REVIEW

Reperfusion injury in acute myocardial infarction: From bench to cath lab. Part II: Clinical issues and therapeutic options

Lésions myocardiques de reperfusion au cours de l’infarctus myocardique aigu du laboratoire au « cath-lab ». Section II : aspects cliniques et options thérapeutiques

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Summary Two forms of reperfusion injury can occur in patients with ST-segment elevation acute myocardial infarction who are undergoing primary angioplasty: no-reflow phenomenon and reperfusion syndrome. No-reflow, defined as low or no distal perfusion despite removal of epicardial occlusion, can be detected by angiographic flow, myocardial blush grade and contrast echocardiography. Reperfusion syndrome involves haemodynamic and rhythmic disturbances, but an overall paradoxical ST-segment increase. A variety of mechanisms give rise to no-reflow, including distal embolization, leucocyte plugging and vasoconstriction. Reperfusion syndrome reflects, at least in part, the cardiomyocyte component of reperfusion injury. Reperfusion injury can be predicted from the initial electrocardiogram, especially when QRS complex distortion is observed. Pharmacological prevention of reperfusion injury has been tested in a number of trials; the most useful drugs available currently are glycoprotein IIb/IIIa receptor blockers and adenosine. Thrombus aspiration leads to faster and greater ST-segment resolution. Postconditioning (also called staccato reperfusion) is a new strategy that has produced highly encouraging results, although it has been tested only in a small randomized study. New tools are required to enable thrombus aspiration and postconditioning to be carried out simultaneously. Pharmacological postconditioning can be anticipated in the future.

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ST-segment elevation myocardial infarction (STEMI) was first described by Krug et al. in 1966 [5], and later by Kloner et al. in 1974 [6], in ischaemia—reperfusion experimental animal models in which coronary occlusion was achieved by ligature without any thrombotic material. Nevertheless, interventional cardiologists continued to regard NR as a technical failure caused by thrombus fragmentation and distal embolism [7,8].

The first positive report of pharmacologically modified reperfusion (using perfluorochemicals) failed to catch the attention of interventional cardiologists [9], as did the surprising results of the Primary Angioplasty in Myocardial Infarction (PAMI) stent study, in which stented patients had a slightly poorer clinical outcome [10]. The failure of, and unconvincing results from, numerous drug trials [11] reinforced the belief that the principal problem during pPCI was vascular, requiring embolism and spasm prevention [12].

However, the first randomized study into postconditioning in humans [13] altered the opinion of interventional cardiologists, who started to accept that a useful link might be made between laboratory research and reperfusion in humans, and that modified reperfusion might have a role in the catheterization laboratory (cath lab). The aim of this review is to demonstrate how experimental modified reperfusion might influence routine pPCI practice in humans.

In an attempt to clarify this complex phenomenon, it is useful to separate the two facets of reperfusion injury—one involving the endothelium and hence postreperfusion flow, and the other involving cardiomyocytes (Fig. 1). Nevertheless, these two consequences of the sudden reopening of the artery are closely interconnected and therapeutic options must target them both. Reopening of the artery is essential to save the myocardium; prevention and treatment of reperfusion injury is the next challenge in the quest to optimize the final outcome.

Abbreviations

- ATP: Adenosine triphosphate
- ECG: Electrocardiogram
- IMR: Index of microvascular resistance
- LVF: Left ventricular function
- MBG: Myocardial blush grade
- MCE: Myocardial contrast echocardiography
- MTP: Mitochondrial transition pore
- NR: No-reflow
- pPCI: Primary percutaneous coronary intervention
- PVF: Peak volume flow
- RISK: Reperfusion injury salvage kinase
- ROS: Reactive oxygen species
- TFC: Thrombolysis in myocardial infarction frame count
- TIMI: Thrombolysis in myocardial infarction

Background

Experimental data have shown that the final myocardial outcome of an ‘ischemic—reperfusion’ sequence depends not only on the time delay between occlusion and reperfusion but also on whether lethal reperfusion injury occurs (see Part I).

