REVIEW

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Shortcomings of coronary angiography and their implications in clinical practice

ABSTRACT

Physicians must interpret coronary angiography with caution and skepticism. Coronary angiography is considered the gold standard for defining coronary artery anatomy, diagnosing coronary artery disease, and guiding intervention. However, it does not provide functional information and may be misleading.

KEY POINTS

Because angiography images a three-dimensional artery in two dimensions, it can either overestimate or underestimate the severity of coronary artery disease.

Most myocardial infarctions are caused by small, unstable lesions that are invisible on angiography, rather than by the large lesions that angiography reveals.

A vessel can actually adapt its structure to accommodate, and thereby conceal, an atheroma.

Atheromas have a tendency to develop at arterial bifurcations, where they are particularly difficult to detect on angiography.

Recent lipid-lowering trials have shown that angiography is surprisingly ineffective at predicting an MI or determining post-MI prognosis.

Physicians should not rely on angiography alone in deciding whether to perform an intervention such as coronary artery bypass grafting or angioplasty, but rather should use angiography in conjunction with a physiologic test such as thallium stress testing.

ALTHOUGH ANGIOGRAPHY is one of the most important diagnostic advances of the 20th century, it has too often been placed inappropriately on a pedestal of infallibility. Angiography is subject to considerable misunderstanding and misuse, and its limitations are many.

For example, although angiography measures the size of the lumen, it does not do so with a high degree of accuracy. Moreover, the size of the lumen does not always correlate with the severity of symptoms, and the composition of the plaque may be more important than the lumen size in predicting a myocardial infarction.

For these reasons and others, no physician should base a treatment decision on an angiogram without understanding its limitations. Although angiography remains an invaluable diagnostic test, caution is warranted in interpreting angiographic results.

ANGIOGRAPHY DOES NOT MEASURE CORONARY ARTERY DISEASE ACCURATELY

For a number of reasons, angiograms can either overestimate or underestimate the degree of coronary obstruction.

The angle of view affects the measurement

An angiogram provides a two-dimensional silhouette of a three-dimensional structure. But many different luminal sizes and shapes can yield the same silhouette on angiography. Moreover, the angle of the angiographic view can misrepresent the degree of stenosis (FIGURE 1).

How severe is the stenosis? Pick a number

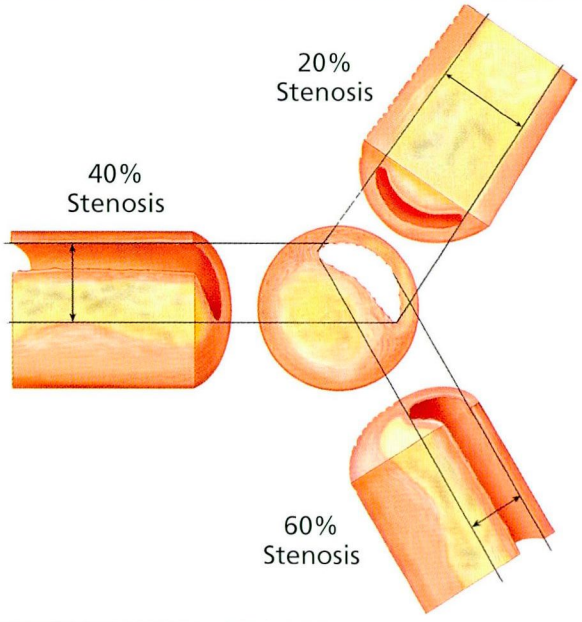

FIGURE 1. The perceived severity of a stenotic lesion can vary according to the angle of the angiographic view. The degree of stenosis in this obstruction can be interpreted as either 20%, 40%, or 60%. Approximately one third of all coronary lesions exhibit this lack of symmetry. Viewing multiple images from different angles does not solve the problem.

Angiography's resolution is surprisingly limited

Most coronary arteries are between 2 mm and 3 mm in diameter, but angiography can resolve only approximately 0.2 mm. This degree of resolution is not sufficient to allow for a precise diagnosis of all lesions. Angiography cannot detect structures smaller than 0.2 mm, and so can miss small but important thrombi.

Reference segments may themselves be narrowed

A common misconception is that coronary artery disease (CAD)—indeed, all vascular disease—consists of a focal narrowing in an otherwise normal vessel. Thus, it is common in angiographic studies to measure the diameter of a narrowed segment and compare it with that of a supposedly "normal" segment nearby to calculate the degree of stenosis.

