REVIEW ARTICLE

Current aspects of correction of neurohumoral system activity in patients after myocardial infarction

Valentin A. Kokorin, Andrey A. Spassky, Nikolai A. Volov, Ilya A. Kokorin

1st Department of Hospital Therapy, Russian National Research Medical University named after N.I. Pirogov, Moscow, Russia

KEY WORDS

heart failure, left ventricular remodeling, myocardial infarction, neurohumoral systems

ABSTRACT

Acute myocardial infarction is still considered as one of the most threatening disorders in internal medicine. Numerous complications of infarction develop due to activation of different neurohumoral systems. The article discusses modern methods of pharmacological correction of neurohumoral system activity in various stages of myocardial infarction. It is emphasized that current guidelines do not always allow to effectively prevent left ventricular remodeling. New drugs used for this aim are discussed.

Correspondence to:
Dr Valentin A. Kokorin,
1st Department of Hospital Therapy,
Veshnyakovskaya 23,
Moscow 111539, Russia,
phone: +7-495-370-46-90,
fax: +7-495-918-72-84,
e-mail: valentinkokorin@yahoo.com
Received: April 16, 2012.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012;
122 (Suppl 1): 47-54

Introduction More than 15 million of new cases of acute myocardial infarction (MI) are reported worldwide every year. The remote effects of MI may occur many months or years later. According to the American Heart Association (AHA),[1] within 6 years after MI, 18% of men and 35% of women have recurrent MI, 7% of men and 6% of women experience sudden death, 22% of men and 46% of women become disabled with severe heart failure (HF), and in 30% to 40% of the cases left ventricular (LV) dysfunction develops despite optimal treatment.

The activation of systemic and local (myocardial) neurohumoral systems plays a key role in the pathogenesis of MI and its complications. In the early stage of MI, an increased release of neurohumoral vasoconstrictors (particularly catecholamines, angiotensin II, and endothelin) promotes coronarospasm that leads to the expansion of infarction zone as well as provokes acute HF and life-threatening ventricular arrhythmias. Initially, neurohumoral activation in MI is compensatory in nature and aims to maintain the heart pumping function, but later may become maladaptive. A long-lasting increased activity of the neurohumoral systems leads to LV remodeling, systolic and diastolic LV dysfunction, dilatation of its cavity, and the occurrence of chronic HF. Most neurohumoral abnormalities are mediated through vasoconstriction or vasodilation. Vasoconstrictive responses occur within the sympathoadrenal system and the renin-angiotensin-aldosterone system (RAAS), and are induced by vasopressin, serotonin, endothelin, and thromboxane A_2. Vasodilative responses involve the kinin system, natriuretic peptides (NP), prostaglandins I_2 and E_2, endothelium-dependent relaxing factor, adrenomedullin, and other mediators.

Correction of the neurohumoral activity in the early and late stages of MI is one of the main aspects of MI treatment and prevention of its complications. β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone antagonists are currently used for this purpose. There are also some new classes of drugs including renin inhibitors, NP, vasopeptidase blockers, endothelin, and vasopressin receptor antagonists, at various stages of clinical investigation.

β-adrenergic blocking drugs β-adrenergic blocking drugs decrease myocardial oxygen need, improve coronary blood flow, promote ischemia improvement, and infarction size reduction. According to a meta-analysis of 22 randomized trials with the participation of more than 25,000 patients,[2] a long-term administration of β-adrenergic blocking drugs resulted in the reduction of all-cause

mortality by 23%, sudden death by 26%, recurrent MI by 41%, atrial fibrillation/flatter by 59%, and life-threatening ventricular arrhythmias by 70%.

The application of atenolol and metoprolol has been investigated in acute MI, while carvedilol, metoprolol, and propranolol have been studied as a long-term treatment. Selective β-adrenergic blocking drugs are preferred, but there is evidence that positive effects are characteristic of the whole class of drugs, except agents with intrinsic sympathomimetic activity.

The earlier the treatment is initiated, the greater the benefits of β-adrenergic blocking drugs. The significance of early routine intravenous administration has been less firmly established. Although Yusuf et al.[3] have shown that early intravenous administration of β-adrenergic blocking drugs in patients with MI leads to a decrease in total mortality by 13%, a number of recurrent MI by 19%, and ventricular fibrillation by 19%, the results of the later conducted Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) and COMMIT/CCS-2 trials did not confirm these findings. According to the AHA/American College of Cardiology (ACC) guidelines,[1] intravenous use of β-adrenergic blocking drugs in patients with acute MI is recommended only in cases when blood pressure control is necessary. Experts of the European Society of Cardiology (ESC) suggest wider indications for intravenous administration of β-adrenergic blocking drugs including tachycardia, arterial hypertension, and recurrent angina.[4] There is no doubt that oral β-adrenergic blocking drugs should be used in all patients since the onset of MI, unless there are contraindications and medication should be continued indefinitely.

