

Is further improvement of the treatment of acute coronary syndromes still possible?

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Abstract

Successful treatment of myocardial infarction related to early reperfusion therapy has caused growing interest in not only ischemic but also myocardial reperfusion injury. Most experimentally confirmed preservation myocardial reperfusion injury methods have failed in clinical practice. Probably one reason for their ineffectiveness was the very narrow "time window" necessitating application of protective methods before obtaining reperfusion. Reducing the myocardial necrosis and preservation of the left ventricular function are the main goals of the therapy. Experimental data suggest that up to 50% of the infarct size may be related to reperfusion injury. Function of the mitochondrial permeability transition pore (mPTP) in the inner mitochondrial membrane, being closed during myocardial ischemia and opening at the beginning of reperfusion, is the common element linking protective methods. Their opening gives rise to metabolic alterations and may lead to cardiomyocyte death (lethal reperfusion injury). That is why successful intervention, very difficult to achieve, has to take precedence over coronary blood flow restoration. Cyclosporin A, an mPTP blocker, was effective in the first small clinical trial in preservation of myocardial reperfusion injury in acute coronary syndrome intervention. Second mitochondrial injury action is related to generation of reactive oxygen species (ROS) including superoxide anions. Reactive oxygen species accumulation results in mitochondrial pH increase leading to mPTP opening. Discovery of a small molecule cationic peptide, readily penetrating cell membranes and concentrating in mitochondria, may give new therapy perspectives. Combining therapy may be possible as well.

Key words: myocardial infarction, reperfusion, cyclosporin A, Bendavia, reactive oxygen species.

Introduction

It is estimated that each year about 15 million people worldwide suffer from myocardial infarction. Myocardial infarction and its consequences lead to the death of about 7 million people worldwide annually and 300 thousand of those are sudden cardiac deaths (SCD). ST-elevation myocardial infarction (STEMI), which is most often caused by total occlusion of the coronary artery, is responsible for approximately 40% of all myocardial infarctions [1-3].

Early reperfusion by means of percutaneous coronary intervention and the use of antiplatelet drugs to prevent thrombosis are the most efficacious methods of treatment of acute myocardial infarction. This kind of treatment started in the first hours of coronary artery occlusion decreases the size of myocardial necrosis (infarction) and improves early- and long-term prognosis.

In Poland, an undoubted success in terms of this type of treatment has been achieved by development of an effective system for invasive treatment of acute myocardial infar-

tion based on a network of hospitals with catheterization laboratories operating on a 24/7 basis. This leads to evident benefits in terms of in-hospital mortality reduction from a dozen to about 4-5% (L. Poloński: Polish ACS Registry 2011 – unpublished data and own unpublished studies). This document is an attempt to, perhaps partially, answer the title question addressed to the author during the Zabrze Cardiology Conference in May this year. At that time I had only 3 min to answer. Since the issue is important and prospective I have discussed it further although some of its aspects (such as prevention of procedural complications) had to be mentioned briefly.

Spectacular progress in this matter is definitely over and it will not be easy to cut down another tenth of a percent. The results of treatment of myocardial infarction depend on its size and possible complications. The latter include mainly in-stent thrombosis and bleeding. Thrombosis is a dangerous, but relatively rare complication.

The problem of bleeding complications is increasing – there was a double increase observed in 2011 (L. Poloński:

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Polish ACS Registry 2011 – unpublished data). This is a price we pay for more and more aggressive (effective) antiplatelet treatment, but also for execution of percutaneous interventions in elderly patients and in patients with concomitant diseases known to increase the risk of bleeding. The solution seems to include individual tailoring of treatment to specific patients and avoidance of new and more powerful drugs in the group of elderly patients and in those at high risk of bleeding due to concomitant diseases. Detailed indications regarding precautions in the use of new drugs are included in the recommendations of scientific societies.

How to reduce the size of necrosis/infarction?

