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EDITORIAL COMMENT

Intermediate Lesions

Retrieving Black From Shades of Gray*

Gabriel Vorobiof, MD,† Y. Chandrashekhar, MD,‡
Jagat Narula, MD, PHD†

Long Beach, California; and Minneapolis, Minnesota

According to the *Oxford English Dictionary*, the adjective "intermediate" is defined as "coming between 2 things in time, place, order or character." Appropriately, therefore, in the context of coronary disease, it refers to lesions that come between mild and severe states of stenosis. Anatomically, intermediate coronary lesions have been defined as lesions discovered on coronary angiography to have a 40% to 69% diameter stenosis usually with minimum luminal cross-sectional area measured by intravascular ultrasound (IVUS) of not less than 4.0 mm^2. Physiologically, intermediate lesions should demonstrate a lack of hemodynamic significance during vasodilatory provocation by fractional flow reserve (>0.75 to 0.80) or during stress-induced testing for myocardial ischemia (shaded region in Fig. 1).

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Natural history of intermediate lesions. Retrospective studies have demonstrated that angiographic progression occurred in 72% (18 of 25) of lesions in patients who had lesions previously deemed insignificant (diameter stenosis <50%) on initial coronary angiography (1) and in 96% who had antecedent stenosis <70% (2). If such patients presented with unstable symptoms, culprit lesions in two-thirds of them had showed only mildly obstructive disease in the angiograms antedating the event. Similar to those of patients with unstable angina, 85% of the infarct-related lesions had <75% diameter stenosis when antecedently examined by coronary angiography (3). Secondary analysis of a multicenter National Institutes of Health registry has demonstrated that 6% of patients undergoing primary angioplasty had acute coronary syndromes develop over the next 1 year, at sites unrelated to the index culprit lesions. These lesions during initial percutaneous coronary intervention were found to be 45% stenotic, and progressed over 1 year to 85% luminal obstruction on follow-up angiography. Plaque progression was seen more frequently in patients with multivessel coronary artery disease detected during original percutaneous coronary intervention (4).

It can be surmised that the lesions in a small proportion of patients with angiographically intermediate lesions may evolve to become bulky and more stenotic, before they rupture to result in an acute event. The remaining lesions may progress variably to produce inducible ischemia. It is therefore important to decipher which lesions will remain stable and only produce anginal symptoms and which will evolve to produce acute events regardless of the extent of luminal obstruction (or anginal symptoms).

Pathology of plaque progression. The atherosclerotic lesions usually develop as intimal xanthomas, or fatty streaks, which are an accumulation of smooth muscle cells in the intima without lipid or macrophage infiltration, whereas accumulation of foam cells without a necrotic core or fibrous cap has been defined as intimal thickening (5). Such lesions usually regress, on the basis of the available animal and human data. Progressive atherosclerotic lesions first evolve as pathological intimal thickening wherein lesions demonstrate smooth muscle cells in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrotic components. Such lesions may develop acute thrombotic complications by characteristic surface erosion, or grow either as thick- or thin-capped fibroatheromas. Fibrous cap atheromas are characterized by a well-formed necrotic core with an overlying thick fibrous cap. Thin fibrous cap atheromas are vulnerable to plaque rupture and contain large necrotic cores covered by thin fibrous caps (usually <65 μm); caps are infiltrated by macrophages and possess rare smooth muscle cells. These lesions are almost always associated with substantial positive remodeling. Fibroatheromas with cap disruption demonstrate luminal thrombus that communicates with the underlying necrotic core. Although small calcific deposits are common in vulnerable plaques, fibrocalcific plaques are usually collagen-rich and associated with significant stenosis with only a few inflammatory cells. To predict acute events, It would be necessary to identify the subset of patients who harbor plaques that have large necrotic cores, are positively remodeled, and are likely to progress as thin-capped fibroatheromas. Such lesions are almost always associated with coronary risk factors. On the other hand, fibrofatty lesions may continue to grow as stable lesions. It will, however, be difficult to predict lesions that are susceptible to erosive complications; the only commonly encountered clinical risk factor is smoking.

