Microemboli and Microvascular Obstruction in Acute Coronary Thrombosis and Sudden Coronary Death
Relation to Epicardial Plaque Histopathology

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Objectives
This study examined myocardial microvascular emboli and obstruction, and related these to plaque in the epicardial coronary arteries supplying the affected microvessels.

Background
Epicardial coronary thrombosis often causes microemboli and microvascular obstruction. The consequences of myocardial microvessel obstruction and myocyte necrosis are substantial, yet histopathologic characterization of epicardial coronary artery plaque has been incompletely characterized. This study examined myocardial microvascular emboli, and related these to plaque in the coronary arteries supplying the microvessels.

Methods
Hearts from sudden coronary death patients underwent examination for coronary artery plaque type and cardiac microemboli.

Results
Forty-four hearts were available for evaluation. Mean age at death was 51 ± 15 years. Coronary artery analysis found 26 plaque ruptures and 21 erosions, and a mean of 4.5 microemboli per heart. Microemboli and microvascular obstruction occurred most often from eroded plaques. Microemboli and occluded intramycocardial vessels were most common in the left anterior descending coronary artery, and all vessels contained fibrin and platelets. Mean stenoses of the culprit lesion was 74% in those with emboli and 75% in those without (p = NS). Intramycocardial microemboli were more common in plaque erosion than in rupture. Microvessels <200 μm were most often those that were occluded.

Conclusions
Microemboli and microvascular obstruction are common in patients dying of acute coronary thrombosis. Plaque erosion is more likely to cause emboli in vessels <200 μm. These emboli and microvessel obstruction have a prominent clinical role since myonecrosis is often associated with these findings. (J Am Coll Cardiol 2009;54:2167–73) © 2009 by the American College of Cardiology Foundation

Epicardial coronary artery thrombosis causes acute coronary syndromes and has long been known to cause myocardial microemboli and microvascular obstruction (MVO) (1–5). Falk (1) reported episodic coronary thrombus growth in studying autopsy-derived hearts from unstable angina patients, describing peripheral myocardial embolization, microvessel occlusion, and microinfarction. Davies et al. (2) furthered this study by an autopsy evaluation of intramyocardial thrombus and found platelet embolic thrombus in 30% of cases, with multiple necrotic regions exhibiting platelet emboli. More recently, Libby (6) summarized the relation of coronary artery thrombosis and plaque in a comprehensive review. Falk (1) and Davies et al. (2) were the earliest to conclude that myocardial platelet thrombi are embolic, and that such emboli are a clinically recognized cause of acute coronary syndromes. Both papers also describe MVO of patients without epicardial thrombi.

Clinical consequences of microvessel obstruction result from myocyte necrosis. Importantly, microemboli and MVO may both occur even when the epicardial coronary arteries are widely patent with excellent angiographic flow (7). Cardiac magnetic resonance imaging detects MVO, and has found it associated with slow myocardial flow and the “no-reflow” phenomenon after coronary intervention (8). MVO is associated with late left ventricular enlargement and heart failure, and it has strong negative prognostic implications (9–12).

Microemboli are histopathologically associated with MVO, myocyte necrosis and edema, and endothelial cell sloughing within the intramyocardial capillaries (13,14). Polymorphonuclear leukocytes are the principal inflammatory cells seen in these regions, and capillary lumina show
Plaque and Acute Coronary Thrombosis

Methods

Human hearts were obtained from a pathologic study of sudden cardiac death due to atherosclerosis and coronary artery thrombosis. These sudden cardiac death cases were sent to the senior author's laboratory (CV Path Institute) by multiple medical examiners for consultation regarding cause of death. All cases used for this study had no known history of coronary disease, and from the histories provided by relatives and investigator no patients were taking statins, clopidogrel, or aspirin. All hearts were from patients experiencing sudden cardiac death, defined as sudden and unexpected death within 6 h of cardiac symptoms. No patients had coronary intervention. Hearts were included in the study if they had at least 1 major coronary artery with ≥75% cross-sectional luminal narrowing by plaque or coronary thrombus. Patients could have no other potentially lethal cardiac or noncardiac cause of death.

Hearts were pressure perfusion fixed. X-rays of the hearts were carried out following contrast injection into coronary arteries to identify stenosis and areas of calcification. The coronary arteries were dissected off the heart and cut serially at 3- to 4-mm intervals to locate thrombus. This was done after arterial decalcification so as not to disrupt the plaque/thrombus during cutting. The X-ray examination thus identified stenoses from calcific or noncalcific plaque.

