An acute thrombotic event resulting in total occlusion of a coronary artery is considered the principal mechanism of ST-segment elevation myocardial infarction (STEMI). De Wood et al. were the first to show that total coronary occlusion was visible on the coronary angiogram in a large majority of patients presenting during the early hours of STEMI. Thrombus could be retrieved in 52 of 59 patients with angiographic, and in 5 of 20 patients without, features of thrombus, suggesting that thrombus formation plays a major role in the pathophysiology of total occlusion and subsequent infarction. Total coronary artery occlusion has also been described, though less frequently, in a range of nonthrombotic events such as intraplaque hemorrhage, vasospasm, spontaneous coronary artery dissection, coronary emboli, coronary arteritis, and compression by myocardial bridging.

Acute coronary thrombosis is caused primarily by the rupture of a coronary atherosclerotic plaque, responsible for approximately 75% of all coronary thrombi leading to myocardial infarction or death, or by plaque erosion or calcified nodules. After rupture of the fibrous cap covering the atherosclerotic plaque, fragments of the lipid-rich core are exposed to the arterial lumen. This highly thrombogenic material causes platelet aggregation within the lipid core and on the ruptured fibrous cap, forming a mural thrombus consisting mainly of platelets, resulting in early coronary obstruction. In this early stage of thrombus formation, intermittent flow is often present, because the platelet aggregates are unstable and embolize into the microcirculation. As a consequence of a balance between thrombotic and thrombolytic factors, episodic growth of thrombus may take place that results in layered thrombus material of different ages. As platelet aggregation continues, the formation of a fibrin network causes stabilization of the white platelet-rich thrombus until eventually the whole lumen is occluded. Persistent obstruction of flow at the site of plaque rupture results in blood coagulation proximally and distally to the occlusion and causes red thrombus formation, consisting mainly of erythrocytes and inflammatory cells entrapped by a fibrin network.

Recently, adjunctive mechanical devices have been developed to retrieve thrombus from the infarct-related lesion during primary percutaneous coronary intervention (PCI) in patients with STEMI. Favorable results have been reported with distal protection devices including distal occlusion devices and distal embolic filters, as well as with antegrade approaches with manual thrombus aspiration catheters or technically more complex mechanical thrombectomy catheters. Currently, the inexpensive and user-friendly manual thrombus aspiration devices seem to hold most promise. With these devices, thrombotic material can be obtained in 73 to 89% of patients. Several studies have reported that thrombus aspiration improves myocardial perfusion and reduces microvascular obstruction in patients with STEMI compared with conventional balloon angioplasty, although the trial results show considerable variability in part due to patient and device selection. Because a strong relation has been established between improved myocardial perfusion, as assessed by angiography or electrocardiography, and lower long-term cardiac mortality, it can be hypothesized that thrombus aspiration will provide clinical benefits. This expectation is confirmed in recent reports showing that thrombus aspiration is associated with a reduction in short- and long-term mortality in patients treated with primary PCI.

The major limitation of thrombus aspiration is its inability to limit microvascular obstruction that has occurred before PCI. Adjunctive pharmacological therapies are therefore still needed to optimize myocardial perfusion. Therapy targeting platelets, for example, a major component in microvascular obstruction, has proven to reduce mortality and reinfarction in patients undergoing primary PCI.

Along with the clinical benefits of thrombus aspiration, retrieval of atherothrombotic material provides us with new possibilities to study the pathophysiology of thrombus formation, and thrombus characteristics may become of value in predicting outcome. In this issue of Circulation, Kramer et al. identify the age of aspirated thrombus as a predictor of long-term mortality in patients with STEMI treated with thrombus aspiration during primary PCI. Previously, these investigators have reported that in many STEMI patients who underwent thrombus aspiration during primary PCI within 6 hours of symptom onset, at least part of the thrombotic material was older than 1 day. Thrombus that was present in the aspirated material of 211 STEMI patients contained older thrombus with lytic (1 to 5 days) or organized (>5 days) changes in 51%, and fresh thrombus (<1 day old) in 49%. These findings show that plaque rupture and thrombus
formation are often initiated days before the development of a total coronary occlusion.

