EDITORIAL COMMENT

The Shadows Leave a Doubt—The Angiographic Recognition of Vulnerable Coronary Artery Plaques*

William C. Little, MD, FACC, Robert J. Applegate, MD, FACC
Winston-Salem, North Carolina

Coronary angiography provides detailed, dynamic images of the coronary arterial lumens. These images provide an explanation for angina and a roadmap to direct surgical or catheter-based revascularization. Although a patient’s prognosis is influenced by left ventricular systolic performance and the number of stenosed coronary vessels, analysis of stenosis severity alone does not accurately identify sites that will subsequently occlude and produce a myocardial infarction (MI) (1). Because the consequences of MI are so important, additional means of evaluating the coronary angiogram to accurately identify the lesions that will produce future events would be an important advance.

STENOSIS SEVERITY

When viewing a coronary angiogram, it is attractive to assume that stenotic sites are at risk for thrombotic occlusion that will produce MI, and that coronary arteries that do not contain obstructive stenoses (<50%) are nearly free of the risk of occlusion. However, this intuitively appealing concept is flawed (1). Serial angiographic studies initially reported both by our group (2) and by Ambrose et al. (3) demonstrated that a coronary artery does not have to contain an angiographically severe stenosis to suddenly occlude and produce MI. In fact, most MI’s occur due to occlusion of arteries that did not previously contain a significant (>50%) stenosis, and the coronary artery that previously contained the most severe stenosis is usually not the culprit. These findings have been consistently confirmed by the results of multiple serial angiographic studies (1).

This seemingly paradoxical finding can be understood by examining the risk of subsequent occlusion and frequency of stenotic and nonstenotic coronary artery segments. Segments of coronary arteries that contain a severe stenosis are several-fold more likely to occlude than segments without a stenosis. However, the risk of occlusion of the nonstenosed segments is not zero, and they are far more numerous (4). Thus, the bulk of occlusions occur in nonstenotic segments. Cardiologists intuitively assign too high a risk of occlusion to stenotic segments while underestimating the risk of occlusion of nonstenotic segments. Furthermore, occlusions of severely narrowed segments may not produce MI because the preexistence of a stenosis acts as a stimulus for the formation of protective collaterals.

Although coronary atherosclerosis produces its clinical manifestations by narrowing or occluding the lumen, it is a disease of the arterial wall. The initial response as atherosclerosis develops in the wall of the artery is usually an outward expansion of the artery that accommodates the atheroma while preserving the lumen (5). Typically, the coronary lumen does not become narrowed until late in the course of the disease. Thus, severe atherosclerosis may be present even when only minimal luminal irregularities are observed on an angiogram, and the rupture of a vulnerable plaque can trigger thrombotic occlusion of an artery without first narrowing the lumen. Consistent with this concept, even patients with minor irregularities of the coronary artery walls but without any angiographically significant stenosis (<50% diameter narrowing), have a substantially lower survival rate than patients with completely normal coronary arteries (6). In addition, even minor changes in the severity of narrowings may indicate active disease in the arterial wall and are associated with the subsequent development of MI (7).

STENOSIS MORPHOLOGY

Because stenosis severity does not adequately define the risk of MI (2,3), subsequent studies have carefully evaluated features of individual stenoses to characterize lesion specific factors predisposing to thrombotic occlusion. The studies have not yielded consistent findings. The fissured plaque with overlying thrombus in patients with unstable angina, non-Q wave MI or following thrombolytic therapy of MI may be angiographically apparent as a convex, intraluminal obstruction with overhanging edges, irregularities or intraluminal defects (8–10). The culprit lesions frequently exhibit these angiographic characteristics after the development of MI or unstable angina (8,10). Some studies suggest that the more complex the morphology of the culprit stenoses responsible for an unstable syndrome, the more likely there will be further progression (11,12). It is possible that stenoses with these characteristics in patients without MI or unstable angina may have a higher risk of subsequent occlusion (13), especially an occlusion that will produce a Q wave MI (14). However, in other studies, the culprit plaque...
usually did not seem complex on angiograms performed before the event (15,16). Similarly, the angiographic morphology of the culprit lesion after thrombolytic therapy may not predict subsequent reocclusion (17).

