

# THE “NO-REFLOW” PHENOMENON: BASIC SCIENCE AND CLINICAL CORRELATES

Thorsten Reffelmann, Robert A Kloner

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162

To achieve early and complete reperfusion of the myocardium in acute coronary syndromes is the daily challenge for every physician in clinical cardiology. However, restoration of epicardial blood flow by thrombolysis, primary angioplasty or bypass surgery does not necessarily imply complete reperfusion, even if the target stenosis is adequately removed or bypassed. The amount of microvascular integrity may limit reperfusion to the previously ischaemic tissue despite complete restoration of epicardial vessel diameters.

A 74 year old man with acute distress is admitted to the emergency room because of acute onset of severe, substernal, crushing chest pain two hours ago. He has never suffered from similar symptoms before. The ECG shows ST segment elevation in leads I, aVL, V2–V4. After aspirin and heparin, the patient is immediately transferred to the catheterisation laboratory. Coronary angiography confirms a thrombotic occlusion of the proximal left anterior descending artery. The guide wire easily crosses the occlusion. After coronary artery balloon dilatation and stent implantation the epicardial artery appears to have gained sufficient luminal diameter. However, the contrast medium is only slowly conveyed to the distal artery and not adequately washed out. Even the final angiogram after glyceryl trinitrate in different projections shows no satisfactory flow albeit no visible flow limiting obstacles, such as coronary artery dissection or recurrent thrombus formation. The battle, undertaken to restore myocardial blood supply, seems to be lost and won, finally leading to compromised tissue perfusion despite a successful restoration of patency to the epicardial blood vessel.

A bolus of abciximab, followed by a continuous infusion, is initiated. ST segment elevations resolve only slightly during the next hours; the patient requires prolonged intensive medical care because of recurrent pulmonary oedema. Finally, the patient is stabilised on cardiovascular medication including an angiotensin converting enzyme (ACE) inhibitor, oxygen, and aspirin. The echocardiography shows a large akinetic segment of the anteroseptal wall with an apical aneurysm, and a global ejection fraction of 30%.

Angiographic no-reflow, as described above, may be one of the clinically most obvious manifestations of microvascular damage. The following discussion will set forward that the so-called “no-reflow” phenomenon is far more frequent, and has important prognostic implications. Combining results from basic science and clinical research, we try to elucidate major mechanisms of no-reflow, methods of assessing microvascular dysfunction, and its significance in the clinical setting.

## WHAT IS KNOWN ABOUT NO-REFLOW FROM ANIMAL STUDIES?

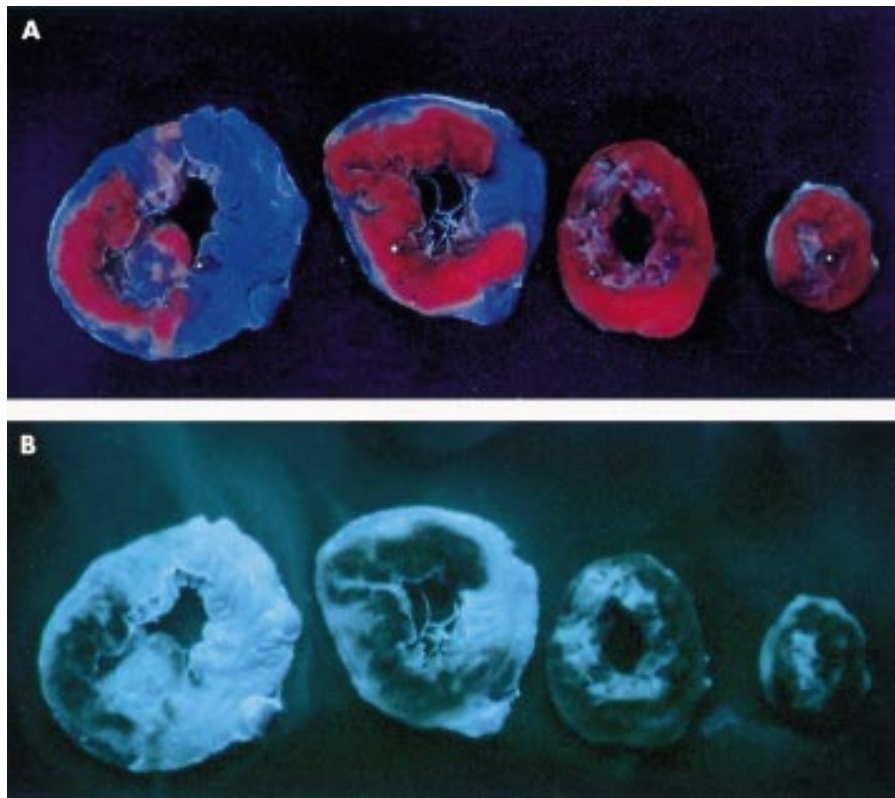
### Anatomical no-reflow

In experimental models of myocardial infarction, injection of various dyes to the circulation has been traditionally used to stain perfused tissue. As shown in fig 1, a substantial part of the myocardium, after being subjected to proximal coronary occlusion and reperfusion of the epicardial artery, may remain unstained after injection of monastral blue or thioflavin S (a fluorescent vital stain for endothelium). The resulting visual perfusion defects represent the so-called “anatomical” no-reflow. Systematic investigations in the canine model of myocardial infarction demonstrated a homogenous distribution of thioflavin S after 40 minutes of ischaemia with subsequent reperfusion. However, after 90 minutes, areas of no-reflow were identified as zones not stained by the fluorescent dye,<sup>1</sup> indicating that a certain duration of ischaemia is necessary for the development of no-reflow. In the canine model, these zones of no-reflow first appeared in the subendocardium.

