EDITORIAL COMMENT

Glycoprotein IIb/IIIa Inhibitors and No-Reflow*

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DEFINITION AND BIOLOGY OF NO-REFLOW

The no-reflow phenomenon is the inability to perfuse a portion of the myocardium after re-establishment of patency of a previously occluded epicardial coronary artery (1–3). This phenomenon has been described in experimental animal models in which the coronary artery is occluded with a mechanical occluder or snare (1). In animal models no-reflow has been detected by using the fluorescent dye Thioflavin S that stains endothelium receiving flow, radioactive microspheres, carbon black, echocardiographic contrast, and magnetic resonance imaging (MRI) techniques.

The phenomenon also has been observed in humans after reperfusion therapy for acute myocardial infarction (MI) in which the occlusion is thrombus mediated, and it has been measured using myocardial contrast echocardiography, nuclear tracers, and MRI (4–6). Perfusion at the tissue level can be severely compromised even when the epicardial coronary artery appears to be fully patent by coronary angiography.

In previous experimental studies we observed the development of the no-reflow phenomenon when the proximal coronary artery was occluded for 90 min or 3 hrs but not 40 min, followed by reperfusion therapy (1). In our models the zone of no-reflow is usually confined to areas of necrotic myocardium (1,2,7–9). There is a tight coupling between infarct size and no-reflow. Outside the zone of no-reflow, there may be an area that is necrotic but that contains an infarct that can be reperfused. Although there is ongoing discussion whether reducing no-reflow can then reduce infarct size, in most of our analyses, myocardial cell death occurs before the disruption of the microvasculature. Thus, in our opinion, no-reflow probably does not exacerbate myocardial cell death but occurs after the myocytes in the area are already dead. This does not mean that no-reflow should be ignored. A large zone of no-reflow may impede the ability of the infarct to heal and prevent delivery of pharmaceutical agents (such as anti-arrhythmics) into the infarct zone. Recently, we observed that a large area of no-reflow predicts worse infarct expansion and left ventricular (LV) dilation (Reffelmann T, Hale SL, Dow JS, Kloner RA, submitted for publication). In humans, the no-reflow phenomenon predicts worse outcome in the post-MI patient (5,10).

In this issue of the Journal, Kunichika et al. (11) clearly show that quantitative myocardial contrast echocardiography (QMCE) is a useful non-invasive tool for measuring myocardial perfusion and diagnosing and quantitating no-reflow in real time. Myocardial blood flow velocity is measured by the rapid destruction of echo contrast microbubbles using ultrasound and then determining the rate at which they refill the myocardium. Findings with QMCE paralleled their measures of regional myocardial blood flow made with fluorescent microspheres. The beauty of the echo contrast technique is that it can be used repeatedly to measure the success (or failure) of myocardial perfusion by a non-invasive technique. It can be used to track perfusion over time, measuring the ability of pharmacologic therapy to affect perfusion of the tissue.

THERAPY FOR NO-REFLOW

A reduction in the size of the anatomic zone of no-reflow might limit infarct expansion, enhance healing, and reduce long-term LV dilation. In our models, any agent that reduces MI size will secondarily reduce no-reflow. We have observed this coupling with agents such as cariporide, preconditioning (12), and hypothermia (13). We have not observed any benefit of thrombolytic agents on infarct size or no-reflow in a mechanical (non-thrombotic) model of coronary artery occlusion. In the present study by Kunichika et al. (11), a fascinating observation was made. Tirofiban, a platelet glycoprotein (GP) IIb/IIIa inhibitor, reduced infarct size and no-reflow in a non-thrombotic coronary occlusion model in the dog. Previous studies in patients with thrombotic coronary occlusions have shown that GP IIb/IIIa inhibitors can enhance reperfusion as would be expected in the setting of a thrombus. GP IIb/IIIa inhibitors were shown to decrease coronary thrombus, improve TIMI flow grade, enhance epicardial reperfusion when combined with thrombolysis, improve 30-day clinical outcomes post MI, speed resolution of ST-segment elevation, and in one study of elective percutaneous coronary intervention improve coronary artery flow reserve and myocardial blush grade. The later two findings support improved microvascular reperfusion (14–17). Kunichika et al.’s (11) observation has an important implication related to the role of platelets in no-reflow. No-reflow in the setting of a thrombotic occlusion may be related in part to microemboli, and platelet aggregates could play a significant role (18). However, the exact cause of no-reflow in a non-

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thrombotic model has remained difficult to trace definitively. Within the zone of no-reflow, discrete ultrastructural abnormalities are observed, suggesting anatomic damage to the microvasculature (Fig. 1). Diffuse and regional endothelial swelling with bleb-like structures appear to occlude the capillaries. Endothelial gaps, fibrin tactoids, rouleaux formation, neutrophil plugging, and compression of capillaries from adjacent swollen myocytes have been identified (1–3). Spasm of the microvasculature at the pre-capillary level also has been implicated (19). However, in our studies of mechanical non-thrombotic occlusion of the coronary artery, ultrastructural identification of platelet or platelet plugs within the microvasculature was an extremely rare finding (1). In the present study, the authors also indicated to me that on histologic analysis they did not observe platelet plugging of the microvasculature either in control or treated animals. If this is the case, then why should a GP IIb/IIIa inhibitor work? One explanation is that inhibition of platelet activation prevents or reduces the release of injurious vasoactive and chemotactic mediators from platelets that may exacerbate tissue injury (11). For example, inhibition of chemotactic mediators might prevent neutrophils from entering the area, thereby reducing damage due to neutrophil-mediated oxygen free-radical release. Of note, in one previous study from our laboratory, Przyklenk et al. (20) showed that oxygen free-radical scavengers given at the time of reperfusion reduced no-reflow as assessed by radioactive microspheres. Inhibiting platelet release of vasoactive mediators theoretically could reduce microvascular spasm, although recently we observed that two agents known to reduce vascular spasm, adenosine and verapamil, did not prevent no-reflow in a similar non-thrombotic model (21). Another possible explanation is that GP IIb/IIIa inhibitors reduce infarct size by some mechanism independent of platelet inhibition and that this is followed by a secondary reduction in no-reflow.

Nevertheless, the fact that Kunichika et al. (11) found that GP IIb/IIIa inhibition reduced no-reflow as well as infarct size in this non-thrombotic model is a fascinating observation. It suggests that the role of platelets in inducing no-reflow, even in a model in which the coronary artery occlusion is created with a mechanical device or snare rather than thrombus, may be far more important than previously appreciated.

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