into an ischemic area results in modulation of the local tissue immune system and altered cytokine production (4). Indeed, BMC transplantation results in local inflammatory changes that activate myofibroblasts, thus reducing infarct size (5). Thus, modulation of pro- and anti-inflammatory intramyocardial cytokine levels by transplanted cells and their crosstalk with the local tissue environment likely affect survival and differentiation of progenitor cells, as well as overall cardiac outcome.

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REFERENCES

1. Yousef M, Schannwell CM, Köstering M, Zeus T, Brehm M, Strauer BE. The BALANCE study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. J Am Coll Cardiol 2009;53:2262–9.
2. Forrester JS, Makkar RR, Marbán E. Long-term outcome of stem cell therapy for acute myocardial infarction: right results, wrong reasons. J Am Coll Cardiol 2009;53:2270–2.
3. Cao F, Sun D, Li C, et al. Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up. Eur Heart J 2009;30:1986–94.
4. Thum T, Bauersachs J, Poole-Wilson PA, Volk HD, Anker SD. The dying stem cell hypothesis: immune modulation as a novel mechanism for progenitor cell therapy in cardiac muscle. J Am Coll Cardiol 2005;46:1799–802.
5. Sun J, Li SH, Liu SM, et al. Improvement in cardiac function after bone marrow cell therapy is associated with an increase in myocardial inflammation. Am J Physiol Heart Circ Physiol 2009;296:43–50.

Reply

The letter by Drs. Thum and Anker touches various aspects of cardiac stem cell therapy (e.g., mortality, paracrine effects, and inflammation), all of which may be briefly addressed as follows.

Intracoronary stem cell therapy seems to represent a safe and effective regimen for treatment of heart failure after acute myocardial infarction (1,2), in an old myocardial infarction (≥8 years) with ischemic cardiomyopathy (3), and in advanced dilated cardiomyopathy (4). Our study (5) did not aim to speculate (Drs. Thum and Anker) on stem cell-induced inflammation (which has not yet been documented in the overwhelming majority of studies) and on possible paracrine effects by stem cells, but fortunately was able to analyze the different parameters of ventricular performance and potential effects on cardiac mortality in large patient groups, treated and untreated, in long-term follow-up after myocardial infarction.

When carefully reading our paper (5), the BALANCE (Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction) study showed that mortality, as a consequence of stem cell therapy, is significantly reduced; in a median follow-up time of 4.6 ± 2.1 years in the bone marrow cell group 1 patient died, and in 4.8 ± 2.2 years, 7 patients in the control group died ($p = 0.03$).

Mortality is dependent on both the degree of ventricular impairment and the amount of arrhythmogenicity. Dependent on the multifactorial mode of action of stem cells, systolic function (e.g., ejection fraction, stroke volume, contractility) and diastolic performance are improved; infarct size, end-systolic volume, and systolic wall stress decrease; and the arrhythmogenicity of the heart is presumably reduced. Thus, several of the main myocardial determinants of cardiac mortality are influenced in favor of reduced mortality by stem cell treatment in chronically ill cardiac patients.

Undoubtedly, further large studies are needed to analyze the action of stem cells on ventricular performance and cardiac mortality in different stages of chronic cardiac failure, especially with regard to the distinct origin of this chronic disease.

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REFERENCES

1. Strauer BE, Brehm M, Zeus T, et al. [Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction]. Dtsch Med Wochenschr 2001;126:932–8.
2. Strauer BE, Brehm M, Zeus T, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002;106:1913–8.
3. Strauer BE, Brehm M, Zeus T, et al. Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT study. J Am Coll Cardiol 2005;46:1651–8.
4. Strauer BE, Brehm M, Schannwell CM. The therapeutic potential of stem cells in heart disease. Cell Prolif 2008;41 Suppl 1:126–45.
5. Yousef M, Schannwell CM, Köstering M, Zeus T, Brehm M, Strauer BE. The BALANCE study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. J Am Coll Cardiol 2009;53:2262–9.

Grade of Ischemia to Assess No Reflow After Reperfusion

We read with great interest the excellent review by Niccoli et al. (1) about the no-reflow phenomenon in humans. In their paper, the authors describe various techniques for the prediction of no-reflow. As far as electrocardiography is concerned, the authors only mention the QRS score as a predictor of ischemia-related injury.

