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Contents

Results of Endovascular Interventions in Patients with Acute Myocardial Infarction and Type 2 Diabetes Mellitus

L.S. Barbarash, A.A. Azarov[1] , O.L. Barbarash, E.V. Tavlueva, S.A. Evtushenko, V.I. Ganiukov
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In-hospital and long-term (in 12 months) results of primary PCI in 140 AMI patients (76 AMI patients without T2DM and 64 AMI patients with T2DM) have been studied. During the in-hospital period, total cardiac complications were more often (by 2,3 times) reported in T2DM patients (2.6% and 6.2%, respectively, p=0.011); stent thrombosis was the reason of such complications in all cases, and for this reason the rate of repeated PCI in T2DM was 2.3 times higher (p=0.011). During the long-term period, total cardiac complications were still more commonly (by 2,9 times) seen in T2DM patients (10.5% and 31.2%, respectively, p=0.011). In the subgroup of incomplete revascularization, the maximum rate of cardiac complications (43.7%) was reported in T2DM patients;, there were no angina-free patients; trend of increased rate of severe (III-IV class CCS) angina was prevailing. Fatal outcomes and IV class CCS angina, being the main distinguishing features of patients with MI and T2DM, were observed in this subgroup only. Additionally, the lowest indices of myocardial perfusion after blood flow restoration in SRA and MA stenosis (II grade MB in 56% of patients) were observed in this subgroup.

Keywords: *percutaneous coronary intervention, acute myocardial infarction, type 2 diabetes mellitus*.

Objective: To identify factors determining unfavorable results of primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) and T2DM .

Materials and methods: 140 AMI patients were included in this study and divided into 2 groups: Group 1 – 76 patients without T2DM , Group 2 – 64 patients with T2DM. After diagnosis confirmation the patients underwent coronarography followed by PCI.

The efficacy of primary PCI during the in-hospital (up to 30 days)/long-term (at 12 months) period was assessed by total cardiac complications (early post MI/unstable angina + recurrent/repeated AMI + fatal outcome), stroke, stent thrombosis, repeated PCI, and need for direct myocardial revascularization. Long-term clinical outcomes (absence/presence of angina pectoris attacks, functional class of angina) were also assessed; correlation between long-term outcomes of primary PCI, completeness of revascularization, and microvascular status were evaluated as well; for this purpose each study group was divided into 2 subgroups: complete and incomplete revascularization in AMI.

Results: According to comparative analysis, patients of both groups had similarly severe coronary lesions as assessed by Yu.S. Petrosyan and D.G. Iosseliani method (39.58±19.86% and 43.67±25.11%, p=0.744) and by Syntax scale (17.59±8.98 and 20.95±10.31, p=0.222). The incidence of three-vessel lesions was 2 times higher in T2DM patients (21.1% and 43.7%). As assessed by myocardial blush (MB), lower myocardial perfusion after the intervention and/or initially more marked distal microvascular disease – II grade MB, was observed twice more often in patients with diabetes mellitus (21% in Group 1 and 40.6% in Group 2, p=0.043), although the restoration of symptom related artery and hemodynamically significant stenosis of the main artery[2] was achieved in 100% in the both groups. Complete myocardial revascularization was performed in 47.4% and 50% of patients in Group 1 and 2, respectively (p=0.112).

During the in-hospital period, total cardiac complications were more often reported in T2DM patients (2.3 times) (2.6% and 6.2%, p=0.011); stent thrombosis was the reason of such complications in all cases, so T2DM patients underwent repeated PCI 2.3 times more often (p=0.011). The analysis of the individual unfavorable outcomes showed no differences in the incidence of early post-MI angina between the groups (p>0.05). Recurrent MI was reported in 3.1% of patients in T2DM group only (p<0.05), which determined significant difference in total cardiac events between the groups.

During the long-term period, total cardiac complications were still more often reported in T2DM patients (2.9 times) (10.5% in Group 1 and 31.2% in Group 2, respectively, p=0.011). However, the incidence of unstable angina during the long-term period in T2DM patients was higher (3.6 times) than that in non-T2DM patients (5.2% and 18.2%, p<0.05), although there were no significant differences in the incidence of non-fatal AMI (5.2% and 6.2%) and stent thrombosis requiring repeated PCI (10.5% and 12.5%, p>0.05) between the groups. Fatal outcomes were reported in 6.2% of patients in T2DM group only and were caused by AMI complicated by cardiogenic shock (p=0.041). There were no significant differences in the need for direct myocardial

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[2] According to the authors, the term « main artery » implies non symptom-related artery with significant stenosis which was stented

revascularization during the long-term period between the groups (10.5% and 12.5%, respectively, p>0.05). Absence of signs of stable angina one year after AMI was observed in non-T2DM patients 4 times higher (47.4% in Group 1 and 12.6% of patients in Group 2, p=0.001). FC I angina was observed in 15.7% and 21.8% of patients, and FC II angina in 28.9% and 40.6% of patients, respectively. Additionally, a trend to an increased incidence of severe functional class angina (p<0.05), FC III in 7.8% and 18.7% was revealed in this group. Moreover, FC IV angina was reported in T2DM patients only – in 6.2% of patients. There were no significant differences in intake of antiplatelet drugs, statins, β-blockers between the groups (p>0.05). However, similarly low compliance with statins (60.5% and 56.2%) and clopidogrel (57.9% and 59.4%, respectively) was observed in the both groups.

After dividing T2DM group into complete and incomplete revascularization subgroups, it was revealed that the maximum incidence of cardiac complications (43.7%) was reported in incomplete revascularization subgroup, there were no angina-free patients; trend of increased rate of severe FC (III-IV) angina was prevailing. The fatal outcomes and FC IV angina determining the main distinguishing features of MI patients with T2DM were reported in this subgroup only. Additionally, the lowest parameters of myocardial perfusion after the restoration of blood flow in SRA and MA stenosis (II grade MB in 56% of patients) were observed in this subgroup.

Conclusions: The presence of T2DM in MI patients is associated with a severe multivessel coronary disease, initially more marked distal microvascular disease and/or low myocardial perfusion after intervention, and generally with a poor prognosis. The main reason for high percentage of unfavorable coronary and clinical outcomes, observed in T2DM patients during the long-term period after AMI is an incomplete primary revascularization of CA during the acute phase of MI.

Abbreviations

CE	– cycle ergometry
CHD	– coronary heart disease
CA	– coronary arteries
MA	– main artery
MB grade	– myocardial blush grade
AMI	– acute myocardial infarction
T2DM	– type 2 diabetes mellitus
SRA	– symptom related artery
FC	– functional class
PCI	– percutaneous coronary intervention

CHD is one of the most common and severe cardiovascular diseases. According to L.A. Bokeria et al. (1) in 2004 the incidence of CHD in the Russian Federation (per 100 000 adults) was 483 which is by 3.2% higher compared to the previous year. Cardiovascular diseases account for 55% of total mortality (2).

T2DM is a serious medical and social problem resulting from its high prevalence, chronic course, tendency to increase in the patient number, high risk of cardiovascular complications leading to early disability and premature mortality. According to WHO data, in 1989 there were 98.9 mln of T2DM patients worldwide. To date, 146.8 mln persons (2.1% of tellurians) are affected with this disease. According to the prognosis made by International Institute of Diabetes Mellitus, in 2010 the number of patients may exceed 215 mln persons and in 2025 - 300 mln persons (3). According to I.I. Dedov's data in Russia, 8 mln persons or 5% of general population have DM, and 90% out of them have T2DM . The mistaken opinion that T2DM is a "milder" form of DM has been existing for a long time. Currently, there are no doubts that it is a severe progressive disease associated with micro- and macrovascular complications, which are the main reasons of patients' death. Thus, T2DM is now considered as not only endocrinological but also cardiological disease.

