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Review Article

High thrombus burden: a review of mechanisms and treatments

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Abstract: This review summarizes current understanding about high thrombus burden (HTB), including the mechanisms underlying the development of HTB and its treatment. HTB has been defined as the occurrence of thrombosis during myocardial infarction, as determined by a thrombus score ≥ 3 in the infarct-related artery (IRA) or as a "cut-off" occlusion pattern and/or large reference vessel diameter (≥ 3.5 mm) in an occluded IRA. Acute myocardial infarction (AMI) with HTB is a major cause of morbidity and mortality worldwide. Several studies have assessed the development of HTB, the impact of HTB on AMI, and medical therapies used to treat HTB. Existing techniques and methods are unable to accurately quantify the thrombus burden, and currently there is no standard treatment strategy. Therefore, the treatment of HTB remains a challenge in current clinical practice. Pre-clinical and clinical markers are especially needed to evaluate HTB.

Keywords: High thrombus burden, inflammation, thrombotic mechanism, thrombus aspiration

Introduction

Acute myocardial infarction (AMI) is a common and critical illness with an in-hospital mortality rate up to 11.9% [1]. As populations age, the incidence of AMI increases, placing an economic burden on both society and families. The primary treatment of AMI remains percutaneous coronary intervention (PCI), which rapidly restores the blood supply to the infarcted region and subsequently improves myocardial perfusion and patient prognosis [2]. Therefore, PCI is a class A recommendation in all major guidelines for the treatment of AMI. AMIs with a high or large thrombus burden are a subset of AMIs, usually detected by coronary angiography. High thrombus burden (HTB) may lead to no-reflow, slow-reflow, and/or distal embolization. HTB may also cause a larger area of myocardial damage, deterioration of left ventricular function, and penetration of the myocardial infarction (MI), which can be revealed by cardiac magnetic resonance image (MRI) [3]. Compared with AMI patients without HTB, AMI patients with HTB have an increased incidence of postoperative adverse cardiovascular events and complications, including cardiac rupture, malignant arrhythmia, and heart failure (HF) caused by inadequate pericardial and myocardial perfusion, as well as having a worse prognosis. This review summarizes the current understanding of HTB and focuses on the mechanisms leading to its pathogenesis and treatment.

Definition and evaluation of HTB

HTB is defined based on evaluation by coronary angiography, for example, by scores associated with angiographic morphological characteristics [4] and by Thrombolysis in Myocardial Infarction Risk Scores (TIMI Risk Scores or TS) [5]. Angiographic morphologic characteristics of HTB include a truncated occlusion pattern of occluded proximal vessels, a floating thrombus at the proximal end, proximal occlusion > 5 mm with a long strip thrombus, occlusion distal to contrast agent residue, an occlusion-related blood vessel with a lumen diameter > 4 mm, and a reference vessel diameter more than three times the length of the thrombus [4].

Alternatively, HTB can be defined according to TIMI Risk Score. On this scale, 0 points indicates no thrombus, 1 point indicates a blurred

thrombus shadow, 2 points indicate that the length of thrombus is less than half the diameter of the blood vessel, 3 points indicate that the length of thrombus is greater than half to two times the diameter of the blood vessel, 4 points indicate that the length of thrombus is more than twice the diameter of the blood vessel, and 5 points indicates that the vessel is blocked and the thrombus cannot be assessed. A thrombus with a score ≥ 4 is defined as HTB [5].

Relative to other methods, coronary angiography has a higher specificity (92-100%) and a lower sensitivity (17-60%) for identifying thrombotic lesions, but was unable to detect small thrombi, and had a low detection of moderate and lateral thrombi [6]. The accuracy of coronary angiography in evaluating HTB is affected by the position of the contrast. In addition coronary angiography, catheter-based techniques such as coronary angioscopy (CAS), intravenous ultrasound (IVUS), and optical coherence tomography (OCT) can be used to evaluate coronary thrombi and assess for HTB.

