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EDITORIAL COMMENT

Angiographic Plaque Complexity: The Tip of the Unstable Plaque Iceberg*

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Coronary plaque rupture is implicated in the pathogenesis of the acute coronary syndromes (1–9). Complex lesion morphology is the angiographic hallmark of these unstable ischemic syndromes, and it correlates with pathologic evidence of plaque rupture (7–9). In this issue of the *Journal*, Kerensky et al. (10) describe the angiographic patterns of plaque instability in 350 patients with nontransmural myocardial infarction (NQWMI) randomized to the invasive arm of the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial (10). Observations from this study demonstrate that a complex culprit lesion could not be identified in nearly one-third of patients; in contrast, a significant number of patients harbored multiple unstable plaques.

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From these results, the investigators conclude that coronary angiography frequently fails to identify the culprit lesion responsible for NQWMI. These findings raise several important issues, including: 1) Does the surprisingly low incidence of identifiable complex culprit lesions observed suggest that patients with NQWMI are pathophysiologically different from patients with ST-elevation myocardial infarction (MI) and unstable angina, who typically manifest unstable plaques by angiography? 2) Are patients with multiple unstable plaques pathophysiologically different from patients with single or no identifiable complex lesions? Alternatively, do most patients with acute coronary syndromes harbor multiple inflamed, eroded or ruptured plaques, but that current imaging techniques are so insensitive that only gross disruptions are apparent, with the majority of unstable plaques “beneath the angiographic radar screen”? 3) How does the angiographic pattern (single, multiple or no unstable complex lesions) influence therapy and prognosis in patients with an acute coronary syndrome?

THE ACUTE CORONARY SYNDROMES: DISTINCT ENTITIES OR OVERLAPPING CONDITIONS?

Traditionally, the acute coronary syndromes have been considered as distinct entities, the conditions of ST-

elevation MI, NQWMI and unstable angina differentiated primarily on the basis of electrocardiographic (ECG) manifestations and myocardial enzyme elevations, rather than coronary anatomy and left ventricular (LV) function. All three conditions share common pathophysiology, characterized by acute coronary insufficiency typically attributable to coronary plaque disruption with superimposed thrombus that may range from superficially adherent to occlusive (1–6).

Plaque rupture induces a dynamic process of clot formation and dissolution that may evolve over minutes or days, a time frame in which resting coronary flow may be intermittently or persistently compromised. Plaque rupture does not inevitably lead to MI, with the clinical expression in an individual patient a function of the interplay among the severity of atheromatous plaque stenosis, magnitude of superimposed thrombus, degree of local coronary vasoconstriction, development of distal plaque-clot embolization and extent of collateral flow (3–6). Plaque erosions and ruptures commonly occur in previously non-flow-limiting lesions and, if minimal superimposed thrombus is generated, may not compromise resting coronary flow sufficiently to induce ischemia; such erosions are initially clinically silent, but they do appear to accelerate plaque growth.

On the catastrophic end of the spectrum, plaque rupture results in abrupt thrombotic occlusion, and unless there are extensive preexisting collaterals, acute transmural ischemia manifests as ST-elevation MI and/or sudden death. Unstable angina and NQWMI constitute intermediate steps in the clinical spectrum of plaque rupture, with both conditions representing acute compromise of coronary blood flow sufficient to provoke unstable symptoms, often with ischemic ECG changes. These two intermediate conditions are differentiated clinically on the basis of biochemical evidence of myocyte necrosis, a function of the interplay of multiple factors including severity of flow compromise, collaterals, duration of ischemia, distal microembolization and myocardial oxygen demand.

Given the common pathophysiologic link of plaque rupture, it seems logical to consider the acute coronary syndromes as a single coronary anatomic-pathophysiologic entity, united by the common thread of plaque instability and differentiated by whether there is sufficient antegrade flow through the culprit complex lesion or via collaterals, which thereby determines whether a patient presents with transmural ischemia, NQWMI or unstable angina. However, despite this common pathophysiologic theme, these three syndromes are distinguished by important clinical, prognostic and therapeutic differences. Acute ST-elevation MI results in LV dysfunction, is associated with increased early and late mortality, and is benefited by acute reperfusion interventions (11). Unstable angina does not typically impact LV performance and usually responds initially to medical therapy, with subsequent revascularization dependent on coronary anatomy and physiology. In contrast,

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NQWMI is a somewhat awkward missing link. On the basis of common coronary pathophysiology, NQWMI appears to be just a bad case of unstable angina, with preservation of global LV performance similar to unstable angina despite biochemical evidence of myonecrosis. Although enzyme elevations without significant wall motion abnormalities could be dismissed as clinically irrelevant, compared to unstable angina NQWMI carries a worse prognosis, based solely on the differentiating factor of biochemical evidence of myocyte necrosis (12-14). Although the precise mechanisms by which such "enzyme leaks" impart an adverse prognosis are unclear, it has been suggested that elevated enzymes may merely be a marker of more severe coronary derangements including severity of underlying obstruction, extent of thrombus, downstream embolization and myocardial damage (13).

