Usefulness of Mean Platelet Volume as a Biomarker for 6-months Outcomes After elective Percutaneous Coronary Intervention

Thesis

Submitted for Partial Fulfillment of Master Degree in
Cardiology

Presented by

Ahmed Mohamed Soliman Nasr eldin
(M.B., B.Ch.)

Under Supervision of

Prof. Dr. Samir Saleh Wafa
Professor of Cardiology
Faculty of Medicine-Ain Shams University

Dr. Ahmed Fathy Tamara
Assistant Professor of Cardiology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2013

ACKNOWLEDGEMENT

*First and above all my deepest gratitude and thanks to **Allah,** for achieving any work in my life.*

*First of all I have to pay **Prof. Dr. Samir Wafa,** Professor of Cardiology, Faculty of Medicine, special thanks for all his guidance, for his sincere supervision, for his valuable remarks and advice and meticulous revision of this work.*

*I would like also to express my fervent appreciation to **Dr. Ahmed Tamara,** Assistant Professor of Cardiology, Faculty of Medicine, for his sound guidance, gentle teaching, honest criticism and generous support; to whom I owe more than mere thank you can ever tell.*

Very warm thanks to my loving family for supporting me the whole course, to my friends who have been always there for me.

Finally, I wish to thank everyone who kindly contributed in any way with this thesis.

Ahmed Mohamed Soliman Nasr eldin

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Introduction

Atherosclerosis and its complications such as acute myocardial infarction (AMI) are regarded as one of the most important causes of death in industrial societies.[1]

Although there are some known risk factors for coronary artery disease such as age, gender, cigarette smoking, diabetes mellitus, hypercholesterolemia, hypertension, and familial history of AMI[1], the detection of some other factors to determine the true risk of acute coronary syndrome seems necessary.[1]

Since platelets play an important role in forming intra coronary vascular thrombosis, they are considered a principal cause of AMI.[2]

An increase in platelet size is concomitant with a rise in platelet reactivity.[3,4]

The mean platelet volume (MPV) has been associated with clinical and angiographic outcomes, patients with a high MPV before balloon angioplasty have been more likely to develop restenosis.[5]

In patients undergoing primary percutaneous coronary intervention (PCI), a high MPV has been associated with

impaired angiographic reperfusion and increased 6-month mortality.[6]

Unlike more expensive or time consuming methods of assessing platelet function[7], the determination of platelet size by quantification of the MPV, using automated hemograms, is simple and inexpensive.[8]

The biologic rationale linking the MPV to clinical outcomes, along with its universal availability, have made it a promising indirect marker of platelet reactivity in the PCI setting.

Aim of the Work

The present study will investigate the utility of the preprocedural MPV as a biomarker in prognosticating the 6 months outcomes after percutaneous coronary intervention (PCI).

Platelets (Thrombocytes)

Platelets are anucleate discs with a diameter of ~1 to 4 nm. They are derived from megakaryocytes in the bone marrow by release of fragments of megakaryocyte cytoplasm.

The normal platelet number is ~150,000 to 350,000 cells/L.

They have pale blue cytoplasm with reddish-purple granules.

Platelets have different types of granules, designated alpha granules and dense bodies. Platelet granules contain clotting factors, adenosinediphosphate (ADP) and adenosine triphosphate (ATP), calcium, serotonin, and catecholamines; many of these stimulate platelet aggregation and are important in the coagulation cascade.

Platelets have a life span of approximately 10 days. Senescent platelets are removed by the spleen.

Platelets, occasionally called thrombocytes, are involved in hemostasis.

They adhere to tears in the endothelial lining of blood vessels, forming a platelet plug.[9]

Platelet: Structural Anatomy

Simple in appearance, the platelet is functionally complex. The structure-function is best understood by dividing the resting platelet into four anatomically distinct zones.[10]

A) Peripheral zone

The peripherial zone consists of a membrane and its invaginations, which form the open canalicular system. It can be divided into three distinct domains: the exterior coat, the unit membrane, and the submembrane region.

Exterior coat

The exterior coat is 10–20 nm thick glycocalyx and rich in Glycoproteins.[11–14]

They serve as receptors for cell-cell and cell-vessel wall interactions. They are discussed in greater detail within the sections to follow on platelet adhesion and aggregation.

Platelet unit membrane

The platelet unit membrane is similar to other blood cell membranes in several ways: (1) it consists of a lipid bilayer rich in phospholipids; (2) it provides a physiochemical separation between intracellular and extracellular processes; and (3) it

contains anion and cation pumps (i.e. Na+/K+ATPase) critical to the maintenance of transmembrane ionic gradients.

