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Mini Review | Journal of Clinical Trials in Cardiology | Open Access

The number of red blood cell-derived microparticles in predicting periprocedural adverse effects in acute ST-segment elevation myocardial infarction patients

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Received: December 27, 2016; Accepted: January 02, 2017; Published: January 10, 2017

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Abstract

The role of the circulating number of Red Blood Cell (RBC) Microparticles (MPs) as predictive biomarker in acute myocardial infarction patients after primary Percutaneous Coronary Intervention (PCI) is widely argued. There are commonly used cardiac biomarkers (i.e., troponins, creatine kinase-myocardial band isoenzymes, myoglobin, heart-type fatty acid-binding protein, copeptin and B-type natriuretic peptide), which have now exhibited broad spectrum limitations regarding short-term and long-term-term mortality rates. Recent clinical studies have shown that the number of RBC-MPs has increased in acute myocardial infarction as compared to healthy volunteers and patients with unstable angina, associated with the extent of myocardial damage and have potential adverse vascular and thrombotic effects. It has been suggested that the number of RBC-MPs might be better predictor compared to other cardiac biomarkers in scintigraphically measured infarct size, periprocedural left ventricular ejection fraction and survival rate.

Keywords: Acute Myocardial Infarction; Primary Percutaneous Coronary Intervention; Cardiac Biomarkers; Red Blood Cell Microparticles; Prognosis;

Abbreviations

ATP - Adenosine Tri Phosphate; BNP - Brain Natriuretic Peptide; CFSE - Carboxy Fluorescein Diacetate Succinimidyl Ester CK-MB - Creatine Kinase-Myocardial Band Isoenzyme; EVs - Extracellular Vesicles; ICAM - Intracellular Adhesion Molecule; LVEF - Left Ventricular Ejection Fraction; MPs - Microparticles; PCI - Percutaneous Coronary Intervention; SPRi Microscopy, Nano-Particles- Surface Plasmon Resonance - Based Imaging Microscopy; STEMI, ST - Segment Elevation Myocardial Infarction;VCAM - Vascular Cell Adhesion Molecule;

Introduction

Microvascular obstruction has remained a prognostic importance for short-term and long-term periprocedural survival after acute ST-Segment Elevation Myocardial Infarction (STEMI) [1, 2]. Although there is a large body of evidence regarding utility of biomarkers of cardiac injury in predicting myocardial functional recovery [3-5], the prognostic information of commonly used cardiac biomarkers (i.e., troponins, creatine kinase-myocardial band isoenzymes (CK-MB), and their combinations) regarding mortality rate is still controversial [6-8]. Indeed, troponin I is an highly sensitive marker of myocardial necrosis or even very minor reversible myocardial injury caused by Percutaneous Coronary Intervention (PCI), which did not influence the death rate [9].

However, in the Selective Inhibition of Delta-protein Kinase C for the Reduction of Infarct Size in Acute Myocardial Infarction (PROTECTION-AMI) trial were determined that only baseline left ventricular ejection fraction (LVEF), infarct size and infarct heterogeneity independently predicted 90-day LVEF, though other biomarkers did not [3]. In the EVOLVE (EValuation Of MCC-135 for Left VEntricular Salvage in Acute Myocardial Infarction) trial, elevated troponin T level was associated with increased 180-day composite clinical events and independently predicted several adverse events, but not death [10]. In contrast, Gollop et al [11] reported that an elevation in CK-MB was best predictor of adverse events including death compared with troponins in post-PCI individuals.

Thus, actual findings suggest that cardiac biomarker of injury (i.e. troponins, creatinine kinase MB isoenzyme, and probably myoglobin) might no longer be the optimal early predictors in STEMI patients undergoing primary PCI, while they are able to depict worsening myocardial perfusion, myocardial infarct size, cardiac function and postponed left ventricular remodeling. Moreover, as a prognostic marker, CK-MB isoenzyme measured on admission was superior to cardiac troponin using a high-sensitivity assay, NTpro-Brain Natriuretic Peptide (BNP) measurement on admission, but myoglobin, heart-type fatty acid-binding protein, copeptin and B-type natriuretic peptide were prognostically equivalent [12]. Consequently, to improve predictive approaches based on biomarker measurement in PCI patients, discovery of novel biomarkers maximally attributed solely to each individual after PCI is required.