LIMITATIONS OF ANGIOGRAPHY IN DELINEATION OF PLAQUE INSTABILITY

Based on this common pathophysiology of underlying plaque rupture, all patients with acute coronary syndromes would be expected to manifest complex unstable lesions by angiography (fissuring, ulceration, haziness and filling defect), with a clear association between location of the culprit lesion with ECG and/or wall motion abnormalities. Furthermore, it might be expected that patients with NQWMI would have a higher likelihood of more severe complex lesions and impaired flow than would those with unstable angina, as such patients are at the far end of the spectrum of ischemic severity as evidenced by the development of myocardial damage. The conspicuous lack of any complex culprit lesion by angiography in fully one-third of NQWMI patients in the present study is, therefore, somewhat surprising and in contrast to prior studies of patients with acute coronary syndromes, in whom a complex culprit plaque is routinely identified (11,15-21). This discrepancy raises the fundamental question as to whether the present findings represent true anatomic and pathophysiologic differences between patients with NQWMI versus patients with other acute coronary syndromes, or whether methodologic considerations may have influenced the results.

The inability to identify a complex culprit lesion in some patients in the present study (10) is likely attributable at least in part to the inherent imaging resolution limitations of angiography, together with the effects of time and therapy administered. Although a crucial tool for assessment of patients with coronary artery disease, angiography is well known to underestimate the presence and severity of coronary artery disease in general and has significant limitations in the precise delineation of plaque architecture and biology. Although angiographic plaque complexity correlates well with pathologic evidence of plaque rupture and thrombus (7,8), angiography is an insensitive tool that is only able to detect those plaques that have relatively gross plaque disruption. It is clear from previous pathologic

studies that the majority of ulcerated plaques are not sufficiently disrupted anatomically to be detected angiographically. Angiography fails to detect the many plaques with subtler but pathologically manifest ulceration and rupture (9), reflecting only a subset of those coronary lesions that are truly unstable and revealing virtually no insight regarding the many vulnerable but not yet ruptured plaques that serve as the substrate for subsequent coronary events.

In the present study, the investigators recognize that performance of angiography three to seven days after the acute event likely further contributed to an underestimation of the prevalence of complex unstable plaques, as the effects of aspirin and heparin together with the tincture of time may have allowed some complex plaques to heal sufficiently such that they appeared angiographically "benign." This healing effect of time is seen in patients with ST-elevation MI, in whom angiography performed acutely identifies a culprit occlusion in nearly all cases (11,15), whereas patients studied later may have a greater frequency of patent although diseased arteries (3).

Another methodologic limitation of the Kerensky et al. (10) study is lack of ECG correlation to guide interpretation of potential culprit lesions, for the angiographic core laboratory analysis was blinded to ECG data and designated a lesion as complex in, and culprit only, if it satisfied rigid angiographic criteria. In the real world of patient care, and in most other studies analyzing culprit lesions, the angiographic findings are correlated with the location of ischemic events by ECG or wall motion abnormalities. Had the ECG data been available to the angiographic observers in this study, a higher incidence of plaques may have been designated as complex and culprit. These considerations emphasize the qualitative nature of such an angiographic evaluation, where complexity may be in the "eye of the beholder."

IMPLICATIONS OF MULTIFOCAL PLAQUE INSTABILITY

The angiographic documentation of multiple unstable plaques in the Kerensky et al. (10) study is consonant with and further supports recent observations from our laboratory demonstrating that many patients with acute MI harbor multiple complex plaques (21). These findings support the concept that plaque instability in many patients is a pan-coronary process reflecting systemic inflammatory and metabolic factors that destabilize plaques not only in the culprit vessel responsible for acute ischemia but also in other locations in other vessels (21,22). Until recently, plaque rupture was thought to reflect local plaque instability attributable to spontaneous or triggered disruption of a lone vulnerable plaque, manifest angiographically or pathologically as a solitary complex unstable lesion. However, the pathophysiologic factors proposed to precipitate plaque instability (4,5), whether due to primary weakening of the fibrous cap attributable to inflammation or the extrinsic influences of intraluminal mechanical forces modulated by

sympathetic tone and catecholamines, would be expected to exert their effects in a widespread pattern throughout the coronary vasculature. Given the potential “pancoronary” impact of these factors adversely influencing plaques, together with the typically diffuse nature of coronary atherosclerosis, it would not be unexpected that plaque instability might develop in a multifocal pattern, resulting in multiple anatomically remote complex unstable plaques, one of which may progress to total occlusion and emerge as the culprit infarct-related lesion.

