About validity of early application of kallikrein-kinin system inhibitors in ischemised myocardium

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Early use of Kallikrein-kinin inhibitor (aprotinin) widens ability to perform intracoronary thrombolisis and decreases risks of reperfusion complications during transluminal coronary angioplasty and aorto-coronary bypass.

Key Words: system, inhibitors, myocardium

Abstract:

Detect the ability of inhibitors of the kalikrein-kinin system (KKS) to avoid early impairment of the microcirculation and low reperfusion damages (RD) in the ischemic area during systemic thrombolisis (T), achieving the optimal results of the thrombolitictherapy (TLT) and in the patients with acute myocardium infarction.

Methods and results:

104 patients with acute myocardium infarction are divided into 4 groups – with TLT infusing kontrikal and heparin earlier (KH) in the first 2-2.5 hours from the disease is spread (group 1), with isolated T on the early stage (2), late T (after 3-6 hours) (3) and traditional therapy (4). The dynamic of the clinical data and ECG data were evaluated. Before the clinical research the experimental-morphological research was done on dogs that showed better retrograde blood flew of the acute ischemized myocardium and decrease of ischemic level, also decrease frequency and area of reperfused intramiocardial haemorrhages (RIMH) in the infarction areas in the conditions of TLT and KH infusion. Significant advantage has revealed of the early T during KH that showed in high antianginal and antiarithmic effect, while there was see no Q or it was deepen unsignifically. With the earlier isolated T (group 2) the worse clinical dynamic was seen, with extrasistols and significant deepen of Q, that was more negative in the patients with later T and traditional therapy (groups 3 and 4). The optimization of the

situation by KH is caused by the suppression of the pathological activation of KKS, decreasing vessel's permeability and RD. The latest thrombolitic drugs ensure faster thromblising, but don't avoid the reperfusion damages, as higher fibrinolitic activity in the moment of T, causes even more activation of KKS and RIMH development, prevents peroxide oxidation of the lipids and may cause higher affectivity of antioxidant's use.

Conclusion:

Earlier admission of KKS inhibitors optimizes the affectivity of TLT and widens the indication to the systemic and intracoronary T, minimizes complications and may cause higher affectivity of coronary angioplasty and aorta-coronary shunting in the patients with acute myocardium infarction.

Introduction:

Thrombolytic therapy (TLT) is an alternative for the existing pathogenetically directed methods of treatment of myocardial infarction. But the improvement of the methods of treatment of myocardial infarction (MI) with the use of new thrombolytic preparations, contributing to the reduction of fibrinolitic hemorrhages, did not, essentially, concern the problem of struggle against such grave complications of revascularization as are reperfusive intramyocardial hemorrhages (RPIH) resulting in an expansion of the infarction area and frequently leading to fatal rhythm disturbances. Previously thrombogenesis processes in the infarction area directed interns (toward TLT as early as possible. Training to avoid reperfusive damages (RD) of myocardium as much possible, the time of revascularization onset was reduced up to 2-3 hours from the beginning of an acute anginous attack (AAA). Moreover, there appeared the first comparatively safe attempts of TLT at the before hospital stage (BHS) and enabled to reduce the time of thrombolysis (T) onset by 1-1,5 hours (13, 14,18,19,27). It might have enabled, somehow, to achieve a more favorable clinical course of the disease, to stop the development of ischemic necrosis and to arrest acute anginous attacks in more than a half of patients at BHS (14).

But the authors of the cites work did not manage to achieve a significant difference in frequency and character of heart rhythm disturbances in TLT at BHS and in hospital. The onset of the successful struggle for the maximum preservation of the function of acute ischemised myocardium (AIM) should be date back to the 1970's of the previous century

when there was revealed a negative effect of pathologic activation of kallikrein-kinin system (KKS) on AIM resulting in increase in vascular wall permeability and myocardial stroma edema and also it was revealed a positive effect of KKS inhibitors wall permeability on a decrease in a painful syndrome and cardiogenic shock appearance (24,25,26,30,34).