Despite the early description of reperfusion syndrome [1—3] and stunned myocardium phenomenon [4], for many years interventional cardiologists failed to acknowledge the concept of lethal reperfusion injury and the reality of its existence in humans. The occurrence of no-reflow (NR) during primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) was first
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The no-reflow phenomenon

First reported 20 years ago after thrombolytic therapy using scintigraphy [14], and again one year later using angiography [15], NR is defined as the absence of or poor myocardial perfusion despite the removal of the epicardiac artery obstruction. Numerous techniques can be used to assess this problem. A final Thrombolysis In Myocardial Infarction (TIMI) grade less than 3 flow is seen with angiography, extending from no-flow to slow-flow, despite the occlusion having been removed with no residual obstacle or vessel dissection [7,16]. The incidence of NR, judged on the basis of the initial TIMI classification, is around 10–15%. The effective myocardial perfusion can be measured more accurately using the TIMI frame count (TFC) [17], which is defined as the number of frames required for dye to reach the distal artery; NR is considered when the TFC is greater than 40 frames [17].

The gold standard measure of myocardial reperfusion is myocardial blush grade (MBG) [18]; MBG 0 is defined as no myocardial opacification; MBG 1 as myocardial opacification without any dye clearance; MBG 2 as myocardial opacification with slow clearance; and MBG 3 as myocardial opacification with quick clearance. Only 21% of patients who reached TIMI grade 3 flow after pPCI had MBG 3. Using conventional angiographic TIMI grade flow assessment, Anderson et al. showed that only TIMI grade 3 flow could be considered to be an indicator of successful reperfusion [19]. MBG is the most powerful predictor of prognosis [20]. Going from MBG 0 to 3, 30-day mortality has been shown to decrease from 6.2 to 5.1%, 4.4 and 2.0%, respectively, in patients with heart failure at presentation [21], with MBG 0 and 1 associated with the worst 400-day follow-up prognosis [21]. Taken together, these data encourage interventional cardiologists not only to achieve but also to go beyond TIMI grade 3 flow [22].

Myocardial contrast echocardiography (MCE) has shown NR to be present in patients even if they have reached angiographic TIMI grade 3 flow; NR was observed in 16–40% of such patients and in 100% of those with TIMI grade 2 flow [23]. Prognosis is linked directly to MCE reflow [24]. Galiuto et al. found that even in patients with TIMI grade 3 flow, a contrast defect greater than 25% was the most accurate predictor of left ventricular remodelling — better than MBG or ST — segment resolution [25]. The degree of contrast defect is linked closely to ST-segment decrease.

Santoro et al. found that the ST-segment decreased by more than 50% in 77% of patients with reflow compared with by 10% in patients with echo NR [26]. Combining MBG and ST-segment resolution makes it possible to predict early and late left ventricular function (LVF) recovery [27]. The combination of MBG 2 or 3 with an ST-segment decrease of more than 50% has been shown to produce seven-day and six-month LVF recovery rates of 65 and 95%, respectively. By comparison, MBG 2 or 3 and an ST-segment decrease of less than 50% resulted in seven-day and six-month LVF recovery rates of 24 and 86%, respectively. In patients with neither MBG 2 or 3, nor an ST-segment decrease, the seven-day and six-month LVF recovery rates were 18 and 32%, respectively.

It may be possible to detect NR ‘on-line’ using a new measure — the index of microvascular resistance (IMR) [28]. Using a pressure sensor wire (as for fractional flow measurement), after injection of adenosine, an IMR greater than 32 units was predictive of poor LVF recovery at three-month follow-up.

NR can also be assessed by intracoronary Doppler flow, with average peak velocity and early systolic retrograde flow correlating well with MCE defect [29], and by magnetic resonance imaging [30–33]. Positron tomography, like magnetic resonance imaging, is a technique that will be developed in the future [34], especially for therapeutic trials. Feldman et al. found a good correlation between coronary flow reserve immediately after pPCI and ST-segment recovery [35]. The criteria defining NR, depending on the assessment technique used, are summarized in Fig. 2.

ST-segment decrease is probably linked to NR, but also depends on cardiomyocyte damage. By pooling the results of two studies comparing MBG and ST-segment resolution [18,27], it is possible to identify four different profiles after pPCI (Fig. 3), providing confirmation that endothelial and cardiomyocyte responses to reperfusion do not always evolve in parallel. The four different profiles are as follows:

- flow recovery with ST-segment resolution;
- flow recovery without ST-segment resolution;
- low-reflow or NR without ST-segment resolution;
- NR alone (as proposed by Santoro et al. [26]).

