

Plaque Instability Frequently Occurs Days or Weeks Before Occlusive Coronary Thrombosis

A Pathological Thrombectomy Study in Primary Percutaneous Coronary Intervention

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Background—Acute ST-elevation myocardial infarction (STEMI) is caused by sudden occlusive coronary thrombosis, after plaque disruption; however, a considerable time interval between plaque disturbance and the onset of symptoms has been suggested. We therefore studied the age of intracoronary thrombi, aspirated during angioplasty in patients with acute STEMI.

Methods and Results—Percutaneous intracoronary thrombectomy during angioplasty was performed in 211 consecutive STEMI patients within 6 hours after onset of anginal symptoms. The aspirated material was histologically screened on thrombus and plaque components, and thrombus age was classified as fresh (<1 day), lytic thrombus (1 to 5 days), and organized thrombus (>5 days). In all patients, intracoronary-derived material was retrieved in the filter of the collection bottle. Thrombus was identified in 199 (95%) of 211 patients. In 12 patients (5%), only plaque components were identified, and in 85 patients (41%), both thrombus and plaque material were aspirated. In 18 (9%) of 199 patients, the thrombus was organized, and in 70 patients (35%), the thrombus showed lytic changes, whereas in 98 (49%), a completely fresh thrombus was found. In 14 (7%) of 199 patients, the thrombus showed combined features of both fresh thrombus and organized thrombus.

Conclusions—In at least 50% of patients with acute STEMI, coronary thrombi were days or weeks old. This indicates that sudden coronary occlusion is often preceded by a variable period of plaque instability and thrombus formation, initiated days or weeks before onset of symptoms. (*Circulation*. 2005;111:1160-1165.)

Key Words: myocardial infarction ■ thrombus ■ occlusion

Acute ST-elevation myocardial infarction (STEMI) typically is caused by occlusive coronary thrombus formation superimposed on a ruptured or eroded atherosclerotic plaque. In many cases of transmural infarction, large occlusive thrombi can be found either angiographically or histologically.¹⁻³ In general, in case of STEMI, a direct relationship between the onset of plaque rupture and acute transmural ischemia is assumed; however, autopsy studies investigating the pathogenesis of the “vulnerable plaque” in patients who had witnessed sudden cardiac death identified signs of old thrombosis, which indicates that plaque complications remain clinically silent days or weeks before the fatal event.^{4,5} The exact time course of events and the frequency of occurrence of older thrombus in patients with STEMI is, however, largely unknown. The presence of intracoronary thrombus and atheromatous plaque constituents may lead to distal embolization and the “no-reflow” phenomenon after percutaneous coronary intervention (PCI),⁶ both associated

with poor clinical outcome.⁷⁻¹⁰ Thus, as an adjunct to primary PCI for acute STEMI, thrombectomy devices were developed to remove the occluding intracoronary material before balloon dilatation and stent placement. We investigated the composition of the retrieved material, aspirated with the Rescue percutaneous thrombectomy (PT) catheter, in a large cohort of patients undergoing primary PCI within 6 hours after sudden onset of symptoms. The aim was to establish the age of the aspirated thrombi to find in vivo pathological evidence of ongoing plaque disturbances and healing processes that occur before the acute occlusive thrombosis of the infarct-related coronary artery.

Methods

Patient Population

Between October 2001 and February 2004, 211 patients who presented at our institution with acute STEMI were treated with percutaneous intracoronary thrombectomy during primary angio-

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plasty. Patients were eligible if there was evidence of acute myocardial infarction with ≥ 2 -mm ST elevation in 2 or more contiguous leads on the admission ECG and symptoms of < 6 hours' duration.

Thrombectomy Procedure

On admission, all patients were treated with 300 mg of aspirin and 5000 IU of heparin, and they underwent percutaneous intervention of the infarct-related artery through the femoral access route with a 7F guiding catheter. Thrombectomy was performed with the Rescue PT system (Boston Scientific), as described previously.^{6,11} Typically, several suctions at the site of the occlusion were performed after smooth introduction and initial passage of the flexible, soft catheter. Aspirated blood and intracoronary material were collected in the collection bottle, which was provided with a filter. Additional balloon angioplasty and stent placement were at the discretion of the operator, as was the use of glycoprotein IIb/IIIa receptor blockers.