In particular, CAS, which uses optical imaging fibers, can clearly reveal the shape and color of the inner vessel wall, and therefore help determine the shape of the plaque, thrombus, and ulcer, as well as identifying treatment strategies. For example, CAS showed that cholesterol plaques with a thick fiber cap are white, whereas cholesterol plaques with a thin fiber cap are yellow. As the size of yellow plaques increases, so does the risk of plaque rupture. IVUS can also reveal the thickness of the thrombus, the lumen area of the coronary arterial wall, and the composition and area of the plaque. IVUS is also used to quantitatively evaluate thrombosis in AMI patients. OCT can clearly discern the shape of the thrombus and quantitatively assess its area and volume, as well as the diameter of the lumen. While these techniques have many advantages in detecting HTB, they are not recommended for evaluating coronary thrombi in AMI patients with HTB prior to PCI because of their potential ability to exacerbate distal embolization and extend treatment time.

Mechanisms of HTB development

The mechanisms underlying HTB development are complex and multifaceted, and are believed to involve the erosion and rupture of plaques. Rupture increases tissue factor (TF), collagen, and HTB, and activates platelets, which link fibrinogen to HTB development.

Abnormal activation of platelets and the coagulation system

Platelets, as a main component of the thrombus, play a key role in the adhesion, activation, and aggregation of arterial thrombi, and their abnormal activation inevitably leads to increased thrombus burden. In addition, platelets promote the formation of blood clots by interacting with the coagulation system. A number of factors and pathological processes play an important role in the formation of HTB.

Heat shock protein-27 (Hsp-27) is a highly conserved intracellular protein that participates in protein trafficking and folding. HSP-27 in heart and muscle induces stress responses and prevents ischemia reperfusion injury [6], whereas Hsp-27 in platelets contributes to platelet aggregation and variations in platelet shape [7]. Hsp-27 has also been shown to positively correlate with the risk of HTB development and the incidence of major adverse cardiac events (MACEs) in patients with ST-elevation MIs (STEMIs) [8]. Mechanistically, Hsp-27 binds to platelet factor XIII and stabilizes the fibrin-platelet clot by regulating transglutaminase activity, which is related to thrombus formation in STEMI patients [9]. These findings suggest that Hsp-27 plays an important role in HTB development. Indeed, plasma Hsp-27 levels may predict the development of HTB and clinical outcomes in STEMI patients [10].

CD40 is a receptor expressed on macrophages and smooth muscle cells (SMCs), is activated by CD40L produced by activated T cells [11], and promotes secretion of TF by macrophages and SMC cells [12]. During the process of thrombosis formation, TF was found to continuously cover the surface of the thrombus, increasing the thrombus burden [13]. Abnormal increases in TF induce both exogenous and endogenous pathways, leading to the activation of the coagulation system. Thus, increases in TF associated with CD40 activation lead to elevated thrombus burden [14].

Endothelial dysfunction has also been associated with HTB. The formation of coronary thrombi is caused not only by the rupture of the

plaque fibrous cap, but also by surface erosion of the arterial lumen. Intact endothelium prevents the formation of thrombi, but endothelial cell injury exposes the intima, which interacts with and activates platelets and induces early pathological processes such as inflammation and thrombosis [15]. The degree of endothelial injury was shown to correlate positively with thrombus burden [16].

Myeloperoxidase (MPO), which is expressed by macrophages at the site of coronary atherosclerosis, produces hypochlorous acid (HOCl) [17], a molecule that induces endothelial cell death through apoptosis, with sublethal concentrations of HOCl increasing TF concentration [18]. HOCl also exacerbates superficial erosion of the endothelium and increases thrombus formation, a process related to the inhibition of the B lymphocyte-2 gene (Bcl-2) and the release of cytochrome C from mitochondria [16].

