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Soluble adhesion molecules in patients with acute coronary syndrome after percutaneous coronary intervention with drug-coated balloon, drug-eluting stent or bare metal stent

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ABSTRACT

Adhesion molecules play an important role in inflammation, atherosclerosis and coronary artery disease (CAD). These molecules are expressed on the surface of dysfunctional endothelial cells, causing inflammatory cells from the circulation to adhere and migrate through the endothelium. Their expression is upregulated in acute coronary syndrome (ACS) and after percutaneous coronary intervention (PCI). The contact between stent struts and endothelium upregulates endothelial cell gene expression, endothelial cell activation and inflammation. The paclitaxel or sirolimus eluting stents inhibited expression of adhesion molecules in several studies and reduced the incidence of major adverse cardiac events (MACE) after drug-eluting stent (DES) over bare metal stent (BMS) implantation. Therefore, we propose that elevated serum levels of the soluble adhesion molecules after primary PCI in patients treated with BMS or DES implantation versus drug-coated balloon (DCB) application to the vulnerable coronary plaque might be a predictor of MACE and further adverse outcomes. Consequently, DCB-only strategy in patients with ACS might be a superior approach in comparison to BMS implantation and non-inferior approach when compared to DES implantation.

Introduction

Acute coronary syndrome (ACS) encompasses a spectrum of clinical conditions caused by prolonged and severe myocardial ischemia due to acute reduction of blood flow through the coronary arteries [1]. Such conditions include ST-segment elevation ACS or ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS) represented by unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) [2]. Coronary artery disease (CAD) is the most frequent cause of death in the world [3,4]. One of six European men and every seventh European woman die from acute myocardial infarction (AMI) [4]. Approximately every 43 s one American suffers from myocardial infarction [5]. The diagnosis of ACS is based on clinical presentation, electrocardiogram (ECG) and cardiac troponin levels [6]. Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in STEMI and urgent or early invasive strategy (PCI) is also recommended in high-risk NSTE-ACS patients up to 24 h after presentation [7]. Early invasive strategy in NSTE-ACS patients improves long-term survival and reduces long-term rates of recurrent major adverse cardiac events (MACE), with shorter hospital stay [8–10]. New-generation drug-eluting stent (DES) implantation is preferred over bare metal stent (BMS) implantation, lowers the incidence of in-stent restenosis (ISR) [11–13] and stent thrombosis after primary PCI [14]. Stent-related adverse events have led to evaluation of drug-coated balloon (DCB) application as a new therapeutic option for patients with ISR, bifurcation lesions, small vessel disease and high-risk patients undergoing primary PCI [15–20]. Adhesion molecules expressed by endothelial cells mediate adhesion of monocytes and platelets to the coronary artery wall. This process plays an important role in the pathogenesis of CAD and contributes to the progression of atherosclerosis, thrombosis, inflammation and restenosis after PCI [21–23].

Hypothesis

We propose that elevated serum levels of soluble adhesion molecules after primary PCI in patients with BMS implantation versus DCB application might be a predictor of MACE and that DCB application is not inferior to DES implantation in primary

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PCI. We will discuss the role of serum adhesion molecules in atherosclerosis progression, vessel wall inflammation, stable CAD and ACS pathogenesis, as well as after PCI, in order to explain our hypothesis.

Evaluation of the hypothesis

Adhesion molecules in pathophysiology of coronary artery disease

Atherosclerotic lesions are hardenings on the inner layer of arterial intima. Lipids, matrix components, debris and cells (mostly macrophages) are responsible for the various lesions formation [24]. Hypercholesterolemia leads to infiltration of LDL-cholesterol particles in the arterial intima. Retained and modified by oxidation and enzymatic attack in the intimal wall, LDL-cholesterol causes inflammatory response and activation of endothelial cells. Such process often appears in the areas of hemodynamic strain [22]. Molecules that are expressed by activation of endothelial cells and on circulating leukocytes cause adhesion of other inflammatory cells from the circulation to the activated areas and their migration through the endothelium [25]. Leukocyte rolling and tethering on the activated endothelial cells is mediated by selectins P, E, L and selectin ligand PSGL-1 [26]. Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), expressed on the endothelium cells, induce leukocyte arrest and firm adhesion to the endothelium [26]. Further occurrences are mediated by platelet endothelial cellular adhesion molecule-1 (PECAM-1) which induces transmigration of leukocytes into the artery wall [25,26].

P-selectin is stored in the granules of endothelial cells (Wiebel-Palade bodies) and platelets (α granules) [27]. It exists in a preformed pool, so it can be mobilized fast to the cell surface after its activation by histamine, thrombin or leukotrienes. Slow mobilization is transcription dependent and therefore occurs within four hours after cell exposure to cytokines such as IL-1 and TNF-α [28]. As well as E-selectin, it binds PSGL-1, which is expressed by monocytes, neutrophils and lymphocytes [27]. E-selectin is expressed by endothelial cells in both acute and chronic endothelial inflammation [27]. Besides PSGL-1, it binds several other ligands. Since it does not exist in preformed pool, the expression of E-selectin depends of transcription regulation with three hour expression peak [28]. L-Selectin is expressed on most leukocytes and it mediates lymphocyte rolling and secondary capture in leukocyte accumulation by adherent leukocytes [27].

