Clinical and Angiographic Correlates in Troponin-Negative Versus Troponin-Positive Patients with Acute Coronary Syndromes Without ST-Segment Elevation

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Presented by

Mohamed Ahmed Bassiouny, M.B.B.Ch

Under the Supervision of

Sherif El-Tobgi, MD

Professor of Cardiology

Cairo University

Mohamed Abd El Ghany, MD

Professor of Cardiology

Cairo University

Sameh Bakhoum, MD

Assistant Professor of Cardiology

Cairo University

Faculty of Medicine

Cairo University

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Abstract

Our study aims to test the hypothesis that troponin positive patients have more severe coronary artery disease (CAD). It also aims to determine the correlation between troponin elevation and myocardial tissue perfusion and assess the incidence of adverse cardiac events. Our data shows that troponin elevation was linked to morphological complexity of the target lesion and to visibility of thrombus formation. Furthermore, troponin elevation was associated with impaired tissue level perfusion, which in turn was translated into a higher risk of morbidity and mortality on 1 year follow-up.

(Key Words: NSTE-ACS, Troponin, TFG, TFC, TMPG, MBG)

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Introduction

Non-ST-elevation (NSTE) acute coronary syndrome (ACS) is a clinical syndrome that encompasses unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI). These life threatening disorders are a major cause of emergency medical care and hospitalization throughout the world. In 1996 alone, the National Center for Health Statistics reported 1,433,000 hospitalizations for UA or NSTEMI in the United States.[1]

NSTE-ACS is characterized by imbalance between oxygen supply and demand. The most common cause of UA/NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a non-occlusive thrombus, which developed on a disrupted atherosclerotic plaque.

UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity; that is, they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I (TnI), troponin T (TnT), or creatine kinase, MB fraction (CK-MB).

The most recently described and preferred biomarkers for myocardial damage are cardiac troponins. They have nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis.[2,3,4,5,6] They also add significant incremental prognostic value to routine clinical and electrocardiographic variables for identifying patients at risk of cardiac events, including death and re-infarction.[7,8,9,10,11]

The percentage of ACS patients presenting with a troponin positive test ranges from 20% in large randomized studies[12,13,14] to up to 60%.[10,15] This wide range of variation reflects improvement of the sensitivity and precision of second

generation troponin assays, in addition to differences in selection of cut-off values above which the case is considered to be troponin positive.

The pathophysiological mechanisms underlying troponin elevation and its ability to identify patients with a worse outcome including worse angiographic results after primary percutaneous coronary intervention (PCI) is still unsettled.[11,16,17,18,19,20,21,22] They may include higher incidence of multivessel disease, complex lesions, and intra-coronary thrombus, more extensive tissue damage due to longer periods of myocardial ischemia, distal embolization of platelet aggregates[23] and microvascular dysfunction and the no-reflow phenomenon.[24,25,26]

Aim of the Work

Objectives of the study are:

1. Test the hypothesis that TnI positive patients have more severe coronary artery disease (CAD), including a higher number of affected vessels, more severe luminal narrowing, and more frequent complex lesion morphology and intraluminal thrombus, and a higher risk score.

2. Determine the correlation between TnI elevation and myocardial tissue perfusion, as assessed by Thrombolysis In Myocardial Infarction (TIMI) flow grade (TFG), corrected TIMI frame count (CTFC), TIMI myocardial perfusion grade (TMPG), and myocardial blush grade (MBG).

3. Assess the differences in incidence of adverse cardiac events, including: post-procedural myocardial injury as measured by CK-MB elevation, and 1 year clinical outcome, in TnI positive versus TnI negative patients.

Review of literature

Pathogenesis of Acute Coronary Syndrome

"Acute coronary syndrome" is a term that encompasses any constellation of clinical symptoms that is compatible with acute myocardial ischemia. It includes myocardial infarction (ST-segment elevation and depression, Q wave and non-Q wave) and UA. These conditions are characterized by an imbalance between myocardial oxygen supply and demand.

The most common cause of UA/NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a thrombus that developed on a disrupted atherosclerotic plaque and is usually non-occlusive. Microembolization of platelet aggregates and components of the disrupted plaque are believed to be responsible for the release of myocardial markers in many of these patients.

