The impact of ischemia-reperfusion injury on the effectiveness of primary angioplasty in ST-segment elevation myocardial infarction

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Abstract

The most effective method of reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) is primary percutaneous coronary intervention (PCI), assisted by aspiration thrombectomy and administration of antiplatelet agents and anticoagulants. However, effective restoration of blood flow in the infarct-related artery may paradoxically result in further damage to the heart muscle. This phenomenon, called ischemia-reperfusion injury (IRI), can significantly reduce the beneficial effects of reperfusion therapy. The rapid restoration of blood flow to the previously ischemic area causes a number of pathophysiological mechanisms leading to increased necrosis of myocytes still viable at the end of the ischemic period. It has been postulated that there are several strategies that can reduce damage to the heart muscle. Attempts to translate the results of experimental trials has been disappointing. More recently, however, some of the clinical benefits of ischemic postconditioning in which reperfusion in patients with STEMI who are undergoing PCI is interrupted with short episodes of ischemia were demonstrated. This renewed the interest in the reperfusion phase as a target for cardioprotective therapy. Research in this field has also been reinforced by the discovery of new potential targets for treatment that protects against IRI, such as the kinase pathway to protect against damage (reperfusion injury salvage kinases – RISK) and mitochondrial permeability transition pore. It seems that these findings will help to develop strategies that will improve the efficiency of mechanical reperfusion and may translate into long-term clinical effects.

Key words: reperfusion, myocardial infarction.

Introduction

Effective reperfusion of the occluded coronary artery led to a reduction of myocardial necrosis and significantly improved the prognosis in acute ST-segment elevation myocardial infarction (STEMI) [1]. For the past two decades mortality in STEMI decreased from more than 15% to less than 5% [2]. Such a significant reduction is mainly due to improvements in the availability and efficacy of reperfusion therapy, in particular primary percutaneous coronary intervention (PCI). Currently, in addition to primary angioplasty with stent implantation, manual aspiration thrombectomy and modern, fast-acting antiplatelet agents and anticoagulants have been widely introduced into clinical practice, which further improved the efficiency of reperfusion.

However paradoxically, effective reperfusion therapy and restoration of blood flow in the infarct-related artery may, in some cases, lead to further damage to the heart muscle. This phenomenon is called ischemia-reperfusion injury (IRI) and it can significantly reduce the beneficial effects of reperfusion.

The rapid blood flow to the previously ischemic area causes a number of pathophysiological mechanisms leading to increased necrosis of myocytes which were still viable at the end of the ischemic period and to extension of the infarct zone [3–5]. It is estimated that IRI is responsible for approximately 50% of the final infarct area [6]. Therefore, almost 30 years ago Braunwald called reperfusion a “double-edged sword” [7].

Exploration how to reduce IRI in clinical practice, and thus further how to reduce myocardial necrosis, is particularly important in the era of rapid development of interventional cardiology. It is known that the area of necrosis, and in consequence the area and the extent of left ventricular remodeling, are the factors determining the patient’s prognosis [8].

The presence and severity of IRI has been the subject of debate. The uncertainty was caused by the inability to
accurately assess the progression of necrosis in vivo in the transition from ischemia to reperfusion [9]. The most convincing way to prove the existence of reperfusion injury is to demonstrate that it is possible to reduce the size of myocardial infarction by interventions applied at the beginning of myocardial reperfusion [3].

In animal and experimental models a number of strategies have been shown to ameliorate lethal reperfusion injury. The translation of these beneficial effects into the clinical setting has been disappointing. Nevertheless, recent demonstrations of the benefit of ischemic post-conditioning, in which myocardial reperfusion in patients with acute myocardial infarction who are undergoing PCI is interrupted with short-lived episodes of ischemia, have regenerated interest in the reperfusion phase as a target for cardioprotection. The identification of the reperfusion injury salvage kinase (RISK) pathway and the mitochondrial permeability transition pore (mPTP) as new targets for cardioprotection has also intensified research in this area. It seems that these findings will help to develop strategies that will improve the efficiency of mechanical reperfusion and possibly translate into long-term clinical effects.

