ADENOSINE ASSOCIATED PRE- AND POSTCONDITIONING IN REAL MEDICAL PRACTICE

Nestor Seredyuk, Mykhailo Fedorchenko, Mykyta Bielinskyi

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Abstract: It has been established that adenosine is a universal trigger of the processes of preparation (conditioning) of the myocardium for ischemic injury, which is confirmed by randomized clinical trials AMISTAD II, TIMI-4, TIMI-9B. Adenosine is included in the guidelines of the ESC Task Force (European Society of Cardiology) as a means of basic therapy, as a representative of the class of potassium channel stimulants (2019) [1]. However, the use of adenosine as an injectable form for intracoronary or intravenous administration is associated with a number of side effects - rapid degradation of the drug in the bloodstream, the need for careful monitoring of systemic hemodynamics (hypotension, tachy- or bradyarrhythmia, ventricular tachycardia, atrioventricular block), frequent development of undesirable gastrointestinal manifestations. All this prompted the search for an alternative form of adenosine use, which would allow wider use of the potentially beneficial effect of adenosine on ischemic pre- and post-conditioning in real medical practice.

More recently, on the pharmaceutical market of Ukraine for the first time appeared a pharmacological agent - Advocard, as a drug with the ability to start the processes of pre- and post-conditioning, with sublingual (oral) form of application. Advocard is an original combined polypill drug with three components: adenosine-5-triphosphate-gluconate-magnesium (II) trisodium salt (magladen) – 18,6-29,25 mg, molsidomine – 0,3 mg and folic acid - 0,45 mg. Recommendations for the use of the Advocard in medical practice are based on the results of clinical studies, which proved that the oral (sublingual) form of adenosine is not only effective and appropriate, but also safe with long-term use.

The therapeutic efficacy of Advocard in chronic coronary syndromes [stable, vasospastic, microvascular angina (pain of small coronary vessels), painless myocardial ischemia] and acute coronary syndromes (STEMI / NSTEMI, instability to stenocardia) before or immediately after coronary stenting is in counteracting the mechanisms of reperfusion injury.

Clinical practice has shown that Advocard is appropriate for the prevention of NO-REFLOW after opening the epicardial coronary artery, even with the result of TIMI-3. Thus, the Advocard opens the prospect of improving the effectiveness of coronary interventions and is an adjunct to complete myocardial revascularization.

Keywords: *preconditioning, adenosine, myocardial infarction, no-reflow, revascularization*

Introduction. Observations and experience of general practitioners have shown that myocardial infarction (MI) occurs more easily in those patients in whom its development is preceded by short-term angina attacks, which disappear spontaneously or after taking nitroglycerin. It is an action of preparation (conditioning) of a myocardium for more expressed ischemia. This phenomenon is called ischemic preconditioning (IschPre-K), i.e. a kind of “training” of the myocardium by prethreshold ischemia [2, 3, 4].

The IschPre-K phenomenon was first described by R. Lange and co-authors in 1984. The authors showed (in an animal experiment) that the decrease in adenosine triphosphate (ATP) reserves after repeated short-term myocardial ischemia is less expressed than in cases of a single long-term episode of myocardial ischemia [5].

Conditioning mechanisms. In 1986, C. Murry and co-authors [6] reported that short episodes of myocardial ischemia (lasting up to 5 min) reduced the size of myocardial infarction by 25% with subsequent occlusion of the dog's coronary artery lasting 40 min (compared to controls where preconditioning was not performed). The authors suggested to designate this syndrome by the term “IschPre-K”.

The phenomenon of ischemic postconditioning (IschPost-K) is defined as protection of the myocardium of reperfusion injury [7]. IschPost-K means the ability to start cardioprotection after critical ischemia, which has already occurred [4].

