PATHOPHYSIOLOGY AND NATURAL HISTORY

UNSTABLE ANGINA

Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death

Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion

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ABSTRACT Extensive microscopic examination of epicardial arteries and myocardium was performed in 25 cases of sudden death due to acute coronary thrombosis. Eighty-one percent of the thrombi had a layered structure with thrombus material of differing age, indicating that they were formed successively by repeated mural deposits that caused progressive luminal narrowing over an extended period of time. This episodic growth of the thrombus was accompanied by intermittent fragmentation of thrombus in 73% of the cases, with peripheral embolization causing microembolic occlusion of small intramyocardial arteries associated with microinfarcts. The period of unstable angina before the final heart attack was, in all but one of 15 patients, characterized by such an ongoing thrombotic process in a major coronary artery where recurrent mural thrombus formation seemed to have alternated with intermittent thrombus fragmentation. The culmination of this "dynamic" thrombotic process in total vascular occlusion caused the final infarction and/or sudden death.


ACUTE myocardial infarction and sudden coronary death are often preceded by a period of recurrent attacks of angina at rest (unstable angina), and it seems likely that the mechanisms underlying these prodromal symptoms and the subsequent major cardiac event basically are the same. Extensive hemodynamic monitoring of patients with angina at rest has shown that transient reductions in coronary blood flow, rather than increases in myocardial oxygen demand, play the major role in resting angina, and the concept of dynamic (vs fixed) coronary stenosis has been introduced. "Dynamic" means that the degree of flow obstruction caused by the stenosis varies, and two main theories have been advanced to explain this phenomenon: (1) focal vasospasm, usually superimposed on an atherosclerotic lesion, and (2) transient platelet aggregation at the site of a severe atherosclerotic stenosis. Both these mechanisms (spasm and thrombosis) have been demonstrated by coronary angiography performed during periods of unstable angina, but uncertainty remains regarding the frequency and the clinical significance of the two phenomena.

Transmural infarction is caused by thrombotic occlusion of a coronary artery. Because unstable angina so frequently culminates in infarction, it seems likely that the thrombotic process in some way is also involved in the dynamic flow obstruction of unstable angina. Thus recurrent episodes of mural thrombus formation alternating with thrombus disintegration could constitute the pathologic basis for unstable angina with the innate risk of occlusive thrombus formation causing infarction or sudden death. This hypothesis is tested in the present study of patients who died soon after the onset of an acute heart attack caused by thrombotic occlusion of a coronary artery. Special attention was focused on changes in coronary arteries and myocardium that had occurred in the days or weeks immediately before the final heart attack.

Materials and methods

Forty-nine patients with clinically suspected fatal ischemic heart disease were selected for postmortem coronary angiog-
raphy at the Institute of Pathology, Randers Hospital. Some of the coronary pathologic data in these patients have been previously reported.14,15 In this study a more extensive examination was performed in 25 patients, all of whom died of acute coronary thrombosis within 24 hr after the onset of acute symptoms. Of the 24 excluded patients, 18 died of acute coronary thrombosis with longer duration of acute symptoms, three died instantaneously of severe coronary atherosclerosis without acute thrombosis, and two had no coronary atherosclerosis; one heart was no longer available.

Autopsy procedure. Postmortem coronary angiography was performed with a barium/gelatine mixture that was gently injected into the coronary arteries under a constant pressure of 150 mm Hg. Angiograms were taken in many different projections. After fixation and decalcification, the epicardial arteries were sectioned transversely at 3 mm intervals, and all thrombosed segments were excised and processed for microscopy by the step-sectioning technique.

The ventricular portion of the heart was cut into 1 cm thick slices parallel to the atrioventricular groove, photographed, and exposed to x-rays with each slice placed directly on the radiographic film. With the angiograms as a guide, great care was taken to identify exactly the perfusion area of each coronary artery (figure 1). Ten histologic sections were prepared from the perfusion areas of thrombosed epicardial arteries, and as a control a similar number was sampled from the perfusion area of a nonoccluded artery without collateral supply from the thrombosed artery, if present. The histologic sections were stained with hematoxylin-eosin and Masson’s trichrome stain.