However, by the time most patients with CAD undergo angiography, their disease is fairly extensive. What their angiograms actually show is a narrow target vessel in a network of other narrow vessels. The physician can underestimate the severity of the target stenosis because the reference segment with which it is being compared is itself stenotic. This is a common reason for false-negative angiograms.

Evidence of this underestimation was gathered in a study[1] in which interventional cardiologists who were about to perform percutaneous transluminal coronary angioplasty (PTCA) were asked to place an intravascular ultrasound probe at the most normal-appearing site in the artery, ie, the site they believed would be least likely to be stenotic. When they did, they found that the average degree of stenosis at the sites they selected was almost 40%; some of these vessels had 60% to 70% narrowing. While there are indeed CAD patients whose disease is restricted to the target lesion, they are few.

The opportunity for underestimation of narrowing is especially rife in persons with diabetes, who often have vessels that are narrower than normal due to diffuse atherosclerosis.

In somewhat the same fashion, angiography can be fooled by a "pseudostenosis." This can occur when the lumen of a target artery is compared with an apparently normal, but in fact overly large, lumen in a nearby artery. For example, next to a dilated distal left main artery, a normal proximal main artery may appear stenotic. If the physician were to rely on angiography alone, the patient may well undergo unnecessary intervention.

Vessel remodeling: Atheroma without stenosis

Another reason why angiography can fail to identify CAD is that a vessel can actually adapt its structure to accommodate, and thereby conceal, an atheroma (FIGURE 2). The mechanism of vessel remodeling was first hypothesized in 1987 by Glagov and colleagues,[2] who found that when an atheroma first develops on the wall of a heretofore normal artery, the adventitia sometimes responds by remodeling outward, while the lumen maintains its original size.

Because angiography shows only the lumen, a remodeled vessel will appear normal when, in fact, it is harboring an atheroma. This can occur even in patients whose level of

Vessel outward remodeling in coronary artery disease

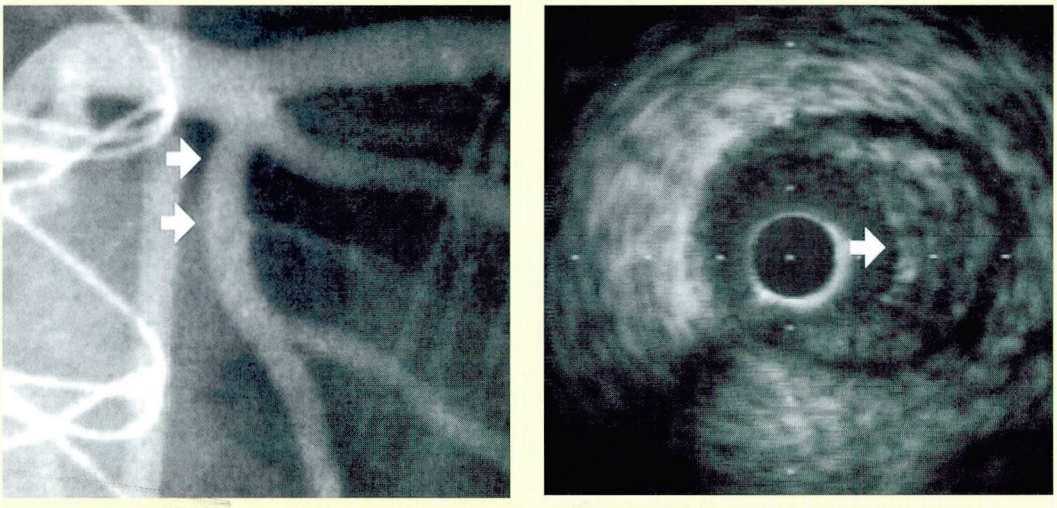

FIGURE 2. Vessels can change their shape to accommodate an atheroma. Left, angiography shows apparently stenosis-free proximal left circumflex artery (arrows). Right, intravascular ultrasonography on the same segment reveals the presence of a large, crescent-shaped atheroma that occupies about 50% of the luminal area. Angiography could not detect the lesion because the adventitia had remodeled outward, which allowed the lumen to remain circular and to maintain the same size as the adjacent uninvolved segment.

SOURCE: FROM TOPOL AND NISSEN, REFERENCE 1.