Tissue Processing and Histopathological Procedure

Immediately after thrombosuction, the filter of the device was placed in formalin, and the aspirated material was fixed for 24 hours. After it was embedded in paraffin, the material was entirely cut in 5- μ m serial sections and stained with hematoxylin and eosin and elastic von Gieson stains, respectively, at ≥ 6 levels. The present thrombi were pathologically classified into 3 groups according to previously published and accepted definitions of thrombus age^{5,12}: (1) fresh thrombus (< 1 day), composed of layered patterns of platelets, fibrin, erythrocytes, and intact granulocytes; (2) lytic thrombus (1 to 5 days), characterized by areas of colliquation necrosis and karyorrhexis of granulocytes; and (3) organized thrombus (> 5 days), which showed ingrowth of smooth muscle cells, with or without depositions of connective tissue and capillary vessel ingrowth. Thrombus material with a heterogeneous composition was graded according to the age of the oldest part. Plaque components were identified on the basis of the presence of inflammatory cells, cholesterol crystals, collagen tissue, and/or calcifications. To optimize visualization of smooth muscle cells and macrophage foam cells, additional immunostaining was performed on specimens that contained thrombus that was classified as > 1 day old. For this purpose, a 3-step streptavidin biotin complex method was used, in which immune complexes were visualized with 3,3'-diaminobenzidine tetrachloride. Primary monoclonal antibodies were anti-CD68, reactive with macrophage foam cells (clone PG-M1, 1/100 dilution, DAKO), and anti-smooth muscle α -actin, reactive with vascular smooth muscle cells (clone 1A4, 1/200 dilution, DAKO). Sections for anti-CD68 staining were pretreated with heat-induced antigen retrieval with citrate buffer pH 6.0.

Statistical Analysis

Continuous baseline and angiographic variables with normal distribution are expressed as mean \pm SD and were compared by 1-way ANOVA. Categorical variables were compared by χ^2 square test or by Fisher exact test where appropriate. A probability value < 0.05 was considered statistically significant.

Results

Patients

In 211 patients, intracoronary-derived material was found in the filter of the collection bottle. Baseline clinical and angiographic characteristics of the patients are summarized in Table 1. Forty-five (21%) of 211 patients experienced preinfarction angina in the days or weeks before presentation of the STEMI, whereas in 14 patients (7%), a history of angina was unclear.

Aspirated Material

Microscopic evaluation of the aspirated material in tissue sections at 6 levels showed that in 199 (95%) of the 211 patients, thrombus was present; in 114 (54%) of these 199

TABLE 1. Baseline Clinical and Angiographic Characteristics of All Patients With Aspirated Intracoronary Material (n=211)

Age, y	59 \pm 13
Male sex, n (%)	154 (73)
Current smoking, n (%)	113 (54)
Hypercholesterolemia, n (%)	53 (25)
Statin use, n (%)	22 (10)
Diabetes mellitus, n (%)	19 (9)
Hypertension, n (%)	58 (28)
Prior angina, n (%)	45 (21)
Prior MI, n (%)	16 (8)
Prior MI in infarct-related artery	7 (3)
Prior CABG, n (%)	8 (3)
Prior PCI, n (%)	19 (9)
Prior PCI in infarct-related artery	4 (2)
Angiographic features, n (%)	
Single-vessel disease	142 (67)
Double-vessel disease	46 (22)
Triple-vessel disease	23 (11)
Infarct-related artery	
RCA	94 (45)
LCx	14 (7)
LAD	95 (45)
Venous graft	8 (3)
Diameter stenosis before PCI, %	99.2 \pm 2.4
Lesion length, mm	15.9 \pm 5.7
ACC/AHA lesion class B2/C, n (%)	209 (99)
Primary/restenotic lesion, n (%)	207/4 (98/2)
Stent placement, n (%)	193 (92)
Stent length, mm*	16.5 \pm 6.0
Stent diameter, mm*	3.4 (2.5–5.0)

MI indicates myocardial infarction; RCA, right coronary artery; LCx, left circumflex; LAD, left anterior descending coronary artery; and ACC/AHA, American College of Cardiology/American Heart Association.

