Promotion of Collateral Growth by Granulocyte-Macrophage Colony-Stimulating Factor in Patients With Coronary Artery Disease

To the Editor:

The study by Seiler et al1 on collateral growth stimulation in humans by granulocyte-macrophage colony-stimulating factor (GM-CSF) received a very optimistic editorial by Schaper.2 The authors should be congratulated on the study concept and the conduct of this first-time approach to assess arteriogenesis directly in humans. However, can we really draw the conclusion that there was a clear-cut effect of GM-CSF on collateral development with a short study time period of 2 weeks? I have 2 main concerns. First, looking at the data in Table 2 shows that the collateral flow index (CFI) differed considerably at baseline between both study groups; this difference of 0.21 versus 0.30 was just the same amount that was ultimately observed as increase in the treatment group (0.21 to 0.31). Surprising and completely unexplained was the fact that in the placebo group, the CFI dropped by almost that same amount, from 0.30 to 0.23. This unexplained drop of the CFI is as significant to study result as the moderate increase in the treatment group. As no balloon dilatation was done at baseline, the CFI should have remained unchanged in the placebo group. Does this change in the placebo group not simply reflect the high intrinsic variability of the applied method? No data on intrainsdividual variability of CFI, which would be essential in the interpretation of the study results, are given. In our experience using Doppler during balloon occlusion, we observed considerable variation of individual collateral flow measurements within 24 hours.3

Also, multiple paired t tests without corrections were used instead of a repeated ANOVA. This test would have probably shown no difference between the groups considering the individual data points (Figure 2). Only 2 patients in the treatment group showed a considerable increase, and at least 2 patients had shown a similar degree of improvement in the placebo group; however, more patients showed an unexplained decrease.

With regard to the many previous experimental attempts to promote arteriogenesis/angiogenesis in humans and the setbacks that have occurred, a cautious approach to the interpretation is important, but limited pilot trial is required. The interpretation of this study in the editorial that “therapeutic arteriogenesis has arrived” is premature.

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Response

We thank Dr Werner for having read completely our article on granulocyte-macrophage colony-stimulating factor (GM-CSF) and collateral growth in humans.1 One of the intentions of the form in which the data were presented, namely as clearly as possible, has obviously been met in at least one reader. Conversely, it is obvious that a study including as few as 21 individuals has a high data variability, one result of which may be that different groups elicit various baseline values in the endpoint variable. Of course, part of this “data noise” very likely stems from inaccuracies related to the method used to measure the outcome variable. Coronary wedge pressure-derived collateral flow measurements are, however, much less “noisy” than the respective ultrasound derived collateral flow index, because the former measurements are less affected by real noise than the latter. In our experience with simultaneous use of pressure and Doppler wires to determine collateral flow,2 the blast encountered often stems directly from the tip of the wire “scratching” the vessel wall instead of gauging flow velocity. This can be easily recognized by the high-pitched, loud signals, and during coronary occlusion and in the presence of low collateral flow it is often hard to correct. In comparison, pressure signals are technically easy to obtain, and they are extremely robust against altering wire positions. The failure to completely occlude the vascular area of interest may also result in a false overestimation of collateral flow. Dr Werner likely has not realized yet that exactly this occurred in the cited study.3 In our experience,4 none of 450 cases encountered was like that in the study by Werner et al, which showed apparently 20% more coronary flow across collateral vessels to the seemingly occluded vessel in comparison to the antegrade flow during vessel patency.3 This finding indicates that absolutely tight vessel blockage is mandatory during collateral assessment, and that it could not have been achieved in the mentioned investigation using coronary probing instead of balloon catheters for occlusion.

We think that at this stage in clinical research on collateral promotion, the best of the numerous potential angiogenic or arteriogenic (theoretically to be preferred) candidates should be picked on the basis of small controlled trials and not open-label trials, the outcome variable relevant to the study object of interest (collateral flow) ought to be measured, the measurement should be performed before and after treatment, and, finally, the measurement should be performed using the best method available in humans. Large-scale trials testing promising candidates for their efficacy with regard to cardiovascular events should await the important selection process.

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