A decrease in RPIH and infarction area expansion could be linked with a decrease in KKS pathologic activation and a reduction of vascular wall permeability. Thus, in the preliminary series of experiments on 130 dogs under the conditions of 2-4-hour AIM reperfusion in the histomorphological and electronmicroscopic investigation, the ischemic area revealed a dissociation of myocardial fibers with myocardial stroma edema and blood formed element extravasation, matrix clearing and mitochondria crist destruction, a reduction of fragmentated sarcoplasmic reticulum ability to absorb Ca (Korotkov A.A. et al., 1980-1084, Kipshidze N.N., Korotkov A.A. et al.,1986).At the same time, in reperfusion against the background of kontrikal and heparin (KH), extravasates are absent and the number of functioning capillaries is increased. Under the conditions of retrograde blood supply maintenance, hypokinesia was reduced that was indicated by an increase in contractibility of glycerized muscular fiber bundles and an increase in Veraguta index. Finally, a satisfactory state of sarcoplazmatic reticulum and mitochondria was registered in 2-hour ischemia and not very pronounced changes in 4-hour ischemia. A considerable supplement to the received results of the favorable effect of KKS inhibitors is an increase in macroerges carrying energetic charge and a significant maintenance of the structure and function of OIM under the influence of a small dosage of Inosie-F (Riboxin) in accompanying cardiac insufficiency. Proved in the experiment by an early injection of KKS inhibitors, the possibility of prevention or sharp decrease in RPIH stimulated the development of new methods of AIM thrombolytic and surgical revascularization (Korotkov A.A. et al., 1985, Kipshidze N.N. et al.,1985). The first success, after an intravenous injection of KKS inhibitors when treating AIM, was reassuring (3, 4, 9, 11 and 12). It should be noted that the ability of KKS inhibitors to improve the retrograde blood supply to the ischemic area after KG injection on the BHS was confirmed by a marked increase in myoglobin and concentration with a significant reduction of myocardial ischemia on the precardialcartogramm (washing out effect)

(Korotkov A.A. et al., 1991). The aim of our work was to study the ability es of KKS inhibitors to prevent early disturbances of microcirculation in the ischemic area and to reduce reperfusive damages in subsequent thrombolysis.

Materials and methods:

One hundred and four patients with acute large focal infarction and the age of 34-67 years (and average age of 53,6 years) were divided into 4 groups taking into account included the time of TLT onset. The first group included 23 patients who, preliminarily within the first 2 hours from AAA onset, received heparin injections, 10 000 u.n. Intravenously in spurt followed by kontrikal, 50 000 u.n. for 5 minutes. TLT (Streptase 1 000 000 M E) began 1-1,5 hours after kontrikal infusion – the period of time necessary to decrease in the inhibitory effect of the preparation on fibrinolitic activity increase. The second group of patients (n-21) underwent an early isolated TJT not later than 2-2,5 hours after acute anginous attack. That is, TLT was started simultaneously in groups 1 and 2 with a slight advantage of an early start for isolated TLT. In-group III (n-21) isolated TLT was performed later (3-6 hours). Group IV (control) consisted of 40 patients who received traditional therapy with nitrates, analgesics, B-adrenoblockers, antiaggregates, calcium antagonists and metabolic preparations used in three preceding groups as well. Six hours later after TLT termination for 5-7 days heparinization was performed, 5000 u.n. every 4-6 hours.

Some fragments of our earlier experimental studies were used for making a more optimum and objective appraisal of KKS inhibitors as an anticipating T basis therapy against microcirculatory disturbances (Korotkov A.A. et al., 1980-1984; Kipshidze N.N.; Korotkov A.A.; et al., 1986). Myocardium contractile function was determined by means of Veragut's index on Mingographe 82, firm Siemens, using glicrinized muscular fibers (Karsanov N.V. et al., 1971).

The material was treated statistically by means of the generally accepted methods of variation statistics using Student's criteria.

Results and discussion:

Table presents the changes in clinical criteria and AIM complications when using isolated TLT and T against the background of KKS inhibitors.

Symptoms and complications		**I** group **n = 23**	**II** group **n = 20**	**III** group **n = 21**	**IV** group **n = 40**
Anginous attack	a	23(100%)	20(100%)	20(95%)	38(95%)
	b	5(21,7%)	10(50%)	13(62%)	24(60%)
	c	3(13%)	4(20%)	11(52%)	21(52,5%)
Rhythm disturbances	a	9(39,1%)	10(50%)	11(52%)	20(50,7%)
	b	4(17,4%)	9(45%)	10(47,6%)	21(52,5%)
	c	0	5(25%)	7(33,3%)	13(32,5%)
Cardiac insufficiency	a	4(17,4%)	9(45%)	11(52%)	19(47,5%)
	b	2(0,7%)	4(20%)	10(47,6%)	19(47,5%)
	c	0	2(10%)	7(33,3%)	12(30%)
Dressler syndrome		1(4,3%)	3(15%)	5(23,8%)	8(20%)
Lethality		0	0	2(9,5%)	4(10%)