In the current study, Kramer et al have sought to investigate the relation between thrombus age and long-term mortality in 1315 STEMI patients in whom thrombus aspiration was performed during primary PCI.14 Fresh thrombus was present in 60% of patients and older thrombus in 40%. In patients with older thrombus, the total ischemic time was longer (4.1 ± 4.3 hours versus 3.3 ± 2.4 hours, P < 0.001) and the incidence of distal embolization was higher (18% versus 12%, P = 0.01) than in those with fresh thrombus. No differences were observed for postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow and enzymatic infarct size as assessed by peak creatine kinase–MB. At 4 years follow up, all-cause mortality was 2-fold higher in patients with older thrombus compared with patients with fresh thrombus (16.0% versus 7.4%, hazard ratio 1.82, 95% confidence interval 1.17 to 2.85, P = 0.008). In a landmark survival analysis, this higher mortality rate of patients with older thrombus versus those with fresh thrombus was apparent during the first 14 days (5.7% versus 2.4%, P = 0.009) but not after 14 days (11% versus 5.2%, P = 0.20). In multivariate Cox regression analysis, the presence of older thrombus was an independent predictor of all-cause mortality at 4 years (hazard ratio 1.83, 95% confidence interval 1.14 to 2.93, P = 0.01) next to well known risk factors such as female gender, age > 60 years, diabetes mellitus, previous coronary artery bypass grafting, cardiogenic shock, and poor postprocedural TIMI flow.

This observation is pivotal because it is the first to show a relationship between thrombus composition and mortality. A plausible mechanism that explains why older thrombus is associated with higher mortality is that patients with older thrombus experience a longer period of nonocclusive thrombus formation. During this phase, the platelet-rich thrombus is unstable and prone to embolize into the distal microcirculation,4 a phenomenon known to be associated with higher long-term mortality.17 This hypothesis is supported by the angiographic data, showing a higher incidence of distal embolization in patients with older thrombus. What remains unclear from the data presented here is whether this effect of the presence of older thrombus was also mediated through poor myocardial perfusion, increased microvascular obstruction, or both, and further studies should elucidate the impact of the presence of older thrombus on these parameters.

Further study should also assess whether retrieval of the thrombus was complete. Incomplete retrieval may have led to thrombus being unclassifiable, together with explanations that also account for the inability to retrieve any thrombotic material from 25% of patients, such as dissolution of the thrombus before aspiration, embolization into the distal vessel, disintegration of organized thrombus, or absence of a thrombotic cause of occlusion. More significantly, although the classification of older thrombus has a high specificity, fresh thrombus could have been misclassified if only thrombus of younger age superimposed on older thrombus was aspirated, thereby confusing the reported findings. Data on the size and composition of the aspirated material and on the angiographic thrombus score after thrombus aspiration might help us in judging whether all thrombus was aspirated.

Coronary angiography is largely used to study the presence or absence of thrombus in the coronary system, although it is probably not very reliable, given that thrombotic material was still retrieved in a considerable proportion of patients without angiographic evidence of thrombus.1,9 Catheter-based imaging modalities such as optical coherence tomography (OCT) may be better instruments to assess the presence of intracoronary thrombus.18,19 OCT may also be able to identify a nonthrombotic event as the pathophysiological mechanism leading to coronary occlusion in patients in whom thrombus aspiration does not result in restoration of brisk antegrade flow in the infarct-related coronary artery.

Some limitations of this study have to be acknowledged. The study was performed retrospectively, and patient selection bias may play a role in the principal findings as well as in the choice to perform regression analysis at 4 years of follow-up. First, it is unclear whether criteria such as angiographic evidence of thrombus or total occlusion of the infarct-related artery were applied for performing thrombus aspiration. Second, the indications for the use of specific devices as well as of concomitant pharmacological treatment were at the discretion of the operator, and it is not reported whether differences were observed in retrieval rates and angiographic and procedural characteristics of different devices. Furthermore, causes of death are not reported, and follow-up at 4 years was incomplete.

Thrombus aspiration now enables the histopathological analysis of platelets, erythrocytes, inflammatory cells, and plaque components in living patients. Characterization of these components may contribute to the current understanding of the pathophysiology of atherosclerosis and myocardial infarction. In addition, ongoing research will elucidate mechanistic relationships between thrombus composition and parameters of myocardial perfusion and microvascular obstruction. This may provide further support in clinical risk assessment, currently based on angiographic, electrocardiographic, and biochemical markers and, very recently, the promising field of genetic markers. In plaque material obtained from carotid atherosclerotic plaques, Hellings et al20 have already demonstrated that the macrophage infiltration rate and lipid core size are associated with restenosis. Ultimately, thrombus characterization may provide us with new information directing us in further development of pharmacological and mechanical therapies.

In conclusion, thrombus aspiration is emerging as an integral component of the interventional approach of acute myocardial infarction, enabling new insights into thrombus composition. It holds great therapeutic as well as diagnostic promise and leads us into a new era of mechanistic and pathophysiological studies.

Disclosures

None.

References


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