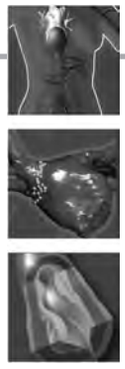

Improving myocardial viability: clinical implications for the use of bone marrow-derived stem cell infusion after acute myocardial infarction

"Improvement of left ventricular ejection fraction is of relevance since left ventricular ejection fraction increase achieved by cell transplantation are within an intriguingly similar range compared with established therapeutic strategies."

KEYWORDS: acute myocardial infarction ■ bone marrow-derived stem cells ■ left ventricular ejection fraction ■ myocardial viability

The treatment of acute myocardial infarction (AMI) has evolved substantially over the past three decades, after an improvement in the mortality rate of AMI due to thrombolytics [1,2] and primary percutaneous intervention for coronary reperfusion [3]. Less than a decade ago, initial reports on the clinical application of mononucleated bone marrow-derived stem cells (BMCs) in patients with AMI opened up a new era of regenerative cardiology and brought with it great enthusiasm [4]. Since then, numerous clinical trials have been carried out, with the aim of assessing the efficacy and safety of bone marrow stem cell therapy. Randomized Phase II trials have demonstrated contradictory results, but finally a significant improvement in cardiac function assessed by left ventricular ejection fraction (LVEF) after cell therapy was highlighted in meta-analyses [5–7]. Some of the discrepancies between some trials may be explained by differences in cell isolation and storage procedures [8]. Nevertheless, there was some evidence to suggest that BMC-based therapy is effective at improving LVEF in certain subpopulations, such as patients with large AMI and decreased LVEF [7,9]. Improvement of LVEF is of clinical relevance, since an increased LVEF achieved with cell transplantation is within an intriguingly similar range compared with established therapeutic strategies [10]. Several mechanisms of action have been suggested, but improvement in myocardial viability had never been assessed before the Bone Marrow in Acute Myocardial Infarction (BONAMI) trial [11].

Myocardial stunning following reperfusion after AMI

Patients with a substantial amount of dysfunctional but viable myocardium are likely to benefit from myocardial revascularization and may demonstrate improvement in regional and global contractile function, symptoms, exercise capacity and long-term prognosis [12]. Nonviable myocardium will usually not resume contractile function after standard revascularization strategies [13]. After rapid reperfusion following acute myocardial infarction, the heart suffers from an alteration of myocardial viability defined as hibernation or a phenomenon termed myocardial stunning [14]. Myocardial stunning is characterized by a prolonged mechanical dysfunction after coronary reperfusion, despite resumption of normal perfusion by coronary angioplasty. Stunning appears to result from alterations in contractile proteins and the generation of reactive oxygen species that impair contractility or by disturbed cellular calcium homeostasis [15]. Specifically, ischemia may lead to decreased responsiveness of the contractile protein machinery to calcium, calcium overload and excitation/contraction uncoupling because of sarcoplasmic reticulum dysfunction. Both mechanisms may not be mutually exclusive and may represent components of the same process. In humans, the return to functional recovery may require days to weeks [15]. Hence, diagnostic methods to distinguish myocardial viability from necrosis are particularly relevant for clinical investigation and patient management in patients with acute and severe left ventricular (LV) dysfunction after revascularization. For example, the ability to distinguish hibernation from stunning could potentially elucidate the prevalence, natural history and relative importance of these two entities in the development of heart failure associated with ischemic heart disease.

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Methods for myocardial viability assessment

One major limitation for detailed myocardial viability is the lack of a true gold standard definition. Moreover, histopathological verification of viability in patients is impossible. Thus, the ideal methodology to assess myocardial viability would provide accurate noninvasive measurements of perfusion, metabolism and cellular membrane integrity, in addition to systolic and diastolic function, with sufficient spatial and temporal resolution for a detailed reconstruction of the entire LV. Increasingly, attempts at assessing multiple aspects of viable myocardium are being made with various noninvasive technologies.