All thrombosed epicardial arteries were step-sectioned at 200 μm intervals and the following were recorded:

Recurrence thrombus. The presence of thrombus material of clearly differing age in the same histologic section was evaluated. Three histologic patterns were differentiated: (1) tightly packed but individually discernible platelets, (2) a structureless eosinophilic (hyalin) mass, and (3) partly organized hyalin material in the process of being incorporated into the atherosclerotic plaque.

Plaque characteristics. Acute changes such as plaque rupture (disruption of the fibrous cap covering the plaque), plaque hemorrhage, and degree of preexisting (fixed) atherosclerotic stenosis at the site of acute thrombosis were evaluated.

The myocardial sections were evaluated blindly without knowledge of sampling site or clinical data, and the presence of the following were recorded:

Microemboli. These were defined as embolic material consisting of (1) tightly packed and individually discernible platelets (aggregated platelets), (2) a hyalin mass, or (3) atheromatous plaque material with cholesterol crystals. Only major platelet aggregates (diameter > 50 μm) were accepted as emboli.

Recent microinfarcts of presumed microembolic origin. Recent microinfarcts were characterized as isolated foci with a diameter greater than 0.5 mm consisting of loose stroma without muscle cells, rich in capillaries, pigment-laden macrophages, lymphocytes, and plasma cells. Only lesions located in the subepicardial half of the myocardium were accepted as being of embolic origin, because severe regional or general perfusion failure may give rise to similar patchy lesions in the subendocardial zone.16,17

Clinical data. Information about prodromal symptoms and the exact time of onset of the final heart attack were obtained from the clinical records (which were reviewed without knowledge of the pathologic findings). Unstable angina was defined as intermittent chest pain at rest in the days or weeks preceding the final heart attack.

Results

Twenty-six acutely thrombosed coronary arteries were found in 25 patients. The male:female ratio was 20:5, and the age range was 42 to 86 years (mean 64). Myocardial tissue was sampled from the perfusion areas of all 26 thrombosed arteries, but in five cases no area was usable as a control because of extensive development of collateral vessels (figure 1, right, illustrates such a case) leaving 20 control areas for sampling.

Thrombosed epicardial arteries. Two zones of differing age could be readily identified in 15 thrombi and three or more zones in another six cases (figure 2). Thus 81% of the thrombi had a layered appearance with evidence of more than one thrombotic episode. The most recent part of the thrombus responsible for the final luminal occlusion consisted of individually discernible aggregated platelets. A preexisting atherosclerotic stenosis (fixed stenosis) greater than 75% was always present and an intimal defect with variable degree of intimal hemorrhage was usually found beneath the thrombi. This intimal defect consisted in 21 cases (81% of the cases) of a ruptured plaque surface, and the concomitant hemorrhage into the plaque was often so extensive that it reached the base of the plaque where it came in close contact with the adjacent muscular media (figure 2, B).

Perfusion areas of thrombosed arteries. Myocardial infarction in the form of coagulation necrosis with polymorphonuclear leukocytic infiltration had developed in 15 cases, equivocal ischemic changes were found in five cases, and the myocardium was morphologically normal in the remaining six cases. No infarct was more than 1 day old (according to the criteria of Mallory et al.,18) and thus the overall morphology of the myocardium was well preserved and no problems were encountered by identifying small emboli and ischemic lesions, if present, which antedated the changes of the major infarct.

Control areas. The myocardium in the perfusion areas of nonthrombosed arteries was normal apart from occasionally small foci of recent necrosis localized entirely subendocardially.

