ment. Enhanced production of EPO could therefore also serve as a compensatory mechanism under ischemic conditions and reflect the severity of ischemic injury.

In the present study, patients with higher EPO levels and smaller infarct size also had lower hemoglobin levels. This is in contrast to previous findings, namely that a low hemoglobin concentration is associated with higher mortality in patients with stable coronary artery disease (7) and acute MI (8).

In addition, a very weak correlation between enzymatic infarct size and endogenous EPO levels should awake cautiousness as to the interpretation of the presumed effect of endogenous EPO on reducing the infarct size. Moreover, the serum EPO levels were measured almost 10 hours after the angioplasty and could thus reflect peri- and postprocedural blood loss, or ischemia-triggered EPO production.

Finally, we believe that the potential mechanism of protective EPO action in these patients might be different from that suggested by the investigators. In an acute ischemic situation, rescuing the cardiomyocytes from cell death (apoptosis) seems a more plausible explanation than increased neovascularization through progenitor cell stimulation. Further studies in larger cohorts of patients should elucidate the precise role of *endogenous* EPO in acute coronary syndromes. Moreover, therapy of patients with MI with *exogenous* EPO may be considered in the future.

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doi:10.1016/j.jacc.2005.10.028

REFERENCES

1. Namiuchi S, Kagaya Y, Ohta J, et al. High serum erythropoietin level is associated with smaller infarct size in patients with acute myocardial infarction who undergo successful primary percutaneous coronary intervention. J Am Coll Cardiol 2005;45:1406–12.
2. Henry DH, Bowers P, Romano MT, et al. Epoetin alfa. Clinical evolution of a pleiotropic cytokine. Arch Intern Med 2004;164:262–76.
3. Lipsic E, van der Meer P, Henning RH, et al. Timing of erythropoietin treatment for cardioprotection in ischemia/reperfusion. J Cardiovasc Pharmacol 2004;44:473–9.
4. Parsa CJ, Matsumoto A, Kim J, et al. A novel protective effect of erythropoietin in the infarcted heart. J Clin Invest 2003;112:999–1007.
5. Volpe M, Tritto C, Testa U, et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol 1994;74:468–73.
6. van der Meer P, Voors AA, Lipsic E, et al. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. J Am Coll Cardiol 2004;44:63–7.
7. Reinecke H, Trey T, Wellmann J, et al. Haemoglobin-related mortality in patients undergoing percutaneous coronary interventions. Eur Heart J 2003;24:2142–50.
8. Lipsic E, van der Horst IC, Voors AA, et al. Hemoglobin levels and 30-day mortality in patients after myocardial infarction. Int J Cardiol 2005;100:289–92.

REPLY

We appreciate the interest and thoughtful comments of Dr. Lipsic and colleagues regarding our study (1). The conclusions of our study were that a higher endogenous erythropoietin (EPO) level can predict a smaller infarct size in patients with acute myocardial infarction (MI) subjected to successful primary percutaneous coronary intervention (PCI), and that this might be attributed to the potentially protective effect of endogenous EPO against ischemia-reperfusion injury in humans. As pointed out by Dr. Lipsic and colleagues, these conclusions may be in contrast to those of studies by Dr. Lipsic and colleagues (2) and by others as well (3). They reported that a lower hemoglobin content was associated with higher mortality in patients with acute MI (2) and stable coronary artery disease (CAD) (3). We would like to emphasize, however, that in our study the hemoglobin concentration was not an independent predictor of the infarct size, whereas the endogenous EPO level was. We believe that we cannot directly compare the results of our study with those of the two studies by Dr. Lipsic and colleagues and by others because they did not measure the serum EPO level in their patients.

Dr. Lipsic and colleagues also reported that, in patients with chronic heart failure, elevated plasma EPO levels are associated with an impaired prognosis (4). The mechanisms of the increased plasma EPO levels in some patients with chronic heart failure are still unclear, and they may be different from those in the patients with acute MI in our study. As described in our report (1), it is possible that current smoking increased the hemoglobin content in the blood and affected the serum EPO levels of the patients in the low EPO group. With regard to the timing of the blood sampling for the serum EPO level, we collected the blood samples 9.9 $\pm$ 5.2 h after the onset of acute MI as described in the Methods section of our study. We believe that Dr. Lipsic and colleagues misunderstood this issue.

We agree with the investigators that a future study with a larger number of patients is needed to draw a more definitive conclusion regarding the role of endogenous EPO in acute MI.

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doi:10.1016/j.jacc.2005.10.029

REFERENCES

1. Namiuchi S, Kagaya Y, Ohta J, et al. High serum erythropoietin level is associated with smaller infarct size in patients with acute myocardial infarction who undergo successful primary percutaneous coronary intervention. J Am Coll Cardiol 2005;45:1406–12.
2. Lipsic E, van der Horst IC, Voors AA, et al. Hemoglobin levels and 30-day mortality in patients after myocardial infarction. Int J Cardiol 2005;100:289–92.
3. Reinecke H, Trey T, Wellmann J, et al. Haemoglobin-related mortality in patients undergoing percutaneous coronary interventions. Eur Heart J 2003;24:2142–50.