Sections with ≥50% luminal stenosis were processed for light microscopy, histopathology, and immunohistochemistry. Sections were stained with hematoxylin and eosin and Movat pentachrome. Culprit coronary arteries with acute coronary thrombi were identified and characterized for cause of thrombosis. Culprit coronary artery plaque was categorized as either plaque rupture or plaque erosion. Plaque rupture was defined as disruption of a fibrocellular cap overlying a pool of lipid with pultaceous debris. Plaque erosion was defined as surface ulceration of the upper plaque layers (containing smooth muscle cells within a proteoglycan matrix close to the luminal thrombus) without rupture into a lipid core, as described previously and shown in Figure 1 (20). Where necessary, and especially in those with underlying necrotic cores, additional serial sections were made to rule out the occurrence of plaque rupture when plaque erosion was seen.

Myocardium was sampled in 3 locations from base to apex; and in each location, 3 myocardial sections were taken transversely and assessed for emboli and infarction. For each artery, 9 myocardial sections were examined, and each section was taken from endocardium to epicardium. In the case of the left ventricular septum, endocardium to epicardium of the right ventricle was examined. By this method, we sampled the myocardium substantially more than as is done in routine autopsies.

Systematic transverse serial myocardial sections of the left ventricle were made to obtain short-axis orientation at 1-cm intervals, and examined from the base, mid-myocardium, and apical myocardium. Vascular myocardial territories were classified as being from the left main and left anterior descending (LAD) coronary arteries in the anterior and mid-septum, the anterior wall, and the anterolateral wall. The circumflex territory was the anterolateral wall and the lateral and posterolateral walls. The right coronary artery myocardial territory was the posterior and posterolateral walls, the posterior septum, and the right ventricle.

**Definitions:** ruptured versus eroded plaque. Culprit plaque and vessels were determined by histopathologic observation. Vulnerable plaques that rupture have a necrotic core with a thin fibrous cap, infiltrated by inflammatory cells, with metalloproteinase-rich macrophages. These plaques rupture in the shoulder region. Ruptured plaque was defined when necrotic material was mixed with thrombotic material at any point in the thrombus.

Conversely, plaque erosion was defined when there was no continuity between the thrombus and the necrotic core, or with the thrombus in contact with the fibrointimal plaque (20,21). Myocardial sections were examined for platelet and fibrin thrombi in intramyocardial arteries and arterioles. Immunohistochemistry was performed using antifibrin II (identifying fibrin) and antigglycoprotein IIIa (CD61, identifying platelets). Microemboli and MVO were defined as confluent aggregates of thrombus consisting of platelets with or without fibrin. Digital morphometry was performed to establish culprit arterial stenosis and size of intramyocardial arteries and arterioles containing thrombus. A control group for comparison was obtained from 9 hearts of patients who died from noncardiac deaths, and without known coronary artery disease.

**Definitions:** myocardial necrosis, acute myocardial infarction (MI), healed MI. Myocardial necrosis was defined as groups of myocytes showing hypereosinophilic
change in the absence of nucleus, or when the nucleus was present showing changes of ischemic damage such as irregular condensation of nuclear chromatin, frank coagulation necrosis, and/or contraction band necrosis. Acute MI was defined as coagulation necrosis involving equal or greater than 1 cm of the myocardium in its widest dimension. Healed MI was defined as an area of scarring ≥1 cm of myocardium in its widest dimension.

Results

Embolization and MVO was sought in 44 autopsy cases of sudden death with proven epicardial coronary artery thrombosis. Death was presumed due to acute coronary syndrome in all cases. No patient had percutaneous or other cardiac intervention. Mean patient age at death was 51 ± 15 years. Sex analysis showed 38 (86%) men and 6 (14%) women.

Histopathologic analysis of culprit plaque underlying the region of epicardial thrombosis showed 26 plaque ruptures (25 hearts, 1 heart with 2 separate plaque ruptures) and 21 plaque erosions (19 hearts, 2 hearts with 2 plaque erosions). Morphology of the occluding thrombus frequently is a mixed platelet-fibrin mixture. Immuno-
staining for platelets (CD61) and fibrin (C and F) components reveal that the typical thrombus frequently is a mixed platelet-fibrin mixture. Images are from patients not included in the study, but illustrate typical coronary thrombus in sudden death due to plaque erosion. CD61 immunostain shows platelets within the thrombus are diffusely scattered throughout slender arrow in B) junction between thrombus and the arterial plaque (thick arrow in B). The ‘cap’ of this thrombus is very fibrin-rich (arrow in C).

