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First Experience with Eliminate™ Thrombus Aspiration Catheter in AMI Patients in Moscow City Center of Interventional Cardioangiology

A.G. Koledinsky[1], D.G. Gromov, O.E. Sukhorukov, I.Yu. Kostyanov, D.G. Iosseliani
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The article addresses the first clinical experience with the new catheter Eliminate™ designed for manual vacuum aspiration of thrombi combined with urgent coronary interventions in patients with acute myocardial infarction. The technical features of this catheter are summarized and compared with the features of existing analogues. The immediate results of this device use in 10 patients with acute myocardial infarction who underwent the urgent thrombus extraction followed by stenting of infract-related artery are described. The high percentage of efficacy for vacuum thrombus aspiration using Eliminate™ catheter is observed, and the absence of complications in studied patients during this procedure should be noted. It was the first clinical approbation of this device in Russia. Based on the obtained results and comparison with the data of literature concerning use of the similar devices, it is concluded that application of Eliminate™ catheter allows achieving the acceptable outcomes of manual vacuum thrombus aspiration in patients with acute myocardial infarction.
Keywords: *acute myocardial infarction, thrombus extraction, systemic thrombolysis, Eliminate™ catheter.*

INTRODUCTION

Currently, it can be considered to be proved that the earliest and most complete blood flow restoration in the infarct-related artery (IRA) improves the clinical prognosis in AMI patients reducing mortality and incidence of serious complications (1,2,3). However, in spite of successful blood flow restoration in the IRA, some patients have in-hospital complications manifested in the extension of myocardial damage area and the reduction in functional capacity of the left ventricle (5). Therefore, the clinicians have focused their efforts on searching the effective preventive methods against multi-level coronary embolization with fragments of thrombus during endovascular procedure.

In this connection, the various pharmacological and non-pharmacological methods of protection of the distal segments of the IRA were tested in the clinical practice (6, 7, 8). Vacuum thromboaspiration allowing complete or considerable removal of thrombus masses from the IRA, is one of the methods preventing from microembolization. The first successful removal of thrombus from coronary artery was reported more than twenty years ago (12). Since then more than thirty various devices were developed and tested. It should be noted that in the first reports concerning efficacy assessment of the thromboaspiration procedures no significant advantages were revealed compared to standard endovascular myocardial revascularization without accompanying thrombus extraction (7, 9). Some authors even observed worsening of blood flow in the IRA and decreasing of the left ventricle function. In our opinion, these complications might be primarily related to the imperfection of the devices (the first catheters had small lumen which did not allow removing completely the thrombus masses from the IRA, and, on the other hand, very large external diameter of catheter might also promote the fragmentation and embolization of the distal coronary vessels with the thrombus particles). Significant improvement of devices for thrombus extraction and accumulation of experience, led to the improvement of the results, which was confirmed in the large, multi-center, randomized study TAPAS (2008), where the superiority of manual vacuum thrombus aspiration over the routine IRA angioplasty was proved in the great number of AMI patients. This concerned both immediate and long-term angiographic and clinical outcomes (4,10). Thereafter, the results of this study were confirmed by a variety of large randomized studies and, as a consequence, the new devices for vacuum thrombus aspiration became available in the medical market (for example, “Quik Kat”, “Export”, etc). Eliminate™ thrombus aspiration catheter (Terumo) is one of the latest in this range.

Eliminate™ catheter (Terumo) was designed with consideration of the disadvantages related to the previous devices. The improvements were related to more safe and effective manual removal of thrombi and restoration of coronary blood flow. When developing this catheter one of the aims was

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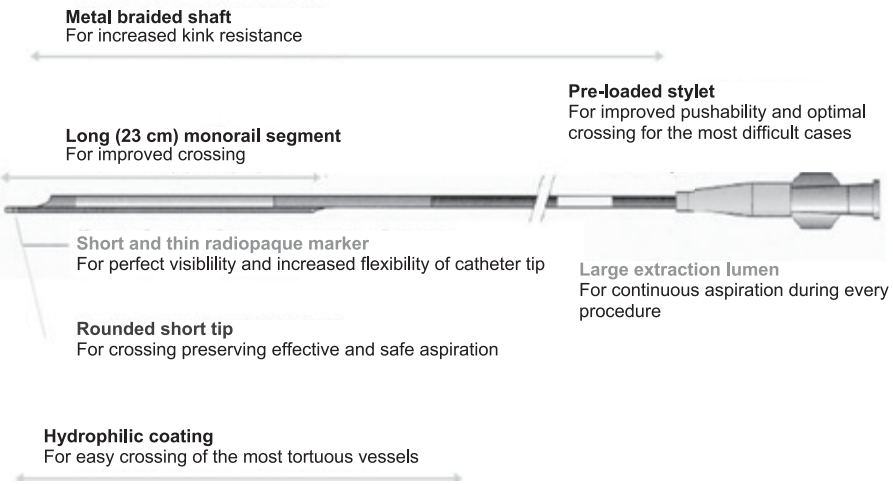

Fig. 1

to make thromboaspiration procedure more visible. First of all, it was related to the creation of optimal balance between such usually ill-matched features as coronary crossing performance, kink resistance and complete thromboaspiration, when possible (Fig.1).

Innovation techniques allowed the catheter to be improved as follows: i) it has 0.016» pre-loaded thin metal stylet ending at 2.5 cm from the distal part of the catheter. This improves the crossing and prevents the catheter from the kinking in difficult segments of coronary arteries; ii) hydrophilic coating of the catheter contributes to its successful advancement through the coronary artery; iii) all-metal braided shaft and long monorail part (23 cm) also contribute to the advancement; Eliminate™ catheter has the optimal internal diameter for thrombus aspiration compared with the similar devices. The important advantage of this type of catheters is that they may be used together with both 6F and 7F guide catheters, which allows this device to be used for transradial approach (Fig.2).

Thus, the presented data indicate that the technical features of Eliminate™ thrombus aspiration catheter (Terumo) demonstrating non-inferiority to the existing analogues developed by other companies are in many aspects superior to them. The rationale for this study was the necessity to evaluate the new catheter Eliminate™ (Terumo) for vacuum thrombus aspiration.

CLINICAL MATERIAL AND METHODS OF THE STUDY

82 endovascular thromboaspiration procedures from the IRA in AMI patients were performed in Moscow City Center of Interventional Cardioangiology from January 2008 till May 2010. Ten patients from this cohort underwent thrombus extraction using Eliminate™ catheter. The obligatory inclusion criteria for AMI patients were: ST elevation >0.1 mV in two adjacent leads; total occlusion of the IRA (TIMI 0). Exclusion criteria were: left ventricle ejection fraction <25%; right ventricle myocardial infarction; acute and chronic renal and hepatic failure; hemopoietic diseases; terminal stage of cancer. Every patient gave the informed consent for thrombus extraction.

Table 1 summarizes the baseline clinical and laboratory data of studied patients. Prior to the endovascular procedure each patient received standard double antiplatelet therapy. The therapy also included acetylsalicylic acid 100 mg/day, clopidogrel 150 mg followed by daily dose of 75 mg/day for the entire in-hospital period. All patients with systolic blood pressure <100 mm Hg received intravenous infusion of nitroglycerine at a dose of 0.25-0.5 μg/kg/min.

As Table 1 shows, mean patients' age was 52.3±8.5 years, they were predominantly males, frequently suffered from arterial hypertension, smoked and had lipid disorders. All patients were hospitalized within the first 2-4 hours after the angina attack onset. All patients had ECG signs of acute ischemic phase of left ventricle myocardial infarction. On admission 3 (30.0%) patients had heart rhythm disturbances presented as single and salvos ventricular extrasystoles. One patient had intraventricular conduction disturbances (incomplete left bundle branch block).

Selective coronary angiography (SCA) and percutaneous interventions (PCI): SCAs and PCIs were performed according to the standard method; each endovascular surgeon had an experience with more than 300 PCIs per year. After diagnostic coronary angiography and determination of angiographic view of acute occlusion of IRA, mechanical recanalization of the vessel was performed followed by angiography, and if it revealed the presence of intraarterial thrombus, thromboaspiration was carried out using Eliminate™ catheter. The procedure was performed by 3-4 slow catheter passages in the area of target lesion. Thereafter, blood flow in the IRA was assessed according to TIMI and MBG classifications, and then the target part of vessel was analyzed using digital computed angiography to select a stent of adequate diameter and length. The standard lead ECG was monitored during the entire intervention, and the 12-lead ECG was registered to evaluate ST dynamics at the end of procedure. Although there are no generally accepted criteria of positive assessment for thrombus extraction, we considered that the procedure was successful in case of: post-interventional antegrade blood flow TIMI 2-3; no evidence of thrombus masses dislocation after intervention; absence of pronounced dissection of the vessel or signs of extravasation

at the occlusion site; no evidence of pronounced generalized spasm. At completion of the IRA stenting, nitroglycerine 200-400 μg was infused intracoronary and the lesion was analyzed using digital computed angiography. The endovascular procedure was successful in all 10 patients: no significant vessel dissection, distal embolization, and deceleration of antegrade blood flow were observed. The volume of used contrast media did not exceed the acceptable limits.

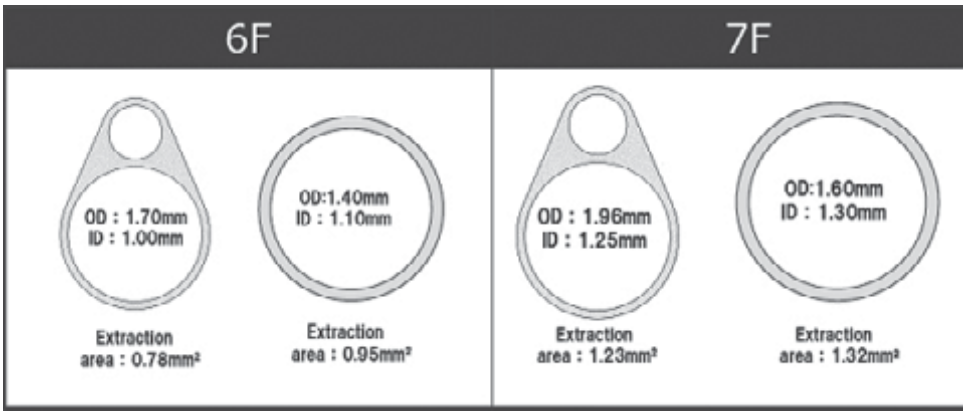

Fig. 2

Intravenous heparin administration was an obligatory condition for thrombus aspiration. Heparin therapy was started with bolus infusion (70 units per kg of body weight) with following drug infusion to achieve activated clotting time (ACT) ≥ 300 seconds. All patients were followed-up in the intensive care unit (ICU) within the first day with subsequent transfer to cardiology department. Here, the patients underwent further examinations including 24-hour ECG monitoring, heart ultrasonography, and cycle ergometry on day 8. Mean in-hospital stay duration was 11.3±2.9 days.

STUDY RESULTS

The principal coronary angiography indices of the studied patients as well as the data of the PCIs are presented in Table 2.

As Table 2 shows, LAD occlusion was observed more frequently than RCA and LCX occlusion. In 80% of cases there was no intra- and intersystemic collateral blood flow to the occluded IRA. As we have already noted, mechanical recanalization with a coronary guidewire was performed in every patient and immediately after control angiography the thrombus extraction using Eliminate™ catheter was performed. Then, the target segment was stented.

The results of thrombus aspiration and IRA stenting are presented in Table 3.

As the presented table shows, every thromboaspiration procedure was performed without previous balloon predilatation. We managed to remove macroscopic thrombus masses in 8 patients.

It should be noted that we used thrombus aspiration catheters of different sizes depending on the IRA diameter: if IRA diameter at the lesion site was > 3 mm, we used 7F catheter; if diameter was < 3 mm, then 6F catheter was applied. Thus, we used 7F and 6F catheters in five cases each. When 7F catheter was applied, thrombus removal was successful in all five cases, and when 6F catheter was used the procedure was successful in three cases only; it may indicate that the lesser diameter of aspiration catheter corresponds to the lesser aspiration ability. However, small number of observations does not allow us to make further conclusions. No major complications were observed during the thromboaspiration procedure: nor generalized spasm neither dislocation of thrombus masses were noted; there was one case of deceleration of antegrade blood flow up to TIMI 2. We observed dissection type C and D after thrombus extraction in two cases out of ten, both cases were successfully resolved by stenting.

Therefore, success rate of ETI using vacuum thromboaspiration by means of Eliminate™

Table 1.

Baseline clinical, historical and laboratory data of studied patients

Age (years)	52.3+8.5
Gender, M	9 (90.0%)
Arterial hypertension	6 (60.0%)
Smoking	6 (60.0%)
Duration of CAD (months)	7.8+1.9
Hypercholesterolemia (%)	7 (70.0%)
MI (in anamnesis)	1 (10.0%)
Acute left ventricular failure	2 (20.0%)

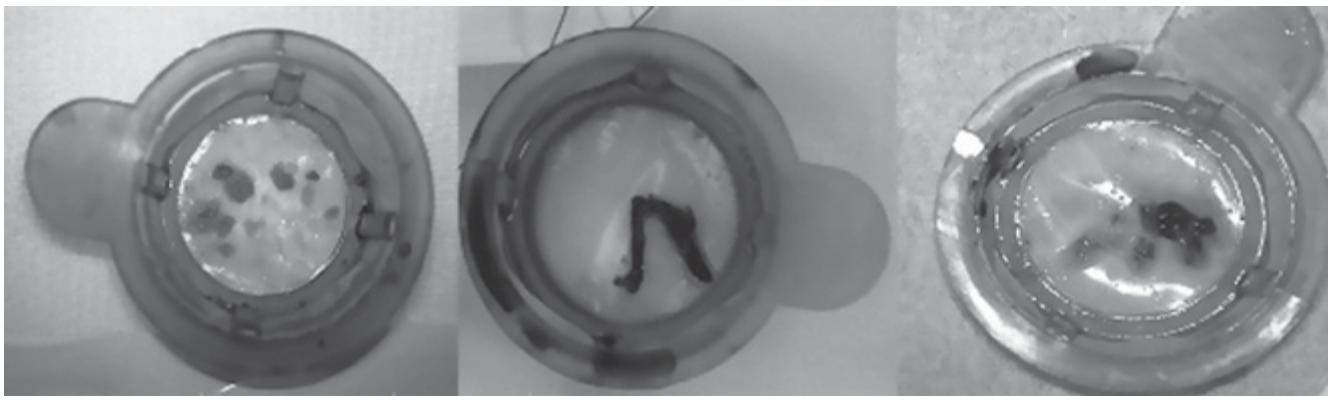

Fig. 3

aspiration catheter in patients with baseline occluded artery was 100%. We analyzed the degree of ST resolution to evaluate ETI efficacy in all patients after the procedure. We observed that in the majority of patients (7; 70%) the ST segment returned to the isoelectric line; it was an indirect marker of adequate endovascular myocardial reperfusion. One patient with partially restored antegrade blood flow (TIMI 2) had no ST resolution. In two more patients the ST resolution was incomplete — from 30 to 70% — compared to baseline ECG. Further in-hospital course of disease was uneventful in all patients; no death, repeated myocardial infarction, acute and subacute stent thrombosis were observed.

Thus, thromboaspiration using Eliminate™ catheter allowed us to restore the lumen of thrombosed coronary artery and to achieve antegrade blood flow TIMI 2–3 in 100% of cases; as a result, the subsequent IRA stenting was performed successfully without serious complications.

DISCUSSION

Currently, thrombus extraction is not a routine treatment in AMI patients. Nevertheless, thromboaspiration is assigned 2B class by European Society of Cardiology Guidelines for Acute Myocardial Infarction (13); it means that further large studies to determine the place of this procedure in patients with AMI and persisting ST elevation should be conducted. A great importance is attached to further studies of thrombus extraction from the IRA in AMI with ST elevation using various devices; moreover, the cardiologists currently have a wide spectrum of different devices for thrombus extraction. Each device should take its own place in AMI treatment. In this study we evaluated the results of new Eliminate™ catheter (Terumo) application. This study showed that this device has a variety of constructional and technical advantages compared with existing analogues manufactured by other companies. Adequate external diameter of the aspiration catheter and its good elasticity facilitate the crossing through the coronary artery lumen altered by the atherosclerotic plaques and thrombus masses. A stylet inside catheter also promotes the better crossing. Besides, the aspiration catheter has sufficiently large internal lumen diameter (Fig. 2), permitting successful aspiration and removal of the thrombi from the

Table 2.

Baseline coronary angiography parameters and data of PCIs

Infarct-related artery (IRA):	
- LAD	5 (50.0%)
- RCA	3 (30.0%)
- LCX	2 (20.0%)
- Number of involved arteries (mean).	1.3+0.3
- Vessel diameter (mm)	2.9+0.7
- Occlusion length (mm)	15.4+6.2
- Presence of intra- and intersystemic collaterals (%)	2 (20.0%)
- IRA stenting (%)	100%
- Time from angina attack onset to procedure of blood flow restoration in IRA (hours)	4.3+0.6
- Interval «door-to-balloon” (min)	37+11
- Mortality (%)	0%

coronary arteries. Especially it is related to the catheters adjusted for the work through the 7F guide catheters. Because of the above, in the vast majority of cases we were successful in performing thrombus extraction from the IRA without any serious clinical and angiographic complications. In two cases only we were not able to obtain macroscopic thrombus masses during thromboaspiration from the IRA.

The volume of thrombus masses removed using Eliminate™ catheter seemed to be somewhat higher than with the use of similar thrombus aspiration catheters developed by other companies (8,9). In no case the balloon predilatation before thrombus extraction was required; it confirms good elasticity, crossing, and deliverability of Eliminate™ catheter. In two cases when Eliminate™ catheter was advanced through the IRA, a small longitudinal dissection type B and D occurred; it did not affect the procedure of thrombus aspiration at all. Further, both cases were successfully stented. Absence of distal embolization or visible dislocation of thrombus and complete ST resolution in the majority of patients indicate the efficacy of the procedure in studied patients; it may equally be a merit of successful thrombus aspiration from the IRA combined with its stenting. Overall, the obtained results correspond to the general conception about thromboaspiration in AMI patients obtained in similar studies (4,8,10). Angiographic assessment of the results also did not reveal any serious inconsistencies with the literature data. In-hospital clinical course of disease was uneventful in all patients. No death or any serious complications including acute or subacute stent thrombosis were observed.

Therefore, the pilot study of thrombus removal from the infarct-related artery using the new aspiration catheter Eliminate™ (Terumo) involving ten patients with ST-elevated AMI and conducted at Moscow City Center of Interventional Cardioangiology has demonstrated that this catheter is every bit as good as the previous similar devices and has some advantages over them and may be recommended for wider implementation into clinical practice. However, definitive solution on its place and role in patients with ST-elevated AMI, necessitates further accumulation of the experience and thorough comparison with the results of other similar devices developed by other companies.

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Table 3.

Results of thrombus extraction and IRA stenting

Antegrade blood flow after thrombus extraction: TIMI 0/1: 2: 3: MBG 0/1: 2: 3:	 0 (0,0%) 1 (10,0%) 9 (90,0%) 1 (10,0%) 5 (50,0%) 4 (40,0%)
Balloon predilatation (%)	0 (0%)
Dissection after thrombus extraction (%)	2 (20,0%)
Distal embolization after thrombus extraction (%)	0 (0%)
Fast ST resolution after ETI <30%, (%) 30-70%, (%) >70%, (%)	 1 (10,0%) 2 (20,0%) 7 (70,0%)
Removal of macroscopic thrombus masses (%)	8 (80%)

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Stenting of the Left Anterior Descending Artery in Patients with Anterior Myocardial Infarction and Low Ejection Fraction within 12-24 Hours

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Treatment of the patients with myocardial infarction during the acute stage complicated by disorder of the left ventricle systolic function and reduction of its global contractility is considered one of the most complex problems of modern cardiology. Clinical picture of such infarction is characterized by increasing heart failure, cardiogenic shock, and pulmonary edema. In the majority of cases these patients are treated conservatively in hospitals without angiographic facilities. At discharge, clinical presentation is often dominated by signs of heart failure (HF) precluding from exercise tests which might cause angina attacks. If delayed coronary angiography (CAG) reveals single vessel lesions, the coronary artery bypass grafting (CABG) or stenting are not offered in most cases. It is related to domination of clinical manifestations of HF, absence of angina attacks, low EF according to the data of the left ventriculography (LV) and echocardiography (EchoCG), and the larger volume of non-viable myocardium revealed by scintigraphy.
Key words: *Stenting, low ejection fraction, myocardial infarction, mortality.*

Relevance: Treatment of the patients with myocardial infarction during the acute stage complicated by disorder of the left ventricle systolic function and reduction of its global contractility is considered one of the most complex problems of modern cardiology. Clinical picture of such infarction is characterized by increasing heart failure, cardiogenic shock, and pulmonary edema. In the majority of cases these patients are treated conservatively in hospitals without angiographic facilities. At discharge, clinical presentation is often dominated by signs of heart failure (HF) precluding from exercise tests which might cause angina attacks. If delayed coronary angiography (CAG) reveals single vessel lesions, the coronary artery bypass grafting (CABG) or stenting are not offered in most cases. It is related to domination of clinical manifestations of HF, absence of angina attacks, low EF according to the data of the left ventriculography (LV) and echocardiography (EchoCG), and the larger volume of non-viable myocardium revealed by scintigraphy.

