Long-term therapy of coronary artery disease: a vascular biology perspective

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When evaluating a patient with known coronary artery disease or a patient with hypercholesterolemia without overt clinical symptoms of coronary artery disease or other vascular disease, it is helpful to understand the vascular biology behind primary and secondary prevention. This article reviews the progression of the atherosclerotic plaque, endothelial function, and the impact of current modes of therapy.

(Key words: coronary artery disease, vascular biology, atherosclerosis, atherosclerotic plaque)

The American Heart Association Committee on Vascular Lesions has categorized the progression of the atherosclerotic lesion from the first lipid deposit in the intima to the ruptured plaque with thrombosis.1,2

The type I lesion, the initial lesion, is the lesion most frequently described in infants and children in all countries. The intima of a type I lesion is infiltrated with microscopic lipid droplets and macrophage-derived “foam cells” (macrophages with intracellular lipid deposit). Macrophages take up a limited number of low-density-lipoprotein (LDL) particles; however, once the LDL is oxidized, the macrophage uptake is markedly increased, leading to accelerated foam cell formation.

The type II lesion includes fatty streaks, which, on gross inspection, may be visible as yellow streaks, patches, or spots on the intimal surface of arteries. In the type II lesion, foam cells are stratified into layers and there are also more macrophages in the thickened intima, including macrophages without lipid droplets. T-lymphocytes have also been identified in these lesions. In autopsy studies among children aged 2 to 15 years, the majority have type II lesions in the aorta; in general, type II lesions develop in the coronary arteries around age 15 and increase in size and number with aging.

Type III lesions are an intermediate or transitional lesion characterized by microscopically visible cellular lipid droplets and particles forming pools among the smooth muscle cells in regions of intimal thickening; however, there is no “lipid-rich core,” a characteristic of the type IV lesion. The type III lesion is still reversible with cholesterol-lowering therapy.

When the extracellular lipid pools of the type III lesion coalesce into a lipid-rich core, the result is a highly disorganized intima, which is characteristic of the type IV lesion. Coronary arteries with type IV lesion may still appear normal on an arteriogram, because the plaque does rupture exposing the lipid core, tissue factor and collagen come into contact with circulating blood, thereby initiating the coagulation cascade. Platelets aggregate and release cytokines, attracting other cells to the region where the rupture is either repaired silently or unstable angina, myocardial infarction (MI), or death results.

Plaque rupture is common. Davies and Thomas4 found at least 103 ruptured plaques in 74 patients who died suddenly of ischemic heart disease. In a later study, they found incidental ruptured plaques in 9% of persons who died of noncardiac causes and 22% of patients with hypertension or diabetes who died of noncardiac causes.

Cholesterol reduction

What impact does cholesterol reduction have on the atherosclerotic plaque? It has been demonstrated that cholesterol reduction, especially through the use of hydroxymethylglutaryl coenzyme A (HMG

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CoA reductase inhibitors (statins), lowers the risk of cardiovascular mortality and the need for cardiovascular intervention. In lipid trials, the decrease in cardiovascular events occurs early in the course of lipid-lowering therapy before plaque regression could occur. As reported in a number of angiographic (regression) studies, only a modest amount of plaque regression occurs (1% to 2%), even after years of therapy; however, the decreased risk of cardiovascular events is on the magnitude of 20% to 40% or more. How can this seemingly insignificant regression account for the large decrease in cardiovascular events?

Several studies have shown abnormal endothelial function in hyperlipidemic patients with and without cardiovascular disease.6-9 In these studies, the lowering of the cholesterol level not only improved endothelial function, but also decreased myocardial ischemia as manifested by the ischemic index via a 48-hour ambulatory monitor or myocardial perfusion via positron-emission tomography.10,11 It has been shown that normal endothelial function can be decreased within minutes of a fatty meal12 and abnormal endothelial function can be improved within minutes of apheresis in hypercholesterolemic patients.13 Because the majority of studies have been done with the statins, the predominant mechanism for this beneficial effect on the endothelium appears to be the lowering of the LDL-cholesterol (LDL-C) level. The statins have been shown to influence cholesterol metabolism in macrophages similar to their effect in hepatocytes. This effect has the potential to reduce macrophage activation, foam cell formation, and the thrombogenicity of the plaque. This reduction alters the lipid-to-cell ratio of the atherosclerotic lesion, which may make the plaque less prone to rupture. Lipid lowering also reduces the production of MMPs. The reduction of MMPs stabilizes the fibrous cap, and a decrease in the presence of cholesterol esters makes the lipid core more stable. Other pleiotropic effects of the statins independent of their lipid-lowering abilities have been suggested as additional mechanisms in plaque stabilization and in decreasing cardiovascular events. Experimental studies have suggested the statins, independent of their ability to lower cholesterol, can interfere with macrophage activation, smooth muscle cell migration and proliferation, inflammatory reactions, and platelet adhesion and aggregation.14,15

Thus, it has been shown that endothelial function can be altered acutely (minutes) or over time (weeks to months) with medications by a variety of mechanisms. This improvement in endothelial function may represent stabilization of the plaque, which in turn may be responsible for the early reduction in clinical events observed in the angiographic trials.

