Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 9178 - 9195
Received 05 March 2021; Accepted 01 April 2021.

High Thrombus Burden among Acute ST Segment Elevation Myocardial Infarction (STEMI) Undergoing Primary Percutaneous Intervention

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ABSTRACT

Background: The degree of severity of coronary artery disease and thrombus burden is associated with poor prognosis in patients presented with acute STEMI. It is important to make risk stratification for these patients on admission and guides the health care team on the most appropriate therapies on the basis of this risk.Coronary artery disease (CAD) is still considered the leading cause of morbidity and mortality in the present world. Risk factor assessment, prevention and treatment of CAD are an important aspect of present-day research.Intracoronary thrombus formation due to atherosclerotic plaque rupture and the interruption of coronary blood flow constitute the main pathophysiology underlying acute coronary syndrome. The quantity of the intracoronary thrombus burden is associated with a poor prognosis in patients with Acute coronary syndrome.

Key words:ST Segment Elevation Myocardial Infarction (STEMI),Coronary artery disease (CAD), Thrombus burden.

Introduction

Myocardial infarction (MI) is defined as myocardial cell death due to prolonged ischemia. Clinically, the term MI is used when there is evidence of myocardial necrosis in a clinical setting, consistent with acute myocardial ischemia and with a rise in cardiac troponin **(1).** MI or acute coronary syndromes, the actual term depending on the current definition under which its various presentations are subsumed, remains the major clinical event in patients with atherosclerosis of the coronary arteries**(2)**. Although myocardial injury is a prerequisite for the diagnosis of MI, it is also an entity in itself. To establish a diagnosis of MI, criteria in addition to abnormal biomarkers are required**(3)**. Approximately 1.5 million cases of myocardial infarction (MI) occur annually; the yearly incidence rate is approximately 600 cases per 100,000 people**(4)**.

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Pathological characteristics of myocardial ischemia and infarction:

MI is defined in pathology as myocardial cell death due to prolonged ischemia. After the onset of myocardial ischemia, histological cell death is not immediate, but takes a finite period of time to develop—as little as 20 min, or less in some animal models **(5).**It takes several hours before myocardial necrosis can be identified by macroscopic or microscopic post-mortem examination. Complete necrosis of myocardial cells at risk requires at least 2–4 h, or longer, depending on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischemia, preconditioning, and individual demand for oxygen and nutrients. The entire process leading to a healed infarction usually takes at least 5–6 weeks. Reperfusion may alter the macroscopic and microscopic appearance **(5)** Atherosclerosis is an important cause of acute coronary syndrome. Atherosclerosis is a disease of intima that can involve both large and medium sized arteries diffusely. Atherosclerosis begins to affect arteries of many individuals in the early decades of life, yet typically, symptoms of atherosclerosis do not occur until several decades later(**6)**.The atherosclerotic lesion in the intima is known as the plaque. The plaque consists of SMCs, extra-cellular lipid, lipid-containing macrophages, T-lymphocytes and some basophils, all of which are embedded in a connective tissue matrix including collagen, elastin and proteoglycans produced by SMCs. The earliest lesion in the pathogenesis of atherosclerotic plaque is the fatty streak**(6)**.