Most of the patients are transferred to our clinic from other hospitals of the Sverdlovsk region, hence the time of admission can be more than 12 hours since the onset of myocardial infarction. To date there is no agreement concerning the reasonability of the stenting of the infarct-related artery after 12-24 hours since onset of myocardial infarction.

Methods and results: 104 patients have been included in this study; all of them had CAD, Q-wave anterior myocardial infarction and their EF on admission was less than 30%. The patients were divided into two groups depending on further management strategy: in Group 1 the stenting of the infarct-related left anterior descending artery (LAD) was performed within the first 24 hours after the admission (n=58), while patients from Group 2 received conservative treatment without stenting (n=46). All patients underwent EchoCG (on Day 1, 21, after 4-6 months), and myocardial scintigraphy (within the next few days after discharging from the hospital and in 4-6 months). Analysis of these investigations has been performed; the clinical presentation and mortality rate were estimated in both groups. Thus, in patients who underwent stenting in the period of myocardial remodeling, the volume of hibernating myocardium had reduced significantly (%) from 42±4.1 to 32±4.3 ($p<0.001$) and ejection fraction (EF) had increased (%) from 23±3.5 to 28±4.1 ($p=0.03$), in comparison with the group of conservative treatment, where the growth of non-viable myocardium was revealed

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from 25±4.2 to 34±3.9 (p<0.001). After stenting of the infarct-related artery mortality during the first year of follow-up is lower (19%) than in the group of conservative treatment (39%). By the end of the 3rd year mortality was 48% and 61% in groups 1 and 2, respectively, without statistically significant difference (p=0.26).

Conclusion. Stenting of the infarct-related LAD is an effective and justified method of treatment in patients with low EF (< 30%) even after 12-24 hours since the onset of anterior myocardial infarction.

ABBREVIATIONS

HF — heart failure
CAG — coronary angiography
CABG — coronary artery bypass grafting
LVG — left ventriculography
EchoCG — echocardiography
LAD — left anterior descending artery
LCxA — left circumflex artery
RCA — right coronary artery
EF — ejection fraction

INTRODUCTION

The influence of stenting on the course of the disease in patients with chronic CAD with EF less than 35% (1) and less than 40% (2) was evaluated in various studies. In most cases these patients had multivessel lesions and a history of previous large-focal myocardial infarction. Mortality in patients with low EF remains high. The lower is contractility, the higher is mortality rate in patients of both sexes in all age groups (3,4,5). The necessity of stenting of the infarct-related artery during the first 6 hours since the onset of myocardial infarction is indisputable. Thrombolysis and stenting of the coronary artery performed later than 12 hours after non-complicated infarction are considered as inappropriate. However, thrombolytic therapy or angioplasty of the infarct-related artery are considered to be justified when cardiogenic shock occurs (6). To date cardiologists don't have a clear position on the use of interventional strategy in patients with myocardial infarction complicated by global reduction of the left ventricle contractility and EF lower than 30% admitted later than 12 hours after the onset of the disease. In most cases in the presence of complications (pulmonary edema, cardiogenic shock) these patients are acknowledged as non-transportable and are left for treatment in local hospitals.

Most of our patients are transferred from other clinics of the Sverdlovsk region. For this reason the time between the onset of the symptoms and the admission can exceed 12 hours (mean, 17±3.5 hours). Our study has begun in 2004 and is still going on, but only patients with follow-up period of 2–3 years were analyzed for this article.

MATERIAL AND METHODS

104 patients with CAD, anterior myocardial infarction and EF less than 30% who were admitted to the emergency cardiology department within the period since 2004 till 2009 are included in this study. At admission all patients received low molecular weight heparin (fraxiparin 1 mg/kg 2 times subcutaneously or enoxaparin 1 mg/kg 2 times a day subcutaneously), Thrombo ASS 100 mg, clopidogrel 300 mg as a loading dose, then 75 mg, statins, prolonged nitrates, β-blockers, ACE inhibitors. In complicated cases an additional therapy was conducted as indicated: nitrates, vasoconstrictors (most often dopamine) intravenously, diuretics. The dosage of ACE inhibitors and β-blockers was adjusted depending on arterial pressure (AP) and heart rate (HR) indices. After the discharge from the hospital patients of both groups received similar treatment (Thrombo ASS 100 mg, clopidogrel 75 mg). Besides, β-blockers, statins, ACE inhibitors, diuretics, nitrates were prescribed; the doses were selected individually depending on the tolerability and the BP level.

The main inclusion criteria were:

1. Ejection fraction less than 30%.according to the data of EchoCG and (or) the left ventriculography
2. Anterior localization of myocardial infarction.
3. The infarct-related left anterior descending artery (LAD) with occlusive thrombosis, according to the CAG data.
4. The patients admitted to the hospital with diagnosed CAD (anterior myocardial infarction with ST elevation) within 12–24 hours.
5. No thrombolysis during the first 24 hours.
6. An obligatory control scintigraphy and EchoCG in 4–6 months.
7. Intake of clopidogrel at a daily dose of 75 mg for 9–12 months.

The patients were divided into 2 groups:

Group 1 (group of study, n=58): patients who underwent successful stenting of the infarct-related LAD on the first day of their admission.

Group 2 (controls, n=46): patients with conservative management strategy. In 2–3 weeks a follow-up diagnostic CAG was performed.

All patients from Group 1 underwent CAG with stenting using the angiographic units Innova 3100 (General Electric) and Integris Allura (Philips). At that, the stents Driver (Medtronic), Pro-Kinetic (Biotronic), Presillion (Cordis) were implanted. The length of stents was adjusted considering the length of stenosis after the preliminary passage of the thrombosed occlusion and angioplasty. In 5 cases Diver CE (Invates) thrombextractor was used. At that, the stent covered the whole stenosed segment and the optimal result was achieved: there was no residual stenosis, dissection of the intima, the blood flow TIMI 2-3 was restored.

As evident from Table 1, no differences in age, gender, by presence of arterial hypertension,

smoking, cholesterol level, history of myocardial infarction, and pulmonary edema were revealed. Statistically significant difference (p=0.032) was revealed only in patients with 1-2 degree cardiogenic shock. These patients more often underwent stenting within the first 24 hours after the admission in comparison with the patients with stable hemodynamics.

All patients underwent EchoCG using ultrasound units Vivid 7 pro and Vivid 4D (General Electric, USA) by 3S and 4MS sector transducers during the first days of the hospital stay and before discharge on Day 18-24. Control EchoCG was performed in 4–6 months.

Scintigraphy was performed on Day 18-24 after MI immediately after discharge from the hospital in the settings of radiological laboratory of the Regional Oncology Dispensary (Ekaterinburg). Control scintigraphy was performed in 4-6 months. Myocardial scintigraphy was performed using the Tc 99m-labeled RP (radiopharmaceuticals) Technetril (Diamed, Russia) from GT-2M generators. Investigation was carried out in the gamma-ray Solus chamber — Epic (ADAS), matrix 64X64X16, by 2 detectors; 32 projections were obtained in Non Circular ECT mode.

The significance of differences in both groups was estimated using Student t-test and z-test. Mathematical processing of results was performed using Primer of Biostatistics, Version 4.03 by Stanton A. Glantz software.

RESULTS AND DISCUSSION

As evident from the Table 2, the indices of LV EF were nor significantly different in both groups on Day 1 (23±3.5 and 24±3.3 in Groups 1 and 2, respectively) and before discharge on Day 18-24 (24±3.7 and 25±3.8 in Groups 1 and 2, respectively) (p>0.05). There were no significant differences (p>0.05) also in the number of revealed acute aneurysms. The further EF analysis conducted in 4–6 months revealed significantly (p=0.016) higher increase of myocardial contractility in the group of stenting (28±4.1) as compared with the group of conservative management (26±4.2). When comparing contractility in Group 1 during the period of myocardial remodeling within 4–6 months, the EF increased from 23±3.5 to 28±4.1 (p<0.001). In Group 2 the EF also increased significantlyfrom 24±3.3 to 26±4.2 (p=0.013) within 3-6 months .

The tissue Dopplerography (TVI) was performed in 35 patients from both groups. It revealed abrupt reduction of the longitudinal systolic speed (S) of the mitral fibrous ring up to 3–6 cm/sec (normal value 8 cm/sec) that significantly correlated with reduction of EF < 30%, abrupt reduction of the early longitudinal diastolic speed (e) up to 2–3 cm/sec, the late longitudinal diastolic speed (a) up to 3 cm/

Table 1.

Baseline clinical characteristics

Parameters	Group 1 n=58	Group 2 n=46	P
Age	52,9±5,4	54,1±5,2	0,255
Male gender	46 (79,3%)	38 (82,6%)	0,862
Arterial hypertension	25 (43,1%)	23 (50,0%)	0,615
Smoking	34 (58,6%)	32 (69,6%)	0,341
Normal level of TC (up to 5.2 mmol/L)	22 (37,9%)	25 (54,3%)	0,141
Elevated level of TC (from 5.2 up to 6.2 mmol/L)	34 (58,6%)	21 (45,6%)	0,262
High level of TC (from 6.2 up to 12 mmol/L)	2 (3,4%)	4 (8,7%)	0,466
History of myocardial infarction without Q-wave	11 (19,0%)	10 (21,7%)	0,925
LV EF, %, according to the ventriculography	18,4±2,8	18,8±2,4	0,443
Cardiogenic shock on admission, 1-2 degree	32 (55,1%)	15 (32,6%)	0,032
Pulmonary edema on admission	5 (8,6%)	2 (4,3%)	0,634
HF 2 by NYHA at discharge	39 (67,2%)	32 (69,6%)	0,961
HF 3 by NYHA at discharge	19 (32,8%)	14 (30,4%)	0,961

sec. These parameters suggest severe myocardial damage. The absence of improvement in parameters in 4-6 months confirms the myocardial necrosis (of the longitudinal and circulatory fibers) and formation of an aneurysm. Diastolic speed (a) ≤ 5 cm/sec is a significant predictor of mortality (7, 8).

Currently, scintigraphy is one of the most sensitive and specific methods for the detection of non-viable hibernating myocardium (9, 10).

As evident from the Table 3, when comparing scintigraphy data within groups the following pattern was revealed:

In patients of Group 1 who underwent revascularization, in 4–6 months the volume of hibernating myocardium reduced from 42±4.1 to 32±4.3 (p<0.001). Some reduction of non-viable myocardium volume from 26±3.6 to 22±3.8 (p=0.004) in Group 1, apparently, is related to the inaccuracy of the method (hibernating myocardium was partly considered as non-viable). A small but statistically significant increase of EF from 24±3.7 to 28±4.1 was observed.

In conservatively treated patients from Group 2 the volume of hibernating myocardium increased insignificantly from 44±3.9 to 45±4.2 (p=0.24). Non-viable myocardium percentage increased from 25±4.2 to 34±3.9 (p=0.000). At that, EF in 4-6 months remained the same, from 25±3.8 to 26±4.2 (p=0.234).

As evident from the Table 4, there were no significant differences in volume of non-viable myocardium at discharge (26±3.6 and 25±4.2 in Groups 1 and 2, respectively) (p=0.194). The volume of hibernating myocardium in Groups 1 (42±4.1) and 2 (43±3.9) groups also was not statistically different (p=0.334). Control scintigraphy performed in 4-6 months revealed significantly lower volume of non-viable myocardium (22±3.8) in patients with revascularization of myocardium comparing to the group of patients with conservative management (34±3.9) (p<0.001). In 4–6 moths the patients from Group 1 also had significantly lower volume of hibernating myocardium (32±4.3) than the patients from Group 2 (45±4.2) (p<0.001).

Clinical condition of patients in one year is shown in Table 5.

When evaluating the quality of life in patients of both groups it should be noted that an increase of exercise tolerance (ET) along with reduced severity of heart failure (HF) related functional limitations was observed in Group 1. The passage of 27% of patients from the IV into II and III NYHA class, the increase of motion activity revealed manifestation of coronary insufficiency (angina). The absence of ET increase in patients of the control group precluded their passage to the lower NYHA class and the extension of the volume of physical exercise that probably would reveal the symptoms of coronary insufficiency. Angina in Group 2 was revealed only in 10% of patients (p=0.05).

Control CAG was performed in 1 year in all patients from Group 1. Restenosis was revealed in 21 patients

Table 2.

EchoCG data

	Group 1 N=58	Group 2 N=46	P
EF EchoCG Day 1 (%)	23±3,5	24±3,3	0,066
EF EchoCG Day 18-24 (%)	24±3,7	25±3,8	0,327
EF EchoCG in 4-6 months (%)	28±4,1	26±4,2	0.016
The presence of aneurysm (cases)	32 (55%)	24 (52%)	0,552
Including the saccular aneurysm (cases)	3 (5%)	4 (8%)	0,827

Table 3.

Myocardial scintigraphy (comparative characteristics within the groups)

	Group 1 (n=58) (after discharge)	Group 1 (n= 58) (in 4-6 months)	P
Non-viable myocardium (%)	26±3.6	24±3.8	0,004
Hibernating myocardium (%)	42±4.1	32±4.3	<0,001
	Group 2 (n=46) (after discharge)	Group 2 (n=46) (in 4-6 months)	
Non-viable myocardium (%)	25±4.2	34±3.9	<0,001
Hibernating myocardium (%)	44±3.9	45±4.2	0,240

(36%). Hemodynamically significant stenosis in other territories developed in 4 patients (1 case RCA, 2 cases LCA), in 3 cases LAD restenosis involving the left main coronary artery was revealed).

Clinical signs of exertional angina were seen in 16 patients with restenosis (27%), in 13 patients (22%) clinical manifestations of HF increased, with reduced exercise tolerance and increased NYHA class, which required adjustment of conservative treatment.

The further management of patients with restenosis and revealed lesions of the coronary arteries in other territories was as follows:

– In-stent angioplasty (12 patients).

– Stent-in-stent placement (2 patients).

– CABG for ostial stenosis involving the left main coronary artery.(3 patients). In one case simultaneous aneurysmectomy was performed .

– Stenting of other coronary arteries (4 patients; among them RCA was stented by two stents in 1 case, and LCxA – in 2 cases).

Clinical presentation in patients of Group 2 was different in one year. Increased breathlessness with increased NYHA class and reduced exercise tolerance was revealed in 19 patients (41%), which is significantly higher comparing to the patients of Group 1.

Angina recurrence was noted in 5 patients (10%) , which is significantly lower comparing to the 1st group – 16 cases (27%). CAG was performed in 5 patients from this group with clinical manifestations of angina. According its results, the patients underwent:

– In-stent angioplasty (3 patients),

– Stenting of the RCA due to newly discovered hemodynamically significant (80%) stenosis (1 patient),

Table 4.

Myocardial scintigraphy (comparative characteristics between the groups)

	Group 1 n=58 Day 21	Group 2 n=46 in 4–6 months	P
Day 21-24			
Non-viable myocardium (%)	26±3.6	25±4.2	0.194
Hibernating myocardium (%)	42±4.1	44±3.9	0.334
EF	24±3,7	25±3,8	0.179
In 4-6 months			
Non-viable myocardium (%)	24±3.8	34±3.9	34±3.9
Hibernating myocardium (%)	32±4.3	45±4.2	45±4.2
EF	28±4,1	26±4,2	26±4,2

Table 5.

Clinical presentation in 1 year

	Group 1 n=58	Group 2 N=46	P
Angina	16 (27%)	5 (10%)	0.054
Shortness of breath HF with increased NYHA class	13 (22%)	20 (43%)	0.037

Table 6.

Mortality evaluation

	Group 1 (n=58)	Group 2 (n=46)	P
1 year	11 (19%)	18 (39%)	0,041
2 years	21 (36%)	24 (52%)	0,15
3 years	26 (48%)	28 (61%)	0,26

– CABG due to ostial stenosis involving the left main coronary artery (combined with aneurysmectomy) (1 patient).

In patients with low EF and symptoms of heart failure the mortality rate by the end of the 1st year reaches 30% (11).

The analysis of 3-year mortality revealed the following pattern. During the 3-year follow-up period the mortality in Group 1 remained lower comparing to Group 2. However statistically significant difference was revealed only at the end of the first year of follow-up: 19% and 39%, respectively, in groups 1 and 2 (p=0.041). By the third year the mortality in two groups was 48% (Group 1) and 61% (Group 2). Despite of the significant percentage difference, it turned out to be statistically insignificant (p=0.26) that might be explained by small numbers.

CONCLUSIONS

1. Stenting is an effective method for the treatment of myocardial infarction, leading to the improvement of myocardial contractility in the long-term in patients with single vessel lesion and EF < 30%, even if myocardial revascularization was performed later than 12-24 hours since the onset of myocardial infarction.

2. Improvement of myocardial contractility is observed during the long-term period (4–6 months) provided myocardial revascularization was performed by the method of stenting of the infarct-related artery.

3. Clinical condition of patients after myocardial revascularization is better than ini those receiving drug treatment.

4. Mortality in the group of patients who underwent stenting of the infarct-related coronary artery within the first follow-up year is lower than in the control group. By the end of the 3rd year of follow-up no significant difference in mortality between two groups was revealed.

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Stent Assistance in Acute Ischemic Stroke: Successful Recanalization

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We present our experience with successful recanalization in acute ischemic stroke with the help of stent assistance in 7 patients with neurologic deficiency scored from 14 to 24. Occlusion involved the anterior part of circle of Willis in 5 cases and the vertebrobasilar territory in 2 cases. Successful recanalization was performed in 6 cases using the stent assistance. During the postoperative period 2 patients had symptomatic hemorrhagic transformation in the form of parenchymatous hematoma of the 2nd type. Brain edema was also observed in two cases. Stent assistance is a rather effective method of blood flow restoration in acute ischemic stroke; however, a strict patient selection is required for a successful procedure.
Key words: *ischemic stroke, stent assistance, intracranial stent, thrombus extraction*

Objective: To present our experience of successful recanalization in acute ischemic stroke with the help of stent assistance.

Material and methods: Intracranial Solitaire stents were used in seven patients with acute ischemic stroke for restoration of the blood flow in intracerebral arteries. Mean age of patients was 64 years. The score of neurologic deficiency ranged from 14 to 24. Five patients had occlusions in the anterior part of circle of Willis, 2 — in the vertebrobasilar territory

Results: After the stent assistance successful recanalization was achieved in 6 patients. Balloon-expandable stent was inserted to one patient after three unsuccessful attempts of thrombus extraction. Four patients required an additional administration of thrombolytic agent r-tPA (Actilyse, Boehringer Ingelheim) in a dose of 2–10 mg due to residual thrombus or development of distal embolism. During the postoperative period 2 patients had symptomatic hemorrhagic transformation in the form of type 2 parenchymatous hematoma. Brain edema was also observed in two cases.

Conclusions: Initial experience with stent assistance in acute ischemic stroke demonstrated rather high degree of blood flow restoration. In order to improve the clinical effectiveness of the method and to lower the risk of postoperative complications a strict patient selection is required considering intervention potential risk and effectiveness.

Ischemic stroke is the third leading cause of death among the adult population in the developed nations (1). In the Russian Federation the stroke causes 175 deaths per 100 000 population (2). Intravenous thrombolytic therapy (IV TLT) is effective in 26-30% of cases in this pathology. However, if the stroke persists for over 3 hours or a major vessel is occluded, the effectiveness of IV TLT remains low, and reocclusion rate reaches 34% (3). According to the data of the PROACT II study (Pro-Urokinase for Acute Cerebral Thromboembolism), the usage of intraarterial thrombolytic therapy (IA TLT) allows to increase the effectiveness of blood flow restoration in intracerebral arteries up to 66%.

After the introduction of self-expanding intracerebral stents for treatment of intracranial stenoses and brain aneurysms into the clinical practice, many authors have studied the possibility of their use in acute ischemic stroke (5,6). The method was called “stent assistance”.

The objective of this work was to present our initial experience with successful recanalization in patients with acute ischemic stroke using stent assistance.

Material and methods: From December 2006 through February 2011, endovascular methods of recanalization were used in 44 patients with acute ischemic stroke. Intracranial Solitaire stents (Ev3) were used in seven patients for restoration of the blood flow. Mean age of patients was 64 years (5 men, 2 women). Neurologic deficiency score ranged from 14 to 24. A mean time since the onset of the disease was 310 minutes. Occlusions in the anterior part of the circle of Willis were observed in five patients (M1, M2 segments of the middle cerebral artery [MCA]), occlusions in the vertebrobasilar territory (the main artery) — in two patients.

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Preoperative diagnostic algorithm included: X-ray computed tomography (X-ray CT), magnetic resonance imaging (MRI), transcranial dopplerography, evaluation of the clinical and biochemical blood parameters.

The operations were performed under the general endotracheal anesthesia using angiographic machines Advantx or Innova 3100 (GE). First of all, for the evaluiation of the level of occlusion, the state of the blood flow in other territories and degree of the development of collateral blood flow, bilateral angiography of the branches of internal carotid and vertebral arteries was performed. After that, the diagnostic catheter was replaced by the guide catheter Envoy (Cordis) 6F. A microcatheter Rebar (Ev3) was placed beyond the occlusion zone and its position was confirmed by the selective injection of the contrast medium. The stent was advanced through the microcatheter and expanded at the level of occlusion. If stent implantation and expansion gave no effect, it was removed (thrombus extraction by expanded stent removal). Throughout the stent removal a simultaneous continuous aspiration from the guide catheter was performed. If the blood flow failed to restore after the first thrombus extraction, the procedure was repeated. In one patient after three unsuccessful attempts of thrombus extraction a balloon-expandable stent Presillion (Cordis) was inserted into the M1 segment of the MCA. Angiographic effect of the blood flow restoration was evaluated using the Trombolysis in Cerebral Infarction (TICI) scale (Table 1).