P-selectin (PS) is a protein present in the alpha granules of platelets and in the Weibel-Palade bodies of endothelial cells. When tissue is damaged, platelets and endothelial cells are activated by thrombin and histamine, resulting in the fusion of platelet alpha granules and endothelial cell Weibel-Palade bodies with their respective plasma membranes and the expression of PS on the surfaces of these cells [19]. PS, together with the activated platelet membrane glycoprotein IIb/IIIa complex (GP IIb/IIIa), plays a role in binding fibrinogen. By interacting with PS glycoprotein ligand-1 (PSGL-1) or glycoprotein Ib (GP Ib) ligands, PS stabilizes the initial complex of GP IIb/IIIa-fibrinogen, resulting in the formation of large stable platelet aggregates [20] and the inhibition of PS binding to ligands.

Fibrinogen is a fibrin precursor that enhances blood coagulation, induces thrombosis, and is an independent predictor of HTB [21]. Hyperfibrinogen is closely associated with endothelial cell damage, with increased fibrinogen levels being a risk factor for AMI and ischemic stroke [22]. Active oxygen, nitrogen, and chlorine can modify fibrinogen molecules produced under inflammatory conditions, such as during tissue ischemia and reperfusion. Fibrinogen can also be modified at different amino acid residues, including nitration and chlorination of tyrosine residues, oxidation of methionine and histidine residues, and formation of dityrosine residues [23]. The structure of fibrinogen can also be modified by glycation and by the presence of homocysteine under conditions of hyperglycemia and hyperhomocysteinemia, respectively [23]. These modifications can render fibrinogen resistant to fibrinolysis, thus increasing the risks of arterial and venous thrombosis [23].

Thrombosis components have also been associated with the development of HTB. For example, a study measuring the surface area of thrombi as a quantitative indicator of thrombus burden found that thrombus burden correlated positively with erythrocyte-rich thrombi, but negatively with platelet-rich thrombi [24]. During thrombosis, the size of the initially formed platelet-rich thrombus increases due to an increase in fibrin components. These thrombi capture large numbers of red blood cells (RBCs) and inflammatory cells, forming RBC-rich thrombi after plaque rupture [25]. Thus, at the beginning of thrombosis, the burden of white thrombi is low, while the burden of red/mixed thrombi is high. However, prolonged ischemia time often results in a red/mixed thrombus with a heavy thrombus burden [26]. Coronary angiography in patients with acute coronary syndrome (ACS) revealed that occlusion, especially distal occlusion, of the right coronary artery and a large IRA diameter (≥ 4 mm) resulted in HTB in the IRA [27]. The components of thrombi were found to differ among coronary arteries [28]. For instance, thrombi in the left anterior descending (LAD) artery tend to be high in platelets, whereas those in the right coronary artery (RCA) tend to be high in RBCs, with thrombi in the RCA readily forming HTB.

Red cell distribution width (RDW) was found to be an independent predictor of HTB [26], with the area under the receiver operating characteristics (ROC) curve predictive of HTB. In addition, RDW-labeled erythrocyte heterogeneity suggests that RDW is associated with some inflammatory markers, such as C-reactive protein (CRP), interleukin (IL)-6, and monocyte chemotactic protein (MCP)-1 [29]. Therefore, the burden and color of a thrombus can be evaluated by both coronary angiography and intravascular imaging methods, including ultrasound, angioscopy, and OCT, all of which can provide important information about the possi-

bility of thrombus aspiration or the requirement for distal protection [24].

RDW strongly correlates with erythrocyte mean corpuscular volume (MCV). The underlying mechanism may be related to aging and the lifespan of RBCs, with elderly individuals having a high proportion of small RBCs, resulting in decreased MCV and increased RDW [30]. With aging, RBCs have a smaller volume and decreased function, making it easier for them to adhere to endothelial cells and form thrombi. In addition, RDW acts on the renin-angiotensin-aldosterone system (RAAS) by activating angiotensin II 1a receptor, enhancing the formation of atherothrombotic thrombi. This process, in turn, facilitates the production of erythropoietin (EPO) and further increases RDW [31].