Along with the angiographic trials, the large-scale statin trials of the past decade have also revealed that consistent decreases in the LDL-C level corresponded with a decrease in clinical cardiovascular events.16

One of these large-scale trials was conducted at the University of North Texas Health Science Center at Fort Worth/Texas College of Osteopathic Medicine (TCOM).17 The AFCAPS/TexCAPS trial (Air Force /Texas Coronary Atherosclerosis Prevention Study) demonstrated the beneficial effects of lowering cholesterol in patients—including women and older patients—who have no evidence of atherosclerotic disease and have an “average” cholesterol level. Of the 6605 participants in AFCAPS/TexCAPS, 2868 were enrolled at TCOM. The participants had a baseline mean total cholesterol level of 221 mg/dL and LDL-C level of 150 mg/dL and received either lovastatin (Mevacor), 20 mg/d to 40 mg/d or placebo plus a low-fat diet. In the lovastatin-treated group, the LDL-C level was decreased to a mean of 115 mg/dL, a 25% decrease, whereas the placebo group had no significant change. The lovastatin-treated group had a significant decrease in the incidence of MI, unstable angina, coronary events, and coronary revascularization procedures. Examination of the composite endpoint of fatal or nonfatal MI, sudden death, or unstable angina shows that the survival curves begin to diverge in the first year and the difference increased as the study progressed through 5 years. This early effect on mortality implies an early effect on the coronary circulation more than just regression or prevention of progression. Although these patients were asymptomatic of any evidence of atherosclerosis at entry into the study, some of these participants probably had clinically silent advanced atherosclerotic disease. We would assume that cholesterol reduction in these asymptomatic patients stabilized the silent advanced lesions, thus decreasing the clinical events within the first year of the study.

As shown, cholesterol reduction may play a role in treating myocardial ischemia, stabilizing high-risk plaques, and decreasing clinical events. Studies utilizing endothelial function, angiographic changes, markers of inflammation, cellular proliferation, and platelet reactivity have all supported the concept of early and late changes of the vascular biology of the endothelium. This concept has been further supported by the reductions in early clinical events in the large-scale trials using lipid-lowering medications.

Role of antiplatelet agents in patients with coronary artery disease

Evidence for antiplatelet agents in secondary prevention of vascular disease was established by the Antiplatelet Trialists’ Collaboration.18 This medical analysis of 145 randomized trials of aspirin, dipyridamole (Persantine), sulfapyrazone, and ticlopidine hydrochloride (Ticlid) showed that aspirin reduced the risk of nonfatal MI and nonfatal stroke and vascular death by 25% in patients at high risk of occlusive vascular disease.

The evidence supporting aspirin in primary prevention is not as impressive. The Physicians’ Health Study, a randomized, placebo-controlled 5-year study using aspirin, 325 mg, in 2271 men, showed no reduction in mortality; however, in a subgroup analysis, there was decreased risk of MI in men older than 50 years. In the Nurses’ Health Study, a prospective cohort study of 87,678 women, those who took 1 to 6 aspirin per week had a decreased risk of MI but no significant decrease in mortality. In the European Stroke Prevention Study 2 Trial,19 the combination of low-dose aspirin (25 mg twice a day) and modified-release dipyridamole (Aggrenox) (200 mg twice a day) was superior to either agent prescribed singly in the secondary reduction of stroke; however, the reduction of MI did not reach clinical significance.

Ticlopidine and clopidogrel bisulfate (Plavix) have mainly been studied in secondary prevention trials. The Ticlopidine Aspirin Stroke Study (TASS)20 compared ticlopidine hydrochloride, 500 mg/d, with aspirin, 1300 mg/d, in patients who previously had a transient ischemic attack or minor stroke. In this trial, ticlopidine was superior to aspirin in reducing ischemic events. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) Trial21 compared clopidogrel bisulfate, 75 mg/d, with aspirin,
increased foam cell formation, and generation of oxygen-free radicals, contribute to proinflammatory and proatherosclerotic changes. Other risk factors for atherosclerosis include mechanical effects and metabolic factors. Mechanical factors include arterial injury, which can result in inflammation and proliferation of smooth muscle cells. Metabolic factors include increased levels of oxidized cholesterol, decreased high-density-lipoprotein (HDL) cholesterol levels, and increased triglyceride levels. These factors are risk factors for CAD, but their quantitative relation to major coronary events remains to be defined adequately in large prospective trials. Predisposing risk factors are those that contribute to the development of the causal and conditional risk factors.

