Thrombus aspirated from patients with ST-elevation myocardial infarction: Clinical and angiographic outcomes

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Abstract

Objective: To investigate differences in clinical and angiographic outcomes between patients with acute myocardial infarction with red and white thrombi.

Methods: A total of 137 patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary interventions were included. Thrombus material was classified as white or red based on its pathology. Information on characteristics of thrombi was available for 97 (70.8%) patients.

Results: The total ischaemic time was significantly longer in the red thrombus group compared with the white thrombus group. The incidence of major adverse cardiovascular events in hospital was higher in the red thrombus group than in the white thrombus group (15.6% vs 0%). Multivariable logistic analysis showed that the total ischaemic time was the only predictor of thrombus composition (odds ratio 1.353; 95% confidence interval 1.003, 1.826).

Conclusion: Red thrombi were present in nearly two-thirds of cases, and were associated with a longer ischaemic time and higher incidence of major adverse cardiovascular events in hospital.

Introduction

Rupture of vulnerable plaques with subsequent thrombus formation can lead to acute myocardial infarction.[1–3] Pathological and imaging studies have demonstrated that thrombi in the coronary artery can be

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classified as red and white thrombi.[4,5] The traditional paradigm is that the type of thrombus in patients with ST-segment elevation myocardial infarction (STEMI) is red, while that in patients with non-STEMI is white.[6] However, Yasushi[7] used optical coherence tomography to analyse the culprit lesion of patients with acute coronary syndrome, and found that 78% of the thrombi in STEMI were red and 22% were white. Abela *et al.*[8] also identified white thrombi by angioscopy in several patients with STEMI. Quadros *et al.*[9] distinguished aspirated intracoronary thrombi by macroscopy, and reported that white thrombi were present in approximately one-third of patients with STEMI and were associated with lower mortality. Thrombus aspiration has enabled study of coronary thrombus *in vivo*.[10] Therefore, the current study aimed to identify whether there was a difference in outcomes in patients with STEMI with various types of thrombi by thrombus aspiration.

Patients and methods

Patients

A total of 137 consecutive patients with STEMI who had undergone thrombus aspiration during primary percutaneous coronary intervention (PCI) within 12 h of symptom onset were included in the study. The study was performed between March 2014 and February 2016 in Zhengzhou University People's Hospital. STEMI was defined as resting chest pain lasting more than 30 min associated with the following: (1) ST-segment elevation of 0.1 mV in two or more contiguous leads on a 12-lead electrocardiogram; (2) elevated myocardial enzymes (plasma creatine kinase and creatine kinase myocardial band fraction levels greater than two times higher than normal); and (3) an identifiable culprit lesion in a native coronary artery by coronary angiography (CAG). Patients with ≥ 50% left main coronary artery stenosis, renal insufficiency with baseline serum creatinine levels of 2.0 mg/dl, thrombolytic therapy before PCI, previous coronary bypass surgery or malignant tumours were excluded.

All of the patients enrolled in this study provided written informed consent. The study was approved by the institutional review board of Zhengzhou University People's Hospital.

Study protocol and angiographic outcomes

All patients were taking aspirin and had received a 300-mg loading dose of clopidogrel before the procedure. Thrombolysis was not performed for any patient. CAG was performed after administration of 0.2 mg intracoronary nitroglycerine. All CAG procedures were performed by two independent observers who were blinded to the clinical presentations. After administration of 5000 IU of heparin and guiding wire crossing, the EXPORT aspiration catheter (Medtronic, USA) was placed proximal of the target coronary segment. Thrombus aspiration was then performed two to four times until thrombi were angiographically invisible. Subsequent PCI was performed for total occlusive lesions or lesions with greater than 75% diameter stenosis. Angiographic analysis was performed by two independent cardiologists, who were unaware of the patients' clinical characteristics. The infarct-related artery was identified on the basis of findings by CAG, as well as an electrocardiogram. Intracoronary thrombus was angiographically identified and scored in five degrees according to the Thrombolysis In Myocardial Infarction (TIMI) score.[11] Coronary flow was assessed according to the TIMI criteria.[12] Distal embolization was defined as an angiographically visible distal filling defect with abrupt cut-off in the distal vessel of the culprit lesion after PCI. In cases of disagreement, consensus was reached by further joint reading.

