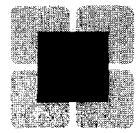

WILLIAM S. WILKE, MD, EDITOR

IMPROVING CORONARY VEIN GRAFT RESULTS

Despite our greater understanding of the process of coronary atherosclerosis, it is still the leading cause of death in the United States. While coronary artery bypass graft (CABG) surgery may substantially improve symptoms and survival, it cannot stop the progression of disease, which continues—at an accelerated pace—in saphenous vein grafts.

Can we slow the atherosclerotic process in patients with saphenous vein grafts? Can risk-factor modification improve vein graft patency or patient survival? Recent findings link elevated cholesterol levels to more rapid vein graft atherosclerosis and reduced event-free survival after coronary bypass.

ACCELERATED PROCESS

The development of atherosclerosis in vein grafts is more accelerated than the process in native vessels, but similar in that it involves trauma to the vessel wall, platelet aggregation, thrombus formation, and lipid deposition. The evolution from normal, thin-walled veins to dramatic, obliterative atherosclerotic lesions typically takes 2 to 12 years following surgery.

Vein graft surgery represents trauma, with transposition of the endothelium from a venous low-pressure system into an arterial high-pressure environment. Platelet aggregation is a part of the process, and antiplatelet therapy has been effective in reducing vein graft occlusion. Lipid accumulates in the walls of vein grafts in foam cells and lipid-rich lesions similar to those occurring in native-vessel atherosclerosis. The difference is that in vein grafts, the foam cells accumulate in surface layers superimposed on intimal proliferation. This predisposes to hemorrhage, ulceration, and thrombosis.

In about 10% of grafts, early flow-related closures occur perioperatively, probably because of aberrations in surgical technique, restrictive anastomotic sutures, or kinks associated with closure of the chest. Intimal proliferation develops in the following 2 to 12 months in all vein grafts and may be an atherosclerosis precursor. Vein graft stenosis occurs in 2% of grafts per year for the first 5 years and in 4% per year thereafter. Half of all vein grafts are closed 10 years postoperatively.

PREDICTING STENOSIS, SURVIVAL

The likelihood of graft stenosis increases with time and elevated preoperative levels of cholesterol and triglycerides, as shown by our study of 6,011 patients who underwent coronary bypass at The Cleveland Clinic Foundation from 1972 to 1981 and who had subsequent cardiac catheterization. The relationship between vein graft narrowing and lipid levels was present after the first 2 years postoperatively, but not during the first 2-year postoperative period. This suggests a different pathogenesis for early *v* late disease in vein grafts.

Preoperative lipid levels also predict event-free survival. A separate study evaluated 5,000 patients (the first consecutive 1,000 patients who underwent coronary bypass at the Cleveland Clinic during each of the 5 years from 1972 through 1976) at 5 years and 10 years postoperatively. We found that event-free survival (events being death, myocardial infarction, recurrent angina, and reoperation) correlated inversely with preoperative cholesterol and triglyceride levels. For example, 10-year event-free survival occurred in 66% of patients with preoperative total cholesterol <199 mg/dL, compared to 59.6% of patients whose total cholesterol ≥300 mg/dL. Event-free survival 10 years after CABG was 67% in patients with triglyceride levels <99 mg/dL, compared to 59.8% with triglyceride levels >250 mg/dL. The study showed that hyperlipidemia affects anatomy and patency as well as symptoms and survival.

IS PREVENTION EFFECTIVE IN THE POST-CABG PATIENT?

Evidence from the Lipid Research Clinics trial and the Multiple Risk Factor Intervention Trial (MRFIT) indicates that risk factor modification reduces the likelihood of atherosclerotic events in native vessels, but its impact on vein grafts is less well understood.