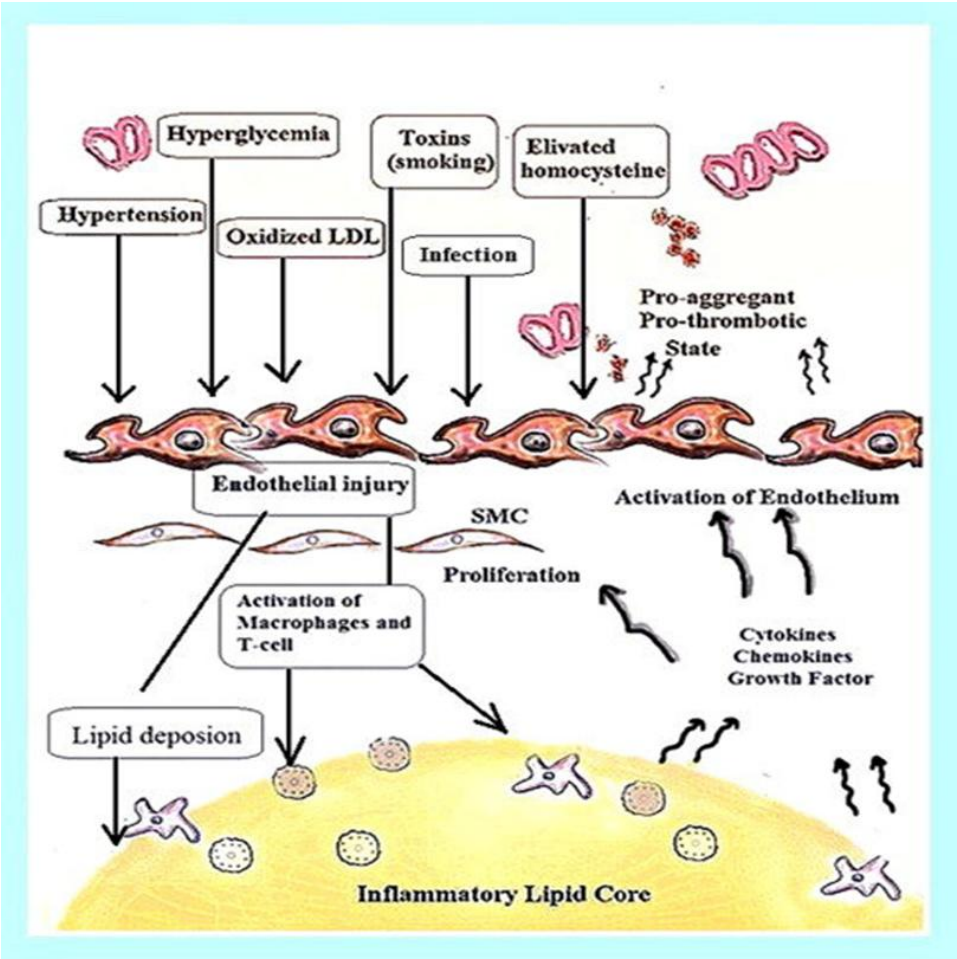

Figure (1) Shows endothelial injury progression for atherosclerosis initiation model **(4).**

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Clinical features of myocardial ischemia and infarction:

Onset of myocardial ischemia is the initial step in the development of MI and results from an imbalance between oxygen supply and demand. Myocardial ischemia in a clinical setting can usually be identified from the patient's history and from the ECG **(7).**

Possible ischemic symptoms include various combinations of chest, upper extremity, mandibular or epigastric discomfort (with exertion or at rest) or an ischemic equivalent such as dyspnea or fatigue **(8).**

The discomfort associated with acute MI usually lasts >20 min. Often, the discomfort is diffuse—not localized, nor positional, nor affected by movement of the region—and it may be accompanied by diaphoresis, nausea or syncope **(9).**

However, these symptoms are not specific for myocardial ischemia. Accordingly, they may be misdiagnosed and attributed to gastrointestinal, neurological, pulmonary or musculoskeletal disorders. MI may occur with atypical symptoms—such as palpitations or cardiac arrest—or even without symptoms; for example, in women, the elderly, diabetics, or postoperative and critically ill patients **(10).**

Careful evaluation of these patients is advised, especially when there is a rising and/or falling pattern of cardiac biomarkers **(11)**

Diagnosis

Chest pain is the usual symptom which brings these patients to medical attention. Pain is severe, diffuse, retrosternal and radiates to arms or from jaws to umbilicus. Pain does not get relieved with sublingual nitrates or usual pain killers **(12).**

It is often associated with eructation and retrosternal burning. Commonly patients mistake it for acid peptic symptoms and waste precious time with antacids **(13).**

It is accompanied with vomiting, sweating and breathlessness. About 15-20% of infarcts can be painless especially in elderly and diabetics. Equal number may have less characteristic pain than described above **(14).**

ECG is generally the first investigation available for making a diagnosis in a patient presenting with acute severe chest pain **(15).**Tall T waves and ST elevation are the hallmarks of early presentation within minutes of onset of pain. The third change− appearance of Q waves is delayed and seen after 6 hours of onset. Q waves denote significant myocardial necrosis **(16).**T wave change is in larger area and it denotes ischemia, ST segment change is in lesser number of leads and denotes myocardial injury and Q waves overlie and denote central area of myocardial necrosis **(16).** Prolonged, new ST-segment elevation (e.g.,>20 min), particularly when associated with reciprocal ST-segment depression, usually reflects acute coronary occlusion and results in myocardial injury with necrosis**(17)**.