Lessons from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial. Results of the PROSPECT trial provide an intriguing look into the

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From the †Memorial Heart and Vascular Institute, Long Beach, California; and ‡Veterans Administration Hospital, Minneapolis, Minnesota. Dr. Vorobiof is on the Speakers' Bureau for Lantheus Medical Imaging. Drs. Chandrashekhar and Narula have reported that they have no relationships to disclose.

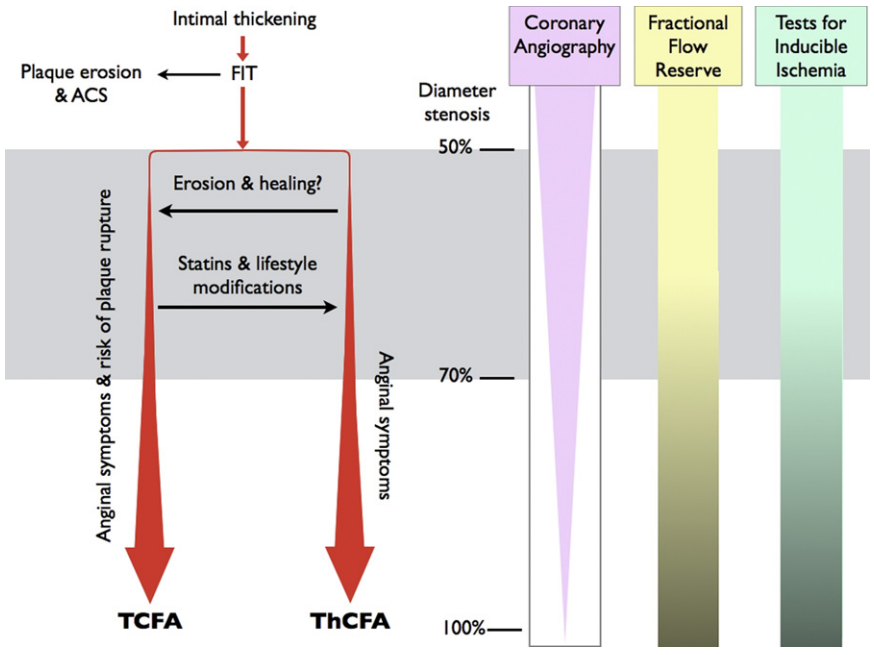

Figure 1. Would It Become Possible to Predict Evolution of Atherosclerotic Plaques Into Thin- and Thick-Cap Fibroatheromas?

Pathologic evolution of atherosclerotic plaques with emphasis on clinical presentation. **Area shaded in gray** represents intermediate lesions. ACS = acute coronary syndrome; FFR = fractional flow reserve; FIT = fibrointimal thickening; TCFA = thin-cap fibroatheroma; ThCFA = thick-cap fibroatheroma.

natural history of plaque progression. In this study of 700 patients undergoing successful percutaneous coronary intervention, 3-vessel intracoronary imaging was performed with gray-scale IVUS and virtual histology (VH)-IVUS. Upon 3-year follow-up, in addition to clinical events associated with intervened target lesions, 11% of subjects also had acute thrombotic complications related to previously nonculprit lesions. Independent predictors for clinical events in such lesions were found to be a minimal luminal area <4.0 mm^2 (odds ratio: 2.77, $p = 0.007$), a shallow necrotic core as defined by VH-IVUS (odds ratio: 3.00, $p = 0.0002$), and a plaque burden at the minimal luminal area of >70% (odds ratio: 4.99, $p < 0.0001$ [6]). The majority of the events were unstable angina rather than cardiac death or myocardial infarction. This study highlighted the importance of large and bulky plaques and necrotic cores that were close to the lumen, and hence likely to be covered by a thin cap. Numerous intravascular studies employing optical coherence tomography have repeatedly demonstrated the importance of defining the fibrous cap attenuation. This and similar smaller studies (7,8) have included patients who have already had an acute event and are on aggressive therapy during follow-up. What is more important is, to identify high-risk lesions for primary prevention, and therefore, it will be important to be able to characterize vulnerable lesions noninvasively.