Formerly cell-derived microparticles (MPs) were determined as cell debris without any diagnostic and predictive information, but now they are considered biomarkers in cardiovascular and metabolic disease including atherosclerosis, unstable angina pectoris, hypertension, heart failure, arrhythmia, thromboembolism, metabolic syndrome, and diabetes, as well as in subjects with implanted cardiac assist devices [11, 13-22]. The aim of the mini review is to discuss possibilities of use of the red blood cell-derived MPs in predicting of PCI-related complications in STEMI patients.

Definition of MPs

MPs are defined a heterogeneous sub-population of Extracellular Vesicles (EVs) with diameter average from 100 to1000 nm originated from plasma membranes of mother' cells. EVs are phospholipid-based endogenously produced particles (30-1000 nm in diameter), which contain cell-specific collections of proteins, glycoproteins, lipids, nucleic acids and other molecules. Abundant cells including cardiomyocites, blood cells, endothelial cells, immune cells, and even tumor cells are capable to secrete MPs of different size and compositions [23].

Depending on their origin EVs are graduated to follow subsets, i.e. the exosomes (30–100 nm in diameter), the microvesicles (50–1000 nm in diameter), ectosomes (100–350 nm in diameter), small-size MPs (<50 nm in diameter) known as membrane particles and apoptotic bodies (1-5 μm in diameter). The exosomes are formed by inward budding of the endosomal membrane and are released on the exocytosis of multivesicular bodies known as late endosomes, whereas the microvesicles are attributed via budding from plasma membranes. However, the exosomes have been predominantly labeled in the case of immune cells (macrophages, T cells, B cells and dendritic cells) and tumor cells. Unlike the exosomes, the ectosomes are ubiquitous microvesicles assembled at and released from the plasma membrane [24].

MPs are released by cellular vesiculation and fission of the membrane of cells [25]. Under normal physiological condition a phospholipid bilayer of plasma membrane of cells represented phosphatidylserine and phosphatidylethanoalamine in inner leaflets, whereas phosphatidylcholine and sphingomyelin represent in the external leaflets. The asymmetrical distribution of phospholipids in the plasma membrane is supported by activity of three major intracellular ATP-dependent enzyme systems, i.e. flippase, floppase, and scramblase. Because aminophospholipids are negatively charged, but phospholipids exhibit neutral charge, the main role of intracellular enzyme systems is supporting electrochemical gradient. Both flippase and floppase belong to family of ATP-dependent phospholipid translocases.

The flippase translocates phosphatidylserine and phosphatidylethanoalamine from the external leaflets to the inner one. The floppase transports phospholipids in the opposite direction. Finally, scramblase being to Ca^{2+}-dependent enzyme system exhibits unspecifically ability of moving of phospholipids between both leaflets of plasma membrane.

Importantly, disappearing of the asymmetrical phospholipid distribution in the bilayer of the cell membrane is considered a clue for vesiculation and forming of MPs. Indeed, both processes of apoptosis or cell activation are required asymmetry in phospholipid distribution that leads to cytoskeleton modifications, membrane budding and MPs release. The mechanisms of vesiculation affect genome and may mediate by some triggers including inflammation [26], while in some cases there is a spontaneous release of MPs from stable cells or due to injury from necrotic cells or from mechanically damaged cells. Particularly, the MPs are released in both constitutive and controlled manners, regulated by intercellular Ca^{2+} and Rab-GTP-ases and activation of μ-calpain. μ-Calpain is a Ca^{2+}-dependent cytosolic enzyme belong to protease, which cleaves talin and α-actin, leading to decreased binding of integrins to the cytoskeleton and a reduction in cell adhesion and integrity. Finally, interaction of the actin and myosin is a main component for cytoskeleton modification that creates a contractile force and drives the formation of membrane MPs.

Recently MPs are considered a cargo for various molecules. Indeed, MPs carry proteins, RNA, micro-RNA, and DNA fragments from their cells of origin to other parts of the body via blood and other body fluids. Within last decade it has become to know that MPs would act as information transfer for target cells. However, the difference between innate mechanisms affected the release of MPs from stable cells, activated cells or apoptotic cells is yet not fully investigated and requires more studies.

