Thrombi in Acute Coronary Syndromes
Revisited and Revised
K. Peter Rentrop, MD

Over the past 35 years, the view has evolved that the acute coronary syndromes, ie, unstable angina pectoris, myocardial infarction, and sudden death, are caused by plaque rupture and formation of a platelet thrombus. There is at least a transient total or subtotal coronary occlusion in all cases of acute myocardial infarction. Q-wave infarcts are thought to differ from non–Q-wave infarcts by more stable platelet thrombi causing more prolonged and/or severe ischemia, leading to more extensive infarction. The greater platelet thrombi causing more prolonged and/or severe ischemia, less stable platelet thrombi that cause less severe, less extensive ischemia and/or infarction.

However, autopsy data and more recent clinical findings require significant refinement of this viewpoint on the basis of the following observations. The occlusive thrombi causing Q-wave myocardial infarction contain more fibrin than the thrombosis found in the other acute coronary syndromes that are characterized by more platelets and less fibrin. The higher fibrin content of thrombi causing Q-wave infarction explains their greater stability. Furthermore, this higher fibrin content suggests that the coagulation cascade is activated to a greater degree during Q-wave infarction than during non–Q-wave infarction in which platelets play a more dominant role. This review analyzes our evolving concepts focusing on the growing divergence of the different mechanisms underlying the different acute coronary syndromes and their clinical and therapeutic implications.

Morphological Basis for the Current Concept of Acute Coronary Syndromes
By the mid-1930s, acute myocardial infarction was shown to be caused by coronary thrombosis resulting from intimal fissuring, which is often associated with dissecting hemorrhage into the underlying plaque.4–7 In the late 1930s, however, intimal fissuring was questioned and subendothelial hemorrhages were ascribed to rupture of capillaries within the plaque.8,9 The causative role of coronary thrombosis became controversial in 1956 when pathologists first reported a low prevalence of thrombi in fatal infarction.10–16

The pendulum began to swing back in the mid-1960s because of improved autopsy techniques. Coronary thrombi were found in >90% of fatal infarcts, most being occlusive. Plaque hemorrhages, which were usually traceable to an intimal tear within the thrombosed segment, were found in most cases.17–21 These observations reaffirmed that intimal rupture was the essential mechanism causing both subendothelial hemorrhage and intraluminal thrombosis.22

Having found that three quarters of occlusive coronary thrombi were composed of layers of different ages, Sinapius17,21 concluded that these thrombi developed in a protracted, recurring course. The oldest portion of thrombus usually sealed the intimal fissure and was rich in platelets. The finding that mural thrombus formation frequently coincided with the onset of preinfarction unstable angina pectoris provided the basis for the present pathogenetic concept of unstable angina pectoris, ie, plaque rupture and deposition of a mural platelet thrombus with an abrupt reduction in coronary artery lumen.17,21,22

These mechanisms were not generally accepted throughout the 1970s. The skeptics suggested that plaque fissures were artifacts caused by sectioning arteries and that coronary thrombi resulted from a prolonged low-output state associated with large infarcts.14,15 The controversy was settled only in 1979 when rapid coronary artery recanalization with an intracoronary infusion of streptokinase provided in vivo evidence of the pathogenetic role of thrombi in acute myocardial infarction.23–25

Plaques complicated by rupture, hemorrhage, and thrombus at histological examination were found to exhibit irregular borders and intraluminal lucencies at postmortem angiography.26 The term “type II eccentric” lesions was introduced when these findings were extended to in vivo angiography.27 The type II eccentric stenosis was commonly found in patients with unstable angina pectoris and in infarct-related arteries in patients with spontaneous or streptokinase-induced recanalization. These findings provided in vivo evidence for a common vascular pathology of unstable angina pectoris and acute myocardial infarction.28

