EDITORIAL

Anatomic-physiologic links between acute coronary syndromes

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THE BEST THERAPY for a given morbid condition is possible only when both its pathoanatomy and pathophysiology are clearly understood. This certainly applies to the acute ischemic syndromes of the heart.

Early in the study of myocardial infarction the term was considered to be synonymous with acute coronary thrombosis.1,2 This theory remained intact for many years, to be challenged only within the past two decades when it was seen that autopsies did not always uncover an acute coronary thrombosis subtending an area of established infarction. While the elegant pathologic studies of Mitchell and Schwartz3 did demonstrate a close relationship, they also found coronary thrombosis less often as death occurred further in time from the acute event. They hypothesized that recanalization might well have occurred in the interim. Roberts4 later proposed that coronary thrombosis might occur secondary to the acute myocardial infarction rather than as a cause. However, during the last few years, technical advances have brought to light a definitive role of thrombosis in the pathogenesis of the acute coronary syndromes.

The role of plaque rupture and thrombosis in the acute coronary syndromes. Recent pathologic studies of the coronary arterial system have revealed that rupture, cracking, or ulceration of atherosclerotic plaques is a common finding at autopsy in patients with coronary atherosclerotic disease.5-8 Disrupted atherosclerotic plaques are often associated with mural or occlusive thrombi, usually anchored in cracks in the ruptured plaque. The part of the thrombus directly overlying the fissure is composed predominantly of platelets. Evidence derived from serial coronary arteriography,9 and that obtained after reperfusion by thrombolysis,10 at operation during acute coronary artery syndromes,11 and from postmortem coronary arteriography,12 have also confirmed the importance of plaque disruption and thrombosis. Indeed, these acute or subacute changes in coronary arterial anatomy appear to be the most frequent cause of all the acute coronary syndromes, including unstable angina, myocardial infarction, and ischemic sudden death.5

Why and how do these acute changes in coronary arterial anatomy occur? Arteries with advanced atherosclerotic plaques often have an alteration and fragmentation of their elastic elements as well as softening of the plaque related to the fatty “gruel,”13 particularly at the margin of the plaque. With such a fragile atherosclerotic plaque, the wall shear stress in regions of focal arterial narrowing, changes in vascular tone, variations in blood pressure, and even the normal bending and twisting of the arteries with every heart contraction may all lead to plaque rupture, tearing, or ulceration.5 While hemorrhage under the plaque was formerly thought to be the mechanism of plaque rupture, recent data indicate that intimal dissection due to a tear in the fibrous cap of the plaque is the usual mechanism of plaque disruption.6,8 Thrombus formation complicating plaque disruption is related to several factors.5 Platelets become activated when the flowing blood comes into contact with the exposed fat and collagen.14 Thromboplastin released from a damaged vessel leads to the formation of thrombin, which results in fibrin formation and further activation of platelets.15 The stenotic plaque predisposes to stasis, which may result in thrombosis, particularly when plaque disruption occurs. We will briefly review recent information concerning the specific role of plaque disruption and thrombosis in three acute or subacute coronary syndromes: unstable angina pectoris, myocardial infarction, and ischemic sudden death.

Unstable angina pectoris. While the clinical presentation of stable angina differs from that of unstable angina, the coronary arterial anatomy is similar with respect to the number of diseased vessels and percentage of stenosis.16,17 However, because in the previous studies coronary anatomy before the onset of unstable

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angina was not ascertained, the significance of the data obtained is unclear. Moise et al.\textsuperscript{9} and Ambrose et al.\textsuperscript{18} reported that in about 75% of patients whose stable angina had become unstable angiographic progression of coronary disease had occurred. In many instances lesions progressed from a previously insignificant stenosis. Among patients with little or no change in symptoms between catheterizations, progression of lesions was found in about one-third. In addition, in patients with acute unstable angina, we described a specific anatomic morphology in the majority of cases. An eccentric lesion in the form of a convex intraluminal obstruction with a narrow neck due to one or more overhanging edges and/or borders that were irregular or scalloped was found in 71% of angina-producing vessels in patients with unstable angina but in only 16% of angina-producing vessels in those with stable angina.\textsuperscript{19} Postmortem angiography and pathologic analysis have confirmed that such eccentric angiographic lesions frequently manifest ruptured atherosclerotic plaques with associated thrombi.\textsuperscript{12}