ICAM-1 and VCAM-1 are the members of immunoglobulin superfamily. ICAM-1 is a transmembrane protein that is expressed by endothelial cells upon thrombin, IL-1 or TNF-α activation, with high concentrations up to 24 h after cell stimulation [29]. ICAM-1 is the endothelial ligand for CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) [30]. The upregulation of VCAM-1 expression is also mediated by cytokine activation of endothelial cells, mostly at atherosclerotic prone sites, with peak values after 6–12 h after stimulation [29,31]. VCAM-1 is the endothelial ligand for α4β1 (very late antigen 4 – VLA-4) [30]. P-selectin, ICAM-1 and VCAM-1 are also upregulated by oxidized LDL-cholesterol, while native LDL-cholesterol upregulates ICAM-1 [27].

Adhesion molecules in acute coronary syndrome

There are few studies that have assessed endothelial inflammation at the site of atherosclerotic plaque in human coronary arteries, and the research has been directed towards animal models, pathology specimens and soluble adhesion serum levels [32]. Radecke et al. [32] reported the first study with direct observation of VCAM-1 upregulation on coronary endothelial cells and endothelial microparticles at the site of atherosclerotic plaque. They have concluded that VCAM-1 is 73% more expressed on endothelium of coronary arteries and 79% more expressed on endothelial microparticles in patients with AMI than in patients with stable CAD. Güray et al. [33] reported that VCAM-1 serum levels were significantly higher in patients with AMI and UA compared to stable CAD patients or healthy controls. Levels of ICAM-1 were similar among AMI, UA and stable CAD groups, but significantly higher than in healthy controls. Levels of E-selectin were significantly higher in ACS group when compared to stable CAD, and similar was the case with P-selectin. They concluded that VCAM-1, P-selectin and E-selectin serum levels might detect plaque destabilization in ACS [33]. Xie et al. [34] also reported higher ICAM-1, VCAM-1, E-selectin serum levels in patients with ACS than in healthy controls, as well as Postadzhiyan et al. [35]. Blankenberg et al. performed a research on 1246 patients and concluded that serum levels of ICAM-1, VCAM-1 and E-selectin predicted the risk of cardiovascular death in patients with CAD. VCAM-1 serum levels were especially related to 2.8-fold risk increase [36]. E and P selectin mediated PSGL-1 plays an important role in plaque rupture and thrombus formation [37], while level of ICAM-1 expression was reported highest 12 h after STEMI [38].

Adhesion molecules after BMS implantation, DES implantation and DCB application

Stent deployment provokes continuous inflammatory response within coronary artery wall. The contact between stainless steel and endothelium upregulates endothelial cell gene expression, endothelial cell activation and inflammation [39]. Punchard et al. [40] found increased expression of ICAM-1, VCAM-1 and E-selectin encoding genes after stent deployment *in vitro* in coronary model artery. Shimizu et al. [41] performed an immunohistochemical analysis using ICAM-1 and VCAM-1 in coronary artery of a pig after BMS implantation and reported higher and more persistent expression of ICAM-1 and VCAM-1 after stent implantation than after balloon angioplasty, which favours restenosis after stent implantation.

Several studies evaluated serum adhesion molecules in patients after BMS implantation [42–44]. Bayata et al. [42] measured VCAM-1 and ICAM-1 serum levels and found that there was no difference in VCAM-1 levels in patients before and after stent implantation. However, a significant difference was found in patients with restenosis in comparison to baseline levels. ICAM-1 levels did not show significant difference. Wexberg et al. [43] reported increased VCAM-1 levels after stent implantation.

Application of DCB provides local drug delivery to the affected segment of the artery wall. Potential benefits over drug eluting stents are the lack of chronic inflammatory response and subsequent restenosis or thrombosis. DCB has no remaining polymer at the site of application and drug is homogenously spread to the vessel wall [45]. The delivery of drug with DCB is faster and local quantity is significantly higher than with DES implantation, since DES covers only 20% of application site [46]. Paclitaxel and several limus family drugs are drugs of choice in DCBs. Paclitaxel is a mitotic inhibitor which prevents neointimal hyperplasia, promoting rapid recovery at the application site [47]. Because of its antiproliferative effect, sirolimus has also been used for stent coating. Voisard et al. [48] evaluated sirolimus effects in *in vitro*/*ex vivo* human models and reported decreased expression of ICAM-1 in human coronary artery endothelial cells, while Rosa et al. [49] concluded that discontinuation of oral sirolimus after coronary stenting causes increase in P-selectin levels. To our best knowledge, no clinical study of serum adhesion molecules in patients treated with DCB have been performed. However, several studies evaluated serum adhesion molecules after DES implantation [50–56]. When