### Ultrastructural changes

Electron microscopy of these areas of no-reflow revealed swollen intraluminal endothelial protrusions and membrane bound intraluminal bodies, which appeared to be free floating and often seemed to obstruct the capillary lumen. Endothelial cells showed decreased numbers of pinocytotic vesicles and nuclear chromatin margination. After 20 minutes of reperfusion, capillaries contained tightly packed erythrocytes, endothelial gaps, sometimes plugged by platelet and fibrin thrombi, with numerous extravascular red blood cells. Occasionally, capillaries seemed to be compressed by

Correspondence to:  
Robert A Kloner, MD, PhD, The  
Heart Institute, Good  
Samaritan Hospital, University  
of Southern California, 1225  
Wilshire Boulevard, Los  
Angeles, CA 90017-2395,  
USA; RKloner@goodsam.org



**Figure 1** Anatomical no-reflow, visualised in a rabbit model of coronary occlusion and reperfusion. Monastral blue (A) and thioflavin S (B, photography under ultraviolet light, Minolta Y48 barrier filter) were injected into the left atrium after 120 minutes of coronary artery occlusion and 120 minutes of reperfusion. Both dyes leave a substantial part of the left ventricle unstained, indicating areas of no or low perfusion. A close look at the slices demonstrates that (although closely correlating) the area not stained by monastral blue is slightly larger than the non-fluorescent area, reflecting the ability of the two dyes to penetrate into areas of hypoperfusion.

subsarcolemmal blebs of neighbouring swollen myocytes.<sup>1</sup> Ultrastructural investigations after different durations (20–180 minutes) of occlusion in a dog model of coronary ligation and reperfusion demonstrated that microvascular damage (first observed after 60 minutes of occlusion) always lagged behind myocardial cell injury (first apparent after 20 minutes of ischaemia) and that microvascular alterations were always located in zones of irreversibly damaged myocytes.<sup>2</sup> Areas not stained by the fluorescent dye were characterised by low regional myocardial blood flow (mean (SEM) 0.13 (0.03) ml/g/min to 0.26 (0.04) ml/g/min), as assessed by radioactive microspheres.<sup>3</sup>

#### Reperfusion injury and microvascular dysfunction

The term “reperfusion injury” has been coined to describe reperfusion related worsening or expansion of various forms of ischaemic cardiac damage, including: alterations of contractile performance; the arrhythmogenic threshold; potential conversion from reversible to irreversible cardiomyocyte injury; and vascular, in particular microvascular, dysfunction. Ambrosio and colleagues demonstrated a more than twofold increase in the area of no-reflow from 2 minutes to 3.5 hours of reperfusion. This increase was accompanied by a progressive decrease of regional myocardial blood flow within the risk area after initial restoration of regional myocardial flow.<sup>3</sup> Thus, on the one hand no-reflow depends on the degree of the initial ischaemic damage, but on the other hand reperfusion injury at the microvascular level is a significant determinant of the final amount of no-reflow.

#### WHAT IS KNOWN FROM CLINICAL RESEARCH?

##### Angiographic no-reflow

Coronary angiography allows a semiquantitative grading of epicardial antegrade flow according to the thrombolysis in myocardial infarction (TIMI) flow grades. TIMI grade 0 refers

to no distal antegrade vessel opacification by the contrast medium, grade 1 means minimal distal flow, grade 2 partial reperfusion, and grade 3 complete reperfusion. After thrombolysis or coronary angioplasty (PTCA) for acute myocardial infarction, TIMI 0–2 grade coronary flow is associated with more complications and worse left ventricular function compared with TIMI 3 grade flow, even without evidence for obstruction of the epicardial artery. In a retrospective review of 1919 elective and emergency percutaneous interventions by Piana and colleagues, “angiographic” no-reflow, defined as TIMI grade flow less than 3 without evidence for obstruction in the proximal artery, occurred in 2% of all interventions. But the incidence varied with the technique and indication for PTCA: the highest incidence of no-reflow was found after recanalisation for acute myocardial infarction (11.5%); the incidence was significantly higher for interventions in degenerated saphenous bypass grafts (4%); and for stenting or directional atherectomy interventions (3%).<sup>4</sup> Recent studies demonstrated that angiographic no-reflow is a strong predictor of major cardiac complications, including congestive heart failure, malignant arrhythmias, and cardiac death after myocardial infarction.<sup>5</sup>

##### Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) has profoundly extended our understanding of myocardial microvascular perfusion after acute myocardial infarction, and intravenous contrast application with bedside imaging is now feasible. Ito and colleagues showed that all patients with TIMI grade 2 flow after PTCA showed substantial no-reflow on MCE, defined as contrast defects after angioplasty of more than 25% of the risk zone (determined before recanalisation). But even with TIMI grade 3 flow, 16% of the patients showed no-reflow, and significant improvement of left ventricular function was only observed in the patients with reflow.<sup>6</sup> Comparing microvascular perfusion and regional myocardial contractile recovery,

Ragosta and associates concluded that microvascular integrity, as assessed by MCE, is closely related to myocyte viability.<sup>7</sup> Sakuma and colleagues demonstrated that the size of the risk area, determined before reperfusion, as well as a low peak grey scale ratio on MCE one day after primary PTCA for acute myocardial infarction, strongly predicted major cardiac events within the next 22 months.<sup>8</sup> Risk factors for the development of perfusion defects on MCE were not consistent in different studies, but most of them reported a higher incidence of no-reflow with longer elapsed time from onset of symptoms to reperfusion, older age, large anterior myocardial infarction, low admission blood pressure, and, interestingly, with the absence of pre-infarction angina, which might be interpreted as a clinical correlate of microvascular preconditioning.

#### Intracoronary Doppler flow velocity changes

Intracoronary Doppler derived flow velocity patterns showed characteristic profiles in patients with evidence for no-reflow on MCE, including early systolic retrograde flow and high diastolic deceleration rates, and a lower coronary flow reserve.<sup>9</sup> Iwakura and colleagues showed that patients with occurrence of these Doppler flow characteristics immediately after PTCA had longer elapsed time from onset of symptoms to reperfusion and more Q waves on the surface ECG before reperfusion. Patients with delayed (within 10 minutes) systolic retrograde flow had a higher incidence of transient ST segment re-elevation after recanalisation.<sup>10</sup> The delayed occurrence of these characteristics in a subgroup of patients might be a correlate of reperfusion associated progression of no-reflow.

#### TIMI frame count and myocardial blush grade

Other angiographic techniques, used for assessing microvascular integrity in patients with reperfused myocardial infarction, are the corrected TIMI frame count, defined as the number of angiographic frames required for the contrast medium to reach standardised distal landmarks of the coronary artery, and myocardial blush grade, as a semiquantitative description of myocardial contrast density on the final angiogram after reperfusion therapy.

#### Scintigraphic techniques

Visualisation of perfusion defects was also achieved by scintigraphic techniques. Intracoronary injection of macroaggre-

gated <sup>99m</sup>technetium albumin after successful percutaneous recanalisation demonstrated substantial perfusion defects. In addition, evidence for a progressive impairment of tissue perfusion during reperfusion was provided by <sup>82</sup>rubidium positron emission in a canine model.

#### Magnetic resonance imaging

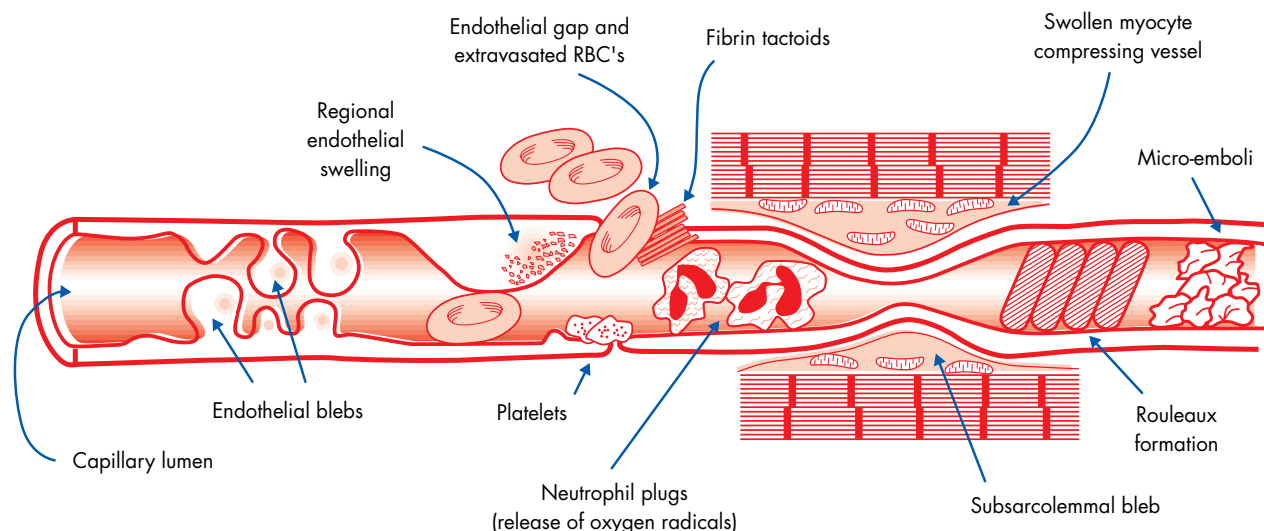
In magnetic resonance imaging (MRI), hypoenhancement 1–2 minutes after contrast injection is assumed to represent zones of no-reflow. A recent study validated the amount of hypoenhancement against anatomical no-reflow assessed by injection of thioflavin S and regional myocardial blood flow in a canine model of reperfused myocardial infarction.<sup>11</sup> Assessing hypoenhancement after contrast injection, visualised in 44 patients 10 days after acute myocardial infarction, Wu and colleagues demonstrated significant prognostic implications of microvascular obstruction for clinical outcome, even after statistical correction for the predictive value of infarct size.<sup>12</sup> Thus, contrast enhanced MRI might be a promising non-invasive future technique for the determination of microvascular obstruction with the opportunity of simultaneous estimation of infarct size (visible as hyperenhancement 5–10 minutes after contrast injection).

