results of several prospective, placebo controlled trials have been published with discrepant findings⁹⁻¹³.

There are several questions concerning the number and phenotype of infused cells, their homing capacity in the myocardium and repair potential depending on the age of patients and on the time of cells transfer. There are also important issues concerning the selection of patients which could be the best candidates for cell replacement therapy and parameters of left ventricular function to be analysed for the assessment of its efficacy. We discuss in this article the last two of these problems.

Left ventricular function evolution after myocardial infarction

There is a great heterogeneity in left ventricular function evolution in patients recovering from acute MI. The natural clinical outcome of acute myocardial infarction depends upon a number of important factors including initial infarct size, its degree of transmural, infarct location, pre-existence of collateral circulation to jeopardised area and number of significantly stenosed coronary arteries. During coronary occlusion most, if not all, of the infarct related territory becomes dysfunctional. After spontaneous, or more frequently therapeutic reperfusion, this functional impairment can recover completely or partially, or progress over time. A complete recovery of contractile regional dysfunction was observed in 22% of patients followed serially by echocardiography in the HEART study¹⁴. In the same study, partial recovery occurred in almost 40% of patients. This regional evolution was associated with a variable evolution of global ejection fraction. Any improvement of global LV ejection fraction was observed at 3 months in 66% of patients with mean change in the whole population of $4.5 \pm 9.8\%$. The recovery of LV ejection fraction is associated not only with the recovery of initially dysfunctional myocardium, but also with compensatory dilation

of LV chamber, observed in the study of Solomon et al¹⁴ in 32% of patients. Whether patients who experience remodelling despite improvement in ventricular function are at increased long-term risk remains to be determined.

The LV dilation can be observed in the very early phase of evolution after MI, as well as in the late phase. Early remodelling occurs mainly in the infarct and peri-infarct zone and is called infarct expansion¹⁵. Late enlargement is related to the changes in non-infarcted regions and global progressive changes in LV size, shape, muscle mass, and function.

Early remodelling that occurs during the hospital phase is not necessarily progressive, and is not necessarily associated with progressive ventricular dysfunction. In the GISSI-3 echo substudy¹⁶ early LV dilation was observed in 41% of patients; the majority of them experienced moderate enlargement (5%-20% increase of end diastolic volume). Importantly 92% of 115 patients with severe early dilation (>20%) did not show further progression of LV enlargement between hospital discharge and the 6 month follow-up. The global ejection fraction decreased slightly in this subgroup during the hospital stay from $47 \pm 7\%$ to $43 \pm 8\%$ and remained stable afterwards. In contrast, late remodelling is associated with progressive deterioration of global ventricular function over time. In the same study, moderate LV enlargement was observed in 28% and severe dilation in 16% of patients. Smaller pre-discharge end diastolic volume, greater regional wall motion abnormality, and the presence of mitral regurgitation were the independent predictors of severe late LV dilation in multivariate analysis.

A 20% increase in end diastolic LV volume was proposed by Bolognese et al as a cut-off value of remodelling based on the upper 95% CI of the intra-observer variability of echocardiographic measurements¹⁷. The prevalence of end diastolic volume enlargement >20% in patients with reperfused MI is estimated at 20%-40%^{16,18-22}. This degree of change is associated with the worsening of long-term outcomes. In this study, patients with LV remodelling had a higher 5 year mortality rate (14% vs 5%, $p=0.005$) and cumulative 5 year combined event-rate (18% vs 10%, $p=0.025$) than those without it. Mengozzi et al¹⁸ have reported, using the same cut off value, that 32% of patients with LV remodelling suffered from congestive heart failure during the 6 months follow-up as compared to 0% in the patients without this condition ($p=0.0001$). The end systolic volume enlargement is also considered as an important prognostic indicator in patients with chronic ischaemic heart disease²³. End systolic volume dilation seems be delayed comparing to the end diastolic volume dilation, at least in patients treated by reperfusion therapy in the acute phase, followed by a modern "anti-remodelling" treatment, as found in the study of Savoye et al¹⁹. Simultaneous end systolic and end diastolic volume enlargement occurring in the first 6 months after an acute event is associated with the worsening of EF and lack of recovery of RWMA. This phenomenon concerned 33% in a group of 75 patients treated by primary angioplasty in our institution²⁴. Currently, the reproducibility of measurement of the LV volumes and function using echocardiography or magnetic resonance imaging is much higher^{16,25}. Whether a lesser degree of LV enlargement is associated with the worsening of outcome remains to be assessed.