There is an unsolved problem consisting of a relatively long delay between the first medical contact and the time to reperfusion. This delay directly affects the size of necrosis (infarction) and therefore also the post-infarction course, which depends on the dynamics and quality of post-infarction myocardial remodeling. This is in line with a promoted slogan that "time is muscle". This in turn determines the occurrence (or not) of heart failure with all its consequences in the long term. Another unresolved problem, closely connected to the previous one, but extending beyond it, is a relatively high double-digit annual mortality (L. Poloński: Polish ACS Registry 2011 – unpublished data and own unpublished studies). It may be assumed that it depends on the extent of myocardial necrosis, but also on in-hospital complications such as peri-procedural bleeding. The idea to reduce the delay to reperfusion discussed above is a basis for multidirectional attempts to improve long-term results made for many years by individual teams as well as advocates of interventional treatment of acute coronary syndromes operating both within societies and present in the media. An improvement of organizational efficacy, as indicated by past experience, is a difficult, long-term and slowly occurring process. It requires a change of thinking of treatment subjects (potential patients), medical rescue teams and those responsible for organization of work at all stages of transport and treatment.

Reperfusion injury

Another factor contributing to the size of myocardial infarction is reperfusion injury. The possibility to reduce the area of myocardial infarction by influencing reperfusion injury was suggested by several experimental studies on animals and a few clinical studies [1, 5].

Previous clinical trials aimed at reduction of this mechanism of infarct zone extension are very limited and their practical use in the clinic depends on further progress of knowledge.

ST-segment elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI) with stenting is a clinical model of ischemia-reperfusion. Early reperfusion achieved by PCI with stenting on one hand prevents

the extension of myocardial necrosis, but on the other hand causes often irreversible injury to previously ischemic cardiomyocytes [2, 4-6]. Similar observations were made in non-ST-segment elevation myocardial infarction (NSTEMI), where both enzymatic examination and magnetic resonance studies showed coexistence of irreversible myocardial injury.

Lethal myocardial reperfusion injury reduces the benefits of early reperfusion, causing expansion of the irreversible injury zone by as much as 50% in comparison to myocardial mass injured by ischemia (animal experimental studies) [2, 6]. It may thus contribute to adverse clinical outcome in the post-infarction period, including higher early and post-hospital mortality, and/or to the onset of heart failure despite successful reperfusion in the acute phase [5].

In summary, the size of necrosis (infarction) in patients undergoing treatment is influenced by time to reperfusion (with PCI, fibrinolysis or spontaneous) and by reperfusion injury. We try to influence the first element by reduction of pain-to-balloon time (so far with limited success).

Is it possible to influence the second element?

Over the years medical teams using reperfusion therapy were helpless in the prevention of post-reperfusion myocardial injury. Several promising experimental studies using animal models and various techniques to prevent reperfusion injury did not work out in the clinic [2, 5]. However, they have led to a better understanding of the mechanism of ischemic and reperfusion injuries. The discovery and confirmation in several experimental animal studies that irreversible reperfusion injury of cells (not only cardiomyocytes) is caused by change in permeability of mitochondrial permeability transition pores (mPTP) localized in the inner mitochondrial membrane resulted in renewed interest of clinical teams in the possibility of reperfusion injury control [1, 2, 5, 6].

According to current knowledge, these channels remain closed during ischemia and "open" during the early phase of reperfusion in response to specific cytosolic proteins and unstable oxidative compounds carrying reactive oxygen species (ROS) [7-10]. The efficacy of these channels is expected to play a crucial role in the maintenance of normal mitochondrial membrane potential and, consequently, proper function of mitochondria and myocardial cells in case of ischemia/reperfusion [6, 10].

Ischemic myocardial cells have reduced ATP resources, accumulate calcium ions and present other electrolytic disorders, which are accompanied by an increase of the amount of free radicals. Activation of mPTP during this period is probably prevented by low pH, caused by ischemia, which is followed by rapid growth of pH in the 1st min of reperfusion unlocking mPTP [7].