Analysis of aspirated samples

Retrieval of thrombus was performed via aspiration through the catheter lumen, and collected from the device filter. The sample was placed in 10% formalin immediately after retrieval and fixed for 24 h. The material was then embedded in paraffin, entirely cut in 3-μm serial sections, and stained with hematoxylin–eosin. On histopathological analysis, the thrombi were pathologically classified into two categories: (1) red thrombi (mainly composed of erythrocyte and fibrin); and (2) white thrombi (platelet-rich thrombi).

Clinical outcome and follow-up

Patients were followed up during hospitalization and telephone contact was made 6 months after discharge. Myocardial infarction was defined by recurrent chest pain with new elevation of serum biomarkers after initial falling of the natural curve, with ST-segment elevation or new Q waves. Urgent revascularization was defined as an unplanned revascularization procedure 6 months after the index STEMI, either by PCI or coronary artery bypass surgery, to treat recurrent myocardial ischaemia.

Statistical analysis

SPSS 17.0 software was used to perform all statistical analysis. Continuous variables are presented as mean $\pm$ SD or median with the interquartile range (25th to 75th percentiles). Categorical variables are presented as frequencies. Differences between patient groups were tested with the Student's *t*-test or the Mann–Whitney *U*-test as appropriate. Categorical variables were compared by the chi-square test or Fisher's exact test. Univariate and multivariable logistic regression were performed to screen the factors of thrombosis type. Univariate analysis included baseline patients' characteristics and previously reported factors and multivariate analysis included significant ($P < 0.05$) factors in univariate analysis. Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). A *P*-value less than 0.05 was considered statistically significant.

Results

Baseline clinical characteristics

Among the 149 patients with STEMI, three with a left main coronary artery lesion, two with renal insufficiency, five with previous thrombolysis, one with previous CABG and one with malignancy were excluded. Therefore, 137 patients were assessed in the present study. Aspiration thrombectomy was successful in 75.2% (n = 103) of the patients. Thrombi were available for analysis in 97 cases. The study flow chart is shown in Figure 1. The mean age of patients was 53 years and 80.4% were men. Red thrombus was present in 66% of cases and white thrombus was present in 34%. Microscopic images of white and red thrombi are shown in Figure 2.

Baseline clinical characteristics are shown in Table 1. The baseline clinical characteristics between the red thrombus group and the white thrombus group were generally similar, except for a history of smoking and ischaemic time. The rate of smoking was more frequent in the red thrombus group than in the white thrombus group ($P = 0.031$). Patients with red thrombi had a longer ischaemic time compared with those with white thrombi ($P = 0.013$). The medications used at admission and after discharge were not significantly different between the two groups.