The platelet membrane is an important catalyst for fluid-phase coagulation.[15,16]

Submembrane region

The area beneath the unit membrane is appropriately called the *submembrane region*. It contains a distinct network of microfilaments that are anatomically (and functionally) associated with both membrane glycoproteins and an extensive cytoplasmic filament system.[17,18]

B) Sol-gel zone

The matrix of the cytoplasm is called the *sol-gel zone* and consists of two fiber systems in varying states of polymerization. Just beneath the submembrane region are tightly coiled microtubules that help maintain resting platelet shape.[19] With activation the microtubules constrict into tight rings around centrally clustered organelles. The driving force for this contractile event is actually provided by the cytoplasmic filaments (not the microtubules).

The second set of fibers within the sol-gel zone are the actin microfilaments. In the resting platelet only 30%–40% of

actin is polymerized into filaments.[20]With activation there is an increase in polymerization, with new filaments appearing at the cell periphery and within developing filopedia.[21]

C) Organelle zone

The organelle zone is not, in the purest sense, a distinct zone but contains storage granules, dense bodies, peroxisomes, lysosomes and mitochondria dispersed throughout the cytoplasm. As such this zone is centrally involved with metabolic processes and also acts as a storage site for enzymes, adenine nucleotides, serotonin, calcium, and a wide variety of proteins.

D) Membrane system

The membrane system constitutes the fourth and final zone. The plasma membrane also contains numerous invaginations that course deep within the platelet. Commonly referred to as the *open canalicular system*, these channels provide a large surface area for cellular transport and remain patent (and functionally active) throughout platelet activation, with shape change, and during the release reaction.[22,23]

The dense tubular system represents a second membrane system located within the cell's interior. Derived from parent

cell endoplasmic reticulum, the dense tubular system acts as a storage site for calcium as well as for the enzymes involved in prostaglandin synthesis.[24,25] The two membrane systems are in direct communication with one another, allowing for an exchange of contents.

Platelet: Functional Anatomy

Under normal conditions, platelets circulate freely in blood vessels without interacting with other platelets or the vascular endothelium. In the presence of endothelial damage, whether from vascular injury or rupture of an atherosclerotic plaque, a chain of events is triggered, leading to platelet-rich clot formation. Depending on the initiating event, this may represent normal hemostasis or pathologic vascular thrombosis. The responsible events represent a complex series of biochemical and cellular processes that can be loosely divided into four general categories: adhesion, activation, secretion and aggregation.[26]

Platelet adhesion

Platelets adhere avidly to damaged, disrupted or dysfunctional vascular endothelium. This is especially true in areas of exposed subendothelial collagen and lipid deposits, as found in eroded or ruptured atherosclerotic plaques. Coverage

of the exposed site by platelets is mediated by adhesive proteins that are recognized by specific platelet membrane glycoproteins. These glycoproteins are also critical for cell-cell interactions.

To date nine of the predominant platelet membrane glycoproteins have been characterized.[10–14] The most common nomenclature for identification is based on polyacrylamide gel separation. With increasing sophistication of the gel systems, increasing separation within groups has beenachieved. Most platelet membrane receptors consist of non-covalent complexes of individual glycoproteins. There is considerable functional overlap as several receptors may bind the same ligand and a specific receptor may response to more than one ligand.

The initiating event for adhesion is contact, a process during which an inactivated circulating platelet “stops” and “sticks” to a site of vascular damage.[27] This important event is accomplished by an interaction between the platelet glycoprotein Ib-IX complex and vonWillebrand (vWF), a large protein synthesized by vascular endothelial cells and secreted on both the luminal and subendothelial surfaces. vWF also has functional domains that contribute to the binding of platelets to vessel wall constituents (collagen, microfibrils).[28,29]

Platelet activation

Platelet activation can be triggered by a wide variety of biochemical and mechanical stimuli in addition to platelet adhesion. Many of the biochemical agonists are produced or released by platelets themselves after vessel wall adhesion, initiating a biological feedback loop that amplifies the response to a given stimulus.

Platelet agonists bind surface glycoprotein receptors and stimulate signal transduction across the membrane via messenger proteins (G-coupled) that, in turn, triggers one of two intracellular pathways.

The first one is the phosphoinositide Pathway and the second pathway involves phospholipase A2.

Platelet secretion

Platelet activation, a complex response to extracellular signals, prompts cytoskeleton rearrangements, membrane fusion, exteriorization and secretion (exocytosis) of contents from within three different types of plateletstorage granules: lysosomes, α-granules, and dense bodies. Fusion of α-granules with each other and with deep invaginations of the plasma membrane (the open canalicular system) followed by an "emptying" of contents to the exterior has been demonstrated. [30,31]