In a 1984 necropsy study of sudden ischemic cardiac death, acute coronary lesions were found in 95% of the 100 test hearts.29 Plaque fissuring was present in nearly all cases. Luminal thrombi were seen in 74%; they were predominantly nonocclusive. These observations suggested that the coronary artery lesions in patients who had died suddenly of ischemic heart disease were identical to those found in unstable angina pectoris.29

From St. Vincent’s Hospital and Medical Center and Columbia-Presbyterian Medical Center, New York, NY.
Reprint requests to K. Peter Rentrop, MD, 38 E 22nd St, New York, NY 10010.
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Dynamic Coronary Obstruction

Unstable Angina Pectoris

Until the late 1970s, unstable angina pectoris was believed to be caused by an increase in myocardial oxygen demand that cannot be met because of a severe fixed reduction in coronary flow reserve. This view was refuted by Maseri et al\(^{30}\) in 1978 when they demonstrated that transient reduction in regional myocardial blood supply and reversible total or nearly total occlusion in the corresponding coronary arteries preceded an increase in myocardial oxygen demand during episodes of preinfarction unstable angina pectoris. They attributed the dynamic changes of the ischemia-producing lesion to coronary spasm.

Another possible mechanism of dynamic coronary obstruction had been demonstrated in a canine model by Folts et al\(^{31}\) in 1976. Severe coronary stenosis associated with endothelial injury was found to cause cyclical reductions in flow to nearly zero, followed by abrupt, spontaneous return to control levels. These cyclic flow variations appeared to be due to transient formation and disintegration of platelet thrombi. Both formation of platelet thrombi and interruption of flow could be eliminated with aspirin.\(^{31}\)

In 1981, Hirsh and associates\(^{32}\) found that a powerful promoter of platelet aggregation and vasoconstrictor, thromboxane, was released into the coronary circulation in patients with continuing unstable angina pectoris but not in those with other forms of ischemic heart disease or nonischemic heart disease. Thromboxane release into the coronary circulation was subsequently also demonstrated in the canine model of Folts et al.\(^{31}\) Cyclic flow variations were inhibited or eliminated by administration of a thromboxane synthetase inhibitor\(^{33}\) or serotoninergic or \(\alpha_2\)-adrenergic receptor antagonists.\(^{34}\) Platelets possess serotoninergic and \(\alpha_2\)-adrenergic receptors, thought to mediate the proaggregatory effects of serotonin and catecholamines.

Isolated coronary artery segments obtained from the site of critical coronary stenosis in the canine model exhibited increased thromboxane and decreased prostacyclin synthesizing capacity.\(^{35}\) Prostacyclin, a key vasodilator and inhibitor of platelet aggregation, is synthesized primarily in endothelial cells that were damaged in this model. There were aggregations of platelets and infiltration of inflammatory cells, both capable of thromboxane synthesis.\(^{35}\) Serotonin tissue concentrations were also found to be elevated; platelet aggregates were considered to be the source.\(^{36}\)

It was hypothesized that endothelial injury in unstable lesions in humans and in the Folts et al\(^{31}\) canine model caused attachment and activation of platelets, which in turn release thromboxane and serotonin. Local accumulation of these 2 substances, combined with reduction in prostacyclin synthesis, would result in an imbalance of mediators, favoring further platelet aggregation and vasoconstriction.\(^{37,38}\)

Subsequent experimental studies demonstrated that intracoronary deposition of activated platelets did trigger local vasoconstriction, mediated by thromboxane \(A_2\) and serotonin.\(^{39}\) Augmentation of prostacyclin synthesis at the site of arterial injury by adenovirus-mediated transfer of the cyclooxygenase gene in a porcine model completely inhibited cyclic flow variations and thrombus formation.\(^{40}\)

Morphological evidence of fragmentation of platelet thrombi in unstable angina pectoris was provided by a 1985 necropsy study of 25 cases of fatal myocardial infarction and sudden death. Old microemboli and corresponding microinfarcts were found in 73% of the perfusion areas of coronary arteries occluded by fresh thrombi.\(^{41}\) Fifteen of the study patients had had unstable angina pectoris before the fatal episode. All but 1 had layering of the thrombus in the epicardial artery, peripheral microemboli, and microinfarctions either alone or in combination. The microemboli, which consisted primarily of platelets, were regarded as evidence that the upstream fatal thrombus had gone through an unstable period of formation and fragmentation before becoming occlusive.