**How is reperfusion injury manifested clinically?**

It has been proven that clinically IRI is the reason for the four major types of cardiac dysfunction. The first type is myocardium stunning – mechanical dysfunction persisting after reperfusion despite the absence of irreversible myocyte damage and despite the restoration of normal coronary flow [10]. Improvement appears usually within a few days or weeks after myocardial infarction. Secondly, IRI leads to the “no-reflow” phenomenon. It is the inability to reperfuse the ischemic area due to changes in coronary microvasculature (endothelial cell swelling, microthrombosis, inflammatory infiltrations) [11, 12]. In coronary angiography, “no-reflow” can be seen as a flow in the infarct-related artery < TIMI 3, despite effective and complete recanalization and/or lack of tarnishing of the myocardium (“blush”) as an expression of reperfusion at the level of the coronary microcirculation (myocardial blush grade or TIMI myocardial perfusion grade < 2) – Table 1. Electrocardiographically the sign of the “no-reflow” phenomenon is the lack of full normalization of the ST segment elevations after successful PCI.

**Table 1.** Angiographic markers of reperfusion in the infarct-related artery and in the coronary microcirculation

| TIMI grade coronary flow | Myocardial Bush Grade (MBG) – is based mainly on the INTENSITY of the opacification of the myocardium in the distribution of the culprit lesion | TIMI Myocardial Perfusion Grade (TMPG) – is based mainly on the DURATION of opacification of the myocardium in the distribution of the culprit lesion |
|-------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| TIMI 3                  | Normal coronary flow                                                                             | Normal entry and exit of dye from the microvasculature. There is the ground glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit artery similarly to the area of distribution of contra- or ipsilateral artery |
| TIMI 2                  | Dye passes the whole artery but significantly slower in the distal part of the vessel than in contra- or ipsilateral artery (> 3 cardiac cycles) | Delayed entry and exit of dye from the microvasculature. There is opacification of the myocardium that is strongly persistent at the end of the washout phase i.e. dye is strongly persistent after 3 cardiac cycles but less than 30 s |
| TIMI 1                  | The contrast material passes beyond the area of obstruction, but “hangs up” and fails to opacify the entire coronary artery distal to the obstruction for the duration of the cine run | Dye slowly enters but fails to exit the microvasculature. There is opacification of the myocardium that fails to clear from the microvasculature, and dye staining is present on the next injection (> 30 s between injections) |
| TIMI 0                  | No antegrade flow beyond the point of occlusion                                                  | Dye fails to enter the microvasculature. There is no blush in the distribution of the culprit artery – lack of tissue level perfusion |

**MBG 3**
- There is well visible ground glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit artery similarly to the area of distribution of contra- or ipsilateral artery

**MBG 2**
- There is visible blush in the distribution of the culprit artery but worse than in the area of distribution of contra- or ipsilateral artery

**MBG 1**
- Minimal blush in the distribution area of the culprit artery

**MBG 0**
- There is no blush in the distribution of the culprit artery or persisted blush (dye staining is present on the next injection) – lack of tissue level perfusion

**The “no-reflow” phenomenon after successful primary angioplasty (i.e., after the residual stenosis ≤ 30% was achieved) is defined as: the flow in the infarct-related artery TIMI ≤ 3 or TIMI 3 flow and MBG/TMPG ≤ 2. TIMI – thrombolysis in myocardial infarction**
Mechanisms of ischemia-reperfusion injury

For the first time reperfusion injury in the heart was demonstrated by Jennings et al. [14]. They described the histological features of reperfused ischemic canine myocardium in which cell swelling, contracture of myofibrils, disruption of the sarcolemma and the appearance of calcium phosphate microparticles in the mitochondria were observed.