Definition of NR according to assessment technique used.

- Epicardial angiography:
  - TIMI 0-2
- Myocardial blush grade angiography:
  - grade 0-1
- Contrast echocardiography:
  - >50 % area at risk
- Endocoronary Doppler:
  - reverse systolic flow
  - *quick diastolic deceleration time
  - *coronary flow reserve <1.6

Figure 2. Definition of NR according to assessment technique used.

Figure 1. The two facets of reperfusion injury, involving endothelium and cardiomyocytes.
Figure 3. Discrepancies between angiographic NR definition and ST-segment resolution: ideal postreperfusion flow is most often (1) but not always (2) predictive of ST-segment resolution, and vice versa (3,4).

- ST-segment recovery despite low-reflow or NR. These conflicting characteristics highlight the two facets of reperfusion injury – endothelial and myocardial.

The time course of NR must be taken into account. Studies in animals have shown that even after early hyperaemia [36] there is a progressive loss of infarct perfusion [36—38]. Twenty years ago, Ambrosio et al. found that after two minutes of reperfusion in a dog model, the area of impaired reperfusion averaged 9.5±3.0%, whereas it was three times as large after 3.5 h of reperfusion (25.9±8.2%) [36]. Few studies have been done in humans to address this evolutive aspect of NR. Tsunoda et al. observed two different groups who had reached angiographic TIMI grade 3 flow [39]. One group experienced an early decrease in average peak velocity followed by a late recovery, while the other experienced a continuous decrease in average peak velocity; the late recovery group showed a greater improvement in LVF.

It is now evident that the different tools that can be used to assess the efficacy of myocardial reperfusion after pPCI show that NR exists in a large number of patients who have a good immediate angiographic result. Classic TIMI grade 3 flow is required, but is not sufficiently accurate to distinguish between distal reflow and NR.

The mechanisms of NR are well elucidated, and include distal embolism, leucocyte and platelet plugging, microvascular spasm, capillary swelling and external compression by hypercontracted cardiomyocytes [34]. A variety of clinical and biological variables may predict the occurrence of NR; these include initial hyperglycaemia [40—42], high leucocyte count [43], troponin elevation at presentation [44], longer time delay, anterior infarcts [45] and lack of preinfarction angina [46].

Cardiomyocyte reperfusion injury

While interventional cardiologists have paid heed to the angiographic results of pPCI, less focus has been placed on the deleterious effects of reperfusion on cardiomyocytes. Stunned myocardium [4] has long been considered to be a reflection of the time needed to repair ischaemic damage rather than a consequence of reperfusion injury.

Reperfusion syndrome [3] combines cardiac arrhythmias such as accelerated idioventricular rhythm, severe bradycardia, arterial pressure drop leading in rare cases to electromechanical dissociation [2], chest pain paroxysm and ST-segment elevation increase [1] (Fig. 4). ST-segment monitoring during and immediately after culprit artery des-obstruction might provide useful information about the

Figure 4. Paradoxical ST-segment increase at reperfusion in acute anterior ST-segment elevation acute myocardial infarction treated with pPCI: (1) initial ECG with QRS distortion (grade 3); (2) immediately postreflow ECG with sudden major increase in ST-segment elevation; (3) slow and delayed ST-segment recovery.
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myocardial response to reoxygenation. An increase in ST-segment shift may be caused by ionic cellular mechanisms such as potassium efflux (see Part I). A paradoxical increase in chest pain and ST-segment elevation can occur immediately after the reopening of the artery or a few minutes later [1]. The fact that even with MBG 3, the ST-segment does not improve in around 15% of patients, supports the existence of two facets of reperfusion injury — vascular and cellular [18]. Santoro et al. tried to differentiate between NR and cardiomyocyte reperfusion injury [26]. Eleven of 37 patients (29.7%) treated with pPCI experienced MCE NR. A sudden postreperfusion ST-segment increase of more than 30% occurred in 10 patients (27.0%), including three of 26 (11.5%) with MCE reflow compared with seven of 11 (63.6%) with MCE NR, which shows that cellular mechanisms can cause the ST-segment to deteriorate even in the presence of reflow. Nevertheless, the additional ST-segment increase was of shorter duration in the reflow group than in the NR group.

