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Contents

Long-Term Prognosis in STEMI Patients Based on the Time Interval Between the Onset of the Disease and the Reperfusion Procedure

Yu.D. Volynsky, V.Yu. Polumiskov, I.E. Chernysheva, O.S. Buraeva, I.E. Kuznetsova, E.V. Yarnykh, Z.A. Aligishieva, D.G. Iosseliani

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The authors present the data on the long-term follow-up of STEMI patients who were treated with the use of endovascular coronary revascularization at different time points following the onset of the disease. The total number of study patients was 780. Five hundred eighty (580) patients who underwent the invasive procedure, entered the main study arm. They were subdivided into 4 subgroups in accordance with the time of surgery. The control arm included 200 patients who were not treated with the use of endovascular coronary revascularization due to various causes. The patients' status was assessed via the annual clinical and instrumental examination, monitoring of the complications and mortality level. The results obtained confirmed the superiority of the endovascular treatment in comparison with the non-invasive management. The best effect of the procedure was observed within the first 6 hours after the onset of the disease. Moreover, it was established that for the patients who are admitted at later terms and have no acute indications for the procedure, the intervention should be postponed by 4 to 6 days and carried out after the complete clinical examination of the patient.

Key words: *STEMI, endovascular coronary revascularization, long-term.*

The widespread implementation of aggressive coronary revascularization, thrombolytic therapy (TLT) and endovascular angioplasty (EVP) has crucially improved the treatment outcomes of the *ST*-elevation myocardial infarction (*STEMI*). Most authors defend the opinion that these procedures, along with the sophisticated pharmaceutical treatment and resuscitation methods, resulted in the essential improvement of in-hospital mortality and reduced rate of severe complications (1). Respectively, the long-term prognosis of patients in terms of vitality and working capacity has improved. The comparative analysis of the outcomes of different methods confirmed the evident advantage of EVP over TLT (2, 3). All this led to the revision of the strategy and tactic of the medical care in *STEMI* patients in order to admit patients as quickly as possible to the hospitals able to perform the 24-hour interventional radiology procedures and the qualified endovascular myocardial reperfusion (2–4).

Most medical professionals agree that EVP in the infarct-related artery (IRA) within 90-180 minutes or, at any rate, within 6 hours after the onset of *STEMI* is the most efficacious (1–4). However, the researchers do not come to a consensus about time limits of the effective reperfusion in *STEMI* patients (4).

For example, Rathore S.S. et al. (2009) allow reperfusion beyond the 6-hour interval after the onset of *STEMI* and include in the analysis the patients admitted within the first 12 hours of the disease, based on the retrospective assessment of the treatment outcomes of 43,801 *STEMI* patients (5).

Other guidelines on the optimal and marginal time for EVP include the period up to 24 hours, i.e. the first day after the onset of the infarction (6). The similar instruction is presented in the order of the Ministry of Healthcare of the Russian Federation No.918n effective as of 15 November, 2012. Therefore, the time limits of effective and appropriate reperfusion intervention after the onset of *STEMI* are under discussion.

This served as the basis for the task-oriented trial aimed to explore the relationship between the delay from the onset of the disease to the moment of IRA endovascular reperfusion, and treatment efficacy in *STEMI* patients. The judgement about clinical effect of this procedure was based on the multiyear data.

Clinical characteristics of patients and methods of the study

To reduce the bias of the analysis and of treatment outcome assessments, the clinical sample was made as much free as possible from any significant age- and gender-related differences. Moreover, to mini-

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mize biases when assessing the delayed outcomes, the data were obtained both from attending physicians and physicians who conducted the medico-social patients' examination.

This was accomplished due to the established Russian practice of referring each AMI patient to the medico-social examination (MSE) with subsequent mandatory yearly re-examination, including the comprehensive cardiological examination.

Accordingly, the retrospective clinical trial used the following documents:

a) computerized medical record repository "DIMOL" of the Moscow City Centre of Interventional Cardioangiology (MCC-IC), which contained the data of >10,000 AMI patients treated from the year 2000 to the year 2012

b) information of the Main bureau of the medico-social examination (MB MSE) from the year 2000 to the year 2012.

Among the data from the MCC-IC repository, the information was gathered concerning 780 *STEMI* patients who underwent the yearly medico-social examination during the following 5 years. The data related to their future fate were extracted from the repository of MB MSE and from the outpatient medical records.

Inclusion criteria were as follows:

- Primary acute myocardial infarction (AMI), confirmed at the hospital level, without any discrepancies concerning its date and time of the onset
- Patient's age at the moment of the disease not more than 55 years (male) and not more than 50 years (female), i.e. before the onset of the disease all patients were able to work
- Follow-up at the cardiology department of MB MSE for 3 years after the primary hospitalization, with yearly re-examination
- No serious concomitant diseases: malignant tumours; congenital and acquired heart malformations; complex heart arrhythmias and conductivity disorders; insulin-dependent diabetes; chronic pulmonary, hepatobiliary, digestive or urinary disorders; significant neurovascular diseases.

Study methods

Among 780 study subjects with *STEMI*, 580 (74.4%) were treated with the use of endovascular myocardial reperfusion (balloon angioplasty and/or angioplasty+stent implantation). These patients formed the main study group. The remaining 200 *STEMI* patients did not underwent coronary reperfu-

Clinical and instrumental data in STEMI patients at the endpoint of the follow-up (n = 780)

Groups of patients			Clinical status after MI	
			Post-infarction aneurysm n (%)	Complex rhythm disturbances n (%)
IM patients Main arm	Overall in the group	n = 580	130 (22,4)*	84 (14,5)*
1th subgroup: EVP: within the first 6 hours after AMI	Overall in the subgroup	n = 249 (100%)	31 (12,3)	33 (13,3)
	Q-wave anterior MI	n = 103 (41,3%)	30 (29,1)	18 (17,5)
	Q-wave posterior MI	n = 127 (51,0%)	0 (0)	14 (11,0)
	Non-*Q*-wave MI	n = 19 (7,7%)	1 (5,30)	1 (5,30)
2th subgroup: EVP 7–72 hours after AMI	Overall in the subgroup	n = 132 (100%)	60 (45,5)**	30 (22,7)**
	Q-wave anterior MI	n = 87 (65,9%)	59 (67,8)**	22 (25,3)**
	Q-wave posterior MI	n = 32 (24,2%)	1 (3,10)	5 (15,6)
	Non-*Q*-wave MI	n = 13 (9,9%)	0 (0)	3 (23,1)
3th subgroup: EVP 4–14 days after AMI	Overall in the subgroup	n = 112 (100%)	20 (17,9)	11 (9.80)
	Q-wave anterior MI	n = 43 (38,4%)	16 (37,2)	4 (9,3)
	Q-wave posterior MI	n = 31 (27,7%)	2 (6,5)	5 (16,1)
	Non-*Q*-wave MI	n = 38 (33,9%)	2 (5,3)	2 (5,3)
4th subgroup: EVP/CABG 15–90 days after AMI	Overall in the subgroup	n = 87 (100%)	19 (21,8)**	10 (11,5)
	Q-wave anterior MI	n = 30 (34,5%)	16 (53,3)**	7 (23,3)
	Q-wave posterior MI	n = 38 (43,7%)	2 (5,3)	2 (5,3)
	Non-*Q*-wave MI	n = 19 (21,8%)	1 (5,30)	1 (5,30)
IM patients Control group	Overall in the subgroup	n = 200	68 (34,0)	77 (38,5)
	Q-wave anterior MI	n = 96 (48%)	55 (57,3)**	49 (51,0)**
	Q-wave posterior MI	n = 84 (42%)	10 (11,9)**	24 (28,6)**
	Non-*Q*-wave MI	n = 20 (10%)	3 (15,0)	4 (20,0)

Notes: * – significant differences between the main arm and the comparator arm ($p < 0.05$)
** – significant differences compared to the 1st subgroup ($p < 0.05$).

sion with the use of EVP or TLT, or the attempted interventions were unsuccessful. These patients formed the control group.

The routine annual examination included the following procedures:

- Electrocardiogram at rest
- Holter's daily ECG monitoring
- Exercise stress test (bicycle ergometry or treadmill-test with ECG recording)
- Heart ultrasound examination (left ventricular ejection fraction [LVEF] and regional myocardial kinetics)
- Clinical laboratory tests

Upon indications, the selective coronarography or CT-coronarography were performed.

The main complications of AMI, defining the severity of patient's status, were established on the basis of the clinical, instrumental and laboratory testing in parallel with the routine methods of the clinical assessment, i.e.: chronic post-infarction heart aneurysm (HA); complex heart arrhythmias and conductivity disorders; congestive heart failure (functional class 2 and higher) (CHF).

STATISTICA for Windows 6.1 (StarSoft Inc., USA, 2006) was used for statistical analysis. The quantitative variables are presented as mean and standard deviation (M ± SD). When nonparametric data were compared, χ^2 test with Yates correction (χ^2) and two-sided Fisher's exact test (F) were used. When qualitative variables were compared to assess the mortality, unpaired Student's test was used, and Mann–Whitney test (U) was used for mortality structure analysis.

Results

According to the study objective, all the patients enrolled in the study were assigned to two groups.

The first (main) group included *STEMI* patients (n = 580), who were successfully treated with the use of EVP at the hospital stage of treatment at MCC-IC (balloon angioplasty and/or stent implantation into the IRA).

The second (control) group included *STEMI* patients (n = 200), who did not undergo EVP or TLT, or these procedures were unsuccessful.

The Table presents the main clinical historical and laboratory data of the studied patients. The table demonstrats the absence of significant inter-group differences in the main clinical laboratory and instrumental data and the good comparability of the study groups.

Clinical status after MI				Mortality distribution	
CHF, 2nd functional class and higher, n (%)	Recurrent MI, n (%)	LVEF, %	Positive stress test n (%)	Mortality during the first 5 years n (%)	Number of subjects who died during the first 5 years due to CVDs, n (%)
173 (29,8)*	53 (9,22)*	53,16*	118 (20,3)*	22 (4,07)*	19 (86,4)
48 (19,3)	14 (5,6)	56,52	27 (10,8)	7 (2,97)	6 (85,7)
32 (31,1) 16 (126) 0 (0)	6 (5,8) 8 (6,3) 0 (0)	54,04 58,02 59,95	14 (13,6) 13 (102) 0 (0)	3 (3,26) 4 (3,20) 0 (0)	3 (100) 3 (75,0) 0 (0)
79 (59,8)**	17 (12,9)**	45,34**	48 (36,6)**	12 (10,2)**	11 (91,7)
57 (65,5)** 14 (43,8)** 8 (61,5)	9 (10,3) 5 (15,6) 3 (23,1)	42,05** 50,84** 53,54	30 (34,9)** 15 (46,9)** 3 (23,1)	9 (11.8)** 3 (10,3)** 0 (0)	9 (100) 2 (66,7) 0 (0)
25 (22,3)	10 (8,90)	54,20	25 (23,3)**	0 (0)	0 (0)
15 (34,9) 8 (25,8) 2 (5,3)	5 (11,6) 4 (12,9) 1 (2,60)	50,95** 52,77** 59,03	12 (27,9)** 10 (32,3)** 3 (7,9)	0 (0) 0 (0) 0 (0)	0 (0) 0 (0) 0 (0)
21 (24,1)	12 (13,8)**	53,77**	18 (20,7)**	3 (3,66)	2 (66,7)
14 (46,7) 4 (10,5) 3 (15,8)**	4 (13,3) 7 (18,4)** 1 (5,30)	49,67** 55,63** 56,67	6 (20,0) 6 (15,8) 4 (21,1)**	1 (3,80) 2 (5,40) 0 (0)	1 (100) 1 (50,0) 0 (0)
115 (57,5)	63 (31,5)	46,48	146 (73,0)	26 (13,2)	24 (92,3)
67 (69,8)** 41 (48,6)** 7 (35,0)**	33 (34,4)** 26 (31,0)** 4 (20,0)**	41,26** 48,96** 55,33**	79 (79,6)** 53 (63,0)** 14 (70,0)**	17 (17,9)** 8 (9,60)** 1 (5,30)	16 (94,1) 7 (87,5) 1 (100)

In accordance with the principal study objective, i.e. for assessing the influence of time from the onset of the disease to the endovascular procedure on the long-term *STEMI* outcomes, the main group was subdivided into 4 subgroups.

The first subgroup (n = 255) included *STEMI* patients who underwent endovascular myocardial reperfusion within the first 6 hours from the disease onset.

The second subgroup (n = 144) consisted of *STEMI* patients who underwent the procedure 7–12 hours after the angina onset.

The third subgroup (n = 99) included *STEMI* patients who underwent endovascular myocardial reperfusion even later, 4 to 14 days from the disease onset.

The fourth subgroup (n = 82) included *STEMI* patients who underwent the delayed myocardial reperfusion 15 to 90 days from the disease onset.

Moreover, *STEMI* patients were subdivided within each subgroup by localization of the necrotic lesion: 1. Anterior left ventricular necrotic lesion, or 2. Posterior left ventricular necrotic lesion.

The patients from the control group (n = 200) were similarly subdivided into 2 subgroups in accordance with the localization of the infarction. The first subgroup included patients with the anterior lesions (n = 106), the second subgroup included patients with the posterior left ventricular lesions (n = 94).

The preliminary comparison of the long-term treatment outcomes in two study groups, i.e. main and control groups, demonstrated, in general, significantly improved outcomes in the main group compared with the patients who received only pharmaceutical treatment, irrespective of the time period of endovascular myocardial revascularization (Figures 1 and 2).

According to the current conceptions, the probability of the essential post-*STEMI* clinical complications depends predominantly on the localization and depth of the necrotic lesion. The anterior left ventricular infarction is generally accompanied with larger myocardial damage and, correspondingly, less favourable outcome compared to the posterior infarctions. However, this can only be applied to the cases of uncomplicated posterior infarctions, i.e. without dysfunction or detachment of the papillary muscles, laceration of the ventricular septum etc.

In general, the results of the present study confirmed the current conceptions (Table). The tables demonstrate that rates of post-infarction heart aneurysm (HA), complex arrhythmias and conductivity disorders, and CHF were statistically significantly higher ($p < 0.01$) in *STEMI* patients with the anterior necrotic lesions, compared to the patients with posterior lesions, irrespective of the treatment group. Accordingly, these complications were accompanied with more pronounced depression of the pumping function of the heart. Thus, the first subgroup of the control group (i.e., patients with anterior localization of the infarction) was characterized by the highest rate of HA (57.3%), complex arrhythmias (51.0%) and 2nd functional class CHF (69.8%), with the most expressed decrease of the left ventricular ejection fraction to 41.26%. No wonder that the anterior *STEMI* was associated with higher mortality. In particular, the mortality rate among the control group patients with anterior *STEMI* was almost twice as high – 17.9% compared with 9.60% ($p < 0.01$) among the patients with the posterior *STEMI*.

Meanwhile, the localization of *STEMI* had virtually no influence on the rate of the recurrent MI, positive results of the exercise stress tests and need for EVP and coronary bypass surgery (CABG) during the distant post-infarction period. The percentages of these events were essentially similar among *STEMI* patients with the anterior and posterior necrotic lesions in both study groups (Table).

This fact can be readily explained, because the relapsed infarctions, as well as the need for the EVP or CABG, or positive stress tests, depend largely on the extent of coronary vessels involvement and post-ischemic myocardial modifications.

When reviewing the clinical course and treatment outcomes in *STEMI* patients in respect to the time of reperfusion treatment, decreased rates of post-infarction aneurysm, complex arrhythmias and CHF are evident after reperfusion within the first 6 hours after the onset of the anginal status compared to delayed reperfusion (Table).

The pump cardiac function in these patients was better. LVEF was 54.04% in patients with the anterior infarction and 58.01% in patients with posterior infarction. These benefits are even more evident compared to *STEMI* patients in the control group with the same localization of the infarctious lesions, who did not undergo EVP or EVP was unsuccessful. In particular, LVEF values in the control group were 41.26% and 48.96%, respectively ($p < 0.01$) (Table). Moreover, in the 1st subgroup (main group) the rate of the positive stress test and the rate of the relapsed MI were 5 times lower than in *STEMI* patients of the control group.

Similarly, the mortality was significantly lower in this 1st subgroup of the main group (Figure 1): 3.26% and 3.20% patients with the anterior and posterior *STEMI* died, respectively. Meanwhile, the mortality of the control group patients was 17.9% and 9.60%, respectively ($p < 0.05$).

The endovascular myocardial revascularization performed within 7 to 72 hours from *STEMI* onset (2nd subgroup of the main group) had a similar positive effect on the course of disease, irrespective of the localization and extent of the necrotic lesion. However,

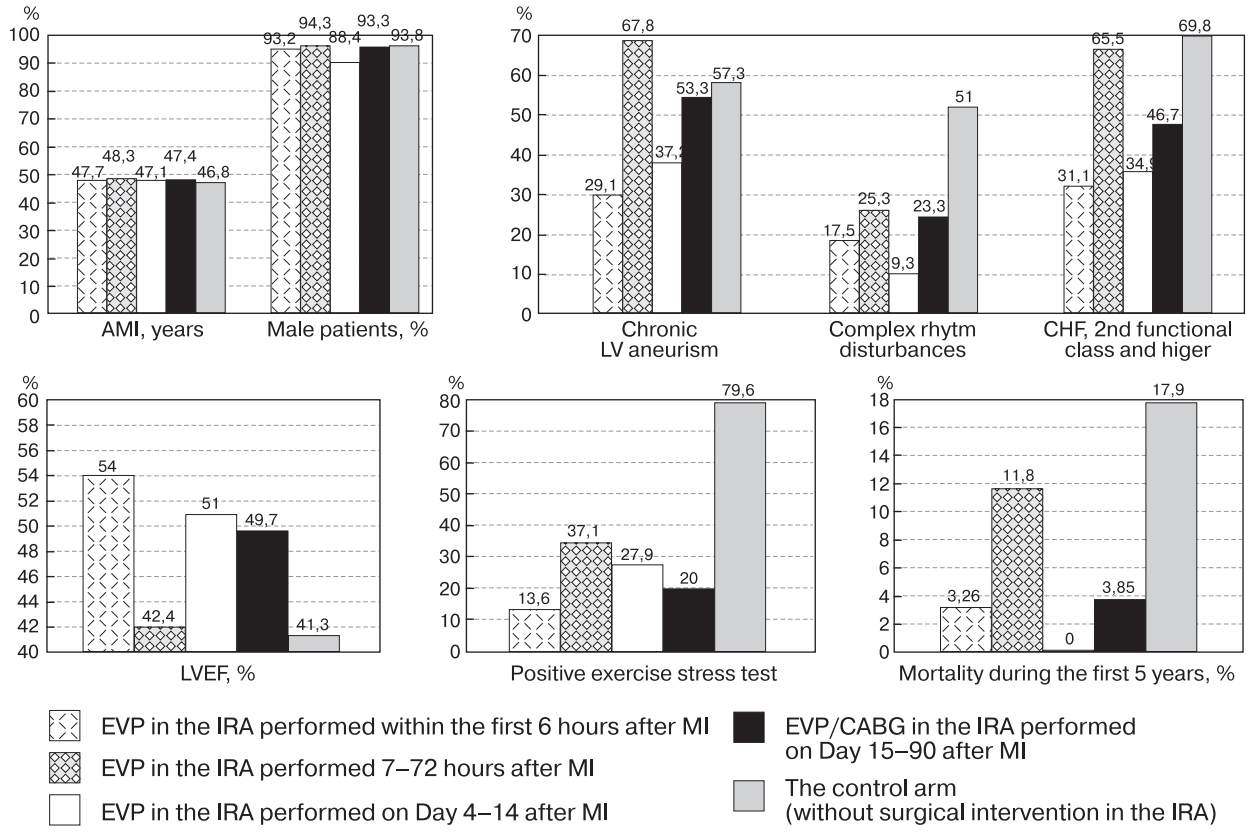

Figure 1. Main clinical and functional parameters in patients with primary Q-wave anterior STEMI (5-year follow-up).