As a result of coronary artery occlusion, a significant number of pathophysiological mechanisms associated with reduced cardiac access to oxygen and glucose occur. The amount of intracellular ATP decreases, functions of ion pumps and enzymes are impaired and the permeability of cell membranes and intracellular calcium concentration increases rapidly [15–17]. In the extracellular space and intracellularly pH drops as a result of accumulation of H⁺ ions (mainly due to the accumulation of excess lactic acid), and osmolality increases due to intracellular accumulation of osmotically active substances [15–17]. Infarct-related artery recanalization and rapid reflow of oxygenated blood to the ischemic area cause a sudden change in the extracellular environment and adverse metabolic changes. Reperfusion leads to rapid correction of pH due to lactic acid leaching and activation of the Na⁺/H⁺ exchanger (pH paradox). This leads to an increase in sodium ion concentration in the cell, then to inhibition of retrograde Ca²⁺ transportation through the Na/Ca exchanger, or even its reversal, which increases intracellular Ca²⁺ accumulation. Consequently, the activation of a number of enzymes and contractile apparatus leads to contraction of the cardiomyocyte in the early stage of reperfusion [3–5]. Sudden reperfusion also induces oxidative stress due to the influx of oxygenated blood and inflammatory cell activation (oxygen paradox) [18]. Reactive oxygen species (ROS) (free radicals) cause lipid peroxidation of the cell membrane and damage to various intracellular enzymes, and DNA [18, 19]. Moreover, the permeability to Ca²⁺ ions and cell calcium overload increases. An important component of the IRI is also infiltration of inflammatory cells and endothelial cell swelling, rapid deterioration of endothelial function and microthrombosis, which lead to the “no-reflow” phenomenon [12, 18]. These mechanisms (calcium ion overload, increased ROS, pH correction) lead to prolonged opening of a non-selective channel in the inner mitochondrial membrane – mPTP [20, 21]. Mitochondrial permeability transition pore plays a central and crucial role in the phenomenon of reperfusion injury. The opening of the channel causes deep and usually irreversible changes in mitochondrial bioenergetics and leads to the start of mechanisms causing necrosis and apoptosis of cardiomyocytes. The rapid increase of mitochondrial membrane permeability to ions and molecules (> 1.5 kDa) leads to swelling of the matrix, the disappearance of membrane electrochemical gradient and inner mitochondrial membrane rupture. This leads to phosphorylation uncoupling, the loss of ATP and NAD⁺, Ca²⁺ ion leakage and, consequently, the disintegration of the mitochondrion. As a result of reduction of the redox potential there occurs additional production of reactive oxygen species (RIRR – ROS-induced ROS release) and leakage of pro-apoptotic enzymes such as cytochrome C [19–22]. These mechanisms lead to rapid necrosis of many hitherto live myocytes and sudden cardiac infarct zone expansion with all clinical consequences. The prevention of mPTP opening seems to be the key mechanism for all cytoprotective strategies against IRI.

Modification of reperfusion (postconditioning)

In 2003, Zhao et al. documented in a canine model the effectiveness of intermittent episodes of ischemia and reperfusion applied after prolonged closure of the infarct-related artery [23]. The left anterior descending artery in dogs was ligated for 45 min and then there were performed intermittent periods of reperfusion and re-occlusion (3 x 30 s). The authors observed 44% reduction in infarct size as compared with the control group. For such a procedure the term postconditioning (POSTCON) was adopted. A few postulated mechanisms of cytoprotective effects of POSTCON exist. It has been shown that modification of reperfusion affects important mediators of lethal reperfusion injury, reducing oxidative stress, rapid washout of adenosine, osmotic shock and intracellular calcium ion overload. POSTCON also improves endothelial function, reduces cardiomyocyte apoptosis, reduces infiltration of neutrophils and, in particular, delay the restoration of neutral pH [3, 6, 24–27]. POSTCON is also a strong impulse which activates the RISK (reperfusion injury salvage kinase) pathway called the survival kinase pathway [28]. POSTCON causes an increase in the extracellular space of endogenous ligands, such as adenosine, opioids, bradykinin and PAR-2 agonists (protease activated receptor-2), which, acting on specific membrane receptors (G-protein-coupled receptors – GPCR), triggers multiple signaling pathways, in this particular pathway MAPK kinase-ERK 1/2 (mitogen-activated protein kinase – MAPK, extracellular signal-regulated kinase 1/2 – ERK 1/2) and PI3K/Akt (phosphoinositide 3 kinase – PI3K). This leads consequently to the closure of key mPTP channels in the mitochondrial membrane [19, 20, 25]. Recently, alternative survival pathways activated by POSTCON were discovered. The most important one is the SAFE (survivor activating factor enhancement) pathway [29]. Two years after the Zhao et al. publication, the first clinical application of modified reperfusion in patients treated with primary percutaneous coronary intervention was made [30]. Research conducted initially in small groups of patients were very promising. Several different algorithms of intermittent reperfusion
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ly all of them have proven to be ineffective, or difficult to use clinically during the acute phase of myocardial infarction. Treatment with antioxidants (reducing the production of free radicals) has been proved to be ineffective [51]. There were also no cardioprotective effects of magnesium treatment and glucose, insulin and potassium infusion [52]. Also ineffective and even harmful was the administration of drugs that block the Na/Ca exchanger (cariporide, eniporide) [53, 54]. Some positive results especially in treatment of the no-reflow phenomenon can be attributed to vasodilator drugs such as verapamil, sodium nitroprusside or nicorandil [55]. Significantly higher hopes are associated with the drugs that have been shown in experimental studies to reduce reperfusion injury through the activation of the RISK pathway. Drugs with this mechanism of action undergoing clinical evaluation include atorvastatin, erythropoietin, atrial natriuretic peptide and analogues of glucagon-like peptide-1.