It was later found that stimulation of adenosine (purine) receptors by adenosine or other agonists of these receptors is required for activation of IschPre-K. It was also found that the use of adenosine receptor antagonists blocks the launch of IschPre-K. In this way, the main trigger of the IschPre-K process was established – adenosine [8]. Two other mechanisms for triggering IschPre-K were soon discovered – bradykinin [9] and opioids [10]. Among the endogenous triggers IschPre-K receptor-dependent (adenosine, opioids, norepinephrine, bradykinin, serotonin, acetylcholine) and receptor-independent factors (NO, IL-1B, IL-2, TNF α , reactive oxygen species, calcium ions) are distinguished. Among the exogenous triggers, the effectiveness of monophospholipids and activators of K_{ATP} channels is studied. An important feature of the trigger stage of IschPre-K is the launch of many, sometimes duplicating signaling paths.

At the mediator stage, signal transmission from

receptors to the target is carried out by protein kinase C, tyrosine kinase, phosphatidyl-inositol-3-kinase, myogen-activated protein kinase (MAPK) and others. [4]. Subsequently, activation of effector proteins of mitochondrial and sarcolemic K_{ATP} channels and NO synthase is observed. Activation of sarcolemic K_{ATP} channels reduces the duration of the action potential and weakens the overload of cardiomyocytes with calcium ions.

Fig.1 Global scheme of signaling mechanisms involved in the conditioning process [11]

In Fig. 1 shows a schematic representation of the signaling mechanisms of conditioning [11].

Therefore, the subanalysis of the randomized clinical trial (RCT) TIMI4 [12] confirmed that patients who had angina attacks before the development of myocardial infarction had a smaller infarct size and more favorable clinical results. For example, the incidence of severe heart failure or cardiogenic shock in the group of patients with previous angina attacks was 1%, while in the control group (without signs of severe heart failure or CABG) - 7% ($p = 0,006$). These data were confirmed in RCD TIMI-9B [13], in which patients with previous angina within the last 24 hours before the first symptoms of MI showed significantly fewer cardiovascular events (CVD) in the first 30 days after MI. In such patients, there was a tendency to lower levels of creatine phosphokinase (KfK) in blood plasma compared with the control group [13].

This was followed by studies that supplemented the list of evidence for the beneficial effects of mild to moderate quantity of angina attacks on the development of myocardial infarction and its complications, including reperfusion syndrome after successful revascularization by coronary stenting or coronary artery bypass grafting.

It has been confirmed that during short-term non-fatal ischemic episodes, cardiomyocytes (CMCs) produce adenosine, which activates the intracellular messenger protein kinase C (PrK-C), under the influence of which

previously closed (normal) ATP-dependent potassium channels are opened. Due to the discovery of ATP-dependent K^+ channels, there is a protective shortening of cardiac action potentials and hyperpolarization of membranes. This effect is energy-saving in the event of a recurrence of myocardial ischemia in the near future. At the same time there is a decrease in metabolic activity, resulting in a decrease in the rate of ATP degradation, slows down glycogenolysis, reduces the rate of growth of intracellular acidosis, slows the entry of Ca^{2+} ions into the cell (closing of calcium channels). Due to this compensatory mechanism, the myocardium better tolerates more profound and prolonged myocardial ischemia (Fig. 2).

Thus, the essence of IschPre-K is to open K_{ATP} channels and close Ca^{2+} channels, the end result of which is vasodilation and a number of metabolic effects aimed at slowing down the breakdown and enhancing ATP synthesis.

Therefore, the phenomenon of IschPre-K is defined mainly by three components: adenosine as the main trigger of this process, protein kinase C as a leading intracellular messenger and ATP-dependent potassium channels as terminal effector factors. Influence on these components in one way or another can either stimulate or inhibit preconditioning [14, 15]. In addition to adenosine, which is a leading stimulator of this preconditioning mechanism, bradykinin, opioids, and other factors can stimulate IschPre-K. It is known that adenosine stimulates IschPre-K by activating protein kinase C, and bradykinin and opioids – by triggering a complex cascade involving phosphatidyl-inositol-3-kinase, protein G, mitochondrial ATP-dependent potassium channels. This variety of ways to activate IschPre-K indicates the exceptional importance of this phenomenon. Even if, due to certain circumstances, one of the paths is blocked, others allow to fully start this protective mechanism. However, the adenosine pathway is the shortest, simplest, and least damaged and is often the main preconditioning mechanism.