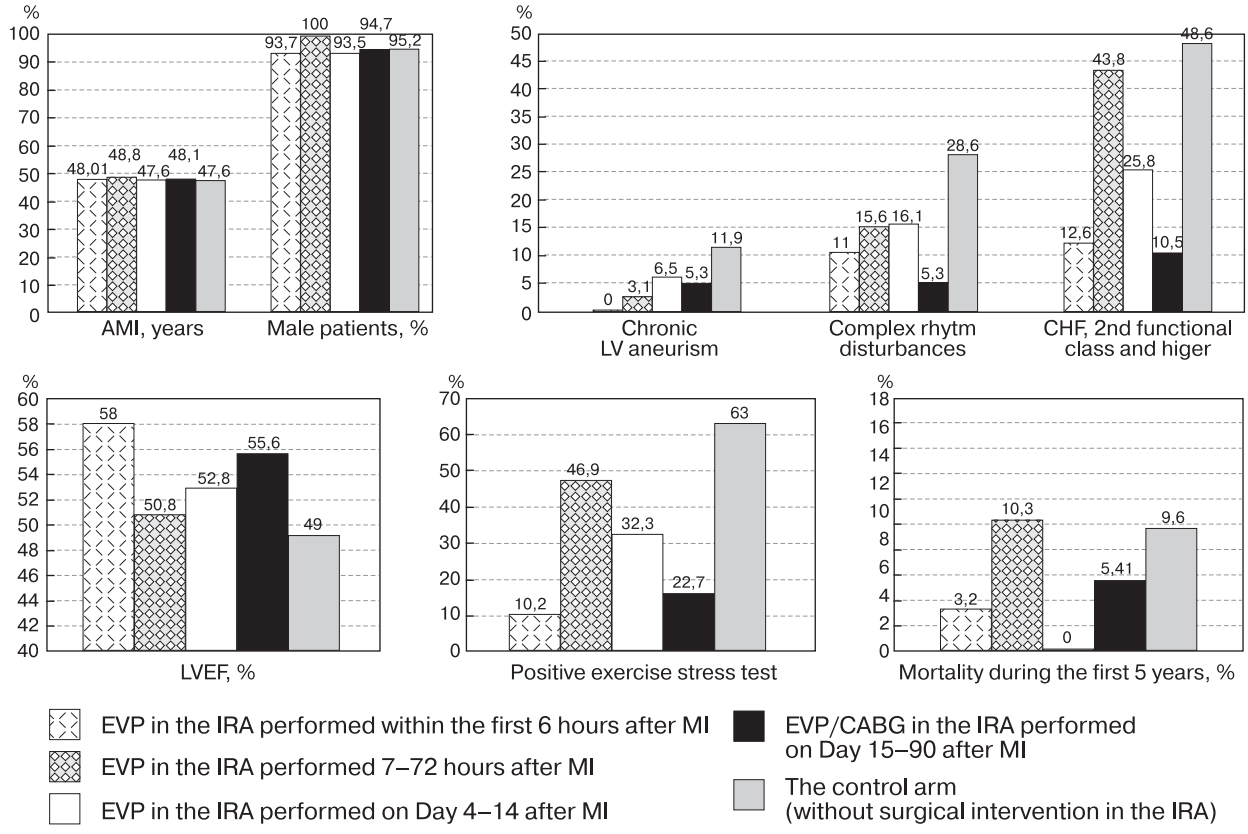

Figure 2. Main clinical and functional parameters in patients with primary Q-wave posterior STEMI (5-year follow-up).

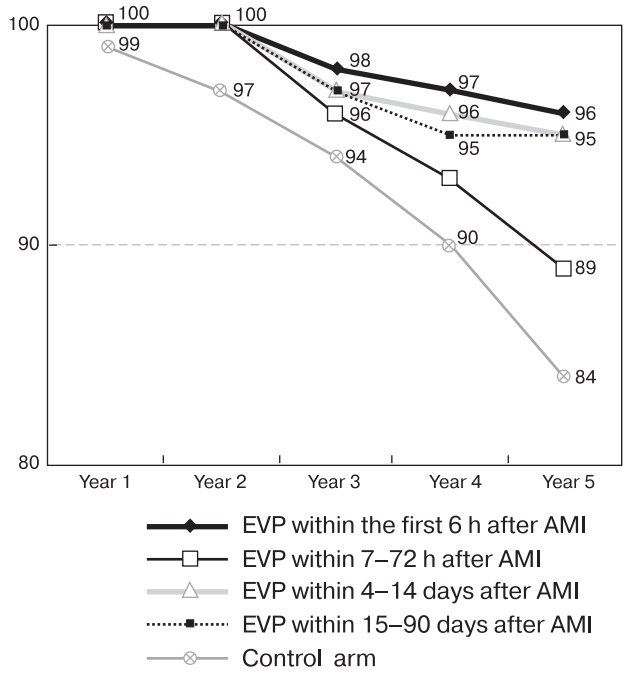

Figure 3. Survival of STEMI patients following successful endovascular reperfusion and in the control arm (%). Note: the averaged data for the anterior and posterior STEMI patients in the subgroups 1–4 of the main arm and subgroup 1 of the control arm are presented.

the positive effect in this subgroup was less evident compared to other groups, except for the group without endovascular procedure or with unsuccessful procedure. The had higher rate of HA, complex arrhythmias and ⩾2nd functional class CHF. The mortality level was similar to the mortality rate in the control group (Table, Figure 1).

The results obtained in the 3rd subgroup (endovascular recanalization of the IRA beyond 72 hours after *STEMI* onset) are of particular importance. These patients had significantly better outcomes compared to the previous subgroup. Namely, aneurysm occurred only in 37.2% of cases compared to 67.8% in the 2nd subgroup. The same applies to the rate of arrhythmias: 9.3% of patients in the 3rd subgroup and 25.3% of patients in the 2nd subgroup. LVEF in the 3rd subgroup was 51% compared to its significant decrease (42.4%) in the 2nd subgroup. The positive stress test was observed in 27.9% and 37.1% of patients, respectively. These facts may explain the lower rate of symptomatic congestive heart failure: 65.5% and 34.9% in the 2nd and 3rd subgroups, respectively.

The outcomes of patients who underwent the X-ray guided endovascular reperfusion procedure 15 days after the heart attack and later, were worse than in the 1st subgroup. In particular, chronic left ventricular aneurysm was observed in 53.3% of cases, complex arrhythmias in 23.3%, CHF in 46.7%, positive stress test in 20% of patients, with mean LVEF of 51%. During the study period, the mortality rate was 3.85%.

In addition to the presented data, the results of treatment have been evaluated using the method of *survival analysis*. This is a method for the study of *life duration up to the moment of its termination* is based on the evaluation of time intervals from the start of study up to the moment of the arising of the "event of interest", in this case – of death in each individual case. This procedure allows to evaluate the *function of survival* more reliably, and for this reason the results of such analysis currently are being used as an important medical index of the effectiveness of various methods of treatment. (7).

The particularity of this and similar studies consists in the presence of individuals, who had been lost from sight for different reasons before the end of study, in each group of patients. Such studies fall within the category of censored studies, that is, the studies with incomplete information.

In order to study such censored data we have used the most natural method of description of the survival function in the samples of study- the construction of tables of life duration after endovascular myocardial reperfusion. For this reason the whole period of observation was divided into the timeslots – years. Then, the number of survived patients and their percentage were estimated for each timeslot. In the same way we have estimated the number and the percentage of patients who had died during the given timeslot, as well as the number and the percentage of individuals for whom no information was available and who had been deleted (censored) in each timeslot. Thus, the table accounted for the complete as well as for the incomplete observations. As a result, the survival curves were plotted (Figure 3).

The analysis of numeric values in the table and the curves on the plot allowed us to make several conclusions concerning the dynamics of mortal outcomes, and the most important among them is the cumulative part of survived patients for each timeslot, that is, for each year of study.

Discussion of the results

At the beginning of this article, we mentioned the confirmed beneficial influence of the reperfusion procedures on the clinical course and outcome of acute myocardial infarction. X-ray guided endovascular revacularization of the infarct-related artery is the most efficacious among the known reperfusion techniques.

However, the time period from the onset of the disease, when this procedure may still be effective, is under ardent debates. Intervals for most successful revascularization procedures are discussed as well. In our opinion, these questions can be answered only after careful comparative analysis of the immediate and distant treatment outcomes in *STEMI* patients

after myocardial reperfusion at different time points from the onset of the disease.

Comprehensive assessment of the long-term treatment outcomes in *STEMI* patients revealed a challenging relationship between the time effect and the delayed clinical status of these patients. In particular, the most pronounced effect was observed following endovascular revascularization of the IRA within 6 hours from the onset of the disease, as expected based on the current knowledge. On the other hand, the reduced efficacy of this procedure during the following 7–72 hours and the subsequent improvement of its effectiveness at later terms require further consideration.

Endovascular reperfusion of the IRA is known to be associated with the myocardial reperfusion injury (MRI), together with the ischemic cascade responses and formation of the necrotic lesion. During this period, the most critical manifestations of MRI during coronary revascularization in AMI patients include reperfusion arrhythmias and reversible post-ischemic myocardial dysfunction lasting from some days to several weeks (8).

It's well known that the myocardial segment, completely or nearly completely devoid of the blood flow, loses the contractile ability. As a result of ischemia, cardiomyocytes disintegrate and their electromechanical activity is disturbed. This may be due both to the ischemic injury or cytolysis of cardiomyocytes, and to the phenomenon of cellular hybernation in the ischemic area. They lose ability to actively contract and relax, reserving the minimal energy resources to maintain viability (8–10).

Early revascularization in *STEMI* prevents cytolysis and contributes to the regression of hybernation. The earlier revascularization, the lower probability of stunning. Nevertheless, even early effective revascularization within one hour does not always result in the complete recovery of the blood flow in the ischemic segment. This is mainly due to the swelling of the endothelial cells in the microcirculation and microcirculatory obstruction by the aggregated platelets. However, these processes are largely reversible: the effective blood flow recovery in the IRA saves up to 50% of the ischemic myocardium in spite of the reperfusion injury and death of some cardiomyocytes. Accordingly, the resulting necrotic lesion can be significantly reduced (8). Evidently, this is a cause of the maximum efficacy of X-ray guided endovascular intervention in the 1st subgroup of patients of the main treatment group.

At later terms (7 to 72 hours after the onset of the disease), i.e. during the necrotic stage of the acute MI, when the membranes of the cardiomyocytes and of their subcellular structures, i.e. mitochondria, are irreversibly damaged, the mechanism and manifestations of MRI change significantly. During this period, the blood flow restoration in the IRA leads to the rapid diffusion of the inflammatory cells throughout the ischemic area. Activated neutrophils produce a lot of active oxygen species (AOS) that potentiate inflammatory injury of the myocardium (8, 11). Moreover, neutrophil adhesion to the capillary walls results in the mechanical blood flow obstruction in combination with the effects of neutrophil-derived factors of vascular constriction and platelet activation, tissue swelling and endothelial injury, with "no-reflow" phenomenon. In this situation, the recanalization of large epicardial coronary vessels does not result in an appropriate myocardial perfusion, which is deleterious to the myocardial reperfusion (8–11). Moreover, "late" (on AMI days 2–3) recanalization of the IRA may increase the risk of haemorrhagic MI (during the systemic TLT or percutaneous catheter-based intervention [PCI] + TLT), aneurysm formation and/or external heart rupture (10).

All this suggests that the clinical and functional effect of myocardial reperfusion performed during the period from 7 to 72 hours after the onset of the disease is reduced due to necrotic processes in the ischemic myocardium during this period.

The present study demonstrated much more beneficial results of blood flow repair on days 4 to 14 after the onset of AMI, i.e. during the resorptive-restorative stage of the disease, in the 3rd subgroup of the main group. It is possibly due to the lowest activity of potential MRI mediators, listed above, at this AMI stage and absence of any MRI prerequisites. On the contrary, myocardial reperfusion during this stage of AMI promotes both faster healing of necrotic focus and restoration of heart contractile function, accelerates resorption and reparation processes due to improved blood supply of necrotic focus and peri-infarction area.

The present data lead to a conclusion about the predominant influence of the duration and severity of ischemia, together with the severity of MRI, on the myocardial survival following reperfusion (10).

Of course, the interpretation of the results of this retrospective clinical trial requires the clarification and confirmation of the data obtained. However, potential more specific approach to X-ray guided endovascular intervention aimed at the IRA recanalization, is of great practical importance in the system of qualified medical care for AMI patients. In particular, in patients with *Q*-wave AMI who are admitted to the hospital beyond 6 hours after its onset and have no progressive symptoms, pain syndrome or arrhythmias, the invasive intervention should be delayed by 5–7 days and performed after the complete clinical, laboratory and instrumental evaluation. The situation of the relapsing early post-infarction angina is an exception. In such

cases, the patient requires urgent examination and appropriate care. This dilemma is the most significant when transportation to the other hospital or for long distances is needed for invasive procedure to be conducted.

Conclusions

1. The long-term treatment outcomes in *STEMI* patients who underwent the X-ray guided endovascular myocardial reperfusion were generally more favourable compared to the patients in the non-interventional group, irrespective of intervention timing.

2. Endovascular reperfusion within the first 6 hours after the onset of *STEMI* have the most beneficial impact on the course of the disease and long-term outcome.

3. In patients admitted to the hospital beyond 6 hours from the onset of the disease, the intervention should be postponed (if no acute conditions are present) by several days and performed after the complete examination.

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Successful Simultaneous Combined Endovascular Treatment of Left Internal Carotid Artery Stenosis and Left Superficial Femoral Artery Occlusion: a Clinical Case

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According to several multicenter trials, surgical or endovascular correction is the most widely used and optimal method of management of atherosclerotic vascular lesions. However the problems of the sequence, the tactics and the volume of revascularization in such patients remain unsolved. It is especially true for the situations when it is necessary to make a choice between surgical and endovascular intervention. The presented clinical case of successful simultaneous endovascular correction of the stenotic atherosclerosis of the carotid and the superficial femoral arteries is an example of a balanced approach to the selection of the tactics of intervention in such patients.

Key words: *stenting of the carotid artery, stenting of the femoral artery.*

Stenotic atherosclerotic process can disrupt the blood supply in almost all the human organs and tissues. Often, this process affects arterial territories of several organs. It is even more important, because the treatment of these diseases involves competing or alternative options, namely surgery and endovascular procedures. (1, 2). In current clinical practice, there are no clearly prescribed and, may be said, established or commonly accepted differential criteria for surgical and endovascular treatment in patients with stenotic and occlusive lesions of major vessels. Only a thorough and rigorous comparison of these methods in terms of their outcomes will allow us in future to develop a differentiated algorithm of indications and contraindications both for surgical and endovascular treatment options. Proper treatment modalities and their sequence are particularly difficult to choose in case of combined lesions of vessels supplying the different organs. In these cases, one should choose not only the most optimal treatment option, but also a right sequence of these procedures in different blood territories. The particularly important question is, whether these interventions should be performed simultaneously or step-by-step with a certain time interval. To resolve all these issues, one must consider many factors including age, comorbidities, lesser invasiveness, probability of serious complications, cost-effectiveness, etc. All the above fully applies to the cases of combined atherosclerotic lesions of the carotid arteries and blood vessels supplying the lower limbs. Severely impaired vascularization of these organs, without adequate treatment, can lead to premature disability and death of patients. To date, significant experience in both surgical and endovascular treatment of these diseases has been accumulated. However, these are separate procedures on these organs with a certain time interval. Meanwhile, there are very few reports on simultaneous combined surgical or endovascular treatment of these diseases. Therefore, we considered it appropriate to publish our clinical observation on simultaneous combined endovascular treatment of stenotic lesion of the right internal carotid artery and occlusion of the middle segment of the left femoral artery.

The male patient K., 62 y.o., was examined in the Center for coronary heart disease. He had a history of several myocardial infarctions in 2012–2013. During examination in the Center, multiple stenotic occlusive coronary artery disease involving almost all major vessels was detected: left coronary artery stenosis up to 50%, LAD stenosis >90%, circumflex artery stenosis up to 70%, and right coronary artery occlusion. Based on the clinical, laboratory and coronarography data, the decision was made to perform a direct myocardial revascularization. However, during examination it was found that the patient suffered from vertigo becoming

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worse when he turned his head, during long-term forced head position, as well as after he got up. Periodically, the patient noted the noise in his head, fatigue, memory loss, confused attention, as well as frequent choking during meal intake. He also suffered from the pain in his left calf occurring when he walked 100–150 meters.

The patient was a smoker; he had no alcohol abuse and did not monitor his nutrition. No diabetes mellitus or impaired glucose tolerance were identified.

Physical examination revealed no murmurs over the femoral and carotid arteries. The palpable pulsation over the right a. poplitea, right a. dorsalis pedis and right a. tibialis posterior was satisfactory, no pulsation was palpable over the lift-sided arteries.

The brachiocephalic ultrasonic Doppler imaging revealed: the S-shaped left subclavian artery was significantly tortuous from the orifice. The antegrade blood flow with a linear blood flow velocity of 1.0 m/sec was registered. The vertebral artery diameter was 2.7 mm; the blood flow was antegrade with a linear blood flow velocity of 0.35 m/sec. The course of the artery between the transverse processes of the cervical vertebrae and in extravertebral segment was nonlinear without hemodynamically significant differences of blood flow. The thickness of the "intima – media" complex in the common carotid artery was 1.3 mm. The internal carotid artery was occluded from the orifice, with a moderately deficient blood flow.

The external carotid artery was unremarkable. The right subclavian artery was S-shaped and insignificantly tortuous. There was an antegrade blood flow with a linear blood flow velocity of 1.0 m/sec. The vertebral artery diameter was 3.6 mm; the blood flow was antegrade with a linear blood flow velocity of 0.35 m/sec. The course in the transverse processes of the cervical vertebrae and in extravertebral segment was nonlinear without hemodynamically significant differences of blood flow. The thickness of the "intima – media" complex in the common carotid artery was 1.0 mm. The internal carotid artery at the orifice was heterogeneous, with a prolonged atherosclerotic plaque narrowing the vessel lumen by 70–75%, the blood flow velocity was 0.8 m/sec. The external carotid artery was unremarkable.

Ultrasound Doppler imaging of the lower limbs revealed US evidence of diffuse atherosclerotic lesions of the arterial walls. On the right: the common femoral artery and superficial femoral artery had antegrade blood flow with signs of turbulence and linear blood flow velocity of 1.07 m/sec. The arterial walls were thickened; there was stenosis up to 25–30%. The posterior tibial artery (PTA) was patent, its wall was indurated, calcified, blood flow was antegrade and two-phase. The anterior tibial artery (ATA) was patent, its wall was indurated, calcified, blood flow was antegrade and two-phase.