Inflammatory factors can counteract the down-regulation of anticoagulant proteins and the up-regulation of pro-coagulant proteins, increasing the likelihood of coagulation. Damage to the coronary artery wall or mild inflammation results in relatively low levels of exposed collagen and released TF, leading to a lighter thrombus burden. By contrast, severe injury to the blood vessel wall or serious inflammation results in the production of higher levels of collagen and TF, leading to a heavier thrombus burden.

White blood cell (WBC) counts, neutrophil counts, and neutrophil-to-lymphocyte (N/L) ratios are independent predictors of thrombus burden [32]. N/L can also be used to predict early and late prognosis in patients with STEMI after PCI [33-35]. Studies in animal models have shown that neutrophils infiltrate atherosclerotic plaques, which release arachidonic acid derivatives and superoxides, leading to coronary thrombosis [36]. Patients with high thrombus stress tended to have a higher percentage of neutrophils [26]. Moreover, the aggregation rate of RBCs was significantly higher in glucose buffer with rather than without a neutrophil suspension [37]. Activation of leukocytes is thought to produce oxygen free radicals and proteolytic enzymes that affect adjacent RBCs on thrombus sites [38]. Through this neutrophil-erythrocyte interaction, neutrophils affect thrombus components and increase thrombus burden.

HTB has also been associated with the monocyte/high-density lipoprotein-cholesterol ratio (M/H). After vascular endothelial injury, monocytes can adhere to blood vessel walls and migrate to the endothelium, developing into macrophages and differentiating into foam cells. The lipid core formed by these foam cells, together with vascular SMCs, forms a fibrous cap, which generates atherosclerotic plaques. Foam cells can also secrete inflammatory factors, TFs, growth factors, and matrix metalloproteinases (MMPs), which promote the growth and rupture of the plaque and increase thrombus burden [39]. Monocytes in patients with hypercholesterolemia were reported to be more sensitive to stimulation by chemoattractants than monocytes in non-hypercholesterolemic individuals [40], which may explain the involvement of monocytes in hypercholesterolemia-associated atherosclerosis. High-density lipoproteins offer cardioprotection by enhancing endothelial function and by suppressing inflammation and oxidation. For example, high-density lipoprotein-cholesterol (HDL-C) and its main component, apolipoprotein AI, were found to exert anti-inflammatory effects by inhibiting the C11b activation by monocytes [41]. In addition, HDL-C and apolipoprotein AI inhibit the oxidation of low-density lipoprotein-cholesterol (LDL-C) by reducing chemotaxis of monocytes and the expression of MCP-1 [42]. Thus, in turn, it was observed to suppress the inflammatory index and inhibit the formation of coronary thrombi. Early M/H levels were shown to be an independent predictor of thrombus burden in 414 patients with STEMI [43]. Moreover, M/H may independently predict the occurrence of in-hospital MACEs [44].

Lipoprotein phospholipase A2 (Lp-PLA2) is an enzyme synthesized in and secreted by macrophages and lymphocytes present in ruptured coronary blood vessels. Monocytes migrate to the intima of coronary arteries and differentiate into macrophages, which phagocytose oxidized LDL (ox-LDL). Lp-PLA2 released during this pathological process adheres to LDL, is activated following LDL oxidation, and reacts with the phospholipid component of ox-LDL, producing two highly efficient inflammatory mediators, oxidized fatty acids and hemolysis phosphatidylcholine. Over time, inflammatory mediators increase and ox-LDL and Lp-PLA2 accumulate in the plaque microenvironment, making late plaques more prone to laceration or rupture and leading to elevated levels of

plasma Lp-PLA2. Plasma Lp-PLA2 levels prior to PCI are independent predictors of HTB in STEMI patients and of blood flow and myocardial perfusion. Preoperative plasma Lp-PLA2 levels were found to be significantly higher in HTB patients than in patients with low thrombus burden (LTB). Thus Lp-PLA2 level serves as a specific marker of vascular inflammation and an independent risk factor for plaque rupture and atherothrombotic events [44].