Results. Successful recanalization (TICI 2a-3) was achieved in 6 patients. 4 patients required additional administration of a thrombolytic agent, tissue plasminogen activator (Actilyse, Boehringer Ingelheim) at a dose of 2–10 mg due to residual thrombus or development of distal embolism. No complications associated with the usage of Solitaire stent were observed.

Discussion: Method of IA TLT in acute ischemic stroke was first described by Zeumer et al. in 1983 (7). The possibility to create high concentration of thrombolytic agent in the area of thrombus is a certain advantage of this method compared to the IV TLT. It is logical to assume that simultaneous mechanical thrombus destruction enhances the area of thrombolytic agent's action and its impact. PROACT I (Pro-Urokinase for Acute Cerebral Thromboembolism) was the first double-blind randomized study to evaluate an effectiveness of IA TLT usage in patients with MCA occlusion and it was conducted in 1994-1995. The study revealed MCA recanalization rate of 58%. The second randomized study (PROACT II) demonstrated the effectiveness of blood flow restoration in 66% of patients; herewith, recanalization rate in the control group was 18%. However, in case of a thrombus of athero-embologenic origin the effectiveness of IA TLT is low (8).

The use of stents for the blood flow restoration in acute ischemic stroke allows us to restore blood flow quickly, as there is no need to wait for the thrombolytic agent to start affecting the thrombus. No need for thrombolytic agents or their use in minimal dose, theoretically, may reduce the risk of hemorrhagic complications. Self-expanding intracerebral stents are of interest. Their use, according to Nogueira et al. (9), allows to restore the blood flow in 79% of patients with acute thrombosis of the intracerebral arteries.

We have used an intracranial self-expanding Solitaire stent (EV3). This type of stent allows to perform the assistance in three ways.

The first one is a “temporary stent-assistance” or the “temporary shunt”. The blood flow restoration occurs due to thrombus masses “pressing” to the artery walls by the stent and the formation of physiological conditions for thrombus lysing. Additional administration of IIb/IIIa receptor inhibitors and thrombolytic agents can speed up this process and prevent the recurrent thrombosis (Figure 1). Blood flow restoration in our practice always started with performing the “temporary shunt”. However, it was effective only in two patients, even though Monofram, the inhibitor of IIb/IIIa receptors, was administered.

The second method is thrombus extraction (Figure 2), especially as the stent which was used

Table 1.

Trombolysis in Cerebral Infarction (TICI) Scale

Degree	Angiographic characteristics of blood flow restoration degree
TICI 0	No blood flow restoration
TICI 1	Blood flow restoration beyond the initial occlusion, limited filling of distal branches
TICI 2A	Blood flow restoration with incomplete or slowed blood flow in less than 50% of the middle cerebral artery basin
TICI 2B	Blood flow restoration with incomplete or slowed blood flow in more than 50% of the middle cerebral artery basin
TICI 3	Complete blood flow restoration with filling of all distal branches of middle cerebral artery including M3 and M4 segments

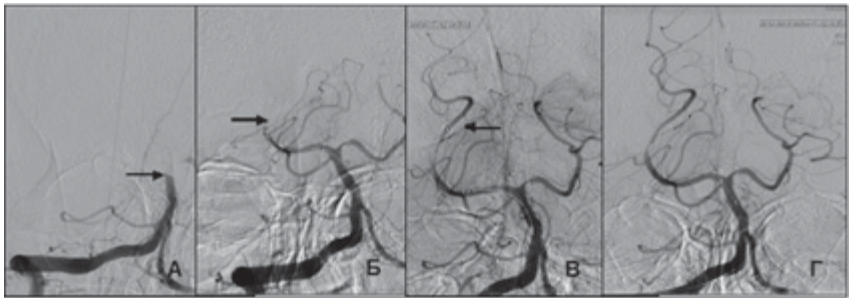

Fig. 1

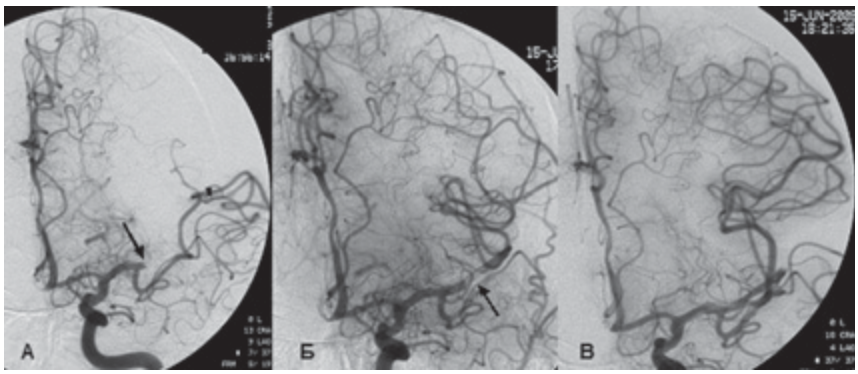

Fig. 2

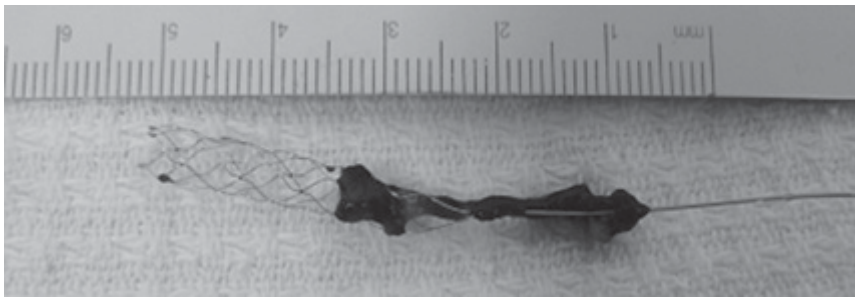

Fig. 3

in our experience has CE mark for thrombectomy performance. We performed thrombectomy in 5 patients. In three cases we saw thrombus masses bound with stent cells (Figure 3). As it was shown in the animal study, thrombus extraction with intracranial Solitaire stent did not affect the endothelium (10). However, if thrombosis was associated with an underlying stenotic lesion of an intracerebral artery, there is a potential risk of endothelium desquamation with serious complications.

Figure 1.

A. Occlusion of the main artery (indicated by an arrow).

B. Blood flow restoration in the main artery after installing the stent as a "temporary shunt" and additional administering 25 mg of Monofram. Embolism in the distal parts of the posterior cerebral artery is visualized (indicated by an arrow).

C. Blood flow restoration in the distal parts of the posterior cerebral artery after installing the stent as a "temporary shunt" (indicated by an arrow) and additional selective intraarterial administering 2 mg of Actilyse.

D. Blood flow restoration in the vertebrobasilar territory after completing the surgery.

Figure 2.

A. Occlusion of M2 segment of the MCA (indicated by an arrow).

B. Blood flow restoration with angiographic signs of parietal thrombus increasing the risk of reocclusion (indicated by an arrow).

C. Complete blood flow restoration after performing IA TLT (Actilyse 6 mg).

Figure 3.

A thrombus extracted during thrombus extraction procedure

The third method is stenting of the occluding segment. The radial force of the Solitaire stent is 0.011 N/mm that is enough for stenting the intracerebral artery if an occlusion is associated with an underlying stenotic lesion. However, the need for simultaneous administration of saturating doses of the double antiaggregant therapy, inhibitors of IIb/IIIa receptors, and heparin to the patients is a disadvantage of intracranial artery stenting in acute ischemic stroke. The use of such a «cocktail» could potentially increase the risk of hemorrhagic complications. Due to ineffectiveness of "temporary shunt" and thrombus extraction, the stenting of M1 segment of the MCA was performed to one of our patients. Thus, the temporary stent assistance was performed in 2 of 7 patients, the temporary stent assistance and thrombus extraction was used in 4, and in 1 patient the temporary stent assistance, thrombus extraction, and stenting were applied.

The effectiveness of the intracranial Solitaire stent in 22 patients had been demonstrated by Roth et al. (11). Successful blood flow restoration was observed in 90.9%. At that, a complete recanalization (TICI 3) was registered in 12 of 22 patients and partial recanalization (TICI 2b) – in 8 of 22 patients. Authors noted that hemorrhagic transformations in postoperative period were observed in 13.6% of patients. We did not observe any complications associated with the usage of this device. During the postoperative period two patients had hemorrhagic transformations in the form of parenchymatous hematoma of the 2nd type, and two had significant brain edema. These complications are related to a significant reperfusion brain injury. In order to lower the risk of such complications, the endovascular recanalization method should be used in strictly selected patients. The time from the disease onset,

the score of neurological deficiency, the volume of ischemia zone assessed by X-ray CT or MRI should be selection criteria (12).

Conclusions: Our initial experience with the use of stent assistance in acute ischemic stroke demonstrated rather high degree of blood flow restoration. In order to improve its clinical effectiveness and to lower the risk of postoperative complications, a strict patient selection is required with precise weighing of potential risk and effectiveness of intervention.

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The Influence of the Viable Myocardium on Parameters of Left Ventricle Remodeling after the Acute Myocardial Infarction

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The influence of the viable myocardium on parameters of LV remodeling after the AMI has been studied. 93 patients diagnosed with ST-elevated ACS were enrolled in this study. All patients underwent stress echocardiography with dobutamine. Electrocardiography and coronary angiography were performed to all patients 1 month and 6 months after the coronary angioplasty. Based on the results of stress echocardiography with dobutamine the patients were divided into two groups: with (group I) and without (group II) viable zones. These two groups were compared by the following parameters: left ventricular ejection fraction (LV EF), regional contractility impairment index (RCII), end-systolic volume index (ESVI), end-diastolic volume index (EDVI). Thus, the absence of residual viability in the infarction zone distinguishes patients with progressive LV dilatation after reperfusion from those with normal geometry of the left ventricle.
Key words: *viable myocardium, remodeling, acute myocardial infarction, echocardiography*

Our objective was to study the influence of viable myocardium on the remodeling of left ventricle (LV) after acute myocardial infarction (AMI).

Methods of study: Two-dimensional echocardiography (within 24 hours after the onset of the AMI) and stress echocardiography with small doses of dobutamine (in 7–8 days after the AMI) were performed in 93 patients diagnosed with ST-elevated acute coronary syndrome (ACS + ST) and successful primary coronary angioplasty. All patients underwent two-dimensional echocardiography and coronary angiography 1 month and 6 months after the coronary angioplasty. Based on the results of stress echocardiography with dobutamine, patients were divided into two groups: with (n=48; group I) and without (n=45; group II) viable peri-infarction areas.

Results of the study: in 1 and 6 months there were no differences between two groups in minimal diameter of lesion and in lumen of infarct-related artery. Patients of Group II had significantly higher end-diastolic (76±18 vs. 53±14 mL/m2; $p<0.005$) and end-systolic (42±17 vs. 22±11 mL/m2; $p<0.005$) indices in 6 months after AMI compared to the patients of Group I. There was a significant inverse correlation between the extent of infracted area viability and percent changes in the end-diastolic volume at 6 months ($r = -0.66$; $P<0.00001$). The extent of infracted area viability ad was the most powerful independent predictor of late left ventricle dilatation.

Conclusion: After reperfusion in AMI, the degree of left ventricular dilatation is inversely related to the residual myocardial viability in the infarcted area. Thus, the absence of residual viability in the infarcted area distinguishes patients with progressing left ventricle dilatation after myocardial reperfusion from those with normal geometry of the left ventricle.

ABBREVIATIONS

RCII — regional contractility impairment index
ESVI — end-systolic volume index
EDVI — end-diastolic volume index
LV — left ventricle
AMI — acute myocardial infarction
AMI + ST — acute coronary syndrome with ST-elevation
TBA — transluminal balloon angioplasty
LV EF — left ventricular ejection fraction
EchoCG — echocardiography

Remodeling of the ventricles after acute myocardial infarction precedes development of expressed heart failure and is an important predictor of mortality (1,2).

Previous investigations demonstrated that the size of the infracted area (3,4) and chronic occlusion of the infarct-related artery (5,6,7) are the two main factors contributing to remodeling of ventricles. However, recent investigations assume that regardless of the

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myocardium preservation, in cases with large volume of necrosis the preservation of the blood flow in the infracted area cannot prevent remodeling (4). On the other hand, at comparable sizes of infarction the volume of transmural necrosis seems to be the main factor of the expansion of the infarcted area (8,9,10,11). Q-wave myocardial infarctions, only partly affecting the whole myocardium depth rarely expand; that is why the degree of expansion is inversely related to the thickness of preserved myocardium within the infarction zone (9). Besides, recent experimental observations revealed that positive influence of reperfusion on the expansion of the infarcted area is related to preservation of little islets of still viable myocytes mainly located in the subepicardium of the scar (12).

Relationships between residual viability of myocardium after reperfusion of myocardial infarction zone and remodeling of ventricles in post-MI patients have not yet been completely studied. In general, it is considered that renewal of regional contractile function indicates clinically significant viability. However, although it is known that restoration of the functionally "sleeping" myocardium is the best clinical result, the presence of non-ischemic viable myocardium can have other advantages. The presence of viable myocardium in the outer layers of the ventricles' wall can actually contribute to preservation of the form and size of the left ventricle, preventing its remodeling (13). Thus, we proposed a hypothesis that the presence of residual viability will favorably influence the ventricle remodeling after the acute myocardial infarction, and that successive changes of the left ventricle size can be closely related to the viability of myocardium in the infarcted area. In order to check this hypothesis we conducted a prospective study on the patients with AMI who underwent primary PCI. To avoid the mixed influence of freely passable infarct-related artery and residual stenosis on further changes of left ventricle size, only those patients were enrolled in the study whose antegrade flow was completely preserved without significant residual stenosis. Echocardiography with small doses of dobutamine was used to determine the extent of infarction zone viability, because the extent of contractile reserve revealed by dobutamine provides an excellent assessment of myocardial viability extent when determining the borders of myocardial necrosis and postischemic myocardial dysfunction without residual stenosis limiting the blood flow (14,15).

Objective of the study: To study the influence of viable myocardium on the parameters of LV remodeling after the AMI.

MATERIAL AND METHODS

93 patients hospitalized in the Cardiac Intensive care Unit of the Republican Scientific Centre of Emergency Care and diagnosed with ST-elevation ACS were enrolled in this study. Mean age of patients was 53.9±9.3 years. Time from the pain attack onset to admission to the clinic was 8.3±3.7 hours. The patients with diabetes mellitus, with previous myocardial infarction or cerebral vascular accident, LV aneurism, atrial flutter, left bundle branch block, significant organ insufficiency and cardiomyopathies were excluded from the study.

All patients underwent two-dimensional echocardiography within 24 hours after hospitalization. On Day 7–8 of treatment stress echocardiography with dobutamine (stress-EchoCG) was performed in order to determine viable myocardium. Under continuous control of ECG and two-dimensional echocardiography, intravenous administration of dobutamine (5 mg/kg body weight per minute) was carried out for 3 minutes. Then the dose was increased up to 10 mg/kg per minute (for 3 more minutes). Criteria for stopping dobutamine administration were hypotension, anginal chest pain, significant ventricular arrhythmias.

All patients underwent two-dimensional EchoCG and coronary angiography in 1 month and 6 months after primary coronary angioplasty.

EchoCG investigations were performed using Siemens Sonoline Omnia ultrasound apparatus (Germany) with 2–4 MHz multi-frequency sensor. EchoECG was performed in B and M modes with patient position on the left side in accordance with American Society of Echocardiography (ASE) guidelines (7,3). The volume of the left ventricle was measured using modified Simpson algorithm from orthogonal apical projections of the long axis. Volume indices were obtained by dividing the volume by body surface area at each time point. Ejection fraction was obtained using the following formula: (end-diastolic volume - end-systolic volume / end-diastolic volume.) Left ventricle was divided into 16 segments (17). Wall movement score was determined for each segment: 1 (normal), 2 (hypokinesia), 3 (akinesia) or 4 (dyskinesia). Regional contractility impairment index (RCII) was calculated for every step of EchoCG with dobutamine. During assessment of regional wall contractility, attention was also paid to the systolic thickening of every segment. Anterior and interior infarction zones were built, and wall movement index was obtained in the whole wall and in the infarction zone for every patient at every step of echocardiography with dobutamine (18).

Selective coronary angiography and transluminal balloon angioplasty followed by coronary stenting were performed in the cath. lab of the Department of Angiography equipped with radioangiographic unit (Integris Allura FD 20, Philips). ECG monitoring was performed using Datex-Ohmeda (Finland) and Philips IntelliVue MP20 (Netherlands) devices.

Statistical processing of the data obtained during this study was performed using personal computer with EXCEL 7.0 package for Windows.

Correlation and regression analysis methods were used in the study. All values in the tables are presented as an arithmetic mean for the set of variate values ± standard deviation. Alternative hypothesis with significance level no less than 95% (p=0.05) was used

as a statistic hypothesis. In order to check hypothesis about equality of means the paired and two-sample Student's t-test were used.

Based on the presence or absence of myocardial viable zones patients were divided into two groups. Contractile reserve was revealed in 48 patients when administering dobutamine, and they were included into the group of viable myocardium (Group I). 45 patients in whom viable myocardium was not revealed formed Group II. Characteristics of both groups are shown in Table 1. There were no statistically significant differences between these two groups regarding the age, sex, assumed lesion, time from the disease onset till reperfusion, localization of infarction, angiographic degree of collateral development, and the number of affected vessels and incidence of coronary risk factors.

In most of the patients the infarct-related vessel was completely or almost closed (TIMI 0 or 1). After the primary coronary angioplasty, the optimal angiographic result was achieved in all patients (residual stenosis <30%, TIMI 3). The infarct-related artery

Table 1.

Main clinical and angiographic characteristics of both groups

	Group 1 (n=48)	Group 2 (n=45)
Age, years	59±11	62±13
Males, %	73 (35)	80 (36)
Diabetes mellitus, %	6 (3)	11% (5)
Arterial hypertension, %	29 (14)	47 (21)
Hyperlipidemia, %	33 (16)	24 (11)
Time of reperfusion, minutes	171±76	167±72
Anterior myocardial infarction, %	56 (27)	53 (24)
Ejection fraction, %	45±11	44±10
LV ESVI (mL/m^2)	35±14	36±9
LV EDVI (mL/m^2)	63±18	64±13
Infarct-related arteries, %		
The right interventricular branch	56 (27)	53 (24)
Right coronary artery	40 (19)	42 (19)
Circumflex branch	4 (2)	5 (2)
Bypasses, %	6 (3)	16 (7)
Multivascular lesions	38 (18)	56 (25)

Table 2.

