We would like to congratulate Sheldon et al. for his efforts in establishing the role of beta-blockers for the treatment of vasovagal syncope. We share his frustrations in the treatment of this disabling and frequent disease. There is no doubt that new randomized and controlled studies are needed to reach a definitive answer. We are happy to have raised doubts on the efficacy of the drugs most commonly used for this pathology.

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REFERENCES

Heterogeneity of Response to Lipid-Lowering Therapy
I read with great interest the article by Penny et al. (1) on changes in endothelium-dependent vasomotor responses in mildly diseased coronary arteries after lipid-lowering therapy. In that report, the investigators studied angiographic responses to acetylcholine (Ach) along successive 3-mm coronary segments. On average there was a small improvement in vasoresponsiveness to Ach after lipid-lowering therapy. Changes in responsiveness correlated with a marker of oxidized low-density lipoprotein (LDL), but not with LDL or total cholesterol levels. As the title implies, the researchers concluded that, overall, lipid-lowering drug treatment reverses coronary endothelial dysfunction.

Although the reported observations generally support the broad concept that, on average, lipid lowering in hypercholesterolemic individuals with atherosclerotic disease can improve endothelial function, they also appear to suggest a potentially important additional and perhaps counterintuitive hypothesis: that the coronary vasomotor responses of some patients may actually react adversely to lipid-lowering therapy. Reiterating the original observations of El-Tamimi et al. (2), who showed adjacent segments in the same artery can show vasodilatory and vasoconstrictive responses, the investigators document an extraordinary heterogeneity in responses of individual coronary segments to Ach, both at baseline and after treatment. More remarkable, the changes in intraindividual coronary artery segment responses after therapy appear to occur in both directions, with a large number of segments showing a decline in vasodilation or vasoconstriction at follow-up. Though the majority of the “most constricted” segments at baseline demonstrated improved responses at follow-up, only 4 of the 29 patients showed arteries that lacked some segmental “deterioration” in function. Judging from Figure 3 in the Penny et al. (1) study, where individual segment response changes were plotted, it appears that 40% to 45% of patients showed a predominantly contraindicated response, with more segments showing a decline in vasomotor responsiveness rather than “improvement.” Whereas this may represent regression to the mean, the mechanism is unclear. Although the graphical expression of the data suggests moderation of responses at follow-up, it leaves some ambiguity with respect to the severity of the deteriorated segmental responses, and it seems possible that the magnitude of the heterogeneity may have been underestimated by the methods employed.

The benefits of lipid-lowering therapy for reducing clinical events in patients with hypercholesterolemia and coronary artery disease have been well established. The observations by Penny et al. (1), as well as the results of the Coronary Artery Reactivity After Treatment with Simvastatin (CARATS) trial (3), which failed to show significant improvement in endothelium-dependent coronary vasomotor and blood flow responses in patients treated for six months with simvastatin, highlight a degree of complexity and inter- and intraindividual variability of response to statin and/or lipid-lowering therapy that is currently poorly understood, and yet one that raises important questions. Are these heterogeneous responses the result of random variability, or do the data imply that there is a subgroup of patients whose coronaries may respond poorly or even adversely to lipid-lowering therapy? Because the investigators have demonstrated a correlation between changes in responsiveness and levels of circulating oxidized LDL (which are not reliably reduced by statin therapy [4]), do the results imply that oxidized LDL levels may help identify those patients who are unlikely to show improvement in endothelial function with lipid-lowering therapy alone, and may need more aggressive additional treatment? Would the clinical benefit of statin therapy be greater if we could select likely patient/coronary “responders” from “nonresponders” or worse, “adverse responders”? Given that multiple mechanisms may be involved in the benefit of statin therapy, this interpretation might be overly simplistic. Nevertheless, the observations of Penny et al. (1) suggest variability in coronary responses to lipid-lowering therapy that may be clinically relevant and warrant further investigation.