#### Resolution of ST segment elevation

The resolution of ST segment elevation after reperfusion therapy was shown to correlate with the amount of myocardial perfusion as visualised by MCE. The so-called ST segment elevation index refers to the sum of ST segment elevation (mV) in the different leads (excluding aVR), divided by the number of leads showing ST segment elevation. While patients without evidence of no-reflow showed a rapid reduction of the ST segment elevation index within the first 30 minutes after successful primary PTCA, ST segment elevation in patients with no-reflow resolved to a significantly lesser degree. Indeed, a (transient) re-elevation was observed in some of these patients.<sup>13</sup>

#### Biochemical markers

Serial measures of serum myoglobin, creatine kinase-MB or troponin I (or T) at baseline and 60 (or 90) minutes after reperfusion therapy have been a useful technique for the assessment of infarct related artery patency. A high ratio of



**Figure 2** Schematic figure, summarising different mechanisms, involved in the development of no-reflow, and accompanying ultrastructural alterations of the microvascular bed (RBC, red blood cell).

the 60 minute value to the baseline value and a higher slope of increase in these markers over time are generally related to successful reopening of the epicardial occlusion, but may also reflect the completeness of microvascular tissue reperfusion. Thus, the amount of tissue reperfusion after reperfusion therapy might in part be estimated even without invasive procedures or sophisticated and expensive technical equipment.

### POTENTIAL MECHANISMS OF NO-REFLOW

Although numerous potential explanations of the development of no-reflow have been put forward (fig 2), the significance of any single mechanism is not yet fully understood. In addition, the importance of these mechanisms might be different immediately after release of the coronary occlusion versus later during the time course of reperfusion. Mechanisms causing no-reflow in experimental mechanical coronary occlusion and reperfusion may differ from those of clinical myocardial infarction or observed during percutaneous coronary interventions (for a list of references refer to eHeart).

#### Endothelial ischaemic damage and microvascular obstruction

The pronounced ultrastructural alterations of the capillary endothelium demonstrated in the canine model suggest that morphological features of the microvascular damage related to ischaemia may directly contribute to the no-reflow phenomenon. Localised areas of endothelial swelling and endothelial protrusions (also called “blebs”) were the most common findings.<sup>1</sup> These protrusions may act to occlude the capillary lumen, and thus play a direct role in causing regional perfusion defects, probably most important directly after reopening of the coronary artery. Following reperfusion, capillaries showed tightly packed erythrocytes suggesting that some flow must have occurred initially into these regions after release of the coronary occlusion.

#### Leucocytes: plugging versus interaction with endothelium, platelets, and myocytes

The pronounced increase of anatomical no-reflow during reperfusion, observed in the experiments by Ambrosio and colleagues, was accompanied by striking neutrophil accumulation within no-reflow areas.<sup>3</sup> Engler and associates demonstrated extensive leucocyte plugging in the microvasculature, that could not be washed out by crystalloid perfusion, after coronary occlusion and five hours of reperfusion. Leucocyte depletion or reperfusion with oxygenated perfluorochemicals led to a reduction of anatomical no-reflow in various studies. However, it should be emphasised that even in isolated saline perfused Langendorff hearts, an anatomical area of no-reflow can be visualised. Thus, leucocytes may exacerbate no-reflow, but do not appear to be a requirement for it to occur.

Even if capillary leucocyte trapping is prominent in the area of no-reflow, the effects of leucocytes are probably not solely confined to mechanical plugging, but may involve complex interactions with the endothelium, platelets, and perhaps with myocytes. Polymorphonuclear cells are able to release reactive oxygen metabolites, proteolytic enzymes, and lipooxygenase products (leukotrienes) that influence platelet and endothelial function. Endothelial cells can modulate leucocyte function by the expression of adhesion molecules—for example, intercellular adhesion molecule-1 (ICAM-1) or P-selectin—and by release of soluble factors including nitric oxide, prostacyclin, endothelin, and platelet activating factor. Platelets affect polymorphonuclear cell activation by release of

thromboxane A<sub>2</sub>, platelet derived growth factor, serotonin, lipooxygenase products, proteases, and adenosine. However, various studies addressing these questions led to partly inconsistent and contradictory results, depending upon the specific model or species investigated. Clinical trials investigating the effect of neutrophil inhibition in myocardial infarction have been in general, negative.