The conditional risk factors are emerging as possible contributors influencing the vascular biology of the atherosclerotic lesion. It is beyond the scope of this review to detail all these factors as they relate to vascular biology; however, a brief review highlighting some salient issues may help to elucidate why these risk factors may take on a larger role in the future. Triglycerides are associated with a number of metabolic and physiologic changes that are risk factors for CAD. Elevated triglyceride levels have been associated with increased very-low-density-cholesterol rich remnants, increased chyomicron remnants, procoagulant changes, decreased high-density-lipoprotein cholesterol, and formation of small dense LDL-C. Small dense LDL-C itself has been proposed as a conditional risk factor because of its affinity to be oxidized, enhance foam cell formation, and contribute to proinflammatory and prothrombogenic activities. Lipoprotein (a) has been implicated in enhanced oxidation and generation of oxygen-free radicals, increased foam cell formation, and impaired fibrinolysis. Homocysteine has been associated with cytotoxic effects, enhanced oxidation, increased platelet activation, smooth muscle cell proliferation, procoagulant effects, and abnormal endothelial function. Plasminogen-activating factor inhibitor-1 is a procoagulant. It has also experimentally been shown to be an inhibitor of smooth muscle cell migration, and it may inhibit removal of necrotic debris from the plaque. Fibrinogen has been associated with procoagulants, enhanced platelet aggregation, and smooth muscle cell proliferation, and it may provide the scaffolding for collagen deposition on the endothelium. C-reactive protein is an acute-phase reactant that is an indicator for low levels of inflammation. Elevated levels have been associated with increased risk of CAD in both men and women. Whether this is a cause or an effect representing other inflammatory factors still needs to be determined. Whether modulation or treatment of these conditional risk factors, independent of other risk factors, will reveal a benefit in the vascular biology of the plaque resulting in a reduction in clinical events is still speculative.

Other therapeutic modalities have been tested experimentally in the treatment of atherosclerosis. Recently, the vasculoprotective effect of the angiotensin-converting enzyme (ACE) inhibitors has been suggested in the Heart Outcomes Prevention Evaluation (HOPE) study. In this study, 9297 subjects with proven vascular disease or diabetes plus one or more other risk factors were studied. These patients were treated with the ACE inhibitor ramipril (Altace) or placebo for 5 years. In spite of a minimal effect on blood pressure (decrease of 3/2 mm Hg) with ramipril, cardiovascular events were decreased 22%. The magnitude of benefit with an ACE inhibitor similar to that seen with lipid-lowering agents and antplatelets. The proposed effect of the ACE inhibitor on the vascular biology includes a proposed antioxidant effect, antiplatelet effect, inhibition of smooth muscle migration and proliferation, and improved endothelial function. Although provocative, several issues are still unresolved from the HOPE study. A large number of participants in HOPE had lipid abnormalities and were not treated; whether treatment of their lipids would attenuate the benefit from the ACE inhibitor is still unknown. Also 75% of the participants in the HOPE study were treated with aspirin, which has been reported to interact with ACE inhibitor to decrease their beneficial effect. The study did show a significant benefit, but it is not known whether the coadministration of aspirin diminished an even greater benefit, added more benefit, or was neutral.

Along with ACE inhibitors, several other therapeutic modalities are under study to see if they can add to our treatment of atherosclerosis.

Comment
Results from clinical trials have consistently demonstrated that reducing LDL-C corresponds with a decrease in clinical events in both primary and secondary
prevention. Smaller angiographic (regression) trials have demonstrated a modest degree of vascular end points which is disproportionate to the substantial reductions in clinical events. This observation suggests that mechanisms beyond the change in lumen size may account for the impressive clinical benefits. Factors mediating risk for plaque rupture, including the functional state of the vascular endothelium and the morphologic and biochemical makeup of the plaque, help to define the vascular biology of atherosclerosis. Medications affecting the vascular biology such as lipid-lowering and antiplatelet medications have been shown to decrease cardiovascular events. Medications such as ACE inhibitors also have been suggested to have a beneficial effect on the vascular biology, and they may represent new areas of research and therapeutic intervention.

References