β-adrenergic blocking drugs are the most effective in patients with LV systolic dysfunction and electrical myocardial instability. They are contraindicated in patients with cardiogenic shock, exacerbation of severe obstructive pulmonary disease, and allergic reactions. In patients with relative contraindications such as diabetes mellitus and obstructive pulmonary disease without exacerbation, and also in cases of severe systolic LV dysfunction, treatment with β-adrenergic blocking drugs should be initiated with minimal doses and patients require careful monitoring. The other relative contraindications to β-adrenergic blocking drugs in MI include systolic blood pressure below 100 mmHg, heart rate below 60 beats/min, prolongation of PQ interval above 0.24 s, second- and third-degree atrioventricular block in patients without artificial pacemaker, and the presence of risk factors for cardiogenic shock.

Nevertheless, it is necessary to note that almost all trials with β-adrenergic blocking drugs were performed before the revascularization era.

Angiotensin-converting enzyme inhibitors ACEIs hinder the conversion of angiotensin I into a strong vasoconstrictor, angiotensin II. Moreover, they decrease norepinephrine release from the neurons as well as vasopressin and aldosterone secretion, increase bradykinin and circulating NP formation, and exert different hemodynamic effects including the reduction of vascular resistance and normalization of diastolic inflation of the left ventricle. ACEIs also diminish platelet aggregation, positively influence blood rheological characteristics and endothelial function, and also have anti-inflammatory, antiarrhythmic, anti-ischemic, and antianginal effects. There is also evidence that ACEIs slow down atherosclerotic plaque formation.[5]

The first studies reporting successful administration of ACEIs in patients with MI that resulted in reduced infarction zone and mortality rate, relief of acute HF symptoms, and prevention of chronic HF, were published in the early 1980s. Later, several trials with more than 100,000 participants focused on the assessment of the efficacy and safety of various ACEIs in patients with MI. Hemodynamic and electrophysiological effects of different ACEIs were examined in the early and late stages of MI.

Early administration of ACEIs (since the first day of MI) was evaluated in the following trials: Second Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS II), Captopril and Thrombolysis Study (CATS), Survival of Myocardial Infarction Long-term Evaluation (SMILE), GISSI-3, ISIS-4, PRACTICAL, Chinese Cardiac Study (CCS-1), and Fosinopril in Acute Myocardial Infarction Study (FAMIS).

The CONSENSUS II trial with intravenous and then oral administration of enalapril since the first hours of MI was prematurely discontinued because of a nonsignificant increase in mortality by 9%, generally due to more frequent development of hypotension. However, in patients with large MI, enalapril reduced LV remodeling, improved prognosis, and significantly reduced the rate of complications. Similar results were obtained with captopril administration during thrombolysis in patients with the first acute MI in the CATS trial.[6] A nonsignificant mortality reduction after early administration of captopril in patients with suspected MI was also shown in the CCS-1 study.[7]

The SMILE study demonstrated that the administration of zofenopril for 6 weeks in patients with anterior MI without thrombolysis nonsignificantly reduced all-cause mortality by 25%, mortality due to HF by 31%, and sudden death by 63%. Risk of severe chronic HF was significantly decreased by 46%. During the first-year follow-up, a significant reduction of total mortality was 29%. More benefits were observed in patients with recurrent MI, arterial hypertension, and diabetes mellitus.[8] In the GISSI-3 trial, the mortality rate in patients with MI after a 6-week treatment with lisinopril was lower by 11%.[9]

Early administration of fosinopril in patients with anterior MI after thrombolysis was associated with a significant reduction in mortality

and severe HF by 36%. Improvement of prognosis did not depend on the effect on LV remodeling since there were no differences in the changes of LV ejection fraction (LVEF), end-systolic volume (LVESV), and end-diastolic volume (LVEDV) between the treatment and control groups during a 2-year follow-up.[10]

In the ISIS-4 study, treatment with captopril during 5 weeks led to a significant reduction in mortality by 7%, especially in patients with anterior MI and older than 70 years.[11]

A positive effect of the early administration of other ACEIs, particularly quinapril, on the clinical course of MI was demonstrated in a number of smaller studies.[12]

Late administration of ACEIs (since the 3rd day of MI) was evaluated in the following trials: SAVE, Trandolapril Cardiac Evaluation (TRACE), Acute Infarction Ramipril Efficacy (AIRE), and Perindopril Remodeling in Elderly with Acute Myocardial Infarction (PREAMI).