The extent of terminal QRS distortion on the admission electrocardiogram, known as the grade of ischemia, is a strong predictor of failure of ST-segment resolution as well as of

angiographic no-reflow and infarct size. We have shown both in patients receiving thrombolytic therapy (2) and in patients undergoing primary percutaneous intervention (3) that grade 3 ischemia is the strongest independent predictor available on admission for the no-reflow phenomenon. Because electrocardiography is the most widely available and least expensive tool at our disposal, and because this simple parameter is a robust predictor of no-reflow, we believe that it should be widely used to predict the risk of no-reflow and possibly to select patients for protective therapies.

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REFERENCES

1. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281–92.
2. Buber J, Gilutz H, Birnbaum Y, Friger M, Ilia R, Zahger D. Grade 3 ischemia on admission and absence of prior beta blockade predict failure of ST resolution following thrombolysis for anterior myocardial infarction. Int J Cardiol 2005;104:131–7.
3. Wolak A, Yaroslavtsev S, Amit G, et al. Grade 3 ischemia on the admission electrocardiogram predicts failure of ST resolution following primary angioplasty for acute myocardial infarction. Am Heart J 2007;153:410–7.

Reply

We thank Drs. Zahger and Wolak for their interest in our paper (1) and for the observation about the role of grade of ischemia on surface electrocardiography (ECG) in the prediction of no-reflow. Many ECG-derived indexes including the QRS score (number of Q waves) (2) and the QRS duration (3) along with terminal distortion of the QRS, known as grade of ischemia (4), have been used in the assessment of no-reflow risk. In our review (1), we mentioned the QRS score because it is the most widely used ECG index in the triage of ST-segment elevation myocardial infarction patients. We acknowledge that other indexes including grade of ischemia may be useful in risk stratification before primary percutaneous coronary intervention. Interestingly, in a previous study performed by Wolak et al. (4), grade of ischemia was associated with infarct size, thrombus burden, and admission glycemia, which may all contribute to the multifactorial pathogenesis of no-reflow. We agree with Drs. Zahger and Wolak that, in an era of superspecialist and expensive tools that are not widely available, such as cardiac magnetic resonance imaging, inexpensive and readily available ECG still has a central role in the management of ST-segment elevation myocardial infarction patients with regard to microvascular obstruction after primary percutaneous coronary intervention. Indeed, ECG is useful for risk prediction and diagnosis of no-reflow, for monitoring the efficacy of mechanical or pharmacological therapies against no-reflow, and finally, for prognostic information.

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REFERENCES

1. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281–92.
2. Iwakura K, Ito H, Kawano S, et al. Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. J Am Coll Cardiol 2001;38:472–7.
3. Kacmaz F, Maden O, Aksuyek S, et al. Relationship of admission QRS duration and changes in QRS duration with myocardial reperfusion in patients with acute ST segment elevation myocardial infarction (STEMI) treated with fibrinolytic therapy. Circ J 2008;72:873–9.
4. Wolak A, Yaroslavtsev S, Amit G, et al. Grade 3 ischemia on the admission electrocardiogram predicts failure of ST resolution following primary angioplasty for acute myocardial infarction. Am Heart J 2007;153:410–7.

Value of a High Exercise Workload to Rule Out Myocardial Ischemia

We read with great interest the paper by Bourque et al. (1) regarding the value of a high exercise workload to rule out significant myocardial ischemia. In that study, only 2 (0.4%) of 473 patients reaching ≥10 metabolic equivalents (METs) and ≥85% of maximum age-predicted heart rate (MAPHR) had ≥10% left ventricular ischemia on myocardial perfusion imaging. Furthermore, of the 430 patients reaching ≥10 METs and ≥85% MAPHR without exercise-induced ST-segment depression, none had significant myocardial ischemia. These results suggest that the information provided by cardiac imaging in these patients is questionable.

Our group previously assessed the prevalence and prognostic value of myocardial ischemia on exercise echocardiography in a population of 1,433 patients with known or suspected coronary artery disease achieving a high exercise workload (defined as ≥10 METs in men and ≥8 METs in women) (2). Of them, in 437 (30%) patients, new or worsening wall motion abnormalities developed during exercise. Over a follow-up of 2.3 ± 1.5 years, 201 (14%) patients underwent coronary revascularization and 57 (4%) patients had a hard cardiac event. Furthermore, exercise echocardiography was shown to provide incremental value for predicting hard cardiac events in these patients.

It might be argued that, in this study, 19% of the patients failed to achieve >85% of MAPHR, and ST-segment changes during the tests developed in 14% of the patients. Thus, we further explored whether the findings obtained by Bourque et al. (1) would