Angiographic control of the two studied groups

	Group 1 (n=48)	Group 2 (n=45)	Significance, p
Passability rate, %			
After the TBA	100	100	.....
In 1 month	98 (1)	100	0,51
In 6 months	98 (1)	96 (2)	0,48
Restenosis (≥50%), %			
In 1 month	4 (2)	2 (1)	0,53
In 6 months	23 (11)	22 (10)	0,57
Minimal diameter of the coronary artery lumen, mm			
Baseline	0,10±0,23	0,07±0,29	0,58
After TBA	2,99±0,54	2,90±0,56	0,43
In 1 month	2,76±0,79	2,90±0,63	0,35
In 6 months	2,38±0,92	2,22±0,99	0,42

TBA — transluminal balloon angioplasty. Values in the round brackets — the number of patients

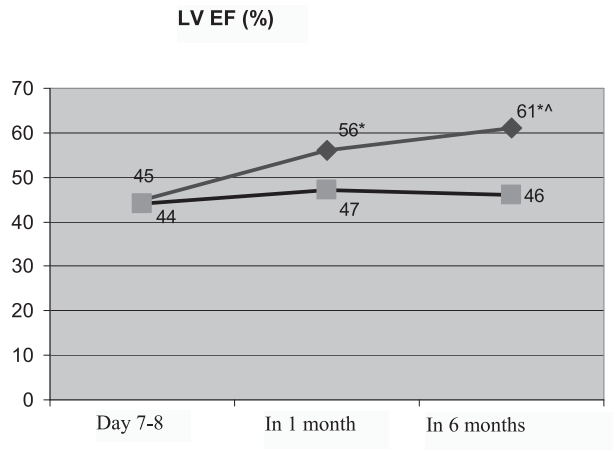

*Fig. 1. LV EF in AMI patients with (◆) and without (■) viable infarction zone; *p<0.05 compared to baseline; ^p<0.05 between the groups*

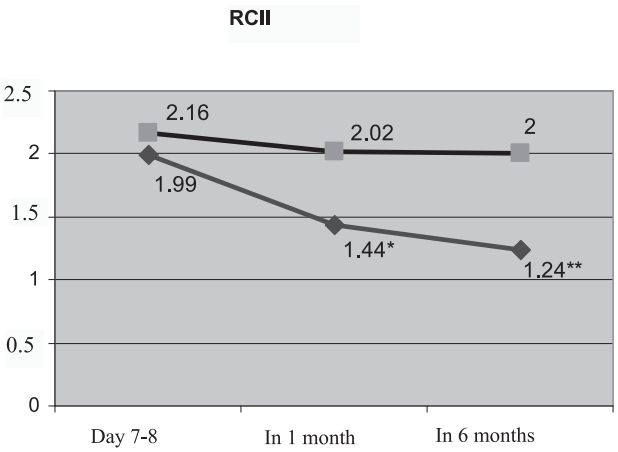

*Figure 2. Change in RCII in AMI patients with (◆) and without (■) viable infarction zone; *p<0.05 compared to baseline; **p<0.05 between the groups*

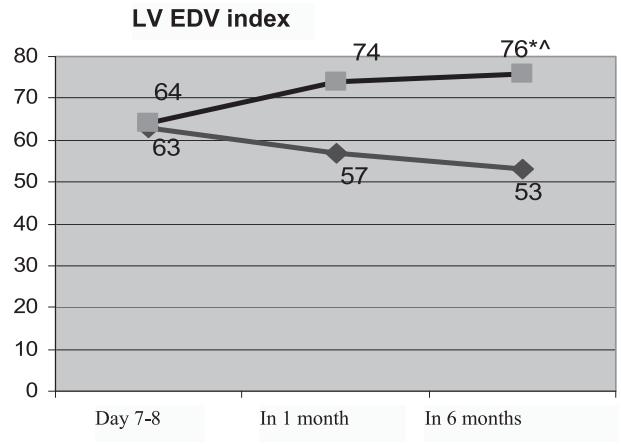

*Fig. 3. Change in the LV EDV index in AMI patients with (◆) and without (■) viable infarction zone; *p<0.05 compared to baseline; ^p<0.05 between the groups*

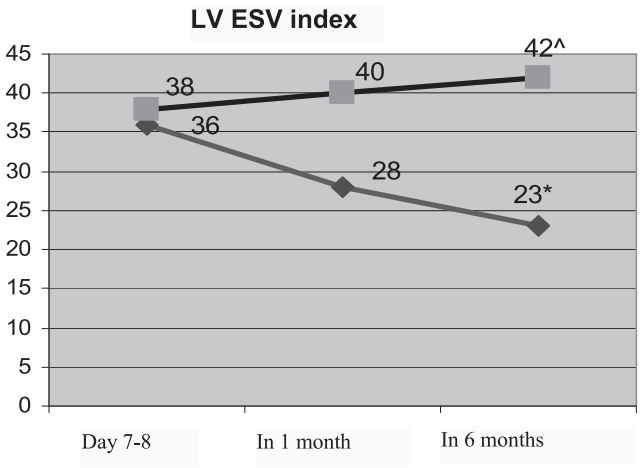

*Fig. 4. Change in the LV ESV index in AMI patients with (◆) and without (■) viable infarction zone; *p<0.05 compared to baseline; ^p<0.05 between the groups*

was stented in 28 patients (17 in Group I and 11 in Group II; p=0.25). Minimal diameter of the affected vessel's lumen increased from 0.10±0.23 mm up to 2.99±0.54 mm after the coronary angioplasty in Group I and from 0.07±0.29 mm up to 2.9±0.56 mm in Group II (Table 2).

Within 1 month angiographic incidence of IRA patency was 98% in Group I and 100% in Group II (p<0.01). Minimal diameter of the vessel was 2.76±0.79 in Group I and 2.9±0.63 mm in Group II (p<0.01).

Within 6 months angiographic incidence of patency of IRA was 98% in Group I and 96% in Group II (p<0.05). No significant difference were revealed between these two groups regarding the minimal diameter of the lumen and the incidence of restenosis (>50%) (Table 2).

At baseline, there was no statistically significant difference between these two groups regarding LV EF (45±11% vs.44±10%; p>0.05), while the regional contractility (RCII parameter) was a bit better in Group I compared to Group II (1.99±0.4 vs.2.16±0.4; p=0.05). There was a significant improvement in LV global function in Group I: compared to baseline, (45±11%) LV EF increased up to 56±8% (p<0.005) during the 1st month and up to 61±8% (p<0.005) after 6 months. No significant improvement of LV EF was revealed in patients of Group II EF (44±10% at baseline, 47±15% in one month; p>0.05; 46±13% in 6 months, p>0.01) (Figure 1). Intergroup comparison showed that patients with viable infarction zone (Group I) in 6 months had significant improvement of the LV global function compared to the patients with non-viable infarction zone (Group II) (Figure 1). Similarly, a significant improvement of RCII was registered in patients of Group I compared to Group II. In 6 months RCII was significantly reduced in the first group (from 1.99±0.4 to 1.24±0.2; p<0.05). In the second group RCII was 2.16±0.4 at baseline, in 6

months insignificant reduction to 2.02±0.5 ($p>0.05$) was observed (Figure 2).

At baseline, EDV and ESV indices did not significantly differ in both groups. During 6 months an insignificant tendency to reduction of EDV index was observed in Group I (from 63±18 mL/m2 to 53±14 mL/m2, $p<0.01$). On the contrary, in the patients of Group II EDV index significantly increased: from 64±13 to 74±18 mL/m2 during the 1st month ($p<0.05$), to 76±18 mL/m2 during 6 months ($p<0.01$), and was significantly higher compared to Group I in 6 months after the AMI ($p<0.05$) (Figure 3). Figure 4 shows changes of ESVI within the follow-up period (6 months) in these two groups. In Group I, ESVI significantly decreased during the period since the onset and up to 6 months, while in Group II there were no significant changes ($p<0.01$). During the 6-months period, ESVI in Group II was significantly higher than in Group I.

In order to estimate the impact of infarcted area viability on development of late left ventricle dilatation, multiple regression analysis was performed. The following variables were used for the analysis: age, ejection fraction, RCII, change in RCII when dobutamine is administered, infarction localization, beginning of reperfusion, collaterals, intake of ACE inhibitors. Factors with $p<0.01$ at one-dimensional analysis were selected for multiple regression analysis. Only the change of the LV RCII caused by dobutamine (assessment of the infarcted area viability) was a significant independent predictor of the EDV change during the 6-months period. At that, the RCII change caused by dobutamine in the infarction zone had higher partial correlation coefficient ($r=0.48$; $p<0.01$).

DISCUSSION

This study demonstrates that dilatation of the left ventricle is observed in patients with acute myocardial infarction despite performing the primary coronary angioplasty, restoration of the lumen of the infarct-related artery, and the absence of significant residual stenosis. At that, an extent of left ventricle dilatation is related to the residual myocardial viability in the infarction zone. Thus, our results suggest that the absence of residual viability in infarction zone distinguishes the patients with progressing left ventricle dilatation after myocardial infarction from those with normal geometry of the left ventricle.

Dilatation of the left ventricle might play a significant role in the development of chronic heart failure (1,2). Dilatation of the left ventricle is a result of chronic shape and structure changes (remodeling) of the left ventricle and is characterized by disproportional expansion of the cavity when LV geometry changes (1).

It is assumed that among factors influencing LV dilatation, the final infarction size (3,4) and perfusion status of the infarct-related coronary artery are the two main determinant factors for LV remodeling in post-infarction patients (5,6,7). Though the large-focal myocardial infarction in any case causes LV remodeling, an assessment of the infarction size cannot be sufficient for predicting dilatation of the left ventricle. Actually, the extent of left ventricle dilatation is inversely proportional to the thickness of preserved myocardium in the range of infarction zone (9). Islets of viable subepicardial myocytes saved by antegrade blood flow can prevent the left ventricle dilatation which was assumed by recent experimental studies on late reperfusion (12). This study confirms that these experimental observations on residual myocardial viability in the infarction zone allow to determine an important and independent predictor of further changes in geometry and function of the left ventricle. According to our data, the extent of asynergy (in order to estimate the size of infarction) was significantly higher in patients without residual viability of myocardium in the infarction zone. Probably, it might, at least partially, be considered as the consequence of the difference in volumes of the left ventricle. However, correlation between the change in end-diastolic volume of the left ventricle and the wall movement index in the infarction zone was lower than between the index of end-diastolic volume and the viability of infarction zone; and after the adjustment for the infarction size the viability of infarction zone was the most powerful independent predictor of the left ventricle dilatation.

A factor balancing the influence of infarction size on further remodeling of the left ventricle is the presence of preserved blood flow in the infarction zone (5,6,7) and the absence of residual stenosis in the vessel (<1.5 mm) (19). In order to avoid the influence of mixing of these two variables on further changes of the left ventricle sizes, only patients with open lumen of the infarct-related arteries and without significant residual stenosis were included in the study. Moreover, further opening of the lumen and incidence of restenosis in both groups of patients were comparable. LV dilatation reduces in accordance to the increase of residual viability extent and assumes that preservation of the blood flow in the infarction zone cannot prevent remodeling in the absence of viable infarcted area. These results also confirm and expand the previous observations of Ito et al. (20) who stated that integrity of capillaries in the infarcted area is a sensitive marker of myocardial viability preventing remodeling of the left ventricle in patients with reperfusion. Our results are consistent with those obtained by Ito et al. who used other methods for the study of different aspects of myocardial viability, and confirm the suggested hypothesis.

LV dilatation as an important feature of remodeling progresses during the long time and is associated with an increase of the end-systolic volume and deterioration of the heart function (1,2,3). In this study, progressive diastolic dilatation in patients with nonviable infarcted area was accompanied by a concerted but not equivalent increase of the end-systolic

volume indicating preservation of the left ventricular ejection fraction during the long time. It is not surprising because left ventricle dilatation in the early phase, probably, is the main compensatory mechanism during the loss of contracting myocardium and leads to restoration of initially reduced ejection volume (18). For this reason at the early stage of the left ventricle remodeling ejection fraction remains unchanged. Gaudron et al. (3) demonstrated that ejection fraction in patients with progressive LV dilatation significantly reduces only 1-3 years after the infarction.

Conclusions

1. After reperfusion of the myocardial infarction area, the presence of relatively large volume of viable myocardium significantly contributes to the preservation of the left ventricle shape and size, thus preventing post-infarction remodeling regardless of the infarction size and the state of the infarct-related artery's lumen.

2. The use of echocardiography with dobutamine in the early phase of disease allows to reveal patients at high risk of left ventricle dilatation progression.

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A Rare Case of Double Lipoma of the Right Atrium

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Primary heart tumors are revealed in 0.0017-0.05% of cases, according to autopsy data (1). Lam K. et al. (2) revealed primary heart tumors in 7 cases of 12,485 autopsies (0.056%); at that, lipoma was discovered only in one died patient (0.008%). Bosset et al. (3) reported the removal of 77 primary heart tumors, 2 of them being lipomas.
As a rule, lipomas are asymptomatic but over time they can lead to cardiac arrhythmia, dysfunction of valves and embolism. The latter is the main indication for surgical removal of lipoma.
We are reporting a case of surgical removal of two closely-adjacent lipomas fixed to the endocardium of the right atrium.
Key words: *lipoma, right atrium, surgical removal.*

CASE DESCRIPTION

The patient L., male, 57-years-old (case history No 33,626), was admitted to the Department of cardiovascular surgery of Moscow City Center of Interventional Cardioangiology diagnosed with the diagnosis: coronary heart disease, vasospastic angina, post-infarction cardiosclerosis (non-Q-wave anterior myocardial infarction in May, 2008); a mass in the right atrium cavity; essential hypertension, stage III.

The analysis of history revealed: Episodes of increased blood pressure up to 160/100 mmHg for 8 years. The patient is adapted to BP 140/80 mmHg. Since 2005 he has angina attacks at physical exertions. In 2008, ECG revealed scars on the lateral wall of the left ventricle. According to the echocardiography data (EchoCG), left ventricular ejection fraction = 50%, and the lateral wall of the left ventricle is hypokinetic. On 08.10.2010 a tumor sized 3.1 – 3.4 x 2.5 cm was discovered in the right atrium cavity. ECG showed regular sinus rhythm. Scars after advanced non-Q-wave anterior myocardial infarction were revealed. According to EchoCG data: cardiac cavities are not enlarged. Left ventricle is unchanged, normokinetic. LV EF = 60%. End-diastolic diameter was 4.7 cm, end-systolic diameter was 3.1 cm (in the parasternal position). Left-ventricular end-diastolic volume was 103 cm3, left-ventricular end-systolic volume was 35 cm3. The thickness of the ventricles walls was within normal limits. The diameter of the aorta was 3.4 cm. Opening of the aortic valve cusps was 2.0 cm. The left atrium size was 3.8 cm, without enlargement. Two middle-echogenicity roundish tumors (sized 2.5 x 1.07 cm and 2.4 x 1.08 cm with a space between them) were visualized in the right atrium cavity near the orifice of the inferior vena cava (Fig. 1). According to the data of multidetector spiral computed tomography (MSCT), there were no stenotic changes in the coronary arteries. There were 2 roundish mildly contrast (density = –100 HU) masses with homogenous structure and well-defined smooth contours (sized 1.8 x 1.9 cm) on the posterior wall of the right atrium laterally to the IVC's orifice. Each tumor had 1 pedicle attached to the wall of the right atrium (Figure 2).

On 21.01.2011, under the normothermic cardiopulmonary bypass (separate cannulation of the superior and inferior vena cava and aorta) and hypothermic cardioplegia (Custodiol), a surgical excision of two right atrial tumors was performed. Duration of the cardiopulmonary bypass was 39 minutes, duration of the aortic cross-clamping — 21 minutes. The right atrium was opened longitudinally. Two closely located nipple-shaped tumors with separate pedicles were revealed in the lower corner of incision adjacent to the IVC's orifice (Figure 3). Tumors were presented as incapsulated fatty yellow tissue of medium density, with rounded apexes sized 2.5 x 2.3 cm and 2.5 x 2.0 cm, with a base of approximately 7 mm (Figure 4). Bases were cut off together with endocardium of the right atrium. Electrocoagulation of lipoma base areas was performed. The right atrium and the cavity of the right ventricle were examined through the right atrioventricular foramen. There were no other tumors. Interatrial septum was without any symptoms of lipomatous hypertrophy. The right atrium was closed with pads. After taking off the clamp from the aorta the heart activity restored spontaneously. The

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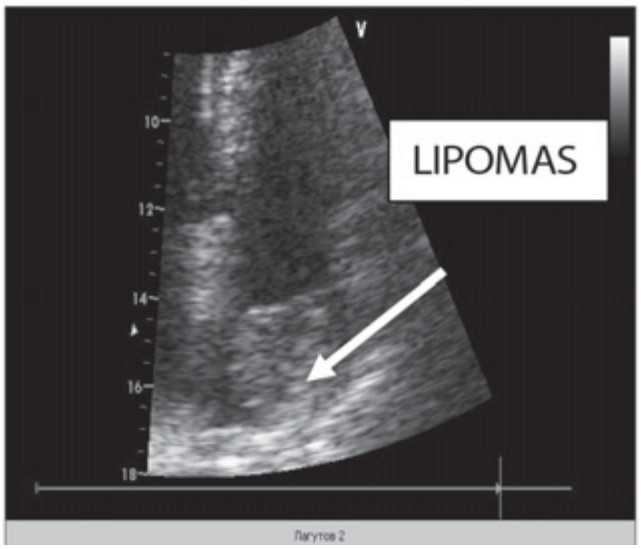

Fig. 1. EchoCG . There is a tumor in the right atrium with the clearing in the center

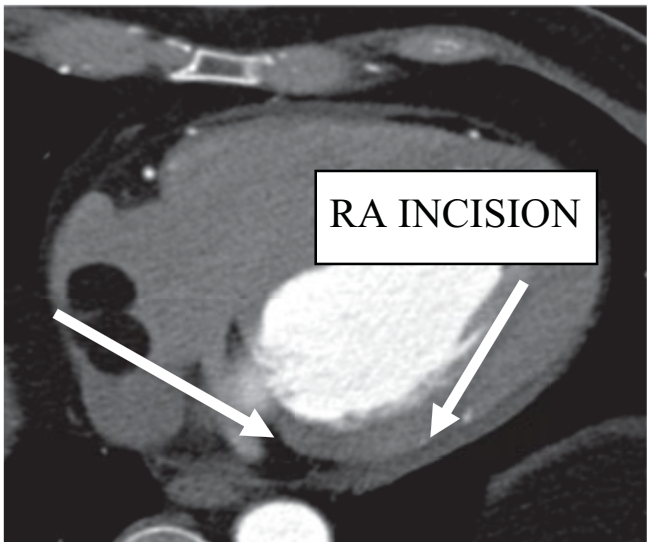

Fig. 2. MSCT. Two tumors are located in the right atrium

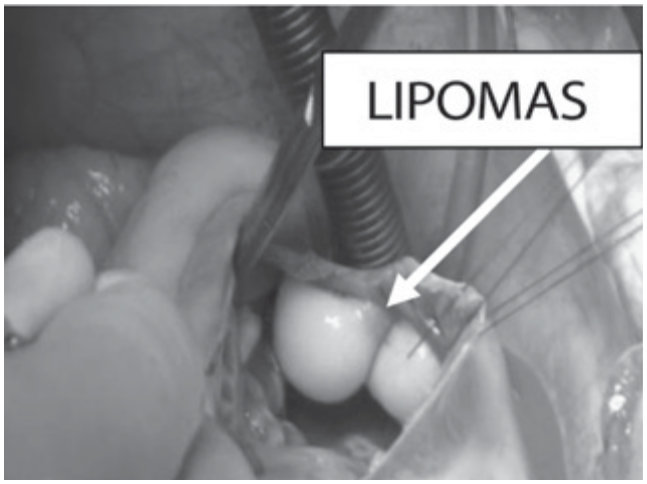

Fig.3. The right atrium near the IVC is opened. Two lipomas on separate crura

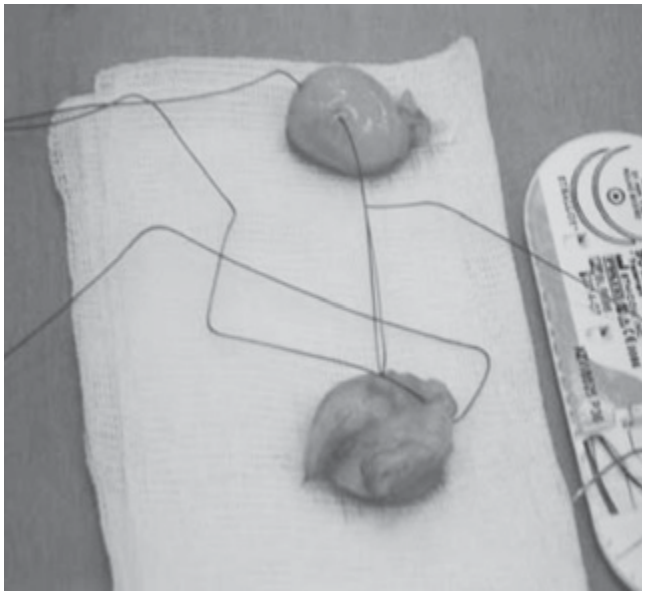

Fig. 4. Dissected lipomas of the right atrium

postoperative period was unremarkable. During repeated EchoCG investigations cardiac cavities were not enlarged, the cavity of RA was without additional formations. On the 12th day after the surgery patient was discharged home in the satisfactory condition.

Removed material was sent for the histological investigation (Sklifosovskiy Research Institute). Macroscopic investigation (24.01.11) showed: the examined consisted of two soft irregular-shaped half-rounded yellow pieces (sized 2.5 x 2.3 x 1.0 cm and 2.5 x 2.0 x 0.9 cm) with rounded surface covered by the thin grayish capsule. Tissue is yellow and lobulated on the section. Histological analysis revealed: the material, stained with hematoxylin-eosin, PAS (para-aminosalicylic acid) and Van Gisone, is presented by the fatty tissue with lobules and unilocular adipose cells of different size, poor content of connective tissue with small vessels without signs of sliming. The definite diagnosis — lipoma.

DISCUSSION

According to the autopsy data, primary heart tumors are present in 0.001% to 0.28% of cases of tumors (5). Lipomas are met in 8% of all primary heart tumors. Clinical manifestations depend on the size and localization of the tumor. As a rule, lipomas are single. According to Smith et al. (8), 60 cases of the right atrium lipomas were reported all over the world; in 3 cases several lipomas were revealed simultaneously. There is a report of a lipoma located near the orifice of inferior vena cava and growing from the upper part of interatrial septum (6).

The following reasons make our case interesting for the practical cardiac surgery:

1. There are single reports about successful removal of such masses in the world literature (5–8, 9, 10).

2. We could not find any description of multiple "twin" lipomas in available literature.

3. Transsternal EchoCG and MSCT gave an opportunity to determine the anatomy, the number and, which is particularly important, interrelation of the tumors with other heart structures.

4. Our patient had a history of angina without the coronary arteries lesion. Courtis et al. (7) reported about the possibility of angina in patients with lipomas.

5. Direct cannulation of the IVC was performed. In case of standard IVC cannulation through the lower part of the right atrium, the integrity of lipomas located near the IVC entry into the right atrium could be destroyed with unavoidable embolism of the pulmonary artery system.

6. Both tumor bases and endocardium were excised; further electrocoagulation of the myocardial wall of the right atrium was performed.

In conclusion, it should be noted that successful removal of the right atrial lipomas is possible with the correct surgical algorithm based on the clear preoperational diagnostics of the disease. EchoCG and MSCT give an optimal opportunity of anatomical and topographic diagnostics of the cardiac cavity tumors as well as of valve tumors (11, 12). At that, MSCT offering the opportunity for more clear diagnostics of so called «soft tissues» and adipose formations is an excellent method for diagnostics of cardiac lipomas (13). In case of mildly contrasting tumor of the RA the presence of lipoma cannot be excluded.