Acute Myocardial Infarction

The above concept of dynamic changes in the culprit lesion was soon expanded to explain the pathogenesis of not only unstable angina pectoris but also myocardial infarction in patients with an open infarct artery at acute angiography. Transient total coronary occlusion at the site of plaque rupture that resolved spontaneously before angiography was postulated.\(^{1,42}\) This view was supported by 3 lines of indirect evidence only, because arteriography and injection of contrast material could cause thrombus dislodgment, leaving an open artery.\(^{43,44}\)

The first line of indirect evidence was derived from the acute angiographic studies of De Wood et al.\(^{45}\) The prevalence of total occlusion of the infarct artery decreased from 86% (320 of 368) among patients evaluated within 6 hours to 68% (58 of 85) among those studied 6 to 12 hours after symptom onset \((P<0.05)\).

Second, left ventricular ejection fraction was found to improve in patients with an open infarct vessel at acute angiography and in those in whom a total occlusion was recanalized with intracoronary streptokinase but not in those with persistent coronary occlusion.\(^{46}\) We suggested that the spontaneous improvement in left ventricular ejection fraction evident in patients with antegrade flow at preintervention angiography results from functional recovery of stunned myocardium.\(^{47}\)

Third, patients with an open infarct vessel at acute angiography had an early peak in creatine kinase (14.6±5.0 hours) comparable to that seen in patients with reperfusion induced by intracoronary streptokinase (15.9±7.1 hours).\(^{48}\) On the basis of this finding, Ong et al\(^{44}\) divided infarct patients who had not undergone thrombolytic interventions or acute angiography into 2 groups: those with an early peak of creatine kinase-MB, presumably resulting from spontaneous reperfusion, and those with a late peak. In both groups, there was a significant linear correlation between left ventricular ejection fraction and total creatine kinase-MB release. The slope of the correlation line was steeper in the group with an early peak, indicating a greater enzyme release per unit of infarcted myocardium, ie, greater enzyme washout, a known marker of reperfusion.\(^{49}\)
In the same study, the time from infarct onset to peak creatine kinase-MB correlated negatively with a change in ejection fraction. This finding suggested that recovery of left ventricular function increased continuously with progressively earlier spontaneous reperfusion.44 Considering time to peak creatine kinase as a continuous variable in this analysis implies the still prevailing assumption that spontaneous recanalization occurs continuously within the first 24 hours of infarction, an assumption consistent with this analysis by definition but not proved by it in fact.

Q-Wave Versus Non–Q-Wave Myocardial Infarction

Coronary angiography within 24 hours of pain onset revealed an open infarct artery in 74% (143 of 192) of patients with non–Q-wave infarction40 compared with only 19% (98 of 517) in those with Q-wave myocardial infarction.51 Collateral flow to the totally occluded infarct artery was present in 86% (42 of 49) of patients with non–Q-wave infarction48 but in only 33% (66 of 199) of patients with predominantly Q-wave infarction.52

Non–Q-wave infarcts differed from Q-wave infarcts by earlier creatine phosphokinase peaks and smaller infarct size as assessed by left ventricular function parameters, thallium scintigraphy, and enzyme release.53 Contraction band necrosis as histological evidence of early reperfusion was more common in nontransmural than in transmural infarcts (57% versus 32% of infarcts with >30% contraction band necrosis, P<0.05).54