#### Reactive oxygen species

The production of oxygen-free radicals peaks during the first 2–10 minutes of reperfusion after coronary artery occlusion. Sources of oxygen free radicals include the xanthine oxidase reaction, mitochondria, and polymorphonuclear cells. The superoxide dismutase pathway, normally responsible for the clearance of superoxide anions, may be altered after an ischaemic insult. Administration of superoxide dismutase in combination with catalase led to a notable reduction of no-reflow, and ultrastructural signs of endothelial injury in animal studies<sup>14</sup>; also free radical scavengers were shown to prevent functional vascular dysfunction after ischaemia and reperfusion.

#### Functional abnormalities of the vessels

Vascular dysfunction after ischemia and reperfusion in animal models is characterised by a decreased vasodilation in response to acetylcholine or platelet derived stimuli. Functional vascular alterations were shown to persist for several weeks. Interestingly, ischaemic preconditioning can prevent functional vascular abnormalities.<sup>15</sup> Clinical observations confirmed a reduced coronary flow reserve after ischaemia and reperfusion. But even if impaired endothelial response to physiologic stimuli is not the primary cause of anatomical no-reflow, functional vascular abnormalities, especially long term alterations, may prevent adaptation of regional blood flow to situations with an increased oxygen or substrate demand.

#### Mechanical compression

Sudden myocardial cell swelling with prominent intracellular and interstitial oedema is one of the very early morphologic changes induced by reperfusion. As tissue oedema might compress the microvascular bed, the no-reflow phenomenon may in part be attributed to changes in total cross sectional vascular area. However, studies investigating the effect of increased serum osmolality to reduce tissue oedema did not show consistent results. It is likely that mechanical compression contributes in some situations, but is not the primary mechanism of no-reflow.

#### Coagulation, tissue factor

Ultrastructural investigations of no-reflow areas did not show direct evidence of a causal role of intravascular thrombus formation for the development of no-reflow in animal models of mechanical coronary artery occlusion and reperfusion. Some electron microscopy studies found rare microthrombi<sup>1</sup>; others did not find any evidence for activation of the coagulation pathway. Administration of acetylsalicylic acid, streptokinase or tissue plasminogen activator did not demonstrate any beneficial effects on microvascular integrity.

Recent observations suggest that tissue factor, a membrane bound glycoprotein that activates the extrinsic coagulation pathway (via activating factor VII) when exposed to flowing blood, contributes to the degree of no-reflow. When active site-blocked factor VII was administered during reperfusion, a pronounced reduction of no-reflow was observed,<sup>16</sup> which

**Table 1** Interventions used in experimental animal models to reduce no-reflow

| Intervention  | Species | Methods for assessing no-reflow             | Comment  |
|---|---------|---|--|
| <b>Adenosine</b><br>Adenosine, intracoronary and intravenous application during reperfusion           | Dogs    | Radioactive microspheres, EM                | Improved regional myocardial blood flow, ultrastructural preservation of endothelial cells, less neutrophil infiltration, in one study only effective in combination with lidocaine  |
| <b>Calcium channel antagonists</b><br>Nisoldipine before ischaemia                                    | Rats    | Fluorescein perfusion                       | Reduced area of no-reflow with nisoldipine in globally ischaemic isolated hearts   |
| Gallopamil during ischaemia   | Rabbits | Thioflavin S                                | Reduced no reflow with gallopamil during ischaemia, accompanied by infarct size reduction  |
| <b>Neutrophil depletion</b><br>Reperfusion with neutrophil depleted blood (filter)                    | Dogs    | Thioflavin S                                | Reduction of anatomical no reflow with concomitant infarct size reduction  |
| Intraperitoneal mustin hydrochloride  | Rats    | Constant pressure perfusion (Langendorff)   | Explanted hearts after global ischaemia for 4 hours (4°C) were transplanted into the abdomen of the recipient. After different times of in situ reperfusion, Langendorff perfusion revealed better recovery of coronary flow after leucocyte depletion |
| Reperfusion with intracoronary oxygenated perfluorochemical   | Dogs    | Thioflavin S, coloured microspheres, EM, LM | Reduced area of no-reflow, less leucocyte plugging, preservation of endothelial structure  |
| <b>Oxygen derived free radical scavenging</b><br>Superoxide dismutase and catalase during reperfusion | Dogs    | Radioactive microspheres, EM                | Preservation of endocardial regional blood flow, less ultrastructural damage to the endothelium within myocardial necrosis, pronounced hyperaemic response in treated animals after 10 minutes of reperfusion  |
| <b>Active site blocked factor VIIa</b><br>Active site blocked factor VIIa during reperfusion          | Rabbits | Thioflavin S                                | Reduction of anatomical no-reflow and infarct size   |
| <b>Endothelin antagonism</b><br>Endothelin A antagonist during reperfusion                            | Dogs    | MCE, radioactive microspheres               | Enhanced microvascular flow after 180 minutes of reperfusion by contrast echocardiography and microspheres   |

EM, electron microscopy; LM, light microscopy; MCE, myocardial contrast echocardiography.

might be of special interest in clinical acute coronary syndromes, associated with vascular and endothelial damage.

