Vascular smooth muscle cell microparticles and coronary no-reflow: another piece of the puzzle?

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Coronary no-reflow is a rare but potentially devastating complication that can occur during percutaneous coronary interventions (PCI). It is defined as the lack of passage of contrast dye into the microvasculature despite relief of the original obstruction in the epicardial vessel and is an angiographic marker of impaired myocardial perfusion at the tissue level (1). Clinically, no-reflow is generally associated with profound ischemia and confers a 10-fold increased risk of complications including ventricular arrhythmias, heart failure, left ventricular systolic dysfunction and death (2). No-reflow occurs in 0.6–3% of PCI cases, with an increased incidence seen in acute myocardial infarction (MI) patients, in patients undergoing saphenous vein graft interventions, and in rotational atherectomy cases (3).

There are two types of no-reflow that have been labeled structural and functional. Structural no-reflow is defined as irreversible changes in microvessels within necrotic myocardium; this form of no-reflow is marked by poor coronary flow throughout the procedure, is irreversible and associated with large myocardial infarctions. Functional no-reflow in contrast, is generally associated with abrupt deterioration in flow immediately following balloon angioplasty or intracoronary stent placement and is caused by compromise of the patency of anatomically intact microvessels due to spasm and/or embolization. Embolic debris can include foam-shaped macrophages, aggregated platelets, cholesterol crystals and thrombi (4). Treatment of no-reflow generally involves intracoronary boluses of vasodilators; but while several agents have been shown to improve flow in small studies, beneficial effects on clinical outcomes are inconsistent (1).

In this issue of Thrombosis and Haemostasis, Essayagh and colleagues describe a mechanism that may potentially contribute to the no-reflow phenomenon (5). Microparticles, derived from smooth muscle cells (SMC) made apoptotic by addition of Fasligand, dose-dependently inhibited acetylcholine-induced vasorelaxation of rings of descending mouse aorta maintained in organ culture. Utilizing an SV40 transformed endothelial cell line, these investigators showed that SMC-derived microparticles were able to bind to cultured endothelial cells and inhibited bradykinin-induced nitric oxide (NO) production and release. This effect was redox sensitive and abrogated when microparticles were pretreated by trypsin. The β3 integrin antagonists abciximab and eptifibatide blocked the inhibitory effects of microparticles on acetylcholine-induced vasorelaxation and eptifibatide inhibited microparticle binding to endothelial cells and blunted the inhibitory effect of microparticles on bradykinin-induced NO release (abciximab was not studied in these experiments because it caused detachment of endothelial cells).

In addition to suggesting a novel mechanism that could contribute to impaired coronary perfusion following PCI, these results add to the evidence that β3 integrin antagonists influence microparticle formation and effects. Previous studies have shown that formation of microparticles from either tissue factor- or shear-activated platelets was inhibited by abciximab (6, 7) and levels of microparticles in peripheral blood were reduced by abciximab at day one and day six in patients with acute MI patients treated with primary PCI (8). Interestingly, eptifibatide had minimal effect on microparticles in this non-randomized study.

There is also evidence that abciximab may limit endothelial dysfunction in patients undergoing PCI, although effects of abciximab on no-reflow are controversial (there are few data on the effects of eptifibatide on endothelial dysfunction or no-reflow). In a study of 48 patients undergoing stent placement, Aymong et al (9) found that acetylcholine-mediated increases in coronary blood flow, were blunted following coronary stenting and this effect was eliminated by treatment with abciximab. The effect of abciximab was specific for acetylcholine-induced blood flow as abciximab had no effect on peak flow or percent change in flow in response to adenosine; these data suggest that the beneficial effects of abciximab on coronary flow are mediated by improving microvasculature endothelial function. Unfortunately, effects of abciximab on no-reflow and myocardial perfusion have been inconsistent. Early studies suggested that there was a de-

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creased incidence of no-reflow and improved myocardial perfusion in patients treated with abciximab. More recently, however, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, a multicenter study of 2,082 patients with ST-elevation MI, found no difference in the incidence of angiographic no-reflow and no improvement in tissue-level perfusion (measured using myocardial blush grade) in patients who received abciximab compared to those who did not (10). Caution must be used in interpreting these results, as patients randomized to the group not treated with abciximab were allowed to receive ‘bail-out’ abciximab if slow coronary blood flow or no-reflow developed during the PCI.

The results of Essayeghe et al (5) are interesting but the significance of their study cannot be fully appreciated until several questions are answered regarding the role of SMC-derived microparticles in vivo. While levels of platelet-derived and endothelial-derived microparticles are elevated in acute coronary syndromes (11), studies on SMC-derived microparticles have only been performed utilizing in vitro systems (12, 13). Important questions remain to be answered including whether PCI elicits the release of SMC-derived microparticles, whether SMC-derived microparticles in vivo resemble microparticles released by Fas-ligand activated cultured cells and whether SMC-derived microparticles reach, bind to, and have effects on, the microvasculature endothelium.

Myocardial tissue perfusion following PCI occurs on a variable spectrum, and while angiographic no-reflow is a rare complication during PCI for acute MI, impaired myocardial perfusion is not. In the CADILLAC trial, myocardial blush grade at the end of the procedure, after the occlusion had been successfully treated, was normal in only 17.4% of subjects whereas 33.9% and 48.7% had moderately or severely reduced myocardial perfusion, respectively. The one-year mortality rate correlated with myocardial perfusion was 1.4%, 4.1%, and 6.2%, respectively, in the three groups. An increased understanding of factors that influence, and the development of agents that improve, myocardial perfusion will represent a significant advance in the treatment of patients with acute MI.

References