It was speculated that in nontransmural infarcts and unstable angina, luminal closure might be a slower process than in transmural infarcts, possibly with recurring, remitting thrombosis or spasm. The extent of myocardial damage was thought to be determined by the duration of the acute obstruction before spontaneous restoration of adequate antegrade flow.59 Time to reflow was considered the essential factor, with total coronary occlusion times of <20 minutes causing unstable angina pectoris, 20 minutes to 2 hours causing non–Q-wave infarction, and >2 hours causing Q-wave infarction.1,2,37,38,42 These occlusion times were not derived from clinical data but were extrapolated from animal models.56

The mechanism of total coronary artery occlusion is initially a platelet thrombus in all unstable syndromes, including Q-wave infarction, according to the present prevailing view.1–3,41,42 The formation of an occlusive, platelet-rich thrombus “head” at the site of plaque rupture and the subsequent development of a fibrin-rich “tail” downstream have been explained by known rheological mechanisms.2 In this presumed mechanism, occlusive platelet thrombi in patients who develop non–Q-wave infarcts are thought to be less stable than those in patients who develop Q-wave infarcts, and the thrombus stability is related in turn to the severity of plaque rupture. The initial event in Q-wave infarction is hypothesized to be a deeper plaque rupture than in other coronary syndromes.2,3

Limitations of the Present Hypothesized Mechanisms of Acute Coronary Syndromes

Spontaneous Recanalization: A Biphasic Phenomenon

Unlike De Wood et al,45 we did not find fewer total occlusions of the infarct artery as the time from infarct onset to angiography increased. In the Second Mt Sinai-NYU Reperfusion Trial, the infarct artery was totally occluded in 70% (95 of 136) of patients studied within 6 hours and in 77% (101 of 131) of those studied within 6 to 14 hours of symptom onset52 (the Table). This confirmed the results of the smaller First Mt Sinai-NYU Reperfusion Trial.48

What could explain the differences between the results of De Wood et al45 and ours? The De Wood et al study was a retrospective data analysis involving patients with Q-wave infarction who were considered “candidates for various therapeutic interventions” by their attending physicians. Only 26.6% (322 of 1210) of those fulfilling inclusion criteria were enrolled. Patients were not studied if they “did not present in the early hours of infarction,” a definition that “varied and was left to the judgment of each physician.”45 Physician judgment is likely to have resulted in preferential enrollment of patients with an open infarct artery in the subgroup presenting after >6 hours, because these patients tend to have a more protracted clinical course. Most patients with persistent total coronary occlusion have completed their infarct within 6 hours of symptom onset.

Our studies were prospective. The standardized enrollment criteria, which included onset of infarction within 12 hours of presentation, did not change with duration of chest pain and were uniformly applied by all participating physicians; 71.3% (393 of 551) of eligible patients were enrolled.52 The main reason for not enrolling patients was their refusal to participate. Therefore, the likelihood of a selection bias would have been greater in the De Wood et al study. Our observations definitively refute the hypothesis that spontaneous recanalization occurs continuously within the first 24 hours of acute myocardial infarction in association with a progressive decrease in the prevalence of total occlusion.52

However, repeated angiography at day 10 to 14 in our reperfusion trials revealed evidence of delayed spontaneous recanalization. Infarct vessels that had been totally occluded at acute angiography were open in 45% of patients who had not received thrombolytic therapy. We therefore further concluded that spontaneous recanalization is a biphasic phenomenon, occurring either earlier than angiography was

### Table: Prevalence of Patency of Infarct Artery at Baseline Angiography in the Second Mount Sinai-NYU Reperfusion Trial

<table>
<thead>
<tr>
<th>Time to Angiography, h</th>
<th>Patients studied, n</th>
<th>Patent artery, %</th>
</tr>
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<tbody>
<tr>
<td>2–4</td>
<td>55</td>
<td>29</td>
</tr>
<tr>
<td>4–6</td>
<td>81</td>
<td>30</td>
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<tr>
<td>6–8</td>
<td>66</td>
<td>27</td>
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<td>8–10</td>
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<td>24</td>
</tr>
<tr>
<td>10–14</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>All</td>
<td>267</td>
<td>27</td>
</tr>
</tbody>
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*As a function of time interval from onset of pain to angiography (time to angiography).
performed in our trial, ie, within <2 hours, or delayed, ie, >14 hours after symptom onset.52