*Stent length and diameter in 193 patients.

patients, only thrombus was found; in 12 (5%), only plaque components were identified; and in 85 (41%), both thrombus and plaque were present in the filter of the collection bottle. Figure 1 illustrates the different combinations of pathological features of the aspirated thrombi, showing that in 17 (9%) of 199 patients, the thrombus was organized (> 5 days old), with at least ingrowth of vascular spindle-shaped smooth muscle cells, which was confirmed with anti- α -actin immunostains. In 70 (35%) of 199 patients, the thrombus showed lytic changes (1 to 5 days old), identified as areas of homogenization of the thrombus structure and karyorrhexis of nucleated cells, whereas in 98 patients (49%) with aspirated thrombi, a completely fresh thrombus was found (< 1 day old; Figure 2, A through H). In 14 (7%) of 199 patients, the thrombus showed combined features of both fresh thrombus and organized thrombus. In total, in 101 (51%) of 199 patients, the thrombus showed lytic or organized changes compatible with an origin of days or weeks before the occlusive event.

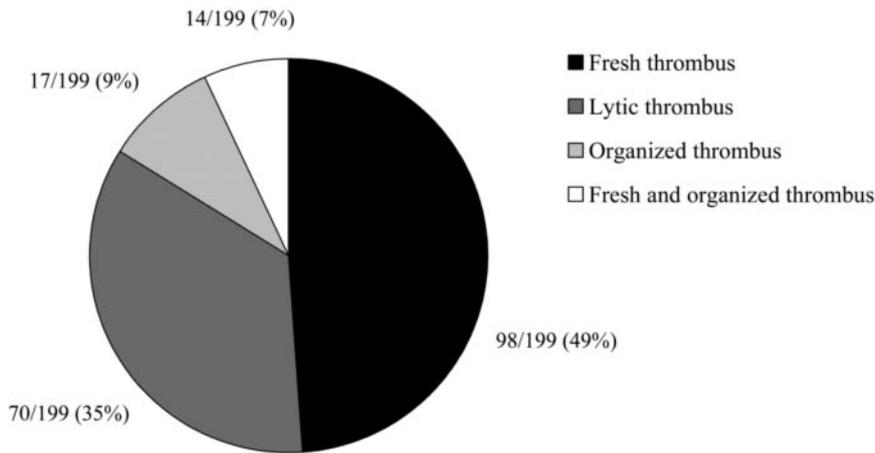


Figure 1. Thrombus age after thrombo-suction: proportions of treated patients (n=199).

All of the 97 specimens that contained plaque tissue showed “soft” plaque constituents: extracellular debris with cholesterol crystals and foam cell macrophages (confirmed by anti-CD68 immunostaining; Figure 2, K through N). A few specimens showed additional small fibrous cap fragments (collagen with or without elastin) and microcalcifications.

Clinical and procedural characteristics did not differ between patients with only fresh thrombus aspirated from the infarct-related artery and patients in whom lytic or organized thrombi were retrieved (Table 2), except that male patients more often had only fresh thrombus or lytic thrombus compared with females ($P=0.024$). Of interest, thrombus age did not differ between patients with and without preinfarction angina in the preceding days or weeks.

Discussion

The main finding of this pathological study is that intracoronary material aspirated by thrombectomy in acute STEMI is frequently heterogeneous of composition in terms of thrombus age. In 51% of cases, older thrombi were present, which suggests an important discrepancy between the time of onset of the thrombotic process and the occurrence of acute clinical symptoms.