High risk factors for coronary artery disease (CAD)

Hyperglycemia promotes thrombosis, inasmuch as erythrocyte aggregation is greater in diabetic than in non-diabetic patients, and hyperglycemia increases the expression of pro-inflammatory cytokines by stimulating inflammatory responses [45]. Autopsy studies have shown that the tendency toward platelet adhesion and aggregation is higher in patients with than without hyperglycemia [24]. Acute hyperglycemia positively correlated with no-reflow in AMI patients [46], and plasma glucose levels at admission were found to be an independent risk factor for mortality in AMI patients [47]. Mechanistically, plasma glucose concentration may affect blood characteristics and contribute to the evolution of thrombosis and thrombus growth [48].

Smoking is a traditional risk factor independently associated with fatal coronary thrombosis [35]. Mechanistically, smoking causes damage to the vascular endothelium through oxidative stress, vasoconstriction, and elevated fibrinogen [49], all of which promote thrombosis. Smoking also enhances platelet aggregation, blood viscosity, and activation of centrosomes [50], resulting in a loss of vascular endothelium and enhanced thrombosis. In addition, smoking induces the expression of intercellular adhesion molecule-1, which triggers immune inflammatory responses, leading to coronary spasm and thrombosis [51].

Treatment strategies for HTB

Mechanical treatments

Interventional mechanical treatments include the use of thrombus aspiration devices, distal protection devices, and stent implantation.

Thrombus aspiration devices are specifically designed to target the thrombus and plaque in an IRA and have been widely used in PCI. Thrombus aspiration devices can prevent coronary microembolisms, improve coronary blood flow, reduce the incidence of no-reflow, and improve the prognosis of STEMI patients after PCI. The Thrombus Aspiration Study (TAPAS) confirmed that thrombectomy after PCI balloon dilatation or stent implantation significantly improved myocardial reperfusion and reduced the incidence of no-reflow and mortality within 1 year [52]. Thrombus aspiration may be manual or mechanical. Manual thrombus aspiration entails the use of a vacuum syringe and an aspiration catheter (e.g., DIVER, EXPORT) to extract the thrombus. This method is not only economical and safe, but is also suitable for elderly patients. However, the suction force is low, reducing its efficiency. Similar to manual thrombus aspiration catheters, mechanical vacuum pumps, such as Rescue and TVAC, remove thrombi through suction, except that the vacuum is generated by a mechanical vacuum pump. The pump slowly pushes and withdraws the catheter to aspirate the thrombus while continuously creating a negative pressure. Another type of mechanical thrombus aspiration device mechanically pulverizes and ejects the thrombi. In 2010, the TCT in the United States recommended manual suction for thrombi with TIMI thrombus grades 2-3 and mechanical suction for those with TIMI thrombus grades 4-5. Although this disagrees with the findings of the randomized controlled EXAMINE (Examination of cardiovascular outcomes with alogliptin versus standard of care) trial, the 2016 Chinese Percutaneous Coronary Intervention Guidelines recommend manual or mechanical aspiration for STEMI patients with HTB, larger culprit vessels, and shorter ischemia time. Multiple thrombus aspirations, generally ≤3, have been recommended for patients with HTB who experience significant effects (TIMI ≥ 3, IIb C recommended) following initial thrombus aspiration [49, 53]. Balloon expansion can also be added if needed [49, 53].

Distal protection devices include obstructive balloons (proximal, distal) and distal filters [54]. An expandable balloon at the proximal end of the coronary artery can be expanded to reduce the impact of coronary blood flow on the thrombus, which can lead to thrombus shedding.