The particular role in the mortality structure of T2DM patients belongs to AMI which is the cause of death in 50% of cases (4). The particular features of AMI in T2DM patients are high risk of complications, and generally with a poor prognosis due to multiple diffuse CA lesions and microcirculation disorders, which makes difficult to choose treatment options for these patients (5).

According to European guidelines high risk patients (i.e. AMI patients with T2DM), should be treated more intensively – using radio-endovascular technique of coronary recanalization in the first 12 hours of AMI, especially stenting (ACC/AHA/SCAI 2005 GUIDELINE). However, the data obtained from ARTS, DIABETES, EPILOG and other trials suggest unsatisfactory long-term results of elective PCI compared to coronary artery bypass grafting in T2DM patients (the greater incidence of cardiac events, death, restenosis, stent thrombosis, repeated revascularization), which questions the efficacy of invasive treatment strategy in such patients (6,7).

The aspects of urgent PCI in T2DM patients with acute myocardial infarction have not been adequately studied. So far, there have been no data on clinical state and PCI outcomes dependence on completeness of myocardial revascularization and microvascular status in such patients. The factors determining the favorable long-term results of urgent PCI in diabetes patients have not been established, which prompted us to study this question.

The objective of the study was to identify the factors determining unfavorable in-hospital and long-term results of primary PCI in T2DM patients with AMI.

MATERIAL AND METHODS

One hundred and forty AMI patients were included in this study and divided into 2 groups: Group 1 – 76 patients without T2DM , Group 2 – 64 patients with T2DM . The inclusion criteria were AMI confirmed by clinical data, ECG recordings, determination of myocardial necrosis markers [troponin I (TnI) and cardiac fraction of creatine phosphokinase (CPK-MB)]. After the diagnosis confirmation the patients underwent coronarography followed by PCI. Bare metal stents were implanted more often than drug eluting stents – in 89.5% and 78.1% cases, respectively. Sirolimus eluting stents were implanted in other patients. In each case of urgent stenting the complete restoration of artery lumen

was achieved with residual stenosis not exceeding 10% and TIMI-III antegrade blood flow. Total coronary lesion was assessed using SYNTAX score (taking into account bifurcation lesions, acute and chronic occlusions, presence or absence of collaterals, arterial tortuosity). The SYNTAX score of 22 and less corresponded to low degree of coronary artery (CA) lesion ; SYNTAX score of 23-32 – to the intermediate degree; and high score of 33 points and more – to high degree of coronary lesions (8). Moreover, CA lesions assessment was performed by Yu.S. Petrosyan and D.G. Iosseliani method (1976) (9). Postinterventional myocardial perfusion was evaluated by MB grade method using myocardial «staining» at the terminal stage of coronary artery opacification (grade from 0 to 3) (10). As known, this parameter not only allows to assess myocardial perfusion immediately after intervention but also is a "surrogate" sign evaluating the initial degree of distal microvascular disease.

One year after PCI all survived patients were re-examined. Physical examination, clinical and laboratory tests, ECG recording, EchoCG, and CE were performed. The efficacy of urgent percutaneous coronary intervention during the in-hospital (up to 30 days) period was assessed by such parameters as total cardiac complications (early post MI angina + recurrent AMI + fatal outcome), stroke, stent thrombosis, repeated PCI, and need for direct myocardial revascularization. The efficacy of urgent percutaneous coronary intervention during long-term (up to 12 months) period was assessed by such parameters as total cardiac complications (unstable angina + non-fatal AMI + fatal outcome), stroke, stent thrombosis, repeated PCI, and need for direct myocardial revascularization. Long-term clinical outcomes (absence/presence of angina pectoris attacks, functional class of angina) were additionally assessed; moreover, correlation between clinical signs, long-term outcomes of primary PCI, completeness of revascularization, and microvascular status were evaluated; for this purpose each study group was divided into 2 subgroups: complete and incomplete revascularization in AMI. Statistical analysis was performed using Statistica 6.0. The values are presented as mean ± standard deviation: M±s. Assessment of significance of the differences was performed using Student t-test and paired t-test (for parametric values), χ^2–test was used for qualitative comparison of the groups. Significance level was $p<0.05$.

Results of the study: According to the comparative analysis, there was no significant difference in average age of patients in studied (p=0.47), however, T2DM patients were slightly older. The majority of patients in the both groups were males (p=0.47). The most common risk factors in the both groups were essential hypertension, smoking, hypercholesterolemia. There was no significant difference in localization of AMI and depth of myocardial necrosis between the two compared groups (p>0.05).

Table 1 presents baseline clinical and historical data on the patients.

Table 1. Cardiovascular risk factors

Parameters	AMI without DM, n=76	AMI and DM, n=64	P
Age, years	55,9±9,7	60,6±11,3	p=0,089
Gender: Males, (%)	81,1	87,5	p=0,47
Arterial hypertension, %	94,7	93,7	p=0,31
Smoking, %	68,4	56,2	p=0,15
Hypercholesterolemia, %	50,2	77,3	p=0,05
Primary myocardial infarction, %	45,7	34,3	p=0,337
Localization of myocardial infarction, % Anterior Posterior	 52,6 37,5	 62,5 47,4	p=0,406
Myocardial infarction, % Q-wave Non-Q-wave	 57,9 42,1	 59,4 40,6	p=0,9

The left anterior descending artery was the SRA in the majority of patients in studied groups. No significant differences in diameter and length of CA lesion, and completeness of revascularization was revealed (p>0.05). The patients from the both groups had similarly severe coronary lesion (by Syntax scale and Yu.S. Petrosyan and D.G. Iosseliani method). However, AMI patients with T2DM had a tendency to higher score of total coronary artery lesions compared to patients without T2DM , but these differences were not statistically significant (p>0.05). The total number of artery lesions did not differ significantly between the patients with and without DM (p=0.1), however, the incidence of three vessel disease was 2 times higher in DM patients, while non-diabetic patients predominantly had one and two-vessel disease. The assessment of microcirculation by MB grade method showed that lower post interventional myocardial perfusion and/or initially more marked distal microcirculatory disease (II grade MB) at baseline was observed significantly more often in diabetic patients (p=0.043), despite that the restoration of SRA lumen and MA stenosis was achieved in 100% cases in the both groups (Table 2).

In general, the results of primary PCI during the in-hospital period were significantly worse in T2DM patients. In this group the incidence of total cardiac complication was 2.3 times higher, stent thrombosis was the reason of such complications in all cases, so T2DM patients underwent repeated PCI 2.3 times more often (p=0.011). The analysis of the individual unfavorable outcomes showed no differences in the incidence of early post-MI angina between the groups (p>0.05). However, recurrent MI was reported in T2DM patients only (p<0.05), which determined significant difference in total cardiac events between the groups (Table 3).