Pathological Findings

The pathophysiological model for the occurrence of STEMI describes sudden vessel closure, mostly due to plaque rupture or erosion and subsequent intracoronary occlusive thrombosis at the onset of symptoms.³ Plaque disruption results in exposure of the lipid-rich core of the plaque to the bloodstream, which causes activation and aggregation of platelets. As a result, a luminal thrombus occurs, which prevents normal blood supply to the myocardium. This explains why in many patients with acute transmural myocardial infarction, a platelet-rich, fresh thrombus can be found.^{12–15} The aspiration of thrombi in 95% of patients in general and fresh thrombi in particular in patients with STEMI in the present study confirms these perspectives and other studies with regard to the pathogenesis of this event. The fact that fresh thrombus could not be identified in all patients may be explained in part by disintegration of the very fragile fresh material by passage through the catheter or in the collection bottle.

Systematic reports on pathological findings of thrombectomy material collected with a thrombo-suction device in large cohorts of patients are limited because the device was introduced only recently.^{11,16,17} The present findings differ substantially from the report by Murakami et al,¹² who studied thrombectomy material of 91 patients with acute MI and reported recent thrombi in 49% of cases but organized thrombi in only 2% of cases. With the use of extensive sampling (≥ 12 stained sections of each case) in a large cohort of patients with < 6 hours of acute anginal symptoms, we identified a much higher thrombus rate (95%). Moreover, with the use of strict criteria of thrombus age, as published previously,^{5,12} and additional immunostaining, we found older thrombi in $> 50\%$ of patients. Of importance, the composition of the thrombus was often heterogeneous, showing in part features of organization, lytic changes, and elements of fresh thrombus in the same tissue fragment. This layered composition suggests episodic growth of thrombus before the onset of occlusive thrombosis and the onset of symptoms. The pathological findings of the present study are compatible with the angiographic report by Ojio et al,¹⁸ who suggested considerable time intervals between the timing of acute plaque complications such as rupture or erosion and the onset of symptoms of acute MI on the basis of the presence of multiple vascular irregularities several days before the occurrence of acute MI.

The present thrombectomy results support the concept of coronary artery disease as a dynamic process, particularly in patients with STEMI. This concept is in accordance with several postmortem studies on the histopathology of the progression of coronary plaques. Plaques can rupture silently without causing symptoms but at the same time increase in size owing to incorporation and organization of intraplaque hemorrhage and thrombosis.^{4,19,20} Moreover, in a postmortem series of 11 young adults with coronary artery thrombosis who had witnessed sudden cardiac death, histological evidence of thrombus organization was found in 8 of 11 cases, which indicates that the thrombus was initiated days or, in some cases, even weeks before the fatal event.⁵ Others demonstrated that patients with a history of myocardial infarction had the highest frequency of healed plaque ruptures (80%) in 1 or several coronary artery plaques identified at autopsy.⁴ The fact that STEMI was not preceded by anginal