Opening of mPTP causes free passage of proteins and electrolytes through the mitochondrial membrane. This

results in mitochondrial edema and loss of their function in intracellular oxygenation [2, 6, 7, 10]. It is believed that blockage of the intra-mitochondrial respiratory chain leads to changes in mitochondrial membrane potential, which results in penetration of pro-apoptotic proteins (including cytochrome C) into the cytosol [3, 7, 9, 10]. Depletion of cytochrome C within the mitochondria increases the disorder of the still existing ischemia respiratory chain disorganization and therefore potentiates dysfunction of the previously injured cells by ischemia [11]. In extreme situations opening of the mitochondrial pores may be irreversible and in consequence lead to mitochondrial disruption [6, 9].

Recent studies suggest that mitochondrial injury may be dependent on the receptor protein known as Nur 77. In normal conditions this protein is located within the cell nucleus. Oxidative stress causes translocation of this protein into the mitochondria, which leads to cytochrome loss and cellular death [12].

It is highly possible that the inner mitochondrial membrane consists of two types of pores responsible for mitochondrial injury during reperfusion. Reperfusion injury may depend, apart from kinase-dependent mPTP, on pores leading to changes of mitochondrial membrane potential in the presence of ROS and to accumulation of excessive anions within the mitochondria [10, 13]. Change of mitochondrial membrane potential in the presence of ROS may lead, independently from mPTP function, to abnormalities of ATP synthesis and in consequence to cellular death [10].

Results of experimental studies suggested that a similar "mitochondrial" mechanism is responsible for microvascular dysfunction known as the no reflow phenomenon accompanying reperfusion [10]. Mitochondrial dysfunction caused by ischemia/reperfusion was also shown to play a significant role in the experimental model of cardiac arrest [7, 9]. It may be assumed that abnormalities caused by ischemia/reperfusion are particularly frequently expressed in well-vascularized organs such as the brain, heart and kidneys. Dysfunction of these organs dominates in the picture of post-reanimation syndrome.

Some of the authors of the published experimental studies believe that cytochrome C, which is considered as a marker of mitochondrial injury in highly vascularized organs, may be an important indicator of the degree of post-reanimation injury, useful in the prognosis of survival after successful reanimation [2, 3, 7, 11].

Studies aimed at confirmation of the clinical value of reperfusion injury prevention run in three directions. The first of them is aimed at the assessment of clinical efficacy of the phenomenon known as ischemic post-conditioning, the second analyzes the value of substances directly blocking mPTP, and the third focuses on the significance of activation of protein kinases (RISKs), which should protect mitochondria of the myocardial cells against reperfusion injury [6].

Initial, single clinical studies assessing the value of the described cardioprotective procedures, mainly in patients

undergoing primary PCI, indicate the need for further research in this direction.

Blockage of mitochondrial inner membrane permeability

Ischemic post-conditioning during reperfusion is based on repeated balloon inflation during PCI in STEMI for several dozens of seconds. Such reperfusion interrupted by ischemia is aimed at activation of protein kinases showing cardioprotective actions by blockage of mPTP permeability [14].

Cyclosporin A is a specific inhibitor of the mPTP permeability and decreases post-reperfusion injury of the organs [1-3, 9]. So far, only one clinical study has shown that administration of cyclosporin A before reperfusion in STEMI treated with primary PCI of the infarct-related artery reduces the size of myocardial injury by about 20% [1, 5]. There were no side effects of such treatment after administration of a single bolus of the drug (2.5 mg/kg of body mass) [1]. There were also no adverse effects of the drug administered before reperfusion on post-infarction remodeling of the left ventricle in a 6-month follow-up [5].