### Microembolisation of atherosclerotic debris and thrombi

Unlike most animal models of mechanical coronary occlusion, the clinical setting probably involves microembolic events in a substantial number of cases. The transition of a stable atherosclerotic lesion to an unstable plaque, induced by inflammatory stimuli or by iatrogenic manipulation, includes the disruption of the fibrous cap with exposure of subendothelial matrix, which subsequently can lead to embolisation of lipid, matrix, endothelial cells or platelet thrombi to the distal vasculature.<sup>17</sup>

In unstable angina, elevation of serum troponin T is a very sensitive marker of myocardial injury, reflecting micronecrosis caused by distal coronary embolisation. The pronounced beneficial effects of glycoprotein IIb/IIIa receptor antagonists in the subgroup of patients with unstable angina and increased troponin T serum concentrations, evident in the CAPTURE (chimeric 7E3 antiplatelet therapy in unstable angina refractory to standard treatment) study, indicates a role of microembolisation followed by platelet activation in this subgroup.<sup>18</sup> Cyclic flow variations in stenosed coronary arteries are regarded as the consequence of the formation of platelet aggregates and subsequent dislodgement of the embolus into the microvascular bed.

Elective angioplasty procedures are associated with a certain incidence of the no-reflow phenomenon.<sup>4</sup> Depending on the technique, the incidence is quite variable. Patients who undergo percutaneous interventions for degenerated saphenous vein grafts have a high risk of periprocedural infarction.

Mechanical devices, designed to trap embolic debris during angioplasty, showed that embolic material could be retrieved during PTCA, especially in angioplasty interventions in degenerated venous grafts, which is “smoking-gun evidence” for the concept of PTCA associated distal embolisation. Directional and rotational atherectomy have a substantially higher risk of no-reflow compared with balloon angioplasty. Thus, microemboli significantly contribute to the no-reflow phenomenon in the clinical situation, leading to micro- and potentially macro-infarcts.

### TREATMENT OF NO-REFLOW: DOES IT MAKE SENSE?

Obviously, the prevention of microembolisation or its consequences should be beneficial in the clinical setting. Glycoprotein IIb/IIIa receptor blockers, that should reduce the detrimental sequelae of coronary embolisation in the microvascular bed, have demonstrated convincing effects on clinical outcome in unstable angina and after percutaneous intervention, in addition to prevention of reocclusion of the target lesion.

However, with respect to the “classical” no-reflow phenomenon in coronary occlusion and reperfusion, the question is more difficult to answer. To date, no study could demonstrate no-reflow zones preceding myocardial necrosis. In 312 biopsies of ischaemic canine myocardium after various times of coronary occlusion (20–180 minutes), no biopsy showed microvascular damage without myocardial cell injury. In addition, ultrastructural myocyte damage greatly preceded microvascular alterations.<sup>3</sup> Even in the experiments of Ambrosio and colleagues, that showed a pronounced expansion of

**Table 2** Interventions used in clinical situations to reduce no-reflow

| Intervention   | Clinical situation                            | Method for assessing no-reflow                        | Comment   |
|--|---|---|---|
| <b>Adenosine</b>   |   |   |   |
| Intracoronary adenosine  | Primary angioplasty for AMI                   | TIMI grade flow                                       | Incidence of angiographic no-reflow could be reduced, and in one study associated with better recovery of left ventricular function and outcome |
| <b>Calcium antagonists</b>   |   |   |   |
| Intracoronary verapamil with glyceryl trinitrate   | Elective and emergency PTCA for AMI           | TIMI grade flow                                       | Improvement of TIMI grade flow after verapamil in elective and emergency PTCA   |
| Intracoronary verapamil  | PTCA in AMI                                   | MCE   | Reduction of perfusion defects and increase in peak intensity, associated with better contractile recovery                                      |
| Intragraft verapamil   | Elective PTCA                                 | TIMI grade flow                                       | Improvement of flow with verapamil in PTCA in saphenous grafts, in contrast: no effect of glyceryl trinitrate                                   |
| <b>Papaverine</b>  |   |   |   |
| Intracoronary papaverine   | Elective PTCA in saphenous grafts             | TIMI frame count                                      | Papaverine reduced the number of TIMI frame counts in patients with no-reflow   |
| <b>Nicorandil</b>  |   |   |   |
| Intravenous nicorandil   | Anterior wall AMI                             | MCE   | Lower incidence of perfusion defects in the nicorandil group  |
| <b>Nitric oxide donor</b>  |   |   |   |
| Intracoronary nitroprusside  | Elective PTCA                                 | TIMI flow grade, modified TIMI frame count            | Improvement of flow after nitroprusside in elective interventions   |
| <b>Glycoprotein IIb/IIIa receptor antagonism</b>   |   |   |   |
| Intravenous abciximab  | Stenting in AMI                               | Coronary flow velocity after 14 days                  | Improvement of coronary flow velocities and left ventricular function after myocardial infarction with abciximab                                |
| Intravenous eptifibatide   | Elective stenting of native coronary arteries | Angiography derived flow reserve and myocardial blush | Eptifibatide improved parameters of coronary flow reserve and velocity of microvascular perfusion in elective PTCA procedures                   |
| Intravenous abciximab  | Elective rotational atherectomy               | Tc-99m sestamibi scintigraphy                         | Abciximab reduced the incidence and amount of scintigraphic perfusion defects after rotational atherectomy                                      |
| <b>Mechanical devices for prevention of microembolisation (distal temporary occlusion versus umbrella technique)</b> |   |   |   |
| For example, PercuSurge GuardWire temporary occlusion system, Dorros/Probing catheter, Angiogard ("umbrella" system) | Elective saphenous graft angioplasty          | First experiences, feasibility                        | In saphenous graft interventions large amounts of atherosclerotic debris could be aspirated.  |