On the left: CFA had antegrade blood flow with signs of turbulence and linear blood flow velocity of 1.19 m/sec. Its wall was thickened; there was a stenosis of 30–35%. The blood flow pattern in the left SFA was changed; there was an occlusion in the middle segment. The PTA was patent, with indurated and calcified walls; the blood flow was collateral, two-phase. ATA was occluded.

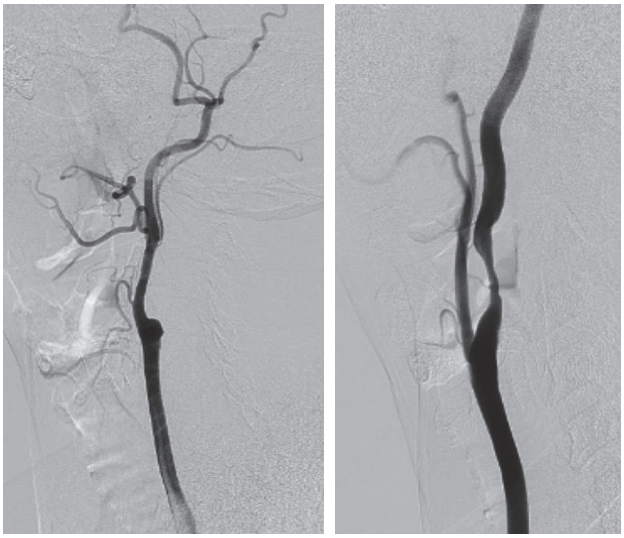

Figure 1. Selective arteriography of the left CCA and ICA (left) and the right CCA and ICA (right) in digital subtraction angiography mode with a frequency of 6 fps in lateral projection (see text for description).

The brachiocephalic angiography revealed: the right common carotid artery had smooth contours; the right internal carotid artery was stenotic from the orifice by 70–75%. The left CCA was unchanged, the left ICA was occluded from the orifice (Figure 1).

The lower limbs angiography revealed: diffusely impaired right CIA, EIA, IIA, CFA, DFA, SFA, popliteal artery, trifurcation and proximal 1/3 of the right crural artery without hemodynamically significant stenosis.

The left CIA, EIA, IIA, CFA, DFA were diffusely impaired without hemodynamically significant stenosis. The left SFA was occluded; the post-occlusion segments, the left popliteal artery, the trifurcation, and the left crural arteries were visualized via collaterals. The left ATA was occluded (Figure 2).

The diagnosis established on the basis of the clinical and medical history, laboratory and instrumental data was: Coronary heart disease; postinfarction cardiosclerosis; multifocal atherosclerosis; occlusive stenotic coronary artery disease (stenosis of the left main coronary artery up to 50%, middle-third LAD stenosis up to 90%, proximal 1/3 of LCX stenosis 60–70%, RCA occluded in the proximal 1/3 – CAG dated May 22, 2013); dislipoproteinemia 2A; stenotic atherosclerosis of BCAs – occlusion of the left CCA, significant stenosis of the right CCA; discirculatory encephalopathy 2A; occlusion of the left SFA and both PTAs, left lower limb ischemia 2B.

The multidisciplinary council of physicians has decided to perform direct myocardial revascularization given the severe lesion of the brachiocephalic vessels and occlusion of the left superficial femoral artery, starting with endovascular interventions in the left internal carotid artery and left

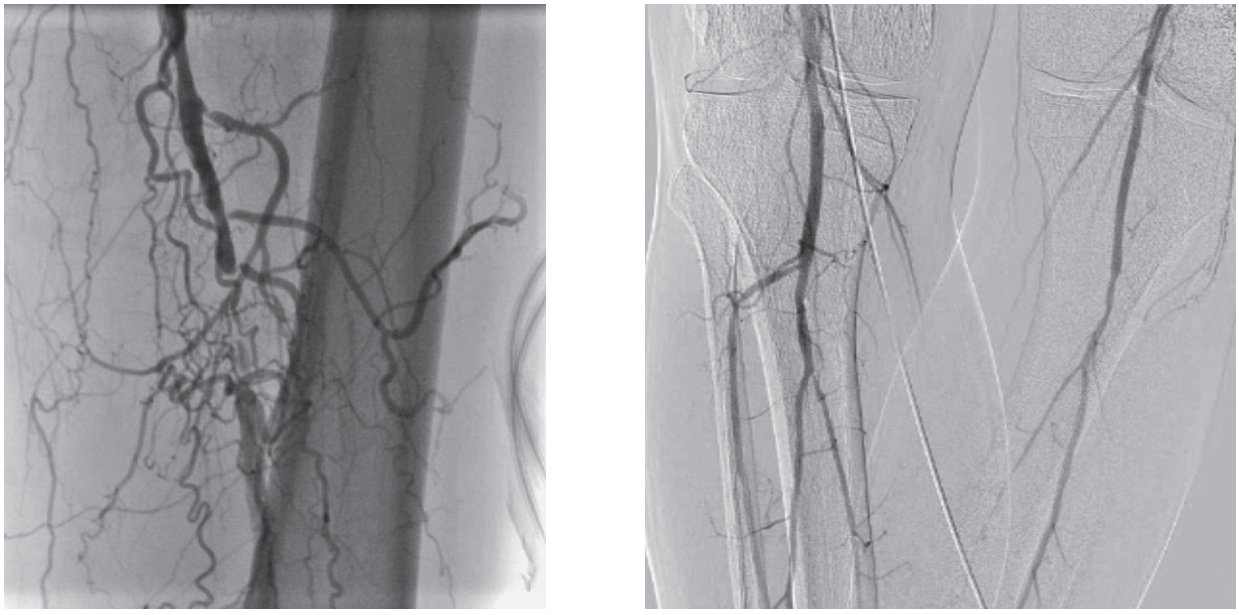

Figure 2. Left: short occlusion of the left SFA; Right: arteriography of both lower legs in DSA mode (right); the occluded left ATA is seen.

femoral artery. To reduce the time period before the direct myocardial revascularization surgery, the decision was made to perform both simultaneous and combined interventional procedures.

Endovascular procedure was started with stenting of the right internal carotid artery according to the standard technique. The arterial access was achieved using retrograde puncture in the right common femoral artery, with the placement of a 8 F sheath. Then using a guiding catheter for the right coronary artery and guidewire 0.35, brachiocephalic trunk and then the right common carotid artery were catheterized. After that, the guidewire was replaced and the distal embolization protection device Filterwire was introduced into the artery and positioned in the distal parts of the internal carotid artery, at a considerable distance from the stenosis. After that, a self-expanding nitinol stent Acculink 8 × 40 mm was delivered, positioned and implanted in the location of the right ICA stenosis. After implantation, the stent was postdilated using the balloon catheter 6.5 × 20 (Figure 3). Then, the distal embolization protection device was removed, and the procedure was finished.

Immediately after this, the left femoral artery was punctured antegradely, and a 8F sheath was placed in it. The multipurpose guiding catheter was advanced in the occluded segment of the left SFA. The consequent wire recanalization using wires Progress 120, Shinobi, and Fielder was performed. The occlusion was dilated consequently using the dilatation balloons 2.0 × 20 mm and 2.75 × 28 mm (Figure 4).

In the area of residual stenosis, the self-expanding nitinol stents Eucatech AG 6 × 40 mm and two stents Eucatech AG 6 × 30 mm were delivered, positioned and implanted, respectively. The control angiography revealed the fully recovered antegrade blood flow in the left SFA, no collateral visualization was observed (Figure 5).

The total contrast media consumption for both procedures was 250 mL (Omnipaque 350); the total scopy time was 23.4 minutes; the total X-ray dose was 3.4 mSv; no clinical and laboratory evidence of acute renal failure in the postoperative period was observed.

Follow-up physical and instrumental examination has confirmed satisfactory and stable condition. There were no murmurs over the femoral and carotid arteries. The palpable pulsation over a. poplitea, a. dorsalis pedis, a. tibialis posterior was satisfactory on both sides.

US Doppler revealed hyperechoic structures of the stents in the left SFA and blood flow without local hemodynamically significant accelerations. The residual stenosis did not exceed 20–25%. The blood flow in the popliteal artery was of modified antegrade type with some expanded

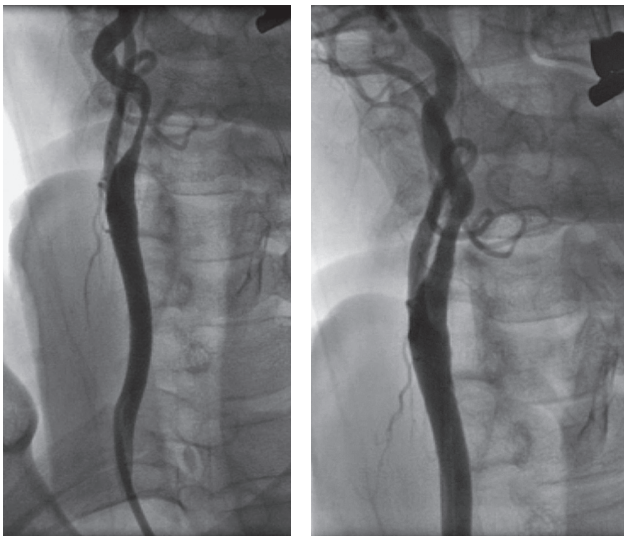

Figure 3. Angiogram of the right CCA-ICA before and after stenting in the left oblique projection with head rotated to the right (see text for description).

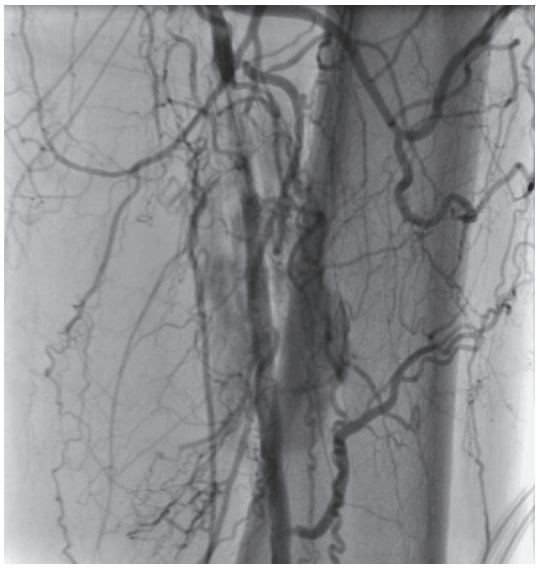

Figure 4. Angiogram after mechanical recanalization followed by the left SFA angioplasty.

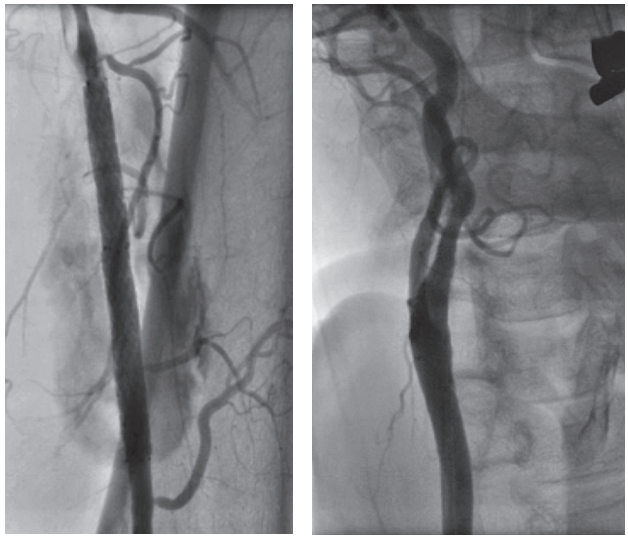

Figure 5. Angiographic results after stenting of the recanalized occlusion of the left SFA (two-level image reconstruction).

systolic component. The hyperechoic structures of the stent were visualized in the bifurcation of the right CCA and ICA. Linear blood flow velocity was up to 1.0 m/sec. The residual stenosis did not exceed 35–40%.

The result of endovascular intervention in the case of carotid and femoral angioplasty followed by stenting was found to be satisfactory, the patient was discharged home.

Thus, we would like to make several important conclusions based on this clinical case. Firstly, the potential of endovascular techniques as alternative options to surgery for critical stenosis of the internal carotid artery and prolonged occlusion of the femoral artery was demonstrated. Secondly, the feasibility of two endovascular interventions involving two different vascular territories together and simultaneously was shown. This feasibility should be recognized favorable for the patient, because it eliminates the need for two interventional procedures and reduces the time of hospital stay; moreover, it provides the economic effect due to shortened bed-days and time expenditures of medical personnel and medical equipment.

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Endovascular Embolization of the Artery Supplying Juvenile Angiofibroma with a Vascular Occluder, and its Impact on the Amount of Operative Blood Loss during Endoscopic Resection of the Tumor

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Endovascular techniques play an important role in diagnosis and treatment of patients with juvenile angiofibroma. CT and MRI/MSCT make it possible to perform non-invasive diagnosis of the tumor. However, carotid angiography is important to determine the exact tumor's localization, assess the type of its vascularization and also perform preoperative embolization of the artery supplying the tumor. Clinical case described in this article demonstrates the value of endovascular embolization in combined treatment of juvenile angiofibroma.
Key words: *angiofibroma, endovascular closure, occluder, Plug, artery.*

Introduction

In recent years, a large number of endovascular interventions performed in the Russian Federation has led to a significant increase in the number of cathlabs functioning both in federal and regional hospitals.

However, in the Russian Federation, in contrast to healthcare systems in the European countries and North America, there are no departments with narrow specialization in cardiologic, neurological and other profiles. Due to the lack of such special cathlabs, the interventionists in a multidisciplinary clinic have to deal with different cardiovascular pathology in daily practice. Thus, they should master the full range of endovascular techniques of diagnosis and treatment. Juvenile angiofibroma (JA) is one of the relatively common pathologies not related to cardiology.

Juvenile angiofibroma is a benign tumor of the nasopharynx. Its structure is characterized by a dense plexus of the connective tissue and many newly formed blood vessels. The tumor is characterized by rapid, uncontrolled growth, and shortly compresses the surrounding tissues with following functional disorders: difficulty in breathing, decreased visual acuity and hearing. JA can recidivate and requires immediate treatment. By the time of initial examination and diagnosis, about 20% of patients demonstrate clinical and morphological signs of angiofibroma invasion into the skull cavity.

In most cases, JA is diagnosed in young males aged from 9 to 19 years (in 70% of cases, age varies from 14 to 15 years.) (1). JA incidence is 50% of all benign tumors of the nasopharynx, or 0.5% of the total number of the head and neck neoplasms (2, 3).

Therefore, the issues of diagnostics, examination and treatment of patients in a multidisciplinary hospital using endovascular interventions are of immediate interest.

Histology and pathogenesis

In 1959 Schiff (4) performed histological study of removed tumors. The basis of JA structure was shown to be a massive deposition of blood vessels and fibrous substrate consisting of collagen fibers and producing fibroblasts. P. Nicolai et al. in 2008–2011 (5) proved that group growth, extended lumen and absolute lack of elastic fibers and muscles is typical for JA-forming vessels. This results in their expansion and potential danger of rupture followed by uncontrolled and life-threatening bleeding. Thus, a quick and adequate treatment is absolutely necessary.

The basis of JA pathogenesis is a massive blood vessels proliferation leading to malformation. There are several hypotheses on JA formation and its pathophysiology. One of the leading hypotheses for JA formation is the impact of male sex hormones, namely, the presence of androgen and testosterone receptors and lack of estrogen and progesterone receptors (6, 7). This is confirmed by the fact that JA is mainly detected in young men in puberty.

JA is typically located in the sphenopalatine foramen of the nasal cavity connecting with the nasal cav-

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Table 1. Juvenile angiofibroma stages (Radkowski, 1996; Fisch, Andrews, 1989)

Stage	
I	The tumor is limited to the nasal cavity, there are no signs of bone destruction
II	The signs of Stage I + the tumor has spread to one or more adjacent structures with the following areas of bone destruction: pterygopalatine fossa, sinuses, retropharyngeal space, ethmoidal or sphenoid sinuses
III	The signs of Stage II + the tumor invades in the orbital cavity or infratemporal fossa, but there is no intracranial growth
IV	The tumors are characterized by intracranial growth and intradural spread involving the pituitary gland and optic chiasm

ity and the pterygopalatine fossa. The precise tumor localization helps to determine its stage and choose the optimal treatment option.

Sings and diagnostics

Juvenile angiofibroma is characterized by rapid growth; however, it often takes 2–3 years since the first signs onset till the initial visit to a physician.

Typical clinical manifestations are:

1. Difficulty in nasal breathing
2. Frequent and recurrent epistaxis (while the tumor is growing, the bleedings become more frequent and more intense)
3. Decreased hearing, often on both ears
4. Headache
5. Decreased visual acuity, exophthalmos, diplopia
6. Deformation of the facial skeleton.

Headache and face pain develop as a result of compression of the nasal sinuses or Eustachian tubes dysfunction due to secretory otitis (8).

The tumor has several developmental stages; the commonly recognized international classification is shown in Table 1.

When the first signs occur, the patient should be examined by an ENT specialist and nasopharyngeal endoscopy should be performed. If the tumor signs are revealed, the contrast enhanced CT should be performed. The tumor will appear on CT slices as an intensive, homogeneous neoplasm of increased intensity (Figure 1).

The CT-related advantage is its superiority over MRI/MSCT for assessing involvement of the JA adjacent bones. MRI/MSCT is mainly used in case of suspected intracranial tumor spreading. The final diagnostic step is the biplane carotid angiography. Angiography helps to localize the tumor-supplying artery; this is necessary not only for its endovascular embolization, but also to guide surgeons during endoscopic excision.

Treatment

Surgical treatment for JA is the sole effective option consisting of 2 steps: endovascular embolization and endoscopic tumor excision. The next day after the embolization of the tumor-supplying artery, the tumor's size reduces by not less than 50%/ thus facilitating its resection at step 2. Moreover, according to P. Eloy (2013), blood loss during the tumor resection is reduced by 60% as a result of arterial occlusion (3, 9, 10). Thus, mean blood loss in patients during open surgery was 1.578 ml, and mean blood loss in case of JA endovascular occlusion followed by endoscopic resection did not exceed 406.7 ml ($p < 0.05$).

Arterial embolization is performed as either elective or emergency surgery. Emergency surgery is performed for uncontrolled, long-term, life-threatening bleeding. Most commonly, it relates to a major branch of the maxillary artery, more rarely – to the branches of the external carotid artery or ascending laryngeal artery. The different types of emboli or vascular occluders are used for embolization of the nourishing artery. In our clinical practice, Plug II vascular occluders (St.Jude, USA) are most commonly used (Figure 2).

