Effect of Cholesterol-Lowering Therapy on Endothelial Function

To the Editor:

In the August 22, 2000, issue of Circulation, Vita et al. found that 6 months of cholesterol-lowering therapy resulted in no significant improvement of coronary endothelial vasomotor function in a study population of patients with coronary artery disease and mildly elevated cholesterol levels. The study was a multicenter, randomized, double-blind, placebo-controlled trial that used simvastatin as the cholesterol-lowering agent. A total of 60 patients completed the invasive protocol, and 1 patient suffered a major complication (acute myocardial infarction).

We recently reported our experience with cholesterol-lowering therapy using pravastatin during a 6-month period and the consequent effect on repeat coronary endothelial function testing in 6 patients with atypical chest pain, normal coronary arteriograms, LDL cholesterol \( \geq 130 \text{ mg/dL} \), and evidence of microvascular endothelial dysfunction during baseline testing (defined as \( \geq 150\% \) increase in coronary blood flow in response to graded infusion of intracoronary acetylcholine). In order to recruit 6 patients who successfully completed the protocol, we screened an additional 8 patients with identical enrollment characteristics, except that in these 8 patients, baseline testing of coronary microvascular endothelial function was normal, excluding them from further participation. To date, we have been unable to identify any other characteristic that seemed to differ importantly among the 6 enrolled and the 8 screened patients.

In our small series, we found significant improvement in LDL cholesterol (157±27 mg/dL to 117±19 mg/dL, \( P=0.02 \)) and corresponding improvement in coronary blood flow in response to acetylcholine (97±32\% versus 160±40\% increase, \( P=0.01 \)) at 6 months. Linear regression analysis showed a significant correlation between change in peak coronary blood flow response and improvement in LDL cholesterol level (\( r=0.87, P=0.02 \)). Improvement in coronary endothelial microvascular function was secondary to reduction in the minimum coronary vascular resistance index (53±12\% to 39±6\%, \( P=0.03 \)). We administered acetylcholine through an infusion catheter into the proximal left main artery (assumed blood flow = 150 mL/min).

We believe that this approach minimizes risk to the patient and permits administration of all graded infusions of acetylcholine in most patients. Because our study population had normal coronary arteriograms, was healthy, and had a specified form and degree of endothelial dysfunction, the group could be characterized as relatively homogeneous with early disease, thus facilitating analyses and avoiding the complexities posed by compensatory mechanisms arising in more advanced disease.

We endorse the conclusion of Vita et al. that the effects of cholesterol-lowering therapy on endothelial function are more complex than previously suspected. Recognizing that this type of research can be tedious, is time and labor intensive, and poses some risk to the patient, and recognizing that the findings ultimately may be of enormous importance, we suggest that simpler protocols and more homogeneous patient groupings may shed some light on this ever-deepening puzzle.

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