

CORRESPONDENCE

Letters to the Editor

Endothelial Progenitor Cells
in Coronary Artery Disease

We have been prompted to write by the small study of Güven et al. (1) showing increased endothelial progenitor cell (EPC) colonies in patients with coronary artery disease (CAD). In contrast, a wide literature demonstrates that the extent of the EPC pool is an indicator of cardiovascular health, as EPCs negatively correlate with severity of both peripheral and coronary atherosclerosis (2,3).

The investigators attribute their paradoxical results to the longer culture method they used to distinguish between true EPCs and circulating angiogenic cells (CACs) in comparison with previous studies. Even if we consider that earlier studies evaluated CACs rather than true EPCs, the findings by Güven et al. (1) are contrasting, because they report higher CACs in patients with CAD. The researchers hypothesize that significantly ischemic CAD triggers the mobilization of EPCs/CACs from bone marrow. However, patients with actual myocardial ischemia, for whom increase in EPCs/CACs have been previously demonstrated, were excluded from the study, and only patients with stable CAD were enrolled. Moreover, whereas EPC colonies directly correlated with maximum stenosis, they did not correlate with the number of diseased vessels, which should be more informative on the extent of myocardial ischemia.

We suggest that the use of intravascular ultrasound may provide further information on coronary atherosclerosis and help explain the paradoxical results when CAD is assessed angiographically. Finally, should the data by Güven et al. (1) really reflect a previously unknown regulation of EPCs in CAD, we would like to offer a counter explanation: the increase in circulating cells with high angiogenic potential dependent on CAD severity may be causally related to plaque angiogenesis and growth (4) the Janus face of EPCs in cardiovascular diseases.

*Gian Paolo Fadini, MD
Carlo Agostini, MD
Angelo Avogaro, MD, PhD

*Policlinico Universitario
Dipartimento di Medicina Clinica e Sperimentale
v. Giustiniani, 2
35100 Padova
Italy
E-mail: gianpaolofadini@hotmail.com

doi:10.1016/j.jacc.2007.01.058

REFERENCES

- Güven H, Shepherd RM, Bach RG, Capoccia BJ, Link DC. The number of endothelial progenitor cell colonies in the blood is increased in patients with angiographically significant coronary artery disease. *J Am Coll Cardiol* 2006;48:1579–87.
- Fadini GP, Coracina A, Baesso I, et al. Peripheral blood CD34+KDR+ endothelial progenitor cells are determinants of sub-clinical atherosclerosis in a middle-aged general population. *Stroke* 2006;37:2277–82.
- Kunz GA, Liang G, Cuculoski F, et al. Circulating endothelial progenitor cells predict coronary artery disease severity. *Am Heart J* 2006;152:190–5.
- George J, Afek A, Abashidze A, et al. Transfer of endothelial progenitor and bone marrow cells influences atherosclerotic plaque size and composition in apolipoprotein E knockout mice. *Arterioscler Thromb Vasc Biol* 2005;25:2636–41.

Reply

We would like to thank Dr. Fadini and colleagues for their comments regarding our study (1) recently published in *JACC*. Dr. Fadini et al. point out that our data, which shows that the numbers of endothelial progenitor cells (EPCs) and circulating angiogenic cells (CACs) in the blood of patients referred for cardiac catheterization are increased in those patients with angiographically significant coronary artery disease (CAD), differs from the results of some previously published studies. We agree. But as discussed in our study and highlighted by Drs. Leor and Marber in an accompanying editorial in *JACC* (2), it is critical when comparing different studies that the type of circulating angiogenic cells be precisely defined. Indeed, a recent study by Yoder et al. (3) suggested that culture techniques commonly used to quantify EPCs actually measure myeloid progenitor cells (3). In our study, we used rigorous histological and flow cytometry techniques to quantify EPCs and CACs (not simply a longer culture method, as suggested by Dr. Fadini et al.). Furthermore, whereas we compared these cell numbers to angiographically defined CAD among patients across a wide spectrum of disease severity, many previous studies identified atherosclerotic disease or its absence noninvasively, which may seriously limit sensitivity and specificity. We agree that a more precise definition of atherosclerosis by, for example, use of intravascular ultrasound, may add to our understanding of the relationship between the different EPC subsets and CAD.

From our observations, we speculated that significant myocardial ischemia may be a proximal determinant of EPC number in the peripheral blood. Dr. Fadini et al. question this, but in support of their opinion they wrongly state that patients with actual myocardial ischemia were excluded from our study. Although patients with acute myocardial infarction and unstable angina were excluded from our investigation, the majority of our patients with significant CAD were symptomatic (and anginal symptoms likely underestimate the frequency of true myocardial ischemia). Importantly, we observed the highest numbers of circulating EPCs and CACs in patients selected clinically to require revascularization. Of relevance, previous studies have shown an increase in circulating EPCs in patients with unstable angina (4) or acutely in response to exercise-induced ischemia (5), observations that appear consistent with the hypothesis that ischemia may be an important factor for the number of circulating EPCs.