Myocardial infarction. Before the use of coronary arteriography in the study of evolving myocardial infarction, most of our knowledge of lesions associated with transmural infarction had been learned at autopsy. Although helpful, these studies included a highly selected and nonhomogeneous sample of the population. Differences in the timing of autopsy after the onset of infarction, in the histopathologic methods of coronary arterial analysis, or in the selection of patients probably explain the reported variation in incidence of thrombosis associated with transmural infarction (20% to 95%).

DeWood et al.\textsuperscript{11} were the first to use coronary arteriography systematically to define the prevalence of total coronary artery occlusion in the early hours after transmural myocardial infarction. Total coronary occlusion was found in 87% of patients evaluated within 4 hr after the onset of symptoms and decreased to 65% when patients were studied 6 to 24 hr later. Among a subgroup of these patients who underwent emergency coronary bypass operations a thrombus was retrieved in 88%. Other angiographic preintervention studies of early myocardial infarction have demonstrated occlusion of the infarct-related artery in 60% to 90% of patients with transmural myocardial infarctions\textsuperscript{10,20} and in some of those with subendocardial (nontransmural) myocardial infarctions as well.\textsuperscript{20,21} The ability to reopen a totally occluded vessel with thrombolytic agents supports the importance of thrombus as the cause of infarction.

Thus, total coronary occlusion is common during the early hours of transmural infarction and decreases in frequency during the first 24 hr, suggesting that superimposed coronary thrombus or spasm, with subsequent dissolution or release, may contribute to the evolution of infarction. To understand the nature of the acute lesion, Ambrose et al.\textsuperscript{22} studied 41 patients with acute (<12 hr) or recent (1 to 12 weeks) transmural infarction and patent infarct-related arteries. Sixty-six percent of infarct-related vessels were eccentrically narrowed, with lesions similar to those described in patients with unstable angina.\textsuperscript{18} Only 11% of noninfarct-related but significantly obstructed vessels had this specific lesion. In that same study analysis of a second group of patients undergoing reperfusion with streptokinase indicated that 61% of the infarct-related arteries had the same characteristic lesion at the site of thrombolysis, while only 9% of noninfarct-related but diseased vessels showed such a lesion. These data suggest that disruption of an atherosclerotic plaque with associated thrombosis is frequent in the pathogenesis of myocardial infarction.

If thrombotic occlusion does play a role in transmural myocardial infarction, why did the trials of anticoagulants in the 1960s and of platelet inhibitors in the 1970s not show a striking benefit?\textsuperscript{23} Unlike the anti-thrombotic trials of unstable angina, these studies were done in patients who survived myocardial infarction. This lack of effect may have been due to the populations selected, differences in study design (including time of entry into the study), and low morbid event rates. For example, a significant effect of aspirin was found when data from six studies were pooled to yield a patient population of 10,000 and the effects of the combination of dipyridamole and aspirin were significant when all coronary events were considered together.\textsuperscript{24,25}

Ischemic sudden death. In most cases of sudden, unexpected death, the terminal event is some form of electrical instability of the heart. Electrocardiographic evidence of acute myocardial infarction, and more commonly ischemia, has been noted in two-thirds of resuscitated survivors of sudden coronary death.\textsuperscript{26,27} In addition, acute, complicated coronary artery lesions were found at autopsy in nearly two-thirds of sudden death victims, and the findings were consistent with plaque rupture and resulting thrombus formation.\textsuperscript{8} Therefore, in a high proportion of sudden cardiac deaths, the pathologic process probably also involves a rapidly emerging coronary lesion in which plaque fissure, rupture, and resultant thrombus formation lead to ischemia with its first and only manifestation being fatal electrical instability.
The anatomic-physiologic link between the acute coronary syndromes. According to the previous discussion, an anatomic substrate consisting of plaque disruption and thrombosis is apparently a frequent common link between the three acute or subacute coronary syndromes. They all share abruptness of onset due to sudden rupture and closure of a vessel. The differences between the syndromes, however, may lie in the completeness of blood flow deprivation (a product of both the intraluminal event and available collateral inflow) and, most importantly, its duration.

