

## Markers of endothelial dysfunction after cardiac surgery: soluble forms of vascular-1 and intercellular-1 adhesion molecules

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**Key words:** endothelial dysfunction; adhesion molecules; inflammation; cardiac surgery.

**Summary.** Endothelium forms an inner layer of vascular wall. It plays an important role in inflammatory process, regulation of vascular tone, and synthesis of thromboregulatory substances.

Leukocyte and endothelium interactions during inflammation are regulated by different families of adhesion molecules. Increased levels of soluble forms of adhesion molecules have been detected in the circulating blood in conditions such as autoimmune diseases, transplant rejection, ischemia-reperfusion injury in addition to neutrophil- and endothelial membrane-bound forms reflecting the level of endothelial dysfunction.

It is known that endothelial dysfunction is a risk factor for ischemic events such as stroke, myocardial infarction, unstable angina pectoris, ventricle fibrillation, necessity of revascularisation procedures, and death from cardiovascular reasons. Clinical studies showed that cardiac surgery has an impact on vascular endothelial function as well. The amount of endothelium-derived soluble forms of vascular-1 and intercellular-1 adhesion molecules increases after cardiopulmonary bypass suggesting endothelial dysfunction. However, further investigations are needed to be done to support the evidence that endothelial dysfunction proceeding heart surgery is one of the reasons of tissue ischemia-reperfusion injury.

### Adhesion molecules

Three structural families of adhesion molecules up to date have been described to be responsible for the leukocyte adhesion, penetration of the vessel wall, and transendothelial migration into the tissue. The immunoglobulin superfamily largely is found on endothelium consisting of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Afterwards, we will concentrate on this family in our review article. Macrophage-1 antigen (MAC-1) and lymphocyte function-associated antigen-1 (LFA-1) are integrins located on polymorphonuclear leukocytes. The third family is called selectins that includes endothelial leukocyte adhesion molecule (E-selectin) found on endothelium, leukocyte endothelial cell adhesion molecule (L-selectin) located on polymorphonuclear leukocytes, monocytes, and some lymphocytes, and granule membrane protein 140 (P-selectin) located on endothelial cells and platelets (1, 2). Soluble forms of adhesion molecules have been detected in the circulating blood in various conditions in addition to neutrophil- and endothelial membrane-

bound adhesion molecules reflecting endothelial activation and damage (3–5). An increase in the levels of soluble forms of VCAM-1 and ICAM-1 results either from increased expression in activated endothelial cells or increased proteolytic cleavage of endothelium-bound forms secondary to endothelial cell injury (6).

Adhesion molecules have been shown to play an important role in the pathogenesis of tissue injury from atherogenesis, autoimmune diseases, transplant rejection, and ischemia-reperfusion injury.

Mediators that stimulate the synthesis of adhesion molecules are histamine, oxygen-derived free radicals, thrombin, platelet-activating factor, activated complement fragments, endothelin, endotoxin, and tumor necrosis factor- $\alpha$ .

ICAM-1 and VCAM-1 seem to be of particular importance for attachment and transendothelial migration of leukocytes (1). ICAM-1 binds to leukocyte integrin LFA-1, and VCAM-1 binds to very late antigen-4 (VLA-4) (7, 8). VCAM-1 expression peaks after 6 to 10 hours of cytokine stimulation and remains ele-

vated for days. The peak of ICAM-1 expression occurs after 12 hours following cytokine stimulation.

### Biochemical markers of endothelial function

Endothelial cells form an inner layer of vascular wall that acts as a barrier of transport of water, electrolytes, and molecules (amino acids, glucose, albumin, lipids, etc.) from the blood to the surrounding tissues. Besides barrier function, endothelium releases vasoactive (vasodilators – nitric oxide, prostacyclin, endothelium-derived hyperpolarizing factor, bradykinin and vasoconstrictors – endothelin-1, angiotensin-1) and thromboregulatory substances that take part in inflammatory process (9–11).