***Daniel C. Link, MD**
Richard G. Bach, MD

*Washington University
Division of Oncology
660 South Euclid
Campus Box 8007
Saint Louis, Missouri 63110
E-mail: dlink@im.wustl.edu

doi:10.1016/j.jacc.2007.01.055

REFERENCES

- Güven H, Shepherd RM, Bach RG, Capoccia BJ, Link DC. The number of endothelial progenitor cell colonies in the blood is increased in patients with angiographically significant coronary artery disease. *J Am Coll Cardiol* 2006;48:1579-87.
- Leor J, Marber M. Endothelial progenitors: a new Tower of Babel? *J Am Coll Cardiol* 2006;48:1588-90.
- Yoder MC, Mead LE, Prater D, et al. Re-defining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. *Blood* 2006 Oct 19; [E-pub ahead of print].
- George J, Goldstein E, Abashidze S, et al. Circulating endothelial progenitor cells in patients with unstable angina: association with systemic inflammation. *Eur Heart J* 2004;25:1003-8.
- Sandri M, Adams V, Gielen S, et al. Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes: results of 3 randomized studies. *Circulation* 2005;111:3391-9.

Adjunctive Thrombectomy in Acute Myocardial Infarction: For Some but Not for All

We read with interest the report by Silva-Orrego et al. (1) regarding the effects of thrombus aspiration on myocardial reperfusion in the setting of primary angioplasty. The study reported a significant enhancement in myocardial reperfusion by a strategy of manual thrombus aspiration before stenting on top of abciximab administration. However, in our opinion some concerns exist about the results of this study. First, the investigators randomized patients with acute myocardial infarction (MI) to a conventional stent-assisted primary angioplasty versus a strategy applying manual aspiration device before stent, regardless of angiographic appearance of thrombus. Early studies evaluating the feasibility of thrombectomy in the setting of thrombus-containing lesion and acute MI clearly reported on the efficacy of thrombectomy devices in reducing thrombus burden at target lesion, consequently limiting distal embolization and no-reflow phenomenon (2,3).

Unfortunately, Silva-Orrego et al. (1) did not provide data concerning thrombus burden at baseline angiography, nor on thrombus removal after device use. Thus, the reported reduction in distal embolization rate may not be univocally ascribed to the device effect, as other factors may affect this result, such as differences in thrombus burden of culprit lesions.

Second, the researchers found a rate of postprocedural myocardial blush grade (MBG) 2/3 in both arms, which is surprisingly higher than expected, based on Thrombolysis In Myocardial Infarction (TIMI) flow achieved after the intervention, and on

time-to-treatment reported in this cohort. In the largest study validating the angiographic reperfusion, MBG was strongly affected by epicardial flow, being that patients showing TIMI flow grade <3 very rarely reached an adequate blush (4). Indeed, it has been shown that the effectiveness of myocardial reperfusion after primary angioplasty, as assessed by ST-segment resolution and MBG is clearly time-dependent (5).

In conclusion, to avoid conflicting results, we believe that future studies evaluating thrombectomy as adjunctive strategy in the setting of primary angioplasty should enroll only patients with angiographically documented thrombus at the lesion site, and that reperfusion findings should be carefully evaluated according to time-to-treatment.

***Massimo Napodano, MD**
Angelo Ramondo, MD
Sabino Iliceto, MD, FACC

*Department of Cardiac, Thoracic, and Vascular Sciences
University of Padova
2 via Giustiniani
35128 Padova
Italy
E-mail: massimo.napodano@sanita.padova.it

doi:10.1016/j.jacc.2007.01.056

REFERENCES

- Silva-Orrego P, Colombo P, Bigi R, et al. Thrombus aspiration before primary angioplasty improves myocardial reperfusion in acute myocardial infarction: the DEAR-MI study. *J Am Coll Cardiol* 2006;48:1552-9.
- Silva JA, Ramee SR, Choen DJ, et al. Rheolytic thrombectomy during percutaneous revascularization for acute myocardial infarction: experience with the Angiojet catheter. *Am Heart J* 2001;141:353-9.
- Napodano M, Pasquetto G, Saccà S, et al. Intracoronary thrombectomy improves myocardial reperfusion during direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1395-402.
- van't Hof AWJ, Liem A, Suryapranata H, Horntje JCA, de Boer MJ, Zijlstra F on behalf of the Zwolle Myocardial Infarction Study Group. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Circulation* 1998;97:2302-6.
- De Luca G, van't Hof AW, de Boer MJ, et al. Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *Eur Heart J* 2004;25:1009-13.

Reply

We appreciated the comments by Dr. Napodano and colleagues and would like to address their concern. The DEAR-MI (De-thrombosis to Enhance Acute Reperfusion in Myocardial Infarction) study (1) included consecutive randomization of acute myocardial infarction (AMI) patients fulfilling the inclusion criteria regardless of angiographic evidence of thrombus based on the assumption that thrombus is always present in AMI. Compared with angiography, the presence of intracoronary thrombus is significantly underestimated by angiography (2). In our randomized population, 73% of controls and 81% of patients undergoing aspiration showed an occluded vessel with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 at the initial angiogram,