Acute coronary syndromes (ACS) result from the rupture of macrophage-rich, inflamed, thin-capped fibroatheroma with superimposed thrombus formation. Unstable plaques are thought to arise from vulnerable lesions that were nonflow-limiting prior to becoming unstable, and therefore, unlikely to produce anginal symptoms or be revealed by traditional stress testing. Although prospective evidence from natural history studies is lacking, retrospective autopsy studies suggest several histological types of suspected vulnerable plaque—the most common of which is an inflamed thin-cap fibroatheroma—that are thought to account for 60% to 70% of coronary events; another 30% to 40% of events are believed to be attributable to plaque erosions, especially in younger women.

Atherosclerosis is a widespread process and most patients harbor diffuse disease. Until recently, plaque rupture was thought to reflect local plaque instability that was attributable to spontaneous or triggered disruption of a lone vulnerable plaque that manifested angiographically or pathologically as a solitary, complex, unstable lesion. However, it is now well appreciated that plaque instability (and vulnerability) is a multifocal, pancoronary process, likely reflecting more systemic pathophysiologic processes with the potential to destabilize atherosclerotic plaques throughout the coronary tree. Recognition that these threatening lesions lurk beneath the clinical radar screen has resulted in a paradigm shift in

Figure 1. Appearance of ulcerated plaques found during computed tomographic angiography (CTA). Invasive angiography in a patient with ACS (A, B) documents a ruptured plaque: a hazy, ulcerated stenotic lesion (white arrows) with distal lesion extension (multiple black arrows) in the left anterior descending artery. Intravascular ultrasound (C) confirms the ulceration and rupture (arrow). CTA of the same lesion reveals similarities in morphology, such as a severe luminal compromise (large black arrow) and evidence of intraplaque contrast penetration into a hypodense plaque (small black arrows), which are indicative of ulceration and rupture (D). The interposed calcific plaque is brighter, thereby differentiating it from the zone of contrast dye penetration into the ruptured plaque. Additionally, CTA shows the extent and bulkiness of the plaque and identifies some other purported signs of vulnerability, such as plaque with low Hounsfield unit density and extensive remodeling. (Reprinted from J Goldstein et al. J Am Coll Cardiol Imag. 2008;1:249-251.)
thinking beyond clinically detectable flow-limiting lesions, with a focus on identifying vulnerable plaques.4

**IDEAL PLAQUE CHARACTERIZATION TOOL**

An appreciation of the information necessary to precisely characterize plaques and the fundamental data provided by plaque-imaging technologies is essential.5 The ideal tool would provide a complete roadmap of atherosclerotic burden throughout the coronary tree and provide per-plaque, lesion-specific data characterizing the architecture, composition, and dynamic biology of each plaque. Comprehensive plaque analysis should include the following parameters:

- **Architecture**: plaque volume, length, eccentricity, remodeling, and impact on lumen area.
- **Physiology**: impact on coronary flow reserve.
- **Composition**: lipid, fibrous tissue, calcium, etc.
- **Pathobiology**: presence of inflammation, neovascularization, fibrous cap metabolism, apoptosis, etc.

**MORPHOLOGY OF VULNERABLE PLAQUE BY INVASIVE IMAGING MODALITIES**

The invasive angiographic hallmark of ACS is a complex culprit plaque characterized by lesion irregularity, haziness, ulceration, contrast dye persistence within the plaque, intraluminal filling defect, and impaired flow.3,6 These angiographic morphological features correlate with plaque rupture and thrombus by direct coronary imaging with IVUS and at pathological examination. Angiography is very accurate in the detection of complex unstable culprit plaques in patients with ACS. However, angiography is an insensitive tool that is only able to detect plaques that have relatively gross plaque disruption. Observations from IVUS, angioscopic, and pathological studies clearly document that the majority of ulcerated plaques are not sufficiently disrupted anatomically to be detected angiographically. Furthermore, it is certain that patients with unstable (and silent) coronary artery disease harbor lipid-rich, inflamed, vulnerable plaques that have not yet ulcerated or ruptured. Angiography fails to detect the many plaques with subtler but pathologically manifest ulceration and rupture. Thus, angiography reflects only a subset of coronary lesions that are truly unstable and provides virtually no insight regarding the many vulnerable but not yet ruptured plaques that serve as the substrate for subsequent coronary events. Therefore, angiographic confirmation of complex plaque undoubtedly represents only the tip of the iceberg of plaque instability and vulnerability.6
IVUS images the vessel wall and delineates its effects on the lumen, thereby providing useful information on plaque architecture, luminal stenosis, and vessel remodeling. When using IVUS, unstable plaques are typically bulky, eccentric, and positively remodeled. Culprit lesions in patients with ACS demonstrate more expansive remodeling by IVUS than by the culprit lesions of patients with stable angina, suggesting that expansive remodeling might be associated with plaque vulnerability. Overall, IVUS features correlate with plaque complexity by angiography and at necropsy. Other direct invasive imaging technologies hold promise for plaque characterization, including IVUS with integrated backscatter imaging, optical coherence tomography (which provides breathtaking images of fibrous cap thickness and integrity), and near-infrared spectroscopy for delineation of lipid core plaque.