In the SAVE trial, in patients with asymptomatic LV dysfunction after MI, long-term administration of captopril was associated with the improvement in survival by 21% as well as with the reduction in severe chronic HF by 37% and in recurrent MI by 25%. These benefits were observed in patients who received thrombolytic therapy, aspirin, and β-adrenergic blocking drugs, as well as in those who did not receive such medications.[13]

In patients with clinical signs of acute HF, administration of ramipril since the third to tenth day after MI significantly reduced mortality by 27%. More benefits were observed in older (>65 years) and hypertensive patients. Ramipril did not alter the rate of stroke or reinfarction.[14] A positive effect of 1-month ramipril treatment on the hemodynamic and LV contractility parameters in patients with acute HF after MI was evaluated by Astakhova et al.[15] The LVEF increased by 31%, LVEDV decreased by 42%, and LVESV decreased by 17%.

A long-term treatment (mean duration, 2.5 years) with trandolapril in patients with reduced LV function (LVEF <35%) soon after MI significantly reduced the risk of overall mortality by 22%, mortality from cardiovascular causes, sudden death, and rate of severe HF.[16]

The PREAMI study demonstrated the efficacy of perindopril in reducing LV remodeling and risk of chronic HF in elderly patients after MI.[17]

Efficacy of different ACEIs in patients with MI was compared in a number of studies. In the PRACTICAL study, the immediate administration of captopril or enalapril improved the LV function and prevented LV dilatation after MI, but survival at 90 days and 12 months was significantly higher in the enalapril group.[18] Sidorenkova et al.[19] showed stronger antianginal and antiarrhythmic effects of fosinopril compared with enalapril in patients with anterior MI.

A meta-analysis of those studies showed that administration of ACEIs after MI was associated with the reduction of all-cause mortality by 26%, risk of recurrent MI by 20%, and hospitalization due to chronic HF by 27%. Important shortcomings of the majority of those trials include the lack of laboratory evaluation of the neurohumoral activity (including the RAAS) and focus only on major cardiovascular events.

There is no doubt that early administration of ACEIs in patients with MI is necessary. Nevertheless, there is no consensus as to whether we should administer ACEIs to all patients with MI or only to those at high risk. The AHA/ACC experts recommend administration of ACEIs to all patients without hypotension with subsequent evaluation (at 6 weeks) of whether they should be continued. According to the ESC guidelines,[20] ACEIs should be given to patients who have impaired LVEF (≤40%) or experienced HF in the early phase. The long-term use cannot be considered to be mandatory in post-MI patients who are normotensive, without HF, or compromised systolic LV function. ACEIs are especially effective in patients with extensive myocardial necrosis, impaired LV function, symptoms of HF or diabetes mellitus. ACEIs offer small benefits even in patients with preserved LV function. Treatment with ACEIs should be started in patients without contraindications as soon as possible after hemodynamic stabilization. Dosage depends on individual blood pressure response and serum creatinine and potassium levels. The dose should be titrated till targeted or maximally tolerated.

Angiotensin receptor blockers Despite proved efficacy of ACEIs in MI, these agents may cause various adverse events, including dry cough, angioedema, headache, and arterial hypotension, which makes it impossible to use them in 10% to 20% of the patients. The action of ACEIs on the RAAS is nonselective – they disturb degradation of bradykinin and modify the effects of angiotensin II on all subtypes of angiotensin receptors. Another factor that limits the action of ACEIs is the presence of alternative ways of local angiotensin II formation. Therefore, use of medications that block the RAAS at the level of the receptors seems to be reasonable. ARBs produce fewer side effects compared with ACEIs (particularly, they have no first-dose effect). In experimental studies, ARBs increased fibrinolytic activity and had a positive effect on endothelial dysfunction.[21]

Comparative clinical studies of ACEIs and ARBs in patients with chronic HF yielded inconsistent results. In the ELITE study (Evaluation of Losartan in the Elderly Study), losartan had a significant advantage compared with captopril in mortality reduction.[22] On the other hand, ELITE II study with the same drugs had not confirmed these findings, although losartan had been found to be better tolerated.[23] The fficacy of combined treatment with ACEIs and ARBs was evaluated in several studies. Simultaneous beginning of treatment had no additive effect on mortality and morbidity, but an increased rate of adverse events was shown. Administration of ARBs (candesartan or

valsartan) to patients who were already on treatment with ACEIs was associated with a significant reduction of mortality and readmission due to chronic HF (by 13%w 15%).[21]

Early data of ARB use in patients with MI have confirmed their positive effect on clinical and hemodynamic parameters, comparable with ACEIs, and the lower rate of adverse events. Choukaeva et al.[24] showed that administration of losartan beginning with day 2 to 5 after MI was not inferior to enalapril in clinical outcomes, improving parameters of LV systolic and diastolic functions. Kots et al.[25] successfully used losartan for treatment of acute HF in acute phase of MI. Parkhomenko et al.[26] examined the safety of combined treatment with irbesartan and captopril since the first day of MI. Similar results were reported for combined treatment with enalapril and losartan.[27]