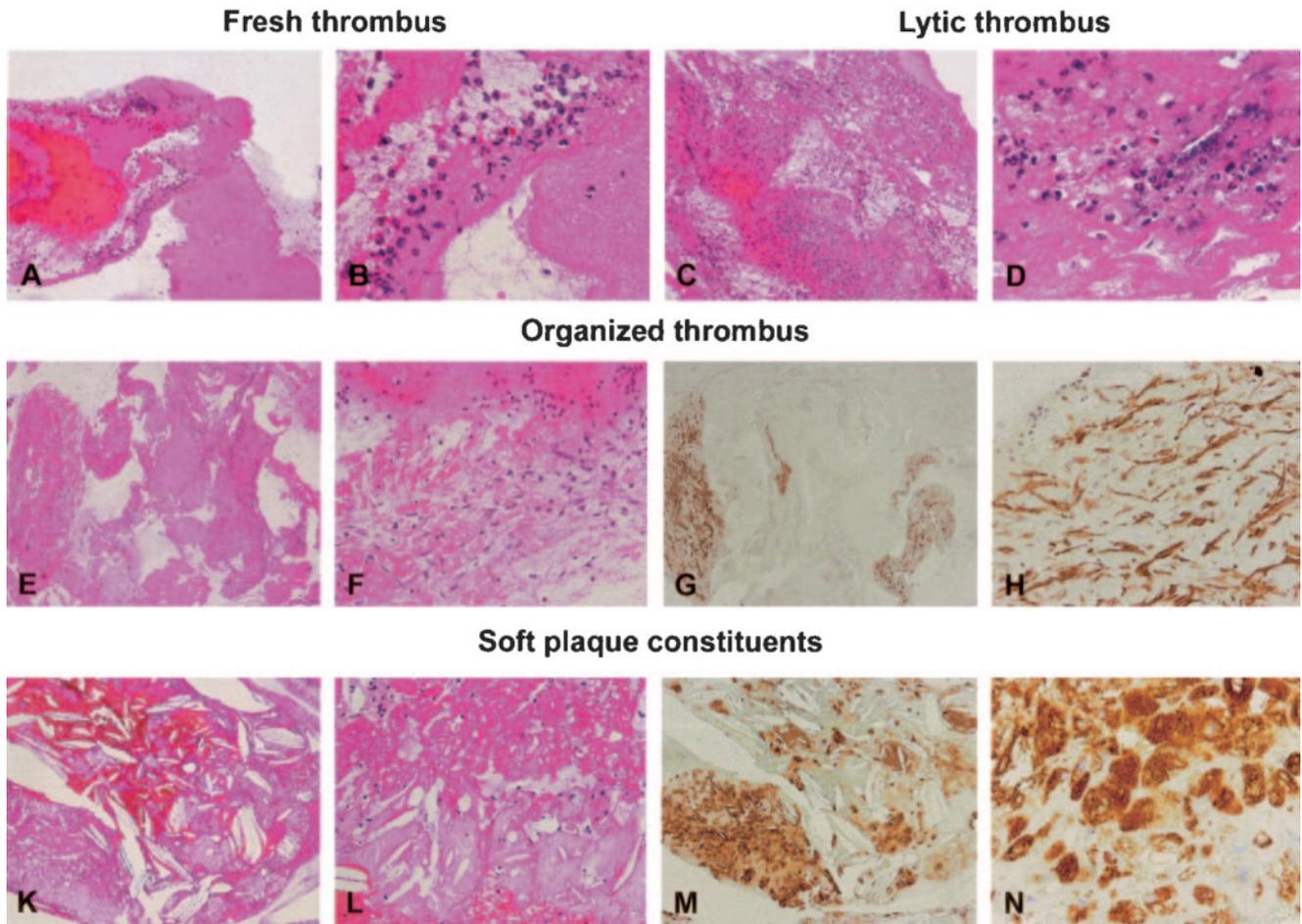


Figure 2. Histological spectrum of thrombus and atherosclerotic plaque tissue retrieved by intracoronary thrombectomy. A, Low-power view of fresh thrombus with layered component makeup (hematoxylin and eosin [H&E] stain, original magnification $\times 40$). B, Detail of panel A showing intact (vital) blood cells (granulocytes, platelets, erythrocytes) amid fibrin (H&E stain, $\times 400$). C, Overview of lytic thrombus with homogenization of structural elements indicating thrombus age of >1 to 2 days (H&E stain, $\times 40$). D, Detail of panel C showing nuclear swelling, fragmentation, and nuclear dust (H&E stain, $\times 400$). E, Overview of thrombus that has fresh, lytic, and organized areas indicating thrombus age of >5 days (H&E stain, $\times 40$). F, Detail of panel E showing ingrowth of spindle-shaped cells and deposition of collagen in homogenized thrombus (H&E stain, $\times 200$). G (overview, $\times 40$) and H (detail, $\times 200$), Immunostains with anti- α -actin antibody confirming smooth muscle cell identity of ingrowing spindle cells. K, Overview of plaque tissue with large amount of cholesterol crystals (H&E stain, $\times 40$). L, Detail of panel K showing border zone of soft plaque and homogenized thrombus (H&E stain, $\times 200$). M (overview, $\times 40$) and N (detail, $\times 400$), Immunostaining with anti-CD68 antibody of same area that visualizes numerous foam cell macrophages amid cholesterol clefts.

symptoms in the majority of the present study population and that thrombus age could not be related to the presence or absence of preinfarction angina is in concordance with clinically silent nonocclusive atherothrombotic events before clinical presentation of occlusive thrombosis. Previous reports with comparable numbers of preinfarction angina have showed the beneficial effects of preconditioning on clinical outcome,^{21,22} whereas the present study was designed to focus on pathological analyses.