GENERAL CONSIDERATIONS

Advances in CTA have now made it possible to accurately image the coronary vasculature noninvasively. CTA produces amazing angiographic images that are comparable (in most cases) to those obtained by invasive angiography, with excellent accuracy for the presence and severity of luminal stenoses. First, an appreciation of the fundamental differences in these techniques is essential to comparing their images. Invasive angiography produces an image of the vessel lumen only, with little insight regarding atherosclerotic plaque other than indirectly by its effects on luminal architecture. Additionally, invasive angiography consistently underestimates the extent of intramural plaque and provides little or no insight regarding plaque character, unless supplemented by adjunctive imaging modalities, such as IVUS. In contrast, CTA provides not only a high-resolution lumenogram but also, by virtue of differential tissue attenuation capabilities, facilitates imaging of the vessel wall, thereby providing insights regarding the presence and nature of intramural plaque, as well as its impact on luminal architecture (Table 1).

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Figure 4. Comparative images in a patient with an unstable ruptured RCA lesion, but stable plaque in the LAD and circumflex arteries. Invasive angiography (A) documents a complex plaque severely narrowing the mid-RCA (dark arrow); left coronary images (C) demonstrate noncomplex plaque in the mid-LAD (white arrows), characterized by minimal luminal narrowing. CTA images are concordant, revealing a bulky, eccentric, and lucent RCA lesion (B) with intraplaque contrast penetration indicative of ulceration and rupture (dark arrow) adjacent to a calcific deposit (white arrow); the LAD lesion (D) exhibits noncomplex features with non-bulky, negatively remodeled, mixed calcific and noncalcific elements (white arrows). (Reprinted from J Goldstein et al. J Am Coll Cardiol Imag. 2008;1:249-251.)
architectural characteristics, such as remodeling.14-16 Previous studies demonstrate that lesions in unstable patients exhibit lower CT tissue attenuation and bulky morphological features, and are positively remodeled.14-16 However, most of the previous studies exhibited a lack of detailed characterization and comparisons of complex lesion morphology by the two imaging modalities.

We recently demonstrated that CTA can detect complex ruptured coronary plaques, depicting morphological features that are strikingly similar to complex unstable lesions proven by invasive angiography.17 In patients presenting with unstable chest pain and proven complex ruptured plaques by invasive angiography, the CTA portrait of an unstable coronary plaque is characterized by a bulky, hypodense, eccentric, positively remodeled lesion with evidence of plaque disruption indicated by ulceration and intraplaque contrast penetration (Figures 1 through 4), which is similar to the vessel wall features of complex ruptured plaques described by invasive angiography and IVUS. Not surprisingly, given its IVUS-like capabilities, CTA has documented that, in most lesions, the bulk and linear extent of intramural plaque were far greater than that seen by invasive lumenography alone. Importantly, in some lesions judged to be noncomplex and stable by invasive angiography, CTA revealed intramural plaques that were eccentric, bulky, hypodense, and positively remodeled, but lacked features of frank rupture (Figure 3). We can only speculate as to whether the bulky, lucent, nonruptured plaque pattern seen by CTA may represent lipid-laden vulnerable plaques that may be the substrate and site for future plaque rupture, necrotic core, intraplaque hemorrhage, or a combination of such elements.

Patients also had other lesion morphologies, including coronary segments with plaque morphologies characterized by nonbulky, high-density, negatively remodeled lesions (Figure 4), as well as densely calcified lesions; it is intriguing to postulate that such lesions represent more chronic stable plaques. However, it is beyond the scope of the presently available data to comment on the precise histopathologic correlates of these various lesion morphologies. Ultimately, characterization of plaque by CTA will require correlation with direct invasive imaging modalities and gross histopathologic correlates.

SUMMARY

These findings demonstrate that CTA delineates the morphology of complex ruptured coronary plaques, demonstrating features strikingly similar to patterns depicted by invasive angiography. CTA, by virtue of its ability to combine imaging of the lumen and vessel wall, produces a novel angiographic portrait providing insights regarding the character and extent of intramural atherosclerosis, which may be an improvement on invasive angiograms that directly image the lumen only. CTA delineation of the character and the extent of plaque throughout the coronary tree, may have clinical implications for patients with acute and chronic coronary artery disease.

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