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) was the first randomized clinical study to compare the efficacy and safety of ARB (losartan) and ACEI (captopril) in patients with MI. A group of 5477 patients with MI and clinical signs of HF were enrolled into the study; the mean duration of treatment was 2.7 years. The overall mortality rate was nonsignificantly higher in the losartan group (18% vs. 16%), but cardiovascular mortality was significantly higher. There were no significant differences in the rate of sudden death and severity of HF, but treatment with losartan was better tolerated.[28] Probably, these findings were related to insufficient dosage of losartan (only 50 mg/day) or inadequate titration scheme.

The Valsartan in Acute Myocardial Infarction (VALIANT) trial evaluated the efficacy of valsartan compared with captopril and their combination in patients with MI complicated by acute HF and/or LV systolic dysfunction. A group of 14,703 patients were randomized and the mean duration of treatment was 36 months. The rates of all-cause and cardiovascular mortality, recurrent MI, and the onset of chronic HF were equal in all 3 groups. Adverse events were less common in the valsartan group compared with the captopril group and significantly more frequent in the group receiving combined therapy. Thus, the hypothesis of the preference of more complete RAAS blocking by the combination of ACEIs and ARB could not be confirmed.[29]

Another attempt to find the difference between ACEI and ARB action was made in the Irbesartan in Patients With Acute Coronary Syndrome Without ST Segment Elevation (ARCHIPELAGO) study, which included 429 patients with acute coronary syndrome without ST-segment elevation treated with irbesartan or enalapril with early (during initial admission) or late (after discharge) initiation. Changes in high-sensitivity C-reactive protein, troponin I, B-type NP (BNP), microalbuminuria, interleukin 6, myeloperoxidase, phospholipase A_2, ischemia-modified albumin, soluble CD40 ligand, matrix metalloproteinase-9, aldosterone, and blood pressure were evaluated. There were no treatment-related differences in any of the above biomarkers. Changes in inflammatory markers were unaffected by the timing of treatment initiation. Both treatments were well tolerated; there were no differences in major adverse cardiac events.[30]

According to the ESC guidelines, ACEIs and ARBs (at least valsartan) can be used alternatively in patients with MI. We have much less experience with long-term treatment with ARBs after MI, so ARBs should be used in patients who do not tolerate ACEIs and have clinical signs of HF and/or the LVEF of 40% or less.

Aldosterone antagonists A positive effect of selective aldosterone antagonist, eplerenone, in patients with HF due to LV systolic dysfunction complicating MI was proved in the EPHESUS trial (Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial).[31] There were fewer overall deaths at 16 months (by 15%), fewer deaths or hospitalizations due to cardiovascular causes (by 13%), and fewer sudden deaths from cardiac causes in the eplerenone group compared with the placebo group. However, serious hyperkalemia was more frequent in the group receiving eplerenone. The benefits were observed only in the case of earlier eplerenone administration (3–7 days) post MI and were not shown when the drug was initiated later (≥7 days).[32]

Additive improvement of LV remodeling and neurohumoral activation by combined aldosterone and ACEI or ARB after experimental MI in rats was described by Fraccarollo et al.[33]

Administration of nonselective aldosterone antagonist, spironolactone, in patients after MI was evaluated only in small studies. Hayashi et al.[34] reported that immediate administration of spironolactone in patients with first anterior MI can prevent LV remodeling by force of the myocardial collagen synthesis suppression. Babak et al.[35] showed that addition of spironolactone to complex treatment of MI complicated by acute HF improved clinical course and reduced LV remodeling. The main humoral effect of spironolactone was an increase in aldosterone and a decrease in plasma atrial NP (ANP) levels. In patients with a tendency to hypotension and limited chance of achieving the optimal dose of ACEIs, low doses of spironolactone were well tolerated. A long-term treatment with combination of spironolactone and ARB (losartan) in patients with MI after successful thrombolysis was associated with lower mortality and delayed progression of chronic HF compared with those receiving losartan alone.[36]

The ESC guidelines suggest that aldosterone blockade may be considered for post-ST-elevation MI patients with the LVEF of less than 40% and HF or diabetes mellitus provided that creatinine is below 2.5 mg/dl in men and below 2.0 mg/dl in women, and potassium is less than 5.0 mEq/l.

Routine monitoring of serum potassium is warranted and should be particularly careful when other potential potassium-sparing agents are used. There is not enough data about the use of aldosterone antagonist later than 2 years post MI.