CAD is moderately severe. Angiography cannot identify the diseased lesion until the adventitia reaches a point of maximum expansion and the lumen is finally reduced in size. Glagov's theory was considered radical at the time, but it was eventually confirmed.

Of interest, there is also a "reverse Glagov phenomenon." Just as atherosclerotic material will induce the adventitia to remodel outward, regression of a lesion will cause the same adventitia to remodel back inward again, while the size of the lumen remains constant. Because angiography cannot detect the reverse Glagov phenomenon, it cannot demonstrate that drug therapy is proving successful in promoting lesion regression.

Plaques in bifurcations are difficult to detect

Atheromas have a predilection to develop at arterial bifurcations. However, the conjoining of two vessels often shields the lesion from view. All bifurcations have some degree of overlap between the "parent" and "child" vessels, and this overlap prevents the angiogram from accurately depicting the lumen. As a result, lesions in the sites that are most likely to become diseased are also the most difficult to detect on angiography. Therefore, some symptomatic patients who have positive functional studies may exhibit no angiographic evidence of a lesion.

Angioplasty distorts luminal shape

Distortion from a previous PTCA can skew the angiographic view. When the balloon is inflated, it can cause plaque to crack or split. When contrast medium is subsequently introduced into the area, the dye fills the cracks as well as the lumen, and the lumen appears larger than it is (FIGURE 3).

Approximately 35% to 40% of patients experience recurrent symptoms after undergoing balloon angioplasty. In my experience, approximately half of these patients did not have a successful PTCA to begin with, but their angiograms led us to believe that those angioplasties had indeed been successful. Approximately two thirds of all PTCAs end

