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IVUS is redefining atherosclerotic disease



Steven E. Nissen, MD

Sensitive new cardiac imaging techniques, which make it possible to measure atherosclerotic plaque in the artery, suggest that regression of atherosclerosis may be possible with aggressive lipid-lowering therapy, said Steven E. Nissen, MD.

For the past 40 years, coronary atherosclerosis has been defined by looking at the coronary lumen with angiography. "The problem with this approach is that angiography doesn't show us the plaque," Dr. Nissen said. "This disease is not a disease of the lumen; it's a disease of the vessel wall. It is the atheroma in the vessel wall that determines the natural history and pathophysiology of the disease."

It is the atheroma in the vessel wall that determines the natural history and pathophysiology of the disease.

Intravascular ultrasound (IVUS) can image lesion characteristics more reliably than angiography and has shown that atherosclerotic burden begins earlier in life than expected. IVUS may also be a more reliable measurement of plaque regression in patients being treated with lipid-lowering agents.

Lessons from IVUS

IVUS involves the use of a 1-mm-diameter catheter rotating at 1800 rpm to produce real-time ultrasound images of the arteries at 30 frames per second.

Coronary disease is not an intraluminal disease; it's an extraluminal disease.

The traditional view that atheroma accumulation in the artery wall gradually narrows the lumen until angina occurs has been proved wrong, said Dr. Nissen. Instead, the detailed imaging provided by IVUS has proved the concept that the lumen does not narrow during atheroma development until very late in the process. Meanwhile, plaque accumulation causes compensatory remodeling in which the external elastic membrane of the vessel remodels outward, resulting in a moderately advanced atherosclerotic plaque with no reduction in lumen size (Figure). "That is to say, only 1 in 20 to 1 in 100 plaques actually appear as luminal narrowing," he explained. "The angiograms we perform so commonly have really misled us."

A vessel that appears completely normal (ie, no luminal narrowing) on angiography is often found to be burdened with atheroma on IVUS. "Coronary disease is not an intraluminal disease; it's an extraluminal disease," Dr. Nissen said. "The disease you don't see on angiography is the disease that will most often lead to the demise of the patient."

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Approximately two thirds of infarction sites are < 50% stenotic on angiography, and only about 1 in 7 acute myocardial infarctions (MIs) occurs at sites of hemodynamically significant stenosis as identified by angiography. "This is the reason epidemiologic studies show that the vast majority of patients do not present with angina. In two thirds of men and about half of women, the first manifestation of coronary disease is not angina, it is sudden death or an acute MI," Dr. Nissen said. "These patients have coronary atheromatosis but not stenosis, and they will not come to easy attention because they are not going to complain of ischemic symptoms."

IVUS studies have also shown that the atherosclerotic process starts at a young age. In 1 such study of hearts harvested for transplantation from young adults who died in motor vehicle accidents, 56% had clinically significant coronary disease, defined as plaques > 0.5 mm in thickness. Only 2% of these hearts

showed an abnormality on an angiogram (*Circulation*. 2001;103:2705-2710).

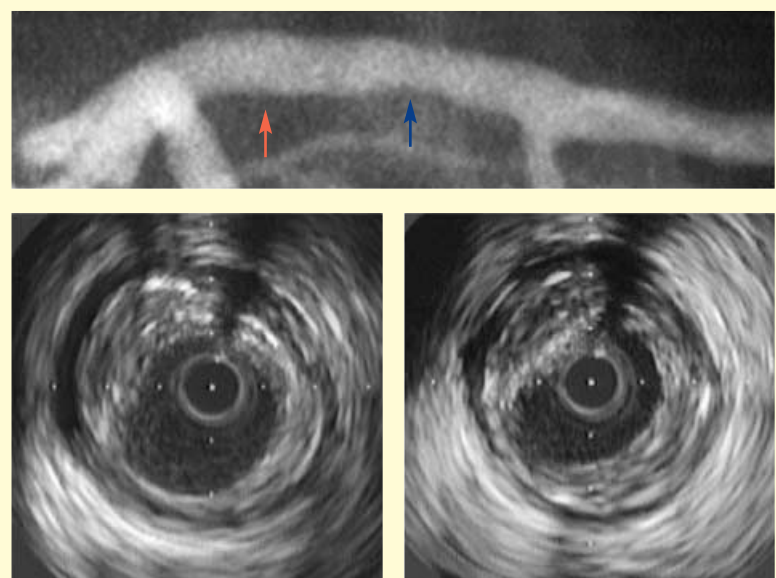
Preventing disease progression

Although relief of angina often occurs when stenotic arteries identified with IVUS are stented, morbidity and mortality from atherosclerotic disease will remain unchanged if only a mechanical approach is used to treat atherosclerotic disease. In every study of treatment of unstable angina with stenting or angioplasty, the risk of death and MI is the same after intervention as it was before, said Dr. Nissen. "And the same thing is going to be true for drug-eluting stents," he said. "Unless you treat this as a systemic disease and change the metabolic milieu that causes this disease to develop, the outcome is not going to be changed."

Two ongoing studies have been designed to test the hypothesis that very aggressive LDL cholesterol lowering can cause plaque regression.

Previous studies using angiography have shown that lipid-lowering therapy may slow progression of atherosclerosis, but does not reverse it. However, the lowest low-density lipoprotein (LDL) cholesterol levels achieved in these regression trials were approximately 100 mg/dL. More study is needed to determine the effects of much more aggressive lipid lowering on plaque regression.

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Figure**Diffuse coronary disease in a patient with diabetes**

Despite limited disease on angiography, both sites indicated by the arrows show severe atherosclerosis by intravascular ultrasound.

IVUS is redefining atherosclerotic disease

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The hypothesis for very aggressive lipid lowering to reduce plaque size was bolstered by observations made when the previously mentioned harvested hearts were transplanted into young patients without coronary disease. In 1 heart, Dr. Nissen said, a large, 8-mm² plaque observed with IVUS before transplantation was reduced to 6 mm² 1 year after trans-

plantation. The lumen size had not changed, but the plaque was reduced.

Ongoing studies

Two ongoing studies have been designed to test the hypothesis that very aggressive LDL cholesterol lowering can cause plaque regression. The ASTEROID trial [A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma

Burden] will measure change in coronary atheroma volume in 450 patients treated with rosuvastatin for 24 months. “This drug, given in the full therapeutic dose of 40 mg, can reduce LDL cholesterol by 60%, and potentially a little more than that,” said Dr. Nissen.

The parallel METEOR trial [Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin] will also evaluate rosuvastatin in

plaque regression using carotid ultrasound. Patients with as little as 20% stenosis will be enrolled in the trial.

With IVUS imaging of plaque mass and with drugs powerful enough to reduce LDL cholesterol to the level of that in children (60 mg/dL), “I think we can turn the clock back on this disease,” he said. “I am convinced that coronary disease is not a disease that is there forever.” ■