

## Platelet Activation in Distinct Forms of Coronary Artery Disease

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Endothelium responds to stimuli, modulates induction and/or regression of several genes, and its autocrine/paracrine activity is responsible for anti-inflammatory, anti-mitogenic, vasodilation, anti-thrombogenic, and homeostatic activity with intravascular components. Intensity and persistence of vascular injury increase the expression of adhesion molecules derived from the selectin-super family (E and P). The nuclear transcription factor (NF) – kappa B expresses these and other adhesion molecules easing parietal entry of monocytes adhered to the endothelium and contributing to the pathogenesis of atherosclerosis.

Rupture of vulnerable plaques modifies their geometry and leads to mural thrombosis. The thrombogenic plaque-dependent substrate, vascular rheology, and systemic pro-coagulant activity influence the magnitude, the stability of the thrombus, and the gravity of the coronary artery disease.

In locations of turbulence (bifurcations, stenosis, or endothelial lesion), erythrocyte hemolysis releases sufficient ADP to mobilize the removal of microtubule calcium ions and activate platelets. The primary aggregation is reversible, and platelet deactivation comes from the return of cytoplasmatic calcium ions to platelet microtubules, a mechanism reliant on prostacyclin produced by integrity and normofunction of the endothelium.

In endothelial loosening and in ruptured plaques, platelets come into contact with subendothelial structures and adhere to microfibrils through a protein from the factor VIII complex (von Willebrand factor) synthesized by endothelial cells and responsible for the interaction of microfibrils with specific glycoproteins of the platelet membrane. Platelets adhere to different types of collagen: in small caliber vessels with strong deformability they adhere to type I collagen, and in large vessels with weak deformability they adhere to type III collagen.

Mural thrombosis repaired by type III collagen increases plaque volume, contributing to the progression of atherothrombosis. In non-activated plaques, arachidonic acid is esterified in cell membrane phospholipids. Intense and prolonged platelet stimuli release large quantities of cytoplasmatic calcium, activate phospholipase, and stimulate metabolism of arachidonic acid via two pathways: by the lipoxygenase route, leukocyte leukotrienes are formed that are responsible for chemotaxis, increased endothelial permeability, and inflammation, and by the cyclooxygenase route, cyclic endoperoxides are produced, which are responsible for prostaglandin formation (D2, E1, and F2).

Cyclic endoperoxides occupy a central position in arachidonic acid metabolism. Depending on the tissue, different metabolites may be formed: thromboxane A2, with aggregant activity, or prostacyclin, an antiaggregant.

Thromboxane A2 has a biological half-life of 30 seconds, and spontaneously transforms into thromboxane B2. Endothelial cells synthesize prostacyclin from their own arachidonic acid or sub-utilize cyclic endoperoxides formed by platelets. The physiological importance of this reaction justifies the platelet aggregate formation within the limits of the damaged vascular segment. In propagation of the aggregate to beyond the damaged limits, endothelial cells transform cyclic endoperoxides into prostacyclin, mobilize calcium ions into microtubules, and undo the platelet aggregate.

Thromboxane A2 is not responsible for the initial platelet activation, but for the result of this activation; with the ADP present inside the platelet, thromboxane A2 is co-responsible for the subsequent growth of the hemostatic plug. Intense platelet stimuli make this aggregation irreversible, and agents such as thromboxane A2 or thrombin induce cellular extrusion of substances accumulated in platelet granules – the “release reaction”.

Products of secretion are available around the platelets: ADP is a chemical messenger that favors adhesion and aggregation; serotonin has a vasoconstriction effect and induces mild aggregation; platelet factor 4, beta-thromboglobulin, von Willebrand factor, platelet fibrinogen, mitogenic factor, and lysosomal enzymes, among others, are products of secretion with diverse activities in platelet aggregation.

Rupture results from physical forces exerted on thinner plaques rich in fat cells and an active mechanism - degradation of the extra-cellular matrix by proteolytic enzymes secreted by intra-plaque macrophages and mast cells<sup>1</sup>. The continuous entry, survival, and replication of monocytes / macrophages are regulated by various factors: ICAM-1, MCP-1, and M-CSF, among others. Modified macrophages express receptors for gamma-interferon, FNT-alpha, and IL-1, which are responsible for cellular apoptosis, and this “defense mission” has the purpose of avoiding accumulation of lipoproteins. In studies by Hutter et al<sup>2,3</sup>, a correlation was identified between the density of macrophages, apoptosis, inflammation markers, and tissue factor.

More specifically, the thrombogenic substrate of the plaque, its rheology, and pro-coagulant activity can influence the magnitude and stability of the thrombus, and consequently, the seriousness of the coronary syndrome with a clinical expression that varies from asymptomatic to unstable angina and myocardial infarct.

In the study performed by Venturinelli et al, (Arq Bras Cardiol 2006; 87: 446-50), “Platelet Activation in Distinct Clinical Forms of Coronary Artery Disease (Role of P-Selectin and other Markers in Stable and Unstable Angina)” *Ativação Plaquetária em Formas Clínicas Distintas da Doença Arterial*

*Coronariana (Papel da P-Selectina e de outros Marcadores nas Anginas Estável e Instável)*, P-selectin, thromboxane B2, and serotonin levels were significantly higher in patients with unstable angina when compared to those with stable angina.

Lipid-rich plaques may evolve with multiple clinical expressions, but they are more vulnerable to ruptures, thromboses, and acute coronary syndrome<sup>4</sup>. Exposure to the thrombogenic substrate is the main determining factor for thrombosis; nevertheless, data on thrombogenicity of the atherosclerotic plaque are limited.

Additionally, thrombogenicity is modulated by the tissue factor located in areas rich in macrophages<sup>5,6</sup>. Perhaps residual mural thrombosis has a thrombogenic effect as a result of monocyte / tissue factor activation and thrombin generation<sup>7,8</sup>.

The analysis of tissues removed by atherectomy in patients with unstable angina showed a large quantity of macrophages (cell-mediated thrombogenicity)<sup>9</sup> and tissue factors in the interior of macrophages in apoptosis<sup>10</sup>. These observations document the importance of the tissue factor in thrombosis and open doors for new strategies in preventing and treating coronary artery disease.

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