PROSPECT Aims to Identify Rupture-Prone Plaque

BY BRUCE JANCIN
Denver Bureau

CHICAGO — A furiously competitive race is on to develop new imaging methods capable of identifying vulnerable coronary plaques.

The first of these technologies to undergo evaluation in prospective clinical trials are virtual histology, palpography, thermography, and multislice computed tomography. They are being assessed in the pioneering Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, a 700-patient international trial whose initial enrollees have completed their first year of follow-up, Dr. Gregg W. Stone said in his Hildner Lecture at the annual meeting of the Society for Cardiovascular Angiography and Interventions.

But PROSPECT is only the beginning. At least 14 different noninvasive and 28 catheter-based invasive diagnostic techniques aimed at detecting vulnerable plaques are in development, according to Dr. Stone, professor of medicine at Columbia University and vice chairman of the Cardiovascular Research Foundation, New York.

The goal of this effort is to identify asymptomatic coronary lesions that are active, inflamed, and prone to rupture so that in theory they can be preemptively treated before they cause an acute MI.

At this point, progress in vulnerable plaque imaging is well ahead of actual treatment. It is clear, however, that statins and lifestyle modification are not going to be sufficient. This was amply demonstrated in the Pravastatin Or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, in which patients with a history of acute coronary syndrome had a 22% coronary event rate over 2.5 years despite being on 80 mg/day of atorvastatin, Dr. Stone said.

Once it's established that vulnerable plaques can reliably be identified, more aggressive interventions might include drug-eluting stents for high-risk lesions, or catheter-delivered cryoplasty or photodynamic therapy for regional treatment, although all of this will require demonstration of clinical benefit in prospective trials, he continued.

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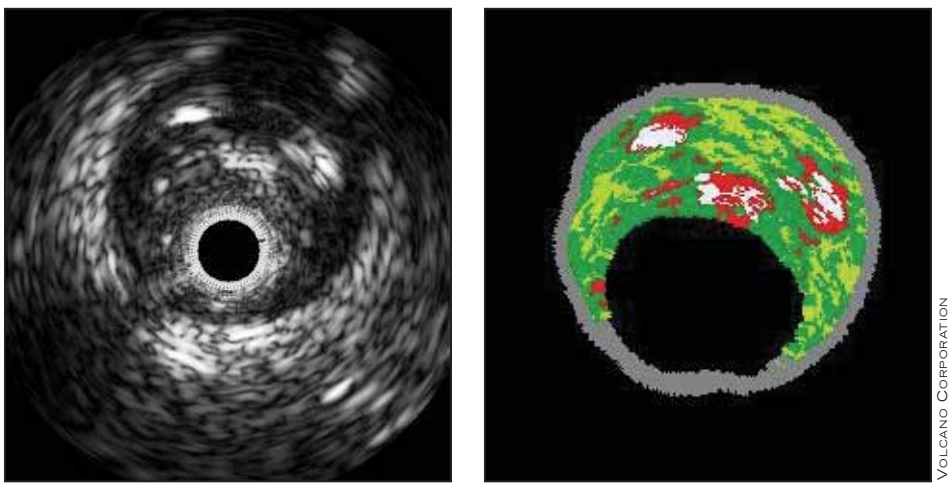
DR. STONE

Noninvasive imaging methods are most attractive as tools for population screening, since they in general pose less risk than invasive methods. That's not always true, though. Multislice CT, the noninvasive method that has garnered by far the greatest interest, entails significant exposure to radiation and nephrotoxic contrast media, Dr. Stone noted.

Invasive imaging techniques are more time consuming. But placing a catheter next to an atheroma yields a wealth of data on structure and function.



VOLCANO CORPORATION

Shown are IVUS image of a coronary atheroma (left) and a virtual histology image (right), which uses IVUS spectral analysis to produce a color tissue map of plaque composition. Green represents fibrous tissue, red indicates a necrotic core within the plaque, and white shows a calcified area.

Invasive imaging methods fall into three broad categories: those that assess plaque morphology, such as virtual histology, optical coherence tomography, and vaso vasorum imaging; tools for evaluating plaque activity or composition, including thermography, spectroscopy, and intravascular MRI; and methods of studying a plaque's physical properties, such as palpography, which measures endothelial sheer stress at the plaque's cap.