Concerns regarding the use of cyclosporin A as an mPTP inhibitor were related to the fact that this drug does not specifically react with cyclophilin D localized within the mitochondria. Irrespectively of the inhibitory effect on mPTP through inhibition of mitochondrial cyclophilin D, cyclosporin also inhibits cyclophilin A localized in the cytosol and playing a role in the calcineurin activity regulating pathway (a protein phosphatase). This pathway, dependent on proteins activated by calcium ions, is believed to be one of the most important parts in generation of compensatory hypertrophy of the remote myocardium [5, 6, 15, 16]. This mechanism may therefore be important in the process of post-infarction left ventricular remodeling.

This was proved in experimental animals by showing that prolonged administration of cyclosporin A led to an increased tendency for post-infarction heart failure [15, 16]. The effect of single dose administration was unknown. Teams of researchers from Lyon and Montpellier demonstrated lack of such an adverse effect of the drug [5].

Administration of cyclosporin A before the reperfusion in the experimental model of cardiac arrest decreased the post-reperfusion injury of the heart, liver and kidneys and increased the chance for survival of the experimental animals [3, 9].

The currently ongoing randomized trial may confirm clinical benefits of cyclosporin A use before interventional treatment in acute coronary syndromes.

The use of antioxidant compounds

The discovery of low-molecular-weight proteins with a positive electric charge, penetrating into the mitochondria – organelles where oxidative processes are very intensive – initiated a study on the possibility of their use in block-

age of damaging effects of ROS under oxidative stress. Peptides studied for this purpose include Bendavia (MTP-131), the effectiveness of which, documented by decrease in the cardiac reperfusion injury, was demonstrated in experimental animals, in which the use of this peptide decreased the infarct zone from a dozen to about 30% [13].

Studies showed no protective effect of this protein during ischemia. The protein showed maximum efficiency during oxidative stress caused by reperfusion after ischemia, when the generation of ROS is high [13]. The effectiveness of the protein was based on neutralization of ROS or on blockage of their generation in the mitochondria. Earlier studies analyzed the dynamics of ROS generation under oxidative stress and showed increase of their level in the first 5 min of re-oxygenation and their disappearance after 20 min of reperfusion [10, 13].

The most intensive degradation of ROS was observed during the first 20 min of reperfusion, which was related to the greatest intensity of cell death at the same time. Bendavia does not directly block mPTP – as demonstrated for previously discussed cyclosporin A. Its protective effect on cardiomyocytes is mainly based on the antioxidant effect and on maintenance of mitochondrial electrochemical membrane potential at the appropriate level, by neutralization of ROS. Therefore, it acts to neutralize free radicals [10]. Free radical scavengers have been considered for a long time, but attempts to use them in the clinical setting were disappointing.

The protective effect of Bendavia on mitochondria sustains the function of these organelles (ATP production) and prevents cardiomyocyte damage [10]. Randomized studies with the use of this protein in humans have just started.

Summary

The problem related to all of the described interventions aimed at reduction of reperfusion injury is caused by a very narrow time window forcing the use of these interventions in an early phase of reperfusion. Pharmacological compounds need to be administered before reperfusion.

Mitochondrial pores (mPTP), which open during the first min of reperfusion, are a common element combining all of these interventions [5]. Their opening should be considered as an irreversible moment generating reperfusion dependent lethal injury. Therefore, successful intervention which is difficult to achieve, must precede this moment.

The second mechanism, which is partially independent, but contributes to the mitochondrial membrane damage, is associated with reactive oxygen species (ROS). Probably ROS take part in the cell damage through their influence on the mPTP function in the mitochondria. It is also possible that these radicals influence mitochondrial membrane damage by a mechanism independent from mPTP [10, 13].

If the clinical significance of these compounds is confirmed, it cannot be excluded that they synergistically protect against reperfusion injury of the ischemic tissues, not only to the myocardium.

The future will show whether, and to what extent, this new perspective of treatment improves early and long-term prognosis of patients with ACS, including patients after cardiac arrest.

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