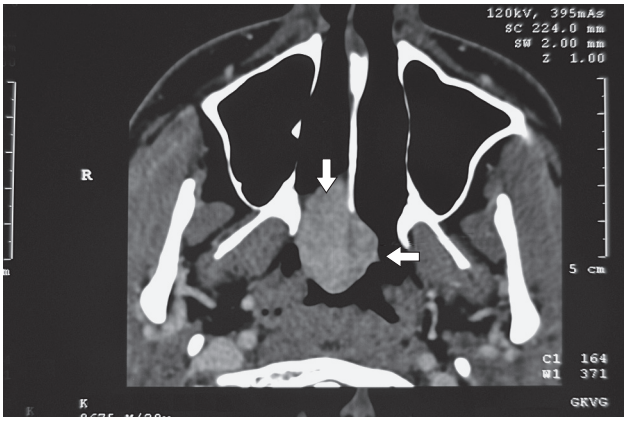

Figure 1. Angiofibroma (arrow) of the posterior regions of the right half of the nasopharynx (contrast enhanced CT).

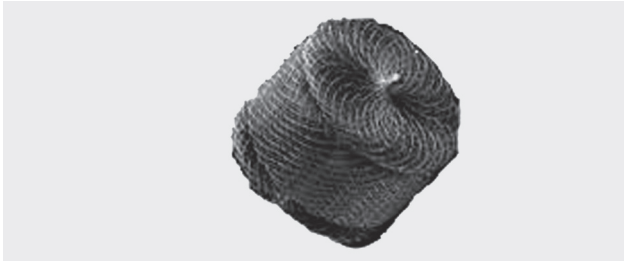

Figure 2. Plug II vascular occluder is made of nickel/titanium alloy and consists of three disks providing guaranteed embolization of the target vessel.

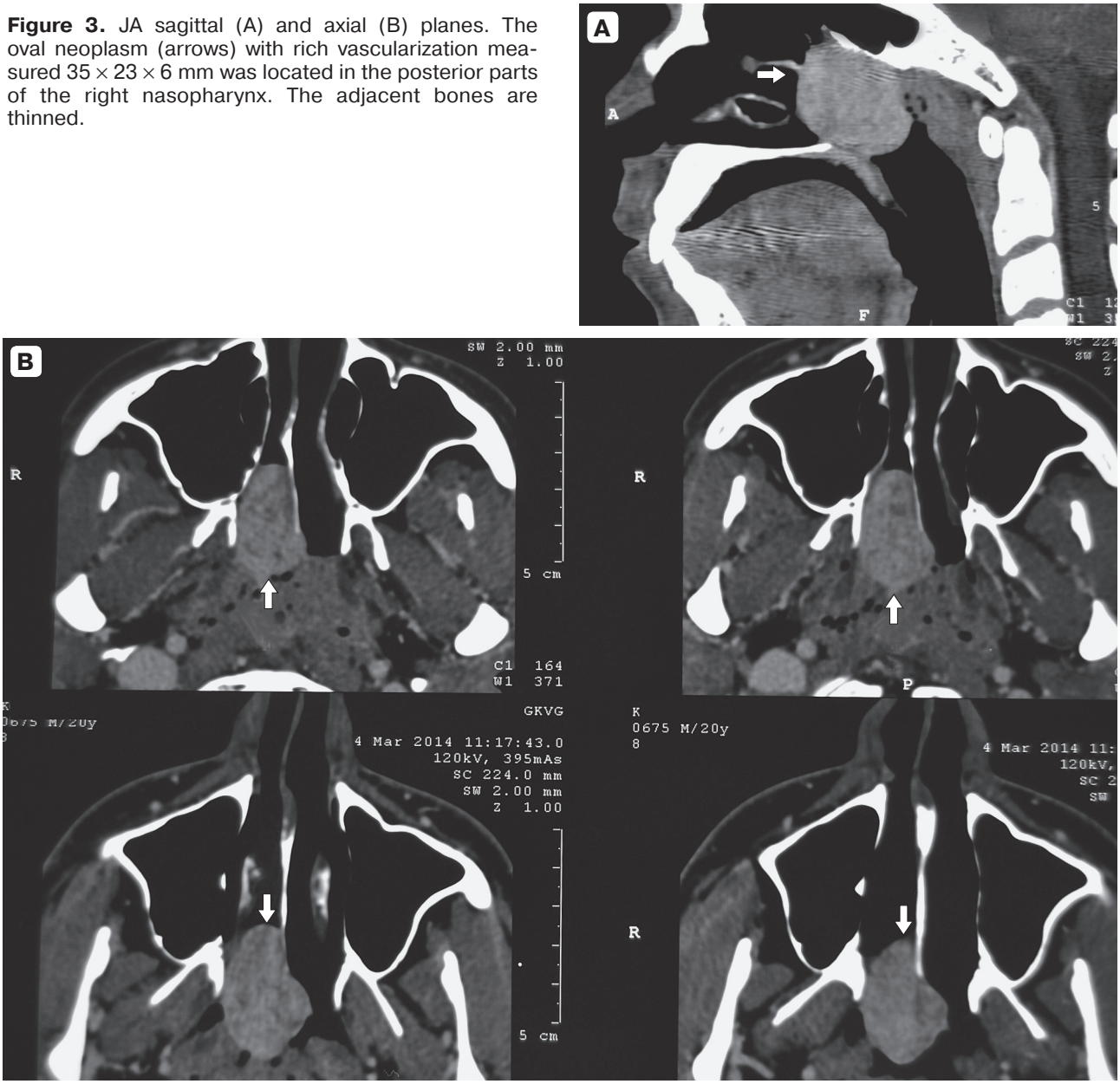

Figure 3. JA sagittal (A) and axial (B) planes. The oval neoplasm (arrows) with rich vascularization measured 35 × 23 × 6 mm was located in the posterior parts of the right nasopharynx. The adjacent bones are thinned.

In our opinion, the main advantage of the occluder is that it can be removed or reposed in case of complications during perioperative or early postoperative periods.

Potential complications related to the arterial embolization do not exceed 2% and include:

1. cerebrovascular accidents (if one of the carotid arteries is embolized)

2. complete vision loss (if the ophthalmic artery is embolized)

3. skin and soft tissue necrosis (if their supplying arteries are involved).

At the second step, in case of stage I-II JA, the tumor is resected endoscopically, and in case of stage III-IV JA an open surgical resection is the method of choice.

It is important to perform a second step within 72 hours after the first endovascular step to avoid the opening of additional anastomoses and restoration of tumor blood supply (11).

JA therapy involving other treatment options, such as hormone therapy, chemotherapy and so on, is used only as a complementary treatment or for recurrent tumor growth.

Clinical case

Patient K., 20 y.o., a military man. On admission he complained of the difficulty in nasal breathing during the previous two years accompanied by constant blood-tinged mucous nasal discharge. In the past year, the patient was diagnosed with acute rhinitis and received repeat cycles of anti-inflammatory and local treatment without any positive effect. Within the previous 2–3 months, he noted a significant deterioration of nasal breathing, frequent nasal bleedings for up to 30–40 minutes. Diagnostic nasopharyngeal endoscopy revealed a purple-pink neoplasm filling the

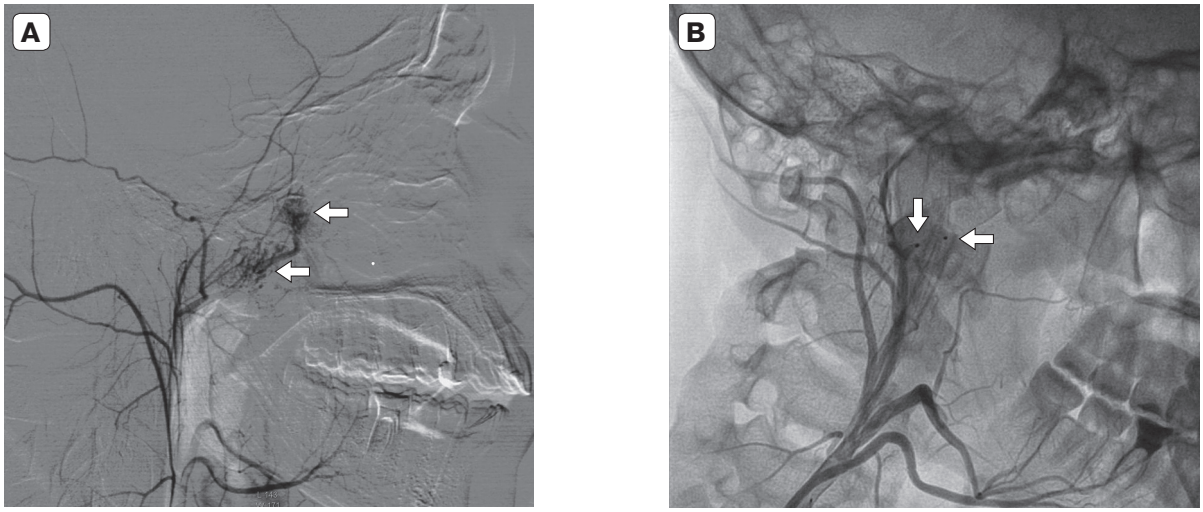

Figure 4. A – Angiographic signs of abnormal revascularization (arrows) in the distal part of the right maxillary artery. B – The vascular occluder was successfully placed with good visualization of the radiopaque markers (arrows) and complete cessation of abnormal blood flow in the JA.

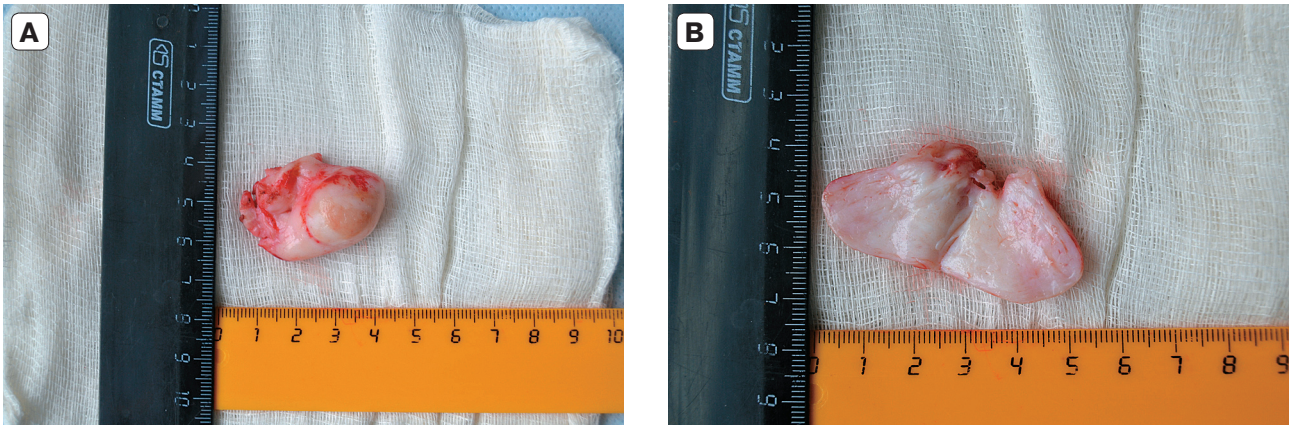

Figure 5. The endoscopically resected tumor. Whitish tissues are noted outside (A) and at cross-section (B) indicating effective embolization of the supplying artery and complete cessation of the neoplasm blood supply.

whole right nasal cavity. Contrast-enhanced CT revealed the oval neoplasm with well-defined smooth contours measuring 35 × 23 × 26 mm, and located in the posterior segments of the right nasopharynx (Figures 3A, 3B). The neoplasm is adjacent to the posteroinferior part of the ethmoid bone. The neoplasm opacified after intravenous contrast administration, the adjacent bones were thinned. Carotid angiography identified the major branch of the right maxillary artery supplying JA (Figure 4A). As there were no signs of intracranial tumor growth, the decision was made to perform arterial embolization simultaneously.

The guide catheter JR 4 6 Fr was placed at the orifice of the right external carotid artery. Then, the interventional wire 0.014" was placed in the distal part of the right maxillary artery and the guide catheter was selectively placed in the middle part of the right maxillary artery. Using the delivery system, we placed Plug II vascular occluder 3.0 × 6.0 mm into the middle part of the artery. The control angiography revealed no blood flow distal to the occluder and no JA vascularization (Figure 4B). The occluder was disconnected from the delivery system. Hemostasis was achieved using bioresorbable collagen placed into the femoral artery.

Endoscopic endonasal JA removal and resection were performed in 24 hours (Figure 5A). The total blood loss did not exceed 150 ml. Macroscopic examination of the cross-sections of the removed tumor revealed whitish tissues (Figure 5B); this indicates the effective cessation of the angiofibroma blood supply. The postoperative period was unremarkable and uncomplicated. The patient noted complete restoration of nasal breathing 5–7 days after the nasopharyngeal edema was eliminated. On Day 10, the patient was discharged from the hospital and returned to his normal life.

Conclusion

Juvenile angiofibroma is common in young males, confirmed by CT and carotid angiography typical pattern. This tumor type is characterized by aggressive and rapid growth involving the surrounding soft tissues and bones. To date, the only effective treatment option is the endovascular embolization of the tumor-

supplying artery with subsequent endoscopic resection of angiofibroma.

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Functional State of Different Types of Shunts Depending on the Revascularization Area

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The function of 649 direct mammary and 505 venous shunts from 6 months to 9.5 years after surgery (mean 60.8 ± 47.5 months) in 421 patients was investigated. The obtained results indicate that revascularization of the left ventricular anterior wall using IMA provides reliable and long-term functionality (91%) specific to this vessel. When the left ventricular anterior lateral wall arteries are revascularized there is no significant difference in functional status between IMA and GSV (78.1% and 84.6%, respectively). When RCA is bypassed, the internal mammary artery should be avoided to be used in favor of venous conduits.
Key words: *myocardial revascularization, long-term results, functional status of shunts (mammary, venous), revascularization area.*

Objective. To investigate the functional competence of different types of shunts depending on the myocardial revascularization area.

Material and methods. 421 patients underwent follow-up coronary angiography (CAG) within 6 months to 9.5 years (mean 60.8 ± 47.5 months). The function of 649 direct mammary and 505 venous shunts was assessed.

Results. The functional competence of the internal mammary artery (IMA) was 85.3%. When the left ventricular anterior wall was revascularized, the shunt patency was 91.0%; meanwhile this parameter for the lateral wall reduced to 72.7%. When the LCX branches were bypassed, normal functioning of the venous conduits was detected in 84.6% of cases. In case of RCA this was seen was 78.1%. When the posterior wall arteries were bypassed with IMA, shunt occlusion occurred in 80% of cases.

Conclusion. When the left ventricular anterior wall is revascularized, IMA provides specific to the vessel reliability and longevity both in-situ and as free flap. When the LV anterior lateral wall arteries were revascularized there was no significant difference in functional status between the IMA and GSV during follow-up ranged from 6 months to 9.5 years (mean 60.8 ± 47.5 months). Therefore, in each individual case, the choice of the graft type should be based on the patient's age, anatomy and topography of the coronary arteries and stenosis degree. RIMA should be avoided for revascularization of the distal branches of the RCA.

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List of abbreviations:

GSV – great saphenous vein
IMA – internal mammary artery
OMB – obtuse marginal branch
DB – diagonal branch of the left anterior descending artery
PDA – posterior descending branch of the right coronary artery
CHD – coronary heart disease
EC – extracorporeal circulation
CA – coronary artery
CAG – coronary angiography
CABG – coronary artery bypass grafting
LIMA – left internal mammary artery
LV – left ventricle
LCA – left coronary artery
RIMA – right internal mammary artery
LAD – left anterior descending artery
RCA – right coronary artery
SG – shuntography

The first direct myocardial revascularizations were performed using IMA implanted in the LAD (1, 25). However, over time, the technique and strategy of CABG have gradually changed based on the analysis of the obtained results (3, 4).

Left IMA use for LAD bypass has become the standard since the beginning of 1980s. Numerous data show better long-term patency of this graft compared to other shunts. Meanwhile, reduced incidence of the cardiac events, decreased need for repeated interventions, improved long-term survival are

observed compared with patients who received only venous grafts (6, 24, 23, 31–33).

Even 20 years later, IMA grafts demonstrated their resistance to atherosclerosis (8, 9, 10). The above mentioned has led surgeons to use both internal mammary arteries along with other available arterial grafts to achieve complete arterial revascularization (2, 11). According to Shah et al. (15), based on 20-year clinical and angiographic experience with two IMAs, on the average, 80 months after surgery, the competence of mammary grafts implanted to the LV anterior wall did not differ significantly from the immediate results. And the RIMA patency grafted to RCA was 79%. The study conducted by Mert et al. (19) showed that on average 5 years after surgery, the incidence of IMA occlusion grafted to RCA was 35%.

According to some authors (17, 18), the functional competence of LIMA depends on the revascularization area. So, if LAD/DB or LCX are grafted, occlusion occurs is 6.6–8.5% and 11.5% of cases, respectively. The comparative analysis of different types of grafts (GSV, IMA) showed the similar competence in all areas, except the LV anterior wall (20, 21).

Given that venous conduits are separated easier, in the vast majority of cases there is no their quantIMA tive limits and even the method of IMA "skeletization" has some contraindications, and the graft length is not always sufficient for complete revascularization, the importance of objectively valid answer regarding the conduit choice for direct revascularization of the lateral and posterior myocardium wall is evident.

There is no doubt that a further improvement of the bypass surgery results should be based on solving the tactical issues. Based on the above mentioned, our study assessing the functional competence of the most popular conduits (IMA and GSV) depending on the revascularization area has real practical significance.

Definitions

1. Satisfactory shunt function is determined as an antegrade filling of the shunt itself and coronary artery in the lack of stenosis ⩾70% in any part of the conduit;

2. Unsatisfactory conduit function:

- shunt occlusion and no antegrade blood flow,
- significant stenosis ⩾70% in any part of the shunt and/or any end of anastomosis,
- so called "String Sign" phenomenon (during selective CAG IMA is visualized throughout its length with diameter less than 1 mm).

3. The group of arteries supplying the anterior myocardium wall – LAD, DB, IA.

4. The group of arteries supplying the lateral myocardium wall – LCX and its branches.

5. The group of arteries supplying the posterior myocardium wall – RCA (PDA), in case of right-dominant coronary blood flow; and terminal branch of LCX in case of left-dominant coronary blood flow.

Materials and methods

The Department of Cardiac Surgery of the Moscow City Centre of Interventional Cardioangiology has experience of more than 1500 direct revascularization surgeries. The mortality rate was 1.4 ± 0.3%. According to the standards accepted in the Center, to further improve surgical tactics and long-term results, all patients regardless of their clinical condition were proposed the follow-up coronary angiography (CAG) 6 months after direct myocardial revascularization.

The inclusion criteria were as follows: 1. primary direct myocardial revascularization (without previous stenting); 2. myocardial revascularization surgeries as well as pre – and postoperative CAG in MCCIC; 3. mammary and venous grafts with one distal anastomosis.

In some cases, the patients' re-examination was limited with refusal from hospIMA lization due to their feeling of well-being. Moreover, nonresidents and foreign patients were rarely admitted for follow-up.

Thus, 421 patients were re-examined within the period ranging from 6 months to 9.5 years (on average, 60.8 ± 47.5 months) after surgery; totally, 649 direct mammary and 505 venous grafts were evaluated in all patients.

Selective coronary angiography and shuntography were performed in radiosurgical operating rooms equipped with angiographic devices "Multi Star" and "Axiom" (Siemens, Germany). Angiometric and morphometric parameters were calculated using the integrated software. Selective coronary angiography was performed in several standard projections for LCA and RCA. The coronary artery lesions were quantIMA tively assessed using the integrated software. The reference diameter of the affected artery and degree and extent of the lesion were calculated. Follow-up CAG and SG assessed the coronary vessels and grafts in general and the intervened segment (stenosis pattern and its degree related to the reference diameter (% and mm)).

