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Interaction between the endothelium and blood cells in acute coronary syndromes

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The introduction of reperfusion strategy in acute coronary syndromes has brought about several new issues. Among others, it has been appreciated that achieving patency of the occluded epicardial vessel may not be sufficient to ensure adequate myocardial perfusion, since significant impairment to flow may occur at the microvascular level. In fact, reperfusion is accompanied by a progressive impairment of blood flow after initial restoration of adequate perfusion, and this phenomenon has thus been termed "no-reflow"[1]. Microvascular obstruction is mostly secondary to the "inflammatory" reaction induced in tissues by the postischemic reflow, that results in trapping of neutrophils in the microvasculature, impaired vasodilation, and intravascular activation of platelet aggregation and of coagulation pathway[1,2].

Neutrophils are large, stiff cells that normally pass through capillaries because the pressure gradient exceeds the adhesive forces[3]. During postischemic reperfusion, reduced perfusion pressure and increased neutrophil adhesiveness to the vessel wall favor cell plugging and vascular obstruction. Several mechanisms contribute to alter vasodilating reserve during postischemic reperfusion[4,5]. First, the presence of a residual coronary stenosis after reperfusion may limit coronary flow reserve. In addition, vasodilation may be impaired by reduced generation of nitric oxide and prostacyclin, while enhanced endothelin formation and damage to vascular β-adrenergic receptors increase vasoconstriction[4]. Reduced nitric oxide production not only impairs vasodilating reserve, but it also stimulates neutrophil and platelet aggregation[5,6].

At the same time, other mechanisms promote neutrophil activation and adhesion to the vessel wall. Postischemic reperfusion induces cytokine production by the endothelium[7,8]; these molecules can in turn activate neutrophils and the endothelium, with exposure of adhesion molecules on cell surface and increased adherence of these cells to the vessel wall[8,9]. Adhesion molecules can also be exposed on the surface of cardiac myocytes[2]. Neutrophil activation is also increased by reduced nitric oxide concentrations[5,6] and increased release of activating mediators, such as the platelet-activating factor, leukotrienes, and complement factors[2]. Activated neutrophils adhere tightly to capillary endothelium, thus mechanically blocking flow. In addition, activated neutrophils and platelets may release vasoconstricting and proinflammatory mediators, further worsening microvascular perfusion[2].

More recently, it has been appreciated that other pathways may also be involved in the pathogenesis of no-reflow in postischemic hearts. First, cardiac release of angiotensin II may contribute to impair tissue microvascular perfusion during reflow, since this molecule is not only a potent vasoconstrictor, but it might also promote neutrophil recruitment and activation[10-12]. Secondly, cardiac mast cells degranulate during myocardial ischemia, releasing preformed mediators, such as histamine and tumor necrosis factor-α, that may play an important role in initiating cytokine release, adhesion molecule exposure and neutrophil recruitment[13]. Finally, the extent of the no-reflow may also be reduced by removal of oxygen radicals, thus suggesting that these molecules are also involved in the pathogenesis of the no-reflow[14]. It is not clear through which mechanisms oxygen radicals may influence the no-reflow; however, in addition to their toxic effects, they

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may also induce various alterations of cell function which favor vasoconstriction, neutrophil activation and release of proinflammatory mediators[6,15,16]. Taken together, these various mechanisms integrate to induce neutrophil plugging in the microvasculature, and vascular obstruction in postischemic tissues.

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