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, microvascular 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...
platelet and fibrin plugging. Epicardial thrombi and microvascular thrombosis may also occur from plaque necrotic core particulate in distal myocardial beds following vulnerable plaque rupture (9,15–19).

Prior histopathologic studies describe intramyocardial microemboli in patients with ischemic cardiac death, but the association between culprit coronary morphology and intramyocardial emboli has not been previously reported. The purpose of this study was to investigate the frequency of intramyocardial microemboli and MVO in sudden cardiac death from acute coronary thrombosis, with specific reference to histopathology based on culprit coronary artery plaque. The study used autopsy-derived hearts from patients suffering sudden coronary death due to thrombosis of a major epicardial coronary artery.

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 ≥50% luminal stenosis by plaque or coronary artery thrombosis, with specific reference to histopathology defining vulnerable plaque rupture in the shoulder region. Ruptured plaque 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 cap overlying 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 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 antiglycoprotein 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

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>LAD</td>
<td>left anterior descending coronary artery</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<td>MVO</td>
<td>microvascular obstruction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>TIMI</td>
<td>Thrombolysis In Myocardial Infarction</td>
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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.
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 showed platelet-rich aggregates in all cases with markedly positive immunostaining for platelets. Fibrin content varied from none to moderately positive immunostaining. Figure 1 illustrates such thrombus, from a patient not included in this study who similarly experienced sudden cardiac death. These microemboli were found distal to culprit lesions, and not in the regions without thrombosis.

Intramyocardial microemboli and MVO were evaluated for frequency. In 44 hearts, 24 of 44 (54%) microemboli and MVO were found, with a mean of 4.5 affected microvessels per heart (range 1 to 22) (Fig. 2). By comparison, no microemboli were found in the 9 control hearts (necoronal deaths).

Table 1 shows that embolization was more common in plaque erosion compared with plaque rupture, and embolization was more severe in epicardial plaque erosion compared with plaque rupture. Microemboli were unrelated to whether epicardial coronary thrombus was occlusive or...
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.

**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 \( \mu \text{m} \) 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.

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