Angiographic findings

Angiographic findings are shown in Table 2. There were no significant differences in
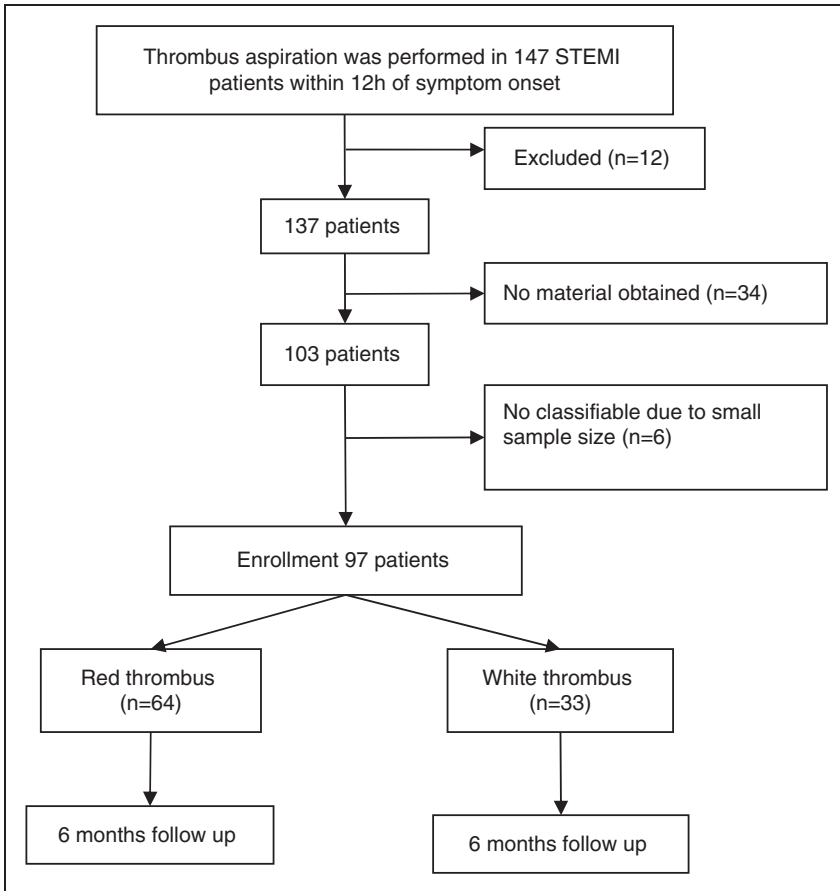
Figure 1. Flowchart of the study.

angiographic findings between the red and white thrombus groups. In the red thrombus group, an associative trend was observed with a higher baseline TIMI score ($P = 0.053$). Additionally, distal embolization was more common in the red thrombus group than in the white thrombus group (10.9% vs 0%; $P = 0.091$).

## Clinical outcomes

Table 3 shows the clinical outcomes in hospital and 6 months after discharge. Ten patients in the red thrombus group suffered from major adverse cardiovascular events (MACE), but none of the patients in the white thrombus group had MACE in hospital ($P = 0.041$). The MACE rate at 6 months after discharge was similar between the two groups.

Univariate and multivariate analyses

The results of univariate and multivariate analyses of factors associated with thrombus type are shown in Table 4. Multivariate logistic analysis identified total ischaemic time as an independent factor for composition of thrombi. Every additional ischaemic hour led to a 1.4 increase in the rate of red thrombus (OR 1.353; 95% CI 1.003, 1.826; $P = 0.048$).
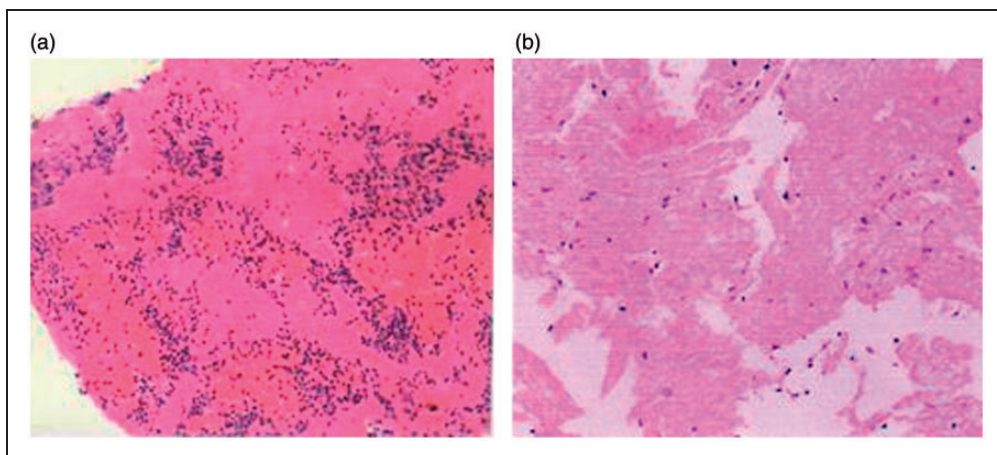
Figure 2. (a) Red thrombus (mainly composed of erythrocytes and fibrin). (b) White thrombus (platelet-rich thrombi).