Detection of patients at risk for post-MI LV remodelling

The extent of remodelling is proportional to the mass of infarcted myocardium, the patency of the infarct-related artery, the quality of microcirculation in the infarct area, and ventricular loading conditions. Because the initially dysfunctional myocardium consists of a mixture of necrosed, stunned, and eventually hibernating muscle, the initial assessments of the infarct size often overestimate the true infarct region. The evolution toward LV remodelling cannot be predicted using simple clinical variables. In patients with initially preserved LV function included in Stent-PAMI study, Mattichak et al²⁶ was unable to predict LV systolic deterioration (defined as a decrease of >15% of global ejection fraction) using baseline clinical and angiographic and outcome variables. Quantitative echocardiography, creatine phosphokinase, haemodynamic status, infarction location, patients' history and other factors can be combined to improve the prediction post MI remodelling. An algorithm has been proposed by de Kam et al²⁷ which can predict, with 80% accuracy, whether an infarction will evolve towards remodelling.

With this model they could predict correctly the 6 month LV dilatation risk for 81% of the 7,842 GISSI-3 patients in whom a pre-discharge echo was available.

There is strong evidence that the evolution towards LV remodelling is at least in part related to the impaired tissue reperfusion. This parameter can be evaluated by assessment of ST-segment elevation resolution, myocardial blush on contrast coronary angiography, contrast echocardiography, and magnetic resonance imaging.

ST segment resolution has been initially used for the evaluation of infarct related patency. When the sensitivity analyses are performed, it appears that the resolution of ST elevation by >70% is the optimal threshold for patients with inferior MI, whereas resolution by >50% may be optimal for anterior MI. Subsequently, it has been demonstrated that the resolution of ST elevation is a reliable predictor of the risk of death and development of congestive heart failure after AMI²⁸. With thresholds of >70% reduction for complete, 30%-70% for incomplete and <30% for absence of ST resolution, the probability of congestive heart failure decreases in a stepwise fashion (7.1%, 13.8% and 17.2% respectively). In a study by Nicolau et al²⁹ the presence of ST segment resolution precluded more favourable LV remodelling at 6 month follow-up.

An impaired myocardial blush assessed on the contrast coronary angiography at the end of primary angioplasty is predictive for LV remodelling in the study of Araszkiwicz et al²⁰. Among 145 patients with anterior MI treated by angioplasty, the impaired myocardial blush (grade 0-1) was observed in 41%. The LV remodelling was observed in 32% of these patients, whereas it occurred in 14% of the patients with adequate tissue reperfusion (grade 2-3, $p=0.014$). A promising tool for the early detection of LV remodelling is the myocardial contrast echocardiography (MCE). This technique allows the appreciation of microvascular dysfunction in dyssynergic segments. Intravenous MCE was performed in 63 patients five days after an uncomplicated first AMI in study published by Mengozzi et al¹⁸. Patients were considered to have microvascular impairment if <50% of segments within the infarct-related area showed abnormal contrast effect. With this criterion, the LV remodelling was predicted

by MCE with a very high sensitivity (94.7%) and specificity (90.9%). In this study, 35% of acutely revascularised patients were not adequately reperfused at MCE despite TIMI grade 3 flows, which is close to the 30% of rate of LV remodelling. In contrast in a study of Ujino et al³⁰, the intravenous MCE was less accurate for the prediction of LV remodelling in 47 patients treated by reperfusion therapy in the acute phase of MI. Although the specificity remains also high (patients with normal contrast opacification have the risk of remodelling <5%), the sensitivity is less satisfactory (in case of abnormal opacification, the risk of remodelling is of 35%). The difference in results between these two studies is perhaps due to the different timing of follow-up studies (6 months for Mengozzi and 2 months for Ujino). In a study published by Bolognese et al³¹, 124 patients treated by angioplasty in the acute phase of MI, underwent intracoronary MCE. Microvascular dysfunction was observed in 19% of them. The prevalence of LV remodelling was significantly greater among patients with microvascular dysfunction than among those without (63% vs 11%, $p<0.0001$).

LV remodelling can also be predicted by analysis of mitral deceleration time on Doppler echocardiography. With the cut-of value of <136 ms, Cerisano et al³² were able to predict 6 month LV remodelling with sensitivity of 75%, specificity of 97% and accuracy of 81%. Of interest, in this study, mitral deceleration time predicted remodelling with higher accuracy than the dosage of BNP.

Mannaerts et al³³ analysed by 3D echo in 33 patients 6.4 days after an AMI. Clinical, electrocardiographic and echocardiographic variables were analysed for the early identification of LV remodelling. The baseline 3D sphericity index was, by far, the most predictive variable with a sensitivity, specificity and positive and negative predictive value for a cut-off >0.25 of 100%, 90%, 87% and 100% respectively.