In patients with unstable angina, occlusion begins as plaque disruption, with compromise of the lumen. This may be followed by thrombus formation with or without spasm. Lysis or breakup of the thrombus or release of spasm, or both, may occur within minutes and yet be recurrent. The obstruction may be so evanescent that subsequent angiographic examination does not reveal its presence or character. The use of aspirin and heparin in such patients appears to have a dramatic beneficial effect, presumably through prevention or dissolution of recurring thrombus.

In patients with myocardial infarction, the same occlusive events occur but duration of blood flow deprivation is prolonged due to unremitting obstruction or delay of recanalization and inadequacy of collateral flow. Indeed, the difference between transmural and nontransmural myocardial infarction may, again, rest on how long obstruction persists as well as on the completeness of obstruction and the availability of collateral blood flow. Angiographic findings and observations at autopsy of more frequent total occlusion with transmural than with nontransmural myocardial infarction may reflect the persistence or the spontaneous dissolution of thrombosis. In patients suffering nontransmural infarction, the vessel may be obstructed for a much shorter time with less attendant damage.

Finally, in patients succumbing to sudden cardiac death unrelated to left ventricular scar and dysfunction, the coronary arteries often show similar plaque rupture and thrombosis.

Moreover, the acute syndromes are points on a continuum. Over 10% of patients with unstable angina develop myocardial infarction or die suddenly within 12 weeks of onset. We now know that a small nontransmural myocardial infarction carrying a good immediate prognosis may simply herald a major transmural myocardial infarction within the next 2 years. Where there is insufficient early collateral blood flow to the infarct zone, the period of deprivation of antegrade blood supply leads to a transmural infarction. Indeed, the presence and functional adequacy of collateral blood supply will moderate or accentuate the ischemic damage with any of these syndromes.

If we accept the premise that all three acute coronary syndromes may evolve from acute plaque disruption followed by thrombosis or spasm or both, then we can construct a unifying theory. The development of the specific syndrome probably depends on three variables: the suddenness, completeness, and duration of blood flow deprivation. The initiating event in each syndrome may be a sudden, significant cessation of segmental blood flow, usually caused by disruption of a preexisting atheroma. The speed of closure by rupture may be greater in some patients who develop a transmural infarction. This is evidenced by the explosive onset, often followed by a self-limited, completed, rarely lingering necrotic event. This contrasts with the stuttering onset of unstable angina or nontransmural infarction, possibly due to slower luminal closure by the plaque, or with recurring, remitting thrombosis or spasm. Ischemia will also be augmented or ameliorated by the collateral blood flow response. The crucial variable determining the extent of damage, however, may be the duration of the acute obstruction before adequate flow is reestablished.

This concept has the advantage of suggesting avenues of therapy that may be beneficial to patients with all these ischemic syndromes. These include prophylactic antithrombotic therapy as well as early use of angioplasty, thrombolytic agents, and arterial vasodilators. Studies of interventions aimed at reopening occluded arteries as quickly as possible or at reperfusing or dilating potential collateral networks early in the course of the acute event should be encouraged. Time to reperfusion may be much more critical than heretofore suspected and may limit or guide our efforts to prevent or confine damage. Whether “coronary artery” therapy during myocardial infarction will favorably alter outcome remains to be seen. In any event, trials of the earliest interventions have brought to light specific causes of the acute myocardial ischemic syndromes and in so doing have offered the greatest hope for future management.

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