Thermography relies on the observation that inflamed, unstable coronary plaques have a consistently slightly higher temperature than indolent ones.

Virtual histology utilizes intravascular ultrasound (IVUS) spectral analysis to assess plaque composition in four colors rather than the standard IVUS gray scale. This imaging tool, which has been validated in an ex vivo histology study using autopsy specimens, is commercially available from Volcano Corp. Virtual histology permits classification of coronary lesions into four types: fibrous, fibro-fatty, densely calcified, or—what is believed to be most worrisome—plaque having a necrotic core, explained Dr. Stone, who is principal investigator of the PROSPECT study.

PROSPECT, funded by Guidant Corp., is a natural history study in which plaque-imaging findings in patients with acute coronary syndrome will be prospectively correlated with future coronary events during 2-5 years of follow-up.

Dr. Stone is a consultant to Guidant, Volcano, and numerous other medical device manufacturers. ■

Invasive Imaging Methods Target Vulnerable Coronary Plaques

BY BRUCE JANCIN
Denver Bureau

CHICAGO — Intriguing invasive methods of identifying vulnerable coronary plaques include vaso vasorum imaging, intraarterial MRI, and several variants of optical coherence tomography, according to speakers at the annual meeting of the Society for Cardiovascular Angiography and Interventions.

▶ **Vaso vasorum imaging.** The vaso vasorum—the microcapillaries that form in the adventitia adjacent to atherosclerotic plaque in response to vascular injury—become more dense as inflammation due to macrophage activity increases. And this inflammation is a key factor in plaque rupture, said Dr. Stephane Carlier of Columbia University, New York.

He and his coworkers have developed an intravascular ultrasound–based technique that uses gas-filled microbubbles for contrast enhancement in order to assess vaso vasorum density and identify areas of intraplaque leakage or hemorrhage.

The hypothesis is that these findings will correlate with high likelihood of plaque rupture, said Dr. Carlier, who is also director of intravascular imaging and physiology at the Cardiovascular Research Foundation in New York.

▶ **Intraarterial MRI.** Conventional magnetic resonance imaging using a big external magnet isn't well suited for evaluating the composition of atheromatous plaques. Adequate resolution is difficult because the coronary arteries are small, are situated deep in the thorax, and move with respiration and systolic motion of the heart.

Intraarterial MRI is a novel imaging method that sidesteps these obstacles. There is no external magnet. Magnet and coil are incorporated within the probe, which also contains radiofrequency transmission and receiver units. Unlike conventional MRI, the intraarterial version doesn't provide pictures of the arteries in cross section; instead, it is designed specifically to analyze the lipid content within the arterial wall.

The current device is No. 6 French and deployed in a No. 8 French guiding catheter. A balloon is inflated to push the probe against an arterial plaque. Interrogation of the lesion takes about 25 seconds, according to Dr. Robert L. Wilensky, a cardiologist at the University of Pennsylvania, Philadelphia.

A 29-patient phase I study has been completed. A larger phase II international trial evaluating higher-risk patients will begin soon. Efforts are also underway to streamline the delivery catheter from No. 8 to No. 6 French, added Dr. Wilensky, who heads the scientific advisory board for TopSpin Medical, the Israeli company developing intraarterial MRI.

▶ **Optical coherence tomography.** This extremely high-resolution, broadband, light-based imaging method provides tremendous structural detail. With a theoretic resolution of 5-7 m and somewhat less in actual practice, optical coherence tomography (OCT) is well suited for in-depth morphologic evaluation of thin-capped fibroatheromas, the plaque type believed to be at greatest risk of rupture and resultant myocardial infarction, said Dr. Gregg W. Stone, professor of medicine at Columbia University and vice chairman of the Cardiovascular Research Foundation.

There is a daunting obstacle to commercial development of OCT, however: At present, the intravascular probe requires arterial occlusion, as do OCT's variants, including optical frequency domain imaging and polarization-sensitive OCT.

Optical frequency domain imaging "is basically OCT on steroids," according to Dr. Stone. "It allows much, much faster acquisition rates. In fact, you can pull back at up to 12 mm/second, so you could image a whole coronary artery in 5 or 6 seconds and get incredibly high-resolution images."

Polarization-sensitive OCT takes advantage of the birefringence of collagen fibers, enabling physicians to readily separate collagen from noncollagen tissues, said Dr. Stone. ■

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