Management of patients with STEMI:

Given the progressive loss of functioning myocytes with persistent occlusion of the infarct-related artery in STEMI initial management aims to restore blood flow to the infarct zone as rapidly as possible. Primary PCI is generally the preferred option, provided that an experienced operator and team can perform it in timely fashion **(18).**

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Missed opportunities for improvement in the care of STEMI include failure to deliver any form of reperfusion therapy in approximately 20% of patients and failure to minimize delays in reperfusion because of inefficient systems of care **(19).**
Given the importance of time to reperfusion, emphasis has shifted to overall medical system goals, starting at the point of first medical contact with the patient Benchmarks for medical systems to use when assessing the quality of their performance are a door-to-needle time of 30 minutes or less for initiation of fibrinolytic therapy and a door-to-device time of 90 minutes or less for percutaneous coronary perfusion **(20).**

Prompt restoration of myocardial blood flow is essential to optimize myocardial salvage and to reduce mortality. A decision must be made as soon as possible as to whether reperfusion will be achieved with fibrinolytic agents or primary PCI **(21).**
For patients who present within two hours of the onset of symptoms, we suggest full-dose fibrinolytic therapy and transferal to a PCI center. This assumes that primary PCI cannot be performed in less than 90 minutes at a local PCI center **(22).**
For patients who present with symptoms that last longer than two to three hours, we suggest transferal for primary PCI. However, there are times when the patient presents after two hours, and PCI cannot be accomplished in less than 120 minutes. In this setting, clinical judgement needs to be exercised; fibrinolytic therapy may be appropriate in patients with up to 12 hours of symptoms **(23).**

Percutaneous coronary intervention (PCI):
Percutaneous coronary intervention (PCI) is lifesaving in patients with acute ST-segment elevation myocardial infarction (STEMI) and has been shown to improve quality of life when performed electively in appropriate patients **(24).**
Initially, PCI was performed at clinical sites with surgical backup as complication rates and rates of urgent surgery were high. Over time as physician experience has increased, techniques have improved, better integration of technology with coronary stents, and antiplatelet and anticoagulation regimens were improved, the need for emergency surgery declined dramatically **(25).** Currently, emergency cardiac surgery rates resulting from PCI procedure are at 0.2%.1 Overall complication rates from PCI are low **(26).**
Primary PCI improves patient outcomes and reduces adverse events in patients with STEMI. Because most patients with STEMI are transported to hospitals without on-site surgical back-up and timely access to primary PCI is important for these situations, it is critical to sustain these programs that are difficult to continue due to financial and human resource issues **(27).**

Coronary Angiography
Coronary angiography, the in vivo contrast study of the coronary artery tree and its lumen, is commonly used to investigate the anatomy of the coronary arteries and to assess the number, location, and severity of coronary stenosis **(28).**
A minimally invasive procedure called coronary catheterization is performed where a small catheter (a thin hollow tube with a diameter of 2–3 mm) is inserted through the skin into an arterial sheath at a point where the artery is fairly superficial and easily palpable in the groin or the arm **(29).**

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The physician advances the catheter often leading with a soft J-shaped guidewire retrograde with the visual guidance of fluoroscopy (a special X-ray viewing instrument), and then the catheter is manipulated in the base of the aorta immediately above the aortic valve until the catheter tip is engaged in the ostium of the coronary arteries, the blood vessels supplying blood to the heart **(30).**
An injection of 5–12 mL of radiographic contrast solution containing iodine, which is easily visualized with X-ray images, visualizes the coronary tree, delineates its branching pattern, and outlines the inner diameter of a coronary artery **(31).**
Both the right and left coronary artery are injected multiple times after changing the position of the X-ray system to visualize the coronary tree from different perspectives **(32).**
The sequential images that are produced over the 3–6 s acquisition time are called the selective coronary angiogram, and the recorded images, if carefully and comprehensively gathered with skill, accurately reveal the extent and severity of all coronary arterial blockages **(33).**
Researchers have attempted to define angiographic CAD burden using quantitative scoring systems. Historically, this was performed by designation of a single-, double-, triple-vessel, and left main disease classification, with luminal stenosis of either ≥50% or ≥70% used to define significance **(34).**However, this simple scoring system was limited in its ability to stratify patients with different levels of disease risk and led to the development of more comprehensive scoring systems for defining atherosclerotic burden and prognosis **(35).**
Current scoring systems are heterogeneous, lack standardization, and have not been directly compared with each other. Some scoring systems are easily reproducible, have been validated in multiple settings, and provide prognostic value, whereas others require sophisticated computer software and are not widely applicable **(36).**Coronary angiography is widely used to define the presence and severity of coronary artery disease; many scoring systems are used for research purposes and clinically. The most frequently used are modified Gensini and SYNTAX score **(37).**
Scores represent a simple, convenient method of risk stratification, in which a number of independent risk factors on presentation are shown to have prognostic significance **(38).**The advantage of scoring systems is that they summaries important prognostic information of the disease in a single number, confidence limits can be easily calculated and survival rates can be easily compared between given treatments **(38).**Several scores have recently been proposed, derived either from clinical trials or from registries and cohort studies **(39)**.