AMI, acute myocardial infarction; MCE, myocardial contrast echocardiography; PTCA, percutaneous transluminal coronary angioplasty; TIMI, thrombolysis in myocardial infarction.

no-reflow during reperfusion, the area of hypoperfusion was always confined to the area of necrosis.<sup>3</sup>

As there is no proof of a contribution of classical no-reflow to myocardial necrosis, one might ask whether treatment that focuses on reduction of no-reflow in necrotic tissue makes sense. In theory, improvement of tissue perfusion, even in areas of irreversibly damaged cardiomyocytes, could have beneficial effects other than myocardial salvage. Improved tissue perfusion might impede infarct expansion, ventricular remodelling or aneurysmic ventricular dilation, and promote scar healing and the delivery of pharmacological agents to the myocardium. Furthermore, blood vessels preserved in an area that might have become a no-reflow zone could serve as a source of future collateral vessels.

The MRI study by Wu and colleagues demonstrated prognostic significance of no-reflow after acute myocardial infarction independent of its relation to infarct size. The presence of microvascular obstruction in this study was significantly correlated with fibrous scar formation, left ventricular remodelling after six months, and worse clinical outcome.<sup>12</sup>

#### TREATMENT OF NO-REFLOW: WHAT TREATMENTS WORK?

Treatment strategies to reduce no-reflow have achieved increasing recognition both in basic animal research and clinical studies. However, pharmacological interventions are

not finally established except for the prevention of the detrimental effects of coronary microembolisation by special devices or therapies that reduce platelet activation. Table 1 summarises a selection of interventions that were shown to exhibit beneficial effects on no-reflow in animal models; table 2 focuses on treatment strategies used to reduce no-reflow in clinical situations. Pharmacological agents with vasodilating properties, such as adenosine, papaverine, and calcium antagonists were investigated in experimental and clinical conditions. The results from animal studies were controversial with respect to adenosine. Clinical studies mainly used angiographic no-reflow as an end point, which might not fully reflect microvascular perfusion. The beneficial effects of leucocyte depletion or oxygen radical scavenging in animal studies did not show convincing usefulness in the clinical setting. As demonstrated recently, nicorandil administered directly after the diagnosis of acute myocardial infarction was effective in both reducing the perfusion defect (MCE) and complications after infarction, accompanied by an increased recovery of left ventricular function.<sup>19</sup> In another study, intracoronary verapamil was also shown to reduce perfusion defects and increase peak contrast intensity in MCE after primary PTCA for acute myocardial infarction.<sup>20</sup>

In summary, the best treatment strategy for no-reflow has not yet been characterised, and future investigations are

**No-reflow phenomenon: key points**

- ▶ Experimental no-reflow is characterised by microvascular dysfunction, evident as distinct areas of hypoperfusion, compromised resting myocardial blood flow, and functional vascular alterations after ischaemia and reperfusion
- ▶ Clinical observations, using TIMI grading of coronary flow, MCE, scintigraphic, and MRI techniques show evidence for similar features of microvascular damage after acute myocardial infarction, and even after elective PTCA interventions
- ▶ Coronary microembolisation is an important mechanism of no-reflow in acute coronary syndromes and PTCA procedures
- ▶ Perfusion defects after acute myocardial infarction—for example, visualised by MCE—are closely related to lack of contractile recovery and irreversible myocyte damage

needed to evaluate the significance and contribution of different mechanisms responsible for no-reflow in order to provide optimal therapy.

**SUMMARY AND CONCLUSIONS**

Both animal models of experimental myocardial infarction and clinical studies have provided evidence of impaired microvascular perfusion after reperfusion. Characteristics of no-reflow found in basic science investigations, such as distinct perfusion defects, progressive decrease of resting myocardial flow with ongoing reperfusion and functional vascular alterations are paralleled by clinical observations demonstrating similar features. Treatment strategies of reducing no-reflow after acute myocardial infarction are under investigation. Coronary microembolisation is significantly involved in clinically observed microvascular dysfunction, and new interventional devices provide hope for capturing these emboli before they cause tissue damage. From a practical standpoint, the best way to reduce no-reflow is to reduce infarct size by early reperfusion and adequate pharmacological treatment. However, whether improvement of microvascular perfusion even in zones of irreversibly damaged myocardium—which theoretically might have beneficial effects on ventricular remodelling, infarct healing, and collateral formation—is feasible with pharmacological interventions, remains to be investigated.