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Scintigraphic Evaluation of the Influence of Endovascular Coronary Angioplasty on Myocardial Perfusion and Cardiopulmonary Hemodynamics in Patients with Coronary Heart Disease

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The influence of endovascular angioplasty (stenting and/or balloon dilatation) of the coronary arteries on the myocardial perfusion and cardiopulmonary hemodynamics had been studied in patients with the coronary heart disease early after revascularization with the help of radionuclide diagnostic methods. The obtained results show that in 4-6 days after endovascular angioplasty cardiopulmonary hemodynamics has already improved as a result of coronary blood flow restoration and improvement of left ventricle's microcirculation.
Key words: *endovascular coronary angioplasty, myocardial perfusion scintigraphy, radiocardiopulmonography, cardiopulmonary hemodynamics.*

Objective of the study is to evaluate the influence of the endovascular coronary angioplasty on the myocardial perfusion and cardiopulmonary hemodynamics in early postoperative period in patients with coronary heart disease (CHD) with the help of radionuclide diagnostic methods.

Material and methods: Using perfusion scintigraphy and radiocardiopulmonography 20 patients with CHD were examined before and 4-6 days after the endovascular angioplasty (EA) of the coronary arteries. The type and the size of myocardial perfusion defects and cardiopulmonary hemodynamics parameters were assessed.

Results: Performing the EA led to decrease in mean sizes of myocardial transient ischemia zones by 59%. Along with perfusion improvement there was a positive change in cardiac hemodynamics parameters in examined patients: statistically significant increase of cardiac output (from 5.19±0.21 to 5.50±0.16 L), cardiac index of the left ventricle (from 2.61±0.10 to 2.79 ±0.09 L/m2), and circulation effectiveness ratio (from 1.0±0.04 to 1.08±0.04). Besides, half-times emptying of the right and left ventricle have shortened (T1/2 RV per sec. reduced from 3.15±0.3 to 2.61±0.13, and T1/2 LV per sec. reduced from 5.81±0.37 to 5.10±0.26).

We observed statistically significant improvement not only in cardiac but also in pulmonary hemodynamics parameters in a group of patients with history of acute myocardial infarction (AMI) and in patients with initial presence of stable perfusion defects even early after the EA. Thus, the mean transit time of the indicator through the lungs (TPULM) reduced from 8.81 ± 0.35 to 8.00 ± 0.35 sec. It happens mostly due to the venous component as a result of a relief in pulmonary circulation, improvement of pulmonary microcirculation, and reduction of left heart preload. Fast improvement of the cardiopulmonary hemodynamics together with restoration of the left ventricle's contractile function in patients with history of AMI can be due to the presence of hibernating myocardium in such patients in the zone of stable perfusion defect.

Conclusions: Thus, radionuclide diagnostic methods allow us to assess the hemodynamics effectiveness of the EA even early after myocardial revascularization in patients with CHD.

ABBREVIATIONS:

CHD — coronary heart disease
EA — endovascular angioplasty;
SPECT — single photon emission computed tomography;
RCPG — radionuclide cardiopulmonography;
RP — radiopharmaceutical;
CER — circulation effectiveness ratio;
TPULM — transit time of indicator's maximal amount through the lungs;
TAM — arterial modal time;
TVM — venous modal time.

INTRODUCTION

Today endovascular coronary angioplasty is one of the most widespread and effective methods of treatment of the coronary heart disease (CHD) (1, 2).

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Immediate results of treatment are assessed visually and by calculating myocardial perfusion reserve during the angiographic procedure (3). During the early and long-term postoperative period clinical follow-up and different noninvasive investigations (electrocardiography, echocardiography, cycle ergometry) are used in combination with stress-tests. However, many of these methods still are not sufficiently sensitive and specific (4).

To date stress myocardial perfusion scintigraphy remains the most objective non-invasive test evaluating the effectiveness of coronary revascularization (5-7). This method allows for highly sensitive semi-quantitative assessment of the myocardial blood flow at the microcirculatory level. Besides, radionuclide cardiopulmonography (RCPG) is widely used for diagnostics of cardiopulmonary hemodynamics disorders and for evaluation of the results of their correction (8-12). It has been shown that the values of the left ventricle's (LV) ejection fraction determined with the help of RCPG for the first pass of the radiopharmaceutical (RP) bolus correlate well (r = 0.83) with the results of the contrast ventriculography (9). At that, the radionuclide method is noninvasive, safe for the patient and easy to perform.

While radionuclide investigation methods allow to receive comprehensive objective information on the functional state of the cardiopulmonary system, there are only single reports in literature about their usage for the assessment of hemodynamic efficacy

Table 1.

Clinical characteristics of patients with CHD treated by endovascular angioplasty

Mean age (M ± SE)	AC (n)			History of AMI (n)	Number of affected CA (M ± SE)	Number of stented CA (M ± SE)
	unstable	II	III			
54,19 ± 1,65	6 (30%)	5 (25%)	9 (45%)	9 (45%)	2,25 ± 0,23	1,42 ± 0,12

Notes: AC — angina class, AMI — acute myocardial infarction; unstable — unstable angina; CA — coronary arteries.

Table 2.

Scintigraphic parameters of myocardial perfusion and cardiopulmonary hemodynamics in patients with CHD before and after endovascular angioplasty (M ± SE)

Parameters	Before EA (n = 20)	After EA (n = 20)	Significance of changes (p)	Normal range*
SD (%)	16,45 ± 3,80	11,44 ± 3,75	0,14	-
TD (%)	14,20 ± 1,52	5,83 ± 1,17	0,01	-
TPULM (sec)	8,36 ± 0,41	7,97 ± 0,36	0,21	5-6,5
TAM (sec)	4,21 ± 0,19	4,13 ± 0,18	0,92	1,5-2,5
TVM (sec)	4,15 ± 0,28	3,85 ± 0,24	0,11	3,6-4,0
T1/2RV (sec)	3,15 ± 0,30	2,61 ± 0,13	0,01	1,7-2,0
T1/2LV (sec)	5,81 ± 0,37	5,10 ± 0,26	0,045	2,2-2,8
CO (L)	5,19 ± 0,21	5,50 ± 0,16	0,02	6-8
SV (mL)	83,79 ± 3,68	82,79 ± 4,13	0,58	70-100
CI (L/m2)	2,61 ± 0,10	2,79 ± 0,09	0,03	3,5-4,5
SI (mL/m2)	41,79 ± 1,59	42,05 ± 1,97	0,33	45-55
CER (1/min)	1,00 ± 0,04	1,08 ± 0,04	0,02	1,1-1,9
CBVPULM (mL)	726,41 ± 38,00	715,29 ± 31,54	0,88	500-900

Notes: EA — endovascular angioplasty; normal range * — normal parameters used in radionuclide diagnostics (16); SD — stable perfusion defect; TD — transient defect; % — size of perfusion defects of the left ventricle's whole size; TAM — arterial modal time; TVM — venous modal time; TPULM — pulmonary time (the sum of TAM and TVM); CO — cardiac output; SV - cardiac stroke volume; CI - cardiac index; SI - stroke index; CBVPULM — circulating blood volume in the pulmonary circulation; CER — circulation effectiveness ratio; T1/2RV, T1/2LV — emptying half-times of the right and left ventricles.

of coronary angioplasty (11, 13). At that, the earliest study of left ventricle's (LV) pump function after successful endovascular treatment was performed in 6 weeks after procedure. The only exception was a study by Van der Vleuten PA et al. (14), who performed a single assessment of the LV's ejection fraction (EFLV) in patients with acute myocardial infarction (MI) in 1-11 days after the primary percutaneous coronary angioplasty using radionuclide balanced left ventriculography. The value of the calculated EFLV was used as an independent predictor of patients' survival during the further 36 months follow-up.

Based on the mentioned above, we had set a goal — to evaluate the influence of endovascular coronary angioplasty on myocardial perfusion and cardiopulmonary hemodynamics in the early postoperative period in patients with coronary heart disease (CHD) with the help of radionuclide investigation methods.

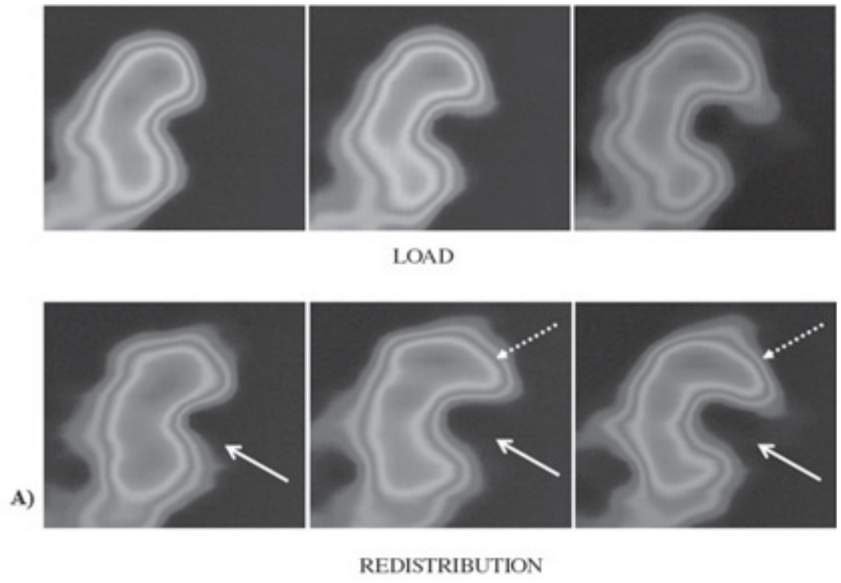

Fig. 1 (a, b). Radiocardiopulmonograms of the patient M. before (a) and after (b) the right coronary artery stenting. There are some scintigraphic signs of the pulmonary circulation relief and improvement of the left and right ventricle's contractility (TPULM reduced due to TVM,T1/2RV and T1/2LV. SV, CI and CER increased).

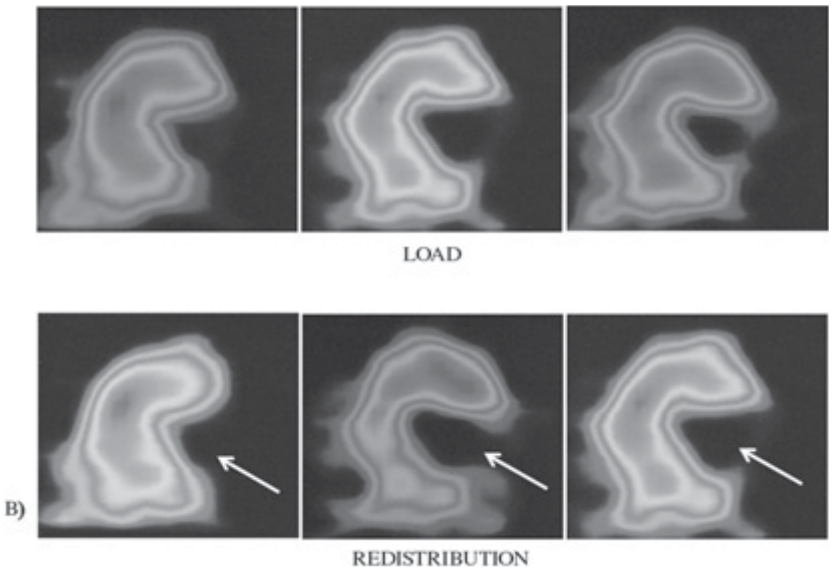

Fig. 2 (a, b). Results of myocardial perfusion scintigraphy with thallium-199 in the patient I. (tomographic sections by the LV transverse axis): a) stable perfusion defect of the lateral wall and posterior-lateral region (pointed with a solid arrow) and transient ischemia of the LV's anterior-lateral region (pointed with a dashed arrow) before the stenting; b) after the stenting of a circumflex artery transient ischemia zones disappeared and the sizes of perfusion SD reduced.

MATERIALS AND METHODS

20 patients with CHD (19 men and 1 woman) aged from 40 to 69 years (mean age 54.19±1.65 years) who had successfully underwent coronary angioplasty – balloon dilatation (BD) and/or stenting of the coronary arteries — were included into the study (BD was performed in 1 patient, stenting – in 16, and BD with stenting was performed in 3 patients).

Selective coronary angiography and left ventriculography using Judkins method were performed in all patients. According to their results, 5 (25%) patients had one-vessel lesion, 10 (50%) had significant stenosis of two coronary arteries, and 5 (25%) had multivessel stenoses. The majority of patients had class III exertional angina (9 patients, 45%). Nine (45%) patients had a history of AMI with post-infarction cardiosclerosis. All patients were in heart failure of at least II NYHA class. Main clinical characteristics of patients are shown in Table 1.

All patients underwent radionuclide cardiopulmonography (RCPG) with 99mTc-pertechnetate and single photon emission computed tomography (SPECT) of myocardium with Thallium-199 chloride (199Tl) (Research Institute of Nuclear Physics, Tomsk Polytechnic University, Tomsk) before and early (4-6 days) after endovascular angioplasty (EA) of the coronary arteries. The first of the listed examination methods is based on the sequential registration of the RP bolus passing through the heart chambers and lungs after its injection in the cubital vein. The

following zones of interest were identified with the help of the software for processing the scintigraphic images: right and left ventricles, the upper lobe of the lung. For each of the chosen zones of interest the "activity-time" curves were built to calculate the main hemodynamic parameters: cardiac output (CO) and stroke volume; circulating blood volume in the lungs (CBVPULM); cardiac index and stroke index (CI, SI); circulation effectiveness ratio (CER); arterial modal time (TAM) (characterizing mostly the blood flow in the major and minor arteries, arterioles, and capillaries in lungs); venous modal time (TVM) (reflecting blood circulation in the veins of the pulmonary circulation and in the left heart); pulmonary time (TPULM) (time period between the peaks of the first and second RCPG waves that represents the sum of TAM and TVM and characterizes the transit time of maximal quantity of indicator through the lungs); emptying half-times of the right (T1/2RV) and left (T1/2LV) ventricle (indirect criteria of their contractility).

Single photon emission computed tomography (SPECT) with 199Tl chloride was performed according to the load-redistribution protocol. Intravenous infusion of adenosine(0.56 mg/kg) was used as the load test. During quantitative processing of the tomograms, the size and localization of left ventricle's perfusion defects (PD) were assessed. Based on the presence or absence of indicator's redistribution on the delayed (in 2 hours) tomoscintigrams, detected PD were divided into the transient (TPD) and stable (SPD) perfusion defects, respectively.

Scintigraphic investigations were performed using the Omega 500 gamma-chamber (Technicare, USA-GFR). Images registration and processing of scintigrams were performed using the Scinti computer system manufactured by the Gelmos Scientific Production Association (Russia).

The obtained data were statistically processed using the STATISTICA software package with descriptive statistics, nonparametric Wilcoxon's test and Sign-test for paired measurements.

RESULTS AND DISCUSSION

As evident from the table 2, the mean number of stable PD in examined patients was almost 17% before the surgery indicating the presence of post-infarction cardiosclerosis zones and the hibernating myocardium in the LV. This confirms the data by Beller (15). Based on the results of RCPG, most of the hemodynamic parameters in examined patients were impaired (decreased mean values of CO, CI, SI, and CER) as a result of reduced cardiac pump function. At that, decreased cardiac output was revealed in 14 (70%), while the stroke index was under the normal values in 12 (60%) patients. As mentioned above, left and right ventricle's contractility can be assessed also by the values of their emptying half-times (T1/2RV and T1/2LV), which were significantly increased above the normal range in examined patients (Table 2). Parameters of pulmonary hemodynamics also deviated from the normal values (Table 2). Thus, a prolongation of the TPULM mostly due to TAM was noted; it was suggestive of pulmonary hypertension development in combination with RV insufficiency. This is consistent with the opinion of Sivachenko et al. (16) (Figure 1, a).

According to the data of coronary angiography and left ventriculography during the direct visual evaluation, the results of balloon dilatation and/or stenting in all examined patients were optimal without residual stenosis.

The quantitative analysis of scintigraphic data obtained in 4-6 days after the coronary angioplasty had shown that the intervention led to decrease in mean sizes of the transient ischemia zones by 59% (from 14.2% ± 2 to 5.8% ± 1.17 of the left ventricle's myocardium size, $p = 0.01$) (Table 2). This is consistent with the results of other authors, according to which direct myocardial revascularization has the most significant influence on the size of transient perfusion defects. For this reason disappearance or reduction of the transient ischemia zones after direct revascularization as a result of coronary blood flow restoration is a proven and well known fact (17).

However, in some cases reversible defects of thallium accumulation persisted after the procedure. This was most likely due to the incomplete myocardial revascularization in patients with multivessel lesion.

The size of stable perfusion defects revealed before the treatment varied from 10.0% to 32.5% (the mean value – 16.45 ± 3.80). Stable perfusion defects are known to be caused by myocardial scars (post-infarction cardiosclerosis) (15, 18) or by the presence of the hibernating myocardium (19).

According to the Table 2, we observed no statistically significant changes of the mean size of the stable perfusion defect. However, early after the CA stenting in 4 examined patients positive scintigraphic changes of the stable perfusion defect were observed (complete resolution in 2 patients and significant reduction in 2 patients) (Figure 2, a, b). Similar data was received by other authors who also observed the disappearance of stable perfusion defects after angioplasty or CABG (7, 20).

Along with perfusion improvement after the surgical treatment there we noted positive changes in some parameters of cardiac hemodynamics (Table 2). Thus, on the 4-6 day after EA we have already observed statistically significant increase of CO and CI, as well as of the circulation effectiveness ratio (CER) that shows what part of the circulating blood volume goes through the LV per 1 minute. The clinical value of CER is determined by its high sensitivity to CO and CBV changes in patients with circulatory insufficiency; thus, even slight negative changes of these parameters lead to significant decrease of CER (16). Besides, emptying half-times of the right (T1/2RV) and left (T1/2LV) ventricle shortened significantly (Figure 1, b). The obtained results indicate the improvement of the LV's pump function after successful

revascularization that is consistent with the results of other authors' studies (11).

Early after the EA we have already observed significant improvement of the parameters not only of cardiac but also of pulmonary hemodynamics in a group of patients with a history of AMI and in patients with sustained hypoperfusion zones at baseline. Thus, the mean TPULM value decreased from 8.81 ± 0.35 to 8.00 ± 0.35 sec. (p = 0.002) after the EA mostly due to the venous component (TVM) that decreased from 4.52 ± 0.19 to 4.02 ± 0.24 sec (p = 0.011). The obtained results indicate a relief in pulmonary circulation and an improvement of pulmonary microcirculation, as well as the reduction of the left heart preload. Meanwhile, Chung et al. (21) showed that improvement of total and regional LV's contractility was not significant in a group of patient with a history of AMI 6 months after the successful angioplasty. The authors believe that after recanalization of a stenotic coronary artery in patients after AMI, a significant improvement of LV function depends on the presence of viable myocardium in the territory supplied by this artery. Considering this point of view, it can be suggested that the fast improvement of the cardiopulmonary hemodynamics together with restoration of the LV's contractile function in patients with history of AMI can be due to the presence of hibernating myocardium in a zone of stable perfusion defect. Conception of cardiac muscle hibernation was firstly suggested by S. Rahimtoola (22) for the areas with low contractility situated in the region of the stenotic artery. Such left ventricle dysfunction developing as a result of chronic myocardial ischemia recovers after its revascularization.

Thus, radionuclide diagnostic methods allow us to assess the hemodynamics effectiveness of EA even early after myocardial revascularization. This is important for the choice of adequate treatment method in such patients and for the determination of the prognosis of the main disease.

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Stents with Bioabsorbable Polymer Coating: State-of-the-Art and Perspectives (a Review)

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Cardiovascular diseases are the main cause of mortality and morbidity worldwide. According to World Health Organization data, cardiovascular diseases kill 16.7 million of people every year that corresponds to 29.2% of total mortality in Earth population (1). In Russia, the last 15 years were marked by an increased cardiovascular mortality (2). The indices of mortality and incapacitation (1477 person-years per 100,000) significantly exceed the corresponding indices in all advanced nations. These rates are 4-fold and more above the same indices in Italy (330 person-years) and France (250 person-years) (3).

Cardiovascular diseases are responsible for 55% of deaths in a general structure of mortality in the Russian Federation, CAD accounts for more than 36%. However, the modern methods of treatment, such as percutaneous interventions (PCI) and coronary artery bypass grafting (CABG) are used 8-10 times less frequently compared with economically developed countries (3).

For a long time pharmacological treatment was the only method of management for CAD. Introduction of new radical methods of myocardial revascularization into the clinical practice extended the possibilities of treatment for CAD patients. Coronary artery bypass grafting proposed by R. Favaloro in 1967 has supassed all expectations resulting in the improvement of the quality of life of such patients and the decrease of the rate of myocardial infarction (4, 5). Development of endovascular methods allowed A. Gruentzig to perform in 1977 three successful intraoperative dilatations of the coronary arteries (6), and in 1986 Jacques Puel has implanted for the first time a stent into a coronary artery (7). Positive immediate results, general improvement of patients' well-being and some other clinical indices suggested the advent of a new era in the treatment of coronary artery disease (8).