After the onset of myocardial ischaemia, cell death is not immediate but takes a finite period to develop (as little as 20 min or less in some animal models). It takes several hours before myocardial necrosis can be identified by macroscopic or microscopic post-mortem examination. Complete necrosis of all myocardial cells at risk requires at least 2–4 h or longer depending on the presence of collateral circulation to the ischaemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischaemia, pre-conditioning, and/or, finally, individual demand for myocardial oxygen and nutrients.

Over the last two decades, converging observations on the close interactions between platelets and the coagulation system, and on the biology of the vessel wall, atherosclerosis, and inflammation, have established the role of intravascular thrombus formation as the immediate trigger for acute coronary syndromes. Two processes cause thrombosis on plaques. In the first (superficial injury) there is endothelial denudation over the plaque. Subendothelial collagen is

exposed and a platelet-rich thrombus forms over the surface. Approximately one in four of larger thrombi that occlude coronary vessels are due to severe superficial injury of this kind. In the second (deep intimal injury) the plaque splits or tears through the cap. Blood enters the lipid core to meet a thrombogenic mixture of tissue factor, collagen and lipid. A platelet-rich thrombus forms within the plaque which may then extend into the lumen. Plaque fissuring covers a wide spectrum of severity; at one extreme there are microfissures no more than a few hundred microns across; at the other, the whole cap may be torn over a centimetre of the artery. When blood enters the core, thrombosis is inevitable but does not always lead to luminal obstruction.

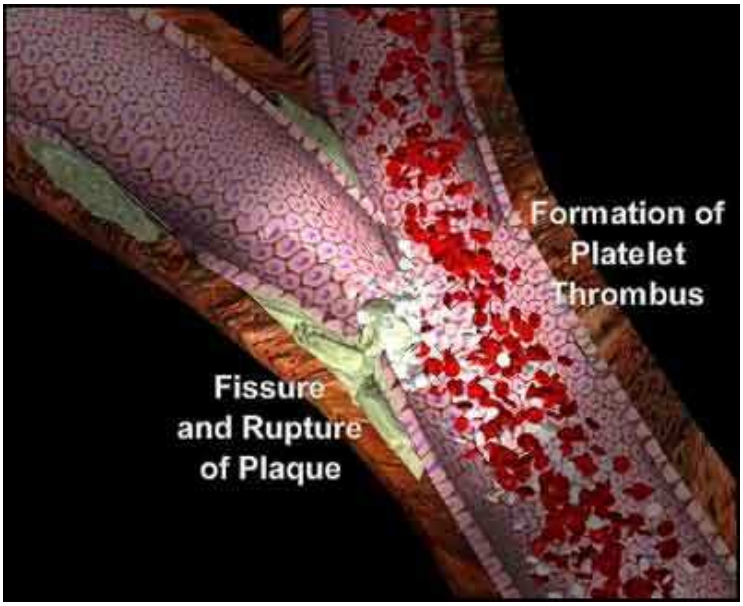

Figure 1: Plaque Fissuring and formation of platelet thrombus

Mechanisms of Plaque fissuring

The mechanisms of plaque destabilization (fissuring and rupture, followed by thrombus formation) are not fully understood. The most common underlying molecular and cellular pathophysiology of disrupted atherosclerotic plaque is arterial inflammation, caused by noninfectious (e.g., oxidized lipids) and, possibly, infectious stimuli, which can lead to plaque expansion and destabilization, rupture or erosion, and thrombogenesis. Activated macrophages and T lymphocytes

located at the shoulder of a plaque increase the expression of enzymes such as metalloproteinases that cause thinning and disruption of the plaque, which in turn can lead to UA/NSTEMI.

Study of plaques in the coronary arteries that have undergone fissuring indicate that the majority are composed of eccentrically situated lipids (i.e., located in an area where the vessel bifurcates) that do not have an internal lattice of collagen supporting the cap of the plaque, which further supports the role of metalloproteinases in plaque destabilization. The vulnerability of such a structure to fissuring also appears to be related to circumferential stress on the plaque cap in systole.