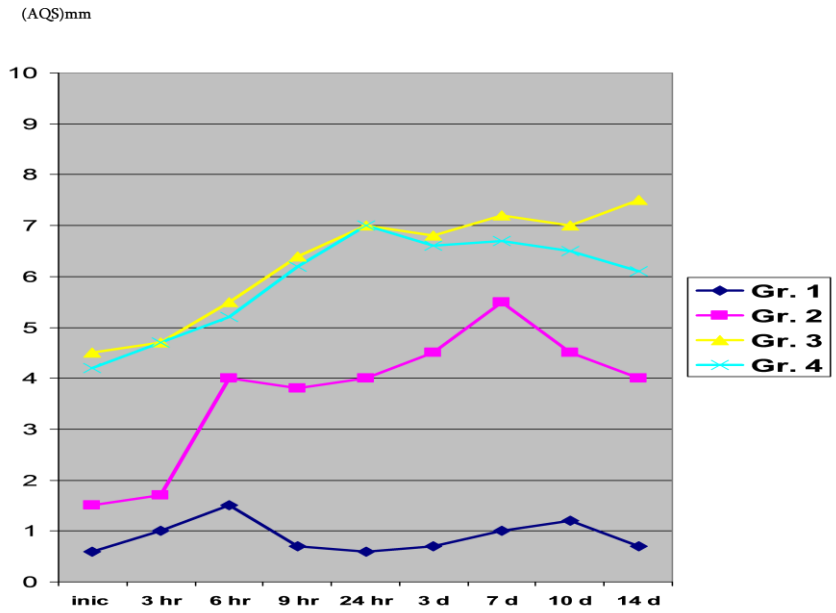
a – before treatment, b – after treatment, c – 5-7 days after treatment

An optimum statistically significant antianginal effect was registered in-group I after KH infusion. In groups II-IV antianginous attacks were arrested by the use of narcotic preparations. The frequency of ventricular extrasistoles (VE) was already reduced when injecting KH. On the 5-7th days their disappearance was registered. In groups 2 and 3, in addition to VE decrease under the influence of antiarythmic agents, new rhythm disturbances were seen coinciding in time with the onset of reperfusion. The best results of treatment of cardiac insufficiency, expressed in congestion phenomena in lesser circulation, were observed in groups I and II with disappearance cardiac insufficiency signs in the patients of the main group I by the end of the list week.

The results of the studies show that a more favorable clinical course of AIM in the patients group I and fewer post infarction complications are caused by maintenance of retrograde and restoration of ante grade blood supply of the infarction area under the conditions of a sharp decrease in vascular wall permeability due to suppression of pathologic activation of KKS and a decrease in RPIH (20, 22). A high antianginal effect in the patients of group I is caused not by an improvement of retrograde blood supply of

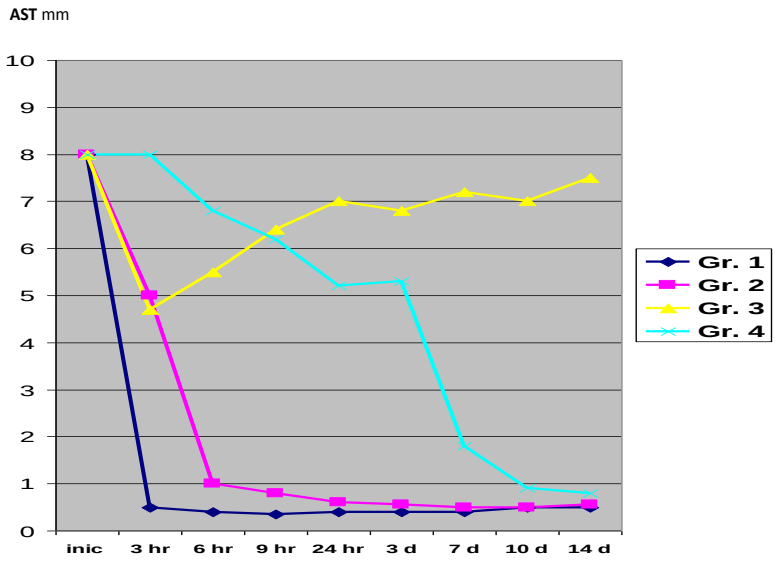
the ischemised myocardium under the influence of KH, but also by an immediate effect of KKS inhibitors on painful receptors. We connect a decrease in the frequency of rhythm disturbances with the earliest infusion of KKS inhibitors and a decrease in vascular wall permeability preventing the development of RPIM. At the same time, in the patients of groups 2-3, in addition to disappearance of rhythm disturbances in some cases, the appearance of new extrasystoles immediately before performing TLT indicates the blood flow restoration in the occulted coronary artery and exudation of plasma and blood formed elements into myocardium, stroma edema and cardyomyocite damage (21).