The majority (more than 90%) of MPs in healthy controls are of platelet origin, whereas less than 10% originate from granulocytes and less than 5% from endothelial cells, red blood cells and monocytes [27]. Since all types of particles contain surface proteins derived from their cell of origin (including antigen-presenting cells), while there are additional biomarkers confirming origin of the MPs. The key features of several MP populations are reported in Table 1.

Biological role and function of MPs

MPs have great potentiality in material science- based applications [28], while initially they were recognized as cell debris beyond any biological function. Developments of technologies that attenuate recognize, determination, and measurements of MPs obtained from various cells appear to be indispensable tool to clinical medicine [29].

Recent investigations have been shown that MPs are a universal biological system with an adaptive cellular response to endogenous or external physiological or stressful stimuli and a genius means for intercellular, inter-organ and even inter-organism communication. MPs as derivate of cellular membrane are discussed powerful paracrine regulators of target cell functions [30-32]. Indeed, MPs possess a wide spectrum of biological effects on intercellular communication by transferring different molecules (autoantigens, cytokines, mRNA, iRNA, hormones, tissue coagulation factors, and surface receptors) able to modulate other cells affected growth of tissue, reparation, vasculogenesis, inflammation, apoptosis, infection,

Table 1: Key features of MP populations

Types of MPs	Markers	Detection
Derived from resting or activated cells		
Granulocytes	CD24+CD11c– CD66b / CD66acde	Flow cytometry western blotting, mass spectrometry, electron microscopic technique, SPRi microscopy
Monocytes	CD14	
Microphages	CD11b+ CD64+/– Ly6Clo	
Endothelial cells	CD144, CD62E	
T cells	CD4 or CD8	
B cells	CD20	
Dendritic cells	CD1a, CD14, CD141, CD80, CD85, CD86	
ICAM(+) cells	CD54	
VCAM(+)cells	CD106	
Platelets	CD41 and/or CD61	
Erythrocytes	CD235a, CD44, CD47, CD55, CFSE, annexin V and anti-glycophorin A	
Derived from activated or tumor cells	Annexin V binding, CD63, CD81, CD9, LAMP1 and TSG101	Flow cytometry, capture based assays
Derived from apoptotic cells	Annexin V, DNA content, histones	Flow cytometry

Abbreviations: ICAM - Intracellular Adhesion Molecule; VCAM - Vascular Cell Adhesion Molecule; SPRi microscopy; nano-particles-surface plasmon resonance - based imaging microscopy; CFSE – Carboxy Fluorescein Diacetate Succinimidyl Ester;

and malignancy [33-39]. Moreover, RBC-MPs act as NO promoter exerted an erythrocrine function by synthesizing, transporting and releasing NO metabolic products contributing in regulation of vascular tone.

However, MPs are not only cargo for biological active substances. Growing evidence supports the idea that regarding association between immune pattern of MPs originated from different cells (RBCs, endothelial cells, mononuclears, dendritic cells, platelets) and nature evolution of various diseases including CV diseases, cancer, sepsis, eclampsia, autoimmune and metabolic states, etc. [40-33].

RBCs-derived MPs may provide an additional pro-coagulant phospholipid surface enabling the assembly of the clotting enzymes complexes and thrombin generation [44-45]. It has noted the release or recruitment of pro-coagulant MPs at sites of endothelium injury or worsening of integrity through P-selectin pathway could be enhanced or triggered by tissue factor activity [46]. Converging evidences from experimental or clinical data highlight a role for MP harboring tissue factor in the initiation of disseminated intravascular coagulopathy.

The majority investigations have now addressed to the endothelial cell-derived MPs, which are marker of endothelial dysfunction and cardiovascular death [47, 48], while MPs originated from other cells (i.e. red blood cells) have exhibited a relation to severity of atherosclerosis and coronary obstruction [49]. Recent studies have shown that the circulating number of endothelial cell-derived MPs originated from activated or apoptotic cells may be markers with powerful independent predictive value in patients with acute myocardial infarction after PCI, although utility of endothelial cell-derived MP measurement is not strongly determined [50]. However, it has suggested that endothelial cell-derived MP assay could be incorporated into multiple biomarkers strategy based on troponins and creatinine kinase MB isoenzyme measurement to improve risk stratification for cardiovascular events in patients at high risk for cardiac death and cardiovascular events [51].The red blood cell-derived MPs in myocardial infarction.