The advantages of stents allowed them to become the main instrument in invasive cardiology during the past years. At present stenting is being performed in 60-90% of all PCIs cases in different cathlabs (9). Active usage of stents allowed for an effective treatment of coronary lesions of different complexity, but at the same time it revealed the weak sides of this method, particularly eventual development of restenosis or repeated luminal narrowing. The main reason for this process is a response of the vessel wall to the injury occurred during stent implantation and to prosthesis itself as a foreign body as well. According to data of different authors, in-stent restenosis is revealed in 10-50% of patients (9).

To prevent in-stent restenosis, drug-eluting stents (DES) were proposed in the 1990's; their coating mainly contained drugs contributing to the decrease of the intensity of cell division (cytostatic agents). DES were considered almost a panacea in the treatment of atherosclerotic damage of coronary arteries (10). The use of phosphorylcholine, polyvinyl acetate, polybutylmethacrylate as polymeric coatings contributed to implementation of such stents into the medical practice (11, 12). Polymeric coatings applied to a metal frame provide controlled local drug eluting into the stented segment of the vessel wall, leading to decreased restenosis rate (13). However, a hydrophobic nature and low biocompatibility of polymers results in a prolonged healing, inflammation of the vessel wall, and thus increases the risk of stent thrombosis (14, 15, 16).

The forthcoming of multicomponent polymers was the further promising trend in upgrading of drug-eluting stents. For example, BioLinx polymer developed by Medtronic company consists of 3 components: C10 polymer being lipophilic (hydrophobic) controls steady drug eluting; hydrophilic C19 polymer possesses high biocompatibility, and polyvinylpyrrolidone (also a hydrophilic polymer) contributes to primary drug eluting (17). Combination of lipo-hydrophilic properties of coatings promotes high biocompatibility and long-term drug eluting. But the main disadvantage of Biolinx polymer is its friability under mechanical impacts such as passage through calcified or tortuous portion of the vessel. As a result, drug eluting is impaired and, as a consequence, the risk of restenosis and thrombosis increases (17).

To date, different companies provide the wide choice of stents with various drug and polymer coatings. The most common stents are those

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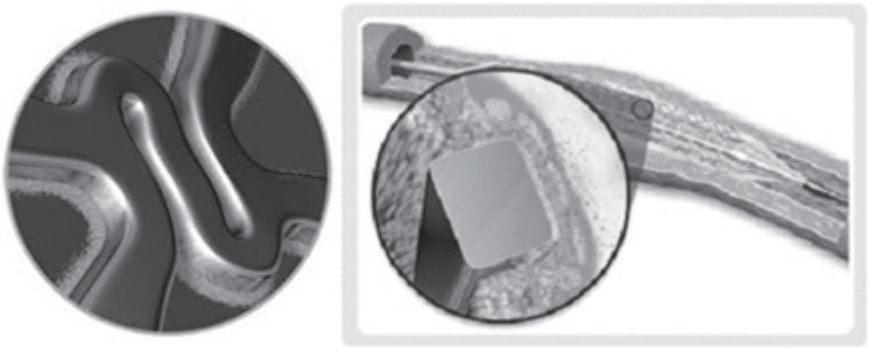

Fig. 3. Abluminal coating of the Biomatrix stent

containing components derived from the «limus family" (18, 19). However, stents containing paclitaxel are not less common (Taxus stent). Derivates of the limus family are represented by Sirolimus (Cypher stent), Everolimus (Xience V), Zotarolimus (Endeavor), Tacrolimus (Jupiter II), Biolimus (Biomatrix and Nobori stents) (20).

Development of technologies, synthesis of new drugs and polymer coatings significantly improved the results of endovascular procedures (21, 22). However, thromboses, particularly late stent thromboses still remain the unsolved problem of interventional cardiology. Insoluble polymer stent coatings, despite their ability to gradually and continuously release the cytostatic agents, are one of inflammation factors themselves and, therefore, a risk factor for clot formation (23, 24).

To solve this problem, the stent with bioabsorbable polymer on the lactate basis has been developed and successfully used. In the long view, a stent with such system of local drug delivery is able to bring together the efficiency of DES and the safety of BMS. One of the first mass-production stents of this type is Biomatrix (by Biosensors). Biomatrix stents are characterized by an abluminal bioabsorbable polymer coating with a cytostatic agent Biolimus A9. It provides timely endotelization of stented segment of the artery. At that, manageable polymer washing out decreases the proliferative response during the acute period of restenosis formation, while the stent eventually becomes a bare-metal stent (25).

Biomatrix stent consists of a bare-metal frame coated by a polylactic acid and biolimus A9 (25).

The S-stent is a platform of Biomatrix stent. The S-stent is produced from medical stainless steel 316 L. The first studies (Future I, Future II) have shown the safety and security of these stents. Incidence of major cardiac events in mid- and long-term periods was comparable with widely used bare-metal stents (26).

Polylactic acid (PLA) is widely used in the production of medical items including drug delivery system, prosthesis implants, and biomaterial for wound closure. PLA and its derivates were tested for biocompatibility in multiple pre-clinical and clinical studies. Bioabsorbable polymer PLA was shown to be safe in humans when used as the drug-eluting implant and polymer. In stents with Biolimus A9-containing coating a small polymer quantity is used. It is due to the fact that PLA polymer is able to carry a high drug dosage. PLA polymer carrying B A9 is absorbed during 6-9 months from the stent surface (25).

An active pharmacologic substance Biolimus A9 was synthesized with the help of chemical modification of Rapamycin, and possess a high lipophilicity and an ability to absorb in tissues. Being a representative of the limus family, this drug has a property to bind to cytoplasm proteins. Besides, it inhibits cells proliferation and blocks the cell cycle between phases J1 and S by binding with cytoplasm proteins FKBP-12, as other "limuses" do. As a result, Biolimus A9 inhibits T-lymphocytes proliferation. Due to high lipophilicity and abluminal stent coating, a fraction of Biolimus A9 reaching systemic circulation and causing a systemic impact is minimized. Figure 3 shows an abluminal coating of the Biomatrix stent (25).

Clinical studies of stents with Biolimus A9 coating.

BEACON I is a multicentre randomized trial aimed to assess major adverse cardiac events during 6 and 12 months after Biomatrix stent implantation. This trial involved 292 patients. In 6 months MACE incidence was 4.8%, repeated revascularization (in the target vessel area) – 2.1%, in 12 months – 6.5% and 2.8%, respectively (27).

STEALTH is the first clinical trial aimed at comparative assessment of Biomatrix stents and their bare-metal analogues (platforms) – S-stents in patients with CAD. One hundred and twenty patients were enrolled in the study. Of those, 80 patients underwent implantation of Biolimus-eluting stents A9, and bare-metal stents were implanted in 40 patients. In six months the lumen loss of the target vessel in the Biomatrix group was less than in the control group: 0.09 ±0.39 mm vs 0.76 ±0.45 mm ($P<0.05$). The rates of major adverse cardiac events (MACE) within 30 and 360-days follow-up period did not differ significantly and were 3.7% vs 2.5% and 5.1% vs 5.0%, respectively. Two-year results demonstrated similar clinical safety of these stents as well; at that, there were no thrombosis cases in Biomatrix stents throughout the follow-up (28).

LEADERS trial involved 1707 patients with 2472 vessel lesions. Of those, 857 patients underwent implantation of Biolimus-eluting stents, while

Table 1.

Results of trials of Biomatrix stent

Trials	Compared groups	Number of patients included in the study	MACE,%			
			Time of follow-up			
			1 month	6 months	9 months	12 months
STEALTH PK	Biomatrix	27	0	3.8	-	-
STEALTH I	Biomatrix/ S-stent	120	-	3.8/ 3.8	-	5.1/5.1
BEACON 1	Biomatrix	292	3.8	4.8	-	6.5
LEADERS	Biomatrix/ Cypher	1707	-	-	9.2/ 10.5	10.7 / 12.2

Sirolimus-eluting stents were implanted to 850 patients (29). Over 50% stenosis of coronary arteries and/or venous grafts was an inclusion criterion. Exclusion criteria were: pregnancy, intolerance of Aspirin, Clopidogrel, Heparin, Sirolimus, Biolimus, contrast media and surgical manipulation within 6 months prior to PCI. The duration of clinical follow-up was 1 and 9 months. The study design envisaged phone monitoring of patients during 5 years. The results of 9-month follow-up were reported at the ESC congress in Munich in September 2008. According to these data, MACE were observed in 9.2% of patients in the Biomatrix group and in 10.5% of patients in the control group (p = n.s.) (29). Within two years of the follow-up, the main results of mentioned stents did not differ significantly as well: cardiac mortality was 3.2% in the group of Biolimus-eluting stents A9 and 4% in the control group (p=0.42); the rate of myocardium infarction was 6.4% and 5.8% (p=0.57); the rate of repeated myocardial revascularization in the territory supplied by the target vessel was 6.6% and 7.3% (p=0.58). During this period "in-stent" thrombosis was observed in 2.2% and 2.5% of cases, late thrombosis – in 0.2% and 0.5% of cases, respectively (p=n.s.). In addition, the rates of stent thrombosis in 1 year after PCI were compared in patients who refused the use of double antiaggregant therapy in the study. In the group with Biolimus-eluting stents A9 such episodes were not observed, whereas in the control group their rate was 1.2% (30).

Three-year results of LEADERS trial reported at the TCT conference in Washington, D.C., in 2010, revealed a tendency to decreased rate of MACE after Biolimus-eluting stent (BES) A9 implantation compared with Sirolimus-eluting stents (SES). Major adverse cardiac events (MACE) were observed in 15.7% of patients with BES and in 19.0% - with SES. Statistically significant difference in MACE incidence (in favour of Biolimus-eluting stents compared with the control group) was obtained in subgroups of patients with MI (9.6% vs 20.7%) and severity of coronary lesion > 16 by SYNTAX score (4.6% vs 10.4%) (31, 32). Results of these and some other comparative trials with Biomatrix stents are summarized in Table 1.

The NOBORI-I, a multicentre randomized trial, involved 85 patients with Biolimus-eluting stents A9 and 35 patients with Paclitaxel-eluting stents. The results of 9-month follow-up revealed that some main indices in the group of Biolimus-eluting stents were better compared with the control group. Mortality, myocardium infarction and restenosis rates were 0%; 4.7%; 7.1% vs 0%; 8.6%; 14.3%, respectively. Clinically relevant restenosis was observed in 0% and 2.9% of cases. During 9 months there were no cases of stent thrombosis in any group. (33, 34).

The NOBORI II trial investigated the results of Biolimus-eluting stent A9 implantation in patients at high risk. The study included 3028 patients. All patients were assigned to 2 groups depending on severity. Group 1 consisted of patients comparable by risk factor level to previously performed studies, whereas patients at high risk of complications were included in Group 2. The study was aimed to assess the indices of cardiac death, myocardium infarction, restenosis, and repeated revascularization. According to the results of 12-months observation, in Group 1 cardiac death was observed in 0.6% of cases, myocardium infarction and restenosis — in 0.7%. In Group 2 these indices were 1.2%, 1.9% and 3.7%, respectively. In general, the incidence of major cardiac events (i.e. MACE) in the NOBORI II trial was lower than in other multicenter studies) — 3.4% (35).

CONCLUSION

It is difficult to overestimate the success achieved in interventional cardiology after wide implementation of antiproliferative drug-eluting stents. However, the problem of coronary artery restenosis is still urgent. One of the main approaches to its solution is a search for more effective lipophilic analogues of cytostatic agents. It is the lipophilicity that promotes increased transmembrane drug permeation into

the cell and thereby potentiates its cytostatic effect. In that respect Biolimus A9 is the most optimal agent.

Another important problem related to the use of DES is the probability of late thrombosis. On this background, an introduction of bioabsorbable polymer-coated stents appears to be most promising. The results of the above-mentioned clinical studies evidently support this assumption.

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The problems brought up and discussed in the article by Drs. K. Laederach-Hofmann, N. Messerli, and B. Meier, fall far outside the scope of interventional cardiology and radiology. For this reason the Editorial Council of the Journal makes a request to its readers whose profession is related to the discussed problems, to present their comments, considerations and suggestions.

Chest Pain, Angina Pectoris, Panic Disorder, and Syndrome X: A Meta-Analytical Study of Psychological Characteristics

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Background: *To review by means of a meta-analysis the body of literature in the field of syndrome-X, including angina pectoris in coronary artery disease and microvascular angina pectoris and to define changes in depression, anxiety, anger, and personality traits.*
Methods: *Meta-analysis of a literature search of MEDLINE, PSYNDEX, and PSYCINFO databases from 1980 to 2002 including 1,326 publications. After a qualitative evaluation, only 25 articles fulfilled the criteria for a thorough statistical analysis. Effect sizes were calculated.*
Results: *Depression, anxiety, and personality traits showed significant differences between patients with syndrome X, angina pectoris due to coronary artery disease, and anxiety disorders. Effect sizes of anger (p=0.0001) and anxiety (p=0.0001) were significantly different between patients with anxiety disorders and syndrome X whereas effect sizes of depression (p=0.005) and anxiety (p=0.01) were significantly different between syndrome X and coronary artery disease patients.*
Conclusions: *Beside newly detected somatic differences between cardiac syndrome X and other cardiac or psychological pathologies, clear cut differences in psychological parameters are discernible.*
Key words: *cardiac syndrome X, panic disorder, chest pain, angina pectoris, meta-analysis*

INTRODUCTION

Chest pain is one of the most disturbing symptoms in medicine with a prevalence of at least 24.6% (1). Overall, one-third of patients' symptoms are either psychiatric or medically unexplained, and most symptoms were associated with an increased lifetime risk of a common psychiatric disorder. However, only 32% of the patients who had had a history of angina pectoris had obtained effective medical therapy for cardiovascular problems (2). In Switzerland 14% to 47% of the respondents with angina pectoris had consulted a physician or had utilized acute medical services (e.g. ambulance to emergency ward) when stricken by chest pain (3-5). In a survey conducted in Germany 54.2% of the men and 56.2% of the women with angina pectoris were on ongoing oral heart medication (6). Noren et al. (7) revealed that internists in North America devote an average of 5.4% of their time to making differential diagnoses of chest pain, which take up almost as much of their time as general check-ups.

On the other hand, apparently 30% of the patients who undergo invasive tests due to typical angina pectoris and to an ergometer test that documents a suspicion of ischemia have normal coronary arteries (8-10). All the same, there seem to be patients whose ECG show typical ST-segment depression in stress tests which do not, however, reveal any cardiovascular dysfunction when measured with invasive examination procedures (11). The definition of anginal syndrome X — which is still used today — dates back to a research paper written in 1967 (12,13). Eight years later Kemp (14) published an editorial on the problem of angina pectoris in normal coronary arteries. He referred to syndrome X for the first time in order to focus attention on the conundrum of the pathophysiological mechanisms, the ischemia-like changes in ECG and the symptom angina pectoris in these patients. By syndrome X (cardiac syndrome X) we mean the following triad: Angina pectoris (often typical) and altered ECG (in particular ST-segment depression and in coronary-ischemia-related abnormality) related to ergometric stress and macroscopically normal coronary arteries in coronary angiography. Abnormal coronary flow characteristics are added to this triad by various authors (15). While many researchers (16-18) have found that patients with syndrome X do not actually display any signs of myocardial ischemia, other abnormalities have also been detected in blood flow similar to those in cardiomyopathy (19), ischemia-specific increase of lactic acid in coronary sinus (20), decreased O_2 in the analysis of arterial veins (21), abnormalities of the clotting system with increased

platelet aggregability (22), or other abnormalities of coronary hemodynamics and myocardial metabolism (23). An updated and simplified overview of the pathogenetic mechanisms in cardiac syndrome X can be found in a recent article by Kaski and Russo (24). The important question as to whether there is a direct relationship between the prevalence of ischemia and angina pectoris has remained unanswered to date (25-27). Angina pectoris presumably corresponds to a change in the heart itself, in neural transmission or in central nervous integration. Psychological factors such as anxiety, depression or hostility influence the strength, severity, and recurrence of the anginal pain. Furthermore, in particular psychological factors as such may lead to complaints indistinguishable from "true" angina pectoris (28,29). Psychopathological processes have repeatedly been assumed to contribute to symptom manifestation and to reactions to pain (30). There is evidence that such patients tend to suffer from anxiety disorders (16,30-36)or other psychiatric disorders (37)such as neuroticism (38).

In addition, there is overall consensus that chronic pain leads to depressive mood and depression, which, in turn, contribute to a lower threshold of perceived pain (39). In patients with chronic depression estimates of prevalence of comorbidity with pain range from about 30 to nearly 100% (40-42). In addition, anxiety is a frequent concomitant of angina pectoris of cardiac origin and in part even replaces actual pain. Anxiety is even what makes for the fatal nature of angina pectoris. Anxiety occurs as an alarm sign in an acute episode of chest pain (43,44) and is detectable as an independent symptom in exercise-provoked myocardial ischemia by intravenous infusion of adenosine (45,46). In a randomized consecutive patient population of 3,705 that had undergone ergometric investigation, Herrmann et al. (47) found high anxiety and depression scores in 19.7% and 9.1% of the sample, respectively.

Despite the fact that the definition of microvascular angina pectoris is narrower than the definition of syndrome X, considerable overlap occurs between the two pathologies (48). The following symptoms may be present in microvascular angina pectoris: endothelial dysfunction (49-52); absence of a specific essential amino acid (L-arginine) as precursor of NO (53); reduced functional coronary flow reserve (54); absence of vasodilatation in response to acetylcholine (55); elevated plasma-endothelial-1 level; decreased endothelial-dependent vasodilatation (56); decreased NO release in response to insulin infusion (56)characteristic of insulin resistance as common in metabolic syndrome (17, 57); dysfunction of the autonomic nervous system with hypersympathetic tone (58), and increased pain perception (59). The question as to whether it is simply a case of dynamic ischemia — a mismatch between demand and need — has likewise been a bone of contention (60).

Since the first publications of syndrome X patients several papers discussed that these individuals seem to experience pain differently to others with coronary artery disease. Cannon (33), for instance, described syndrome X patients more often react with angina pectoris when electric stimulation of the right ventricle is performed or contrast medium is injected into the coronary artery concurrently during coronary an-

Table 1.

Results of literature search (actualized January 1st 2003)

	Medline	PsycINFO	PSYNDEX
heart	420'610	11'790	1'381
psych*	87'447	544'078	125'188
syndrome X	354'320	403	17
cardiac	201'437	3'101	254
cardiac syndrome X	12'567	0	0
angina pectoris	18'763	158	40
chest pain	13'067	292	8
anxiety	46'289	43'810	6'260
panic	6'292	6'795	508
heart + psych*	1'143	7'527	1'259
heart + psych* + chest pain	59	80	1
heart + anxiety	2'336	1'529	240
heart + panic	431	382	60
psych* + chest pain	172	219	8
psych* + angina pectoris	59	100	35
angina pectoris + anxiety	124	23	4
angina pectoris + panic	33	8	0
heart + panic + chest pain	51	27	0
heart + anxiety + chest pain	84	30	1
chest pain + anxiety	264	91	3
chest pain + panic	168	92	1

giography — which basically amounts to temporary O2 withdrawal and thus is equivalent to strain. In a study of the psychiatric comorbidity of symptoms in patients with chest pain and a normal coronary arteries, Beitman et al. (61)found panic disorder in 34% of 94 patients. In an effort to ascertain central (i.e. alternating pain processing) pathologies Rosen et al. (62) recently found that patients with syndrome X suffer from a central thalamic gate disorder of pain. Their standpoint is that increased pain perception is exclusively due to altered activation of the cerebral processing centers in particular the fronto cortical insula area and connections to the frontal operculum. Therefore, they concluded that the origin of cardiac syndrome X cannot be ischemic. Frobert et al.'s (63) findings coincided with Rosen et al.'s that central pain processing in patients with syndrome X must be altered. However, a recent study using cardiovascular magnetic resonance imaging to detect abnormal subendocardial perfusion provided conclusive evidence that syndrome X patients exhibit subendocardial ischemia, in particular of the left ventricle, compared to control subjects (64). These data had sparked a heated debate (65,66). Smith et al. (67) reported a significant correlation between anxiety and the incidence of anginal complaints. In their overview, Kaski and Russo (68) defined syndrome X as a disorder of coronary microvascular regulation, the mechanism of endothelial dysfunction being of prime importance (69) that is triggered by multiple causal mechanisms. This is in line with recent publications (70-72) and leaves the question open whether and to what extent both mechanisms add to the symptom of angina pectoris in syndrome X.

The present meta-analysis aims to elucidate the data on psychological factors in patients with syndrome X, coronary artery disease, and overt panic disorder using strict criteria and reliable psychometric instruments. Thereby, our hypotheses include that patients with syndrome X are more depressed and anxious than those with coronary disease. On the other hand, syndrome X patients will show less anger than patients with coronary artery disease. Additionally, concerning personality characteristics (somatization, compulsiveness, general complaints) we hypothesize that patients with syndrome X focus more attention on physical symptoms than do patients with coronary artery disease and exhibit less general complaints and compulsiveness than others with panic disorder.

METHODS

All of the works considered in this article were collected by means of public accessible data banks. Medical articles were collected with the help of MEDLINE databank published by the U.S. National Library of Medicine. The search for relevant psychological literature was undertaken via PSYNDEX and PsycINFO (American Psychological Association). The search restricted itself to works published after 1980 and before the end of November 2002. For an overview of search terms and the number of articles elicited from the databanks see table 1.

