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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 acetlycholine 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 variablity 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 atherogenesis. 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 neoangiogenesis (1,2).

Those intriguing studies raise many questions. Particulary, 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

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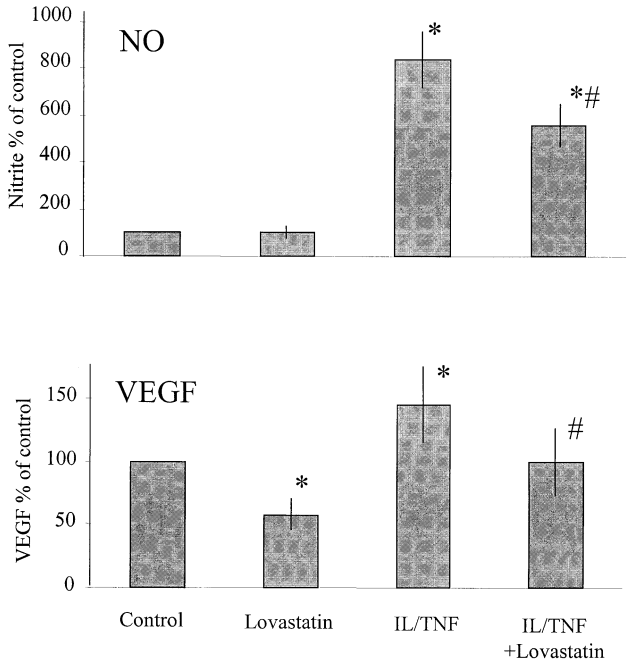

Figure 1. Lovastatin decreases cytokine-induced nitric oxide (NO)-generation and vascular endothelial growth factor (VEGF) synthesis in vascular smooth muscle cells (VSMC). Rat thoracic aorta VSMC were treated for 24 h with lovastatin (10 μmol/liter) and/or interleukin (IL)-1β (10 ng/ml) and tumor necrosis alpha (TNF)-α (10 ng/ml). The VEGF protein and nitrite concentrations were determined in media after 24 h of culture, using an ELISA kit (R&D System) and the Griess reagent method, respectively. Only background amounts of nitrites, not derived from inducible NO synthase activity, have been detected in cells not treated with cytokines. Mean ± SD (three independent experiments), analysis of variance followed by the Scheffè test. $^{*}p < 0.02$ vs. control; $^{\#}p < 0.01$ vs. IL/TNF. Lovastatin also decreased VEGF synthesis in human VSMC (not shown).

HMG-CoA reductase, which efficiently decrease cholesterol levels, may also influence VEGF production by interrupting the lipid-mediated enhancement of VEGF production. In our recent study (9) we have demonstrated that atorvastatin therapy for two months decreased VEGF plasma levels in hypercholesterolemic patients. Additionally, we have shown that lovastatin decreased both basal and cytokine-induced VEGF production, and it also diminished the iNOS-mediated cytokine-induced NO generation (Fig. 1). Thus, statins may modulate VEGF level including lipid-dependent and lipid-independent pathways.

More than ten years after discovery of VEGF we still do not fully understand how to face the facts that it exerts ambiguous influence. It is possible that only a narrow range differentiates its beneficial effects from harmful ones.

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