Physiologically Assessed Collateral Flow and Intracoronary Growth Factor Concentrations in Patients With 1- to 3-Vessel Coronary Artery Disease

To the Editor:

We enjoyed reading the article by Fleisch et al but would like to point out several potential factors that detract from our data reported. In particular, we are concerned about the measurement of growth factors and collateral flow index (CFI).

As the authors acknowledge, both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are heparin-binding peptides and, thus, their levels are significantly altered in the presence of heparin. The administration of “nearly identical doses of heparin” does not normalize for heparin’s effects, because plasma heparin levels will vary according to the patient’s body mass, plasma volume, and age. We have found that after a standard 10 000-unit heparin bolus, both arterial and venous plasma VEGF levels can be undetectable when using the same enzyme-linked immunosorbent assay (ELISA) as Fleisch et al, even when there is a 50-fold difference in baseline sample concentrations before heparin administration. This probably explains why one-fifth of the study patients had undetectable VEGF levels.

Conversely, arterial bFGF levels are elevated after heparin administration. There is a 3- to 5-fold increase at 30 minutes after heparinization for cardiopulmonary bypass, probably because heparin displaces bFGF from the subendothelial extracellular matrix and luminal surface of blood vessels. Similarly, we have found up to a 10-fold increase in arterial bFGF 5 minutes after the administration of 10 000 units of intravenous heparin before angioplasty.

The effects of heparin on VEGF and the variable effect of bFGF displacement from the arterial luminal surface are fundamental confounding factors that were not adequately accounted for in this article.

The accurate measurement of CFI is heavily dependent on a correct evaluation of right atrial pressure at the time of balloon inflation. In our experience, if the mean right atrial pressure is assumed to be 5 mm Hg, CFI is overestimated by an average of 30%. This may explain why Fleisch et al used a CFI of 0.3 as the cut off point for sufficient collateral vessel development to protect against ischemia, as opposed to the theoretical and experimentally validated ratio of 0.25. Therefore, significant differences exist in the true CFI of the patients studied, which could alter their assignment to the high and low CFI groups.

In summary, we question the reliability of the measurements of growth factors and collateral flow and believe that their relationship may be less certain than the authors conclude.

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Response

We thank Lambiase and coworkers for their interest in our recent publication on angiogenic growth factors and directly measured coronary collateral flow among patients with coronary artery disease. The points they raise are valid. That is why we discussed them extensively in our original publication. In fact, the entire discussion focused on “pointing out a number of potential factors detracting from the data reported,” as Lambiase et al stated. Referring to Figure 3 of our publication, we stated that “...75% of the collateral flow variability is related to factors other than the sum of the concentrations of bFGF and VEGF.” Later in the article, the points raised by Lambiase and coworkers were considered in detail. In addition, data not reported that could have influenced heparin plasma levels and, therefore, the growth factor concentrations in the group of patients with insufficient and sufficient collaterals are provided as follows: the age in the 2 groups was 61±10 and 61±11 years, respectively; body weight was 81±10 and 77±13 kg, respectively (not significant); and body mass index was 28±2.3 and 26.3 kg/m², respectively (not significant).

With respect to the way the collateral flow index (CFI) was calculated, we cannot confirm the experience of Lambiase et al that the pressure-derived CFI is overestimated by 30% using an assumed (5 mm Hg) instead of measured central venous pressure. Among 50 of our patients with pressure-derived CFI measurements (of a total of ~450 CFI measurements in our laboratory), central venous pressure (CVP) was also obtained. CVP was equal to 8.4±5.1 mm Hg (range, 1 to 22 mm Hg). CFI calculated by measured CVP was equal to 1.02×CFI calculated by assumed CVP minus 0.03 (r²=0.92; standard error of estimate=0.04). The standard error of estimate relative to average CFI was 17%, a value that was approximately half of that given by Lambiase et al.

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