Our studies of thrombolysis efficiency against the background of preliminary KH infusion, compared to an early, at the same period isolated infusion of streptase, elucidate the solution of the problem on optimum periods of TLT performance and on the, possibility of prevention or a considerable reduction of manifestations of seemingly inevitable reperfusive syndrome. Table I shows obvious advantageous effects of preliminary KH infusion on the frequency of reperfusive arrhythmias and somehow on the severity of MI clinical course. A still clearer pattern of differences in thrombolysis efficiency between groups 1 and 2 is revealed by dynamics of the wave Q on ECG (fig.1).



In the first group a maximum, by 11,5%, increase in Q wave amplitude was registered by 6 hours from the treatment onset, the initial level being already reached by 24hours, while

in isolated TLT, the Q wave increased by 30% by 6 hours and grew up to the 7-th day. An increase in the Q wave amplitude in groups III and IV was identical within the first 6 hours, growing on, correspondingly, within the period of 7 and 10 days of MI course that clearly indicates a further progression of necrotic processes in myocardium. So, in TLT against the background of KKS inhibitors, only a slight increase in Q wave is explained by minimum disturbances of microcirculation. At the same time, in such an early, but isolated TLH, a considerable increase in the Q wave, as early as 6 hours after T onset, is connected with a sharp activation of KKS, RHIM and myocardial stroma edema. Still more pronounced processes of AIM necrotisation in late TLT are caused by depletion of plasminogene pools and a decrease in fibrinolitic activity (21). We did not attach great importance to the examination of ST segment dynamics on ECG (fig. 2) when estimating the severity of ischemic lesion.



It only expressed a blood supply restoration in the infarction area. An insufficient inform ability of ST segment change can be judged by its rather quick approaching to the isoline in the first 3 groups, while a considerable increase in Q wave was seen in…… % of groups II and III after TLT.

According to the data of Chasov E.I. and Ruda M.Y. (15), "the probability of cardiac decompensation development depends directly on the size of the lesion focus, the mass of

damages myocardium and, with certain reservations; this proposition can be also extrapolated to the case of cardiorrhexis". In doing this, it is important to determine if there exists a relation among the degree of cardiac decompensation, the severity of reperfusive syndrome and cardiorrhexis. What is the main cause of this terrible complication? And if it is largely due to the severity of reperfusive syndrome, then an early correction of microcirculation disturbances in the infarction area acquires a greater importance. Thus, a disconnection of myocardial fibers, a development of hemorrageous MI and a creation, to a certain degree, of the conditions for cardiorhexis were revealed in our early experiments in isolated T according to the findings of histomorphological examination of biopsy material and considerable RP. Hence the urgency of RPJH's correction has been preserved to nowadays though their danger and expansion of the ischemic damage area were mentioned in early studies by 17, 23, 30 and others. A shortening of periods of THT onset is important for the reduction of myocardial damage volume thought it does not avoid RP completely. In this connection it is worthwhile to keep in mind that thrombolytics infusion causing an increase in fibrinolitic activity results in a further increase in KKS activation in IM (1). Proceeding from this we should mention, that isolated TLT with streptase having a high fibrinolitic activity, results in a still higher KKS activation, an increase in RP and an expansion of the infarction area. Thus, it was shown objectively, that in efficient intracoronary TLT, leading to the restoration of the coronary artery potency, the necrosis mass was increased 1.8 times, in inefficient THT – 1.2 times while in traditional therapy – 1.4 times (2). When making comments on the received results, we should also pay attention to the fact, that TLT was performed in average 6.5 hours after the onset of AAA when severe alterations began in myocardium under the conditions of KKS pathologic activation.

The results of our studies confirm the above-mentioned facts by the example of early isolated TLT. Late TLT is followed by still greater structural disturbances in AIM. For all this, under the conditions of KKS increased activation, blood pumping into the damaged and ischemised myocardium makes late T even more dangerous than traditional therapy. At the same time, a marked decrease in mortality was revealed when appraising IM severity against the background of KKS inhibitors. Thus, under the conditions of an early injection of KM at BHS, it amounted to $3,9 \pm 2.7$ % ($P < 0,05$), at the hospital stage –

6.1±4. 1, while in the control group 12.8 ± 3.6% (9). No lethal outcomes were registered in the early isolated T and TLT against the background of KKS inhibitors. a\cording to the evidence of the European society of cardiologists (32), a significant (by 30%) decrease in mortality among the patients with IM is connected with creation of intensive care units. Mortality was still decreased by 25 % owing to the introduction of TLT. Nowadays mortality from IM amounts to 5-7% in the leading clinics of the world. However, a researching decrease in hospital lethality, a reassuring decrease in hospital lethality, was accompanied by a mortality decrease of the stage of the primary medical aid. Thus, in about 1/3 of the cases IM is terminated by a lethal outcome still before hospitalization (16.28) mainly within the first hour and more often in younger patients. Hence, in addition to an earlier T performance at BHS, it is necessary to have a sue of maximum pathogenetically directed agents improving microcirculation, promoting antianginal and antiarythmic effects and maintenance of AIM function.