Thrombus burden

Thrombus burden is defined based on evaluation by coronary angiography, for example, by scores associated with angiographic morphological characteristics and by Thrombolysis in Myocardial Infarction Risk Scores (TIMI Risk Scores or TS). Angiographic morphologic characteristics of thrombus burden 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 **(40).**

Alternatively, thrombus burden 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

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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 thrombus burden **(41).**

Grade 0	No angiographic evidence of thrombus
Grade 1	Angiographic features suggestive of thrombus (decreased contrast density, haziness of contrast, irregular lesion contour, a smooth convex meniscus at the site of a total occlusion, suggestive, but not firmly diagnostic of thrombus)
Grade 2	Definite thrombus present in multiple angiographic projections (marked irregular lesion contour with a significant filling defect—the greatest dimension of thrombus is <1/2 vessel diameter)
Grade 3	Definite thrombus appears in multiple angiographic views (greatest dimension from >1/2 to <2 vessel diameters)
Grade 4	Definite large size thrombus present (greatest dimension >2 vessel diameters)
Grade 5	Definite complete thrombotic occlusion of a vessel (a convex margin that stains with contrast, persisting for several cardiac cycles); angiographic detection of a grade 5 TIMI thrombus leads to further exploration of the occlusive thrombotic content. Either a PCI guidewire or a small balloon is advanced across the thrombotic total occlusion. Crossing the thrombus results in restoration of antegrade flow in the treated vessel. Consequently, the ensuing coronary angiogram enables restratification of the underlying residual thrombus (final TIMI thrombus grade).

Abbreviations: TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention.
[a]Data taken from references.[5,9,10]

Figure (2) classification of thrombus burden **(42).**

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. The accuracy of coronary angiography in evaluating thrombus burden 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 thrombus burden **(43).**

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. **(44)**

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. **(44)**

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 thrombus burden, they are not recommended for evaluating coronary thrombi in AMI patients with thrombus burden prior to PCI because of their potential ability to exacerbate distal embolization and extend treatment time **(44).**

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 in-creased thrombus burden. In addition, platelets promote the formation of blood clots by interacting with

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the coagulation system. A number of factors and pathological processes play an important role in the formation of thrombus burden **(45).**

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, whereas Hsp-27 in platelets contributes to platelet aggregation and variations in platelet shape. Hsp-27 has also been shown to positively correlate with the risk of THROMBUS BURDEN development and the incidence of major adverse cardiac events (MACEs) in patients with ST-elevation MIs (STEMIs) **(46).**

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. These findings suggest that Hsp-27 plays an important role in thrombus burden development. Indeed, plasma Hsp-27 levels may predict the development of thrombus burden and clinical outcomes in STEMI patients **(47).**

CD40 is a receptor expressed on macrophages and smooth muscle cells (SMCs), is activated by CD40L produced by activated T cells, and promotes secretion of TF by macrophages and SMC cells. During the process of thrombosis formation, TF was found to continuously cover the surface of the thrombus, increasing the thrombus burden. 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 **(48).**

Endothelial dysfunction has also been associated with thrombus burden. 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. The degree of endothelial injury was shown to correlate positively with thrombus burden.**(49)**

Myeloperoxidase (MPO), which is expressed by macrophages at the site of coronary athero-sclerosis, produces hypochlorous acid (HOCl), a molecule that induces endothelial cell death through apoptosis, with sublethal concentrations of HOCl increasing TF concentration. 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 **(49).**