Direct renin inhibitors The idea of RAAS blocking at its origin by inhibition of renin has existed since the 1970s. The first generation of orally active renin inhibitors (enalkiren, remikiren, and zankiren) has never been used clinically because of low bioavailability and weak blood-pressure-lowering activity.[37] Success came to kirens after the synthesis of aliskiren – non-peptide low-molecular direct renin inhibitor. In 2007, aliskiren was approved in Europe and the United States for treatment of arterial hypertension, and the first results of its efficacy in patients with chronic HF were reported a year later.[38] In 2010, the results of 2 trials with the use of aliskiren in patients with acute coronary syndrome were presented.

The ASPIRE trial has assessed addition of aliskiren to help limit changes to cardiac structure and function in patients with signs of LV dysfunction (LVEF <45% and the zone of akinesia >20%) 2 to 6 weeks after MI. The study involved 820 patients who received aliskiren or placebo for 36 weeks in addition to standard therapy with statins, β-adrenergic blocking drugs, ACEIs, and antiaggregant agents. A small reduction in the LV volume was seen in patients who received aliskiren compared with those given standard therapy only; however, this finding was not statistically significant. The combined rates of cardiovascular death, hospitalization for chronic HF, recurrent MI, stroke, and nonfatal cardiac arrest were similar in both groups. The rate of hyperkalemia, hypotension, and kidney dysfunction was higher in patients receiving aliskiren.[39]

In the AVANT GARDE-TIMI 43 trial, the hypothesis that early inhibition of the RAAS in patients with preserved LV function but elevated BNP following acute coronary syndrome would reduce hemodynamic stress by a greater reduction of BNP compared with placebo was evaluated. A total of 1101 patients stabilized after acute coronary syndrome without clinical evidence of HF or LV dysfunction but with an increased level of N-terminal pro-BNP (NT-proBNP) 3 to 10 days after admission were randomized to aliskiren, valsartan, the combination of both, and placebo. By week 8, NT-proBNP levels decreased significantly in each treatment arm, including placebo, though there were no differences in the reduction between the groups (42% in placebo, 44% in the aliskiren, 39% in the valsartan, and 36% in the combination arm). There were no differences in clinical outcomes but there were more adverse events, including serious events and adverse events leading to early discontinuation of aliskiren, in patients treated with active therapy.[40]

The results of the ASPIRE and AVANT GARDE-TIMI 43 trials put in doubt the future use of renin inhibitors in patients after MI.

Vasopeptidase blockers The inhibition of neutral vasopeptidase (NVP) is a very promising approach in the treatment of HF. NVP blockers decrease degradation of NP and thus prolong its activity. It is supposed that vasopeptidase blockers are more effective in patients with hypertension and chronic HF. Clinical studies on several agents blocking neutral endopeptidase and ACE are ongoing. Simultaneous inhibition of ACE and NVP intensifies natriuretic and vasodilating effects of NP, suppresses angiotensin II formation, and increases the half-life of other vasodilators, such as bradykinin and adrenomedullin. Preclinical and early clinical studies of NVP/ACEIs demonstrated their high efficacy in the treatment of chronic HF: they reduced vascular remodeling and myocardial hypertrophy and showed natriuretic, diuretic, and antiproliferative action.[41] The most examined NVP/ACE blocker is omapatrilat. Initial clinical data have shown the effectiveness of this agent in patients with hypertension and chronic HF, but further studies did not reveal any benefits of omapatrilat vs. ACEIs (enalapril) in this patient group.[42] The rate of a serious adverse event, angioedema, was much higher with omapatrilat, and this is a significant barrier for its introduction into clinical practice. Nevertheless, new NVP/ACE blockers (gemopatrilat, sampatrilat, and fasidotril) are currently being investigated. In experimental models of MI in animals, omapatrilat decreased the rate of mortality and ventricular arrhythmias and was more effective than ACEIs in preventing LV dysfunction and remodeling.[43]

Currently, there are not enough clinical data to support the practical recommendation of using vasopeptidase blockers in patients with MI.

Endothelin receptor antagonists Blockade of endothelin receptors can be a new alternative direction of HF treatment applicable in patients after MI. There are antagonists to nonselective ET_A- and ET_B-receptors (bosentan, enrasentan, and tezosentan) and selective ET_A-receptor (ambrisentan, atrasentan, darusentan, and sitaxentan). The results of these medications in the treatment of pulmonary arterial hypertension are the most encouraging.