Results

The study demonstrated that on average 63 ± 7.1 months after surgery, 85.2% and 79.4% anastomoses to IMA and GSV were patent, respectively (p = NS).

In the vast majority of cases (97%), LAD was grafted with IMA and only in 3.0% of cases LAD was bypassed with venous conduits (Table 1).

Satisfactory functioning of IMA grafted to LAD was found in 91.9% cases, which was the highest value among all graft types. When LAD was bypassed with GSV, the unsatisfactory competence was identified in 53.4% of cases that was the lowest value for this graft

Table 1. Number of anastomoses among the different types of conduits

Grafted coronary artery	Number of grafts	
	IMA	GSV
LAD	406 (62.6%)	15 (3.0%)
DB/IA	51 (7.8%)	56 (11.0%)
MA/OMB	187 (28.8%)	201 (39.8%)
RCA	5 (0.8%)	233 (46.1%)
Total	649 (100%)	505 (100%)

type. The analysis of the results showed that in 4 (0.8%) cases LAD was bypassed for CA stenosis ⩽60%, 6 patients (1.2%) were operated on emergency basis and in 5 (1.0%) cases LAD had severe atherosclerotic lesions and its diameter was less than 1.5 mm, and therefore IMA was used to bypass other LV arteries. When DB/IA were bypassed, the competence of 84.3% and 75.0% mammary and venous grafts was observed, respectively. The normal functioning of the venous grafts bypassed to LCX (MA/OMB) was observed in 84.6% cases. In turn, the value for IMA was only 72.7% (Table 2).

Despite the small number of grafts from RIMA to RCA or its branches (5 cases), our results showed that this strategy is unfavorable. Graft patency was observed only in 1 case (20%), while 4 remaining grafts were occluded (80%). At the same time, satisfactory functioning of the venous graft to the RCA territory was observed in 78.1% of cases.

The following results were obtained when the mammary grafts were assessed depending on revascularization of the different myocardium walls: anterior wall – the highest patency (91.1%), lateral wall – 72.7%.

When the results for venous grafts to different areas of the left ventricle were analyzed, the worst patency (69.1%) was observed for anterior wall revascularization. At the same time, the patency for lateral and posterior walls was 84.6% and 78.1%, respectively (Table 3). Thus, according to the obtained results, significant advantage of the mammary grafts over venous shunts for the LV anterior wall revascularization completely disappears if the vessels of lateral myocardium wall are bypassed.

Due to the huge number of conflicting opinions on RIMA and its patency when it is used in different coronary territories, 39 direct RIMA grafts in situ were separately analyzed (Table 4).

The total number of patent grafts was 27 (69.3%). The analysis of the functional status of these grafts depending on the topography of bypassed CA (Table 3) showed that RIMA was used for revascularization of the lateral and posterior walls in 87.1% (34 grafts) and 12.9% (5 grafts) of cases, respectively. According to CAG and SG, the satisfactory function of the arterial conduits was observed in 76.5% and 20% of cases, respectively. When the relatively adjacent vessels were bypassed (OMB or 1st MA), the functional competence amounted to 84.6% (22/26 grafts), while this value for the 2nd MA was 50% (4/8 grafts). However, it is obvious that a satisfactory functioning of the graft bypassed to PDA is more likely incidental than evident (20% vs 80%).

Discussion

More than one million direct myocardial revascularizations are annually performed worldwide. The further improvement of the surgery results and efficacy depends mainly on correct surgical strategy, which has not been definitively determined.

The standard for the left IMA to be used for LCA grafting based on the numerous data on the long-term competence of this transplant type (3, 24, 23) and its resistance to atherosclerosis (9, 10) was developed in the 1980's. Our results are fully consistent with these data. LIMA was bypassed to LAD in 96.4% of cases.

Table 2. Functioning of conduits to different coronary arteries

Conduit	Satisfactory results		Unsatisfactory results	
	IMA	GSV	IMA	GSV
LAD	373 (91.9%)	7 (46.6%)	33 (8.1%)	8 (53.4%)
DB/IA	43 (84.3%)	42 (75.0%)	8 (15.7%)	14 (25.0%)
LCX/OMB	136 (72.7%)	170 (84.6%)	51 (27.3%)	31 (15.4%)
RCA/PDA	1 (20%)	182 (78.1%)	4 (80%)	51 (21.2%)
Total	553 (85.2%)	401 (79.4%)	96 (14.8%)	104 (20.6%)

Table 3. Comparative functioning of different grafts depending on the revascularization area

Area	Shunt	Number	Satisfactory results	Unsatisfactory results
Anterior wall	IMA	457	416 (91.1%)	41 (8.9%)
	GSV	71	49 (69.1%)	22 (30.9%)
Lateral wall	IMA	187	136 (72.7%)	51 (27.3%)
	GSV	201	170 (84.6%)	31 (15.4%)
Posterior wall	IMA	5	1 (20.0%)	4 (80.0%)
	GSV	233	182(78.1%)	51 (21.9%)
Total	IMA	649	553 (85.2%)	96 (14.8%)
	GSV	505	401 (79.4%)	104 (20.6%)

Table 4. Comparative analysis of the RIMA function depending on the LV revascularization area

RIMA in situ 39		Lateral wall 34 (87.1%)		Posterior wall 5 (12.9%)	
Satisfactory function	Unsatisfactory function	Satisfactory function	Unsatisfactory function	Satisfactory function	Unsatisfactory function
27 (69.3%)	12 (30.7%)	26 (76.5%)	8 (23.5%)	1 (20%)	4 (80%)

The satisfactory functioning within the period from 6 months to 9.5 years (on average, 60.8 ± 47.5 months) was observed in 91.9% of cases. Similar results (satisfactory function in 91.0% of cases) were obtained when LV anterior wall arteries (DB, IA) were grafted. This is explained by the convenient location of these vessels for a surgeon during the distal anastomosis formation; in the vast majority of cases, the middle third of IMA is used, which is an elastic artery, and its usual diameter in this part is 2.0 mm or more that is optimal for long-term graft patency (22). Therefore, risks of technical errors (iatrogenic stenosis and occlusion) are minimized. Vessel topography is more physiological if diameters and histological structure of the graft and native artery are similar.

Despite commonly recognized standards, according to which LAD should be bypassed with IMA , we bypassed LAD with venous grafts in 15 cases (3.0%). This strategy was caused by emergency situation (6 cases (1.2%)), LAD stenosis ⩽60% (4 cases (0.8%)) and small diameter LAD with diffuse atherosclerotic lesions (5 cases (1.0%)). In the latter case, IMA was used to bypass other CAs.

Satisfactory functioning of GSV bypassed to LAD in these cases was achieved only in 46.6% of cases. Obviously, in this situation, this type of graft is a "hostage" of circumstances where surgeons were not eager to perform mammary anastomosis that will likely become a failure. Although, Mert M. et al. (34) argue that IMA for non-critical stenoses (<50%) does not affect the long-term patency of the mammary graft; the small number of his cases (3 patients), as well as the data obtained by other authors, including own results, justify our opposite opinion (5). Based on these data, it can be confidently assumed that the mammary grafts in such cases would not result in a significant increase in the competence rate compared to GSV.

Furthermore, influence of CA lesion degree cannot be excluded. Many investigators have shown that in case of diffusely affected native coronary arteries (including chronic occlusion, distal lesion) (7) grafts of any type become incompetent more frequently (26–28).

Obviously, the desire to use both mammary arteries requires research of functioning of IMA s bypassed to coronary arteries supplying different myocardial areas.

Functioning of grafts bypassed to the LV lateral and posterior wall arteries is of the greatest interest.

Some articles demonstrate satisfactory function of the IMA bypassed to the LV posterior lateral areas (16, 17). Tatoulis et al. (2011) showed that IMA results are always better compared with GSV and RA in the identical coronary areas. 10-year mammary graft patency was 91%, 84%, and 86% in LCX, RA, and PDA, respectively. However, the authors do not describe actual topography of these vessels, which suggests that these CAs were located on the lateral but not on the posterior lateral wall of the left ventricle. Most investigators consider that IMA grafts bypassed to LCX and RCA are characterized with high incompetence rate (18). The main reasons for this is that the distal mammary graft, rather muscular than elastic, is used. As a result, graft spasm and occlusion are more likely (18, 29). It cannot be excluded that a high incompetence rate is caused by technical issues during anastomosis formation due to small diameter of the distal IMA (usually it is <1.5 mm) (30).

Our results on LV lateral wall revascularization suggest the mammary grafts used on the posterior lateral myocardium wall actually have lower patency for this graft type. When this LV area is bypassed, the total competence associated with mammary grafts was only 72.7%. In contrast, satisfactory function of venous grafts to LCX was observed in 84.6% of cases, i.e. was the highest for venous grafts bypassed to any coronary artery.

When mammary graft in situ is bypassed to the LV posterior wall, its unsatisfactory functioning is observed. According to Pallav J. Shah et al. (15), IMA as a free flap is better in these cases. Our results are supported by those investigators who consider that GSV is better for RCA grafting. Similar functioning of GSV and IMA bypassed to LCX and RCA is most likely due to the fact that surgeons are not limited by venous graft length and coronary artery remoteness on the LV lateral wall.

Therefore, the obtained data indicate that if so-called remote myocardial arteries (RCA branches, 2nd MA) are bypassed with GSV, the results would be better than in case of arterial grafts.

Conclusion

Revascularization of the left ventricle anterior wall arteries with IMA provides reliability and longevity specific to this vessel. Venous conduits perform similarly to IMA when the left ventricle anterior lateral wall arteries are bypassed and better when the posterior lateral arteries are grafted. Therefore, the choice of the graft type should be based on the

coronary topography, patient's age, urgency, comorbidities, and so on. When the RCA territory is bypassed, internal thoracic artery should be avoided in favor of venous conduits.

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Current Trends of Reperfusion Therapy in Patients with Acute Coronary Syndrome with *ST*-elevation

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Based on the myocardial infarction national registry data over the period 2010–2012, the volume and structure of emergency medical care provided to the patients with ST-elevation acute coronary syndrome were analyzed. Proportions of emergency endovascular interventions out of the total number of ACS patients with ST-elevation were 22.3%, 22.1%, and 28.5% in 2010, 2011, and 2012, respectively. Thrombolytic therapy was performed in 27.6%, 30.2%, and 30.3% of cases in 2010, 2011, and 2012, respectively. Proportions of patients without any reperfusion were 50%, 46%, and 42% in 2010, 2011, and 2012, respectively. Meanwhile, percentage of patients admitted to the hospital within 12 hours after the pain onset but received no revascularization was 25.7%, 19.3%, and 16.9% in 2010, 2011, and 2012, respectively. In-hospital mortality rates related to ACS with ST-elevation were 7.7%, 7.0%, and 6.8% in 2010, 2011, and 2012, respectively.
Reduction in the in-hospital mortality rate related to myocardial infarction is caused by both the widespread introduction of high-technology medical care and increasing use of the most accessible reperfusion method (thrombolytic therapy) within the "therapeutic window".
Key words: *myocardial infarction, acute coronary syndrome with ST-elevation, endovascular intervention, thrombolytic therapy.*

Acute coronary syndrome with *ST*-elevation is an unfavorable complication of coronary heart disease associated with high mortality rate in both out-hospital and in-hospital settings, even if medical care is timely provided. Reduction of mortality related to this pathology has long been a top-priority social economic issue in many countries including the Russian Federation.

Blood flow restoration in the infarct-related artery as soon as possible after the disease onset (most preferably within the first 6 hours) significantly improves the immediate and long-term outcomes in patients with acute coronary syndrome and reduces life-threatening complications (1, 2, 3, 4).

Introduction of the thrombolytic therapy into clinical practice in the middle of the last century is a significant breakthrough in the treatment of acute coronary syndrome with *ST*-elevation. Over a half-century of thrombolytic therapy history, the mortality related to myocardial infarction has decreased considerably due to the wide clinical use of this treatment option (5, 6, 7).

Nevertheless, to date, its limitations are well known – successful reperfusion is achieved in 70–80% of cases only, hemorrhagic stroke incidence is high, making thrombolytics clinically dangerous in patients at high risk of hemorrhagic complications (especially in elderly patients) (8, 9).

Mechanical recanalization of the infarct-related coronary artery (IRA) using endovascular technologies was limited for a long time. The wide availability of the method was hampered by its high cost, the need for highly skilled surgical team and fine-tuned interaction of various services for rapid patient transportation. In addition, balloon angioplasty was accompanied by high incidence of re-occlusion and relapses of acute myocardial infarction (10, 11). The situation changed when coronary stents were developed; this technology increased the primary success of the antegrade blood flow restoration in IRA up to 96–98% with the minimal risk of hemorrhagic complications (12, 13, 14).

High clinical efficacy of this option promoted its rapid development as a priority treatment for acute coronary syndrome with *ST*-elevation. An additional advantage of this method is elimination of morphological substrate of coronary heart disease – atherosclerotic plaque; hence, re-infarction and angina recurrence are reduced compared to thrombolytic therapy (15, 16).

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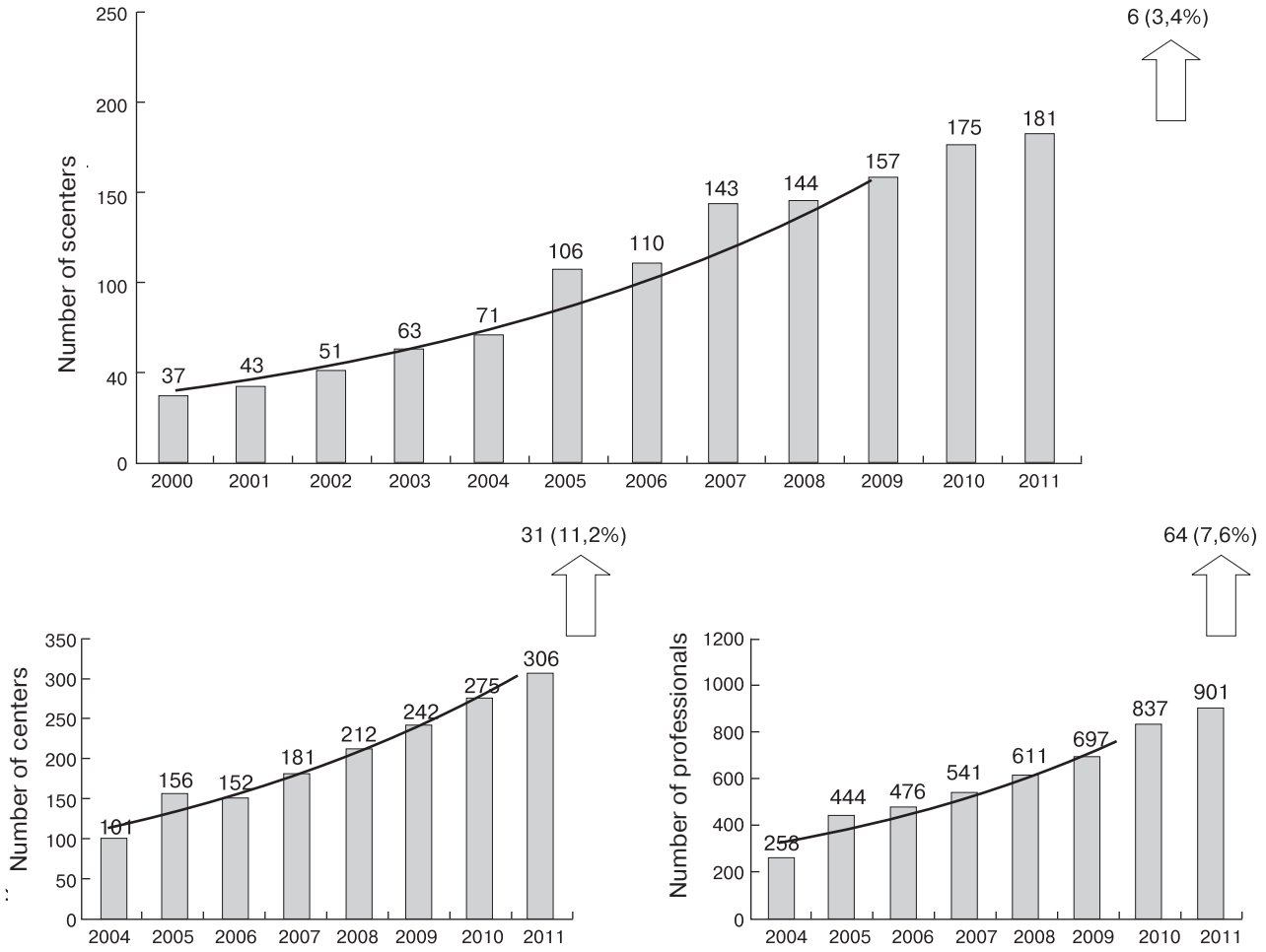

Figure 1. High-technology endovascular medical care in the Russian Federation (L.A. Bokeria, B.G. Alekyan, 2012).

Introduction of endovascular method in daily clinical practice was associated with a further improvement of treatment results in ACS with ST-elevation, decreased in-hospital and long-term mortality in this disease compared to thrombolytic therapy. ACCF/AHA recommendations of 2013 on treatment of acute coronary syndrome with ST-elevation indicate that endovascular techniques should be preferred in case of timely hospitalization of patients for reperfusion within the "therapeutic window" (17).

As already noted, disadvantages of endovascular method can include its high cost, need for well-developed infrastructure for rapid patient transportation and 24-hour cathlab. To perform safe and effective endovascular interventions, a highly qualified operating team is required, which is also indicated in the available recommendations (17). Hence, availability of high-tech medical care is significantly inferior to less effective but simpler and cheaper method – thrombolytic therapy.

Over the last ten years, a broad program of high-tech medical care has been developed in our country with aim to reduce myocardial infarction mortality. In our country, mortality rate related to acute coronary syndrome with *ST*-elevation in hospitals without cathlabs averages 15% (18). At the same time, in developed European countries with a wide network of centers providing emergency endovascular treatment in 90–95% cases of acute myocardial infarction, the in-hospital mortality rate ranges from 4 to 7% (19).

In the Russian Federation, the number of centers providing high-technology endovascular care has grown rapidly over the last decade. For example, in 2000 there were 37 endovascular centers performing emergency interventions across the country, but by 2011 their amount reached 181 (B.G. Alekyan, L.A. Bokeria, 2012) (20). The number of specialists who perform such interventions increased from 250 in 2000 up to 900 in 2011 (20) (Figure 1). However, despite an impressive growth, endovascular treatment options in ST-elevation ACS in our country over the past decade were used in only 8.8% of hospitalized patients with this

diagnosis; it is obviously inferior to this parameter in developed European countries (from 60% to 95%) (20).

It should be noted that in different countries demographic and geographic factors play an important role in emergency care provision. Apparently, availability of high-technology medical care and efficacy of high-technology center network largely depend on population compactness. In most European countries, the population density per area unit is quite high; this facilitates timely high-tech medical care. In Russia, there are many territories with low population density and areas difficult to access; this impedes emergency endovascular interventions in many non-European regions of the country. A similar situation is in the North America, despite a developed economy, the percentage of primary endovascular interventions (on average 48%) is lesser than in developed European countries, which may also be caused by the geographical and demographic characteristics [20].