The results of primary PCI during the long-term period were significantly worse in T2DM patients. Total cardiac complications were still more often reported in this group (2.9 times) (p=0.011). However,

Table 2. Angiographic features of patients

Parameters	AMI without DM, n=76	AMI and DM, n=64	P
Symptom related artery, % LAD CA RCA	 57,8 5,2 36,8	 62,5 9,4 28,1	P=0,646
of Affected artery diameter, mm	3,12±0,44	3,02±0,44	P=0,340
Affected segment length, mm	15,92±8,51	14,19±5,24	P=0,718
Number of affected arteries: 1 2 3	 44,7 34,2 21,1	 37,5 18,7 43,7	P=0,1
Complete myocardial revascularization, %	47,4	50	P=0,112
Total lesions by Yu.S. Petrosyan and D.G. Iosseliani method[1], (%)	39,58±19,86	43,67±25,11	P=0,744
Total lesion by SYNTAX scale[2], (scores)	17,58±8,98	20,95±10,31	P=0,222
Assessment by Myocardial Blush[3] Grade II,% Grade III, %	 21 79	 40,6 58,4	 P=0,043 P=0,075

(1) Total lesion calculated using Yu.S. Petrosyan and D.G. Iosseliani method (1976)
(2) Total lesion calculated by SYNTAX scale (2005), >17 scores – severe coronary disease
(3) intensity of myocardial «staining» (perfusion of microcirculatory vessels)
LAD – left anterior descending artery, CA – circumflex artery,
RCA – right coronary artery

Table 3. In-hospital results of primary PCI (up to 30 days)

Parameters	AMI without DM, n =76	AMI and DM, n=64	P
Total cardiac complications, abs. (%)	2(2,6%)	4(6,2%)	p=0,011
Early post-MI angina, abs. (%)	2(2,6%)	2(3,1%)	p>0,05
Recurrent MI, abs. (%)	-	2(3,1%)	p<0,05
Death, n (%)	-	-	-
Stroke, abs. (%)	-	-	-
Repeated PCI (stent thrombosis), abs. (%)	2(2,6%)	4(6,2%)	p=0,011
Direct revascularization, abs. (%)	-	-	-

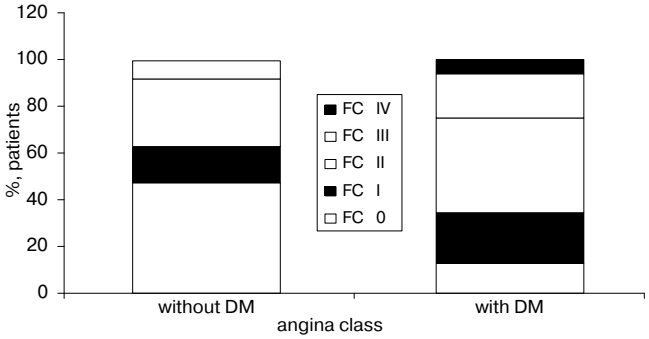
Table 4. Long-term PCI result at 1 year (including data obtained during the first 30 days)

Parameters	AMI without DM, n=76	AMI and DM, n=64	P
Total cardiac complications, abs. (%)	8 (10,5%)	20 (31,2%)	p=0,011
Unstable angina, abs. (%)	4 (5,2%)	12 (18,7%)	p<0,05
Non-fatal MI, abs. (%))	4 (5,2%)	4 (6,2%)	p>0,05
Death, abs. (%)	-	4 (6,2%)	p=0,041
Stroke, abs. (%)	-	-	-
Repeated PCI (stent thrombosis), abs. (%)	8 (10,5%)	8 (12,5%)	p>0,05
Direct revascularization, abs. (%)	8 (10,5%)	8 (12,5%)	p>0,05

the analysis of the individual unfavorable outcomes also showed the incidence of unstable angina during the long-term period in T2DM patients higher (3.6 times) than that in non-T2DM patients, although there were no significant differences in the incidence of non-fatal AMI, stent thrombosis requiring repeated PCI between the groups (10.5% and 12.5%, p>0.05). Fatal outcomes were reported in T2DM patients only and were caused by AMI complicated by cardiogenic shock. There were no significant differences in the need for direct myocardial revascularization during long-term period between the groups (p>0.05) (Table 4).

Signs of stable angina one year after AMI were observed more frequently in DM patients (p=0.001). The absence of signs of stable angina one year after AMI was observed 4 times more often in non-T2DM patients (47.4% in Group 1 and 12.6% patients in Group 2, p=0.001). FC I angina was reported in 15.7% and 21.8% of patients, FC II angina was observed in 28.9% and 40.6% of patients, respectively. Additionally, a trend to an increased rate of severe functional class angina (FCIII-IV) (p<0,05) was revealed in this group, moreover, FC IV angina was reported in T2DM patients only (Figure 1).

Fig. 1. One-year clinical results



The number of individual favorable outcomes i.e. the absence of angina attack, negative CE test (28.9% versus 9.3%) one year after AMI was more than 3 times higher in non-T2DM patients (p=0.001).

There were no significant differences in intake of antiplatelet drugs, statins, β-blockers between the groups (p>0.05). However, similarly low compliance with statins and clopidogrel was observed in the both groups. Compliance with of β-blockers was slightly lower in T2DM patients, but these differences were not statistically significant (Table 5).

Characteristics of the subgroup of AMI patients with T2DM were the most unfavorable: they had incomplete myocardial revascularization during urgent primary PCI. The maximum incidence of cardiac complications (43.7%) was reported in this subgroup, there were no angina-free patients; a trend to an increased rate of severe functional class angina was prevailing. The fatal outcomes and FC IV angina

Table 5. One-year therapy (12.5±2.2 months)

Parameters	AMI without DM, n=76	AMI and DM, n=64	P
Clopidogrel 75 mg, abs. (%)	44 (57,9%)	38 (59,4%)	p=0,264
Statins, abs. (%)	46 (60,5%)	36 (56,2%)	p=0,756
β-blockers, abs. (%)	70 (92,1%)	46 (71,8%)	p=0,190
Aspirin, abs. (%)	76 (100%)	64 (100%)	p=0,9

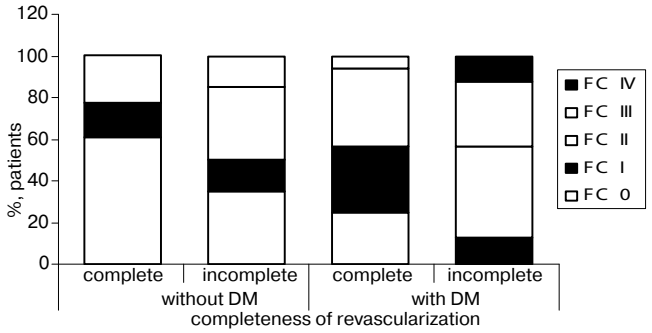
Table 6. One-year long-term PCI results (up to 12.5±2.2 months) depending on completeness of myocardial revascularization in AMI patients

Parameters	AMI without DM, n=76		P	AMI and DM, n=64		P
Revascularization	Complete n=36	Incomplete n=40		Complete n=32	Incomplete n=32	
	47,3%	52,7%		50%	50%	
Cardiac complications, abs. (%)	2 (5,5%)	6 (15%)	p<0,05	6 (18,7%)	14 (43,7%)	p<0,05
Death, abs. (%)	-	-		-	4 (12,5%)	p<0,05
Unstable angina, abs. (%)	-	4 (10%)	p<0,05	4 (12,5%)	8 (25%)	p<0,05
Non-fatal MI, abs. (%)	2 (5,5%)	2 (5%)	p>0,05	2 (6,25%)	2 (6,25%)	p>0,05
Repeated PCI (stent thrombosis), abs. (%)	2 (5,5%)	6 (15%)	p<0,05	4 (12,5%)	4 (12,5%)	p>0,05
Direct revascularization, abs. (%)	2 (5,5%)	6 (15%)	p<0,05	4 (12,5%)	4 (12,5%)	p>0,05

Table 7. One-year clinical results (up to 12.5±2.2 months) depending on completeness of myocardial revascularization (Fig. 2)

Parameters	AMI without DM, n=76		P	AMI and DM, n=64		P
Revascularization	Complete n=36	Incompletea n=40		Complete n=32	Incomplete n=32	
	47,3%	52,7%		50%	50%	
Absence/presence of angina attacks, abs. (%)	22 (61,1%)/ 14 (38,9%)	14 (35%)/ 26 (65%)	p<0,05	8 (25%)/ 24 (75%)	0/100%	p<0,05
FC I angina, abs. (%)	6 (16,6%)	6 (15%)	p<0,05	10 (31,25%)	4 (12,5%)	p<0,05
FC II angina, abs. (%)	8 (22,4%)	14 (35%)	p>0,05	12 (37,5%)	14 (43,7%)	p>0,05
FC III angina, abs. (%)	-	6 (15%)	p<0,05	2 (6,25%)	10 (31,2%)	p<0,05
FC IV angina, abs. (%)	-	-		-	4 (12,5%)	p<0,05

Fig. 2. One-year clinical results depending on completeness of revascularization



determining the main distinguishing features of MI patients with T2DM were reported in this subgroup only. The lowest parameters of myocardial perfusion after the restoration of blood flow through SRA and MA stenosis (II grade MB in 18 (56%) patients, III grade MB in 14 (43.7%) patients) were observed in this subgroup.