The findings of clinical studies that investigated use of nonselective endothelin receptor antagonists in patients with HF were disappointing. Enrasentan added to standard therapy in patients with chronic HF was found to have no additive effects,[44] and no difference in efficacy compared with placebo was shown when high doses of tezosentan were given intravenously in patients with acute decompensated HF associated with acute coronary syndrome, but symptomatic hypotension developed much more frequently.[45]

The preliminary results of clinical studies with selective ET_A-receptor antagonists gave evidence of their higher efficacy and action selectivity. Darusentan improved the cardiac index in patients with severe chronic HF, especially in a long-term treatment.[46] The EARTH trial, performed later, was not equally optimistic: darusentan neither improved cardiac remodeling nor reduced clinical symptoms or improved outcomes in patients with chronic HF.[47]

Application of endothelin antagonists in MI has been investigated only in experimental studies. A possible premise of their clinical use might be the study by Niccoli et al.[48] who found that plasma endothelin-1 levels predicted angiographic no-reflow in patients with MI after successful primary or rescue percutaneous coronary intervention (PCI). These findings suggest that endothelin-1 antagonists might be beneficial in the management of no-reflow phenomenon.

Natriuretic peptides Nesiritide is structurally identical to endogenous human BNP agent, which is produced by *Escherichia coli* using recombinant DNA technology. In 2001, nesiritide was approved by the U.S. Food and Drug Administration for treatment of acute HF and recommended as a first-choice drug in patients with acute decompensated HF. In 2005, Sackner-Bernstein et al.[49] performed a meta-analysis of several trials evaluating nesiritide application in patients with decompensated chronic HF. It showed that nesiritide may increase short-term mortality and worsen renal function, but fortunately these findings have not been confirmed later. Nevertheless, the role of nesiritide in the treatment of HF remains uncertain.

There is also a lively practical interest in NP use in patients with MI. Chen et al.[50] demonstrated that infusion of low doses of nesiritide for 72 hours in patients with anterior MI suppresses aldosterone and preserves the LV function and structure, improving the LVEF and smaller LVEDV at 1 month.

Hillock et al.[51] showed that nesiritide, administered soon after MI, induced an increase in plasma cyclic guanosine monophosphate and C-type NP as well as a decrease in other endogenous cardiac peptides with a neutral effect on renal function and a trend towards favorable LV remodeling.

Kitakaze et al.[52] established that patients with acute MI who were undergoing reperfusion treatment and were given ANP had lower infarct size, fewer reperfusion injuries, and better outcomes than controls. In the J-WIND trial, 569 patients were enrolled, and they received 72-hour infusion of ANP or placebo after PCI. Patients treated with ANP had a reduction of 14.7% in infarct size and a significantly increased LVEF at 6 to 12 months compared with the placebo group, but they also had severe hypotension more often.

Thus, primary results demonstrate that NPs could serve as a safe and effective adjunctive treatment in patients with MI, but this hypothesis should be confirmed in further clinical studies. Currently, nesiritide is not registered in most European countries.

Vasopressin receptor antagonists Vasopressin receptor antagonists diminish vasoconstriction and promote aquaresis without a negative effect on electrolyte balance. There are nonselective V_{1A}/V_2-receptor antagonists (conivaptan) and selective V_{1A}- (relcovaptan), V_{1B}- (nelivaptan) and V_2- (tolvaptan, satavaptan, mosavaptan, and lixivaptan) receptor antagonists. Administration of conivaptan and tolvaptan was approved in the United States and Europe for correction of hyponatremia, including in patients with chronic HF. Addition of tolvaptan to standard treatment in patients with acute decompensated HF was associated with reduction of clinical symptoms without influence on mortality and other major cardiovascular endpoints.[53] There is only experimental evidence for use of vasopressin receptor antagonists in patients with MI.

Conclusion Currently, there are several methods of pharmacological correction of the activity of neurohumoral systems in patients with MI and those after MI applicable in clinical practice. Some new groups of neurohumoral modulators are at different stages of research. The most promising agents preventing LV remodeling and development of HF in patients with MI seem to be NPs. The search for optimal combinations and examination of other pharmacological groups in these patient groups should be continued.

REFERENCES

1 Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. Circulation. 2008; 117: 296-329.

2 Dargie HJ. Beta blockers in heart failure. Lancet. 2003; 362: 2-3.

3 Yusuf S, Sleight P, Held P, McMahon S. Routine medical management of acute myocardial infarction. Lessions from overviews of recent randomized controlled trials. Circulation. 1990; 82 (Suppl 3): 117-134.

4 Van de Werf F, Bax J, Betriu A, et al. Management of Acute Myocardial Infarction in patients presenting with ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008; 29: 2909-2945.

5 MacMahon S, Sharpe N, Gamble G, et al. Long-term effects of the ACE inhibitor, ramipril, on atherosclerosis in patients with coronary heart disease or other occlusive arterial disease. J Am Coll Cardiol. 1999; 33 (Suppl A): 899-904.

6 Kingma JH, van Gilst WH, Peels CH, et al. Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction. Results from the Captopril and Thrombolysis Study (CATS). Eur Heart J. 1994; 15: 898-907.

7 Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). Lancet. 1995; 345: 686-687.