It was found that all known mechanisms of myocardial conditioning are reduced to the impact on the inner membrane of mitochondria – mitochondrial permeability transition pore, mPTP. It is important in which way the signal from protein kinase C is transmitted to the effector K_{ATP} channels. Three such pathways are known: reperfusion injury salvage kinase pathway (RISK), the last link of which is mPTP activation; survivor activating factor enhancement pathway (SAFE), the endpoint of which is also mPTP; eGMP / PKG pathway – the path of entry of Ca^{2+} in the mitochondria [16]. The actual activation of mitochondrial pores (mPTP), observed in the early period of reperfusion, has a number of undesirable consequences for the cell – rapid swelling of the

Fig.2 Mechanisms of ischemic preconditioning

mitochondrial matrix, decreased ATP production, activation of apoptosis. Inhibition of mPTP pore opening weakens the manifestations of reperfusion damage [17].

The most unfavorable factors for IschPre-K are old age and diabetes mellitus (DM), in which the normal adaptive capacity of the myocardium is sharply suppressed [18]. At the same time, regular physical activity prolongs the effects of IschPre-K - prolongation of "myocardial youth", which was studied by Mokhort MA, Kutovyi Yu.M. [4]. Testosterone and estrogens also have a positive effect on IschPre-K, as they stimulate the formation of NO synthase, which is important for the opening of K_{ATP} – dependent mitochondrial channels, and hence the initiation of ischemic preconditioning [19]. At the same time, hypercholesterolemia and atherosclerosis have a negative value for IschPre-K, but this thesis needs further study. Left ventricular hypertrophy (LVH) also has a negative effect on the development of IschPre-K. LVH regression has been shown to enhance myocardial response to ischemia [20]. Thyroid hormones partially eliminate the undesirable suppression of natural cardioprotection, but this effect also requires further investigation [3, 21].

The practical significance of IschPre-K. Convincing evidence of the positive impact of IschPre-K

is presented in the work of SH Rezkalla et al. [22] and RCD – TIMI-4, TIMI-9B [12, 13], AMISTAD-II [23].

The antiarrhythmic effect of IschPre-K in clinical conditions is presented in the study of ZK Wu et al. [24]. It was found that aortic compression before coronary artery bypass grafting (CABG) reduced the incidence of ventricular tachycardia during and during the procedure. IschPre-K can be caused also by balloon dilatation of a coronary artery (KA) during percutaneous coronary intervention (PCI). This provides optimization of the implanted stent and better results after coronary stenting. In a study by L. Argaud et al. [25] it was proved that short-term ballooning of the blood pressure cuff does not increase the level of collateral perfusion, but contributes to less profound ischemia caused by the intervention. This means that we are talking about the stimulation of the actual processes of ischemic preconditioning, rather than collateral blood flow.

The so-called remote preconditioning deserves special attention, the essence of which is to create short-term episodes of ischemia in tissues far from the heart.

The effect of remote ischemic preconditioning on the dynamics of troponin I in patients with severe forms of acute coronary syndrome during coronary artery stenting was studied by S.F. Veremchuk and co-authors [26]. The authors proposed the following method of

remote preconditioning. A cuff of appropriate size was measured on the lower limb in the thigh area to measure blood pressure. Ischemia was caused by 4 cycles of inflating the cuff to a pressure of 200 mmHg (for 5 minutes) followed by reducing it to zero. After 5 minutes, the procedure is repeated, the total duration of the technique – 40 minutes. The time from the beginning of remote preconditioning to recanalization of the infarct-dependent coronary artery was 13.3 ± 1.4 minutes. At the same time postoperative level of troponin I in patients of the main group changed towards decrease, and in control – on the contrary increased ($p = 0,00386$). This means that remote preconditioning has a positive effect on the effectiveness of coronary revascularization.