Following complete revascularization, DM patients had 2.3 times fewer cardiac complications (18.7%) than patients with incomplete revascularization ($p<0.05$), and unstable angina developed in them 2 times less frequently (12.5%) over 1 year ($p<0.05$). No deaths were observed in this subgroup, stable angina attacks were absent in 8 (25%) patients, none had FC IV angina (Table 7), parameters of myocardial perfusion after the restoration of blood flow were better (grade III MB in 24 (75%) patients and grade II MB in 8 (25%) patients) ($p<0.05$). In general, the prognosis in T2DM patients who had complete myocardial revascularization was comparable to that in AMI patients without DM who had incomplete revascularization.

DISCUSSION

Thus, in this study the incidence of individual unfavorable outcomes i.e. non-fatal MI and stent thrombosis, repeated PCI, need for direct myocardial revascularization during the long-term period was similar in T2DM patients and non-diabetic patients; that could be attributed to initially severe coronary lesion in patients from the both studied groups as well as low compliance with statins and clopidogrel (on average 58.5%).

However, the results of primary PCI during the in-hospital and long-term period were significantly worse in T2DM patients. Comparative analysis of the incidence of unfavorable AMI outcomes in the both studied groups over one year follow-up demonstrated poorer survival, higher percentage of stable and unstable angina, tendency to increased rate of severe FC classes in T2DM patients that could be attributed to severe multivessel coronary disease and initially more marked distal microvascular disease in T2DM patients. However, more detailed analysis established that the abovementioned negative tendency was most apparent in T2DM patients who had incomplete myocardial revascularization during primary PCI.

Based on the abovementioned, it can be concluded that incomplete primary CA revascularization during the acute phase of MI in T2DM patients is one of the reasons of high percentage of unfavorable coronary and clinical outcomes observed in T2DM patients. Positive tendency (no deaths, lower complication rate, more frequent absence of stable angina attacks, no severe FC angina) was most apparent in T2DM patients who had complete myocardial revascularization. Moreover, high indices of myocardial perfusion after the restoration of blood flow in SRA and MA stenosis (grade III MB in 75% and grade II MB in 25%) were observed more often in, while patients with incomplete revascularization more often demonstrated low indices (grade II MB in 56% and grade III MB in 43.7%).

Comparing our data with the results of the DEBATE I, DEBATE II and DESTINI studies evaluating percutaneous coronary angioplasty outcomes in CHD patients, which showed that the *clinical status and long-term cardiovascular prognosis in the majority of CHD patients depend highly on how the restoration of stenosed artery lumen improves blood flow at the level of microcirculation* (11), and taking into account the fact that significant functional and structural disorders of distal microvascular segment is a “trademark” of diabetes (12), it can

be concluded that complete myocardial revascularization provides greater improvement of myocardial perfusion more frequently than incomplete revascularization (blood flow at the microcirculatory level), probably due to minimizing the functional disorders, therefore, it is a factor determining favorable coronary and clinical outcomes of urgent PCI in T2DM patients with AMI.

Based on the abovementioned, it should be recommended to perform complete myocardial revascularization to the extent possible during primary (urgent) PCI and/or to decrease timing of elective PCI of non-target lesion in AMI patients with T2DM .

CONCLUSIONS

1. 1. The presence of T2DM in MI patients is associated with severe multivessel coronary disease, initially more marked distal microvascular disease and/or low post-interventional myocardial perfusion, and generally with a poor prognosis.
2. 2. Incomplete primary PCI during the acute phase of MI in T2DM patients is one of the main reasons of high percentage of cardiac complications and unfavorable clinical outcomes during the long-term period after AMI.

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Comparative Evaluation of Everolimus- and Sirolimus-Eluting Stents in Patients with Coronary Heart Disease and Coronary Atherosclerosis

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The efficacy of everolimus- and sirolimus-eluting stents was compared, which allows to optimize the use of these stents in clinical practice. One hundred and sixty five CHD patients were divided into 2 groups: sirolimus- and everolimus-eluting stents were implanted in 94 and 71 patients, respectively. Good results were achieved in 6-12 months of follow-up. During the long-term period only 4.2% of patients following EES implantation and 6.3% patients following SES implantation required the repeated revascularization due to in-stent restenosis. There were no stent thromboses or other cardiovascular complications. The use of everolimus- and sirolimus eluting stents in CHD patients showed comparable good immediate and long-term results.

Keywords: *coronary atherosclerosis, stenting, everolimus-eluting stent, sirolimus-eluting stents.*

Objective: Investigation of immediate and long-term results of the use of everolimus-eluting stents in CHD patients and comparative evaluation with well-known Cypher stent that has become well-established over the recent years.

Background:

The use of drug-eluting stents decreased the rate of restenosis and other complications following endovascular interventions. Currently, more than 20 types of drug-eluting stents are being used. Xience V is a second generation stent; it was developed using the technologies designed to reduce the complications. The comparison of EES and SES is of major clinical interest as it allows to optimize the use of drug-eluting stents.

Methods:

The evaluation of endovascular treatment using everolimus- and sirolimus-eluting stents was performed. Patients with various CHD forms were included in the study and divided into 2 groups: EES were implanted in Group 1 (71 patients), and SES were implanted in Group 2 (94 patients). Endovascular intervention was performed by the conventional technique. After the discharge the status of patients was assessed during out-patient examination, by telephone interview, or during repeated hospitalization. The following endpoints were evaluated: death from any cause and cardiovascular death, non-fatal myocardial infarction, cerebrovascular accident. The rate of repeated myocardial revascularization was analyzed.

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Results:

Good results after coronary stenting were achieved in both groups at 6-12 months of follow-up. There were no stent thromboses and other serious cardiovascular complications. Low percentage of in-stent restenosis and need for target vessel revascularization (4.2% versus 6.3% for EES and SES, respectively) as well as a decreased rate of non-fatal myocardial infarction were revealed.

Conclusions: This paper demonstrates that EES is at least non inferior to SES, and it may be used safely and effectively during PCI in patients with CHD and coronary atherosclerosis.

Abbreviations

CHD – coronary heart disease
DES – drug-eluting stent
PCI – percutaneous coronary intervention
EES – everolimus-eluting stent
SES – sirolimus-eluting stent
ACE – angiotensin converting enzyme
ECG — electrocardiogram
LAD – left anterior descending artery
CA – circumflex artery
RCA — right coronary artery

Endovascular treatment methods for coronary heart disease (CHD) have been used in the clinical practice since the end of the 70s of the last century. Firstly, in 1977 A.R. Gruentzig successfully performed balloon dilatation of coronary artery pioneering the development of endovascular treatment methods (1). The era of coronary artery stenting began in 1987, for the first time a stent was implanted in the coronary artery to prevent its occlusion and restenosis after transluminal coronary balloon angioplasty (2). Since their appearance, the endovascular treatment methods are being continuously developed, and indications for clinical use are being extended. Coronary interventions involving stenting are widely used in practice, and the risk of restenosis, which

was of 30-45% for balloon angioplasty, significantly reduced up to 17-20% in patients following a bare metal stent implantation. Subsequently, the use of drug-eluting stents (DES) led to greater reduction in the rate of restenosis and other complications following percutaneous coronary interventions (PCI) (3, 4). Endografting is one of the effective methods of definitive elimination of myocardial ischemia symptoms. To date, multivessel disease and complicated vessel morphology are not contraindications for PCI.