8 Ambrosioni E, Borghi C, Magnani B, et al. The effect of angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995; 332: 80-85.

9 GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet. 1994; 343: 1115-1122.

10 Borghi C, Marino P, Zardini P, et al. Post acute myocardial infarction: the Fosinopril in Acute Myocardial Infarction Study (FAMIS). Am J Hypertens.1997;10 (10 Pt 2): 247S-254S.

11 ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1994; 345: 669-685.

12 Grouzdeva GV, Sidorenko BA, Sedov VP. [Usage of quinapril in acute period of myocardial infarction]. Kardiologiia. 2001; 1: 25-29. Russian.

13 Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992; 327: 669-677.

14 Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence heart failure. Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993; 342: 821-828.

15 Astakhova ZT, Kaitova ZE, Mrikzev VK, et al. [Clinical efficacy of ACE inhibitor ramipril in left ventricular failure followed myocardial infarction]. Rus J Cardiol. 1999; 4 (Suppl): 9. Russian.

16 Kober L, Torp-Pedersen C, Carsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study. N Engl J Med. 1995; 333: 1670-1676.

17 Ferrari R; Perindopril and Remodeling in Elderly with Acute Myocardial Infarction Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. Arch Intern Med. 2006; 166: 659-666.

18 Foy SG, Crozier IG, Turnr JG, et al. Comparison of enalapril versus captopril on left ventricular function and survival three months after acute myocardial infarction (the "PRACTICAL" study). Am J Cardiol. 1994; 73: 1180-1186.

19 Sidorenkova NB, Plyasheshnikov MA. [Comparative efficacy of enalapril and fosinopril in acute myocardial infarction]. Rus J Cardiol. 1999; 4 (Suppl): 150. Russian.

20 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008; 29: 2388-2442.

21 Sun YP, Zhu BQ, Browne AE, et al. Comparative effects of ACE inhibitors and angiotensin receptor blocker on atherosclerosis and vascular function. J Cardiovasc Pharmacol Ther. 2001; 6: 175-181.

22 Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet. 1997; 349: 747-752.

23 Pitt B, Poole-Wilson P, Segal R, et al. Effects of losartan versus captopril on mortality in patients with symptomatic heart failure: rationale design, and baseline characteristics of patients in the Losartan Heart Failure Survival Study - ELITE II. J Card Fail. 1999; 5: 146-154.

24 Choukaeva II, Oshepkova MV, Bogova OT, et al. [Influence of treatment with angiotensin II receptor antagonist losartan and ACE inhibitor enalapril on postinfarction remodeling of the left ventricle]. Rus J Cardiol. 2001; 5: 41-45. Russian.

25 Kots YI, Lebedyantsev LV, Saifutdinov RI, et al. [Usage of angiotensin II receptor blockers in treatment of left ventricular failure in acute stage of myocardial infarction]. Kardiologiia. 2001; 1: 30-33. Russian.

26 Parkhomenko AN, Irkin OI, Bril GV, et al. [Experience of ACE inhibitor captopril and angiotensin receptor blocker irbesartan usage in early period of myocardial infarction]. Ukrain J Cardiol. 2000; 3: 5-8. Russian.

27 Amosova EN, Zaporozhets OB, Kazakov VE, et al. [Influence of ACE inhibitor enalapril and angiotensin receptor blocker losartan on early left ventricular remodeling in patients with acute myocardial infarction and its clinical course]. Ukrain Med J. 1999; 4: 91-96. Russian.

28 Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002; 360: 752-760.

29 Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Eng J Med. 2003; 349: 1893-1906.

30 Montalescot G, Drexler H, Gallo R, et al. Effect of irbesartan and enalapril in non-ST elevation acute coronary syndrome: results of the randomized, double-blind ARCHIPELAGO study. Eur Heart J. 2009; 30: 2733-2741.

31 Pitt B, Williams G, Remme W, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction: Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther. 2001; 15: 79-87.

32 Adamopoulos C, Ahmed A, Fay R, et al. Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHESUS trial. Eur J Heart Fail. 2009; 11: 1099-1105.

33 Fraccarollo D, Galuppo P, Schmidt I, et al. Additive amelioration of left ventricular remodeling and molecular alterations by combined aldosterone and angiotensin receptor blockade after myocardial infarction. Cardiovasc Res. 2005; 67: 97-105.

34 Hayashi M, Tsutamoto T, Wada A, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation. 2003; 107: 2559-2565.

35 Babak OY, Knyazkova II. [Hemodynamic and humoral effects of spironolactone in patients with acute myocardial infarction, complicated by heart failure]. Ukrain J Cardiol. 2004; 4: 23-28. Russian.