In addition, the usefulness and relevance of all the documents elicited via the search terms syndrome X and cardiac syndrome X were examined on the basis of their titles and whenever available — the respective abstracts were studied as well. A total of 1,326 publications were elicited by means of combined search procedures and an additional 42 were found based on the abstract search outlined. We included studies using a thorough description and physical examination of the patients and fulfillment of the above-mentioned diagnostic criteria — namely, evidence of an abnormal stress test with electrical signs of an ischemia and a completely normal coronary angiography, if possible with no coronary reaction to ergonovine (exclusion of vasospastic angina pectoris). Articles on older theoretical models (e.g. type A/B behavior) were included provided they were based on relatively up-to-date methods of data evaluation. Furthermore, participants may not be under 16 or over 70 years old.

Articles dealing with the following topics were not included: the therapeutic setting, effectiveness of medication, theoretical models of bodily perception, isolated panic disorders or isolated coronary artery disease, classification of diseases and psychosomatic complaints in disorders that were not related to our topic. In addition, patients are not allowed to display any changes in heart function, in particular no arterial hypertension with left-ventricular hypertrophy, diabetes mellitus, or obesity. We also excluded case reports and chapters of books that referred to studies that were available in their original form or book articles that were of a narrative nature failing to do justice to the topic of interest.

Of the 1,326 titles referring to cardiac syndrome X that had been ordered in the literature search 243 publications were reviewed in their completeness as published and sorted according to cardiac and psychological indexing terms (depression, anxiety, anger, and personality traits such as compulsiveness, neuroticism, general complaints and somatization). The studies included have been sorted on the basis of relevance and underwent qualitative evaluation using a questionnaire that was designed based on the Critical Appraisal Standard of evidence-based medicine as proposed by the Cochrane Society (73) and adapted to our needs by ourselves. The literature management program Endnote Version 6 was used to organize the articles cited. The qualitative data from each article was stored and organized in an excel table using Microsoft Excel Version 2000.

Quantitive synthesis of results was performed using the procedure described by Whitehead & Whitehead (74). Statistical analysis is driven by the fixed effect model (FEM) as well as by the random effect model (REM). REM analysis is used as sensitiv-

ity analysis for the results of FEM analysis. If there is considerable divergence between the two results the FEM results cannot be trusted. Even though REM is the appropriate model for certain forms of heterogeneity, the REM result does not represent all situations correctly. Meta-analysis was undertaken with the help of the Comprehensive Meta-Analysis Program engineered by Biostat (Engelwood, New Jersey, 07631, USA).

The fact that only 25 references were actually incorporated in meta-analysis is related to various problems. First; in many of the studies the distinction between coronary artery disease and syndrome X as well as the definitions of both disorders that were exclusively based on non-invasive investigations were unclear or incomplete. The participating patients often suffered from non-cardiac chest pain with or without a history of coronary artery disease. These articles were excluded

Table 2.

Effect sizes of different psychological variables between panic disorder (PD), coronary artery disease (CAD), and cardiac syndrome X (SYX) compared to Normal Controls (NC)

Psychological Variables			Fixed Effect		Random Effect	
		N		p=		p=
Depression						
PD	NP	216	0.893	0.001	1.075	0.001
PD	SYX	106	0.632	0.007	0.667	0.058
SYX	CAD	52	0.873	0.005	0.873	0.005
Anxiety						
PD	CAD	152	-0.343	0.041	-0.347	0.233
PD	NP	728	0.936	0.001	1.097	0.001
PD	SYX	352	0.944	0.001	0.971	0.001
SYX	CAD	260	1.535	0.0001	1.535	0.0001
Anger						
PD	NP	40	1.183	0.001	1.183	0.001
PD	SYX	532	-3.329	0.0001	-3.329	0.0001
SYX	CAD	457	0.589	0.0001	0.674	0.414
Personality Factors						
Compulsiveness						
PD	NP	40	1.322	0.001	1.322	0.001
PD	SYX	38	0.718	0.086	0.718	0.086
Somatization						
PD	CAD	38	0.163	0.619	0.163	0.619
PD	NP	256	0.812	0.0001	1.372	0.02
PD	SYX	38	0.862	0.043	0.862	0.043
General Complaints						
SYX	CAD	104	1.536	0.0001	1.536	0.0001

from meta-analysis since they were not relevant to our research question. Second; the disorders were not clearly distinguished from each other and the diagnostic groups were not homogeneous either. In some publications there was overlap between panic disorder and chest pain of non-cardiac origin, and between coronary artery disease and normal population. Third; in some publications the statistical data were incomplete or contradictory so that they could not be used either for determining effect sizes or odds values. What was particularly regrettable was that statistical problems could not be resolved even by consulting with the respective authors.

These difficulties seem to suggest that only a limited number of references actually addressed the problem of syndrome X or related aspects (depression, anxiety, anger, tendency to somatization, and personality factors). There is still a great need for studies which fulfill these criteria. The incredibly large number of narrative reviews — some of which are highly selective — and often include unclearly defined patient groups and do not call for replication.

RESULTS OF THE EMPIRICAL META-ANALYSIS EFFECT SIZES

The effect sizes calculated ensure a relatively substantial sample size which, in turn, represents as good a match as possible between the hypotheses we formulated and the diagnostic instruments employed (table 2).

Additionally, all ranges of effects of the comparisons between different pathologies are depicted in figure 1.

Panic Disorder vs. Cardiac Syndrome X

There are significant differences between patients with panic disorder and those with syndrome X as to depression, anxiety, anger, and somatization (as part of personality characteristics). On the other hand, no differences were detectable between other personality dimensions such as compulsiveness; no data was to be found in the studies reviewed concerning neuroticism and general complaints.

Cardiac Syndrome X vs. Coronary Artery Disease

Significant differences between patients with cardiac syndrome X and patients with coronary artery disease were found as to depression, anxiety, anger and general complaints. None of the research work incorporated in meta-analysis yielded data about the dimensions compulsiveness, neuroticism and somatization.

Panic Disorder vs. Normal Volunteers

Significant differences between patients with panic disorder and normal volunteers were found as to depression, anxiety, anger, compulsiveness, and somatization. None of the research work incorporated in meta-analysis yielded data about general complaints.

DISCUSSION

Our meta-analysis shows that cardiac syndrome X differs significantly in its clinical presentation and psychological features from coronary artery disease as well as from panic disorder. This is in line with clinical experience and most of the published original papers and reviews. Our assumption that patients with cardiac syndrome X are more depressed and more anxious than patients with a coronary artery disease was confirmed. In contrast, the hypotheses regarding anger were shown to be untenable. The data indicates that syndrome X patients have a greater tendency to become angry than patients with a coronary artery disease (opposite to our assumption). On the other hand, as regards to general complaints the result points in the right direction in that the patients with syndrome X reported more complaints. Moreover, we had hypothesized that depression, anger, and somatization would significantly differ in that patients with panic disorder would score higher in all of these areas than patients with syndrome X. Meta-analysis data yielded conclusive evidence to this effect. Regrettably, we were unable to locate any research on the remaining dimensions of personality characteristics.

DEPRESSION

In our first hypothesis we assumed that the amount of depression must be different between patients with panic disorder, coronary artery disease, syndrome x, and normal controls. Patients with syndrome X were hypothesized to be more depressed than those with coronary artery disease. In our meta-analysis we found depression to be higher in patients with cardiac syndrome X than others with a coronary artery disease.

This finding has been found in a small number of 22 patients with syndrome X compared to 30 patients with coronary artery disease (75). Other research work pointing to the same direction entered also our meta-analysis. However, there was no paper describing whether patients with syndrome X (and a higher depression score) have lower cardiovascular mortality compared to those with coronary artery disease. One could assume that depression with its similar effects on vascular local hormones and clotting factors as well as higher vascular wall stress should have similar effects on mortality as it has been proved for patients suffering from coronary artery disease. Additionally, we found no paper which investigated the long-term course of patients with syndrome X and their probability to switch into the group of patients with coronary artery disease during their disease course (76).

Moreover, we had hypothesized that depression would significantly differ in that patients with panic disorder would score higher in all of these areas than patients with syndrome X. Meta-analysis data yielded conclusive evidence to this effect, making the same arguments valuable which were discussed in respect

to syndrome X and coronary artery disease. However, in the case of panic disorder a higher mortality has been proved compared to normal controls (77,78) or patients without panic disorder (79) but not to others suffering from coronary artery disease (80).

ANXIETY

We assumed that anxiety would significantly differ between patients with panic disorder, or syndrome X compared to coronary artery disease, and normal controls. Indeed, in our meta-analysis syndrome X patients were found to be more anxious than patients with coronary artery disease.

Various authors have examined the question of anxiety. Beck et al. (34) compared chest pain patients, panic disorder patients and control subjects. While trait anxiety and phobic fears were strongest among patients with panic disorder, chest pain patients displayed the highest degree of situation-related anxiety. Additionally, the researchers found a lower level of anxiety and avoidance in chest pain patients who did not have an organic heart disease than in panic disorder patients. In addition, the former group of patients did not need as much anxiolytic medication to alleviate symptoms. Serlie's group (81) on the other hand, could not find any significant differences in state or in trait anxiety between patients with chest pain of non-cardiac etiology and heart patients. However, this group found a significantly higher level of basic anxiety in chest pain patients who had no organic disease - a finding that had already been reported by Elias (35) more than a decade beforehand. Roy-Byrne et al. (82) compared panic disorder patients and patients with microvascular angina. The differences in anxiety were thought to suggest either panic disorder comorbidity or two possible categories of microvascular angina. In a later study chest pain, dyspnea and paresthesias as well as substantially greater anxiety prior to myocardial infarction was found significantly more often in both patient groups than in the control group, whereby panic disorder patients' symptoms were the most intense and frequent (83). Beck et al. (84) succeeded in lending even greater support to these results by conducting a provocation test with hyperventilation. As opposed to Beck et al., Beitman et al. (32, 85) described a sub-group of panic disorders which met all the diagnostic criteria for panic disorder with the exception of subjective fear. As a result, these patients had been designated as suffering from «nonfear panic disorder». In studies on the family-related prevalence of panic disorders, both groups of patients were found to be at greater risk

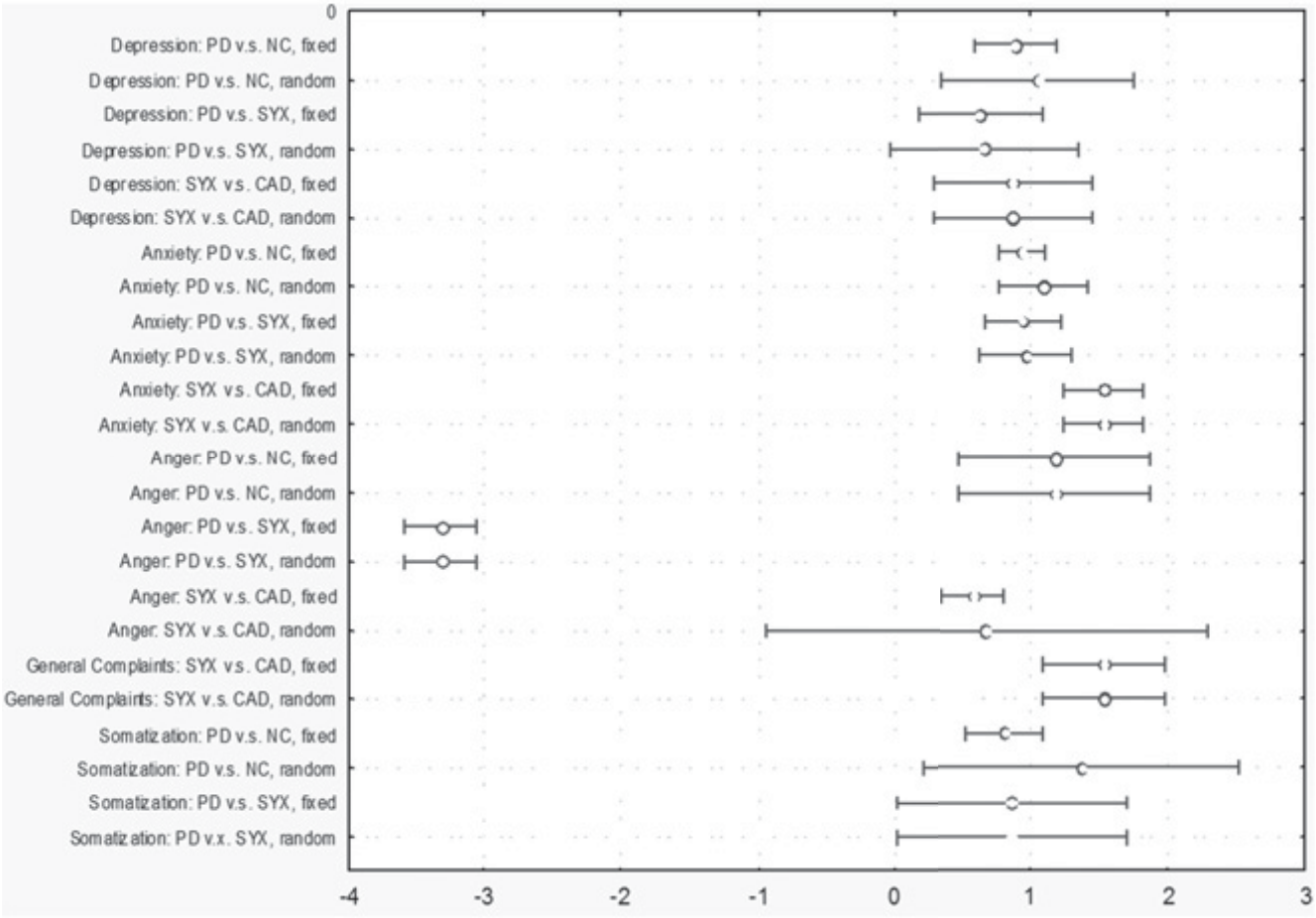

Fig. 1. Effect Sizes of Psychological Characteristics of Patients with Angina Pectoris and Syndrome X (SYX), Coronary Artery Disease (CAD), or Panic Disorder (PD) compared to Normal Controls (NC). An effect size of >0.35 is generally accepted as relevant (dotted line)

than the normal population if they had a close relative with panic disorder history (86,87).

ANGER

In contrast, the hypotheses regarding anger were shown to be untenable in that data indicates syndrome X patients to have greater an anger tendency than patients with a coronary artery disease.

With regard to the association between chest pain and these personality factors, Schocken et al. (36) report on a study with angina patients in which patients with silent ischemia showed less of a tendency to become angry than patients with ischemia. In addition, patients with angina were rated as more angry and neurotic than those without chest pain. Beck (34) compared patients with persistent chest pain, panic disorder patients and control subjects. Therein, neither Beck nor Serlie (81) found any significant differences with regard to anger nor could Ruggeri et al. (75) demonstrate any differences between syndrome X patients' and heart patients' anger, related coping and management strategies. On the other hand, Eifert el al. (88) found significantly higher anger potential in panic disorder patients than in healthy controls. Tennant et al.'s (89) goal was to distinguish between the two groups based on indices of myocardial thallium scintigraphy. They detected a significant difference in anger between ischemia patients and those with normal thallium scans.

Personality traits (compulsiveness, general complaints, somatization)

The initial assumption that patients with cardiac syndrome X report more complaints than others with a coronary artery disease was confirmed. Thereby, it was assumed that syndrome X patients focus more attention on physical symptoms than do patients with coronary artery disease and exhibit less general complaints than those with panic disorder.

Various attempts were made to develop a better and simpler method of assessing the symptoms and the psychiatric-psychological problems of persons who experience chest pain. An approach was developed by Fraenkel et al. (90) to identify the differences in cognitions during chest pain between patients with angina pectoris and those with panic disorder. All patients with normal coronary angiograms experienced frightening cognitions during chest pain. While in 83% of this group, the cognitions were the predominant experience, only 18% of the patients with proven symptomatic coronary artery disease complained of their symptoms and only 4% of them attributed their frightening cognitions to chest pain. On the other hand, Ladwig (91) suggests grouping chest pain symptoms of non-cardiac origin as a somatoform pain disorder rather than as an anxiety and panic disorder. The question as to whether there ought to be differences in pain perception between patients with chest pain and coronary artery disease and syndrome X patients has remained controversial. Cannon (92) found exaggerated or abnormal cardiac pain perception in patients with chest pain, normal coronary angiograms and ischemic signs under stress. In a study comparing pain perception in patients with syndrome X , patients with mitral valve disease and coronary artery disease, and heart transplant recipients, Chauhan et al. (93) found typical anginal chest pain more often in syndrome X patients (94%) than in the other groups (0-19%) when stimulated intracardially. The authors concluded that the results of their study suggested that abnormal cardiac pain perception is a fundamental abnormality in syndrome X.

LIMITATIONS:

First of all, we must assume that our selection criteria were very straight and excluded e.g. unclear diagnostic description of patients, non-validated psychometric instruments, and lacks of diagnostic workup. However, this would only have been avoidable if we had access to the raw data of the respective studies what was not the case in most studies. Second, the various psychological measuring instruments pretend — as was stated in the respective manuals — to measure the same constructs. We had to include these different measuring instruments to augment the number of research work assessed. To compare the various instruments we had to normalize the values and adapt them into a preformed scale in order to becoming able to include them in the effect size calculation. Therein it was assumed that the intervals be the same over the whole Likert scales of the respective instrument included. This could also have an effect on the reliability of our findings in that the comparability has not been tested beforehand. Additionnally, the publication bias in studies using psychometric instruments and medical diagnoses is known to be substancial (94). This could only be refuted if we could depict that the best and most strenuous articles were found in high-ranked journals. This was, however, not the case. Moreover, we could even prove that there was no correlation whatever between numbers of patients included, valuable instruments used, or thorough diagnoses groups and the impact factor of the respective journal.

CONCLUSIONS

All in all, the results of our meta-analysis show that syndrome X is an entity characterized by distinct clinical and psychological features that can be clearly distinguished from coronary artery disease, panic disease and non-cardiac chest pain. Differences in complaints, such as angina pectoris - which is indistinguishable between coronary artery disease and syndrome X - appear to be less pronounced than in pathophysiology and psychological parameters. Nevertheless, many patients who showed negative results in coronary angiography complain of per-

sistent chest pain in the course of illness and suffer under decreased social and vocational function in the long term 95 96.

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Polymorphisms in eNOS and Gpx-1 Genes are Asociated with the Risk of Restenosis after Coronary Stenting with Bare Metal Stentss

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Coronary artery stenting is widely used for the treatment of patients with coronary artery disease (CAD). However, in-stent restenosis leading to the recurrence of the symptoms of myocardial ischemia still remains the main problem after a successful intervention, and drug-eluting stents cannot solve this problem once and for all. The search for new risk factors of in-stent restenosis development, including genetic ones, is still vital. Correlation between functional polymorphisms in genes encoding antioxidant enzymes, as well as the frequency and the degree of restenosis after stenting of the coronary arteries with bare metal stents has been assessed. Minor alleles of eNOS G298T and Gpx-1 Pro198Leu polymorphisms were shown to be associated with restenosis incidence, and the minor allele of Gpx-1 Pro198Leu polymorphism was associated with increased degree of the coronary artery restenosis.

Key words: *coronary stenting, genetic risk factors, restenosis, antioxidant enzymes.*

Objective: To study correlations between polymorphism genotypes in genes encoding 6 antioxidant enzymes and the risk of restenosis development after coronary artery stenting with bare metal stents.

Material and methods: The study comprised male patients who underwent intracoronary stenting using bare metal stents and control coronary angiography in 6 months after it. Frequencies of genotype polymorphisms (262 C/T in the CAT gene, L55M and Q192R in the PON-1 gene, G298T and -786T/C in the eNOS gene, Pro198Leu in the Gpx-1 gene, Ile105Val in the GSTP gene and C242T in the NAD(P)H gene) were studied.

Results: A total of 101 patients enrolled into the study were divided into 2 groups – with (n=44) and without restenosis (n=57). L-allele of Pro198Leu polymorphism in the Gpx-1 gene (Odds Ratio (OR) = 2.9; 95% Confidence Interval (CI): 1.23–6.82) and T-allele of G298T polymorphism in the eNOS gene (OR = 2.79; 95% CI: 1.17–6.66) were associated with the risk of in-stent restenosis.

Conclusion: In Russian population, Gpx-1 Pro198Leu and eNOS G298T polymorphisms can be used as additional risk markers of restenosis development after coronary artery stenting with bare metal stents in males.

To date coronary artery stenting is widely used for the treatment of coronary artery disease (CAD). However, in-stent restenosis leading to the recurrence of myocardial ischemia symptoms still remains the main problem after a successful intervention, and drug-eluting stents do not solve this problem once and for all (1). Hence, the search for new risk factors of in-stent restenosis development, including genetic ones, is still of great importance.