Thus, the components of reperfusion injury are clearly interwoven and angiographic reflow must be combined with immediate ST-segment shift after pPCI (Fig. 2) [47].

Initial electrocardiogram and reperfusion injury

The initial electrocardiogram (ECG) is a reliable predictor of ST-segment and angiographic outcome after pPCI. The greater the sum of ST-segment elevation in acute anterior infarctions, the worse the ventricular prognosis as a result of severe ischaemia and reperfusion injury [48,49]. Kurisu et al. found a sum of ST-segment elevation greater than 10 mm to be an appropriate cut-off value [49]. Patients with less severe ST-segment elevation presented more frequently with prodromal angina and may therefore have been protected by preconditioning [49]. Greater ST-segment elevation in the D1 lead than in the aVL lead is associated with impaired myocardial reperfusion (assessed by MBG) and less myocardial salvage in patients with recanalized anterior infarctions [50], as well as with ST-segment depression in the aVR lead in patients with acute inferior infarctions [51]. In patients with inferior infarctions, a larger sum of ST-segment depression in the V4—V6 leads than in the V1—V4 leads is also considered to be a marker of poor prognosis, although a clear relationship with reperfusion injury has not been established [52].

The most studied feature of the initial ECG is QRS complex distortion [52—54]. The initial ECG can be categorized as follows on the basis of repolarization: grade I, T-wave peaking; grade II, ST-segment elevation without distortion of the terminal portion of QRS complex; grade III, ST-segment elevation with distortion of the QRS complex, defined as disappearance of the S wave in the VI—V3 leads or appearance of ST-segment elevation (measured at the J point) greater than 50% of the R wave in the same lead (Fig. 5). A grade III ECG can be observed in around 30% of patients [52] and predicts a poorer prognosis despite infarct-related
artery reopening, due to more frequent NR and less frequent ST-segment decrease as a consequence of reperfusion injury.

It is clear, therefore, that admission ECG and ST-segment changes after pPCI may be valuable predictors and markers of global reperfusion injury. Immediate ST-segment changes after pPCI can be used reliably to unmask reperfusion injury, which in turn enables appropriate modifications to be made to the reperfusion strategy; given the association of reperfusion injury with mortality rate and final LVF, this measure may emerge as a strong surrogate endpoint in future clinical trials.

**Therapeutic options**

**Unexpected failures**

Following robust experimental results, a variety of molecules have been tested for their ability to counteract either NR or cardiomyocyte reperfusion injury: of these, reactive oxygen species (ROS) scavengers [55], inhibitors of the sodium-hydrogen exchanger [56] and inhibitors of the inflammatory cascade [57—59] have failed to produce significant benefits. The reasons for these surprisingly negative results cannot be discussed in detail here and for each type of molecule, but may include the multifactorial mechanisms of reperfusion injury and the need for these mechanisms to be acted upon simultaneously, the intravenous mode of drug delivery, the timing of delivery (during ischaemia or during reperfusion), the gap between the experimental setting and STEMI in humans, and the low risk level of patients included in the studies.

The therapeutic options discussed below have all produced some positive results and are either available for immediate use or are under development for future use.

**Thrombectomy and filter devices**

Given that distal embolization is one of the causes of NR [60], various devices have been proposed for use in the removal of thrombi or the prevention of distal embolisms into arterioles and small coronary branches. Numerous small trials have demonstrated the efficacy of these devices in terms of improved flow and ST-segment regression; MBG 3 can be reached in around 85% of patients compared with 45% after conventional pPCI, and immediate complete ST-segment regression is noted in around 70% of patients with 45% after conventional pPCI, and immediate complete 3 can be reached in around 85% of patients compared terms of improved flow and ST-segment regression; MBG trials have demonstrated the efficacy of these devices in

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ized, placebo-controlled study using a low adenosine dose (10 μg/kg per min) infused intravenously for six hours in patients undergoing thrombolysis [76]. At the six-month follow-up of 292 patients with anterior infarcts, the adenosine group showed a trend for less all-cause mortality (8.4% versus 15.3%; \( p = 0.07 \)) and cardiovascular mortality (8.4% versus 14.6%; \( p = 0.08 \)). Furthermore, in a post hoc analysis of a subgroup with anterior infarcts and severely depressed LVF, the six-month death rate was significantly lower in the adenosine group (2.0% versus 12.1%; \( p = 0.007 \)).