More than 20 types of drug-eluting stents are currently used in European countries: Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson), Taxus (Boston Scientific) and Co star (Conor) paclitaxel-eluting stents, Endeavor (Medtronic) and Zo maxx (Abbot) zotarolimus-eluting stent, A9 biolimus-eluting stent (Biomatrix), Xience V everolimus-eluting stent (Abbot) etc. In recent years DES coated with a substance from limus family – everolimus (EDS) – has appeared and gained attention.

Everolimus manufactured by Novartis Pharma AG (Basel, Switzerland) has antiproliferative properties and affects a wide range of cells including vascular smooth muscle cells, inducing cell proliferation cycle arrest at G1 stage (5,6). This effect is mediated by binding with intracellular protein FKBP12 and caused by inhibition of mTOR (Target Of Rapamycin) kinase activation – the site of rapamycin action (7, 8). Everolimus is chemically similar to sirolimus and also has an immunosuppressive effect. Combination of smooth muscle cells inhibition and high lipophilicity suggests the best prevention from neointimal hyperplasia.

Xience V is a second generation stent with a cobalt-chromium platform developed using the technologies to reduce the risk of early (thrombosis) and late (restenosis) complications. This stent with thin polymer coating allows to maintain vessel lumen patency, thus, reducing the rate of restenosis and subsequent revascularizations. This is the main advantage of Xience V over the standard stents. The stent releases approximately 80% of the drug over 1 month and 100% of the drug over 4 months (9).

Xience V (Abbot) was launched in 2006. It was approved for use in the Russian Federation in 2007.

The objective of our study was to investigate immediate and long-term results of the use of everolimus-eluting stents in CHD patients and to compare it with well-known Cypher stent that has become well-established over the recent years.

MATERIAL AND METHODS

Evaluation of immediate and long-term results of endovascular treatment using Xience V and Cypher drug-eluting stents in patients with atherosclerotic coronary stenosis including patients with acute coronary syndrome was performed in the laboratory of endovascular treatment methods at A.L. Myasnikov Research Institute of Cardiology. Patients with various CHD forms were prospectively included in this study: 94% of patients (n=155) had stable angina, 6% of patients (n=10) had unstable angina; they underwent coronary stenting as indicated in the period from February 2007 till February 2009.

The patients were allocated to 2 groups: Xience V was implanted in Group 1 (71 patients), Cypher was implanted in Group 2 (94 patients). Preparation of patients to the stenting was conventional. During 12-month follow-up the patients received standard medical therapy for underlying disease (according to 2006 Guidelines by European Society of Cardiology) including aspirin + clopidogrel for one year after intervention, ACE inhibitors, statins, and beta-adrenoblockers (as indicated).

Ninety nine everolimus-eluting stents (EES) were implanted in 71 patients from Group 1, and 138 sirolimus-eluting stents (SES) were implanted in 94 patients from Group 2. Table 1 presents clinical characteristics of patients. In both groups 1 to 3 DES were implanted in each patient. Table 2 presents angiographic characteristic of patients. As is evident from baseline angiographic data (number of affected arteries, initial degree and lesion morphology) the groups were not significantly different.

Endovascular intervention was performed according to the standard technique using Coroscop-33 and Axiom-artis angiography units (Germany) and coronary software to assess the degree and length of coronary stenoses. Either direct stenting or stenting with balloon pre-dilatation was performed at the discretion of the surgeon.

Table 1. Clinical characteristic of patients with everolimus- and sirolimus-eluting stents

Parameter	Xience V (n=71)	Cypher	P
(n=94)	P	59.08+9.7	НД
Males (%)	88,7%	89,3%	НД
Females (%)	11,2%	10,6%	НД
Smokers (%)	70,4%	72,3%	НД
Arterial hypertension (%)	56,3%	60,6%.	НД
Diabetes mellitus (%)	11,2%	14,8%.	НД
Stable angina (%)	92,9%	91,4%.	НД
Unstable angina (%)	5,6%	5,3%	НД
Previous PCI (%)	15,4%	15,9%.	НД
Previous CABG (%)	5,6%.	6,3%.	НД
Hyperlipidemia (%)	71.8	73.4%.	НД
Mean follow-up (months)	9+-6 мес.	10+-7 мес.	НД

Note: CABG – coronary artery bypass grafting, NS - non significant, PCI – percutaneous coronary intervention (angioplasty with stenting).

Prior to the intervention all patients received double antiplatelet therapy including aspirin 100 mg/day and clopidogrel 75 mg/day; in case of urgent intervention, clopidogrel 600 mg was given before PCI. At the beginning of PCI heparin was administered intravenously taking into account the activated partial

Table 2. Angiographic characteristic of patients with everolimus (n=71) and sirolimus (n=94) eluting stents

Parameters	EES	SES
1. Number of affected vessels (%):		
1 vessel	52	51
2 vessel	36	38
3 vessel	12	11
2. Stenosis location (%):		
Main LCA	5	2
LAD (DB)	42	44
CA (OMB)	17	25
RCA	36	29
3. Lesion type (AHA/ACC,%):		
A	32	34
B	34	30
C	34	36
4. Mean reference diameter (mm)	3.02±0.51	3.04±0.49
5. Mean stent length (mm)	20.8±5.34	21.3±4.27
6. Mean number of stents per patient	1.4	1.5
7. Lesion degree (%):		
before stenting	81±9.7	79±8.9
after stenting	5±0.34	6±0.38

Note: LAD – left anterior descending artery, DB – diagonal branch of LAD, CA – circumflex artery, OMB - obtuse marginal branch of CA, RCA – right coronary artery, LCA – left coronary artery. (There were no significant differences between the groups, P> 0.05.).

Table 3. Clinical outcomes in patients with everolimus- and sirolimus-eluting stents (at 12 months).

Parameter	Xience V (n=71)	Cypher	P
Subacute thrombosis	P	0	
Non-fatal myocardial infarction	1 (1,4%)	2 (2,1%)	NS
Patients referred to CABG after PCI	1(1,4%)	0	NS
Repeated revascularization	3 (4,2%)	6 (6,3%)	NS
Recurrence of angina	2 (2,8%)	4 (4,2%)	NS
Death	0	0	

thromboplastin time and activated clotting time. After PCI and the discharge from hospital double antiplatelet therapy was prescribed for at least 12 months.

After the discharge the status of patients was assessed during out-patient examination, by telephone interview, or during repeated hospitalization, if needed. The patient's complaints, functional class of angina, clinical course and complications of CHD, treatment after PCI and its tolerability were assessed. Hematology, ECG at rest and on exertion (bicycle ergometry test, treadmill test), and, if indicated, 24-hours ECG monitoring and repeated coronary angiography were performed in out-patient settings or during the hospitalization. The following end-points were evaluated: death from any cause and cardiovascular death, non-fatal myocardial infarction, cerebrovascular accident. The rate of repeated myocardial revascularization (PCI or coronary artery bypass grafting due to in-stent restenosis or development of significant stenosis in non-target coronary arteries and non target lesions) was also analyzed. Classification of stent thrombosis set by the Academic Research Consortium (ARC) was used (10).

Statistical processing of the data was performed using Statistica 6.0 software (stat Soft Inc).

RESULTS AND DISCUSSION

All examined patients (165 persons in both groups) with implanted DES were alive during the follow-up of 6 to 12 months (mean follow up was 9±6 months), there were no fatal myocardial infarctions. PCI success during the in-hospital period was 100%; there were no failed stenting procedures, acute or subacute stent thrombosis.