Discussion

Analysis of aspirated thrombi from the coronary artery can provide interesting insight into the pathophysiology of STEMI. The type of thrombus can guide clinical decision-making on various antithrombotic and anticoagulants strategies.

The traditional paradigm is that intracoronary thrombi in patients with STEMI are red thrombi, which are mainly composed of erythrocytes and fibrin. Fibrinolytic therapy should be provided to patients within 12 h of symptom onset when it is anticipated that primary PCI cannot be performed within 120 min of first medical contact.[12] In contrast, thrombi in patients with non-STEMI are mainly composed of platelets (white thrombus) and thrombolytic therapy is not permitted to be adopted.[13] The current study included 97 patients with STEMI within 12 h of symptom onset and showed that nearly two-thirds of the cases were red thrombi and more than one third were white thrombi. The current study also showed that the white thrombus group had a shorter ischaemic time compared with the red thrombus group. This finding is similar to that of another study in which thrombi were distinguished by macroscopy.[9] One reasonable explanation for this finding is that the composition of thrombi may change as the ischaemic time is prolonged. In the process of thrombi formation, platelet aggregation is followed by fibrin deposition and red blood cells embrace. Silvain *et al.*[14] investigated the composition of coronary thrombi aspirated from patients with acute myocardial infarction (AMI). They found that fibrin content increased from 48.4% in thrombi that were collected less than 3 h from symptom onset to 66.9% in those that were collected after 6 h, whereas platelet content decreased from 24.9% to 9.1%. Multivariate analysis in their study showed that fibrin content could increase two-fold per ischaemic hour. Therefore, white thrombi are more likely to present in the beginning of ischaemia, while red thrombi may have a major role as the ischaemic time extends. However, further research in this field is required to verify the pathophysiological mechanism, which could be of important for the therapeutic strategy of AMI.

The current study showed that patients with red thrombi had a higher incidence of

Table 1. Baseline clinical characteristics of the patients.

	Red thrombus (n = 64)	White thrombus (n = 33)	P
Age, years	52.3 ± 9.4	54.9 ± 10.3	0.213
Male sex	52	25	0.526
Diabetes mellitus	18	5	0.155
Hypertension	29	18	0.389
Dyslipidaemia	24	12	0.913
Smoking	47	17	0.031
Prior MI	2	0	0.546
Prior PCI	3	1	1.000
Prior stroke	2	4	0.176
Total ischaemic time	5.6 (4.0–6.6)	4.5 (3.3–5.9)	0.013
Peak CK-MB	238 (200–321)	212 (147–368)	0.991
LVEF, %	50.4 ± 6.8	52.6 ± 5.8	0.108
Killip class ≥ 2	8	3	0.870
White blood cells, 10^9/L	10.8 ± 3.1	11.2 ± 3.1	0.592
Neutrophil count, 10^9/L	9.0 ± 2.7	9.3 ± 3.2	0.573
Platelets, 10^9/L	194.3 ± 41.8	209.6 ± 51.9	0.120
Medications (within 24 h of hospital admission)			
Glycoprotein IIb/IIIa inhibitors	35	16	0.562
Unfractionated heparin	59	29	0.746
Beta-blockers	3	1	1.000
Statin	52	26	0.772
Nitrates	22	7	0.180
ACE inhibitors/ARB	16	7	0.678
Medications (after discharge)			
Beta-blockers	57	31	0.678
ACE inhibitors/ARB	56	30	0.870
Aspirin	62	32	1.000
Clopidogrel	57	28	0.786
Ticagrelor	8	5	0.961
Statins	62	32	1.000
Nitrates	61	31	1.000

MI, myocardial infarction; PCI, percutaneous coronary intervention; CK-MB, creatine kinase-MB; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

smoking history than those with white thrombi. Yunoki *et al.*[15] reported that smoking was an independent factor for erythrocyte-rich thrombus. A previous study showed that long-term smoking increases the neutrophil count in the circulation.[16] Activated neutrophils then increase aggregability of red blood cells by releasing inflammatory mediators, such as myeloperoxidase, into the blood. Myeloperoxidase finally leads to formation of erythrocyte-rich thrombi after a serious of signal conductions.