Pharmacological conditioning. Noteworthy is the idea of using for the purpose of pharmacological pre- and postconditioning potassium channel activator nicorandil [27]. It is an activator of potassium channels and at the same time a donor of nitric oxide. This double effect of Nicorandil is attractive to the general practitioner. In a study by C. Murry et al. [6] it was found that nicorandil significantly reduces the risk of developing Q-MI. Moreover, the use of nicorandil 5 minutes before coronary transluminal angioplasty (balloon inflation) in patients with angina causes a significantly lower degree of ischemia than was observed in the control group [28].

The IONA-N10 study (Impact of Nicorandil in Angina) confirmed a reduction in the number of serious coronary events in patients with stable angina on the background of continuous use of Nicorandil [29].

The cardioprotective effects of valsartan (a component of the complex drug Entresto), levosimendan, diazoxide, nitrates, estrogens, testosterone are studied. However, regarding the activation of preconditioning processes, they have been insufficiently researched [30, 31, 32].

Still, adenosine has the largest evidence base for pharmacological pre- and post-conditioning.

Studies AMISTAD- I ($n = 236$), AMISTAD-II ($n = 2118$) investigated the effect of intravenous adenosine at doses of 50 and 70 $\mu\text{g} / \text{kg} / \text{min}$ 15 min before PCI on the clinical results and the size of MI in patients with STEMI, in which reperfusion was performed. It was found that adenosine at a dose of 70 $\mu\text{g} / \text{kg} / \text{min}$ significantly reduces the size of MI (by 57%; $p = 0,023$).

It should be noted that the reduction of the lesion area is the most important clinical evidence of cardioprotection [33]. However, intracoronary and intravenous administration of adenosine has certain, well-founded limitations: the need for device for long-term infusion, careful monitoring of hemodynamics, as there are possible complications: hypotension (18,4%), bradycardia (2,7%), ventricular tachycardia (4,39%), AV blockade (0,03-0,04%), nausea / vomiting (7,8%) In

addition, the drug rapidly degraded in the bloodstream. Therefore, it is important to create a drug with an oral form of administration, with a more favorable pharmacological profile.

Today on the pharmaceutical market of Ukraine there is the first domestic analogue of adenosine – adenosine-5-triphosphategluconate-magnesium (II) trisodium salt (ADVOCARD). It is a combined polypill containing magladen (a mixture of adenine nucleotides) (18,6-29,25 mg), molsidomine (0,3 mg) and folic acid (0,45 mg). Adenosine induces mechanisms that are manifested by antiischemic, membrane stabilizing, antiarrhythmic and antithrombotic effects. Molsidomine (the second most important component of Advocard) is a donor of NO (nitric oxide), which potentiates the activation of K_{ATP} channels and the closure of calcium channels, thus enhancing vasodilation. Folic acid actively reduces the level of homocysteine, thus causing antihypertensive and antiatherogenic effects of the drug. Advocard, in contrast to nitrates, is not addictive (tolerance), reduces myocardial oxygen demand, improves myocardial metabolism [23].

The possibility of clinical use of Advocard in acute coronary syndromes, angina and heart failure was studied by MT Vatutin and co-authors [34, 35, 36], V.O. Shumakov and co-authors [37], NM Seredyuk and co-authors [38, 39], S.O. Andrievska [40], O.M. Bilovol and co-authors [41].

Patients with myocardial infarction with ST-segment elevation (STEMI) [34, 35, 36] immediately after urgent percutaneous coronary intervention (coronary angiography followed by angioplasty and stenting of the infarct-dependent artery) were prescribed Advocard sublingually at an initial dose of 30 mg and after that another 60 mg of the same drug, followed by constant intake of this drug 30 mg every 8 hours for 3 weeks. Patients in the control group did not receive Advocard. It has been established that Advocard increases the effectiveness of treatment of patients with STEMI in the acute period due to the improvement of myocardial contractility, which the authors associated with a decrease in myocardial damage due to the development of the phenomenon of preconditioning [34]. Confirmation of the favorable effect of the Advocard on the blood supply to the myocardium is the positive dynamics of the resolution of the ST segment: a decrease of 60% in the main group against the same dynamics by only 12,5% in the control group [36]. The authors also associate the fact of long-term retention of the antianginal effect achieved by revascularization and Advocard with the phenomenon of pharmacological postconditioning [35].