Endothelium cells are source of hemostatic regulatory molecules such as von Willebrand factor (vWF), tissue factor pathway inhibitor (TFPI), and thrombomodulin (TM). vWF participates in platelet adhesion and plays a role in thrombus formation (12). TFPI is the main physiological inhibitor of tissue factor (TF)-induced coagulation. The free form of TFPI (f-TFPI) in plasma reflects the level of endothelial cell-associated TFPI and has potent anticoagulant activity (13). TM is an endothelial cell surface receptor for thrombin that functions as an anticoagulant by accelerating thrombin-induced activation of protein C. A soluble form of TM circulates in plasma (14). During endothelial damage, plasma levels of these molecules have been shown to increase suggesting that they could be reliable markers of endothelial dysfunction (15–17). The Prospective Epidemiological Study of Myocardial Infarction (PRIME) found that vWF and f-TFPI plasma levels were independent risk factors for myocardial infarction and angina pectoris in healthy men (18).

Inflammatory process is caused by the initial injury resulting from tissue ischemia, stimulation of phagocytes, and interactions with endothelial cells (19). Accumulation of leukocytes in tissue appears to be essential for effective host defence in repair and healing processes (20). Under physiological conditions, endothelium prevents leukocyte migration into the vessel wall. Interactions of leukocytes and the endothelium are regulated by different families of adhesion molecules inducing contact with the endothelium followed by firm adhesion where integrins and immunoglobulins play an important role (1, 21, 22). Neutrophils roll along the endothelium, adhere to it, and subsequently release superoxide radicals, proteolytic enzymes, cytokines that initiate endothelial abnormalities and cause tissue damage (23). After neutrophils are attached, they migrate transendothelially and further contribute to inflammation. This complex process

is initiated and maintained by interactions of circulating leukocytes and endothelium via cell- and organ-specific adhesion molecules (1).

Imbalance between endothelium-derived vasodilators and vasoconstrictors, abnormal inflammatory cell-endothelial interactions, and increased expression of adhesion molecules are referred to endothelial dysfunction. That is known to be a risk factor for various ischemic events such as stroke, myocardial infarction, unstable angina pectoris, ventricle fibrillation, necessity of revascularisation procedures, and death from cardiovascular reasons (24–26).

### Adhesion molecules in cardiac surgery

Heart surgery is an aggressive procedure that has an impact on vascular endothelium. The majority of surgical procedures are still performed using artificial circulation. Blood contact with extracorporeal circuit, ischemia/reperfusion injury, increased endotoxin permeability from the gut, and surgical trauma are associated with the activation of complement system, increased plasma levels of circulating adhesion molecules and polymorphonuclear leukocytes. It leads to the development of systemic inflammatory response syndrome and organ dysfunction (27–32). Increased levels of soluble adhesion molecules is a result of higher expression on the endothelial surface or increased proteolytic cleavage of endothelium-bound forms secondary to endothelial cell damage (5).

Only patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) and not those having the major abdominal or pulmonary surgery showed an elevation of P-selectin, sVCAM-1, and sICAM-1 levels 2 and 5 hours after cardiac surgery (33). Blume et al. showed that infants and children undergoing cardiac surgery with CPB with longer pump time had higher levels of soluble adhesion molecules (34). We also measured sICAM-1 and sVCAM-1 concentrations in serum of the blood perioperatively in 42 patients undergoing on-pump coronary artery bypass grafting (CABG) surgery. Levels of both adhesion molecules increased after surgery compared to preoperative values suggesting the impact of coronary artery bypass surgery with CPB on endothelial function. Concentration of sICAM-1 raised from 201 (146–336) to 268 (215–375) ng/mL ( $P=0.022$ ), and level of sVCAM-1 increased from 1003.5 (709.5–211) to 1638.2 (1268.25–2094.125) ng/mL ( $P=0.023$ ) (35).

Not only cardiopulmonary bypass itself but also blood temperature during artificial circulation has an impact on endothelial function. Grünenfelder et al. in the prospectively controlled randomized study analyz-

ed the effect of CPB temperature on the dynamics of sICAM-1 in 50 patients undergoing elective coronary artery bypass grafting using normothermic or hypothermic CPB. sICAM-1 level was measured before surgery and 24 hours, 36 hours, 48 hours, and 6 days after surgery. All patients had significantly increased levels of sICAM-1 postoperatively as compared to preoperative levels; however, higher levels of sICAM-1 were determined in those patients who underwent hypothermic CPB. Postoperative course showed no significant difference in morbidity and mortality rates. Intubation time, infection rate, length of intensive care unit (ICU) and hospital stay did not reach statistical significance comparing both groups. Age, gender, and artificial circulation or aorta cross-clamp time showed no correlation with adhesion molecule levels (36). CABG surgery without extracorporeal circulation is associated with the lower activation of endothelium as compared to on-pump procedures. Wei et al. investigated the changes in the levels of soluble adhesion molecules perioperatively (sICAM-1, sP-selectin, and sE-selectin) in patients undergoing CABG surgery with or without CPB. After cardiac surgery, sP-selectin and sICAM-1 levels increased in both groups of patients being higher in the on-pump group (37).