Finally, the Acute Myocardial Infarction Study of Adenosine II (AMISTAD-II) was a double-blind, placebo-controlled, randomized study in 2118 patients with anterior STEMI undergoing thrombolysis or pPCI [77,78]. Two doses of adenosine were tested: 50 and 70 μg/kg per min. Despite the lack of difference between the two groups in terms of major clinical endpoints, a marked reduction in infarct size was observed in the high-dose group. In a post hoc analysis, among patients receiving reperfusion therapy within three hours of symptoms, adenosine reduced one-month analysis, among patients receiving reperfusion therapy within three hours of symptoms, adenosine reduced one-month mortality rates significantly: 5.2% versus 9.2% (\( p = 0.014 \)) and 7.3% versus 11.2% (\( p = 0.03 \)), respectively [78]. Adenosine can be considered to be an effective adjunctive therapy that minimizes infarct size and clinical events in patients with anterior infarcts treated with reperfusion therapy within 3–4 h of chest pain onset.

Nicorandil

Nicorandil is another molecule that has the potential to limit reperfusion injury [79]; this hybrid of an ATP-sensitive potassium-channel activator and a nitrate contributes to the reduction in preload and afterload, works as a ROS scavenger, and has neutrophil-modulating properties. The opening of potassium-ATP channels is known to be involved in preconditioning and postconditioning (see Part I). In two randomized studies, patients undergoing pPCI received nicorandil by intravenous infusion (4 mg bolus plus 6 mg/h for six hours) [80], or by a combination of intracoronary administration (1–2 mg) and intravenous administration (4 mg bolus plus 6 mg/h for 16 h) [81]; in both studies, patients who received nicorandil had a better final flow, a greater ST-segment resolution and fewer major clinical events, including deaths. The strategy of combining intracoronary and intravenous drug administration appears to be the most effective.

Postconditioning or modified reperfusion

Jakob Vinten-Johansen’s group (Atlanta, USA) has probably launched a new era in the treatment of reperfusion injury and the protection of ischaemic but viable myocardium (see Part I). This group has demonstrated that gradual and haemodynamically controlled reperfusion is more effective than abrupt ‘off-on’ artery reopening, and has transformed preconditioning from a random phenomenon to a feasible therapeutic strategy that may become established as a second stage in STEMI reperfusion treatment.

Postconditioning reduces infarct size, preserves vascular endothelial function, decreases polymorphonuclear neutrophil accumulation and activation, decreases calcium overload, delays the restoration of neutral pH, reduces apoptosis, inhibits ROS production and decreases cellular oedema. Hence, mechanical manipulation of the early phase of reperfusion can reduce post-ischaemic endothelial and myocardial injury, while providing conclusive proof of the existence of reperfusion injury. The first randomized clinical study showed that postconditioning during pPCI saved 32% of enzyme release, and turned a laboratory curiosity into a successful clinical application [13].

Proposals for the mechanisms underlying the efficacy of postconditioning have come from molecular biology studies. Yellon’s group has shown that it is possible to protect reperfused myocardium by activating the prosurvival kinase signalling pathway, now called the reperfusion injury salvage kinase (RISK) pathway (see Part I). The effectors of these salvage kinases are the recently discovered mitochondrial transition pores (MTPs) and potassium—ATP channels. When opened (an effect promoted by calcium overload, oxidative stress and ATP depletion), MTPs lose their mitochondrial protective role, causing mitochondria to undergo massive swelling, and to become uncoupled and unable to maintain pH gradient and membrane potential; instead of producing ATP they start to degrade residual ATP. A second consequence of mitochondrial swelling is mitochondrial inner membrane architectural changes that result in the release of cytochrome c, which in turn activates proapoptotic caspases. The first postconditioning mechanism seems to prevent MTP opening and to preserve mitochondrial function. The second effector of postconditioning may be the opening of mitochondrial potassium—ATP channels, provoking a partial mitochondrial membrane depolarization and preventing calcium overload. The opening of potassium—ATP channels in sarcoplasmic reticulum may also decrease calcium overload and hence prevent myofibrillar contracture.