A group of other authors [37] studied the effectiveness of the Advocard according to the dynamics of myocardial contractility with the assessment of areas of impaired kinesis and exercise tolerance in the early postinfarction period. It was found that the efficiency of the work performed had the advantages

of positive dynamic in the Advocard group against the control group (31,6% vs 4,5%, $p < 0,001$). Therefore, the authors proved that the benefits of Advocard are especially noticeable in more severe patients with incomplete revascularization after PCI. It is to such patients VO Shumakov and co-authors recommend prescribing Advocard.

Interesting are the observations of S.O. Andrievska and co-authors [40]. The authors compared the therapeutic efficacy of Advocard in patients with painful myocardial ischemia (PMI) and painless myocardial ischemia (PLMO). It was found that the duration of PLMI in the Advocard group decreased by 57,4% against 48,5% in the control group. In patients with PMI (stable angina), efficacy in the Advocard and control groups was defined as 46,1% vs 39,1% ($p < 0,05$). The dynamics of the ratio of the total duration of ischemia (PMI + PLMI) in the group of Advocards was significantly better than in the control group – 22,25 vs 15,0%; $p < 0,05$. Therefore, Advocard is also appropriate for patients with stable angina, painless and total (PMI + PLMI) myocardial ischemia. Only one in 16 patients receiving Advocard had an adverse effect – headache in the first 3 days of admission (6,25%). Three patients with nitrate tolerance successfully underwent Advocard treatment and did not experience angina during the entire course of treatment [40].

The team found that Advocard reduces the frequency of angina attacks and the number of nitroglycerin tablets used by 75,8% in patients with functional class II (FC) stable angina (SA) and by 53,5% in patients with FC III. In control, these indicators were 49,4% and 46,9%, respectively. The indicator of the total duration of ischemia per day in the group of Advocard decreased from $84,3 \pm 4,4$ min to $57,3 \pm 3,6$ min ($p < 0,05$). In the control, such dynamic was much less clear-cut - from $76,5 \pm 3,6$ min to $68,8 \pm 1,6$ minutes after treatment [42].

In our observation [38, 39] there was also a positive dynamic of pain syndrome (HR = 0,73 [0,57 – 0,94]) and ECG criteria STEMI / NSTEMI; UA. Thus, the resolution of the ST segment tended to decrease (HR = 0,57 [0,26 – 1,23]), and the Q wave also to decline (HR = 0,75 [0,57 – 0,94]). LV EF in patients of the Advocard group increased from $48,43 \pm 0,61\%$ to $51,97 \pm 0,78\%$ ($p < 0,05$) against less pronounced dynamics in the control group – from $45,72 \pm 1,88\%$ to $47,54 \pm 1,82$ after treatment ($p > 0,05$). Left ventricular myocardial mass index (LVMMI) in the main group decreased by 21,2% ($p < 0,05$) against a decrease of 8,4% ($p < 0,05$) in the control group, indicating regression of left ventricular hypertrophy (LVH).

Therefore, the inclusion of Advocard in standard therapy of patients with STEMI immediately after revascularization (coronary stenting) is an effective and safe method of pharmacological postconditioning. According to our results, the most proven criteria for

the effectiveness of Advocard in patients with STEMI are the positive dynamic of typical anginal pain, ST-resolution, reduction of LVML and amplitude of the depth of the Q wave.