According to the recent international and national guidelines (11) patients received clopidogrel (Plavix) and aspirin regularly throughout follow-up. During long-term follow-up in Group 1, where Xience V was implanted, 3 patients only (out of 71 persons) had angina recurrence and signs of myocardial ischemia on exertion tests in 3.5 and 8 months; in two patients deterioration was caused by restenosis, which was confirmed by coronary angiography. These two restenoses (one located in the left anterior descending artery, another – in the right coronary artery) were successfully eliminated during repeated PCI. One patient developed significant stenosis in non-target arteries; this patient underwent successful coronary artery bypass grafting. One patient developed myocardial infarction in 7 months, which was confirmed by blood chemistry, increased troponin levels, specific ECG pattern, and coronary angiography (CA occlusion was eliminated successfully during repeated PCI). The other patients did not require control angiography. Four patients from Group 2 (out of 94 persons) where Cypher was implanted had angina recurrence and signs of myocardial ischemia on exertion tests at the target vessel area in 2, 3, 5, and 8 months; restenoses were confirmed by coronary angiography. These restenoses (two located in the left anterior descending artery, one in the right coronary artery and one in the circumflex artery) were successfully eliminated during repeated PCI. Two patients developed myocardial infarction confirmed by coronary angiography (RCA occlusion and LAD occlusion) in 1 and 6 months after PCI, respectively. These occlusions were successfully eliminated during repeated PCI. Therefore, the need for target lesion revascularization (TLR) was 4.2% and 6.3% in Group 1 and 2, respectively (see Table 3), which is considered as a good index for DES, however, a larger number of observations is required to make a definitive conclusion regarding the low incidence of adverse events with everolimus-eluting stents.

EES were compared to other stents in many large trials. Thus, in FUTURE-1 trial (First Use to Underscore Restenosis Reduction with Everolimus) intravascular coronary ultrasound demonstrated significant reduction of vessel diameter loss (-0.11 mm) in the EES group versus 0.85 mm ($p<0.001$) in the bare metal stent group; reduction of neointimal hyperplasia was also observed (12,13).

Another trial –SPIRIT FIRST (Comparison of a Durable Polymer Everolimus-Eluting Stent with a Bare-Metal Coronary Stent) assessed not only short-term results of EES implantation but also long-term clinical results. Xience V was compared to Multi Link Vision bare metal stent. No late stent thrombosis was observed in the Xience V group over 2-year follow-up (14). Thus, SPIRIT FIRST study confirmed the efficacy of the everolimus-eluting stent and initiated SPIRIT-II, SPIRIT-III, and SPIRIT-IV trials.

In the European clinical trial SPIRIT II EES was compared for the first time to another DES (paclitaxel-eluting stent) (15). Three hundred patients were followed during one year after stenting (Xience V was implanted in 233 patients and Taxus was implanted in 77 patients). The study results demonstrated that the number of severe cardiovascular complications was by 71% lower (p=0.04) in Xience V patients (2.7%) compared to patients with implanted Taxus (9.2%). The one-year rate of late thrombosis was 0 and 1.3%, respectively.

Further, SPIRIT III – a large randomized trial involving 1002 patients was carried out (16). Xience V was compared to Taxus. Artery segment lumen loss was the primary endpoint in this study. After 8 months EES has shown its benefits demonstrating statistically significant reduction of late lumen loss compared to Taxus (0.14±0.41 mm and 0.28±0.48 mm for EES and Taxus, respectively, p=0.004). Any clinically significant coronary events in target artery, including repeated revascularization, sudden cardiac death, and repeated cardiac attacks were the secondary endpoint in this study. EES was similar to Taxus after 9 month follow-up. Clinically significant coronary events in target artery were observed in 9.0% of Taxus patients and in 7.2% of Xience V patients (by 21% lower than in Taxus patients, p<0.0001). After the primary and main secondary endpoints were achieved in SPIRIT III trial, the development of major adverse cardiovascular events such as sudden cardiac death, myocardial infarction or target vessel revascularization over 9 months was analyzed. The complication rate was 8.1% and 4.6% in Taxus and Xience V patients, respectively, i.e. the use of EES significantly (p=0.028) reduced the rate of severe cardiovascular complications (by 44%).

The analysis of pooled data from SPIRIT II and SPIRIT III trials demonstrated the greater safety and efficacy of EES over 2-year follow-up: meta-analysis showed statistically significant reduction of combined mortality from any cause or myocardial infarction, as well as further reduction in the need for repeated PCI. Thereby, it was proved that EES – a second generation stent – truly improves the results of treatment in patients with atherosclerotic coronary lesion.

Prospective, multicenter trial SPIRIT IV started in 2006 and included 3690 patients with native coronary artery lesion. The length of lesion did not exceed 28 mm, reference diameter varied from 2.5 to 4.25 mm. The patients were randomized in a 2:1 ratio to compare two DES: EES (XIENCE V) and PES (TAXUS EXPRESS-2), respectively. The follow-up examination was performed in 30, 180, and 270 days, 1 year and than annually up to 5 years, and currently is ongoing. Such endpoints as death, myocardial infarction, presence of ischemia, need for target vessel revascularization, and stent thrombosis were assessed in this study. At one year of follow-up, the rate of stented vessel revascularization with everolimus- and paclitaxel-eluting stents was 2.5% and 4.4%, respectively, which demonstrated doubtless superiority of EES. Currently SPIRIT IV is the largest randomized trial comparing two DES, which allows to perform the most accurate comparison of their clinical safety and efficacy. The fact that the largest cohort of diabetes mellitus patients (1100 persons) was included in the study is very interesting. Publication of five-year follow-up data is expected in the nearest time; which will allow to determine the differences in the clinical efficacy of these stents. (17).

Comparison of the safety and efficacy of EES and zotarolimus-eluting stent (Endeavor) between two groups of 200 patients each also demonstrated the superiority of EES. Although both stents had good immediate results, the significantly lower rate of acute myocardial infarction (3.5% versus 0%), repeated target vessel PCI (7% versus 2%, p=0.04), and serious cardiovascular complications (9.5% versus 2% for Endeavor and EES, respectively, p=0.001) were observed in patients with implanted EES at one year (18).

The comparison of EES and Cypher sirolimus-eluting stent, which has maintained a leadership position for a long time, is of most clinical interest. Thus, meta-analysis involving 16 clinical trials performed by Biondi-Zoccai G. et al. (19), demonstrated that EES is as effective as Cypher sirolimus-eluting stent. The results obtained in our prospective trial comparing everolimus- and sirolimus eluting stents were comparable: the incidence of myocardial infarction (1.4% for EES and 2.1% for SES), repeated revascularization (4.2% for EES and 6.3% for SES), recurrence of angina (2.8% for EES and 4.2% for SES) did not differ significantly.

CONCLUSION

Low percentage of in-stent restenosis and need for repeated coronary intervention on target vessel (4.2% versus 6.3% for EES and SES, respectively), and low incidence of non-fatal myocardial infarction during both immediate and long-term periods (up to 1-year follow-up) were demonstrated in both groups of CHD patients with implanted EES and SES. Further accumulation of clinical data and comparison of everolimus-eluting stent with sirolimus-eluting stent and other drug-eluting stents will permit to establish the benefits and eventual disadvantages of the studied stent. This paper demonstrates that EES is at least non-inferior to SES and may be safely and efficiently used during PCI in patients with CHD and coronary atherosclerosis.

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Clinical and Angiographic Evaluations of Immediate and Long-Term Results of Transluminal Balloon Angioplasty Using EucaTAX Coronary Stent in Patients with Coronary Ctherosclerosis

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Restenosis after stenting remains the main problem in the endovascular treatment of coronary atherosclerosis. The sirolimus-eluting stents (Cypher) have shown the best results.
The double-coated EucaTAX stent was developed using the technologies to reduce early and late complications. Comparative study of EucaTAX versus Cypher was performed in patients with angiographically documented stenosis of ⩾ 70% in one or two coronary arteries. The superiority of Cypher in reduction of the rate of target lesion revascularization (TLR) and major adverse coronary events (MACE) was shown.

Key words: *coronary stenting, thrombosis, restenosis, EucaTAX.*

Objective: to evaluate the efficacy and safety of EucaTAX drug-eluting stent versus Cypher in patients with coronary atherosclerosis.