Not all of the signalling molecules that induce salvage pathways are known, although adenosine is recognized as being one of these triggers. The postconditioning technique may slow down adenosine washout by ‘ramped’ reperfusion. Bradykinin, which is synthesized during ischaemia, may also initiate salvage mechanisms. Other drugs that mimic postconditioning, such as opioids, insulin, cyclosporin A, angiotensin inhibitors, glucagon-like peptide-1, erythropoietin, statins, cardiotrophin-1, protein kinase C and transduction inhibitors, such as opioids, insulin, cyclosporin A, may slow down adenosine washout by ‘ramped’ reperfusion. Bradykinin, which is synthesized during ischaemia, may also initiate salvage mechanisms. Other drugs that mimic postconditioning, such as opioids, insulin, cyclosporin A, angiotensin inhibitors, glucagon-like peptide-1, erythropoietin, statins, cardiotrophin-1, protein kinase C and transforming growth factor beta-1, may also activate these pathways and/or inhibit apoptosis directly by blocking caspases [82]. Some of these drugs (cyclosporin A, insulin and opioids) may be in clinical use in this setting in the near future.

Minimalist and low pressure reperfusion

A novel strategy has been proposed recently, based on the hypothesis that achieving a TIMI grade 3 flow (having crossed the occlusion with the wire or a small balloon, but leaving the stenosis), postponing the implantation of a stent for 12–24 h and preventing reocclusion with strong antithrombotic treatment, might protect myocardium against reperfusion injury [83]. Such a scheme results in low distal pressure reperfusion, delays washout, decreases mechanical stretch and may mimic postconditioning. Indeed, low pressure reperfusion is known to induce the RISK pathway, suggesting that such minimalist reperfusion might be comparable with postconditioning. In a pilot, non-randomized study of minimalist reperfusion, ST-
Figure 6. PCI tools available for the prevention and treatment of reperfusion injury: (1) coaxial perfusion balloon catheter allowing drug infusion; (2 + 3) thrombus aspiration and occlusive balloon catheter permitting simultaneous thrombus aspiration and postconditioning; (4) thrombus aspiration and perfusion catheter without balloon (5, 6).

Unresolved issues and future options

Current data demonstrate that while there is no unique ‘magic bullet’ for preventing reperfusion injury, a variety of therapeutic options do exist. If postconditioning is adopted as the principal strategy it will be necessary to identify the optimal sequences for balloon inflations and deflations (length and number), as differences can exist between animal models and humans. The question remains as to whether the postconditioning technique must be driven by ST-segment monitoring and prolonged until a significant decrease in ST-segment elevation is achieved.

In the future, pharmacological postconditioning may be adopted via the intravenous route or intracoronary injection. Intravenous pharmacological postconditioning may also be beneficial for patients treated with thrombolytic therapy. Finally, pharmacological reperfusion injury treatment must be continued for a number of hours to counteract the second delayed window for reperfusion injury.

Conclusion

Reperfusion injury is a proven event, occurring immediately after coronary reopening in STEMI patients but enduring thereafter. Prevention of reperfusion injury might optimize myocardial salvage, acting on the vascular bed as well as on cardiomyocytes. Glycoprotein IIb/IIIa receptor blockers and adenosine are two pharmacological treatments that are applicable immediately, as are thrombus aspiration and perfusion.
mechanical modified reperfusion (postconditioning), pro-
vided that both of these strategies can be used almost simulta-

eously. More trials are needed, but a new era of myocardial 
reperfusion is certainly starting, dedicated not only to the 
epicardial artery but also to microvascular reperfusion and 
cardiomyocyte salvage. On-line ST-segment monitoring, 
available in every cath lab, provides an excellent means of 
measuring the immediate effects of such therapies.

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