There are numbers of studies demonstrating the impact of modulation of synthesis of adhesion molecules on different organ function after ischemia-reperfusion injury. Appleyard and Cohn using a sheep model showed that myocardial stunning that occurs following ischemia and reperfusion of the heart can be diminished by blocking neutrophil-endothelial cell interaction with monoclonal antibodies against CD18 or ICAM-1 receptors (38). Continuous perfusion of pulmonary arteries in infants with congenital heart defects undergoing surgery with CPB has been shown to preserve lung function and to decrease concentration of sICAM-1 postoperatively (39). Chello et al. found that patients treated with simvastatin before CABG surgery had significantly lower levels of sICAM-1 postoperatively compared to control group (40).

#### **Adhesion molecules and organ damage**

Increased levels of adhesion molecules are determined in those patients who suffer from organ damage. Higher expression of myocardial ICAM-1 (in atrial myocytes and vascular endothelium) has been demonstrated by Kilbridge et al. in pediatric patients undergoing CPB (41). The role of ICAM-1 induction in neutrophil-mediated myocardial damage after car-

diopulmonary bypass was demonstrated by Entman and colleagues (42). Boldt et al. found that critically ill patients suffering from trauma or postoperative complications had elevated levels of soluble VAM-1 and ICAM-1 during admission to the ICU. Significantly higher sICAM-1 concentrations were found in nonsurvivors compared to survivors already at admission to the ICU. None of hemodynamic or laboratory parameters correlated with the time course of adhesion molecules, except for PaO<sub>2</sub>/FiO<sub>2</sub> ratio that was negatively correlated with plasma levels of sICAM-1 and sVCAM-1 in nonsurvivors (43). Cowley et al. found elevated plasma levels of soluble adhesion molecules in patients with systemic inflammatory response syndrome and organ dysfunction (44). A significantly increased level of L-selectin was measured in plasma by Donnelly et al. in patients with the progression of adult respiratory distress syndrome (45).

Low cardiac output syndrome is one of the most common causes of postoperative mortality after heart surgery. It is not only a consequence of preoperatively impaired ventricle function but also a myocardial damage following ischemia/reperfusion injury. In cases of angina pectoris, acute myocardial infarction, or ischemia/reperfusion during CPB, patient's plasma contains a variety of stimuli capable for the activation of polymorphonuclear neutrophils (PMNs) and endothelial cells (46–48). It causes adhesion of PMNs to vascular endothelium leading to coronary capillary plugging, reduction in coronary flow, and myocardial infarction. Activated PMNs are the source of free oxygen radicals that also damage myocardial cell membranes (49). Following stimulation, endothelial cells start to produce more adhesion molecules that may be shed from their surface to circulating blood and detected there in soluble forms. The plasma levels of adhesion molecules indicate the intensity of endothelial activation during reperfusion of ischemic myocardium (48).

Soluble ICAM-1 and VCAM-1 are well-known markers of endothelial cell activation that occurs during CABG surgery with extracorporeal circulation (50). Administration of antibodies that block the function of adhesion molecules attenuates PMN-mediated tissue destruction during on-pump CABG surgery (47). Kalawski et al. found increased levels of sICAM-1 and sVCAM-1 in patients after ischemia-reperfusion injury following on-pump CABG. However, concentrations of both adhesion molecules were higher in those patients who received cold crystalloid cardioplegia compared to cold blood cardioplegia (51). The results support the possible superior cytoprotective effect of blood cardioplegia in coronary bypass surgery.

