An Alternative Pathophysiological Mechanism for Unstable Angina

A study recently published in Circulation by Flugelman et al. proposed a mechanism of sudden precipitation of unstable angina that may be an alternative to plaque rupture and thrombus formation, namely, smooth muscle cell (SMC) proliferation leading to plaque expansion and coronary luminal narrowing. This conclusion is based on the observation that atherectomy specimens obtained from selected patients with unstable angina exhibited significant SMC proliferation compared with specimens obtained from patients with stable angina.

There are some limitations in the study design that must be highlighted. First, patients in the unstable angina group were included in the study only if they had no angiographic evidence of intracoronary thrombus. This exclusion criterion introduces a significant bias to the study design, since previous studies have evidenced presence of intracoronary thrombi in the vast majority of patients with unstable angina.2-3 Sherman et al. have in fact reported that intraluminal thrombi were present in about 70% of patients with unstable angina undergoing coronary angiography.

This figure increased to 100% if the analysis was limited to patients who exhibited angina at rest.2 In another study, Mizuno et al. reported the presence of intracoronary thrombi in patients with unstable angina undergoing angiography in nearly 100% of the cases (14 of 15 patients). Of note is the fact that only patients with angina at rest were included in the study of Mizuno et al. Although this limitation is acknowledged by Flugelman et al. in their article, it should be pointed out that when angiography is used, intracoronary thrombi can be detected in nearly all patients with unstable angina. Thus, the results of the study of Flugelman et al. apply to a very limited subset of patients with unstable angina. Second, the time elapsed between hospital admission and accomplishment of atherectomy also represents an important limitation. All patients were referred to a tertiary referral center for angiographic diagnosis and therapy. Although not specified, it is likely that several days had elapsed before the procedure was performed. It is therefore possible that during this time frame the thrombus had spontaneously lysed and plaque rupture/dissection had healed. The authors acknowledge this as a possible cause of underestimation of the presence of intracoronary thrombi in unstable angina. Besides that, however, the fact that atherectomy was performed at a later time with respect to hospital admission does not allow one to exclude that the SMC proliferation observed by Flugelman et al. in the specimens of patients with unstable angina might actually be a late consequence of plaque rupture, platelet activation, and thrombus formation.

In fact, release of mitogenic factors under these conditions might have promoted SMC proliferation after the acute event had occurred. Finally, a brief consideration regarding clinical studies enrolling patients with unstable angina: This syndrome is a complex, nonuniform condition. As Braunwald stated in 1989,4 a broad spectrum of patients with ischemic episodes varying widely in cause, severity, prognosis, and responsiveness to therapy are lumped together under the broad umbrella of unstable angina pectoris. In the study of Flugelman et al, 32 patients were included in the unstable angina group. However, of these, only 17 (53%) had angina at rest, whereas the others had angina of recent onset (10 patients) or accelerated angina (5 patients). According to Braunwald's classification,4 these patients clearly belong to different categories of unstable angina, which recognize different pathophysiological mechanisms. This lumping of different patients into a single category obviously affects the interpretation of the results of the present study as well.

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References


Reply

We would take issue with Dr Golino that exclusion of patients with angiographic evidence of intracoronary thrombus represents a limitation in study design. Thrombosis and plaque rupture has already been unequivocally demonstrated to contribute to the development of unstable lesions. We therefore deliberately excluded such patients so that we could determine whether any other mechanism might also contribute to the development of this syndrome. Thus, we were not trying to determine the relative incidence of different mechanisms responsible for precipitating unstable angina—we were searching for the existence of another such mechanism.

Dr Golino appears totally dedicated to the belief that the only cause of unstable angina is plaque rupture and the development of intracoronary thrombi. He states, as we discussed in our article, that during the time from onset of symptoms to the time of atherectomy, any existing thrombus may have spontaneously lysed. This surely occurred, but can Dr Golino be certain that it occurred in all or even in the majority of our patients? Dr Golino also uses angiographic evidence to infer that thrombi are present in “nearly 100%” of cases. However, these angiographic studies also investigated selected patients, casting doubt on any conclusion that “all” patients with unstable angina have intracoronary thrombus; in addition, it is not at all certain that the color and appearance of a coronary atheroma can unequivocally identify a clot (none of the published angiographic studies correlated the angiographic findings with histopathology of the coronary lesions).

Dr Golino then suggests that the smooth muscle cell (SMC) proliferation we observed might actually be a late consequence of plaque rupture, platelet activation, and thrombus formation. This is a reasonable working hypothesis. However, a good scientist would not ignore an alternative possibility—that it is the proliferation of SMCs that may be primary and that this process, by leading to an expanding and less stable neointima...
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