When appraising the results of clinical examinations and the previous experiments, e KKS inhibitors at BHS as optimum cardioprotektors. Thus, KH, having a powerful antianginal effect, activates the capillary bed, improves retrograde blood supply and decreases in myocardial ischemia. Moreover, suppressing pathologic activation of kinin and coagulative systems of blood in subsequent TLT, KH prevents the development of RPIH and an increase in the mass of necrotisized myocardium, thrombus formation and facilitates its lysis.

Finally, when the patient is admitted to the hospital with periods of development of irreversible changes in the ischemic lesion focus being postponed under KH effects, it becomes possible to successfully perform not only systemic but also intracoronary thrombolisys and, if necessary coronary angioplasty and even ACSH operations. On these grounds successfully used the given method for urgent indications to perform ACSH surgery in connection with balloon angioplasty complicated by coronary artery occlusion (10).

Without casting doubt on cytoprotecting actions of trimetasidine, mildronate, magnesium sulfate and others, the known mechanisms of reperfusive damages and arrhythmias can be successfully blocked by an early preliminary infusion of KKS inhibitors. Thus, in experiment with preservation of collateral circulation in the ischemic area and retrograde

blood flow and stimulation under the influence of KH causing a decrease in myocardial ischemia, the formation of free radicals in reperfusion almost comes to naught. An absence or a considerable decrease in extravasation of blood formed elements against the background of KH in antegrade blood flow restoration indicates not enough urgency of a possible mechanic damage of cardiomyocites (CMC). Finally, mitochondria filling with calcium followed by a damage of their function, a decrease in ATP contents, a development of CMC contracture and their death were revealed in experiment in AIM reperfusion, against the background of KH accompanied by slight swelling of mitochondria, their structure and function being preserved.

In conclusion it should be noted that the earliest isolated T, in large focal myocardial infarction, inevitably results in RP. And for the time being there seems to be no alternative for prevention of significant RPJH other than a preliminary infusion of KKS inhibitors at BHS. At the same time a high realization of various ways of blood supply to the ischemic are with minimization of RD is possible with providing KKS inhibitors at the before hospital stage and a slight reorganization of emergency service.

Conclusions:

1. An optimum effect of early (within 2,5 hours)TLT against the background of an preliminary infusion of KKS inhibitors is caused by a decrease in vascular wall permeability prevention or considerable reduction of RPIH, removal, in majority cases, of anginous pains, rhythm disturbance and the signs of cardiac insufficiency in patients with AMI.
2. An early isolated thrombolysis, under the conditions of KKS pathologic activation, is often characterized by a less favorable clinical course of MI, appearance of RPIH, more pronounced rhythm disturbances and, frequently, bu aggravation of myocardium infarction. The performance of a late thrombolysis accompanied by still graver structural changes in myocardium and aggravating reperfusion complications has no advantage over traditional therapy.
3. An increase in Q wave at the moment of AMI reperfusion, appearance of new extrasystoles as well as observed episodes of ventricular fibrillation within the first 1-3 hours of T indicate the presence of RP which can be prevented by an early infusion of KKS inhibitors.

4. The ability of kontrikal and heparin to suppress pathological activation of kinin and blood coagulative systems, accumulated experience of a successful use of KKS inhibitors at BHS and positive results of TLT AMI at their background enable us to use kontrikal and heparin at BHS not later than 2 hours after AAA onset followed by TLT in hospital.

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კალიკრეინ-კინინური სისტემის ინჰიბიტორები მიოკარდიუმის ინფარქტის რეპერფუზიული გართულებების პრევენციისათვის

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კალიკრეინ-კინინის ინჰიბიტორის (აპროტინინი) ადრეული გამოყენება აფართოებს ინტრაკორონარული თრომბოლიზის ჩატარების შესაძლებლობას და მნიშვნელოვნად ამცირებს რეპერფუზიული გართულებების რისკს ტრანსლუმინური კორონარული ანგიოპლასტიკის და აორტო-კორონარული შუნტირების დროს.

გასაღები სიტყვები: სისტემა, ინჰიბიტორები, მიოკარდიუმი.