> "*In several animal studies, bone marrow cell transplantation has induced angiogenesis, prevented ventricular dilatation and improved function.*"

Noninvasive assessment of myocardial viability has been studied using multiple imaging techniques, including single-photon emission computed tomography (SPECT), MRI, PET and dobutamine stress echocardiography. These techniques have been extensively evaluated for assessment of viability and prediction of clinical outcome after myocardial revascularization. SPECT imaging uses various tracers to assess perfusion and cell integrity as hallmarks of viability. This technique is widely used and available in most centers, with a reproducible quantitative assessment of viability expressed as a percentage of tracer intake for each myocardial segment. Cardiac MRI is now considered as a gold standard for the evaluation of cardiac function and LV remodeling owing to its high reproducibility and low inter-/intra- observer variability. When imaging at the acute phase of MI, cardiac MRI and SPECT imaging do not evaluate the same pathophysiological pattern. Detection of MI by MRI requires first myocardial gadolinium wash-in when injected. Accordingly, MRI results reflect the integrity of microvasculature. Then, contrast is based on washout differences of contrast agent between injured myocardium and remote regions. It relates to an increased distribution volume related to increased extracellular space and cell membrane rupture (necrosis). Thus, post-gadolinium cardiac MRI, which is performed most commonly 10 min after injection in reperfused AMI, demonstrates a mix of necrosis and myocardial edema (i.e., myocardial damage) while thallium-201 SPECT impairment demonstrates, from a metabolic point of view, the absence of cellular viability (i.e., myocardial salvage). The increase in extracellular space (resulting from necrosis but also myocardial edema) leads to an overestimation of MI size by MRI in the order of 10–15% in the acute phase. Both experimental and clinical studies indeed demonstrated the decrease of myocardial late enhancement a few weeks after MI, and once edema disappeared replacement fibrosis becomes the only mechanism responsible for an increase of extracellular space [16].

Implication of bone marrow-derived stem cells in the recovery of myocardial viability

Alteration in myocardial viability is a logical target for cell therapy to accelerate recovery of contractile left ventricular function. However, so far, little is known about the mechanisms of action when autologous bone marrow-derived stem cells are targeted to the infarct zone after reperfusion. In several animal studies, bone marrow cell transplantation has induced angiogenesis, prevented ventricular dilatation and improved function [17]. In clinical studies, modern noninvasive bio-imaging techniques are of paramount importance to evaluate the true extent of myocardial restoration and justify the concurrent use of stem cells. Rest-redistribution thallium 201-SPECT was chosen in the BONAMI trial to evaluate changes in myocardial viability since it provides a good estimate of myocyte cellular membrane integrity. Indeed, 34% (16 out of 47) of patients treated with autologous BMC had improved myocardial viability compared with the control group (16%; 7 out of 43), although this was only statistically significant in multivariate analysis. Importantly, although MRI is sensitive enough to detect myocardial fibrosis, and superior to SPECT in case of small infarct with subendocardial necrosis [18,19], patients who were included in the BONAMI trial suffered from an inaugural large infarction with severe decrease of EF (mean EF of ~36% as demonstrated by radionuclide angiography) and a large scar extent of approximately 40%, as assessed by MRI. In this case of large MI, MRI may not be superior to SPECT in evaluating myocardial viability [18,19].

The commonly hypothesized mechanisms for cell therapy efficacy, namely myocardial regeneration, salvage and local perfusion, should lead to improvement of myocardial viability as a primary event that would later translate into an improvement of LVEF and/or limitation of LV

remodeling. In the BONAMI trial there was no significant improvement of LVEF 3 months after cell therapy, although myocardial viability was enhanced. There is a complex relation between viability and contractility after STEMI, with contractile dysfunction related not only to the balance between necrosis and viability, but also to the extent of metabolic damage in viable myocytes [20]. Hence, recovery of contractility in some but not all regions with preserved metabolic viability might be observed [21]. Interestingly, the strong tendency towards improvement in myocardial viability observed in the BONAMI study can be placed alongside the restoration of microvascular function observed in the REPAIR-AMI cardiac cell therapy clinical trial [9] study and the probable importance of restoring a microvascular function [22]. More than restoration of blood flow; BMCs may act against myocardial stunning and thus accelerate the recovery of cardiac function. Nevertheless, the relationship between cell therapy and cardiac recovery needs further preclinical investigations and large clinical trials.