Moreover, an expandable balloon and a distal filter at the proximal end of the coronary artery can be expanded to prevent the thrombus from escaping to the distal end of the coronary artery. A study in 78 patients treated with the PercuSurge distal protection device found that the mean thrombus size was significantly greater in the TIMI ≥ 2 group than in the control group, with the PCI control group having no-reflow in the distal vessels [55]. In addition, the rates of embolism formation and of MACEs within 30 days were higher in the thrombosis than in the control group [55].

Delayed stent implantation has also been associated with HTB. Acute stent implantation by PCI in HTB patients may cause acute thrombosis-related events, such as slow blood flow, no-reflow, distal coronary embolism, and increases in MACEs (cardiac shock, malignant arrhythmia, and death). Thrombectomy after PCI stent implantation was found to reduce mortality and improve prognosis in patients with heart disease [56]. Delayed stent implantation after enhanced antithrombotic therapy was found to ameliorate perfusion in patients with HTB after thrombus aspiration [57]. By contrast, the DANAMI3-DEFER study showed that delayed stent implantation within 48 hours did not improve the prognosis of STEMI patients [58]. More comprehensive findings will be obtained from other trials, including MINI, INNOVATION, and PRMACY, which explored the effects of delayed stent implantation in patients with HTB [56]. Although delayed stent implantation may have negative effects, it is regarded as important in treating HTB.

Drug treatments

Drugs used in the treatment of HTB include antiplatelet agents, anticoagulant drugs, thrombolytic agents, statins, and vasodilators.

Antiplatelet drugs include cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate receptor antagonists (clopidogrel, ticagrelor), and platelet GP IIb/IIIa receptor antagonists (GPIs). Aspirin has been shown to play a role in the secondary prevention of MI, stroke, and transient ischemic attack (TIA), but its mechanisms of action in primary prevention may differ, as shown in the ARRIVE [59], ASCEND [60], and ASPREE [61-63] trials. The strongest antiplatelet drugs, which can be selectively applied to STEMI patients with HTB, include monoclonal antibodies such as azizumab and peptide inhibitors, such as eptifibatide and tirofiban [64]. Intracoronary injection of these drugs was shown to be superior to intravenous injection [65]. GPI inhibits platelet IIb/IIIa receptors, protects endothelial cells, restores reperfusion of the IRA, and reduces endpoint events and MACEs [66]. However, although drug treatment can immediately diminish the size of coronary thrombi, it cannot permanently abolish them. Moreover, the recommended dose and timing of drug administration vary among patients with HTB, as patients are not uniform. The 2015 guidelines for the diagnosis and treatment of STEMI in China [67] recommend tirofiban for high-risk patients, patients with type IIA indications, and patients with HTB without PIIY12 therapy. The INFUSE-AMI study showed that thrombus aspiration combined with a GPI (abciximab, tirofiban) synergistically reduced the MI area and the incidence of HF after 1 year [68]. Very different findings, however, were observed in the AIDA-STEMI trial [69]. The reasons for this discrepancy are not clear, but may be due to the use of microcatheters, which allow better local application of GPIs [70].

Anticoagulant drugs include unfractionated heparin, low molecular weight heparin, and bivalirudin. Conventional antiplatelet aggregation and anticoagulant agents may not have an effect in HTB patients. However, these patients may benefit from strengthening anticoagulation or the administration of warfarin [71].

Thrombolytic medications include alteplase and urokinase. Low-dose intracoronary thrombolysis washout was not only found to be appropriate and safe for STEMI patients with HTB who failed treatment by thrombus aspiration, but also reduced coronary thrombus burden and improved epicardial blood flow and myocardial perfusion [72]. The combined administration of urokinase and abciximab did not cause distal embolization or slow blood flow, but significantly reduced the thrombus burden [73].

Statins have a broad spectrum of activity. For example, they were found to improve endothelial function and oxygen supply. Moreover, these agents have anti-hypersensitivity C, anti-infection, and antithrombotic activities, reducing platelet thrombosis, thrombus burden, MI area, and myocardial reperfusion injury. Early treatment with statins has been recommended for AMI patients with HTB [74].