Figure 1 Coronary Artery Occlusion From Eroded Plaque

Epicardial coronary arteries with occlusive macroscopic thrombus (A to C) due to plaque erosion. Longitudinal sections (A, B, and C) and transaxial sections from a different vessel (D, E, and F) show the deep lipid core is not exposed. Immunostains for platelet (CD61, B and E) and fibrin (C and F) components reveal that the typical thrombus frequently is a mixed platelet-fibrin mixture. Images are from patients not included in the study, but illustrate typical coronary thrombus in sudden death due to plaque erosion. CD61 immunostain shows platelets within the thrombus are diffusely scattered throughout slender arrow in B) junction between thrombus and the arterial plaque (thick arrow in B). The ‘cap’ of this thrombus is very fibrin-rich (arrow in C).
nonocclusive. Myocardial necrosis was more common in plaque erosion, and women were more likely to have plaque erosion. Finally, microemboli were unrelated to the histopathologic stenosis severity of the culprit coronary artery, with mean epicardial lumen area stenosis 74% in those with emboli and 75% in those without (p = NS).

Left main thrombus was associated with no myocardial emboli (0 of 4), whereas 73% (16 of 22) of LAD thrombi had myocardial emboli, and respectively, 25% (2 of 8) of left circumflex coronary artery (LCx) thrombi, and 44% (4 of 9) of RCA thrombi. Only 4% of emboli were found in vessels >200-μm diameter, whereas 7% were found in vessels 120 to 200 μm, and 89% in vessels <120 μm. Of those thrombi in vessels <120 μm, 15% occurred in vessels 81 to 120 μm, 46% in vessels 40 to 80 μm, and 39% in vessels <40 μm. The majority of vessels with intramyocardial occlusion were thus ±120-μm diameter (Fig. 3).

Myocardium in the region of the occluded microvessel was associated with focal myocardial necrosis (e.g., see Fig. 4) in 57% of cases. Of these necrotic segments, 83% were associated with multiple emboli (86% in vessels <120-μm diameter). Twenty-three percent were associated with acute MI, and 5% with myocardial scar (healed MI). Fourteen percent were associated with no myocardial changes.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plaque Morphology</th>
<th>Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolization rate</td>
<td>Erosion</td>
<td>71% (15/21)</td>
<td>0.01</td>
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<td></td>
<td>Rupture</td>
<td>42% (11/26)</td>
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<tr>
<td></td>
<td>Total</td>
<td>55% (26/47)</td>
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<tr>
<td>Percent of hearts with ≥5 emboli</td>
<td>Erosion</td>
<td>43% (9/21)</td>
<td>0.05</td>
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<tr>
<td></td>
<td>Rupture</td>
<td>12% (3/26)</td>
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<tr>
<td></td>
<td>Total</td>
<td>26% (12/47)</td>
<td></td>
</tr>
<tr>
<td>Totally occlusive thrombus</td>
<td>Erosion</td>
<td>61% (14/23)</td>
<td>NS</td>
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<tr>
<td></td>
<td>Rupture</td>
<td>48% (12/26)</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>55% (26/47)</td>
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<tr>
<td>Myocardial necrosis</td>
<td>Erosion</td>
<td>86% (18/21)</td>
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<td></td>
<td>Rupture</td>
<td>19% (5/26)</td>
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<tr>
<td></td>
<td>Total</td>
<td>49% (23/47)</td>
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</tr>
<tr>
<td>Women</td>
<td>Erosion</td>
<td>71% (15/21)</td>
<td>0.001</td>
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<td></td>
<td>Rupture</td>
<td>38% (10/26)</td>
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<tr>
<td></td>
<td>Total</td>
<td>53% (25/47)</td>
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Discussion
Prior autopsy studies of epicardial coronary thrombus documented myocardial embolization, microvessel occlusion, and microinfarction, often from platelet aggregation. These papers focused on the coronary artery events, and founded the fundamental concept that embolic
myocardial platelet thrombi cause acute coronary syndromes (2,22).