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Bibliography

1 Bonnefoy E, Steg PG, Boutitie F *et al.*: Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur. Heart J.* 30(13), 1598–1606 (2009).

2 Roncalli J, Brunelle F, Galinier M *et al.*: Pre-hospital fibrinolysis followed by angioplasty or primary angioplasty in acute myocardial infarction: the long-term clinical outcome. *J. Thromb. Thrombolysis* 15(3), 181–188 (2003).

3 Grines CL, Browne KF, Marco J *et al.*: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N. Engl. J. Med.* 328(10), 673–679 (1993).

4 Strauer BE, Brehm M, Zeus T *et al.*: Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation* 106(15), 1913–1918 (2002).

5 Abdel-Latif A, Bolli R, Tleyjeh IM *et al.*: Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch. Intern. Med.* 167(10), 989–997 (2007).

6 Lipinski MJ, Biondi-Zoccai GG, Abbate A *et al.*: Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a collaborative systematic review and meta-analysis of controlled clinical trials. *J. Am. Coll. Cardiol.* 50(18), 1761–1767 (2007).

7 Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM: Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. *Eur. Heart J.* 29(15), 1807–1818 (2008).

8 Seeger FH, Tonn T, Krzossok N, Zeiher AM, Dimmeler S: Cell isolation procedures matter: a comparison of different isolation protocols of bone marrow mononuclear cells used for cell therapy in patients with acute myocardial infarction. *Eur. Heart J.* 28(6), 766–772 (2007).

9 Schachinger V, Erbs S, Elsasser A *et al.*: Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N. Engl. J. Med.* 355(12), 1210–1221 (2006).

10 Reffelmann T, Konemann S, Kloner RA: Promise of blood- and bone marrow-derived stem cell transplantation for functional cardiac repair: putting it in perspective with existing therapy. *J. Am. Coll. Cardiol.* 53(4), 305–308 (2009).

11 Roncalli J, Mouquet F, Piot C *et al.*: Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial. *Eur. Heart J.* DOI: 10.1093/eurheartj/ehq455 (2010) (Epub ahead of print).

12 Allman KC, Shaw LJ, Hachamovitch R, Udelson JE: Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J. Am. Coll. Cardiol.* 39(7), 1151–1158 (2002).

13 Wu KC, Lima JA: Noninvasive imaging of myocardial viability: current techniques and future developments. *Circ. Res.* 93(12), 1146–1158 (2003).

14 Braunwald E, Kloner RA: The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 66(6), 1146–1149 (1982).

15 Bolli R, Marban E: Molecular and cellular mechanisms of myocardial stunning. *Physiol. Rev.* 79(2), 609–634 (1999).

16 Fieno DS, Hillenbrand HB, Rehwald WG *et al.*: Infarct resorption, compensatory hypertrophy, and differing patterns of ventricular remodeling following myocardial infarctions of varying size. *J. Am. Coll. Cardiol.* 43(11), 2124–2131 (2004).

17 Flynn A, O'Brien T: Stem cell therapy for cardiac disease. *Expert Opin. Biol. Ther.* 11(2), 177–187 (2010).

18 Wagner A, Mahrholdt H, Holly TA *et al.*: Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 361(9355), 374–379 (2003).

19 Ibrahim T, Bulow HP, Hackl T *et al.*: Diagnostic value of contrast-enhanced magnetic resonance imaging and single-photon emission computed tomography for detection of myocardial necrosis early after acute myocardial infarction. *J. Am. Coll. Cardiol.* 49(2), 208–216 (2007).

20 Beygui F, Le Feuvre C, Helft G, Maunoury C, Metzger JP: Myocardial viability, coronary flow reserve, and in-hospital predictors of late recovery of contractility following successful primary stenting for acute myocardial infarction. *Heart* 89(2), 179–183 (2003).

21 Panza JA, Dilsizian V, Laurienzo JM, Curiel RV, Katsiyiannis PT: Relation between thallium uptake and contractile response to dobutamine. Implications regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation* 91(4), 990–998 (1995).

22 Werner C, Bohm M, Friedrich EB: Progenitor cell therapy and myocardial infarction: the importance of microvascular function. *Nat. Clin. Pract. Cardiovasc. Med.* 5(2), 78–79 (2008).