Material and methods: the patients with angiographically documented stenosis in one or two main coronary arteries of at least 70%, who underwent coronary stenting using drug-eluting stent were enrolled. Our objective was to evaluate mortality, the incidence of MI, repeated CAG, TLR, stent thrombosis and composite endpoint - MACE, including mortality, MI, need for TLR and stent thrombosis in 9 months and 2 years.

Main results: two groups of patients were enrolled into the study: 320 patients in whom 368 Cypher stents were implanted and 282 patients in whom 344 EucaTAX stents were implanted. The significant differences in the number of repeated CAGs (12.2% versus 19.1%, respectively, p=0.02) and the TLR rate (4.7% versus 9.2%, respectively, p = 0.03) were revealed between the Cypher and EucaTAX groups in 9 months. The significant differences in the TLR rate (6.25% versus 16.3%, respectively, p=0.0001) and composite MACE endpoint (7.8% versus 18.4%, respectively, p=0.001) were observed in 2 years. The incidence of restenosis in repeated CAG in 2 years was significantly higher in the EucaTAX group compared to the Cypher group.

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Conclusion: our experience of EucaTAX use in the comparative study with Cypher stent demonstrated the superiority of Cypher in reduction of TLR and MACE rates.

Abbreviations:
TBA — transluminal balloon angioplasty
MI — myocardial infarction
CAG — coronary angiography
TC — total cholesterol
TG — triglycerides
HDL — high density lipoprotein
LDL — low density lipoprotein
DM — diabetes mellitus
TLR — target lesion revascularization
MACE — major adverse coronary events

Restenosis after stenting remains the main problem in the endovascular treatment of coronary atherosclerosis (1,2). Many stents of various types and modifications, which are used in invasive cardiology for coronary atherosclerosis have appeared over the last few years, The sirolimus-eluitng stents (Cypher) have shown the best results.

The transluminal balloon angioplasty (TBA) using double-coated EucaTAX stent developed using technologies to reduce the risk of early and late complications, is of interested. The mechanism of complication risk reduction is realized via double-coating with synthetic glycocalyx (synthetic endothelium) and paclitaxel. Artificial glycocalyx reduces the thrombosis rate. The synthetic endothelium allows to achieve biomimicry by imitation of glycocalyx of the endothelial membranes. This determines formation of anti-thrombotic stent layer. The synthetic glycocalyx consists of highly hydrated dense polysaccharides forming a spatial barrier preventing the non-specific adsorption of plasma proteins. The imitation of glycocalyx anti-adhesive

properties should contribute to resolve the problem of stent thrombosis (3).

Paclitaxel penetrates into endothelium and arterial smooth muscle cells at the place of stent implantation (i.e. at the place of endothelial lesion) thus reducing the risk of restenosis. Paclitaxel has a number of complex actions at the cellular level affecting microtubule dynamics participating in cell dividing. As a result, synthesis and secretion of extracellular matrix, smooth cell proliferation and migration are reduced, thus, neointimal hyperplasia resulted to in-stent restenosis is diminished (4).

In contrast to other cytostatic substances, paclitaxel has several properties allowing its use as an anti-proliferative stent coating to prevent restenosis. Firstly, it is a lipophilicity due to which paclitaxel rapidly passes through endothelial membranes. Secondly, it is an unique set of properties allowing to achieve long-term antiproliferative effect even when paclitaxel affects endothelial cells at a very low doses and over short time (5-6). Thus, EucaTAX stent allows to affect stent thrombosis and restenosis due to imitation of intact endothelium and inhibition of endothelial proliferation.

Taking into account the individual features of EucaTAX, its comparison to Cypher – the gold standard of modern interventional cardiology, which has been established as a reference stent in many studies, seems important.

MATERIALS AND METHODS

Patients and study protocol

This study enrolled patients with angiographically documented stenosis of at least 70% in one or two main coronary arteries, who underwent coronary stenting using drug-eluting stents.

Patients who had myocardial infarction (MI) within less than 6 months prior to the study start, congestive heart failure, severe rhythm and conduction disturbances, type 1 diabetes mellitus (T1D) or decompensated type 2 diabetes (T2D) family hypercholesterolemia, liver and kidney failure, and tumors were excluded from the study. Before and after the intervention, the patients received standard therapy: aspirin, β–adrenoblockers, and statins; calcium antagonists and ACE inhibitors were prescribed as indicated. During the angioplasty nitroglycerin 250 μg intracoronary and heparin 70 IU/kg intra-arterially were administered to each patient. The patients received Plavix for 3-5 days before stenting and for 12-18 months after the intervention.

Angiographic analyses

TBA with stenting was performed according to standard method (7) using Axiom Artis, Siemens (Germany) equipment. The nominal stent diameter corresponded to the reference artery diameter at the site of stenosis (mean diameter of the artery segments proximal and distal to stenosis). After the last dilatation and removal of balloon catheter and coronary guidewire from the coronary artery, the contrast-enhanced visualization of the dilated vessel using at least 2 orthogonal scans for the better imaging was performed.

The repeated coronary angiography (CAG) was performed as indicated in patients who returned to the clinic over 2 years using the same equipment and projections.

The analysis of obtained angiograms was performed using Axiom Artis quantitative computed analysis (Siemens, Germany). The parameters used for analysis of the angiographic data were as follows: the diameter and length of implanted stent, reference artery diameter, minimal artery diameter at the site of maximal stenosis before the intervention, immediately after the intervention and during repeated CAG; artery stenosis (stenosis percentage) before the intervention, immediately after the intervention and during repeated CAG; late loss – the difference between minimal diameters immediately after stenting and during repeated CAG; increase of stenosis – the difference between the artery narrowing degree during repeated CAG and immediately after stenting.

Evaluation of lipid panel

Total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) concentrations were determined by enzymatic method using FP-900 Labsystems Oy biochemical analyzer and Boehringer test sets. TC content in HDL was determined after precipitation of low density lipoproteins (LDL) and very low density lipoproteins by manganese-heparin reagent (8). TC content in HDL was calculated from the Friedwald formula:

TC LDL = TC – (TG/2.2 + TC HDP). The obtained data were presented as mmol/L.

Statistical analysis

Statistical processing of the study results were performed using STATISTICA 6.0 software. For quantitative comparison of the groups the parametric (Student t-test) and non-parametric (Mann-Whitney test) methods were used. χ^2–test and exact Fisher test (for binary parameters) were used for the qualitative comparison of the groups. The non-parametric Spearmen correlation test was used to determine the relationship between the parameters. The parameters with normal distribution were presented as mean and standard deviation (Mean+STD), and the parameters with non-normal distribution were presented as median and low and high quartiles (Med (LQ - HQ)). Differences were considered to be significant at $p < 0.05$.

RESULTS AND DISCUSSION

Six hundred and two (602) patients with revealed coronary lesion were enrolled in this study. They were divided into 2 groups by the implanted stent type:

- Group 1 - 320 patients with 368 antiproliferative sirolimus-eluting Cypher stents implanted.

- Group 2 - 282 patients with 344 paclitaxel-eluting EucaTAX stents implanted.

After the hospitalization the patients were followed for over 2 years via the control instrumental and invasive examinations performed in patients who returned to the clinic. The control CAG to confirm or exclude restenosis was performed in 155 patients. The analysis of clinical parameters was performed on the sample of patients, and the angiographic data were analyzed by the number of the stented segments.

At baseline patients with implanted Cypher and EucaTAX stents were comparable by main clinical characteristics such as gender, age, history of MI, arterial hypertension (AH), T2D, smoking status, and lipid profile (Table 1).

The main angiography parameters of coronary lesions (localization, reference artery diameter, minimal artery diameter, percentage stenosis) both at baseline and immediately after the intervention were comparable between the Cypher and EucaTAX groups. There were significant differences between groups in the diameter and length of implanted stents (Table 2).