Vessels sometimes respond to atheroma by remodeling outward

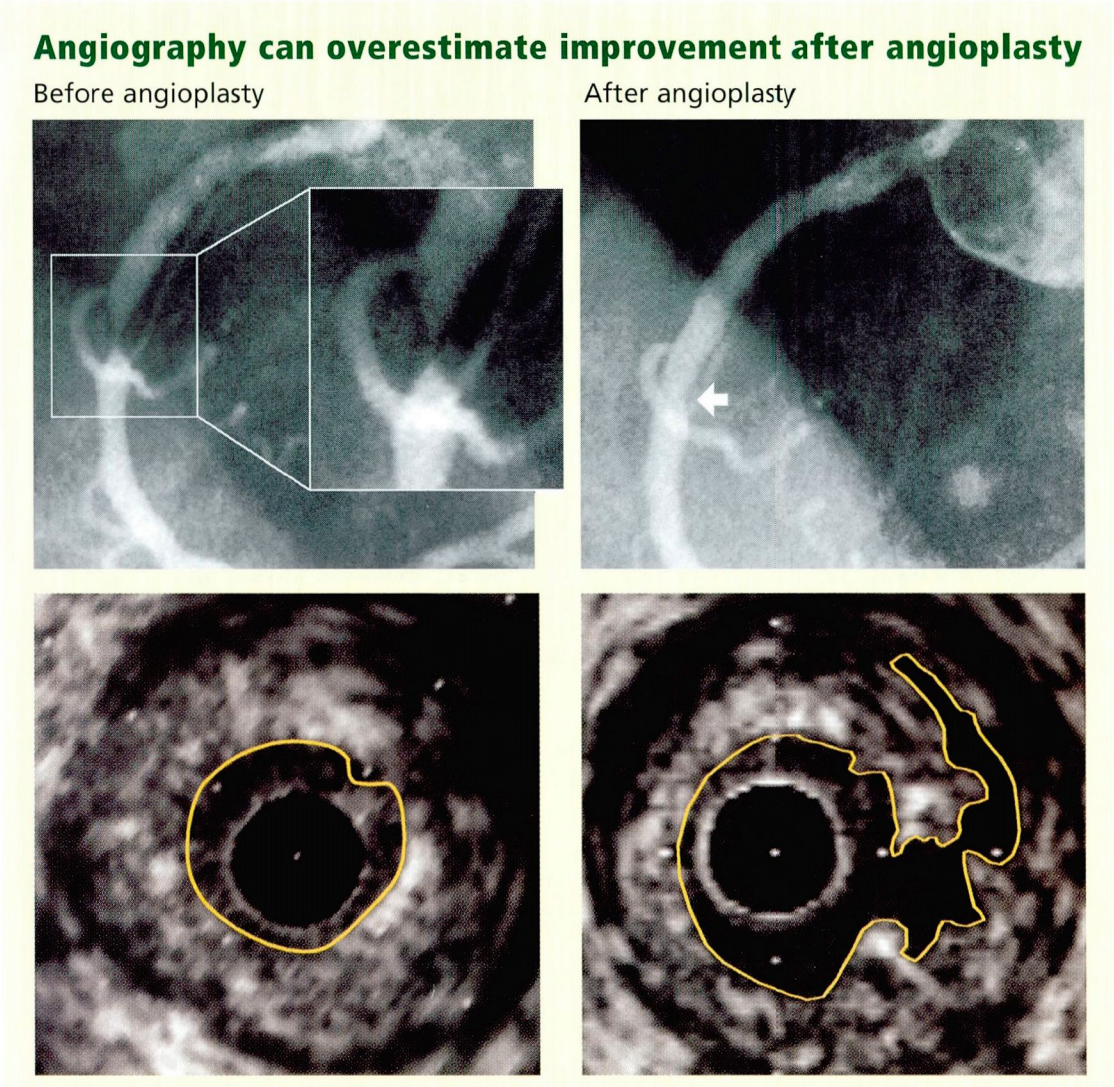

FIGURE 3. Left, preangioplasty angiogram (top) and intravascular ultrasonogram (bottom) of the right coronary artery show a concentric, fibrotic lesion and a lumen cross-section area of less than 0.25 mm^2. Top right, postangioplasty angiography indicates a 25-fold increase in cross-section area to 6.25 mm^2. Bottom right, postangioplasty ultrasonogram shows that the actual increase in lumen cross-section area was only about twofold. During angiography, the contrast medium infiltrated the scimitar-shaped tear in the plaque, which the angiogram misidentified as part of the lumen.

Lumen diameter may be less important in MI than once thought

with a good result. The difficulty is in relying on angiography to identify the sizable minority of patients who did *not* achieve a successful result.

ANGIOGRAPHY CORRELATES POORLY WITH PHYSIOLOGIC MEASURES

Another drawback of angiography is that it cannot discriminate between small differences in stenosis that may make a large difference in exercise tolerance.

At the start of exercise, the heart responds almost instantly to oxygen demands by increasing blood flow. The magnitude of the increase in flow is called "coronary flow reserve," and its measurement is the most precise indicator of the physiology of the coronary circulation. A normal flow reserve

is a fivefold to sevenfold increase. Patients whose reserve is sufficient to meet oxygen demands can exercise without angina. Patients whose reserve is inadequate experience symptoms.

The difficulty arises when the degree of stenosis in a coronary artery approaches 70% to 80%. Most patients with 70% stenosis have minimal diminution in coronary flow reserve in the affected vessel. Despite the significant amount of obstruction, they do not usually experience angina during exercise. However, in a vessel with an 80% stenosis, the coronary flow reserve is only about half as great (FIGURE 4). Such patients would very likely experience angina during moderate exertion. The difference between a 70% and an 80% stenosis can represent the difference between a normal and a markedly impaired coronary flow reserve.

Physicians should not rely on an angiographic estimate of the degree of stenosis as the basis for a decision to intervene. Thus, it would not be prudent to perform coronary artery bypass graft (CABG) surgery solely on the basis of an angiographic estimate of 75% stenosis, because the angiogram cannot distinguish small differences in stenosis.

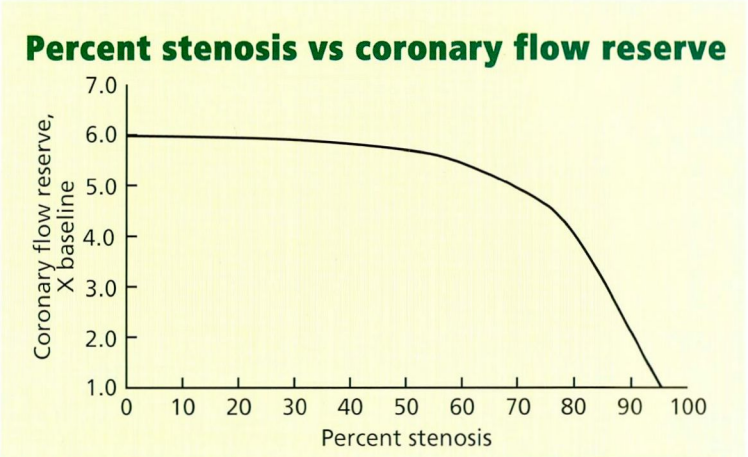

FIGURE 4. Coronary flow reserve remains normal until the degree of stenosis reaches approximately 60%. Thereafter, flow reserve declines, slowly at first and then rapidly and exponentially.