The number of Red Blood Cell (RBC) MPs has increased in acute myocardial infarction as compared to healthy volunteers and patients with unstable angina and probably associated with the extent of myocardial damage. Wang L et al [52] have reported that the baseline levels of MPs received from peripheral red blood cells were significantly higher in the none-ST elevation myocardial infarction (none-STEMI) patients than in healthy controls. Moreover, after PCI and stent implantation, a remarkable increase of RBC-MPs was observed. Specifically, the peak concentration of RBC-MPs was determined at 18 hours following stent implantation. Authors have pointed that the circulating RBC-MPs might cooperate with other MPs mostly derived from platelets and leukocytes and contribute to markedly shortened coagulation time and sufficiently increasing thrombin and fibrin generation after PCI. In ST elevation myocardial infarction (STEMI) patients treated with primary circulating level of PCI RBC-MPs have exhibited significant approximately double elevation compared to volunteers. Moreover, the concentration of PCI RBC-MPs appears to be strongly positively associated with adverse clinical events in short-term follow-up [53].

There is evidence regarding close relationship between circulating number of RBC-MPs and biochemical infarct size, circulating troponins, associate with microvascular obstruction and reverse of ischemia-induced myocardial dysfunction [53], although the exact pathophysiologic routes for these interactions remain to be uncertain. Probably, the pro-coagulant activity of RBC-MPs seems to provide beneficial intrinsic and extrinsic clotting in patients after primary PCI. Indeed, pro-coagulant thrombotic activity of RBC-MPs and their ability inducing platelet activation and aggregation might explain the role of them in the pathogenesis of periprocedural microvascular obstruction and left ventricular remodeling [54, 55]. Therefore, RBC-MPs are able to activate endothelium in visceral organs and thereby influence vasoconstriction and direct injury of them [56, 57]. In this context, RBC-MPs measured in the peripheral blood may be sensitive markers of the thrombo-occlusive vascular process developing in the coronary arteries of STEMI-patients [58, 59]. Although RBC-MPs have usually not been incorporated into predictive analysis due their small sizes and limited resolution of traditional equipment, their relations to the biomarker of cardiovascular repair and their impact on prognosis after primary PCI in STEMI subjects and probably in non-STEMI patients appears to be plenty promising.

Moving across this issue, it would be suggested that RBC-MPs as a player in the myocardial reperfusion injury might attenuate the benefit of PCI after acute myocardial infarction. Whether RBC-MPs would be potentially useful for risk stratification after primary PCI is not fully clear. Therefore, it is not understood whether RBC-MP count would be prognostically superior to high-sensitivity cardiac troponins, creatinine kinase MB isoenzyme, myoglobin, natriuretic peptides, copeptine, heart-type fatty acid-binding protein, and scintigraphically measured infarct size, which remains a better correlate of 1-year mortality than either biomarkers. However, measurement of circulating RBC-MP number after primary PCI appears to be promising because lack of individualized biomarkers with predictive value regarding survival in subjects with microvascular obstruction remains to be challenged. All these findings require more investigations in future.

Conclusion

There are no strong evidence regarding the advantages of periprocedural use of RBC-MPs compared to widely used biomarkers including high-sensitivity cardiac troponins, creatinine kinase MB isoenzyme during PCI to provide prognostic information about the degree of myocardial injury and risk of morbidity and mortality. However, the need of discovery of novel biomarker with higher predictive value is obvious fact. RBC-MPs could be discussed as attempt to individualize risk stratification amongst acute ST-segment elevation myocardial infarction patients after primary PCI, because other routinely used biomarkers have exhibited some serious limitations. In future more investigations are required to explain in detail the role of the number of RBC-MPs in prediction of survival amongst acute ST-segment elevation myocardial infarction patients after primary PCI.

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