Microemboli and recent microinfarcts. The essential findings are presented in table 1 and illustrated in figures 3 and 4. A total of 460 transmural myocardial sections were examined (260 and 200 sections from perfusion areas of thrombosed and nonthrombosed arteries, respectively). A total of 76 microemboli were found in 31 histologic sections. All except four (two sections) of these microemboli were located in perfu-
FIGURE 1. Postmortem coronary angiography was used to identify exactly the perfusion areas of thrombosed epicardial arteries and to guarantee that suitable areas were selected for control (areas without collateral supply from thrombosed arteries). Left, Guided by angiograms of the entire heart and of 1 cm thick transventricular sections, myocardial tissue was sampled from perfusion areas of the LAD (thrombosed artery; arrow) and the LC and R (control). Right, As a result of old occlusions of the LC and R, the thrombosed LAD supplies the original perfusion areas of the LC and R via collateral vessels. Thus no area remains for control, illustrated (bottom) by the finding of a small atheroembolus (arrow) with associated microinfarct (asterisk) in the posterior wall of the left ventricle (microinfarct “at a distance”). (× 100.) LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; R = right coronary artery.
FIGURE 2. Two cases illustrating episodic thrombus formation in epicardial arteries. A. Occlusive thrombus formed in three stages, with the oldest part (1) incorporated into the fibrous cap covering the atheromatous “gruel.” B. Nonocclusive thrombus formed in two stages with associated hemorrhage into the plaque (asterisks) (both thrombus and hemorrhage commenced a little further proximal in the artery where the fibrous cap was ruptured). Possible mechanisms underlying a concomitant vasospastic phenomenon, if present, are illustrated: stimulation of the medial smooth muscle by the disruptive plaque hemorrhage (short arrows) or vasoactive substances liberated from the platelet mural thrombus (long arrows). (×20.) cap = fibrous cap; c = contrast medium.
sion areas of thrombosed epicardial arteries, i.e., downstream to a thrombus in a major coronary artery. Fourteen (54%) perfusion areas of thrombosed arteries contained microemboli while only one (5%) control area did so (p < .002, Fisher's exact test). Emboli of aggregated platelets were located in morphologically normal small arteries, while emboli of hyaline material were often partly incorporated into the vessel wall and endothelialized. Some emboli consisted of a mixture of hyaline material and individually discernible platelets. Sixteen atheroemboli were found in four cases. The impacted atheromatous material usually had elicited an extensive inflammatory cell reaction with many eosinophils. In all cases of atheroembolism a ruptured atheromatous plaque was found upstream beneath an occluding thrombus in the supplying epicardial artery.

Recent microinfarcts in various stages of healing were found in 10 (38%) of the 26 perfusion areas of thrombosed arteries while only a single similar lesion was found in one (5%) of the 20 control areas (p < .02, Fisher's exact test). Microemboli and/or recent microinfaracts were present in 19 of the 26 perfusion areas of thrombosed arteries (73%). The size of the ischemic myocardial lesions corresponded to the size of the occluded intramyocardial arteries.

Clinicopathologic correlations. The duration of the terminal heart attack was in all cases in accordance with the morphologic age of the myocardial infarct, if present. Coagulation necrosis with polymorphonuclear leukocytic infiltration was not present in 11 patients, all of whom had died within 8 hr after the onset of acute symptoms. In 24 patients the clinical records contained information about the condition of the patient in the period immediately before the final heart attack. Fifteen had experienced unstable angina, two had had uncharacteristic chest discomfort, and only five had been without any prodromal symptoms. No differences between these groups were noted regarding the degree of preexisting atherosclerotic (fixed) stenosis at the site of thrombosis or the presence or absence of an underlying plaque rupture (table 2). There was a trend toward more episodes of thrombus formation in epicardial arteries, more peripheral microemboli, and more embolic microinfarcts in the group of patients with unstable angina (table 3), but none of these differences were statistically significant. However, all but one of the patients with unstable angina had morphologic evidence of repetitive episodes of thrombus formation/fragmentation in the form of a layered epicardial thrombus with thrombus material of differing age and/or peripheral microemboli and/or microembolic infarcts.