Effects of polymorphism in genes encoding different enzymes and receptors on in-stent restenosis are being actively studied all over the world. Polymorphisms in homeostasis system genes (2), inflammatory system genes (3,4), renin-angiotensin system genes (5,6), and also Glu298Aps and - 786T/C polymorphisms in the endothelial nitric oxide synthase (eNOS) gene (7,8,9) are currently known to play a role in the development of in-stent restenosis. It is known that the oxidative stress in the vascular wall develops immediately after the lesion. Its symptoms persist during all stages of in-stent restenosis, including the stage of neointimal hyperplasia (proliferation and migration of smooth muscle cells (SMC) and synthesis of extracellular matrix) (10,11) which is the leading mechanism of the restenosis development after coronary stenting (12). Active forms of oxygen are known

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to modify the aggregation functions of thrombocytes and are also the inflammation mediators (13,14,15); besides, thrombosis and inflammation also play an important role in the process of restenosis. Up to date there has been no system approach to the study of the influence of polymorphisms in genes encoding main antioxidant enzymes on the process of restenosis. Meanwhile this is is particularly important considering the great role of these polymorphisms in the mechanisms of restenosis development. At the same time the impact of functional polymorphisms in genes encoding antioxidant enzymes, such as catalase (CAT), paraoxonase-1 (PON-1), eNOS, glutathione peroxidase-1 (GPx-1), glutathione-S-transferase (GSTP), NAD/NAD(P)H-oxydase (NAD(P)H), on the development of cardiovascular diseases and their complications (16,17,18,19,20, 21, 22) has been shown. Basing on the above we have evaluated effects of functional polymorphisms in genes encoding antioxidant enzymes on the frequency and degree of restenosis after the stenting of coronary arteries using bare metal stents in groups of patients with and without in-stent restenosis.

MATERIAL

Patients and study protocol

Male patients with CAD who underwent the intracoronary stenting using bare metal stent and control coronary angiography (CAG) on average in 6 months after the procedure were included into the study. Patients with myocardial infarction (MI) and the stroke within less than 6 months prior to the study start, severe congestive heart failure, severe rhythm and conduction disturbances, family hypercholesterolemia and hypertriglyceridemia, type 1 diabetes mellitus (T1D) or decompensated type 2 diabetes (T2D), oncological diseases, hepatic and renal failure, alcohol abusers, those who had been taking antioxidant drugs and had the type C atherosclerotic lesion of the coronary arteries according to the ACC/AHA classification (1988) were excluded from the study.

Before and after PCI all patients received standard therapy including Plavix for 3-5 days before stenting and for 6-12 months after it. During the angioplasty heparin (70 U/kg intra-arterially) and nitroglycerin (250 μg intracoronary) were administered to each patient.

ANGIOGRAPHY DATA

Transluminal coronary angioplasty with stenting was performed according to the standard technique using Axiom Artis, Siemens (Germany) equipment. After the intervention the contrast study of the stented fragment was performed at least in 2 orthogonal projections. The control CAG was performed in each patient on average in 6 months after the stenting using the same equipment and same projections. The analysis of obtained angiograms was performed using Axiom Artis quantitative computed analysis system (Siemens, Germany). Angiographic restenosis was determined as artery narrowing of the stented segment > 50%. Patients after stenting of two coronary artery segments and restenosis in one of them on the control CAG, were included into the restenosis group.

GENETIC INVESTIGATION

The following parameters were determined: -262 C/T polymorphism in the CAT gene (rs#564250), L55M (rs#854560) and Q192R (rs#662) polymor-

Table 1.

Parameters of the restriction analysis

Polymorphism	PCR product length (base pairs)	Restrictase	Restriction fragment length (base pairs)
CAT-262 C/T: allele C allele T	185	SmaI	30 and 155 185
PON-1 L55M: allele L allele M	170	Hin1 II	170 44 and 126
PON-1 Q192R: allele Q allele R	99	BspPI	99 33 and 66
eNOS G298T: allele G allele T	206	MboI	206 87 and 119
eNOS -786 T/C: allele T allele C	236	MroNI	236 33 and 203
Gpx-1 Pro198Leu: allele P allele L	337	HaeIII	79 and 258 337
GSTP Ile105Val: allele I allele V	436	BstMAI	108 and 328 105, 108 and 223
NAD(P)H C242T: allele C allele T	509	RsaI	113 and 396 80, 113 and 316

phisms in the PON-1 gene, G298T (Glu298Asp; rs#1799983) and -786T/C (rs#2070744) polymorphisms in the eNOS gene, Pro198Leu polymorphism in the Gpx-1 gene (rs#1050450), Ile105Val polymorphism in the GSTP gene (rs#1695) and C242T polymorphism in the NAD(P)H gene (rs#13474332).

Genomic DNA was extracted from whole blood samples as described earlier (23). Fragments of respective genes were amplified by polymerase chain reaction (PCR) under the conditions described earlier (19,24,25,26,27,28). The following primers were used for amplification of the GPx-1 gene's fragment: direct 5'-TGT GCC CCT ACG CAG GTA CA-3' and reverse 5'-CCA AAT GAC AAT GAC ACA GG-3'. The genotype was determined by the method of analyzing restriction fragment length polymorphism which is based on creating a natural restriction site in one of the alleles during PCR. After the end of PCR, 3 μg of 10X buffer for restriction and enzyme 2 U were added into the tubes individually for each polymorphism and incubated for 14 hours. Restriction products were analyzed with electrophoresis in 2.5% agarose gel containing ethydium bromide 1μg/ml. Fragment sizes were determined with the help of weight standards 50 bp.-Ladder, Fermentas (Table 1).

STATISTICAL ANALYSIS

The obtained results were processed statistically using STATISTICA 6.0 software. Conformity of received genotype frequencies to the Hardy-Weinberg distribution was determined with the help of Fisher's test. For quantitative comparison of the groups the parametric (Student t-test) and non-parametric (Mann-Whitney test) methods were used. X^2–test and exact Fisher test were used for the qualitative comparison of the groups. In order to determine the odds ratio (OR) a logistic regression analysis was used. The parameters with normal distribution were presented as the mean and standard deviation (Mean; 95% CI), and the parameters with non-normal distribution were presented as the median and lower and higher quartiles (Med: (LQ; HQ)). Differences were considered to be significant at $p < 0.05$.

Table 2.

Clinical characteristics of the patients and angiographic parameters of coronary artery lesions

Parameters	Restenosis group (n=44)	Group without restenosis (n=57persons)	P (intergroup differences)
Age	56.5 (47.5-62.5)	58 (53 - 62)	0.4
History of MI	28(64%)	33 (58%)	0.68
AH	25(57%)	34(60%)	0.84
- type 2 diabetes mellitus - other disorders of carbohydrate metabolism	4 (9%) 4 (9%)	5 (9%) 8 (14%)	0.75
Smoking status: -current smoker - gave up - non-smoker	9 (21%) 12 (27%) 23 (52%)	13 (23%) 12 (21%) 32 (56%)	0.77
TC (mmol/L)	4.83 + 1.09	4.95 + 0.81	0.29
LDL-C (mmol/L)	3.29 + 0.96	3.12 + 0.72	0.4
HDL-C (mmol/L)	1.08 + 0.32	1.18 + 0.33	0.25
TG (mmol/L)	1.4 (1.06 - 1.97)	1.36 (1.02 - 2.18)	0.85
Artery: -RCA -LAD -CA	14 (32%) 22 (50%) 8 (18%)	21 (37%) 30 (53%) 6 (10%)	0.53
Artery reference diameter (mm)	2.84 + 0.55	2.78 + 0.63	0.63
min d at baseline (mm)	0.93 + 0.55	1.13 + 0.44	0.1
Stenosis at baseline (%)	86.5 + 10	81 + 10	0.08
Stent's length (mm)	16 (13 - 18)	13 (9 - 18)	0.09
min d after stenting (mm)	2.5 + 0.52	2.43 + 0.54	0.44
Stenosis after stenting (%)	9 + 6	10 + 4	0.96

AH — arterial hypertension; RCA — right coronary artery; LAD — left anterior descending artery; CA — circumflex artery; min d — minimal diameter, MI — myocardial infarction; TG — triglycerides; LDL — low density lipoproteides,; HDL — high density lipoproteides.

RESULTS

We examined two groups of patients who underwent coronary artery stenting with bare metal stents and control CAG in average 6 months after the procedure. The patients were divided into two groups: with (n=44) and without restenosis (n=57). Patients in both groups were comparable in terms of clinical parameters. The lipid profile (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)) also did not significantly differ in both groups. According to angiographic characteristics of the coronary artery lesion there were no significant differences between the groups both before and immediately after the intervention (Table 2). In 6 months after the procedure the mean degree of narrowing at the site of stent implantation was 71% in the group with restenosis and 30% in the group without restenosis.

The frequencies of genotypes polymorphisms (-262 C/T in the CAT gene, L55M and Q192R in the PON-1 gene, G298T and -786T/C in the eNOS gene, Pro198Leu in the Gpx-1 gene, Ile105Val in the GSTP gene and C242T in the NAD(P)H) gene were determined in all patients in groups with and without in-stent restenosis. Polymorphism genotype distribution in both groups was in accordance with the Hardy-Weinberg's law. Taking into account insignificant number of homozygous minor allele observations for polymorphisms (Q192R in the PON-1 gene, G298T in the eNOS gene, Pro198Leu in the Gpx-1 gene and Ile105Val in the GSTP gene), homozygotes for minor allele were combined into one group with heterozygotes for statistical calculations of these polymorphisms. Significant differences between groups were obtained for 2 polymorphisms: G298T in the eNOS gene and Pro198Leu in the Gpx-1 gene (Figure 1). There were more minor allele carriers of eNOS G298T polymorphisms in the group of patients with restenosis (54.5% compared with 28% in the group without restenosis, $p<0.01$). There were also more minor allele carriers of Gpx-1 Pro198Leu polymorphisms in the group of restenosis (61% compared with 35% in the group without restenosis, $p<0.01$).

The comparison of homozygotes for wild-type allele (PP genotype) and carriers of minor allele (PL+LL) Gpx-1 Pro198Leu polymorphism did not reveal any significant difference between the groups in terms of clinical parameters. The degree of restenosis in minor allele carriers is by 21% higher than in the group of PP wild genotype carriers (54% against 42.6%, $p = 0.01$). In minor allele carriers the frequency of restenosis is 1.9-fold higher (59% against 31%, $p = 0.0085$) (Figure 2). The minor allele of Pro198Leu polymorphism in the Gpx-1 gene was associated with increased risk of in-stent restenosis (OR = 2.9; 95%CI: 1.23-6.84). As for G298T polymorphism in the eNOS gene, differences between the groups were revealed only in the frequency of restenosis. In minor allele carriers (genotype GT+TT) the frequency of restenosis is 1.8 times higher than in the group of GG genotype carriers (60% against 33%, $p = 0.008$) (Figure 3) and G298T polymorphism minor allele in the eNOS gene was associated with increased risk of in-stent restenosis (OR = 2.79; 95%CI: 1.17-6.66).

DISCUSSION

Oxidative stress palys a certain role at all stages of the restenosis process: thrombogenesis, inflammation, and neointimal hyperplasia (29). Lipoperoxides and other AOS (active oxygen species) are an important factor in regulation of SMC growth signals and inflammatory response to the vessel lesion (30). Considerable influence of oxidative stress on the processes of restenosis is also proved by the fact that among diverse clinical risk factors for cardiovascular diseases only type 2 diabetes mellitus (T2DM) predicts restenosis after the stenting (12,31). The intensification of lipid peroxidation (LP) in patients with DM is evidenced by accumulation of considerable concentrations of malondialdehyde (a secondary product of LP) in patients' blood plasma, while the antioxidant activity of plasma in patients with T2DM is considerably reduced (32). Antioxidant enzymes are the main protectors of the body from the oxidative stress, and their content in the blood plasma

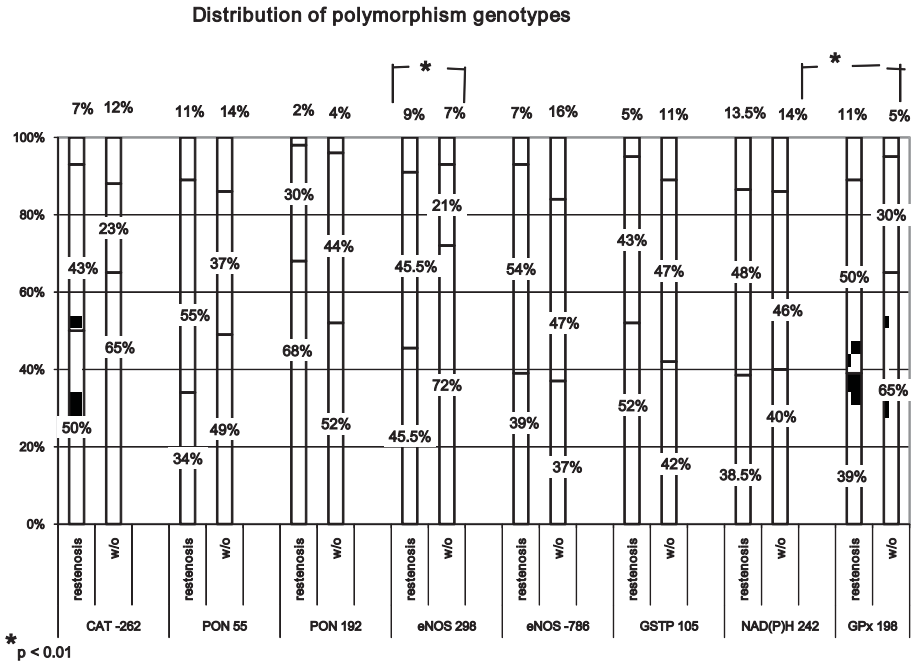

Fig. 1. Distribution of polymorphism genotypes in groups with restenosis and without restenosis

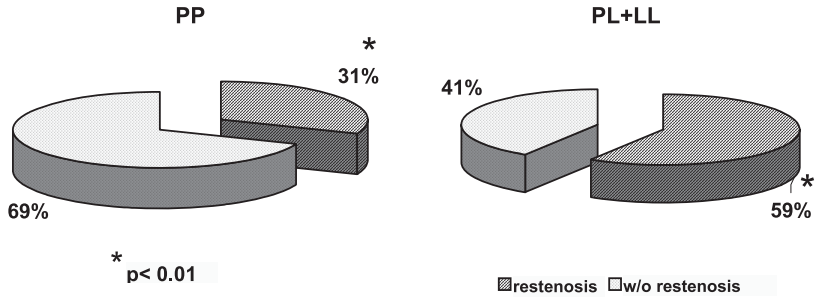

Fig. 2. Frequency of restenosis in groups of PP and PL+LL genotypes of P198L polymorphism in the Gpx-1 gene

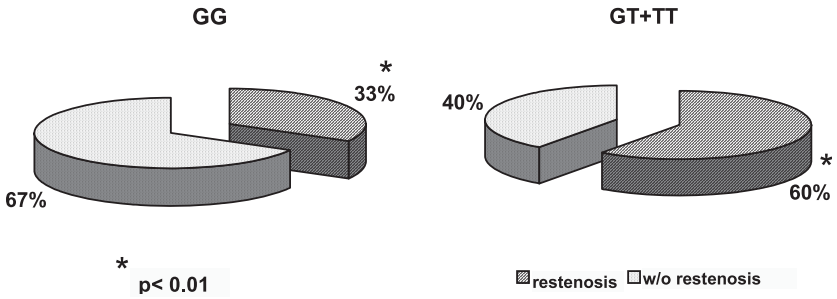

Fig. 3. Frequency of restenosis in groups of GG and GT+TT genotypes of G298T polymorphism in the eNOS gene

and their activity can be genetically determined. Accordingly, the correlation between polymorphisms in genes encoding antioxidant enzymes and the risk of restenosis development after the coronary stenting was being investigated in our study.

It is known, that Gpx participates in the metabolism of peroxynitrite and also destroys organic peroxides in the body including lipoperoxides (13) that are cytotoxic for macrophages, endothelial cells, and vessels' SMC, leading to their death (33). It was shown in earlier studies that the risk of cardiovascular complications increased in patients with reduced catalytic activity of Gpx and documented CAD (20,34). The influence of Pro-198Leu polymorphism in the Gpx-1 gene on restenosis development was not investigated in earlier studies, although the role of this polymorphism in cardiovascular diseases' development was revealed. It was shown that the carriers of minor allele had higher thickness of the intima-media complex of the common carotid artery ($p = 0.0028$). They also had higher prevalence of cardiovascular diseases ($p = 0.035$), peripheral vessel diseases ($p = 0.027$) (35), and the coronary calcium score according to the data of multispiral computed tomography ($p = 0.006$) (21).

The eNOS is known as one of the key enzymes in the production of nitric oxide (NO) which, in its turn, acts as a vasodilator, inhibits SMC growth (36), prevents thrombocyte aggregation, inhibits adhesion of leukocytes to the vessel wall (37), and also has the antioxidant activity (38). Our data indicate that T-allele of G298T polymorphism in the eNOS gene increases the risk of restenosis after the coronary artery stenting, which is in conformity with previously received data. Thus, the study conducted in 226 patients after coronary artery stenting, revealed higher risk of restenosis in carriers of T-allele G298T polymorphism in the eNOS gene (OR = 1.88; 95%CI: 1.01–3.51; $p = 0.043$) (7). T. Suzuki et al. (2002) have shown that T-allele is an independent predictor of restenosis development (OR = 3.09; $p = 0.036$) (8). At the same time it is known that T-allele leads to reduced eNOS enzyme activity (39) and G298T polymorphism in the eNOS gene is associated with reduced NO level (40) that eventually leads to respective decrease of its protective role. Probably, this might explain the negative influence of these eNOS gene polymorphisms on the processes of restenosis development.

CONCLUSION

Thus, our data allows to consider eNOS G298T and Gpx-1 Pro198Leu polymorphisms as possible risk factors for restenosis development after coronary artery with bare metal stents in male patients in Russian population.

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4th Russian Congress of Interventional Cardioangiology. Information Report.

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The 4th Russian Congress of Interventional Cardioamgiology took place in Moscow from March 21st to 23rd, 2011 in the World Trade Center. The Congress was organized by Russian Society of Interventional Cardioangiology (RSICA) with the support of All-Russian Scientific Society of Cardiology, Russian Scientific Society of Angiology and Vascular Surgery, Moscow City Center of Interventional Cardioangiology, Medical Scientific Center of Radiology of the Ministry of Healthcare of Russia and the Center of Endosuregry and Lithotripsy. Over 1000 delegates from Russia and different countries, including Germany, USA, Spain, France, Switzerland, Italy, Japan, etc, participated in the Congress.

After the opening speech of the President of RSICA, Professor Zaza Kavteladze, the Congress started its work. World-renowned leaders and experts M. Dake, J. Bilbao and J. Moses presented the lectures on the state of the art and perspectives of development of interventional radiology in the 21st century.

Two plenary sessions held during the first day of the Congress two plenary sessions were dedicated to endovascular interventions in acute coronary syndrome. Leading Russian specialists — V.I. Ganyukov, A.M. Babunashvili, E.Yu. Vasilieva, E.V. Merkulov — presented their viewpoint on this problem. The presentations dedicated to the problem of ACS management in patients with the lesions of the left main coronary artery, the use of radial approach for primary coronary angioplasty in patients with ACS and the use of thromboextraction in patients with acute myocardial infarction. A special session was dedicated to the new generation of drug-eluting stents, drug-eluting balloons and biodegradable stents. A special session under the auspices of EuroPCR, held for the first time in Russia, dealt with one of the thrilling problems — the management of patients at high risk for surgical interventions, including the use of hybrid procedures for their treatment. A great interest was provoked by plenary sessions on the problems of endovascular interventions in critical leg ischemia, the treatment of extra- and intracranial arterial pathology and endovascular interventions in gynecological patients.

Plenary sessions held during the second day of the Congress were dedicated to several most complicated trends in modern interventional cardioangiology — the treatment of chronic occlusions and bifurcation lesions of the coronary arteries. The organizers did not overlook important problems of modern interventional radiology: separate sessions were dedicated to the management of cancer, the interventions for the lesions of the abdominal aortic branches and the treatment of venous pathology.

The most memorable event during the second day of the Congress was the jubilee session held to celebrate the 60th anniversary of the eminent interventional cardiologist of our time Antonio Colombo. During this session the hero of the day presented the lecture «My view on modern interventional cardiology» and received the Special Lifetime Career Achievement Award for his contribution into the development of our speciality.

A special session with the participation of scientific societies from the former Soviet republics held during the third day of the Congress allowed to exchange opinions on the state of the art and perspectives of the development of interventional cardiology. The participants of a jubilee session held on the occasion of 20 years of the method of aortic aneurysms stent-grafting brought back to mind the history of this technique and its development, and also discussed current approaches to the treatment of the aneurysms of thoracic and abdominal aorta. During the session “Meeting the industry” held for the first time the top-managers of the leading world companies-producers of expendable materials and instruments for endovascular and transluminal surgery shared their strategic vision on the development of technical equipment for this booming field of medicine. Special attention was paid to unsolved problems of modern interventional cardioamgiology — the necessity of stenting of renal and carotid arteries, the advantages and disadvantages of this method in comparison with pharmacological and surgical treatment. As usually, a great interest was manifested toward the session dedicated to the presentation of complex clinical cases met by interventional cardiologists. During the session on new technologies in endovascular surgery Professors A. Colombo and C. Neinaber made presentations on transcatheter aortic valve implantation. The Congress ended by a session held to hear reports and elect a new management of RSICA. The President of RSICA, Professor Z. Kavteladze reported on the work performed during the last three years. The Board highly appreciated the work of Professor Kavteladze and thanked the Organizing Committee for its efforts on holding the Congress at a good international level. According to the Status of the Society, the Board conducted a ballot vote and elected the Corresponding Member of Russian Academy of Medical Sciences, Professor Leonid Kokov to the presidency of RSICA for the next 3 years.