An evaluation of emergency endovascular care in our country will help to answer the main question – how positive growth dynamics of the high-technology medical centers affects in-hospital mortality rate related to myocardial infarction. In order to objectively assess this parameter in Russia, acute myocardial infarction registry was initiated in 2008 involving medical institutions engaged in endovascular interventions. Over the period from 2010 to 2012, the registry included 48 vascular centers from different Russian regions, where amounts of high-technology medical care were comparable with developed European countries.

According to the registry data, percentage of emergency endovascular interventions out of the total number of acute coronary syndrome patients with *ST*-elevation in registry member centers was 22.3%, 22.1%, and 28.5% in 2010, 2011, and 2012, respectively. In-hospital mortality rates related to ACS with ST-elevation were 7.7%, 7.0%, and 6.8% in 2010, 2011, and 2012, respectively. Thus, a trend to reduced in-hospital mortality was observed within 3 years. Meanwhile, parameters of timeliness of pre-hospital medical care provision and patient admission to the hospital remained almost unchanged during the specified follow-up period. Thus, “pain-to-thrombolytic”, “pain-to-balloon” time intervals averaged 180 min and 300 min, respectively, and did not significantly change during the 3-year period.

Did the extent and structure of medical care for myocardial revascularization have a significant impact on the reduction of in-hospital mortality? Based on the dynamics of different revascularization types during the follow-up period, we clearly observe an increase in both endovascular interventions and thrombolyses within 3 years. Over 2010–2011, primary endovascular interventions did not change significantly (approximately 22%). The amount of thrombolytic therapy increased from 27.6% in 2010 up to 30.2% in 2011. During this period we observe a clear reduction in the in-hospital mortality rate from 7.7% up to 7%.

If one looks at the reperfusion therapy structure over 2011–2012, a distinct increase in revascularization frequency is observed for endovascular interventions (from 22.1% up to 28.5%), while the use of thrombolytics remained approximately the same (30.2% and 30.3%). A slight decrease in the in-hospital mortality rate (from 7% to 6.8%) was observed during this period, despite a significant increase in the extent of endovascular care for acute myocardial infarction. Thus, a significant increase in emergency endovascular interventions was not properly reflected in reduction of the in-hospital mortality rate, despite seemingly undeniable advantages of endovascular compared to thrombolytic therapy.

Apparently, to reduce AMI-related mortality, a total number of completed reperfusions matters and not the ratio of its different types. According to the registry, percentages of patients without any reperfusion were 50%, 46%, and 42% in 2010, 2011, and 2012, respectively. Meanwhile, proportions of patients admitted to the hospital within 12 hours of the pain onset, but who did not receive any revascularization were 25.7%, 19.3%, and 16.9% in 2010, 2011, and 2012, respectively. As noted above, the time of revascularization is the main predictor of both immediate and long-term AMI outcomes. Current advantages in the AMI treatment explicitly contrast with a fairly high percentage of patients who were timely hospitalized but receive no reperfusion in timely manner. This trend may be caused by several factors.

High efficacy of emergency endovascular interventions for acute myocardial infarction formed an approach of predominant hospitalization of patients to hospitals with cathlabs for such procedures. However, despite rapid development of industry and expansion of the network of endovascular centers, it's not always possible to carry ACS patients and perform interventions within reasonable timeframes. Multidisciplinary centers with many elective

endovascular interventions sometimes are not able to promptly provide X-ray operating room for emergency endovascular treatment. In such circumstances, priority performance of endovascular intervention is not always justified and leads to loss of precious time which significantly reduces patient's chances for a favorable outcome.

Moreover, in practice, a negative attitude has formed in recent years to endovascular intervention after thrombolytic therapy. This is due to study data on increased bleeding risk and unsatisfactory endovascular intervention outcomes. In clinical practice, endovascular treatment after thrombolysis was named a pharmacoinvasive approach. This approach was proposed to improve outcomes in ACS patients, achieve guaranteed reperfusion and reduce in-hospital mortality. However, greater efficiency of this approach was not confirmed in several randomized studies. For example, PRAGUE-1, ASSENT-4 trials (21, 22) demonstrated increased in-hospital mortality, re-occlusion of the infarct-related vessel rate, and reduced rate of successful recanalization.

Therefore, priority with respect to mechanical recanalization can play a negative role when emergency intervention is impossible, thus leading to unnecessary delay in any reperfusion. Negative attitude of medical practitioners to pharmacoinvasive approach also leads to the fact that during transportation of patients to the cathlab most professionals prefer not to use thrombolytics, even when there is a risk of missing a favorable "therapeutic window" for reperfusion.

This strategy, in our opinion, is not justified, because the time is the main predictor of survival after myocardial infarction. For example, according to PAMI, PRAGUE-2 trials, the long-term survival after myocardial infarction is inversely proportional to the time interval "pain-to-infarct-related vessel recanalization" (23, 24). It is logical and reasonable to use a reperfusion option which is currently available and in most cases, a thrombolytic therapy is still important. In recent years, an attitude to endovascular intervention after thrombolytics has changed. American and European Societies of Cardiologists recommend so-called "rescue" angioplasty after unsuccessful and so-called facilitated angioplasty after successful thrombolysis within 3 to 24 hours after thrombolytic administration. Another important factor is wide introduction of radial access into clinical practice, especially in patients with acute coronary syndrome. Endovascular interventions via the radial artery minimize risks for bleeding from the puncture site.

Therefore, in our opinion, a choice of reperfusion method in patients with *ST*-elevation ACS should be balanced and focused on as early reperfusion as possible. Endovascular interventions are highly effective and reliable for reperfusion and should be preferred if there are technical conditions. Nevertheless, it is advisable to resort to available reperfusion method (currently it is still a thrombolytic therapy) if the "therapeutic window" is likely to be missed and a patient cannot be quickly carried to the X-ray operation room.

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Our First Experience with Specialized Medical Care for Acute Coronary Disease in Chelyabinsk

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In recent years, the number of percutaneous coronary interventions including those performed for acute coronary syndrome has increased in our country. In each region, the emergency endovascular coronary interventions are introduced on individual basis at different times given financial provision and opportunities of cardiological and endovascular services, as well as emergency medical care. This article presents the first results from one of the Chelyabinsk regional vascular centers, which was the first in the region to start working in this direction.

Key words: *percutaneous coronary intervention, acute coronary syndrome, acute myocardial infarction, regional vascular center.*

Objective. To improve the treatment results in patients with acute coronary disease.

Material and methods. The study was conducted in the regional vascular center "Railway Clinical Hospital at Chelyabinsk station, JSC Russian Railways", providing specialized cardiological and endovascular medical care for patients with acute coronary disease who are residents of Chelyabinsk and surrounding municipalities. The article presents retrospective analysis of case histories of patients admitted with a diagnosis "Acute coronary syndrome" in 2012 and 2013 (416 and 506 patients, respectively). The mortality was assessed depending on the reperfusion therapy.

Results. The proportions of patients with the final diagnosis "Acute myocardial infarction" in 2012 and 2013 were similar (59.6% and 59.3%, respectively). The emergency coronary angiographies were performed: in 79.8% and 77% of cases in 2012 and 2013, respectively; the emergency coronary stenting was performed in 67.7% and 64% of cases in 2012 and 2013, respectively. After endovascular techniques were introduced for the patients with acute coronary patology, the mortality rate was decreased from 16% in 2007–2011 to 12% in 2012–2013. The lowest mortality rate was observed in patients who underwent primary emergency coronary stenting with/without thrombolytic therapy. The highest mortality rate was observed in patients who did not receive any reperfusion treatment (19.6% and 21.6% in 2012 and 2013, respectively).

Conclusion. The first experience of the Railway Clinical Hospital at Chelyabinsk station, JSC Russian Railways, Chelyabinsk, in provision of specialized medical care for patients with acute coronary disease can be considered as positive. Further improvement in results is related to a reduction of the time interval "door-to-balloon", strict adherence to clinical guidelines, accumulation of experience and its critical analysis.

Introduction

The cardiovascular diseases (CVD) are one of the priority problems of the Russian healthcare (3). The proportion of cardiovascular diseases in the structure of overall population mortality is consistently above 50% (6). Annually, approximately 180,000 patients with newly diagnosed acute myocardial infarction (AMI) are registered in our country (1).

According to ChelyabinskStat data, CVD mortality and all-cause mortality rates in 2008 were 828.5 and 1509.2 per 100,000 population, respectively. Despite the positive trend over the last 6 years (CVD mortality and all-cause mortality rates in 2013 were 726.3 and 1387.5 per 100,000 population, respectively), this value remains high (5).

The Decree No 598 "On Improvement of the State Policy in Healthcare" issued by the President of the Russian Federation on May 7,

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2012, has identified the reduction of CVD mortality to 649.4 per 100,000 population as one of the main goals of the Government of the Russian Federation until 2018. The achievement of this goal as well as further reduction of the given index is connected with the improvement of medical care for patients with acute myocardial infarction (AMI), which has a serious impact on cardiovascular mortality. The AMI consequences, in addition to reduction of patient's working capacity and quality of life, are eventual prerequisites for the development of other forms of coronary heart disease, which can lead to death.

Material and methods

Till 2011, only conservative therapy for acute coronary disease was used in Chelyabinsk, according to which, patients were routinely administered thrombolytic therapy (TLT), if there were no contraindications. At the same time in Russia, there was a steady increase in the number of coronary angiography and percutaneous coronary interventions including those in the settings of acute coronary syndrome (2). Therefore, according to the Healthcare Modernization Program, since September 2011, an invasive method of coronary blood flow restoration – emergency coronary stenting – has been introduced. The medical institutions providing emergency interventional medical care to the Chelyabinsk residents were determined: Railway Clinical Hospital at Chelyabinsk station, JSC Russian Railways (RCH), Regional Clinical Hospital No3 and since the beginning of 2012 – Chelyabinsk Regional Clinical Hospital. Since 2013, these institutions have become regional vascular centres.

Medical institutions providing specialized medical care to patients with acute coronary disease perform in similar conditions; therefore, the immediate results can be assessed using the example of one specific healthcare institution – namely, the Railway Clinical Hospital (RCH).

In 2012, 416 patients diagnosed with acute coronary syndrome were hospitalized in RCH. As a result of the diagnostic and treatment interventions the following clinical diagnoses were established: AMI – 248 (59.6%), unstable angina – 140 (33.7%), unconfirmed acute coronary disease – 28 (6.7%). In 2013, the number of admitted patients with diagnosis of acute coronary disease was increased – 506 subjects, including AMI – 300 (59.3%), unstable angina – 192 (37.9%), unconfirmed acute coronary disease – 14 (2.8%). In the first half of 2014, a significant increase in the number of patients with acute coronary disease was observed. Within these 6 months, the number of admitted patients already exceeded the similar value for the whole 2013. 628 patients with acute coronary disease were hospitalized in RCH, including: AMI – 314 (50%), unstable angina – 296 (47.1%), unconfirmed acute coronary disease – 18 (2.9%).

168 and 208 emergency coronary stentings were performed in RCH in 2012 and 2013, respectively. The endovascular activity increased in 2013 due to increased flow of regional patients. In 2012 and 2013, the proportions of urban and regional patients were 147 (87.5%) vs 18 (10.7%) and 130 (62.5%) vs 72 (34.6%) patients, respectively. At the end of 2013, the Ministry of Healthcare of Chelyabinsk region expanded RCH service area in duty days (Wednesday-Saturday) up to 4 districts of Chelyabinsk municipality and 7 adjacent municipalities. Hence, in the first half of 2014, the number of emergency coronary stentings increased – 201 interventions (the 1st half of 2013 – 122 interventions), the urban/regional patients ratio was similar to 2013 – 120 (59.7%) and 81 (40.3%) patients, respectively.

Since RCH starting (2011), all patients admitted with acute coronary disease have undergone coronary angiography. If there are indications, the coronary arteries are examined on emergency/urgency basis or at discharge. In 2012, 239 (61.6%) emergency coronary angiographies were performed, in 2013 – 321 (65.2%), and in the 1st half of 2014 – 386 (63.3%). The coronary angiographies were performed in AMI patients: 2012 – 198 cases (79.8%), 2013 – 231 cases (77%), and the 1st half of 2014 – 298 cases (94.9%).

The portions of emergency coronary stentings in patients admitted with acute coronary disease are similar – 168 (43.3%) in 2012, 208 (42.3%) in 2013, and 213 (34.9%) in the 1st half of 2014. The proportions of AMI patients who underwent emergency coronary artery stenting out of the total number of AMI patients during the study period are without significant fluctuations: 2012 – 67.7% (168 interventions in 248 patients), 2013 – 64% (192 revascularizations in 300 patients), 1st half of 2014 – 64% (201 interventions in 314 patients).

Results

The mean time interval "sign-to-balloon" is more than 3 hours (see Table 1), suggesting

Table 1. Time intervals depending on the type of acute coronary disease, mean ± error of mean

ACS type	Time intervals			
	"sign-to-balloon", hr		"door-to-balloon", hr	
	2012	2013	2012	2013
Overall ACS	4.5 ± 0.27	7.38 ± 0.56	75 ± 4.5	144 ± 14
ST-elevation ACS	4.4 ± 0.22	9.97 ± 2.6	71 ± 4.1	123.1 ± 10
Non-*ST*-elevation ACS	5.4 ± 0.35	9.3 ± 2.0	86 ± 6.2	157 ± 35

that invasive interventions are performed for at least subendocardial AMI. Thus, it was not a prevention, but limitation of AMI only.

The reason for "sign-to-balloon" interval lengthening in 2013 was likely an increased flow of regional patients. In 2012 the portion of regional patients amounted to 10.7% and in 2013 it increased up to 34.6%. Thus, in 2012, specialized medical care for acute coronary disease was provided only in Chelyabinsk municipality. All urgent patients with regional registration, who were hospitalized in duty medical institutions, were delivered exclusively from the urban locations. From May 2013, the RCH service area was added with 4 municipal areas located at a distance of 50–70 km from the city. When the diagnosis of acute coronary syndrome with/without *ST*-elevation was established by ambulance team, most of these patients were sent to local district hospitals, and then to the regional vascular centre RCH. In these cases, strategically important time was seriously lost. Since the end of 2013, after the situation was analyzed, the intermediate part of routing represented by central district hospitals was maximally abolished and the patients were directly sent to RCH.

The time interval "door-to-balloon" in RCH in 2012 was consistent with the recommended standards (60–90 minutes), while in the 2013 this value was increased more than 1.5-fold (123 min on average). There are several reasons for the delay of invasive intervention.

Simultaneous hospitalization of several patients with acute coronary disease leads to a "queue" in the cathlab and, for some patients, increased time from hospitalization till percutaneous coronary intervention. The second reason for the delay is referring regional patients with acute coronary disease in accordance with the routing of the Ministry of Healthcare of Chelyabinsk region in the 7/24 regimen, while RCH staff provided 24-hour endovascular medical service only on duty days in Chelyabinsk – "Wednesday–Saturday". If percutaneous coronary interventions were not performed, patients underwent TLT and/or X-ray surgical team was called from the house, which also extended "door-to-balloon" time interval. Due to active applications to the Ministry of Healthcare of Chelyabinsk region, since the end of 2013 the regional patients have been hospitalized in RCH only on duty days.

Mean interval "AMI onset-to-TLT" in 2012 was 2.4 ± 0.36 hours. In 2013 it increased up to 3.45 ± 0.8 hours, most likely due to the late appealability of the regional patients. In 2013, almost all patients after TLT underwent coronary angiography – 65 patients (91.5%), and 51 (71.8%) patients underwent coronary stenting. In 2012, these values were slightly below – 80% and 63.8%, respectively.

The time interval "TLT-to-CAG" was increased from 98 ± 13 min in 2012 up to 183 ± 37 min in 2013. Increasing this interval should be considered positive due to mitigation of risk for hemorrhagic complications related to invasive reperfusion therapy with previous TLT, which is the highest in the first 180 minutes.

While the endovascular techniques were introduced for patients with acute coronary disease, systemic thrombolytic therapy (sTLT) started to be less frequently performed by both the ambulance and in hospital. AMI patients admitted to RCH in 2012 underwent 80 (32.3%) sTLTs, 58 (23.4%) and 22 (8.9%) out of them were performed in the pre-hospital and in-hospital settings, respectively. In 2013, sTLTs were performed in 71 (23.7%) patients; 59 (19.7%) and 12 (4%) out of them were performed in the pre-hospital and in-hospital settings, respectively. In the 1st half of 2014, sTLTs were performed in 37 (11.8%) AMI patients; 32 (10.2%) and 5 (1.6%) of which were performed by ambulance staff and duty cardiologists, respectively.

Mortality in AMI patients in RCH over the period from 2007 to 2011 was similar (15–16%). Once this value was increased (in 2010 up to 20.37%), which can be explained by a small number of patients (about 100 per year). Mean 5-year mortality rate corresponds to the average mortality rate in Russian (16%). Significant reduction in mortality rate in AMI patients (to 12%) was achieved when emergency endovascular coronary interventions were intro-

Table 2. The mortality rates in AMI patients by reperfusion type

Type of reperfusion	2012		2013	
	abs.	%	abs.	%
All reperfusions	20/197	10.2	18/212	8.5
Any stenting	17/168	10.1	14/192	7.3
– stenting w/o TLT	10/117	8.5	11/141	7.8
– TLT with stenting	7/51	13.7	3/51	5.9
TLT w/o stenting	3/29	10.3	4/20	20.0
Neither TLT no stenting	10/51	19.6	19/88	21.6

duced. Mortality rates in AMI patients in 2012 and 2013 were 12.1% (30 cases) and 12.3% (37 cases), respectively.

The mortality rates in AMI patients by reperfusion type are presented in Table 2.

In 2012, the mortality in AMI patients who underwent reperfusion was 2 times lower compared to non-TLT-and-non-stenting arm – 10.2% and 19.6%, respectively. In 2013, this difference even more increased: 8.5% versus 21.6%. Although time intervals "sign-to-balloon" and "door-to-balloon" were prolonged in 2013, the mortality rate in AMI patients who underwent primary or post-TLT invasive reperfusion was lower compared to values observed in 2012.

The vast majority of AMI patients who underwent reperfusion are those after emergency coronary stenting. Mortality rate in this arm was decreased from 10.1% in 2012 to 7.3% in 2013. The lowest mortality rate in 2013 was those who underwent coronary stenting after previous TLT (5.9%). Low percentage of deaths was also observed in patients who underwent primary coronary intervention without prior TLT – 7.8% (in 2012 – 8.5%).

Discussion

The obtained results indicate the advantage of endovascular interventions compared to TLT. The mortality rates in AMI patients who underwent emergency coronary stenting without TLT in 2012 and 2013 were lower than in patients with isolated TLT (8.5% and 7.8% versus 10.3% and 20.0%, respectively). These data should not be interpreted in favour of TLT abolition or restriction, because this method of primary coronary blood flow restoration can and should be used where timely endovascular interventions are not available. In contrast to coronary stenting, TLT is available for ambulance and its application is determined individually based on severity of patient's condition, as well as conditional terms of patient transportation in the hospital where percutaneous coronary interventions are performed. Interaction between ambulance and hospital staff when choosing the reperfusion type is most clearly regulated in the Russian guidelines "Diagnosis and Treatment of Patients with Acute Myocardial Infarction with *ST*-elevation on the Electrocardiogram" (4).