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REPLY

We appreciate Dr. Bach’s interesting comments regarding our study of the changes in coronary endothelial dysfunction occurring after lipid lowering (1). We certainly agree that the segmental heterogeneity of these changes in response to acetylcholine suggests a level of complexity that has been previously underemphasized.

The reduction in clinical events in groups of patients on lipid-lowering therapy is irrefutable. Our work confirms previous reports that this therapy can also improve endothelial function in a group of patients. However, as in all therapies, not all patients respond equally, and the inclusion of all analyzable coronary segments in our study expands on the original observation of El-Tamimi et al. (2) that not all areas of the artery respond equally.

As pointed out in our current study (1) as well as in our earlier work (3), it is difficult to separate true physiologic heterogeneity from methodologic variability inherent in all analytic techniques. We reiterate that the phenomenon of regression to the mean may well account for some of the findings of most constricted and most dilated segmental responses being moderated on follow-up. However, the conclusion that some responses are actually adversely affected by lipid reduction cannot be made by our study given the lack of a comparative placebo group—a more abnormal response might be expected at follow-up given the natural history of atherosclerotic coronary disease, and some of these "worsened" responses could have been an improvement over that seen in the absence of lipid reduction.

We agree that the pattern of vasomotor response and the correlation with oxidized low-density lipoprotein may possibly reflect a given patient’s clinical response to lipid-lowering therapy. This observation deserves further study.

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Vascular Endothelial Growth Factor: Angiogenesis, Atherogenesis or Both?

Vascular endothelial growth factor (VEGF), a specific mitogen for endothelial cells, was initially regarded to be a remedy for impaired reendothelialization of arteries in patients treated with balloon angioplasty. Supplementation with VEGF was also expected to induce the formation of blood vessels nourishing ischemic heart or peripheral muscles.

Among the studies demonstrating the therapeutic efficiency of VEGF were reports suggesting the opposite (1,2). It took, however, several years until stronger evidence was obtained. In recent issues of JACC (1) and Nature Medicine (2) Celletti et al. (1,2) have published data demonstrating that VEGF promotes atherosclerosis. They used two animal models: double knockout mice (apoE/ apoB100), in which spontaneous atherosclerosis was aggravated by a single injection of a low dose of VEGF protein (2), and cholesterol-fed rabbits, which when treated by VEGF developed larger plaques (1,2). The investigators showed that VEGF increased the total number of blood and plaque monocytes/macrophages and enriched the pool of circulating CD34+/flk−1+ progenitor cells that might enhance neangiogenesis (1,2).

Those intriguing studies raise many questions. Particularly, it remains to be established how those experimental data relate to the results of the clinical trials with angiogenic growth factors, which so far did not report any significant side effects. In our opinion the results presented by Celletti et al. (1,2) force us also to reinvestigate the role of VEGF using more basic approaches. One of the crucial aims will be to understand the mechanisms governing VEGF synthesis and angiogenic activity in normal and atherosclerotic vessels.

We have recently demonstrated that nitric oxide (NO) enhanced VEGF synthesis in vascular smooth muscle cells (VSMC) (3,4). Nitric oxide synthesis is inhibited by modified low-density lipoprotein (LDL), which is elevated in atherosclerosis (5). However, this does not result in attenuation of VEGF production. In fact, lipid components of modified LDL enhanced VEGF expression in VSMC independently of their inhibitory effect on the generation of NO by inducible nitric oxide synthase (iNOS) (5).

Those data, which are supported by others (6), show that different factors can enhance VEGF in the vessel wall and initiate or promote atherosclerosis. In fact, VEGF is strongly expressed in the plaque (7,8). Thus, probably the inhibition, but not the supplementation, of VEGF has to be regarded for the treatment of atherosclerosis. Application of a strong antiangiogenic treatment might not be a good option for patients with already impaired blood supply and developing plaques. However, an interesting, safer alternative might already exist. The statins, inhibitors of