Potential Outcomes of Plaque Fissuring

Most advanced plaques appear to progress from the early lesion very rapidly by means of Type II injury with resulting thrombus formation and its incorporation into the plaque.[27]

Thrombosis and incorporation of the surrounding thrombus into the plaque have been demonstrated in various stages of atherogenesis. In autopsy study of coronary arteries in patients with atherosclerotic syndromes, for example, nearly 17% of patients had fissures in atherosclerotic plaques and some cases overlying thrombi.[28]

Moreover, studies have suggested that thrombus formation/organization and acute or subacute progression of atherosclerotic plaque is probably part of the same phenomenon.[29] Acute episodes of transient ischemia and ischemic stroke (as well as myocardial infarction, unstable angina, as sudden death) may be precipitated by thrombosis on atherosclerotic plaques.

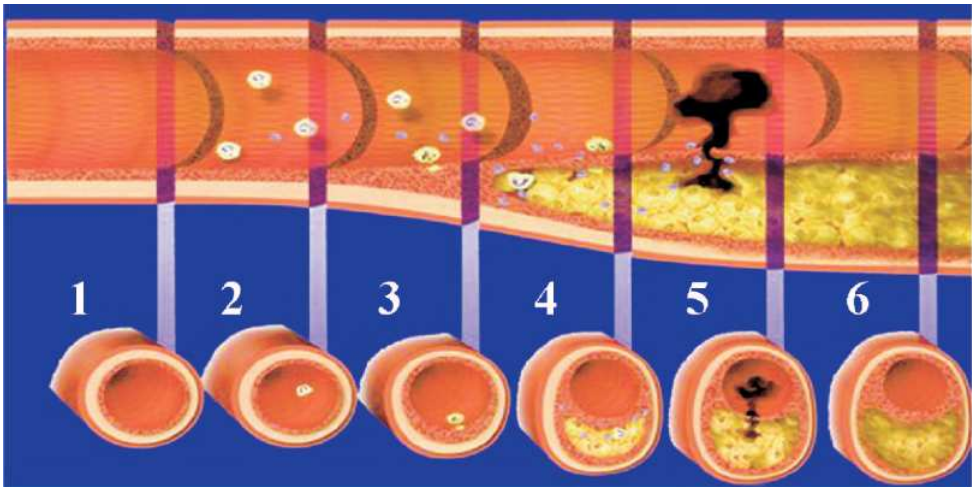

Figure 2: Plaque formation and outcome of fissuring

Thrombus Formation

Rupture of the atherosclerotic plaque exposes the subendothelial collagen to the bloodstream.[30] On contact with collagen, platelets become activated, with platelet adhesion, secretion of platelet contents, and platelet aggregation at the site of injury (figure 3). The activated platelet surface is an essential catalytic surface for several coagulation reactions that generate thrombin, a key factor in the coagulation sequence.[31]

Platelets adhere to exposed subendothelium through interaction with a variety of platelet surface receptors, the most important of which is GP-Ib-IX.[32] This glycoprotein is the main receptor for the subendothelial protein ligand von Willebrand factor (vWF).

Platelet aggregation requires the platelet membrane glycoprotein integrin receptor (GP IIb-IIIa), which -- at least under low fluid shear stress conditions -- is involved in calcium-dependent interplatelet bridging by bound fibrinogen. Under high fluid shear-stress conditions, there is evidence that platelet aggregation depends on the binding of vWF to platelet GPIIb/IIIa.[33] It has also been shown that blockade of vWF-GPIIb/IIa interaction inhibits platelet aggregation and thrombus formation without disturbing the initial platelet adhesion.[34] Thus, vWF appears to play a crucial role in both platelet adhesion and platelet aggregation under high

shear-stress conditions, such as turbulent blood flow in atherosclerotic vessels. The importance of vWF is further supported by an association between elevated vWF concentrations and arterial thrombosis.[35]

When platelets are activated, they acquire enhanced capacity to catalyze interaction between activated coagulation factors.[36] These factors circulate in the form of inactive precursors (zymogens). Rupture of the atherosclerotic plaque leads to activation of the coagulation cascade: Each zymogen in converted into an activated coagulation factor, which in turn activates the next zymogen in the sequence. This process culminated in the generation of thrombin, an enzyme that converts the soluble protein fibrinogen to the insoluble one, fibrin, forming a blood clot.