**REFERENCES**

- 1 Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in dogs. *J Clin Invest* 1974;**54**:1496–508.
  - ▶ This is the first article describing anatomical no-reflow after experimental myocardial infarction in the canine model, using thioflavin S as a marker of anatomical no-reflow. The corresponding ultrastructural changes of the microvasculature are evaluated by electron microscopy.
- 2 Kloner RA, Rude RE, Carlson N, et al. Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: which comes first? *Circulation* 1980;**62**:945–52.
  - ▶ The spatial and temporal distribution of ultrastructural alterations of the microvascular bed is evaluated in comparison to myocyte fine structure. Microvascular changes lagged behind myocyte changes of irreversible ischaemic damage.
- 3 Ambrosio G, Weisman HF, Mannisi JA, et al. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. *Circulation* 1989;**80**:1846–61.
  - ▶ This landmark article provides evidence of reperfusion injury at the microvascular level, demonstrating a substantial increase of anatomical no-reflow with ongoing reperfusion and a progressive decrease of tissue perfusion.
- 4 Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994;**89**:2514–18.

- ▶ In a retrospective analysis, the incidence of angiographical no-reflow in elective PTCA procedures as well as in primary PTCA for acute myocardial infarction is evaluated.
- 5 Morishima I, Sone T, Okumura K, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. *J Am Coll Cardiol* 2000;**36**:1202–9.
  - 6 Ito H, Okamura A, Iwakura K, et al. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. *Circulation* 1996;**93**:1993–9.
    - ▶ Systematic analysis of the relation between TIMI grade flow and MCE and its significance for functional recovery.
  - 7 Ragosta M, Camarano G, Kaul S, et al. Microvascular integrity indicates myocellular viability in patients with recent myocardial infarction: new insights using myocardial contrast echocardiography. *Circulation* 1994;**89**:2562–9.
  - 8 Sakuma T, Hayashi Y, Sumii K, et al. Prediction of short- and intermediate-term prognoses of patients with acute myocardial infarction using myocardial contrast echocardiography one day after recanalization. *J Am Coll Cardiol* 1998;**32**:890–7.
  - 9 Iwakura K, Ito H, Takiuchi S, et al. Alteration in the coronary blood flow velocity pattern in patients with no-reflow and reperfused acute myocardial infarction. *Circulation* 1996;**94**:1269–75.
    - ▶ First description of characteristic changes of intracoronary Doppler profiles in patients with no-reflow after acute myocardial infarction with a section of potential explanations of its pathophysiology (see discussion).
  - 10 Iwakura K, Ito H, Nishikawa N, et al. Early temporal changes in coronary flow velocity patterns in patients with acute myocardial infarction demonstrating the "no-reflow" phenomenon. *Am J Cardiol* 1999;**84**:415–19.
  - 11 Rochitte CE, Lima JA, Bluemke DA, et al. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. *Circulation* 1998;**98**:1006–14.
    - ▶ Even if a substantial percentage of the included patients were not available at follow up after 16 months, this elegant study was able to relate the occurrence of microvascular obstruction, visualised as magnetic resonance hypoenhancement after contrast injection, to cardiovascular complications. This is the first study that demonstrated a prognostic significance of microvascular dysfunction independent of its relation to infarct size.
  - 13 Santoro GM, Valenti R, Buonamici P, et al. Relation between ST-segment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with direct angioplasty. *Am J Cardiol* 1998;**82**:932–7.
  - 14 Przyklenk K, Kloner RA. "Reperfusion injury" by oxygen-derived free radicals? Effect of superoxide dismutase plus catalase, given at the time of reperfusion, on myocardial infarct size, contractile function, coronary microvasculature, and regional myocardial blood flow. *Circ Res* 1989;**64**:86–96.
  - 15 Richard V, Kaeffer N, Tron C, et al. Ischemic preconditioning protects against coronary endothelial dysfunction induced by ischemia and reperfusion. *Circulation* 1994;**89**:1254–61.
  - 16 Golino P, Ragni M, Cirillo P, et al. Recombinant human, active site-blocked factor VIIa reduces infarct size and no-reflow phenomenon in rabbits. *Am J Physiol* 2000;**278**:H1507–16.
  - 17 Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;**101**:570–80.
    - ▶ Excellent review on the role of coronary microembolisation in various clinical situations of unstable coronary syndromes and percutaneous interventions.
  - 18 Hamm CW, Heeschen C, Goldman B, et al, for the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;**340**:1623–9.
    - ▶ One of the most convincing studies on glycoprotein IIb/IIIa receptor blockade, which demonstrates the beneficial effects of glycoprotein IIb/IIIa receptor antagonism in unstable angina on clinical outcome.
  - 19 Ito H, Taniyama Y, Iwakura K, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol* 1999;**33**:654–60.
    - ▶ This study demonstrated beneficial effects of intravenous nicorandil, initiated before reperfusion therapy, on microvascular function and myocardial viability by MCE.
  - 20 Taniyama Y, Ito H, Iwakura K, et al. Beneficial effect of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. *J Am Coll Cardiol* 1997;**30**:1193–9.



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