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 **(50).**

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 and the inhibition of PS binding to ligands **(50).**

Fibrinogen is a fibrin precursor that enhances blood coagulation, induces thrombosis, and is an independent predictor of THROMBUS BURDEN. Hyper-fibrinogen is closely associated with

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endothelial cell damage, with increased fibrinogen levels being a risk factor for AMI and ischemic stroke. 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. The structure of fibrinogen can also be modified by glycation and by the presence of homocysteine under conditions of hyperglycemia and hyperhomocysteinemia, respectively. These can render fibrinogen resistant to fibrinolysis, thus increasing the risks of arterial and venous thrombosis **(51).**
Thrombosis components have also been associated with the development of thrombus burden. 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. 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. 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 **(52).**
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 thrombus burden in the IRA. The components of thrombi were found to differ among coronary arteries. 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 thrombus burden **(53).**
Red cell distribution width (RDW) was found to be an independent predictor of thrombus burden, with the area under the receiver operating characteristics (ROC) curve predictive of thrombus burden. 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. 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 possibility of thrombus aspiration or the requirement for distal protection **(54).**
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. With aging, RBCs have a smaller volume and de-creased 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**(51).**
This process, in turn, facilitates the production of erythropoietin (EPO) and further increases RDW **(51).**
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 tissue factor, leading to a lighter thrombus burden. By contrast, severe injury to the blood

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vessel wall or serious inflammation results in the production of higher levels of collagen and tissue factor, leading to a heavier thrombus burden **(49).**

White blood cell (WBC) counts, neutrophil counts, and neutrophil-to-lymphocyte (N/L) ratios are independent predictors of thrombus burden. N/L can also be used to predict early and late prognosis in patients with STEMI after PCI. Patients with high thrombus stress tended to have a higher percentage of neutrophils. Moreover, the aggregation rate of RBCs was significantly higher in glucose buffer with rather than without a neutrophil suspension. Activation of leukocytes is thought to produce oxygen free radicals and proteolytic enzymes that affect adjacent RBCs on thrombus sites. Through this neutrophil-erythrocyte interaction, neutrophils affect thrombus components and increase thrombus burden **(55).**

Treatment Strategies for Thrombus Burden

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 micro embolisms, 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 **(56).**

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 **(49).**

In 2010, *Ren et al*, recommended manual suction for thrombi with TIMI thrombus grades 2-3 and mechanical suction for those with TIMI thrombus grades 4-5 **(55).**

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 THROMBUS BURDEN, larger culprit vessels, and shorter ischemia time. Multiple thrombus aspirations, generally ≤3, have been recommended for patients with THROMBUS BURDEN who experience significant effects (TIMI ≥ 3, IIb C recommended) following initial thrombus aspiration. Balloon expansion can also be added if needed **(57).**

Distal protection devices include obstructive balloons (proximal, distal) and distal filters. 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 **(55).**

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

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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. In addition, the rates of embolism formation and of MACEs within 30 days were higher in the thrombosis than in the control group **(58).**

Delayed stent implantation has also been associated with thrombus burden. Acute stent implantation by PCI in thrombus burden 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 **(59).**

Delayed stent implantation after enhanced antithrombotic therapy was found to ameliorate perfusion in patients with thrombus burden after thrombus aspiration. By contrast, the DANAMI3-DEFER study showed that delayed stent implantation within 48 hours did not improve the prognosis of STEMI patients **(59).**

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 thrombus burden. Although delayed stent implantation may have negative effects, it is regarded as important in treating thrombus burden **(60).**

Drug treatments:

Drugs used in the treatment of thrombus burden 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). **(61).**

The strongest antiplatelet drugs, which can be selectively applied to STEMI patients with thrombus burden, include monoclonal antibodies such as azizumab and peptide inhibitors, such as eptifibatide and tirofiban. *Intracoronary* injection of these drugs was shown to be superior to intravenous injection. GPI inhibits platelet IIb/IIIa receptors, protects endothelial cells, restores reperfusion of the IRA, and reduces endpoint events and MACEs **(49).**

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 thrombus burden, as patients are not uniform. **(49).**

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. Very different findings, however, were observed in the AIDA-STEMI trial. The reasons for this discrepancy are not clear, but may be due to the use of microcatheters, which allow better local application of GPIs **(49).**