Whether treatment can slow or stop the progression of disease in coronary saphenous vein grafts is being addressed in the 5-year multicenter Post-CABG Inter-

vention Trial, funded by the National Heart, Lung, and Blood Institute. The Cleveland Clinic Lipid Research Clinic and four other clinical centers will evaluate the effects of cholesterol-lowering and antithrombosis therapy on the rate of stenosis and patency of aortocoronary saphenous vein grafts. The trial, to involve 1,200 patients, will compare high- with low-dose lovastatin therapy, and low-dose anticoagulation with placebo.

WILLIAM J. STEWART, MD
Department of Cardiology

BIBLIOGRAPHY

Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco MD, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol niacin treatment for coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987; 257:3233–3240.

Stewart WJ, Goormastic M, Healy BP, et al. Clinical outcome 10 years after coronary bypass: effects of cholesterol and triglycerides in 4913 patients (abstr). J Am Coll Cardiol 1988; 11:7A.

Stewart WJ, Goormastic M, Lytle BW, et al. Saphenous vein graft patency after 2 years is related to preoperative serum cholesterol and triglyceride levels (abstr). J Am Coll Cardiol 1988; 11:7A.

INTERFERON FOR CHRONIC HEPATITIS

Until recently, the treatment of chronic viral hepatitis was entirely supportive, with no practical therapy that could be directed against the underlying hepatic infection. The recent promise shown by interferons against some cases of chronic viral hepatitis signals a new era in the treatment of this disorder.

RATIONALE FOR THERAPY

Interferons are approved by the Food and Drug Administration for use in hairy-cell leukemia and approval is being sought for their use in chronic hepatitis C. Interferons are glycoproteins whose production in the body is stimulated by a variety of viruses, including those that cause hepatitis. Liver biopsies from patients with chronic active hepatitis demonstrate focal clusters of alpha interferon-containing mononuclear cells and fibroblasts, and interferon may be briefly detected in the serum within a few weeks of exposure to hepatitis B.

Chronic hepatitis develops when the infection fails to clear, possibly because of a deficiency in interferon production. Accordingly, the administration of exogenous interferon may result in improvement.

CHRONIC HEPATITIS B

Although hepatitis B usually resolves spontaneously, there is enthusiasm now for immunoregulatory therapy, especially interferon. It is unknown whether one preparation is better than another, what the optimal dosage and duration of therapy may be, and whether the promising short-term benefits of interferon will be sustained long after treatment is stopped.

A promising regimen employs pretreatment with prednisone, 60 mg per day, for 2 weeks, and then tapered by 20 mg every 2 weeks. This is followed by the administration of alpha interferon, 5 million units daily for 3 months. This regimen resulted in a 44% clearance of viral B replication and improved liver histology; in 50% of patients, liver enzymes remained normal after treatment was stopped. The hepatitis B surface antigen (HBsAg) usually remains positive during and after therapy, but markers of viral replication, including the hepatitis B e antigen (HBeAg), hepatitis B virus DNA, and DNA polymerase may disappear.

A recent multicenter randomized trial confirmed the benefits of alpha interferon and suggested that pretreatment with prednisone was not statistically significantly better than the use of interferon alone. Many investigators use longer treatment periods, from 6 to 9 months.

It is not unusual for clinical hepatitis to flare during interferon treatment. Such a flare could have serious consequences for the patient with advanced cirrhosis because of the lack of hepatic reserve, and treatment probably should be withheld from these patients.

Unfortunately, only a minority of patients with chronic hepatitis B will benefit from interferon therapy. Those less likely to respond include males, patients who are HIV positive, individuals of Chinese descent, and patients with childhood onset of disease. Patients with high levels of viral replication also respond less often.

CHRONIC HEPATITIS C

Interferons show promise for some patients with hepatitis C. The dosages are usually lower than those used for hepatitis B. In one multicenter, 26-week study, 180 patients with chronic hepatitis C were randomized to receive 1 million units three times a week, 3 million units three times a week, or no treatment. The pretreatment SGPT averaged 175 U/L and this value fell to a mean of 95 U/L at a dose-dependent response rate. At the end of the trial, 46% of the high-dose group and 28% of the low-dose group had normal or near-normal SGPT levels. Among those who responded to treatment, nearly one