ANGIOGRAPHY DOES NOT DISTINGUISH DIFFERENT TYPES OF PLAQUE

Angiography shows an image of the lumen only, not the vessel wall. But CAD is not a disease of the lumen, it is a disease of the vessel wall. The analogy is that angiography shows the hole in the doughnut when it would be more useful to see the doughnut itself. Certainly, the goal of PTCA and stenting is to enlarge the lumen, but the target of these procedures is the vessel wall.

When planning to intervene, it is important to know the composition of the target lesion to avoid complications and to ensure the best opportunity for a successful result. Although all narrowings look the same on an angiogram, every atheroma is different—not only in size but in composition. And angiography does not reveal the makeup of a lesion.

Interventions are risky in calcified lesions

This shortcoming is particularly evident when angioplasty is planned on a lesion that the physician does not know is calcified. The risk of failure and complication is substantially higher in a calcified vessel than in one that is not calcified.

For example, a PTCA attempted on a circular, "napkin ring"-shaped calcification may well prove futile. The stenosis may not dilate, regardless of how many atmospheres were forced into the balloon. A more dangerous situation arises if the target lesion is a horseshoe-shaped calcification, in which the open end of the horseshoe is made up of soft plaque (FIGURE 5). Upon dilation, the balloon would expand toward the open end of the horseshoe, where the resistance is least. The force might push the two prongs of the horseshoe apart, and they could puncture the vessel wall and cause a vessel-threatening dissection.

A small difference in stenosis can make a big difference in symptoms

Tuzcu et al[3] conducted a study on the prevalence of calcification in arteries that had been targeted for intervention. The investigators showed a series of angiograms to a group of experienced angiographers and asked them to identify which lesions were calcified. The angiographers reported that 27% of the lesions were calcified—17% of them extensively so. However, when intravascular ultrasonography was performed, the investigators found that the angiographers had identified only half of the calcified lesions that were present: 52% of the lesions were calcified, 33%

A horseshoe calcification can be hazardous during angioplasty

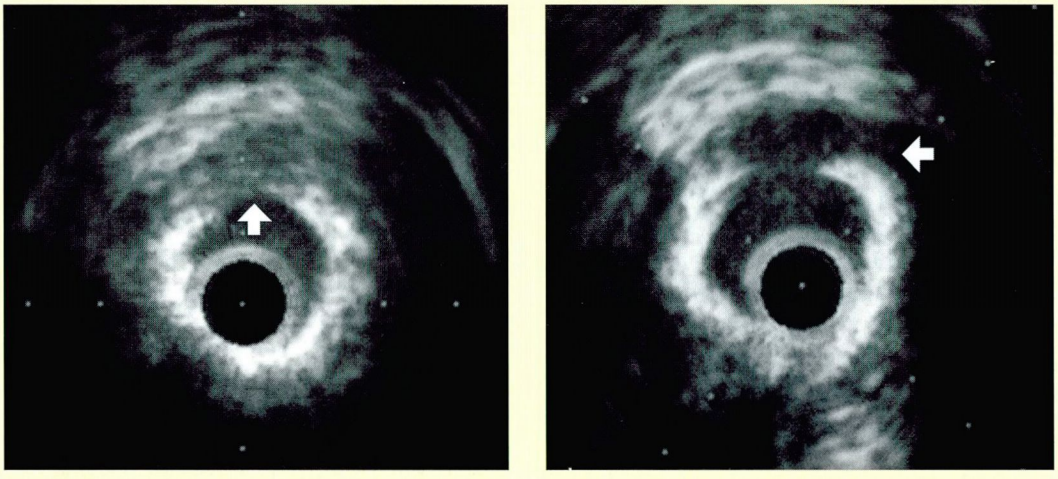

FIGURE 5. Intravascular ultrasonography illustrates the hazards of undetected calcification. Left, the arrow points to the open end of a horseshoe-shaped calcium deposit after Rotablator treatment. Right, the same lesion after balloon angioplasty. When the balloon was inflated, it expanded toward the open end, which was composed of soft plaque, and it forced the ends of the horseshoe to separate and puncture the vessel wall (arrow). The complication was serious and the patient required multiple stents.