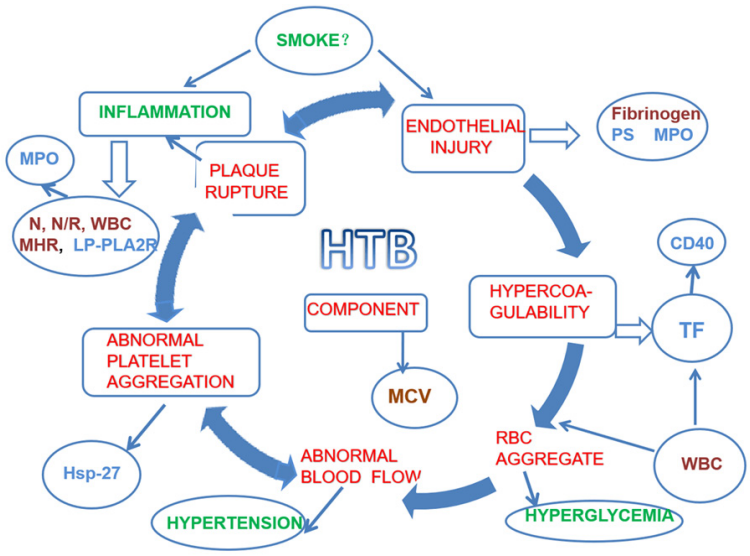

Figure 1. Summary of the mechanisms underlying the development and treatment of HTB.

Vasodilators, such as calcium antagonists, nicorandil, nitrates, and sodium nitroprusside, may be injected into the coronary artery to reduce no-reflow caused by thrombotic lesions [75-77]. One of these drugs, verapamil, is commonly used to treat HTB patients with no-reflow. Intracoronary administration of these drugs improves myocardial perfusion and vascular function and increases wall motion scores. Intracoronary sodium nitroprusside can immediately enhance TIMI blood flow. Adenosine and alprostadil can dilate blood vessels, inhibit platelet aggregation, suppress the activation of inflammatory cells and the production of oxygen free radicals and intracellular calcium, reduce reperfusion injury, and improve myocardial perfusion. In addition, the PEOPEN-AMI study suggested that increased adenosine levels after thrombus aspiration significantly improved microcirculation without elevating the risk of MACEs [78].

Other treatments

Intra-aortic balloon pump (IABP) has been used to treat patients with HTB. Timely treatment with an IABP can efficiently improve coronary blood flow and cardiac function in HTB patients with slow blood flow after PCI.

Extracorporeal membrane oxygenation (ECMO) was shown to be effective in the treatment of cardiogenic shock and respiratory failure in patients with HTB [79]. Because ECMO also interfered with coagulation, risk assessment is necessary in patients with cardiogenic shock before ECMO is administered.

Coronary artery bypass grafting (CABG) may improve outcomes in STEMI patients with HTB. These patients may experience potentially fatal complications including coronary dissection, thrombus shedding, and heart rupture. Endoscopic CABG is regarded as the best method to reduce these complications.

Hypothermia treatment has been shown to reduce apoptosis, protect the myocardium, and promote survival, especially in AMI patients with HTB who had severe myocardial involvement [80].

Summary

The mechanisms involved in the pathogenesis and treatment of HTB are summarized in **Figure 1**. Current techniques and methods are not able to accurately quantify the thrombus burden, and there is no standard treatment strategy at this time. Therefore, the treatment of HTB remains a challenge in current clinical practice. Pre-clinical and clinical predictors are especially needed to evaluate HTB. Clinical follow-up endpoints; large-scale, multicenter randomized clinical trials; and long-term assessment of clinical prognosis are required to provide better guidelines for the clinical management of HTB.

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Disclosure of conflict of interest

None.

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