Multiple Plaque Rupture in Acute Coronary Syndrome

To the Editor:

Rioufol et al1 recently reported a lower incidence of plaque rupture in culprit arteries than in non-culprit arteries (37.5% versus 79%) in acute coronary syndrome (ACS). The low incidence in culprit arteries was explained by thrombi that masked underlying ulcerations, but findings suggest that plaque rupture/thromboses do not directly induce symptoms in ACS (or ACS/infarction). There are other problems with the plaque rupture/thromboses mechanism. These include low (around 25%) incidences of thromboses in ACS,2,3 failure of thrombolyis to benefit non-ST-segment elevation infarction,4 rising incidence of thromboses over time in infarction,2,3 common occurrence of asymptomatic plaque rupture,1 failure of platelet glycoprotein IIb/IIIa receptor blockade to benefit most cases of ACS,2 and apparent inability of thromboses in very stenotic arteries to explain infarction.2,3 To my knowledge, nobody has seen plaque rupture directly cause ACS. ACS is attributed to plaque rupture because of the association of plaque rupture with ACS, but this is only evidence consistent with this mechanism. Findings as rising incidences of thromboses in infarction seem to be inconsistent with ACS due directly to plaque rupture/thromboses, and such findings raise the possibility of falsifying this mechanism. The mechanism of plaque rupture/thromboses was threatened by the finding that stenosis significantly reduced the incidence of infarction in the absence of significant improvement in coronary artery disease (CAD), and stabilization of "vulnerable" plaques provided an explanation for this apparent discrepancy.2,3 Although rupture of vulnerable plaques is accepted overwhelmingly, this explanation is also only consistent with the validity of the plaque rupture mechanism. The spasm of resistance vessel (S-RV) concept,5 which asserts that S-RV directly induces symptoms in ACS, offers another explanation for the action of stenins in preventing infarction; stenins, which are anti-spastic,2,3 operate basically by reducing the tendency toward S-RV. The S-RV concept asserts that risk factors operate by causing S-RV, and the major risk factor of stenotic CAD is considered to cause S-RV through ischemic injury (ischemic injury-induced S-RV or ischemia-induced S-RV). The concept avers that plaque rupture in culprit arteries favors ACS mainly through stenoses; consistent with this, plaque rupture in the study by Rioufol et al was significantly more stenotic in culprit than in non-culprit arteries (70% versus 39%). Platelets probably play only a minor role in most cases of ACS,5 and operate mainly by release of vasoconstrictors.5 In addition to antiplatelet therapy for ACS, consideration should be given to reversing ischemia-induced S-RV, for example by α-adrenergic blockade.5

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Response

Dr. Hellstrom raises the interesting physiopathological hypothesis that coronary microcirculation may play a fundamental spastic role in the genesis of acute coronary syndrome (ACS). He considers the presence of ruptured atherosclerotic plaque accompanied by culprit artery thrombus as an epiphenomenon that may promote and maintain the spasm of resistance vessel (S-RV) phenomenon via the stenosis caused. These ideas, however, fail to convince us for a number of reasons:

1. It is the moderately stenosis-inducing coronary plaques that cause the largest number of acute atherothrombotic events,1 not the more severe lesions implicated by the S-RV concept.
2. It has yet to be directly proven that unstable plaque causes ACS; however, intravascular ultrasound studies have nevertheless shown that so-called vulnerable plaques (ie, at risk of cap-rupture) that are less than 50% in diameter and non-stenosis-inducing both precede and predict future ACS occurring precisely in their neighborhood.2
3. Inflammatory syndromes are believed to be both risk factors and consequences of ACS.3 Resistance-stage vasospasticity is now included in the phenomena of coronary vasoactivity as a whole.4 Vasospastic angina, however, may involve a degree of ischemia as intense as in ACS patients, but gives rise to no inflammatory phenomenon;3 thus arguing against the S-RV concept.
4. Several unstable lesions are frequently found up- or down-stream from the ACS culprit lesion.5 Under the S-RV theory, all these ought to be thrombotic, whereas in fact, in the vast majority of cases, a single ACS culprit lesion is identified and tends to contain thrombus.

Atherothrombosis is a complex multi-factor condition with stochastic evolution; it therefore appears difficult to tie it down to just one dominant theory, even one focusing on microcirculation.

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