Endovascular techniques for acute coronary disease started to be used in 2011 according to the Healthcare Modernization Program, and led to the creation of modern system of specialized medical care in Chelyabinsk and adjacent regional districts with annual growth in the number of emergency stentings – from 523 in 2012 up to 975 in 2013.

As exemplified by a specific medical institution having the status of regional vascular centre (RCH), the number of admitted patients with acute coronary disease and emergency coronary stenting increased on average by 20% in 2013 compared to 2012. The data obtained during the 1st half of 2014 show significant growth by the end of this year.

RCH adheres to the tactics of active use of endovascular interventions for acute coronary disease, as evidenced by the frequency of emergency coronary angiographies and stentings in AMI patients. The percentage of emergency coronary angiography increased from 79.8% in 2012 up to 84.1% in the Quarter 1 of 2014. Two thirds of AMI patients annually undergo emergency invasive coronary revascularizations (2012 – 67.7%, 2013 – 64% and Q1 2014 – 59%).

Further improvement of specialized medical care for AMI patients in RCH is connected with an active cooperation with the regional healthcare institutions (ambulance services, central district hospitals) attached to the regional vascular centre, in terms of timely admission of patients without organizational delays, rational use of TLT, pre-hospital medical support of patients. The roundtable discussions on AMI, current dialogue on specific clinical cases and other forms of interaction will contribute to the improvement of time intervals ("sign-to-balloon", "door-to-balloon") and compliance with the state criteria of accessibility and quality of medical care.

Conclusion

The first experience of the Railway Clinical Hospital at Chelyabinsk station, JSC Russian Railways, in provision of specialized medical care for patients with acute coronary disease can be considered as positive. Being one of three regional vascular centres of Chelyabinsk, RCH intensively hospitalizes urban and regional patients with routine use of modern endovascular technologies for AMI treatment. Further accumulation of experience, application of world guidelines for the treatment of acute coronary disease in clinical practice, review of interim and final results will improve the strategic parameters both at the level of RCH and in the region as a whole.

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Our Experience with Femoral Access for Emergency Percutaneous Coronary Interventions

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The number of coronary interventions in general and in acute coronary syndrome in particular is annually increasing in the Russian Federation. In settings of intensive practical activities, complications are inevitably observed, among which there is a special group related to arterial puncture. A specific complication of femoral arterial access which remains the "classical" one in X-ray surgery is the formation of false post-puncture aneurysms. This problem is very topical for emergency PCI-centers, where anticoagulants from various pharmacological groups are used particularly aggressively. To eliminate this complication, radial access can be used. Our clinic adheres to conservative opinions and offers its experience of "upgrading" femoral access in the settings of extensive flow of emergency cardiology patients.

Key words: *percutaneous coronary interventions, acute coronary syndrome, pulsatile hematoma, false aneurysm, closure device.*

Objective. To improve outcomes of emergency percutaneous coronary interventions performed via femoral access by preventing post-puncture pulsatile hematomas.

Material and methods. Retrospective analysis of 927 medical histories of patients who were admitted with acute coronary syndrome and underwent emergency coronary angiography alone or followed by coronary stenting via femoral access was performed. The proven false femoral aneurysms including those in patients with arterial puncture site closure using special vascular closure devices were registered. Therefore, all patients were divided into 2 groups: group 1 – vascular closure device (VCD) group – 589 subjects (63.5%) and group 2 – non-vascular closure device (non-VCD) group – 338 subjects (36.5%). Cordis Exoseal and St.Jude Angio-Seal devices were used in group 1 (89% and 11%, respectively). The indications were as follows: previous thrombolytic therapy; patients at high risk for pulsating femoral hematomas (grade 2–3 exogenous constitutional obesity, grade 2–3 arterial hypertension, application of 2b/3a receptor blockers).

Results. There were no deaths caused by bleeding from the puncture site. In total 24 false femoral aneurisms were revealed: 2 (0.3%) in VCD group and 22 (6.5%) – in Non-VCD group, 6 out of them were treated surgically. A surgical revision of the groin area (increasing haematoma) was performed in 1 female patient with myocardial infarction after thrombolytic therapy and coronary angiography. The source of bleeding was not found, the femoral arterial puncture site was closed using Cordis Exoseal with no evidence of bleeding or inflammation.

Conclusion. The selective use of the femoral artery puncture site closure devices in patients with acute coronary pathology who received intensive cardiac treatment was associated with the minimum number of pulsating hematomas. Among hemostasis puncture closure devices, Cordis ExoSeal device (over 500 closings) was proven to be effective, reliable and easy to use.

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Introduction

In our country there is a stable tendency to annual growth in the number of coronary angiography and coronary stentings including those in acute coronary syndrome (4). Modern PCI-centers, especially targeted at emergency interventions, obtain the newest pharmacological agents with various mechanisms of action on all hemostasis components. Under emerg-

ing trends, the risk for hemorrhagic complications related to the puncture site increases, which, in turn, necessitates searching for reliable methods of their prevention. One of the possible local hemorrhagic complications is post-puncture femoral false aneurysm (5, 7). Endovascular coronary interventions in comparison with interventions on other vessels are accompanied by a larger number of local complications including pseudoaneurysms (8). These circumstances are one of the reasons for refusal from femoral access in favor of radial puncture (6) and in some centers – ulnar puncture (1). There are reports on numerous applications of these approaches (2, 3).

However, femoral access remains principal for many PCI sites. Therefore, to reduce hemorrhagic complications, effective preventive measures are required.

Material and methods of the study

The study was conducted in the Department of Endovascular Techniques for Diagnostics and Treatment of the InterRailway Cardiovascular Surgery Center of the Railway Clinical Hospital at Chelyabinsk station, JSC Russian Railways (RCH). This medical institution works as a duty regional PCI center and provides specialized cardiological and endovascular medical care for patients with acute coronary disease. The territory of service includes 4 districts of Chelyabinsk municipality and 7 surrounding regional municipalities.

RCH routinely uses femoral access for angiographies and interventions. In case of coronary interventions in emergency patients, the vascular closure devices are used to prevent hemorrhagic complications. We have adopted the conventional indications for their use: previous thrombolytic therapy; patients at high risk for pulsating femoral hematoma (grade 2–3 exogenous constitutional obesity, grade 2–3 arterial hypertension, previous application of 2b/3a receptor blockers).

To assess the efficacy of the closure devices, a retrospective analysis of case histories of patients who were admitted to RCH with a diagnosis of acute coronary syndrome and underwent emergency coronary angiography alone or followed by coronary stenting via femoral access was performed. Clinically and instrumentally proven false femoral aneurysms after percutaneous coronary interventions were registered, including those in patients with arterial defects closed using special vascular closure devices. Therefore, all patients were conditionally divided into 2 groups: group 1 – vascular closure device (VCD) group and group 2 – non-vascular closure device (non-VCD) group. The groups were comparable by sex, age, and volume of reperfusion treatment. Further, an efficacy of treatment for puncture complications through compression and surgical techniques was assessed.

All cases of pulsatile femoral hematomas were diagnosed based on clinical data (painful and pulsating formation at the puncture site, systolic murmur) and ultrasound data. The way of elimination of femoral artery defect was determined individually, a vascular surgeon was invited for consultation in all cases. The surgical method was selected in cases of significantly reduced hemoglobin levels (20–25% from baseline) and expanding hematoma. In case of stable hematology parameters, a pressure bandage was put on the groin area, strict bed rest was prescribed, with modification of antiplatelet and anticoagulant therapy. This treatment was performed up to 7 days with daily clinical examination of hematoma and change of pressure bandage. The process was controlled by ultrasound once every 2 days to assess the efficacy of compression therapy. If the compression therapy was ineffective, the defect of femoral artery was sutured.

Two types of special vascular closure devices were used to close the puncture defects (Cordis Exoseal and St.Jude Angio-Seal). They were placed by endovascular specialists of similar qualification category in accordance with the manufacturers' recommendations. In some clinical cases where special devices were temporarily absent, an approach of delayed sheath removal was used in the above clinical cases (after 24 hours on average). Vascular closure device was selected solely based on its availability in the medical institution. Usually, only one out of two options was available for use.

Results

1550 patients with a diagnosis of acute coronary syndrome were admitted to RCH from January 01, 2012 to July 01, 2014. As a result of the diagnostic and therapeutic interventions, the following clinical diagnoses were made: acute myocardial infarction – 862 patients (55.6%), unstable angina – 628 patients (40.5%), unconfirmed acute coronary disease – 60 patients (3.9%).

Since the beginning of activities in acute coronary syndrome, almost all admitted patients

with acute coronary disease undergo coronary angiography (emergency, delayed coronary angiography and elective coronary angiography prior to discharge). 946 emergency coronary angiographies (61.0%), 589 (62.3%) out of them followed by emergency coronary stenting, were performed during the reporting period.

727 (84.3%) patients with a final diagnosis of myocardial infarction underwent emergency coronary angiography. The proportion of patients with myocardial infarction who underwent emergency coronary stenting was 65.1% (561 patients) out of the total number of patients with myocardial infarction.

Patients with acute coronary disease who were admitted to RCH underwent 188 (12.1%) systemic intravenous thrombolysis. In the vast majority of cases (79.3%) thrombolytic reperfusion was performed in the prehospital settings.

The proportion of femoral access for percutaneous coronary interventions was 98.0% (927 cases). The radial and brachial accesses were used in 19 patients (2.0%). Sheaths and catheters 6F were routinely used.

All patients were conditionally divided into 2 groups. Group 1 consisted of patients in whom special vascular closure devices were used – 589 cases, which accounted for 63.5% out of the total number of completed femoral punctures for percutaneous coronary intervention. Cordis Exoseal (524, 89%) was used in the vast majority of cases (St.Jude Angio-Seal – in 65 patients (11%)).

Group 2 included patients whose femoral artery puncture site was closed without special vascular closure devices – 338 cases (36.5%). This group presents a variety of cases, when vascular closure devices were not used in accordance with the above mentioned conditional indications, and in situations where these devices were not available.

The mortality rate in AMI patients was 10.2% (88/862 cases). In both groups there were no deaths caused by puncture site bleeding. Totally, 24 false femoral aneurisms (2.6%) were revealed. In pooled group, surgical treatment was used in 7 patients, which accounted for 0.8% of all cases.

The vast majority of patients with false femoral aneurysms belongs to non-VCD group – 22 patients (6.5%). 6 patients (1.8%) in whom the special vascular closure devices were not used, needed open suturing to close the femoral artery defect: 4 cases – after coronary angiography, 2 cases after coronary angiography followed by stenting. 3 patients needed surgery in emergency settings due to reduced hemoglobin levels and hematoma increasing; two of them needed blood transfusion. Three other patients after surgery demonstrated no required effects of the compression therapy.

In 16 subjects from this group, the compression treatment was effective; the puncture defect was closed in almost all patients by Day 3–4 of conservative treatment. In group 1, the compression treatment was also effective in all 2 cases (0.3%) of pulsating hematomas observed after Cordis Exoseal and St.Jude Angio-Seal (1 case each).

In the VCD group, there were no false femoral aneurysms requiring surgical treatment. Open surgery was performed in one female patient with myocardial infarction and increasing groin hematoma after coronary angiography. In addition to cardiac diagnosis, this female patient suffered from Grade 3 exogenous constitutional obesity and Grade 3 arterial hypertension with hypertensive crisis pattern. After successful thrombolytic therapy, multivessel coronary artery disease was revealed that required coronary artery bypass grafting. The puncture site was closed using Cordis Exoseal without significant hematomas for 3 observational days. On Day 4, hematoma size was increased, mild groin pain appeared. There was no systolic murmur over the femoral artery; US did not confirm false aneurysm or puncture defect. In spite of compression treatment, on Day 5 hematoma size increased and hemoglobin level decreased to 87 g/L (127 g/L at admission), US revealed no circulatory problems in the femoral artery. The groin region was revised because of ineffectiveness of compression treatment, extensive therapy targeted at blood thinning, clinically significant reduction in hemoglobin level and suspected bleeding from the femoral artery or its branches. The hematoma was evacuated (about 800 mL of the blood with clots), and soft tissues were coagulated diffusely to achieve hemostasis. The source of bleeding was not found, closed femoral puncture defect was seen without evidence of bleeding or inflammation. Single blood transfusion (400 mL) was done, the postoperative period was unremarkable. On Day 16 after admission, the female patient was discharged for out-patient therapy and elective heart surgery.

No specific complications or problems with the placement were observed in the group where femoral artery puncture defect closure devices were used.

Discussion

Till September 2011, specialized endovascular medical care was provided in RCH on elective basis only. Subsequently, our clinic has become as emergency PCI center within the Healthcare Modernization Program. All our practical efforts were focused on accumulation of clinical experience with emergency cardiac patients. This refers primarily to percutaneous coronary intervention.

An idea of switching from the femoral to radial access appeared several times, and most likely, it would be realized for elective patients. The first difficulties associated with the radial puncture, catheterization of the coronary artery ostia, and spasm problems are easily overcome due to sufficient time reserve, always available in elective percutaneous coronary interventions.

Switching from femoral to radial access in the settings of extensive flow of emergency patients with acute coronary disease is much more difficult. If there are no relevant skills, the time interval "door-to-balloon" will increase due to prolonged coronary angiography and placement of delivery catheter. This time delay can have serious consequences for severe patients. Therefore, femoral access is used in our clinic in emergency settings, allowing the fastest possible diagnostics and immediate preparation for percutaneous coronary intervention.

In terms of hemorrhagic complications, transradial access is potentially more effective compared to femoral one. In our study, femoral access was accompanied with only 6 (0.6%) false post-puncture aneurysms and 1 (0.1%) increasing groin hematoma that required surgery. These results were obtained when special vascular closure devices were used only in patients at high risk of bleeding or when these devices were not available. In contrast to elective patients who undergo percutaneous coronary interventions, those admitted with acute coronary disease receive more intense and more prolonged medical treatment aimed at blood thinning. Therefore, the obtained results on prevalence of significant pulsating hematomas after femoral access are considered to be positive.

The advantage of transradial access associated with the lack of strict bed rest appeared to be leveled by staying in the intensive care unit and mandatory restriction of motor activity with existing myocardial infarction.

The best results were observed when special vascular closure devices for femoral puncture sites were used, both in terms of pulsating hematomas and need for surgical treatment. The used device (Cordis ExoSeal and St. Jude Angio-Seal) proved to have equally high hemostatic efficacy.

Cordis ExoSeal device was used in the majority of cases due to several advantages. First of all, it can be easily placed by a novice. It is almost impossible to cause any harm to the patient when using Cordis ExoSeal. In the worst case scenario, the device does not close the femoral puncture site without any significant morphological consequences for the vessel. Due to its simplicity, the device can be applied directly at the bedside. In our practice, when the sheath was left for possible re-interventions, which ultimately were not performed due to the patient's status stabilization, the puncture site was closed in the intensive care unit. Among other less important advantages compared to St. Jude Angio-seal, we can note longer storage period, absence of special storage conditions, and absence of X-ray control during placement.

Conclusion

In our study, selective use of vascular closure devices for femoral artery puncture sites in patients with acute coronary disease receiving intensive cardiac treatment was accompanied with the minimum incidence of pulsating hematomas (0.8%). We consider justified to use these devices in patients at possible high bleeding risk. Low coagulation potential is observed in patients after thrombolytic therapy, as well as in patients who received 2b/3a receptor blockers. In grade 2–3 exogenous constitutional obesity as well as in arterial hypertension, compressive bandage over punctured femoral artery is less effective.

In the settings of extensive flow of emergency patients with acute coronary disease requiring PCI, the vascular closure devices for femoral arterial puncture site minimize post-puncture complications. More than 500 femoral closings were performed using Cordis ExoSeal during the reporting period. These devices have proven themselves as effective, reliable and very easy to use.

In our clinic, the femoral access is the principal one. Despite the low rate of false femoral aneurysm over the last 2.5 years, we associate further improvement of specialized interventional medical care for acute coronary disease with radial access. When performing coronary interventions, we choose arterial access taking into account own skills, technical abilities, as

well as prevention of puncture complications in individual patients.

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Comparative Analysis of Thrombolytics' Effectiveness: the Research Continues

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«...If thou examinst a man for illness in his cardia, and he has pains in his arm, in his breast, and in side of his cardia ... say: "Death threatens"»
Papyrus Ebers, 1550 B.C.

Treatment of acute myocardial infarction still remains one of the most important tasks of Russian and world healthcare. Cardiovascular diseases are the leading cause of death in developed countries and among them in Russia. Introduction of thrombolysis into clinical practice resulted in lowering of 30-days mortality to 5–8%, whereas during pre-thrombolytic era it reached 17–18%. According to ESC, ACC and Russian scientific society of interventional cardiology guidelines thrombolysis is method of choice for achieving reperfusion as soon as possible, or when primary coronary intervention is unavailable.

Primary coronary intervention allows achieving reperfusion in 90–95% with low incidence of early and late reocclusions and statistically significant lower rate of stroke compared to thrombolysis. Organizational difficulties of redirection of patients into specialized hospitals, time losses during transportation and pre-treatment are serious obstacles for widespread of primary percutaneous coronary interventions (PPCI). Finally, the costs of this treatment are high enough.

Over 80% of Europe population lives compactly and nearest cathlab is available for them in 30 minutes, therefore over 80% of patients can be directed there via optimally functioning emergency service. But even in this, close to "ideal", situation some patients during fist hours of AMI can only receive thrombolysis due to some reasons, e.g. living on an island.

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Situation differs in countries with vast territories. For example, in USA only 20–25% (!) of hospitals can perform PPCI 24/7 and most patients need to be redirected to another hospital for PPCI to be performed. As a consequence, only 4% of redirected patients receive coronary angiography in 90 minutes from fist medical contact. (12) For example, in Dallas county 14 of 16 hospitals have cathlabs, but only 2 (!) of them work 24/7 (19).

It is also fair for Russian Federation. There are vast territories with regional medical centers, where availability of PPCI in first hours is low. There are also large megapolises where traffic jams sometimes make possible only hospitalization to the nearest hospital.

Thus thrombolysis is still the most common and available method of reperfusion in AMI despite continuing spreading of endovascular treatment.

Thrombolysis in AMI is used for more than 50 years since W.S. Tillett in 1955. (4) A.P. Fletcher in 1958 reported successful use of streptokinase in AMI. (5) E.I. Chazov in 1976 was first to administer fibrinolisine intracoronary. (6) But necessity of thrombolysis in AMI was universally recognized only recently. DeWood in 1980 performed a study with coronary angiography in 517 patients within first 24 hours of AMI and proved that thrombus is the reason of acute occlusion of coronary artery in 80–95% (7). Coronary angiography played an important role in development of thrombolytic therapy, as well as morphological studies that showed that the reason of AMI is the intracoronary thrombus, developing most frequently on the damaged atherosclerotic plaque.

Lysis of intravascular thrombus is mediated by plasmin. It is trypsin-like enzyme that catalyzes fibrinolysis, thus leading to reperfusion.

Plasmin is the main component of fibrinolytic system and is produced as a result of plasminogen activation. Lysis of occlusive thrombus is performed via fenestration that is formation of one or more tortuous courses in the thrombus with subsequent total resorption.