Anticoagulant drugs include unfractionated heparin, low molecular weight heparin, and bivalirudin. Conventional antiplatelet aggregation and anticoagulant agents may not have an effect in thrombus burden patients. However, these patients may benefit from strengthening anticoagulation or the administration of warfarin **(52).**

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Thrombolytic medications include streptokinase, alteplase and urokinase. Low-dose *intracoronary* thrombolysis washout was not only found to be appropriate and safe for STEMI patients with thrombus burden who failed treatment by thrombus aspiration, but also reduced coronary thrombus burden and improved epicardial blood flow and myocardial perfusion. The combined administration of urokinase and abciximab did not cause distal embolization or slow blood flow, but significantly reduced the thrombus burden **(56).**

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 thrombus burden **(62).**

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. One of these drugs, verapamil, is commonly used to treat thrombus burden 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 **(57).**

Intravascular ultrasound:

Standard X-ray angiography provides a qualitative 2-dimensional assessment of the caliber of the interior surface of coronary arteries in the long axis **(63).**

Intravascular ultrasound (IVUS) can provide additional information regarding vessel geometry (diameter, cross-sectional area) and plaque dimensions **(64).**

IVUS is performed by passing a coronary artery catheter with an inbuilt ultrasound array over a guide wire. A cross-sectional image of the coronary artery wall is displayed showing the relationship of the intima, media and adventitia, which in health are closely associated. Measurements obtained by IVUS are more accurate than angiography particularly in the left main stem and ostial lesions where vessels overlap **(65).**

Due to its higher resolution, IVUS may reveal presence of plaques that have not yet expanded into the lumen or ruptured. This occult disease is clinically significant as the minimally occlusive plaque has been shown to be more likely to rupture and cause acute cardiac ischemia **(58).**

The main disadvantage of IVUS is the cost and the length of time it adds to any diagnostic procedure. There is also increased risk of intimal damage to the coronary artery which must be balanced against the additional data gained from an IVUS study **(58).**

Ventriculography and valvular assessment:

Ventriculography can be performed before or after angiography. A catheter is advanced through the aortic valve into the LV and radiocontrast injected **(57).**

The contraction of the LV is then assessed to detect any wall motion abnormalities and provides data on stroke volume, ejection fraction and cardiac output. Gross diagnoses of aortic and mitral valve regurgitation can be made during left ventriculography **(58).**

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 9178 - 9195
Received 05 March 2021; Accepted 01 April 2021.

Coronary computed tomography angiography (CCTA)

Coronary CT angiography is a non-invasive method of examining the coronary arteries. No arterial catheterization is required and instead intravenous radiocontrast is injected and timed scans of the heart performed. In the past, CCTA was limited by the number of (0.5 mm) slices a scanner could image per rotation of its emitter/detector tube, leading to movement artefact from the heart and respiratory cycle. The advent of sub-second tube rotations and 64, 128, 256 and 320 slice scanners enable the heart to be imaged quickly and have a high enough resolution to allow accurate assessment of CAD **(64).**

Radiation doses are comparable to invasive, catheter angiography but can be significantly reduced with technologies such as prospective ECG gating where CCTA images are obtained only in diastole, when the heart is motionless **(63).**

Images can be reconstructed to give a 3D representation of the heart. A disadvantage of CCTA is that images can become difficult to interpret in the presence of significant vessel wall calcification and, in the event of discovering an amenable lesion, no intervention is possible **(64).**

Magnetic resonance (MR) coronary angiography

At present, the indications for cardiac magnetic resonance angiography (MRA) are limited. This is mainly due to relatively long scan times of five to 15 minutes versus fraction of a second with CCTA. Image resolution is also considered inferior; 1 to 1.5 mm versus a slice thickness of 0.5 mm with CCTA **(64).**

However, cardiac MRA emits no ionizing radiation making it suitable for children requiring multiple scans. Furthermore, it is not affected by vessel wall calcification **(65).**

Advances in MR scanner field strength, use of MR contrast and the number of coils means that more of the heart can be imaged simultaneously thereby improving resolution and decreasing scan times. Currently cardiac MRA is mainly used for diagnosing anomalous coronary artery origins (in children) and coronary artery aneurysms in Kawasaki Disease **(66)**

Conflict of Interest: No conflict of interest.

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