36 Aroutunov GP, Rozanov AV, Vershinin AA. [Influence of complete blockade of rennin-angiotensin-aldosterone system with angiotensin II antagonist and aldosterone antagonist on course of heart failure in patients with acute myocardial infarction after successful thrombolysis]. Journal of Heart Failure. 2000; 1: 20-26. Russian.

37 Staessen JA, Li Y, Richart T. Oral renin inhibitors. Lancet. 2006; 368: 1449-1456.

38 McMurray J, Pitt B, Latini R, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. Circ Heart Fail. 2008; 1: 17-24.

39 Solomon SD. Effect of the Direct Renin Inhibitor Aliskiren on Left Ventricular Remodelling Following Myocardial Infarction with Left Ventricular Dysfunction: ASPIRE. Late breaker presentation at American College of Cardiology 59th Annual Scientific Sessions 2010.

40 Scirica BM, Morro-DA, Bode C, et al. Patients with acute coronary syndromes and elevated levels of natriuretic peptides: the results of the AVANT GARDE-TIMI 43 Trial. Eur Heart J. 2010; 31: 1993-2005.

41 Rossi GP. Dual ACE and NEP inhibitors: a revie-of the pharmacological properties of MDL 100 240. Cardiovasc Drug Rev. 2003; 21: 51-66.

42 Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002; 106: 920-926.

43 Eliseev OM. Natriuretic peptides. Evolution of knowledge. Ter Arkh. 2003; 75: 45-49.

44 Cosenzi A. Enrasentan, an antagonist endothelin receptors. Cardiovasc Drug Rev. 2003; 21: 1-16.

45 O'Connor CM, Gattis WA, Adams KF, et al. Tezosentan in patients with acute heart failure and acute coronary syndromes: results of the Randomized Intravenous TeZosentan Study (RITZ-4). J Am Coll Cardiol. 2003; 41: 1452-1457.

46 Ruschitzka F, Enseleit F, Hurlimann D, et al. [Effects of long-term selective ETA receptor blockade on neurohumoral activation in congestive heart failure]. J Am Coll Cardiol. 2001; 37: 171. Russian.

47 Anand I, McMurray J, Cohn JN, et al. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor antagonist Trial in Heart failure (EARTH): randomised, double-blind, placebo-controlled trial. Lancet. 2004; 364: 347-354.

48 Niccoli G, Lanza GA, Sha-S, et al. Endothelin-1 and acute myocardial infarction: a no-reflo-mediator after successful percutaneous myocardial revascularization. Eur Heart J. 2006; 27: 1793-1798.

49 Sackner-Bernstein J, Aaronson KD. Nesiritide for acute decompensated heart failure: does the benefit justify the risk? Curr Cardiol Rep. 2007; 9: 187-193.

50 Chen HH, Martin FL, Gibbons RJ, et al. Low-dose nesiritide in human anterior myocardial infarction suppresses aldosterone and preserves ventricular function and structure: a proof of concept study. Heart. 2009; 95: 1315-1319.

51 Hillock RJ, Frampton CM, Yandle TG, et al. B-type natriuretic peptide infusions in acute myocardial infarction. Heart. 2008; 94: 617-622.

52 Kitakaze M, Asakura M, Kim J, et al. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet. 2007; 370: 1483-1493.

53 Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. JAMA. 2007; 297: 1319-1331.

ARTYKUŁ POGLĄDOWY

Współczesne aspekty korekcji aktywności układu neurohumoralnego u chorych na zawał serca

Valentin A. Kokorin, Andrey A. Spassky, Nikolai A. Volov, Ilya A. Kokorin

1st Department of Hospital Therapy, Russian National Research Medical University named after N.I. Pirogov, Moskwa, Rosja

SŁOWA KLUCZOWE

niewydolność serca, przebudowa lewej komory serca, układ neurohumoralny, zawał serca

STRESZCZENIE

Ostry zawał serca wciąż jest postrzegany jako jedna z najgroźniejszych chorób w medycynie wewnętrznej. Liczne powikłania zawału serca są wynikiem aktywacji układu neurohumoralnego. Praca omawia współczesne metody farmakologicznej korekcji aktywności układu neurohumoralnego u chorych na zawał serca. Zwrócono uwagę na fakt, że aktualne wytyczne nie zawsze pozwalają na skuteczne zapobieganie przebudowie struktury lewej komory serca. Poddano dyskusji stosowanie nowych podawanych w tym celu leków.

Adres do korespondencji:
Dr Valentin A. Kokorin,
1st Department of Hospital Therapy,
Veshnyakovskaya 23,
Moskwa 111539, Rosja,
tel.: +7-495-370-46-90,
fax: +7-495-918-72-84,
e-mail: valentinkokorin@yahoo.com
Praca wpłynęła: 16.04.2012.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2012;
122 (Suppl 1): 47-54