Main goal of thrombolysis in AMI is minimizing the volume of necrosis. The key factor, influencing the efficiency of thrombolytic therapy is time delay from coronary occlusion to reperfusion. This in turn depends on time of beginning of thrombolysis and thrombolytic efficacy.

Reperfusion as soon as possible leads to reduction of necrosis volume through saving myocardium in peri-infarction zone. This is the zone of hibernating myocardium which is reversibly damaged. Necrosis volume increases dramatically with time thus most lives can be saved if reperfusion is begun during first hour of symptoms onset. It is called "golden" hour of thrombolysis. Thrombolysis in first 30–60 minutes can save 60–80 lives among 1000 patients, and 30–50 lives in 1 to 3 hours (1).

In experimental study 40–60 minutes after occlusion of coronary artery most cardiomyocytes in subendocardial layer are damaged. If ischemia persists, damage spreads to all layers of myocardium, reaching subepicardial zone in 3–6 hours. 60% of myocardium dies within 4 hours with the rest dying in 20 hours.

Thus thanks to reperfusion necrosis volume is reduced. Secondarily, saving subepicardial layer of myocardium may lead to lesser remodeling of diseased heart tissue. Finally it leads to increase in so called "residual" function of left ventricle thus increasing quality of life and lifespan.

Thrombolysis in AMI is effective due to early reperfusion of infarct-related artery, thus it must be already administered on pre-hospital stage. Results of international and Russian studies lead to widespread of thrombolysis and nowadays it is one of most important methods of treatment of AMI. It reduces in-hospital and late mortality by 20–25%.

Meta-analysis of 9 large randomized trials shows that thrombolysis in first hour of AMI reduces 35-days mortality by 27%, whereas therapy in 7–12 hours – only by 13%. Thrombolysis in 13–24 hours almost did not influence mortality (20).

Medicine used for thrombosis must be effective, safe for patient and easy to administer.

Continuing studies are searching for "ideal" thrombolytic agent. It must possess following properties: fast reperfusion, 100% of TIMI III flow incidence, high specificity to "new" thrombus, low incidence of reocclusion, high resistance to first type of plasminogen activator, no blood pressure influence, no antigenic properties, acceptable cost and easy and convenient administration.

Bolus introduction of drugs has several advantages. First, easy administration leads to earlier beginning of AMI treatment, leading to increase in patient's survival. (10, 13) Respectively, increase in door-to-drug time leads to increased mortality. (14) Time delay to beginning of thrombolytic therapy can be reduced by using bolus administration of thrombolytic. Door-to-drug time in patients that received bolus administration of thrombolytic was 15 minutes less than in infusion of alteplase (14). Secondly, bolus administration of drug is more convenient strategy for pre-hospital stage. Meta-analysis of several studies shows 19% reduction in mortality in pre-hospital thrombolysis compared to in-hospital (15). Third potential advantage of bolus thrombolytic therapy – lesser incidence of medical errors. E.g. large amount of incorrect dosing and timing of administration were seen in bolus+infusion administration of alteplase. For example, among 41021 patients in GUSTO-1 in 12% of cases drug administration was incorrect, thus 30-days mortality was higher (7,7% compared to 5,5% in alteplase; 11,3% compared to 6.4% in streptokinase, $p < 0.001$). National register of myocardial infarction including over 71000 patients shows 2,3 times increase in hemorrhagic stroke among patients that received alteplase dose > 1,5 mg/kg.

Hemorrhagic complications including intracranial hemorrhage are among most frequent and dangerous complications of thrombolysis. Meta-analysis of 9 studies including 58600 patients shows 0,39% incidence of intracranial hematomas (ICH). 268 of 41021 patients (0.65%) in GUSTO-1 study developed ICH with 59.7% mortality!

Another type of hemorrhagic complication is gastrointestinal bleeding (GIB), its incidence is roughly 5%. Incidence of life-threatening GIB is 1.1%. Some complications are specific to streptokinase and anistreplase, such as fever in 5%, arterial hypotension in 10–25%, rash in 2–3%.

Increase in fibrinolyic activity of patient's blood can be achieved by 2 ways:

1. Administration of activated plasmin (fibrinolysine). This method is of historical importance only and is not used nowadays. Exo-

genous plasmin acts slowly and is not effective enough in solving arterial thrombi. Besides, it causes pyrogenic and allergic reactions frequently and can lead to serious bleedings.

2. Administration of plasminogen activator, increasing plasmin production. Continuous search for newer drugs nowadays is centered on this group.

Modern thrombolytic drugs can be divided into 3 groups:

1. First generation of drugs, that activates both free and fibrin-binding plasminogen. This drugs (streptokinase, urokinase) have low $T_{1/2}$.

2. Second generation of drugs, that are more specific to fibrin-binding plasminogen and has longer $T_{1/2}$ (prourokinase, anistreplase, alteplase).

3. Third generation of drugs, highly selective to fibrin-binding plasminogen has the highest thrombolytic activity (metalyse, fortelysin).

Streptokinase (SK) is one of the first widely used drugs. It is direct plasminogen activator, a single-stranded polypeptide with molecular mass of 47000 D, produced from group C β-hemolytic Streptococcus. Streptokinase is a non-enzyme protein that can form a stoichiometric complex with plasminogen, exposing its active site. Streptokinase-plasminogen complex acts as an enzyme, converting both free and fibrin-binding plasminogen into plasmin. Its $T_{1/2}$ is 15–25 minutes and the complex can be partially inactivated by antistrepococcus antibodies. Streptokinase has antigenic properties since is produced from bacterial culture. Due to high incidence of streptococcus infections there always are antistrepococcus antibodies in human blood, but the incidence of anaphylactic reactions is low – 0,1% (8). The quantity of antistrepococcus antibodies rises fast and is maximal in several weeks after thrombolysis sometimes rising 1000 times higher than before thrombolysis. Some patients may have normal level of antistrepococcus antibodies in 6 months, but in numerous cases resistance and allergic reactions were seen in patients that received thrombolysis 2–4 years back. Thus repeated administration of streptokinase or its administration immediately after streptococcus infection is not recommended.

Some authors recommend administration of 180–240 mg of prednisolone or antihistamines as a prophylaxis of allergic reactions. Studies show that effectiveness of streptokinase varies strongly. It can be the consequence of different quantity of antistrepococcus antibodies. Nowadays dosage of 1 500 000 U of streptokinase IV in 60 minutes suggested by R. Schroeder in 1981 is universally accepted. (9)

Effectiveness of streptokinase in AMI was actively studied in eighties, along with GISSI-1 study (Gruppo Italiano per lo Studio della Streptochinasi nell`Infarcto Miocardico) (10). This study included 11 806 patients with AMI, roughly half of them received 1 500 000 U of streptokinase within 12 hours from symptoms onset. It was first to show that thrombolysis in AMI reduces mortality and to show the correlation between time of thrombolysis and its result. Administration of drug within 1 hour, 2–3 hours and 3–6 hours led to mortality of 8.2%, 9.2%, 11.7% respectively compared to 14.6% in control group.

Same conclusions were made after ISIS-2 study (10). Over 17000 patients were randomized into 4 groups: streptokinase therapy, aspirin therapy, streptokinase plus aspirin and control group. Reduction of 5-weeks mortality was 25, 23 and 42% for first 3 groups respectively. Thus combination of streptokinase and aspirin almost doubled treatment effectiveness. Results of this study contributed to modern strategy of thrombolysis in AMI.

Meta-analysis of studies with angiographic control shows that incidence of reperfusion in streptokinase therapy is 44% in 60 minutes, 48% in 90 minutes, 72% in three hours, 24 hours to 21 days 75–85%, that is significantly higher than in control group. (11)

Urokinase (UK) in human is produced by renal tissue cells and endothelium. Unlike streptokinase, urokinase is an enzyme and converts plasminogen into plasmin directly. It is known that endothelial cells produce 2 types of plasminogen activator: tissue-type and urokinase-type. There are two molecular forms of urokinase-type plasminogen: low molecular weight (33000 D) and high molecular weight (54000 D). Urokinase is low molecular weight form of urokinase type double-stranded plasminogen activator. Urokinase $T_{1/2}$ is 15–20 minutes. Unlike streptokinase, urokinase doesn't lead to antibodies production, allergic reactions occurs much rarely. Like the streptokinase, urokinase activates both free and fibrin-binding thrombolytic, leading to systemic lytic state, or plasminaemia.

Prourokinase. New form of single-stranded urokinase was developed in 1979. It was called prourokinase. It can also split plasminogen thus producing plasmine and is fibrin-selective. Prourokinase is a natural enzyme, that can be produced from human urine, embryonic

renal tissue cell culture but for clinical practice it is produced by DNA-recombinant method. Prourokinase is produced by cells as a protein, consisting of 411 amino acids. First human use was reported in 1986 by Van der Werf. $T_{1/2}$ of prourokinase is 3–9 minutes.

New thrombolytic agent – recombinant prourokinase (purolase) was developed and registered in Russia in 2000. In genetic engineering lab of Myasnikov's RCSIC modified molecule with 24 amino acid residues changes was developed. Amino acids modifying led to increasing of $T_{1/2}$ up to 30 minutes. Recommended dosage of prourokinase is 20 mg IV bolus and 60 mg as an infusion during 1 hour. Study including 237 patients with AMI within 6 hours from symptom onset was performed. Reperfusion was evaluated using ECG data and CK levels.

Repeated administration of purolase did not led to any adverse effects, including allergic reactions.

Alteplase (actilyse) is tissue plasminogen activator (tPA). It is produced by endothelial cells in human. Alteplase (actilyse) was produced using DNA-recombinant method. Alteplase is a sequence of 527 amino acids with molecular weight of 70000 D. Actilyse is different from other tPA, it only converts plasminogen into plasmin in presence of fibrin, which means that it is fibrin-specific and has no systemic effect. Its selectiveness results from several factors, among them high affinity to fibrin and fibrin-dependent activation of plasminogen. Therefore tPA acts mostly within the thrombus. As a result tPA in vivo solves thrombus with minimal systemic effect. 100 mg of actilyse caused reduction of circulating fibrinogen to 54–60% within 4 hours of thrombolysis. Plasminogen and alpha-2 antiplasmin levels lowered to 52–70% and 25–35% respectively within 4 hours, and increased to 80% within 24 hours. $T_{1/2}$ of drug is 4–8 minutes, thus long infusion is needed. Recommended dosage is 90 mg within 90 minutes. Thrombolysis by tPA leads to active thrombin producing and platelet activation, therefor heparin infusion is also needed.

Comparative studies of streptokinase and alteplase were performed in eighties. Studies with angiographic control showed that 3 hours of alteplase infusion led to reperfusion significantly more often, but TIMI-1, GISSI-1 and ISSIS-3 studies showed no significant difference in mortality. Only GUSTO-1 study (41021 patients) showed that accelerated infusion of alteplase (100 mg in 90 minutes) led to lowering of 30-days mortality compared to streptokinase (6.3 against 7.2, p = 0,001). More strokes were seen in alteplase group (0.72 against 0.54%, p = 0.03).

85 patients with AMI received coronary angiography and reperfusion was seen in 71% and 85% within 90 and 120 minutes after thrombolysis respectively.

ASSET study (n = 5013) compared actilyse with placebo within 5 hours from symptoms onset. 30-days and 6-months mortality was significantly lower in actilyse group (7.2 versus 9.8%, p = 0.001 and 10.4 versus 13.1%, p = 0.008 respectively)

Double-blind randomized study (n = 721) compared actilyse and placebo within 5 hours from symptoms onset. Patients in actilyse group had significantly better left ventricle ejection fraction, measured by ventriculography (50.7 versus 48,5%, p = 0.01), infarction zone size was 19% less, cardiogenic shock incidence was significantly lower (p = 0.02), 21-days mortality was 3.7 versus 6.3%, p = 0.05.

Tenecteplase (metalyse) is a recombinant fibrin-specific plasminogen activator. It alteplase molecule, modified by genetic engineering. 3 different genetic mutations were needed to increase $T_{1/2}$ (8 times compared to alteplase), plasminogen activator inhibitor 1 resistance (200 times compared to alteplase) and thrombolytic activity and specificity.

The drug binds with fibrin and catalyses plasminogen to plasmin conversion, thus solving thrombus. Tenecteplase has more affinity to fibrin and plasminogen activator inhibitor 1 resistance compared to natural tPA. Increased affinity to fibrin leads to reduced incidence of bleeding, as fibrinolysis only occurs in thrombus. Thus fibrinogen, V and VIII clotting factors decomposition can be avoided. Inhibition by plasminogen activator inhibitor 1 is 80 times less than in alteplase.

Tenecteplase molecular weight is 65000 kD.

Dose-dependent consumption of α-2-antiplasmin occurs after administration of tenecteplase, followed by rise of systemic plasmin matching expected effect of plasminogen activation. Comparative studies in patients received maximal dose of tenecteplase (50 mg) marked fibrinogen lowering by less than 15%, plasminogen lowering by less than 25%, compared to 50% decrease in fibrinogen concentration after alteplase administration. Tenecteplase $T_{1/2}$ is 24 minutes, 5 times longer than $T_{1/2}$ of native plasminogen, allowing to administer it as a single bolus thus facilitating its prehospital use. Tenecteplase metabolism is pri-

marily hepatical, thus renal function impairment does not impair its pharmacodynamics.

Effectiveness of tenecteplase was studied in many clinical researches, among them TIMI 10A, TIMI 10B, ASSENT-2, ASSENT-3, ASSENT-3 PLUS.

Effect of different doses of tenecteplase was studied in TIMI 10B study, 886 patients enrolled. According to coronary angiography, tenecteplase bolus of 30, 40 and 50 mg led to TIMI III flow restoration in 55%, 63% and 66% respectively within 90 minutes.

III phase double-blind randomized study ASSENT-2 (16949 patients enrolled), planned to evaluate effective dose of tenecteplase depending on bodyweight and accelerated alteplase 90 minutes infusion, showed that decrease in 30-days mortality in tenecteplase group was no less than in alteplase group, but tenecteplase showed greater safety. Prospective randomized multicenter study ASSENT-3 (6095 AMI patients enrolled) showed that tenecteplase combined with low molecular weight heparin (enoxaparin) lowers the incidence of recurrent infarctions and refractory myocardial ischemia. Meta-analysis of 12 international studies showed that tenecteplase is no less effective than accelerated infusion of alteplase, but exceeds it is safety and usability (bolus administration).

Tenecteplase decreases 30-days mortality in AMI by 6.2%. Bleeding incidence is 26.4% (ICH excluded), compared to 28.9% in alteplase ($p = 0.00003$). Major bleedings incidence was 4.68% versus 5.94%, $p = 0.0002$, blood transfusion was needed in 4.25% versus 5.49%, $p = 0.0002$. ICH incidence was 0.93% in tenecteplase group versus 0.94% in alteplase group. 30-days mortality was significantly less than in alteplase group (4.3% versus 9.6%), along with stroke incidence (0.4% versus 3.3%) and ICH incidence (0 versus 1.7%) if thrombolysis was performed after 6 hours from symptoms onset.

Thus tenecteplase is at least noninferior to alteplase regarding effectiveness, but excels in safety and has more convenient route of administration (bolus).

Fortelysin is innovative fibrin-selective thrombolytic agent, developed by "SupraGen" pharmaceutical company. It is recombinant protein, produced from E. Coli by genetic engineering containing non-immunogenic staphylokinase. Unlike native staphylokinase, 3 amino acids in fortelysin molecule are changed thus antistaphylococcus antibodies are not produced after single administration and are minimally produced after repeated administration (antibody titer to 45 days: 100 for fortelysin, 12000 for staphylokinase). Drug represents a single-stranded molecule of 138 amino acids with molecular weight of 15.5 kD.

Fortelysin is not an enzyme. It activates plasminogen forming a stoichiometric 1 : 1 complex

Free plasminogenof blood has closed α-conformation, whereas plasminogen, binded with intact fibrin has semiclosed β-conformation and finally plasminogen binded with partially degraded fibrin has open γ-conformation. Fortelysin only reacts with open γ-conformation plasminogen, that is situated in thrombus, and does no react with α-conformation plasminogen thus being fibrin-selective. Fortelysin-plasminogen complex converts plasminogen to plasmin, that solves the thrombus.

Active research of fortelysin is underway since there is still very little data regarding clinical experience.

Multicenter randomized study performed in 6 Russian clinical centers enrolled 54 AMI patients, that received thrombolysis (41 patient received fortelysin, 13–100 mg of actilyse). First group was divided into two subgroups, first one ($n = 20$) received fortelysin as bolus + bolus (10 and 5 mg), second one received fortelysin as bolus+infusion (10 and 5 mg).

Coronary angiography was performed, revealing TIMI 2–3 flow in 85% of patients in fortelysin group (34 of 41), and in 77% of actilyse group (10 of 13), TIMI III flow 54% and 31% respectively. Incidence of reperfusion did not differ significantly in double bolus and bolus + infusion group (80 versus 80 b 86%).

No lethal outcomes, ICH, allergic reactions were seen in both groups. Blood fibrinogen decrease within 24 hours was less in fortelysin group. (17)

Pharmacoeconomic analysis shows that cost of thrombolysis in 1 patient for actilyse (100 mg) was 43778 RUR, whereas cost thrombolysis in 1 patient for fortelysin was 28 660 RUR(18).

Thus, nowadays arsenal of cardiologist contains variety of thrombolytic drugs, represented in chart 1.

Thrombolysis nowadays greatly reduced mortality due to AMI. Besides, it is also used for treatment of several other thrombotic and thromboembolic diseases. Taking into account incidence of hemorrhagic complications, research is now focused on third generation of

Table 1. Comparative characteristics of thrombolytics, used for treatment of AMI

Characteristics	Purolase	Actilyse	Metalyse	Streptokinase	Urokinase	Fortelysin
Production	Genetic engineering	Genetic engineering	Genetic engineering	Bacterial protein	Human urine protein	Genetic engineering
Generation	Third generation	Second generation	Third generation	First generation	First generation	Third generation
Fibrin-selective	+	+	+	–	–	+
Plasminogen type	Urokinase	Tissue	Tissue	Tissue	Urokinase	Tissue
$T^{1}/_{2}$	30–42 min	4–8 min	20–24 min	15–20 min	10–20 min	
Immunogenic	–	–	–	+	+/–	–
System fibrinolysis	–	–	–	+	+	–
Administration	Bolus+infusion	Bolus+infusion	Bolus	Infusion	Bolus+infusion	Double bolus
Reperfusion in 90 minutes		75%	80%	50%		80%
Available for pre-hospital use	+	++	+++	+	+	+++
Cost, RUR		35–40 000	45–55 000			28600
Reocclusion incidence	4–5%	10–15%	10–15%	10%	5%	Not enough data

thrombolytics, that have lesser incidence of adverse effects. Besides, numerous attempts to improve fibrin-specificity, $T^{1}/_{2}$, plasminogen inhibitor resistance are being performed by genetic engineering.

According to MHSD statistics, 162 000 cases of AMI were registered in Russia in 2009 (2). 68 000 of them died (41.9%) (3). One of the reasons for this disastrous number is low rate of reperfusion therapy use, much because of absence of thrombolytics in hospitals and ambulance service. Thrombolysis in Russia is used in 6–17% of patients, mostly in cities. Thus one of the most important goals of healthcare is development of effective, safe and economically available thrombolytics and their introduction into clinical practice.

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