An associative trend was observed with a higher TIMI thrombus score and distal embolization in patients with red thrombi in the current study. Yunoki *et al.*[17] studied the relationship of thrombus characteristics and angiographically visible distal embolization in patients with STEMI. They

Table 2. Angiographic findings.

	Red thrombus (n = 64)	White thrombus (n = 33)	P
IRA			0.689
LAD	30	14	
LCX	6	5	
RCA	28	14	
Lesion location			0.410
Proximal	30	13	
Middle	20	11	
Distal	11	9	
Number of diseased vessels			0.134
1	12	12	
2	34	12	
3	18	9	
Baseline TIMI score $\geq$ 3	59	25	0.053
TIMI flow grade 3, %			
Pre	3	4	0.224
Post	54	32	0.130
IABP use	6	2	0.863
Stent implantation	54	28	0.951
Stents per lesion	1.37 ± 0.56	1.28 ± 0.64	0.477
Stent size, mm	3.42 ± 0.43	3.36 ± 0.47	0.530
Stent length, mm	26.68 ± 6.17	24.48 ± 8.12	0.139
Quantitative coronary angiographic analysis (baseline)			
Reference diameter, mm	3.48 ± 0.52	3.38 ± 0.42	0.342
Minimum lumen diameter, mm	0.08 ± 0.18	0.12 ± 0.21	0.330
Diameter stenosis, %	98.2 ± 5.57	96.4 ± 6.28	0.152
Quantitative coronary angiographic analysis (after PCI)			
Minimum lumen diameter, mm	2.89 ± 0.55	2.76 ± 0.48	0.253
Acute gain, mm	2.83 ± 0.56	2.64 ± 0.49	0.102
Diameter stenosis, %	12.2 ± 13.7	11.3 ± 10.4	0.741
Distal embolization	7	0	0.091

IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; IABP, intra-aortic balloon pump.

demonstrated that erythrocyte-rich thrombi might be correlated with the incidence of angiographically visible distal embolization during primary PCI. In their study, the erythrocyte component was significantly associated with a high thrombus burden, which increased the risk of distal embolization. The mechanism of erythrocyte-rich thrombus being positively related to a high thrombus burden is that platelet-rich thrombus initially includes a large fibrin component and erythrocytes, and a large number of inflammatory cells as the thrombus grows. Finally, this becomes an erythrocyte-rich thrombus.

Importantly, in the current study, the incidence of in-hospital MACE was higher in the red thrombus group than in the white thrombus group. Several previous studies showed similar results. In Quadros *et al.*'s study, white thrombi were associated with less mortality and a trend toward less

MACE compared with patients with red thrombi. White thrombi were associated with a shorter ischaemic time and smaller thrombus volume. In Yunoki *et al.*'s[17]

Table 3. In-hospital and 6-month out-of-hospital clinical outcomes.

	Red thrombus (n = 64)	White thrombus (n = 33)	P
In hospital			
MACE	10	0	0.041
All-cause death	2	0	0.546
Urgent revascularization	1	0	1.000
Cardiac shock	4	0	0.296
Cardiac arrest/VF	2	0	0.546
Stroke	1	0	1.000
MACE 6 months after discharge	6	8	0.095
All-cause death	0	1	0.340
MI	1	0	1.000
Urgent revascularization	0	1	0.340
Cardiac shock	4	4	0.544
Cardiac arrest/VF	1	2	0.266

MACE, major adverse cardiovascular events; VF, ventricular fibrillation; MI, myocardial infarction.

study, erythrocyte-rich thrombi were correlated with a larger thrombus burden and higher incidence of angiographically visible distal embolization. Another study conducted by Yunoki *et al.*[15] showed that erythrocyte-rich thrombi contained more inflammatory cells and reflected a high thrombus burden, which led to impaired myocardial reperfusion in patients with STEMI. Therefore, a longer ischaemic time, larger thrombus burden, and other factors that relate to poor myocardial perfusion may account for a higher MACE rate in patients with red thrombi.