Our study examined such emboli and related them to epicardial coronary plaque and characterized the MVO that results. Coronary atherosclerotic plaque typically forms thrombus from 2 principal plaque morphologies, rupture and erosion. Plaque rupture is characterized by a necrotic core and a thin, ruptured fibrous cap that causes luminal clot on a thrombogenic necrotic core. By comparison, plaque erosion has a luminal surface rich in proteoglycans and smooth muscle cells, often with only mild or minimal inflammation. Many plaque erosions lack necrotic cores (23,24).

This autopsy-derived study evaluated intramyocardial microemboli and MVO related to epicardial plaque morphology. Microemboli and MVO were found in 55% of hearts with acute epicardial coronary artery thrombosis and were often associated with focal myocardial necrosis. Whether there were emboli that were missed is unclear.

The culprit epicardial coronary artery was most often the LAD with associated emboli. The most commonly affected microvessels were 120–262 μm or less in diameter. Importantly, although patient numbers in this study were small, women more often had plaque erosions than ruptures, consistent with a prior study (21).

Plaque type has not been previously examined for its association with myocardial thromboemboli. We found plaque erosions were more often associated with MVO than plaque rupture, but not related to whether thrombus was occlusive or not in the epicardial artery. Plaque rupture is due to erosion only very rarely (25). Although mechanisms were not evident from this study, the implications are that epicardial atherosclerotic plaque structure and morphology may preferentially predispose to microembolic events. Similarly, iatrogenic plaque disruption occurs with percutaneous coronary intervention (PCI) of acute coronary syndromes,
and microembolic MVO is a major clinically recognized cause of angiographic no-reflow.

Kloner described reduced epicardial coronary flow in acute MI (26,27). These studies suggest that angiographic no-reflow (a surrogate for MVO) may in fact be worsened by coronary artery reperfusion. Progressively decreased coronary artery flow occurs over 2 to 3 days after an acute coronary artery event, and worsened by reperfusion injury (28,29).

Normal epicardial flow visualized by coronary angiography is insensitive for detecting thromboemboli and MVO. Wu et al. (30) found MVO in 17% of patients with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and in >50% over patients with TIMI flow grade 0, 1, or 2. Costantini et al. (31) found that good flow restoration in acute MI is a powerful predictor of prognosis, but is achieved in a minority of patients. In 96% of patients with angiographic TIMI flow grade 3 following PCI, myocardial perfusion was normal in only 17.4%.

Long-term prognosis is directly related to adequacy of myocardial perfusion, even after thrombolysis (30–34). This may relate to adverse ventricular remodeling (35,36). Patients with MVO have higher end-diastolic and -systolic volumes compared with patients without MVO (37,38). Myocardial segments without MVO have increased wall thickness early and better late functional recovery compared with late wall thinning in MVO segments at 5-month follow-up (39). Late clinical cardiac events occur more often in patients with MVO than those without it, suggesting that acute microemboli and MVO are important prognostic markers even after controlling for infarct size (32,37,40–42).

This study found microvascular thrombus was platelet rich in the obstructed microvasculature, with fibrin also occurring often but less frequently. MVO is a complex histopathologic phenomenon, comprising thrombus-filled myocardial arterioles and capillaries, abnormal capillary structure with endothelial cell swelling, compression, myocyte edema and necrosis, and neutrophil infiltration. Reperfusion injury promotes myocardial edema, endothelial disruption, capillary plugging by neutrophils and microthrombi, inflammation due to oxygen-free radicals and activation of complement components, and contracture of neighboring myocytes (43). PCI potentially worsens the process by causing embolic showers (5,14).

Study limitations. Although histopathologic sampling and evaluation was systematic and included multiple sectioning, relatively little of the myocardial risk region could be sampled due to the large specimen volume that would be necessary. The extent of microvascular thrombosis and obstruction is thus likely underestimated in this study. The study was performed in autopsy-derived hearts, a source of selection bias, but necessary for histopathologic evaluation.

Conclusions

This study examined epicardial plaque morphology in sudden cardiac death, and found that plaque erosion was the dominant histopathology in clot embolization causing cardiac death. Clots universally were comprised largely of platelets and fibrin-rich regions. MVO occurred most often in vessels <120 μm, and was associated with focal myocardial necrosis.

References


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Key Words: acute myocardial infarction ● sudden cardiac death ● microemboli ● microvascular obstruction.