Multiple complex plaques are evident though not necessarily commented on in previous pathological and angiographic studies of patients with acute coronary syndromes. Multifocal plaque rupture and multiple coronary thrombi are evident in autopsy studies of fatal acute ischemic heart disease (1,2,9). In fact, extensive multifocal coronary ulceration and multicentric clot formation may be the rule rather than the exception, with one detailed necropsy study documenting multiple ulcerated plaques in 71% and four or more lesions in 20% of patients (9).

Multifocal plaque instability is also evident in prior angiographic studies of patients with unstable angina (23–29), with one study documenting an average of 2.6 complex lesions per patient (29). Recent angioscopic observations in patients with acute coronary syndromes confirm a significant subset of cases with multiple unstable plaques (30). The concept of multifocal plaque instability is also supported by angiographic natural history studies documenting rapid progression of culprit and nonculprit complex lesions in patients with acute coronary syndromes (23–28). Studies in patients with acute MI have demonstrated striking rapid multifocal progression of both infarct-related and nonculprit complex lesions over one month (24). Angiographic natural history studies in patients with unstable angina also demonstrate that rapid progression is not confined to the initial culprit lesion but is evident in nonculprit complex lesions as well (25–28), consistent with the concept of multifocal plaque instability. Multifocal plaque instability is evident both in coronary vessels and in peripheral vessels, including the thoracic aorta as well as carotid and femoral arteries (31–34). Patients with unstable carotid artery disease often harbor unstable plaque in the contralateral nonculprit carotid artery and are prone to acute coronary events (31), consistent with the concept of systemic processes leading to panvascular plaque instability in both coronary and noncoronary beds.

There is a striking association among complex lesion morphology, clinical instability and prognosis (21–29,35–37). The prognosis is particularly foreboding in patients with multiple unstable plaques. In our study of patients with acute MI, the presence of multiple complex unstable plaques was associated with adverse clinical outcome, as such patients were less likely to undergo primary angioplasty, more frequently required early coronary artery bypass surgery or staged multivessel percutaneous interventions, and had

greater depression of LV function compared to those with single unstable lesions (21).

Observations in the present study (10) are strikingly similar, as patients with multiple unstable plaques were less likely to undergo percutaneous transluminal coronary angioplasty and more frequently required bypass surgery. In our study, the presence of multiple complex plaques was also independently predictive of future adverse clinical events over one year, including an increased incidence of recurrent angina and acute coronary syndromes, higher rates of repeat percutaneous revascularization not only in the initial culprit vessel but also in non-infarct-related lesions previously documented as complex, and greater likelihood of requiring coronary artery bypass surgery (21). These findings emphasize that the angiographic documentation of multiple unstable plaques not only influences initial revascularization strategies but also identifies a subset of patients particularly predisposed to rapid plaque progression associated with greater risk for recurrent ischemia.

In aggregate, these pathological, angiographic and clinical observations support the concept that plaque instability is not merely a local vascular accident, but likely reflects pancoronary pathophysiologic processes with potential to destabilize atherosclerotic plaques throughout a diffusely diseased coronary tree. However, 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 and ruptured. Therefore, angiographic documentation of plaque rupture undoubtedly represents only the “tip of the iceberg” of plaque instability. We do not yet possess techniques sufficiently sensitive and accurate to delineate all eroded-ruptured plaques, let alone the many vulnerable but not yet ruptured plaques. Although results of the Kerensky et al. (10) study emphasize the limitations of angiography, the findings are nevertheless relevant; both patients with multiple unstable plaques and those without obvious complex culprit lesions may pose revascularization decision dilemmas. Clearly, higher-resolution imaging techniques are necessary to better define coronary plaque architecture with respect to thickness and stability of the protective fibrous cap, presence of thrombus and extent of the lipid-rich plaque pool.

Finally, there is also a pressing need for reliable biomarkers that can delineate the local coronary and systemic metabolic and inflammatory processes underlying plaque destabilization, with the ultimate goal to facilitate detection of vulnerable and unstable plaques prior to catastrophic rupture.

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