Experimental studies have reported that a high dose of atorvastatin may reduce the extent of IRI. Promising results have been demonstrated by the ARMYDA-ACS study, which showed that 80 mg of atorvastatin administered to patients with acute myocardial infarction without ST-segment elevation 12 h before PCI reduced the infarct size [56]. The Statin-AMI study examined the effectiveness of high- and low-dose atorvastatin before primary PCI in STEMI. In a randomized group of 171 patients (a relatively small study group), a high dose of atorvastatin resulted in no significant clinical improvement, but it was associated with significant improvements in angiographic para-meters after treatment [57].

Erythropoietin has been assessed in the REVEAL study. Four-hour infusion of erythropoietin did not reduce the infarct size measured by MRI between the 2nd and 6th day of admission. In the group treated with erythropoietin adverse cardiovascular events were more frequently observed [58].

In the J-WIND study the authors tested whether the addition of atrial natriuretic peptide improves the results of reperfusion therapy [59]. The study patients were eligible for both thrombolytic and primary angioplasty. 72-hour infusion of atrial natriuretic peptide caused a 15% (p = 0.016) reduction in enzymatic infarct size and improved left ventricular ejection fraction after 6–12 months by 2.2% (p = 0.024).

In a recently published study, a group of Danish researchers evaluated exenatide (BYETTA, Amylin-Lilly USA) – an analog of glucagon-like peptide-1, which is used in the treatment of type 2 diabetes [60]. One hundred and seventy two patients with STEMI were randomized to receive an infusion of the study drug starting 15 min before PCI or placebo. Infusion was maintained 6 h after the procedure. It was confirmed that administration of the drug in the acute phase of myocardial infarction is safe and there was a significant reduction in infarct size assessed by MRI.

Clinical application of cardioprotective methods during primary percutaneous coronary intervention

May successful reperfusion therapy with primary angioplasty be supplemented by additional cardioprotective strategies to effectively protect against reperfusion injury? At present, none of them is still found to be fully recognized and the routine in clinical practice. Based on previous studies, both POSTCON and other methods used to prevent IRI can benefit patients with a high risk of STEMI, i.e. with a large area of ischemia (proximal closure of large coronary arteries) and with total ischemia time shorter than 3–4 h, or in those patients who still retain a relatively large area of viable myocardium. Final confirmation of the effectiveness of cardioprotective strategies, supporting optimal reperfusion therapy, and the widespread adoption of these methods as the standard for treatment of primary percutaneous coronary intervention therefore require further clinical trials, multi-center and in larger groups of patients, as well as the careful selection of protocols and clinical endpoints. It seems, however, that these studies are promising due to the significant potential benefits for patients with STEMI.

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