Editorial comment

The transition from stable to unstable coronary artery disease: a key research target

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The report by Ambrosio's group in this issue of the Journal[1] raises the question of the mechanisms of acute thrombotic coronary artery occlusion at the site of fibrous coronary lesions, most likely related to radiation therapy received 10-32 years earlier. As discussed by the authors, thrombosis at the site of non-ruptured plaques either poor in lipids, rich in smooth muscle cells and proteoglycans[2,3] or just fibrous[4] is not uncommon in patients who died of acute coronary syndromes (ACS). In his comprehensive review Davies[5] reports that, among patients who died of ACS, the overall ratio between fissures and endothelial erosions in culprit coronary plaques is 3:1 and the ratio decreases to 1.3:1 in younger patients. Thus it appears that fissure of a plaque is not a necessary cause of coronary thrombosis, nor does it appear a sufficient cause, as coronary plaque fissures are commonly found in coronary patients who died of non-cardiac causes[6]. Accordingly, if a fissure does not appear a necessary or a sufficient cause for acute coronary occlusion, then also an endothelial erosion appears unlikely to represent, by itself, a sufficient explanation for an acute coronary occlusion. Yet, in the search for a readily available, plausible explanation a plaque fissure is generally considered the cause of coronary instability and of acute infarction.

What causes coronary instability?

The triggers of the sudden, unpredictable transition from stable, symptomatic or chronic coronary artery disease to coronary instability with the development of ACS are still a matter of speculation. Such triggers are likely to be multiple and not necessarily the same in all patients.

A "reductionist" view tends to focus on finer and finer details of a single, common, pathogenetic mechanism, largely related to the gradual progression of the atherosclerotic process. This view is based on the assumption that sudden coronary instability is merely a consequence of the same mechanisms generally involved in atherogenesis or of their exacerbation. However this view does not easily explain the inconsistent relation between severity of coronary atherosclerotic disease and development of ACS, and/or the varied clinical presentation and temporal evolution of ACS.

The spectrum of clinical presentation and temporal evolution of acute coronary syndromes

ACS develop suddenly, unpredictably, often as the very first clinical manifestation of coronary artery disease, but the pattern of their clinical presentation and evolution is varied and such variability is likely to reflect a different prevalence of underlying mechanisms of instability. At one extreme end of the spectrum are patients who present with acute myocardial infarction totally unheralded, not preceded nor followed by anginal episodes, and who subsequently remain asymptomatic for years or decades (type I pattern). At the other extreme are patients in whom myocardial infarction is preceded by unstable angina for a few days up to 2 months (according to current definitions), and who subsequently continue to develop recurrent episodes of instability and/or reinfarction during the following weeks or months (type II pattern). Patients with type I pattern are characterized by a high prevalence of circulating acute soluble and cellular markers of inflammation, suggestive of a lymphocyte

Th1 response. The prevalence of elevated serum levels of C-reactive protein (> 3 mg/l) ranges from 70% in unstable angina (Braunwald class IIIB) to nearly 100% in acute myocardial infarction preceded by unstable angina, and to less than 50% in myocardial infarction not preceded by unstable angina. Persistent elevation of C-reactive protein after discharge is associated with a 5-7-fold increase in the incidence of recurrent instability of an acute myocardial infarction in the following months. Thus, a type II pattern of clinical presentation of instability is characterized by elevated circulating markers of inflammation which, conversely, are much less frequent in a type I pattern[7].

The spectrum of coronary atherosclerosis in unstable and stable patients

Both acute myocardial infarction and unstable angina, when they present as the very first clinical manifestation of coronary disease, are on average characterized by a much smaller severity and extension of angiographically detectable coronary atherosclerosis than patients with long-standing uncomplicated chronic stable angina[8,9]. Thus in some patients extensive and severe coronary atherosclerosis can remain stable for years, whereas patients with much less obvious lesions may present with acute infarction. Moreover, also in obvious contrast with a reductionist view, after acute infarction many patients with a type I pattern remain stable for decades, although their coronary atherosclerotic burden is unchanged or gradually increases.

The 4 patients described in the report by Ambrosio's group present an example of the multiplicity of the potential atherogenic stimuli and of the potential sudden development of acute infarction. The authors postulate an endothelial erosion caused by elevated wall shear stress in the stenotic segment. However such explanation, developed from the study of acute animal models[10], appears rather unlikely, first because the patients had no history of effort angina, and second because patients with effort angina and severe coronary stenoses can remain stable for years.

Patient-guided research strategies

In the quest for the actual causes of sudden coronary instability we must look for distinctive features among patients, beginning from the clues offered by the pattern of their clinical presentation. The inclusion into the same research protocol of patients with different pathogenetic components of instability would cause a dilution of specific triggers prevalent in one subset of patients but not in others. Persistence and recurrence of coronary instability suggest a high prevalence of persistent or recurrent triggers. Conversely, an isolated myocardial infarction suggests a high prevalence of random, unfavorable events concurring simultaneously to produce an acute, persistent coronary occlusion.

The study of biological reactions to self and non-self danger signals[11] such as heat shock protein production, antigenic mimicry and autoimmune mechanisms[12-14], are opening novel avenues for research on atherogenesis in general and on the potential triggers of its very occasional transition from a stable to an unstable phase. This line of investigation could also explain the observation of a widespread coronary inflammation in patients with unstable angina[15].

For inquisitive minds the investigation of unexplained inconsistencies could be more stimulating than the study of finer and finer details of only apparently plausible paradigms.

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