Boldt et al. measured sICAM-1 and sVCAM-1 levels in 15 children and the same number of adults scheduled for CABG surgery before and after cardiopulmonary bypass, at the end of surgery, on the first and second postoperative days. Plasma levels of soluble adhesion molecules before cardiopulmonary bypass were significantly higher in pediatric compared to adult patients and inversely correlated with oxygenation index ( $\text{PaO}_2/\text{FiO}_2$ ). However, no significant correlations between plasma levels of sICAM-1 or sVCAM-1 and other clinical and laboratory data were seen (52). Microcirculatory abnormalities, release of proteinases from white blood cells, activation of the complement, coagulation system, or platelets may contribute to an increased expression of membrane-bound adhesion molecules and the release of soluble forms into circulating blood. Preferential expression of adhesion molecules, leukocyte adhesion and emigration take place in venules where the shear rates are lower compared to arteries (53). Hypoxia and low flow states are important stimuli for activating the inflammatory cascade (54). The reduced plasma levels of sICAM-1 and sVCAM-1 during and after CPB in children may reflect improved circulation and tissue oxygenation after correction of congenital heart defects (52).

Wei et al. found that sICAM-1 concentration in plasma was significantly higher in patients with necessity of norepinephrine infusion in the ICU after CABG surgery. Nevertheless, levels of sICAM-1 did

not correlate with the duration of bypass, aortic cross-clamping, or creatinine kinase-MB concentration (55). Patients with postoperative respiratory insufficiency had a significantly higher level of sICAM-1 and white blood cell count compared to patients with uneventful postoperative course after CABG (56).

### Conclusions

Duration of cardiopulmonary bypass, aortic cross-clamp time, and bypass temperature are factors that activate the endothelial cells and influence the production of adhesion molecules. Increased levels of soluble forms of endothelium-derived adhesion molecules may represent increased synthesis, the rate of cleavage from the surface, or reduced their clearance. The data concerning long-term detrimental effects of elevated adhesion molecules are scarce.

Various drugs have been used to inhibit the migration of leukocytes through the endothelial level in order to diminish the inflammatory response induced by cardiopulmonary bypass and to prevent the tissue ischemia/reperfusion injury (57, 58). In particular, salicylates, complement receptor- and adhesion molecule-blocking agents, were used for this purpose. Further controlled studies, confirming that blockade of adhesion receptors by monoclonal antibodies may limit tissue destruction in inflammatory disease, or prevention of the elevation of circulating adhesion molecules may be associated with improved organ function, e.g. pulmonary function, or even outcome, are needed.

## Endotelio disfunkcijos žymenys po širdies operacijų: tirpios kraujagyslių-1 ir tarpląstelinės sąveikos-1 adhezijos molekulės

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**Raktažodžiai:** endotelio disfunkcija, adhezijos molekulės, uždegimas, širdies operacija.

**Santrauka.** Endotelio ląstelės sudaro vidinį kraujagyslių sluoksnį. Jos dalyvauja formuojantis uždegimui, kraujagyslių tonuso reguliacijos procese bei vykstant kraujo krešėjimo sistemos faktorių sintetinimui.

Leukocitų ir endotelio sąveika uždegimo metu sąlygota skirtingų adhezijos molekulių rūšių. Sergant autoimuninėmis ligomis, atsiradus transplantanto atmetimo reakcijai, išemiam/reperfuziniam audinių pažeidimui, greta adhezijos molekulių, susijungusių su neutrofilais ir endotelio ląstelėmis, aptinkama tirpių šių molekulių formų. Kraujyje cirkuliuojančios adhezijos molekulės naudojamos kaip biocheminiai endotelio disfunkcijos žymenys.

Klinikiniais tyrimais įrodyta, kad endotelio disfunkcija yra tokių išeminių įvykių kaip išeminis insultas, miokardo infarktas, nestabili krūtinės angina, skilvelių virpėjimas, poreikio revaskulizacijos procedūroms bei staigios mirties nuo širdies ir kraujagyslių sistemos patologijos rizikos veiksnys. Širdies operacija su dirbtine



kraujo apytaka taip pat turi įtakos kraujagyslių endotelio funkcijai. Po širdies operacijų nustatytas padidėjęs kiekis endotelio sintetinamų tirpių kraujagyslių-1 ir tarpląstelinės sąveikos-1 adhezijos molekulių. Tačiau būtini tolesni klinikiniai tyrinėjimai, norint įrodyti, kad endotelio disfunkcija po kardiochirurginės operacijos su dirbtine kraujo apytaka yra viena iš audinių išeminio/reperfuzinio pažeidimo priežasčių.

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