Lessons from computed tomography (CT) angiography studies. Coronary CT angiography is an established noninvasive tool to exclude the presence of coronary disease and to define the location of a coronary plaque. In addition to the luminal obstruction, plaque attenuation (by Hounsfield unit [HU] measurement) on CT angiography shows acceptable correlation to plaque composition verified by IVUS or post-mortem histological analyses (9–13). On CT angiography, the culprit lesions in acute coronary events were >110% positively remodeled. Such lesions included low attenuation plaque (LAP) areas of <30 HU measurement, which corroborated with IVUS-verified necrotic cores; positively remodeled plaque and LAP have been termed 2-feature positive plaques. In a prospective analysis, 2-feature positive plaques were found to be precursors of acute events, with a 22.5% likelihood of development of acute coronary syndrome over a 2-year follow-up; <0.5% of subjects with 2-feature negative plaques had an acute event, with a hazard ratio of 22.8 ($p < 0.001$) (14). The greater the plaque and necrotic core volumes and the greater the extent of positive remodeling, the higher the likelihood for the development of an acute event. Furthermore, the greater the extent of these 2 characteristics, the earlier the event occurred. In a study that serially performed CT angiography and optical coherence tomography (15), it was demonstrated that circumferential necrotic cores, termed "napkin-ring" cores (16), were usually associated with thin-

capped fibroatheromas, further underscoring the importance of noninvasive imaging. It is noteworthy that positively remodeled and LAP attenuate substantially in response to statin treatment (17). Although these studies suggest that coronary CT angiography may reasonably elucidate plaque composition, heavily calcified plaque and need for iodinated contrast as well as ionizing radiation pose substantial limitations for repeated investigation, especially in asymptomatic subjects.

The present study. Should CT angiography noninvasively and reasonably accurately replicate the IVUS findings, it may be logical to define the composition of intermediate lesions with the expectation that LAP may progress to high-risk lesions. Conversely, intermediate attenuation plaques (30 to 150 HU), which represent IVUS-verified fibrous plaques, may evolve as stable lesions, lead to anginal complaints, but not result in an acute event. With probably a similar expectation, the study presented in this issue of *JACC: Cardiovascular Interventions* by Voros et al. (18) compares VH-IVUS and coronary CT angiography characteristics of intermediate lesions. Both over- and underestimation by CT of various plaque morphologies was found, with wide ranges of −22% to 102% compared to VH-IVUS. Modest correlation was found for percent atheroma volume ($r = 0.51$) between the 2 techniques. Although it is reasonable to compare noninvasive studies with intravascular tools, the accuracy of VH-IVUS to quantify individual plaque components, in particular the size of the destabilizing necrotic core, was recently found to have little correlation with histology (19).

Since the relation between the anatomy and physiology of coronary artery disease remains poor (20), debate will continue on how to improve our understanding about the physiologic significance of lesions. This approach, however, is only likely to predict suitability for revascularization and improvement in anginal symptoms. A far greater goal would be to identify and prevent the unpredictable acute coronary events. The imaging techniques such as CT angiography and IVUS allow pathologic or compositional information but such techniques, as the current studies show, still leave much uncertainty. Even if these techniques offered precision, it would be prudent to question the justification of recommending a widespread imaging strategy for the management of intermediate lesions, because only a small fraction of nonculprit vessel plaques progress to acute events. Approximately 4% per year from the PROSPECT study (6) and 6% from the National Heart, Lung, and Blood Institute registry (4) had acute events. This event rate may be somewhat lower among patients without an event that brought them to the catheterization laboratory, or somewhat higher in the absence of an aggressive medical therapy. Plaques form, rupture, and heal all the time, and it would be difficult to accurately identify a high-risk plaque likely to be associated with a subsequent event, let alone identify it in a treatable proximity to an event. Finally, ever-evolving medical therapy changes the natural history of plaques, and imaging techniques will need to be continually assessed to ensure that they continue to perform in face of a rapidly decreasing probability of events. Despite these caveats, studies such as by Voros et al. (18) remain important for helping us understand plaque anatomy, the actual composition of plaque, and the physiological relevance of the lesion. They will, however, only be clinically fruitful if they can also, hopefully in future, identify its temporal-spatial proclivity for events (21).

Reprint requests and correspondence: Dr. Jagat Narula, Memorial Heart and Vascular Institute, 2801 Atlantic Avenue, Long Beach, California 90801-1428. E-mail: narula@uci.edu.

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