Prospects for application. Clinical observations have shown that postconditioning with the drug Advocard is an effective way to counteract the development of syndrome of unrestored blood flow and myocardial perfusion (NO-REFLOW) after successful restoration of blood flow in the epicardial infarct-dependent coronary artery. Currently, there is reason to believe that patients after successful percutaneous coronary intervention with the results of TIMI-III according to control coronary angiography, but whose value of myocardial saturation MBG is 0-I (no blush / min blush), and ST-resolution is $\leq 30\%$ may be prescribed Advocard at a dose of 2-3 tablets 2-3 times a day sublingually for 4-6 weeks (Fig. 3).

Comorbid pathology, particularly hypertension, diabetes and anemia, are not contraindications to the prescription of Advocard. Moreover, Advocard potentiates the therapeutic efficacy of ACE inhibitors / ARBs II and CCB, as well as anticoagulation when co-administered with DOAC in patients with atrial fibrillation. Advocard 2 tablets 3 times a day in the complex therapy of patients with chronic heart failure (CHF) NYHA II-III leads to improvement of their clinical condition, increases tolerance to physical exertion, improves quality of life. The authors also noted that under the influence of Advocard there is a significant reduction of the level of endothelin-I (by 32,7% vs. 20,3%) and increase of the quantity of cyclic adenosine monophosphate (cAMP) (by 43,9% vs. 19,4%). Analysis of the dynamic of plasma concentrations of endothelin-I in severe patients (CHF stage III) showed that the addition to standard therapy of Advocard significantly reduced the level of this potent vasoconstrictor and proaggregant [41, 43].

In a COVID-19 pandemic Advocard can be used to counteract hypercoagulation, the development of calcium paradoxes (arrhythmias), and the progression of heart failure.

Discussion. The ability of the myocardium to ischemic preconditioning and postconditioning and the proven ability to stimulate conditioning by pharmacological means should be part of clinical management guidelines for patients with chronic and acute coronary syndromes. In this context, the strategy of protecting the myocardium from damage during revascularization (NO-REFLOW syndrome – failure to restore blood supply to the myocardium after successful PCI) is of particular importance. Postconditioning after coronary stenting can be a new path for improving the effectiveness of treatment and cardiac rehabilitation of revascularized patients with acute and chronic coronary syndromes. The relevance of this strategy is confirmed by the CADILLAC study, which showed that only 35%

Fig.3 Mechanisms of pharmacological preconditioning

of patients can achieve complete revascularization [44]. The same is said in the study by OM Parkhomenko et al. [45], KM Amosova et al. [46], Niccoli et al. [47]. The results of different studies also show that the syndrome of unreturned blood flow (NO-REFLOW) after reperfusion can also be caused by microvascular obstruction and intramyocardial hemorrhage [48]. The presence of adenosine, molsidomine, and folic acid in the Advocard opens up a new possibility of using this drug before and after coronary stenting [49, 50].

Adenosine-containing complex polypill drug Advocard is an effective, safe and affordable drug for real medical practice of treatment primarily of patients-candidates for urgent and planned revascularization. A special indication for the appointment of Advocard (2 tablets 3 times a day) should be considered to prevent syndrome of unreturned blood flow (NO-REFLOW) after revascularization. Advocard may be recommended for patients with chronic coronary syndromes, including patients with stable angina, asymptomatic patients with painless myocardial ischemia, vasospastic angina, microvascular angina, postinfarction cardiosclerosis and chronic heart aneurysm. Advocard can be recommended for patients with the following comorbid diseases – hypertension, type II diabetes.

Conclusions

The analysis of literature and own clinical observations give the basis for the following conclusions:

1. The induction of pre- and postconditioning of

the myocardium can be an important component of the health care system both in urgent situations (STEMI / NSTEMI; UA) and for primary and secondary prevention of atherosclerotic cardiovascular diseases and their complications.

2. Adenosine-containing drug Advocard provides an opportunity to reduce ischemic myocardial injury during myocardial revascularization (PCI, CABG) and after critical myocardial ischemia, which has already occurred.

3. The presence of comorbid diseases, such as hypertension, diabetes mellitus, including their complications are not contraindications to the prescription of Advocard.

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