The article of Ledru et al. (18) expands our knowledge of the angiographic characteristics of the culprit lesion before MI. First, the findings of their serial angiographic study again confirmed that a future culprit site is usually not stenotic. (The mean stenosis of the culprit site before MI in their study was 45%.) Second, they made the new observation that coronary artery narrowings with steeper outflow angles were more likely to occlude. It is possible that this relates to shear stress that might play a role in the distribution of inflammatory cells that may destabilize plaques (19). Finally, Ledru et al. (18) made the surprising observation that symmetrical narrowings are more likely to occlude than eccentric lesions. This differs from the previous finding that eccentric stenoses are an angiographic sign of an unstable or ruptured plaque.

LIMITATIONS OF SERIAL ANGIOGRAPHIC STUDIES

All serial angiographic studies such as that by Ledru et al. (18) have limitations, which Ledru et al. fully acknowledge. First, the patients were highly selected and did not include patients who did not have angiograms both before and immediately after their MI. Thus, most patients with MI would not have been included in this study, and no patients with fatal MI’s were included. Second, only patients who had MI were included. Thus, we do not know how many lesions with the highest risk characteristics (severe symmetrical stenosis with steep outflow angle) will subsequently occlude. Even in the study patients, all of whom had MI, the positive predictive value of the highest risk stenosis that was both concentric and with an abrupt angle was only 49%. Moreover, 13% of the lowest risk areas subsequently occluded. It is also important to recognize that the “low” and “moderate” risk areas were far more numerous than “high” risk areas; thus, two-thirds of the MI’s occurred due to occlusions of “low” and “moderate” risk areas. This limited predictive power is similar to previous studies evaluating lesion characteristics before MI.

The two-dimensional shadows of the arterial wall obtained by coronary angiography provide only indirect and limited information about the atherosclerotic process within the arterial wall. No matter how well multiple angiographic characteristics correlate with coronary occlusion, it seems unlikely that coronary angiography will ever be able to precisely define all potentially dangerous vulnerable plaques within the arterial wall. It is possible that improved direct imaging of coronary arterial wall with intravascular ultrasound or magnetic resonance imaging, or characterizing the plaque by spectroscopy or thermal imaging will be more successful in evaluating the status of disease within the wall of the artery (20,21).

THERAPEUTIC IMPLICATIONS

The study by Ledru et al., (18) and others like it, point out the limitation of using the coronary arteriogram to help direct therapy aimed at preventing subsequent coronary events. Coronary artery bypass surgery and percutaneous transluminal coronary angioplasty are effective in eliminating ischemia when they are appropriately directed at angiographically significant (i.e., stenotic or flow limiting) narrowings. Because most occlusions occur at sites that did not previously contain a flow limiting stenosis, these interventions are not likely to be effective in preventing many subsequent MIs (22).

Dilating or stenting a nonflow limiting area with angiographic characteristics that suggest it may be a vulnerable plaque is also unlikely to benefit the patient. First, the absolute risk of subsequent occlusion of this site is low. Second, dilation or stenting has not been proven to decrease the risk of subsequent occlusion. Third, this strategy exposes the patient to the risk of the procedure itself, as well as to the risk of restenosis. If restenosis occurs, it can convert a nonflow limiting area into an ischemia producing stenosis.

Although mechanical treatment of high-grade coronary stenoses relieves angina and improves exercise tolerance, slowing or reversing the progression of atherosclerosis in the walls of the coronary arteries by altering serum lipids may be a more powerful intervention to prevent the catastrophic complications of coronary artery disease (unstable angina, MI and death) (22). This concept is supported by the recent preliminary report of the Atorvastatin Versus Revascularization Trial (AVERT) study at the American Heart Association meeting in Dallas.

CONCLUSIONS

In conclusion, coronary atherosclerosis is a disease of the arterial wall that produces clinical manifestations by narrowing the lumen. Angiographic imaging of the coronary lumen provides an accurate assessment of the extent and severity of atherosclerotic coronary narrowing. Although angiographic correlates of vulnerable plaques that may subsequently trigger MI have been described, the shadows of the coronary lumen provide only indirect and incomplete information concerning the extent, severity and activity of the atherosclerosis process in the arterial walls. Thus, coronary angiography cannot be expected to accurately identify all plaques that are vulnerable or will become vulnerable to rupture and subsequently produce an MI.

Reprint requests and correspondence: Dr. William C. Little, Cardiology Section, Wake Forest University School of Medicine, Bowman Gray Campus, Winston-Salem, North Carolina 27157-1045. Email: wlittle@wfubmc.edu.
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