EDITORIAL COMMENT

Carotid Atherosclerosis: Is It Treatable?

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Carotid atherosclerosis can be detected by ultrasound and is a risk factor for myocardial infarction and stroke.[1,2] It is a consequence of endothelial dysfunction;[3] thus, understanding the role that the endothelium plays in maintaining vascular tone has provided new insights into the evaluation and treatment of atherosclerosis. Some of the most important vasoactive substances produced by the endothelium are nitric oxide (NO) and NO-containing donors. NO exerts its vasodilatory effect by activating guanylate cyclase, a major cellular initiator of vascular relaxation.[4]

Endothelial dysfunction has not been well studied in patients with carotid atherosclerosis. However, Hsu et al[5] used brachial-artery flow-mediated dilatation (FMD), a promising, noninvasive tool for detecting endothelial dysfunction, to evaluate endothelial dysfunction in patients with carotid atherosclerosis, and found that systemic endothelial dysfunction might contribute to atherosclerosis in these patients. The authors also evaluated changes in FMD, cytokines and carotid arterial stenosis during atorvastatin administration to patients with normocholesterolemia.[6] The investigators found that endothelial dysfunction was significantly improved after 4 months of atorvastatin treatment. However, the 2 questions below should be posed.

Is the assessment of brachial-artery FMD reliable and reproducible?

In the 1990s, high-frequency ultrasound imaging of the brachial artery to assess endothelium-dependent FMD was developed.[7] Over the past decade, this test has proved to be a quantitative, noninvasive and reproducible means of detecting the severity of endothelial dysfunction. The sensitivity, specificity and positive predictive value for brachial-artery FMD were 71%, 81%, and 95%, respectively.[8] Nonetheless, the measurement of brachial FMD has some limitations. Firstly, measurement of brachial-artery diameter is difficult, and intraobserver variations exist. Secondly, with the wide baseline variability that exists in a normal response to increased flow, the present techniques may fail to detect the true peak FMD. Thirdly, there is currently no standardized "normal range" for FMD. Fourthly, brachial FMD reflects only 1 facet of endothelial dysfunction; factors such as age, sex, serum markers of inflammation, and serum markers of vascular homeostasis may all influence endothelial dysfunction. Although no gold-standard method exists for measuring endothelial dysfunction, brachial-artery FMD is widely used as a reliable and reproducible research tool.

If 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have direct anti-inflammatory effects, how long do they need to achieve significant benefit?

Hsu et al[6] found that atorvastatin significantly decreased serum levels of total and low-density lipoprotein (LDL) cholesterol after 1, 2 and 4 months' treatment, although levels of inflammatory cytokines showed no significant reduction within 4 months, suggesting that longer periods of statin therapy may be needed to cause significant anti-inflammatory effects. However, Albert et al[9] reported that pravastatin had anti-inflammatory effects, as evident from reduced levels of C-reactive protein (CRP) at 12 and 24 weeks. Ridker et al[10] reported that CRP levels were significantly reduced within 8 weeks of starting cerivastatin therapy. Although levels of inflammatory cytokines were not significantly reduced in the study by Hsu et al,[6] a trend towards a progressive reduction after atorvastatin use was demonstrated. Furthermore, if the latter study had continued

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beyond 4 months, atorvastatin might have displayed significant anti-inflammatory effects.

Summary

The assessment of brachial-artery FMD is a reliable, reproducible and noninvasive tool for evaluating endothelial dysfunction, which, together with endothelial inflammation, causes carotid atherosclerosis. Atorvastatin therapy can reverse endothelial dysfunction after 4 months, and may have significant anti-inflammatory effects if continued for more than 4 months. Importantly, statin therapy can be used to treat carotid atherosclerosis.

References

1. Craven TE, Ryu JE, Espeland MA, Kahl FR, McKinney WM, Toole JF, McMahan MR, et al. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis. A case-control study. *Circulation* 1990;82:1230–42.
2. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340:14–22.
3. Nabel EG, Selwyn AP, Ganz P. Large coronary arteries in humans are responsive to changing blood flow: an endothelium-dependent mechanism that fails in patients with atherosclerosis. *J Am Coll Cardiol* 1990;16:349–56.
4. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373–6.
5. Hsu HY, Chen YT, Sheu WH, Sheng WY, Chao AC. Comparison of brachial artery flow-mediated vasodilatation in symptomatic and asymptomatic patients with carotid arterial stenosis. *Am J Cardiol* 2002;90:814–6.
6. Hsu HY, Wang PY, Chen YT, Sheu WHH, Hu HH, Sheng WY. Changes in flow-mediated dilatation, cytokines and carotid arterial stenosis during aggressive atorvastatin treatment in normocholesterolemic patients. *J Chin Med Assoc* 2005;68:53–8.
7. Laurent S, Lacolley P, Brunel P, Laloux B, Pannier B, Safar M. Flow-dependent vasodilation of brachial artery in essential hypertension. *Am J Physiol* 1990;258:H1004–11.
8. Enderle MD, Schroeder S, Ossen R, Meisner C, Baumbach A, Haering HU, Karsch KR, et al. Comparison of peripheral endothelial dysfunction and intimal media thickness in patients with suspected coronary artery disease. *Heart* 1998;80:349–54.
9. Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64–70.
10. Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 2001;103:1191–3.