Comparison of patients with and without older thrombi did not identify differences in clinical or lesion characteristics in the present study, except that males had fresh thrombi significantly more often than females. All patients were treated with heparin and aspirin at the start of the PCI procedure, which prevented “artificial” thrombus formation secondary to catheter handling during the procedure.

The reason a nonocclusive coronary thrombus apparently heals at first but subsequently gives rise to occlusive throm-

bosis days to weeks later remains to be elucidated. Clearly, plaque disruption is only part of the process. The results of the present study suggest that the absence of adequate, complete healing of an aging thrombus may play an important role in the occurrence of sudden occlusive coronary thrombosis.

Study Limitations

The present study was performed in patients who underwent primary PCI who were admitted to our hospital. Therefore, the results may not be representative for all patients with STEMI.

Conclusion

The present study demonstrated the presence of older coronary thrombi in $>50\%$ of patients with acute STEMI, which indicates that acute coronary occlusion is often the final stage in a series of successive thrombotic events that occurred in

TABLE 2. Comparison of Baseline Characteristics of Patients With Fresh, Lytic, or Organized Thrombus

	Fresh (n=98)	Lytic (n=70)	Organized (n=31)	P
Age, y	58±14	61±13	55±13	0.083
Male sex, n (%)	79 (81)	47 (67)	18 (58)	0.024
Current smoking, n (%)	51 (52)	34 (48)	22 (71)	0.10
Hypercholesterolemia, n (%)	27 (28)	17 (24)	6 (19)	0.64
Statin treatment, n (%)	12 (12)	9 (13)	0 (0)	0.11
Diabetes mellitus, n (%)	9 (9)	6 (9)	3 (10)	0.98
Hypertension, n (%)	30 (31)	22 (31)	5 (16)	0.24
Prior angina, n (%)	24 (26)	14 (23)	4 (13)	0.36
Prior myocardial infarction, n (%)	7 (7)	9 (13)	0 (0)	0.077
Prior CABG, n (%)	3 (3)	3 (4)	0 (0)	0.51
Prior PCI, n (%)	10 (10)	8 (11)	1 (3)	0.41
Angiographic features, n (%)				
Single-vessel disease	66 (67)	46 (66)	22 (71)	
Double-vessel disease	22 (22)	14 (20)	7 (23)	
Triple-vessel disease	10 (10)	10 (14)	2 (6)	0.82
Infarct-related artery				
RCA	41 (42)	37 (53)	14 (45)	
LCx	7 (7)	3 (4)	3 (10)	
LAD	46 (47)	27 (39)	14 (45)	
Venous graft	4 (4)	3 (4)	0 (0)	0.66
Diameter stenosis before PCI, %	99.4±1.7	99.2±2.4	99.1±2.3	0.88
Lesion length, mm	16±5	17±5	18±10	0.097
ACC/AHA lesion class B2/C, n (%)	98 (100)	70 (100)	29 (94)	0.49
Primary/restenotic lesion, n (%)	95/3 (97/3)	69/1 (99/1)	31/0 (100/0)	0.36
Stent placement, n (%)	88 (90)	65 (93)	30 (97)	0.43
Stent length, mm*	18±4	19±5	18±6	0.34
Stent diameter, mm*	3.4±0.38	3.5±0.33	3.4±0.26	0.53

RCA indicates right coronary artery; LCx, left circumflex; LAD, left anterior descending coronary artery; and ACC/AHA, American College of Cardiology/American Heart Association.

*Stent length and diameter in 193 patients.

the preceding days or weeks. These findings confirm and extend previous smaller autopsy studies, which demonstrates the frequency of older thrombus in the clinical arena. Moreover, we provide new insights in the heterogeneous timing of distinct processes that lead to the occlusive thrombotic event and underline the importance of identifying the vulnerable and the already-disturbed plaque before the acute clinical event.

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