Practitioners too often treat lesions without knowing that they are calcified

extensively so. The implication is that practitioners far too often treat lesions without knowing that they are calcified.

Small, unstable lesions cause myocardial infarctions

Angiography offers surprisingly little value in predicting a myocardial infarction because it does not identify the small, unstable lesions that are more likely to cause a myocardial infarction or death.

This shortcoming came to light during the past decade, when a spate of lipid-lowering trials[4–6] consistently showed that lipid-lowering drugs reduce morbidity and mortality but produce virtually no increase in lumen diameter. For example, in the FATS (Familial Atherosclerosis Treatment Study),[4] patients who received nicotinic acid and the bile acid sequestrant colestipol had an 80% lower incidence of morbid coronary events than did placebo controls. But when investigators performed follow-up angiography on these patients, they found a mean increase in lumen diameter of only 0.7%. Likewise, the STARS (St. Thomas' Atherosclerosis Regression Study)[5] found an 89% reduction in events with only a 1.9% increase in lumen diameter. Other studies showed similar results.[6]

The disparity between the large reduction in coronary events and the minimal improvement in lumen diameter seems to indicate that the diameter of the lumen does not play as dominant a role in myocardial infarction as one would expect. A meta-analysis found that 68% of the lesions that caused a myocardial infarction were small (< 50% stenosis), and only 14% were severe (> 70% stenosis).[7]

These small, dangerous lesions are made up of soft, lipid-rich plaque that is prone to rupture and subsequent thrombosis. However, over time, lipid-rich plaques tend to become fibrotic, and finally calcify. Lipid-lowering therapy prevents a myocardial infarction by altering the composition of these unstable lesions, though not affecting their size very much. On angiography, these small lesions may be barely visible or not visible at all, as may the response to lipid-lowering therapy.

Angioplasty opens high-grade stenoses and alleviates angina, but it does not prevent

a myocardial infarction or prolong life because it is not directed against the small, unstable lesions that cause a myocardial infarction and death. The same holds true for stenting. CABG, on the other hand, does prevent a myocardial infarction and improve survival because it provides an alternate conduit for blood to follow in the event that a plaque ruptures and occludes a vessel.

RECOMMENDATIONS

Angiography has a vital clinical role, but physicians should keep in mind its limitations. Angiographic findings should not be the sole criterion for intervention. Short of finding a 99% stenosis, there is no such thing as "angiographically significant" (or insignificant) lesions. Anatomy does not define the need for surgery or angioplasty, physiology does. In addition to stenosis, it is necessary to have evidence of reversible ischemia. Therefore, if a patient's symptoms are suspicious, I believe it is often prudent to first perform a physiologic test such as a thallium stress test, and reserve angiography for patients in whom one anticipates the need for CABG or PTCA. We should also remain open to additional methods, such as intravascular ultrasound and Doppler studies.

OTHER IMAGING STUDIES

Angiography can be augmented by other imaging studies.

Intravascular ultrasound is an excellent technique that, unfortunately, is not feasible for every patient. Its cross-sectional image of the coronary artery provides a view of both the hole *and* the doughnut. Furthermore, it can easily distinguish the different types of plaque morphology. For example, the sonographic signature of a cholesterol-rich atheroma is sonolucence, because lipid does not reflect much ultrasound. Ultrasound can identify fibrous plaques more easily because these lesions are more echogenic, and it can detect calcified plaques because the sound waves cannot penetrate calcium. On angiography, all types of atheromas look the same.

Until now, no head-to-head studies have compared the value of angiography and intravascular ultrasound in gauging the response to medical therapy. My colleagues at the Cleveland Clinic and I are about to launch the first large multicenter comparison. We will perform baseline ultrasound and angiography on patients with early, minimal coronary artery disease who do not yet have any need for intervention, and we will follow these patients for 18 months. Patients with hypercholesterolemia will be randomized to treatment with one of two drugs. At the conclusion of the study, we will perform repeat ultrasound and angiography to determine how well each procedure can detect disease progression or regression. I predict that despite significant changes in atheromas, which will be detected by intravascular ultrasound, we will not see any corresponding change on angiography.

Magnetic resonance angiography (MRA), a new technique, shows promise. It provides an excellent view of aortic disease, although it is not adequate for viewing the coronary arteries. A study now being organized will attempt to determine whether aortic MRA can detect lesion regression that is not apparent on standard aortic angiography in patients receiving lipid-lowering therapy.

Angiographic findings should not be the sole criterion for intervention

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