Assessing the Time Frame of Spontaneous Reperfusion by Indirect Parameters

The duration of total occlusion in patients with early spontaneous recanalization can be estimated from left ventricular function data. We observed a specific relation between the change in ejection fraction after reperfusion with intracoronary streptokinase and the duration of total coronary occlusion.46 In the same database, patients with an open infarct artery at acute angiography exhibited an average increase in ejection fraction of 7.6%. Using this value with our observed relation of improved ejection fraction to duration of occlusion indicates that the mean occlusion time in patients with an open infarct artery at acute angiography is <2 hours.

To examine the effects of delayed spontaneous recanalization, we analyzed several retrospective studies. In a study of creatine kinase release after early reperfusion with intracoronary streptokinase, we used historical control patients not treated with a thrombolytic agent who had had angiography in the acute and chronic stage of infarction.57 Control patients with spontaneous delayed recanalization did not exhibit an early creatine kinase peak as did patients acutely reperfused with intracoronary streptokinase. In fact, the enzyme curves of patients with delayed spontaneous recanalization were indistinguishable from those seen in patients with persistent total occlusion.

ECG changes in patients with acute left anterior descending artery obstruction were assessed in another study using a group reperfused with intracoronary streptokinase and non-treated historical control patients.58 Control patients with delayed spontaneous recanalization did not display the rapid decrease in ST-segment elevations, regression of Q waves, or increase in the sum of R-wave amplitudes that occurred within 24 hours after early streptokinase-induced recanalization.

Left ventricular ejection fraction was determined before short-term angiography and predischARGE in the Second Mt Sinai-NYU Reperfusion Trial.47 A post hoc analysis revealed that ejection fraction decreased in patients with delayed recanalization (−6.3±1.2%, P<0.001) and in those with persistent occlusion of the infarct artery (−4.5±1.1%, P<0.001), whereas it increased after acute recanalization with intracoronary streptokinase (2.8±0.9%, P<0.01).

These data suggest that delayed spontaneous recanalization, in contrast to early induced recanalization, does not alter enzyme kinetics or the evolution of the ECG, nor does it prevent deterioration of left ventricular function. Delayed spontaneous recanalization occurs too late to limit infarct size.

Morphological and Interventional Findings

Severity of Plaque Rupture and Thrombotic Response

Detailed autopsy studies do not support the assumption that the extent of intimal injury determines the extent and stability of the intraluminal thrombus and associated clinical syndrome. For example, microscopic fissures only 0.1 mm deep were found to be covered by massive, occlusive thrombi, and large plaque ulcers were sealed by flat mural thrombi. This study explicitly demonstrated that extent, composition, and thickness of coronary thrombi are not related to the severity of the intimal injury.18 This report has been confirmed by other studies showing that the amount of thrombus within the lumen was not proportional to the extent of the exposure to plaque contents. Minimal fissuring was commonly found in association with a massive thrombotic response.1

Histology of Mural Thrombi

Intimal injury causes the formation of a platelet thrombus; however, even microthrombi in human arteries are frequently “mixed” in nature; ie, they contain significant quantities of erythrocytes and fibrin in addition to platelets,59 suggesting that the coagulation cascade is often activated at an early stage after plaque rupture. Mural thrombi often extend beyond the rupture site to cover adjacent intact endothelium.60

Within 24 to 72 hours, mural thrombi undergo regressive changes, beginning with compression, which is followed by hyalinization. Fibrinolytic agents cannot diffuse easily into compressed mural thrombi, which makes them poor targets for such drugs.17