The current study showed no significant difference in outcomes 6 months after discharge between the two groups. A possible reason for this lack of finding is that the present study followed up patients for only 6 months and there was no difference in long-term mortality between them. In Kramer *et al.*'s[18] study, the all-cause mortality rate at 4 years was significantly higher in patients with older thrombus (16.0%) compared with those with fresh thrombus (7.4%). They concluded that older thrombus is an independent predictor of long-term mortality in patients with STEMI treated with

Table 4. Univariate and multivariate analyses for predicting thrombus type.

Variables	Univariate	P	Multivariate	P
Age	0.973 (0.931,1.016)	0.213		
Male sex	1.387 (0.503,3.822)	0.527		
Hypertension	0.690 (0.297,1.605)	0.390		
Diabetes mellitus	2.191 (0.732,6.560)	0.161		
Smoking	2.602 (1.080,6.271)	0.033	2.367 (0.939,5.969)	0.068
Prior stroke	0.234 (0.040,1.351)	0.104		
Total ischaemic time	1.438 (1.075,1.925)	0.015	1.353 (1.003,1.826)	0.048
Peak CK-MB	1.000 (0.997,1.002)	0.745		
LVEF	0.947 (0.886,1.012)	0.110		
Platelets at admission	0.993 (0.983,1.002)	0.123		
Lesion location	0.696 (0.407,1.191)	0.186		
Number of diseased vessels	1.426 (0.792,2.567)	0.237		
TIMI score ≥ 3 pre-aspiration	3.776 (1.125,12.679)	0.032	2.782 (0.768,10.082)	0.119

CK-MB, creatine kinase-MB; LVEF, left ventricular ejection fraction; TIMI, Thrombolysis In Myocardial Infarction.

thrombus aspiration during primary PCI. Although the red thrombus group had a longer ischaemic time than the white thrombus group in the current study, whether red thrombus was associated with old thrombus was unclear. Therefore, further studies should be conducted to investigate this issue.

In the present study, multivariate logistic analysis identified total ischaemic time as an independent factor for the composition of thrombus, which is similar to Silvain *et al.*'s study.[14] The current study showed that every additional ischaemic hour led to a 1.4-fold increase in the incidence of red thrombus. Administration of antiplatelet agents at an early stage has been shown to reduce mortality in primary PCI,[19,20] which is consistent with our study. Despite our finding that the composition of thrombus changes as the ischaemic time is prolonged, this finding does not contradict the notion that thrombolysis treatment is most efficient during the first 3 h of STEMI. A previous study showed that at the beginning of STEMI, the clot is relatively small and soft.[14] Therefore, thrombolysis is more efficient during this period.

Study Limitations

The present study has several limitations. First, this study was nonrandomized and had a small sample size. We did not include patients with no material or small thrombus obtained by aspiration. We also had no access to information on the thrombus type of patients who died before admission to hospital. Therefore, there was a certain degree of bias for selection of patients. Second, we could not guarantee complete retrieval of intracoronary thrombus by thrombus aspiration. Therefore, possible residual thrombus was neglected, which might have resulted in bias of the sample. Third, the aspiration catheter might have damaged the thrombus and might have affected the pathological composition of

the aspirated sample. Fourth, we did not assess the thrombus size or volume, which might correlate with thrombus type. Moreover, we followed up patients for only 6 months. Whether the thrombus type affects the long-term mortality of patients with AMI is unclear.

Conclusion

In a summary, the current study shows that red thrombi occur in nearly two-thirds of patients with STEMI, and are associated with a longer ischaemic time and poorer prognosis in hospital. The present findings suggest that thrombus type might play a major role in the treatment strategy of STEMI.

Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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