4. van der Meer P, Voors AA, Lipsic E, et al. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. J Am Coll Cardiol 2004;44:63–7.

Intravascular Ultrasound Analysis of Polymer-Based Paclitaxel-Eluting Stents

With great interest I read the report by Weissman et al. (1) regarding intravascular ultrasound (IVUS) analysis of polymer-based paclitaxel-eluting stents. The investigators stated in the text that "positive remodeling assessed as the absolute increase in the external elastic membrane volume over time tended to be slightly more prominent with the TAXUS stent (7.66 ± 48.64 mm^3 vs. −12.29 ± 36.05 mm^3, respectively, $p = 0.064$)." Also Figure 1 suggested positive remodeling in the TAXUS stent. However, Table 2 of their article (1) shows an inconsistent result, that is, decrease of external elastic membrane volume in the TAXUS-stent group (283 ± 91 mm^3 at postimplantation vs. 280 ± 89 mm^3 at nine-month follow-up). Because a previous IVUS analysis has also suggested positive remodeling in the TAXUS stent (2), it may be of great importance to better clarify this result.

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doi:10.1016/j.jacc.2005.10.033

REFERENCES

1. Weissman NJ, Koglin J, Cox DA, et al. Polymer-based paclitaxel-eluting stents reduce in-stent neointimal tissue proliferation: a serial volumetric intravascular ultrasound analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1201–5.
2. Tanabe K, Serruys PW, Degertekin M, et al. Chronic arterial responses to polymer-controlled paclitaxel-eluting stents: comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial. Circulation 2004;109:196–200.

REPLY

We appreciate Dr. Kaneda's astute observation about the data contained in our report (1) on the intravascular ultrasound (IVUS) results from TAXUS-IV. It is indeed true that there was a trend for the vessel receiving a TAXUS stent to demonstrate positive remodeling, similar to prior drug-eluting stent (DES) reports. The analysis for remodeling used only TAXUS and non-TAXUS patients with complete volumetric IVUS data of the external elastic membrane (EEM) throughout the stent length at *both* the time of stent implantation and at follow-up. As it states in the Methods section, "Volumes were calculated only if the vascular interface was visualized every millimeter throughout the stent" (i.e., we did not extrapolate the EEM border for images in which it was not visualized). Thus, not all patients with EEM volume data at stent implantation had EEM volume data at follow-up, and vice-versa. Table 2 of the study (1) reports all the volume data at one time point (postimplantation or follow-up) and the statistical analysis for change (and Figure 1 of the report [1] displaying change over time) used only patients that had *paired* postimplantation and follow-up EEM volume data. Hence, the results of a trend toward positive remodeling in the TAXUS stent are indeed accurate and in concordance with other DES studies.

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doi:10.1016/j.jacc.2005.10.034

REFERENCE

1. Weissman NJ, Koglin J, Cox DA, et al. Polymer-based paclitaxel-eluting stents reduce in-stent neointimal tissue proliferation: a serial volumetric intravascular ultrasound analysis from the TAXUS-IN trial. J Am Coll Cardiol 2005;45:1201–5.

Restenosis, Statistics, and Reasonable Inferences

We appreciate the accompanying editorial (1) to our recent report entitled "Relationship Between Angiographic Late Loss and Target Lesion Revascularization After Coronary Stent Implantation: Analysis From the TAXUS-IV Trial" (2) but we wish to clarify several apparent misconceptions. Our principal messages are that in the era of drug-eluting stents (DES), it is not only the mean value but also the shape of the distribution curve (variance and skewedness) that will determine the population target lesion revascularization (TLR), and that with a homogeneous response in-stent late losses up to about 0.75 mm may provide acceptable clinical results (2). That DES may have rightward skewed late loss histograms has been previously reported (3). The fact that the individual patient late loss/TLR relationship is curvilinear with an apparent inflection point, rather than linear, had not been reported and is a novel and unique observation that has since been replicated in several other DES trials (DELIVER, ENDEAVOR-II). Most importantly, given the rightward skew in patient population data seen in all these trials (including the pivotal SIRIUS trial of the sirolimus-eluting stent), a certain lower level or "floor" of TLR may be unavoidable, somewhat independent of the mean late loss.

Moreover, recent data reported at the most recent American College of Cardiology meetings substantiate our findings. The ENDEAVOR-II trial, with a considerably higher mean late loss (0.62 mm) but with rather a homogeneous effect (standard deviation of late loss 0.46), reported a low TLR of 4.6% with the ABT-578-eluting stent. The large-scale REALITY trial, comparing the sirolimus-eluting and paclitaxel-eluting stents, found significantly greater in-stent late loss with the latter (0.09 vs. 0.31 mm, respectively, $p < 0.001$), but nearly identical eight-month TLR rates (5.0% vs. 5.4%, $p = 0.81$). Thus, given the patient and lesion complexity studied in the pivotal DES trials to date, an "acceptable" TLR can be achieved with a relatively high in-stent late loss, providing that a homogeneous response is seen.

In addition, other variables beyond angiographic late loss that may affect TLR rates must be considered, including the inaccuracies and variability of quantitative measures of late loss. Variable thresholds of patient angina perception, follow-up ischemia detec-