Histology of the Occlusive Thrombus

There is now agreement that in transmural myocardial infarctions, most occlusive thrombi develop in a protracted and recurring course, which is reflected by their layered appearance.1,17,41 However, controversy remains about the composition of the terminal thrombus that causes total occlusion of the vessel. The concept that total coronary occlusion always results from growth of mural platelet thrombus was first proposed in 196961 and gained wide acceptance, although it is unconfirmed by scientific data.1,3,41,62

In the most thorough autopsy study to date involving 91 cases of fatal transmural acute myocardial infarction, the composition of occlusive coronary thrombi was assessed by transverse sectioning and related to the underlying plaque pathology.63 In only 15% (14 of 91) did the transverse sections at the site of plaque injury, corresponding to the “head” of the thrombus, reveal a pure platelet thrombus containing little or no fibrin. In 85% (77 of 91), occlusion was caused by thrombi rich in fibrin and erythrocytes. Slightly more than half of these latter thrombi (n=41) were coagulation thrombi, which were frequently superimposed on an older, mural platelet thrombus. The remaining 36 thrombi were mixed in structure, with areas rich in thrombocytes adjacent to areas rich in fibrin and erythrocytes. The platelet component dominated in a small subgroup of mixed thrombi, comprising ≈5% of the total study group. Therefore, no more than ≈20% of all occlusive thrombi consisted exclusively or predominantly of platelets.63

Plaque rupture frequently resulted in extrusion of atheromatous debris into the vessel lumen.19,63 In rare cases, a prolapsed atheroma caused subtotal occlusion. Extrusion of atheromatous material into the lumen was usually associated with a red or a mixed thrombus, not with a platelet thrombus.63

Regressive changes in occlusive thrombi were not visible microscopically for ≥3 days after the infarct, which is
Appositional Thrombus Growth
Distal extension of the thrombus beyond the site of plaque rupture, corresponding to the "tail," was found in 50% of the 91 cases of fatal infarction mentioned above. Proximal apposition was seen in 25%. Most appositional thrombi were rich in fibrin and erythrocytes. Two distal appositional thrombi consisted of platelets only, and 2 proximal appositional thrombi were mixed.63

The average length of coronary thrombi including the appositional portion was 20.2 mm; however, one third of thrombi were longer, up to 80 mm.63 It has been proposed that proximal thrombus apposition could cause infarct extension by occlusion of side branches,64 even that distal thrombus apposition could transform nontransmural into transmural infarcts. This hypothesis was based on a canine model in which coronary artery ligation resulted in nontransmural infarcts, whereas coronary ligation, combined with injection of a nonresorbable polysulfide polymer into the distal arterial lumen, resulted in transmural infarcts. The polysulfide material occluded distal branches, which functioned as conduits for collateral flow.65 Occlusion of major side branches by appositional thrombus was specifically examined in the above-mentioned postmortem analysis of coronary thrombi, but no evidence of it was found.63 Longitudinal thrombus growth does not appear to be of importance in theogenesis or evolution of transmural myocardial infarction.

Coronary Angioscopic Findings
Coronary thrombi assessed at autopsy are necessarily subject to a selection bias. In vivo evidence regarding the composition of occlusive thrombus has been provided by transcutaneous transluminal coronary angiography.66 Of 16 patients with acute myocardial infarction undergoing coronary angiography, 15 had thrombi, all reddish. Thrombi were also found in 14 patients with unstable angina pectoris. Only 4 of these thrombi were reddish; the remaining 10 were grayish or whitish. If proximal thrombus apposition occurs in only 25% of cases as suggested by autopsy findings,63 one would have to assume that the "head" of the occluding thrombus was directly visualized by angiography in three quarters of the patients.66 The red color of all thrombi in the acute myocardial infarction group was consistent with the histological finding of a coagulation or mixed thrombus, rich in erythrocytes, at the site of plaque rupture in most cases of fatal transmural myocardial infarction.63