Discussion

Evolution of an occlusive thrombus. It has previously been shown that the final thrombotic occlusion of an atherosclerotic coronary artery usually occurs at the site of a severe stenosis where an acute intimal lesion (a ruptured plaque) initiates the thrombotic process in the vascular lumen. This observation is extended by the present study, which shows that the occluding thrombus is seldom formed abruptly in a single event but is usually formed successively over an extended period of time. In full agreement with other observations, two or more episodes of thrombus formation were readily identified in the majority (81%) of the thrombi. The layered structure suggests that most thrombi were formed by repeated mural deposits, which progressed to total vascular occlusion in an episodic way. However, for the first time firm evidence is presented that intermittent thrombus fragmentation is a phenomenon as frequent as recurrent thrombus formation. Thus in 73% of the cases small fragments of thrombus material (microemboli) and/or recent microinfarcts were found in the myocardium distal to evolving coronary thrombi, indicating that thrombus material may break off and be carried away with the blood (peripheral embolization). This sets the stage for a dynamic coronary stenosis: recurrent episodes of thrombus formation alternating with thrombus fragmentation. Such a "dynamic" thrombotic process is in full agreement with results of experimental animal studies, in which thrombus formation caused by arterial injury often continues for weeks with fragmentation, embolization, and rebuilding of the platelet thrombus. Furthermore, it has also been shown that experimentally induced platelet microemboli may give rise to microinfarcts and/or may initiate a lethal arrhythmia.
FIGURE 3. Two cases illustrating microemboli with associated subepicardial microinfarcts. **Top.** Two partly endothelialized hyalin microemboli (arrows and inset) with associated small foci of granulation tissue (asterisks). (×30, inset ×125.) **Bottom.** Atheroembolus containing cholesterol clefts clinging to the vessel wall at a bifurcation (arrow and inset) with associated recent microinfarct (vital stroma without muscle cells). (×30, inset ×100.) c = contrast medium.
Plaque rupture: the missing link between the atherosclerotic lesion and focal vasospasm? The severity of coronary artery disease appears to be similar in patients with stable and unstable angina despite the worse prognosis of the latter. However, instability of the atherosclerotic plaque (rather than severity of stenosis) caused by a rupture of the plaque surface could constitute the difference that makes the atherosclerotic lesion of the unstable condition more susceptible to spasm and early thrombotic occlusion. A ruptured plaque surface allows luminal blood to enter the plaque and the exposed subendothelial tissue triggers the thrombotic process in the vascular lumen. However, an occlusive thrombus is not formed unless a severe pre-existing stenosis is present, causing local flow disturbances at the rupture site. Accordingly, the severity of fixed atherosclerotic stenosis also seems to be a major determinant for the outcome of vasospastic

| TABLE 2 |
| Pathology of coronary thrombi with reference to the presence (+) or absence (−) of unstable angina before the final heart attack |

<table>
<thead>
<tr>
<th>Preexisting atherosclerotic stenosis (%)</th>
<th>Plaque rupture</th>
<th>Thrombotic episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>75–79</td>
<td>80–84</td>
<td>85–89</td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ (n = 15)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>− (n = 7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No statistically significant differences could be detected for any parameter.
angina. On the other hand, hemorrhage into the plaque may be extensive and disruptive (referred to as intimal hemorrhagic dissection by Fulton) even in a nonstenotic lesion, and such hemorrhage probably could stimulate the vascular smooth muscle mechanically (like catheter-induced spasm) or chemically through breakdown products of erythrocytes (analogous to cerebral vasospasm after subarachnoid hemorrhage) (figure 2, B). A concomitant focal vasospastic phenomenon could also result from vasoactive substances liberated from aggregated platelets at the rupture site (figure 2, B). Thus plaque rupture with variable degrees of intimal hemorrhage and luminal thrombosis could be the missing link between morphology (atherosclerosis) and function (spasm).

Platelet aggregates and sudden coronary death. It has been suggested that some cases of sudden coronary death could be caused by a systemic enhancement of the platelet function (reactive platelets) with the formation of platelet aggregates in the flowing blood leading to microembolic occlusion of small myocardial vessels. The present study confirms that platelet microemboli are frequently found in intramyocardial vessels of victims of sudden coronary death, but an extensive and systematic myocardial sampling from exactly defined perfusion areas revealed that these aggregates were almost selectively located in the microcirculation distal to thrombosed epicardial arteries. This clearly speaks against an underlying systemic cause to the aggregates observed in the present study.