High accuracy in the prediction of LV remodelling was also obtained by Hombach et al³⁴ using the magnetic resonance imaging technique 6 days after AMI in 110 patients, 58% of whom presented ST elevation MI. The combination of three MRI parameters (infarct size, persistent microvascular impairment and transmural extent of necrosis) predicted LV remodelling with the sensitivity of 80% and specificity of 84.6%. An important study assessing the importance of transmural extent of infarction and microvascular obstruction on left ventricular remodelling was recently published by Tarantini et al²¹. The infarct size and transmural extent as well as microvascular obstruction were assessed by contrast-enhanced magnetic resonance imaging, whereas the volumes evolution was evaluated by echocardiography in a group of 76 patients treated by angioplasty in the acute phase of MI. It was seen that 71% of patients had MRI evidence of transmural necrosis in ≥ 1 LV segment, whereas 36% showed severe microvascular obstruction. This latter phenomenon was exclusively observed in segments with transmural (>75% of LV wall thickness) extent of delayed enhancement. LV end diastolic volume enlargement >20% was observed in 37% of patients. Using receiver-operating characteristic curve analysis, 4 LV segments (in the 17-segment model) with transmural necrosis at MRI showed the best sensitivity (70%) and specificity (82%) for major adverse remodelling (AUC 0.80, 95% CI [0.70 to 0.92]). Severe microvascular obstruction did not remain an independent predictor of remodelling when trans-

mural necrosis was included in the model of multivariate analysis. It seems to occur later than transmural necrosis, suggesting that, from pathophysiologic point of view, severe microvascular obstruction lags behind transmural necrosis. These findings are important in view of data published recently by Janssens et al⁹. In this double-blind, randomised trial of intracoronary infusion of autologous bone marrow-derived stem cells (BMS), the presence of microvascular obstruction precluded LV function recovery. In contrast, improved function in the BMS group was observed in segments with the most severe transmural extension of MI (51%-75% and >75%) without microvascular obstruction.

Although scintigraphic imaging techniques are unable to assess the intermediate degrees of transmural MI, we have recently found good correlations between Tc-99m-mibi uptake on SPECT imaging and the most severe transmural extension (>75%) of late enhancement on magnetic resonance imaging as well in the territory of the left anterior descending as in that of right coronary artery³⁵. The predictive value of these findings for LV remodelling is under way. We have also studied a group of twenty nine patients with acute MI and early PTCA by rest Tc-99m-sestamibi ECG-gated SPECT was performed 21±5 days after PTCA¹⁵. Myocardial perfusion was quantified using a semi-automatic sectorial analysis. The patients were separated in two groups according to the absence (group I, n=21 patients) or presence (group II, n=8 patients) of LV remodelling. The perfusion index in the infarct sectors was -2.29 ± 2.9 SD in group I and $-6.40 - 2.85$ SD in group II ($p < 0.01$). With a perfusion cut-off value of -2.46 SD, the sensitivity and specificity of Tc-99m-sestamibi SPECT for the prediction of end systolic volume enlargement was 100% and 62%, respectively. When the functional data from ECG-gated acquisitions was added, sensitivity and specificity were 87% and 86%, respectively. The possibility of prediction of LV remodelling earlier after the AMI with low dose dobutamine by rest Tc-99m-sestamibi ECG-gated SPECT is currently being investigated in our centre.

Taking all this data together, it appears at present time that it is possible to predict adverse left ventricular remodelling after AMI with relatively high accuracy. Patients who are at low risk for remodelling have a good long-term prognosis, and probably will not benefit from cell replacement therapy. The question remains open for patients at high risk of remodelling who present with severe microvascular obstruction. The efficacy of intracoronary delivery of stem cells could be impaired in these cases and other methods of cell delivery might prove to be more useful in these situations.

Which parameter of LV function should be measured for assessment of cell therapy in post-MI patients?

Recently published controlled trials assessing the efficacy of BMC in acute MI have used changes in global LV ejection fraction as a primary endpoint⁹⁻¹¹. The use of this parameter as a surrogate endpoint of thrombolytic therapy in comparative trials was criticised already several years ago by Califf et al³⁷. Lack of correlation between ejection fraction and survival, little change over 6 months, better correlations between volumes evolution and survival, and the effects of compensatory hyperkinesia of non-infarcted regions

on global ejection fractions were the arguments posited against the use of ejection fraction as an endpoint. It is entirely probable that these arguments are still valuable in 2007. Instead, the use of global LV ejection fraction, the analysis of LV volumes, regional wall motion and thickening, as well as infarct size and transmural extension could be used as surrogate endpoints for the efficient assessment of the use of cell stem therapy. If the “anti-remodelling” effect of stem cell therapy is further researched, demonstration of a significant reduction of the proportion of patients with severe end diastolic volume dilation would certainly become an important argument in favour of this approach as well.

Conclusions

A task force of the European Society of Cardiology has recently published a consensus paper concerning the clinical investigation of the use of autologous adult stem cells for us in the repairing the heart³⁸. The use of cell therapy has not been currently recommended for use in routine clinical practice. Several problems in stem cells therapy have been identified, among them being how to measure outcomes. The necessity to find appropriate surrogate endpoints for the assessment of the efficacy of this treatment has been underscored. The selection of patients at risk for the development of left ventricular remodelling, and the use of pertinent surrogate endpoints, would be of great interest for further assessing the place of this therapeutic modality in clinical practice.

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