Response to Pharmacological Interventions
Failure of fibrinolytic therapy to achieve angiographically apparent improvement of the culprit lesion in patients with unstable angina pectoris was first reported by us24 and definitively proven in the TIMI IIIA trial.67 “Substantial improvement,” ie, reduction of diameter stenosis by ≥20% or improvement of flow by 2 TIMI grades, was seen in 7% of patients with unstable angina pectoris treated with tissue plasminogen activator and heparin and in 4% of those treated with heparin alone. This finding indicates that significant amounts of fresh fibrin were not present in the coronary arteries of patients with unstable angina pectoris. Fibrin-containing mural thrombi >24 hours old have undergone regressive changes and would be expected to be resistant to fibrinolytic therapy. Alternatively, resistance to fibrinolytic therapy would be consistent with the suggestion that unstable angina pectoris is caused by extensive plaque dissection with luminal encroachment66 and/or formation of unstable platelet thrombi.41

Among patients with non–Q-wave infarction in the TIMI IIIA trial, one third of those treated with tissue plasminogen activator and heparin showed substantial angiographic improvement compared with 8% of those treated with heparin alone (P=0.003). Non–Q-wave myocardial infarction, an a priori–specified variable in the multivariate analysis of the TIMI IIIA trial, was found to be an independent predictor of angiographic improvement; unstable angina pectoris was not.67 These results suggested that fresh, fibrin-containing intracoronary thrombus was more prevalent among patients with non–Q-wave infarction than among those with unstable angina pectoris. However, neither patients with unstable angina pectoris nor those with non–Q-wave infarction benefited clinically from fibrinolytic therapy. Conversely, blockade of platelet aggregation with glycoprotein IIb/IIIa inhibitors, tested in several trials, invariably reduced death or nonfatal infarction at 30 days in both groups.68 These findings are consistent with autopsy studies that point to the formation of platelet thrombi as a central pathogenetic mechanism in both of these unstable syndromes.

Rapid reflow was achieved in 80% of patients with total coronary occlusion treated with intracoronary streptokinase within 6 hours of infarct onset.52 This finding parallels the postmortem observation of a fibrin-rich occlusive thrombus in 80% of fatal transmural infarctions. Lysis time was found to increase when therapy was initiated >6 hours after onset of infarction.69 This finding may be related not only to cross linking of fibrin70 but also to appositional thrombus growth. Full resistance to fibrinolytic therapy in 20% of patients corresponds to the observation of occlusive platelet thrombi in the same percentage of autopsy cases.63

Revision of the Hypothesized Mechanisms Underlying Acute Coronary Syndromes
The view that all myocardial infarcts are caused by occlusive thrombi, which are more stable in Q-wave than in non–Q-wave infarcts, is supported by the body of published research.2,3,55,62 However, the assumption that the occluding thrombus is a platelet thrombus in both types of infarction, the stability of which is determined by the extent of underlying plaque rupture, is not consistent with the results of autopsy studies65 or prospective clinical trials.48,52 Rather, available evidence indicates that 80% of occlusive thrombi causing Q-wave myocardial infarction owe their greater stability to a greater fibrin content. Such fibrin-rich thrombi commonly recanalize spontaneously because of clot retrac-
tion or endogenous fibrinolysis; however, these processes require too much time to salvage myocardium.

This analysis indicates that in 80% of patients with transmural infarction, the coagulation cascade is activated to a greater degree than it is in other acute coronary syndromes at the time of the final event when an occlusive thrombus develops. Expression of tissue factor, which initiates the extrinsic coagulation cascade leading to thrombin formation, was found to be higher in lipid-rich atheromatous core than in other vessel wall substrates, including collagen-rich matrix. Thrombus formation and platelet deposition were up to 6 times higher on the lipid-rich core than on other arterial wall components. Plaque thrombogenicity was reduced by local inhibition of tissue factor activity.