Artifactual peripheral displacement of thrombus material caused by the postmortem contrast injection could account for such a regional distribution of the microemboli. However, firm evidence was encountered that it was a real antemortem phenomenon. First, in 12 of the 14 cases the emboli had caused a vital reaction in the form of endothelialization, an inflammatory cell response, or a recent microinfarct (figures 3 and 4). Second, emboli were also found in cases of total thrombotic occlusion where artifactual peripheral displacement is impossible. Furthermore, if gentle contrast injection can cause peripheral displacement of thrombus material, would not pulsatile flow of the blood do the same? Herem, in a study of sudden coronary death, found a positive association between thrombus formation and the occurrence of platelet aggregates in the same epicardial artery, and he did not use contrast injection.

Clinicopathologic correlations. All but one of the patients with unstable angina had evidence of an ongoing thrombotic process in a major coronary artery during the unstable period. The culmination of this process in total vascular occlusion caused infarction and/or sudden death. A concomitant vasospastic phenomenon cannot be excluded, but the study demonstrates that the thrombotic process is usually involved in the pathogenesis of unstable angina with a fatal outcome. The mechanisms underlying unstable angina with a more benign course may be different, although thrombus formation also seems to play a role in at least some of these cases. No significant difference in coronary pathology could be demonstrated between patients with and without preinfarct angina, probably in some degree because of the small number of patients without prodromal symptoms. However, that an apparently similar thrombotic process may manifest itself quite differently clinically should not be surprising, since even severe myocardial ischemia may be totally asymptomatic (painless myocardial ischemia and infarction).

Clinical implications. Treatment with potent antispasmodic drugs (nitrates, calcium antagonists) and β-blockers usually relieves pain in the unstable condition, but the incidence of myocardial infarction or death is not reduced to any extent, if at all. Anti-thrombotic therapy, on the other hand, has been shown to give some protection against the development of myocardial infarction and probably also improves the survival. In accordance with this, a recent pathologic study of sudden coronary death stressed the pathogenetic significance of the thrombotic process, and it was suggested that the same mechanism could be responsible for unstable angina. This suggestion is supported by the present results, which once more bring the thrombotic process in focus as a significant mechanism underlying many acute cardiac events. With the objective not only of relieving pain but also of improving the prognosis, more attention should be paid to the potentially fatal thrombotic process that apparently is going on in a major coronary artery of many patients with unstable angina.

### TABLE 3
Morphologic evidence of recurrent mural thrombosis with peripheral embolization with reference to the presence (+) or absence (−) of unstable angina

<table>
<thead>
<tr>
<th>Unstable angina</th>
<th>&gt;1 thrombotic episode</th>
<th>Microemboli</th>
<th>Microinfarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ (n = 15)</td>
<td>13 87</td>
<td>8 53</td>
<td>7 47</td>
</tr>
<tr>
<td>− (n = 7)</td>
<td>5 71</td>
<td>3 43</td>
<td>2 29</td>
</tr>
</tbody>
</table>

No statistically significant differences could be detected for any parameter.

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Conclusions. The period of unstable angina preceding a fatal heart attack is usually characterized by an ongoing thrombotic process in a major coronary artery in which episodes of mural thrombus formation alternate with thrombus fragmentation and peripheral embolization. This dynamic thrombotic process (with or without a concomitant focal vasospastic phenomenon) at the site of an atherosclerotic lesion is probably the pathologic basis for unstable angina with the innate risk of progression to total thrombotic occlusion causing infarction or sudden death. Platelet aggregates are frequently found in the myocardial microcirculation of victims of sudden coronary death, but this is usually a secondary phenomenon to an evolving thrombus in a major epicardial artery and cannot be taken as evidence for a systemic platelet hyperaggregability of pathogenetic significance.

I thank Dr. Preben Johansen, Aalborg Hospital, for critical review of the manuscript.

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Circulation. 1985;71:699-708
doi: 10.1161/01.CIR.71.4.699

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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