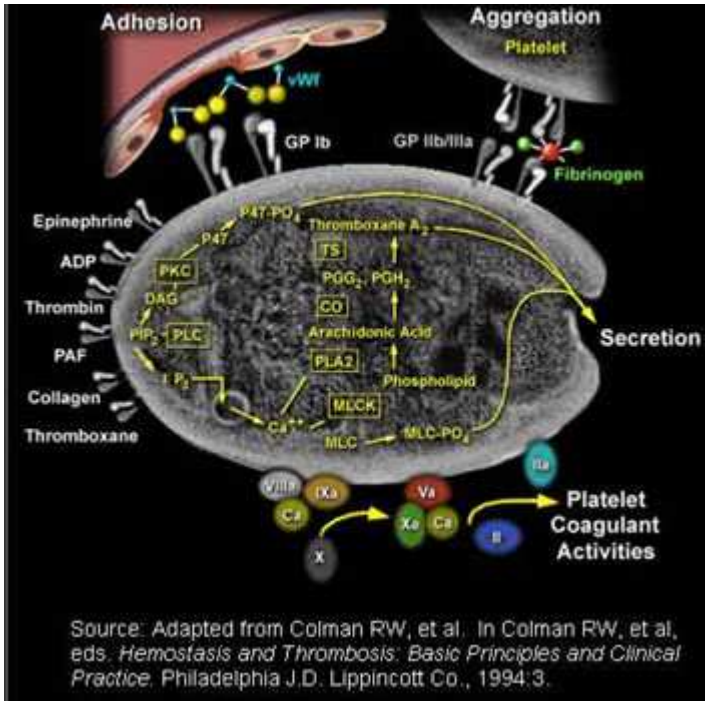

Figure 3: Platelet activation

The clotting cascade consists of two separate initial pathways ("intrinsic" and "extrinsic") that ultimately converge on the "common" pathway" to activate the precursor protein prothrombin to the active enzyme thrombin (Figure 4).[37] The extrinsic system, the principal initiating pathway of in vivo blood coagulation, involves both blood and vascular elements. The critical component is

tissue factor (TF, sometimes referred to as thromboplastin), a glycoprotein embedded in association with phospholipid (PL) in the surface membrane of fibroblasts within and around blood vessels and in various other tissue cells. Under physiologic conditions, tissue factor is not exposed to blood, but with vascular or endothelial cell injury, this substance acts in concert with activated Factor VIIa and phospholipid to convert Factor IX (from intrinsic system) to IXa and Factor X (from the extrinsic system) to Xa. The coagulant activity of Factor VII, the major plasma component of the extrinsic pathway, is increased by Factor IXa of Factor XIIa of the intrinsic system. These events take only about 15 seconds.[38]

The intrinsic pathway can be viewed as coagulation initiated by components entirely contained within the vasculature. This pathway results in the activation of Factor IX by Factor XIa, providing a pathway independent of Factor VII for blood coagulation. A major difference between the intrinsic and extrinsic pathways is that whereas the activation of Factor IX by XIa requires only the presence of ionized calcium, the activation of Factor IX by VIIa (in the extrinsic system) requires both calcium and tissue factor. Importantly, Factor IXa converts Factor X (in the extrinsic system) to Factor Xa in concert with the "tenase" complex (PL/VIIIa).

Factor Xa, regardless of how it is formed, is the active catalytic component of the "prothrombinase" complex, which converts prothrombin to thrombin. Thrombin cleaves fibrinopeptides (FPA, FPB) from fibrinogen, allowing the resultant fibrin monomers to polymerize, and converts Factor XIII to XIIIa, which crosslinks (XL) the fibrin clot. Thrombin accelerates the process by its potential to activate Factors V and VIII.

The fibrin molecules aggregate together, trapping platelets, erythrocytes, and leukocytes to form the clot. The clot then contracts, pulling together the edges