These findings emphasize the importance of the external coagulation pathway in unstable coronary syndromes and suggest that the nature of the plaque component exposed by rupture determines the degree of its activation. However, they do not fully explain why some thrombi are rich in fibrin while others consist of platelets, primarily because thrombin not only leads to fibrin deposition but also is the most potent platelet activator. Tissue factor staining score and quantitative platelet deposition on various plaque and vessel wall components correlated positively. Inhibition of tissue factor inhibited both fibrin and platelet deposition. Thus, additional factors that could shift the thrombotic response to vessel injury toward fibrin deposition need to be considered in pathogenetic models of transmural infarction.

Such factors included increased plasma fibrinogen levels, which have been found in patients with acute ischemic syndromes and in smokers. Elevated levels of LDL cause endothelial dysfunction, which might contribute to the formation of a fibrin-rich thrombus by increasing extrinsic factor activity, reducing fibrinolytic activity, and increasing levels of plasminogen activator inhibitor.

Clinical Implications

Intravenous thrombolytic therapies fail to achieve restoration of early and complete coronary flow in 50% of patients. Fibrinolysis enhances platelet aggregation by exposing thrombin, a very potent platelet activator, which is abundantly bound within the clot. It has been suggested that exposure of thrombin results in growth of the platelet core of the occluding thrombus. Because activated platelets secrete plasminogen activator inhibitor type 1, the most powerful inhibitor of fibrinolysis, a vicious circle ensues.

The recanalization rate of 50% achieved with intravenous thrombolytic therapy corresponds approximately to the prevalence of fibrin-rich coagulation thrombi at autopsy. Such thrombi present the most promising targets for fibrinolytic therapy. The older, platelet-rich mural thrombi, which are often found at the base of coagulation thrombi, have usually undergone regressive changes and are therefore unlikely to become a nidus for the vicious circle of platelet aggregation and activation.

These latter mechanisms are most likely to occur in the “mixed thrombi,” in which areas rich in thrombocytes lie adjacent to areas rich in erythrocytes and fibrin; such thrombi were found in approximately one third (36 of 91) of the cases at necropsy. Intracoronary streptokinase infusion, which achieves TIMI grade 3 flow in 80% of total occlusions, appears to lyse not only the coagulation thrombi but also most mixed thrombi. This may be due to the greater concentration of fibrinolytic agent at the thrombus site and the anticoagulant activity of fibrinogen degradation products, primarily fragments X and Y, generated by this nonselective thrombolytic agent.

Intravenous treatment modalities could theoretically be modified to lyse mixed thrombi more efficiently. Administration of a glycoprotein IIb/IIIa inhibitor without exogenous plasminogen activator improved flow in 85% of 13 patients with acute myocardial infarction, although TIMI grade 3 flow was achieved in only one patient. Combined administration of a fibrinolytic agent and a glycoprotein IIb/IIIa inhibitor, which is currently under investigation, would prevent platelet aggregation in mixed thrombi. Overall recanalization rates of total occlusions could be expected to increase from 50% to 80% with such therapy, an improvement that is in keeping with results of the TIMI 14A trial.

In the 20% of patients whose occlusive coronary thrombi consist predominantly of platelets, glycoprotein IIb/IIIa inhibition may be particularly useful. It appears quite possible, however, that brisk reflow can be achieved in these patients only with the use of mechanical interventions.

In patients with unstable angina and non-Q-wave infarction, the benefit of blocking fibrin formation long term with warfarin in addition to reducing platelet activation is being explored. Such studies would be in keeping with the concept that activation of the coagulation cascade is a central mechanism in the pathogenesis of Q-wave infarction.

Structural features and cellular components that render plaques vulnerable to fissuring and mediators that promote platelet and fibrin deposition have been identified. However, the factors that determine the nature and extent of the thrombotic response to plaque disruption and the ensuing clinical syndrome remain incompletely understood.

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