The patients were clinically followed for over 24 months after the intervention to analyze the long-term results of coronary stenting. In case of angina relapse or occurrence of other cardiac complications (myocardial infarction, heart failure), the patients underwent angiography to evaluate in-stent restenosis. These patients were followed for over 2 years to assess mortality (cardiac, non-cardiac), MI (Q-wave, non-Q-wave), the incidence of repeated CAGs, need for target lesion revascularization (TLR), thromboses (acute, subacute, late, and very late) as well as the composite endpoint - major adverse cardiac event(s) (MACE) consisting of mortality, MI, need for TLR and stent thrombosis. The assessment of the above parameters 9 months after the intervention was the first control point in our study.

9-month clinical outcomes in the Cypher group

No deaths were observed in the Cypher group. There were two non-fatal non-Q-wave MIs (0.6%) in the Cypher group. Thirty nine patients had repeated CAG in the Cypher group (12.2%). Fifteen patients out of these (4.7%) had repeated TLR at the site of the stent implantation. Two patients had stent thrombosis (0.6%). Notably, both thromboses were acute and developed during the first day after angioplasty. Thus, 19 patients (5.9%) from the Cypher group had MACE (Table 3).

9-month clinical outcomes in the EucaTAX group

One death caused by Q-wave MI was observed in the EucaTAX group (0.4%). Fifty four patients had repeated CAG in the EucaTAX group (19.1%). Twenty

Table 1. Clinical characteristics of patients

Parameters	Cypher (n=320)	EucaTAX (n=282)	(p)
Age	56 (52 - 61)	57 (52-62)	0,12
Gender · Males · Females	 283(89%) 37(11%)	 246(87%) 36(13%)	0,65
History of MI	206 (64%)	180(64%)	0,89
AH	211(66%)	171(61%)	0,18
T2D	70 (22%)	62 (22%)	0,97
Smoking status: · smoker · gave up · non-smoker	 85 (27%) 148 (46%) 87 (27%)	 73 (26%) 137 (49%) 72 (25%)	0,84
TC (mmol/L)	4,78 (4,2-5,33)	4,69 (4,17-5,4)	0,7
TC LDL (mmol/L)	2,86 (2,15-3,59)	2,7 (2,14-3,7)	0,59
TC HDL (mmol/L)	1,12 (0,9-1,36)	1,12 (0,9-1,37)	0,95
TG (mmol/L	1,36 (1,02 - 2,18)	1,42 (1,07 - 2,48)	0,41

AH – arterial hypertension; MI – myocardial infarction; T2D – type 2 diabetes mellitus, TG – triglycerides. TC – total cholesterol; TC LDL– low density lipoprotein cholesterol; TC HDL– high density lipoprotein cholesterol.

Table 2. Angiographic parameters of coronary lesions.

Parameters	Cypher (n=368)	EucaTAX (n=344)	(p)
Artery: · RCA · LAD · CA · OMB	 125 (34%) 180 (49%) 55 (15%) 8 (2%)	 120 (35%) 172 (50%) 42 (12%) 10 (3%)	0,66
Reference diameter (mm)	2,88 (2,59-3,18)	2,81 (2,44-3,2)	0,13
Min d at baseline (mm)	1,07 (0,79-1,44)	1,06 (0,49-1,43)	0,88
Stenosis at baseline (%)	82 (74-90)	83 (76-90)	0,47
Stent diameter (mm)	3 (2,75-3,25)	3 (2,75-3,25)	0,96
Stent length (mm)	18 (13 - 23)	18 (13 – 23)	0,24
Minimal diameter after stenting (mm)	2,46 (2,2-2,75)	2,37 (2,07-2,76)	0,21
Stenosis after stenting (%)	12 (8-18)	12 (7-18)	0,71

OMB – obtuse marginal branch; CA – circumflex artery; RCA – right coronary artery; LAD– left anterior descending artery; min d – minimal diameter.

Table 3. 9-month clinical outcomes after the intervention.

Parameters	Cypher (n=320)	EucaTAX (n=282)	P
Mortality · Cardiac · Non-cardiac	0 0 0	1 (0,4%) 1 (0,4%) 0	0,29
Myocardial infarction · Q-wave · Non-Q-wave	2 (0,6%) 0 2 (0,6%)	1 (0,4%) 1 (0.4%) 0	0,64
Repeated CAG	39 (12.2%)	54(19,1%)	0,02
TLR	15 (4,7%)	26 (9,2%)	0,03
Stent thrombosis · Acute (<1 day) · Subacute (up to 1 month) · Late (1-9 months)	2 (0,6%) 2 (0,6%) 0 0	1 (0,4%) 0 1 (0,4%) 0	0,18
MACE (mortality/MI/TLR/thrombosis)	19 (5,9%)	29 (10,3%)	0,07

CAG – coronary angiography; MACE – major adverse coronary events; TLR – target lesion revascularization.

six patients out of these (9.2%) had repeated TLR at the site of the stent implantation. One patient (0.4%) developed stent thrombosis 2 weeks after discharge. Thus, 29 patients (10.3%) from the EucaTAX group had MACE (Table 3).

Eventually, there were significant differences between the Cypher and EucaTAX groups in the number of repeated CAG (12.2% in the Cypher group versus 19.1% in the EucaTAX group, p=0.02) and the TLR rate only (4.7% versus 9.2%, respectively, p=0.03) (Table 3).

We analyzed angiographic parameters of coronary lesions during repeated CAG performed within the first 9 months after the intervention. There were no significant differences in the angiographic parameters of coronary lesions during repeated CAG between the Cypher and EucaTAX groups (Table 4).

2-year clinical outcomes in the Cypher group.

No deaths were observed in the Cypher group. There were 2 non-fatal non-Q-wave MIs (0.6%) in this group. Seventy five patients had repeated CAG (23.4%). Twenty patients out of these had repeated TLR (6.25%). Three patients had stent thromboses (0.9%); 2 thromboses out of these (0.6%) were acute and developed within the first day after angioplasty and 1 case (0.3%) of very late thrombosis developed more than 12 months after the angioplasty. Thus, 25 patients (7.8%) from the Cypher group had MACE.

2-year clinical outcomes in the EucaTAX group.

There were three deaths in the EucaTAX group (1.1%): two cardiac deaths (0.7%) caused by Q-wave MI and 1 non-cardiac death (0.4%). Eighty patients (28.4%) had repeated CAG in this group. Forty six patients out of these had repeated TLR (16.3%). %. One patient (0.4%) had stent thrombosis that developed 2 weeks after discharge. Thus, 52 patients (18.4%) from the EucaTAX group had MACE.

There were significant differences between the Cypher and EucaTAX groups in the TLR rate (6.25% versus 16.3% respectively, p=0.0001) and the composite endpoint - MACE (7.8% versus 18.4%, respectively, p=0.001) (Table 5).

We analyzed angiographic parameters of coronary lesions during repeated CAG performed 2 years after the intervention in the Cypher and EucaTAX groups. The comparison of the angiographic parameters of coronary lesions during repeated CAG in the Cypher and EucaTAX groups showed that the incidence of restenosis (minimal artery diameter, restenosis degree, late loss and increase of stenosis) was significantly higher in the EucaTAX group than in the Cypher group (Table 6).

Paclitaxel-eluting stents as well as sirolimus-eluting stents showed good results in large international trials (9,10,11), however, stent thrombosis still remains a vulnarable spot of drug-eluting stents (12,13,14). The decision to influence on this process using glycocalyx coating appeared to be quite reasonable. Indeed, the rate of thrombosis in our study was lower in the EucaTAX group than in the Cypher group, although the difference was not significant, while the MACE rate was significantly higher in the EucaTAX group compared to the Cypher group (18.1% versus 7.5%) primarily due to the increase in the TLR rate (16.3% versus 6.25%). For the angiographic parameters, coronary lesions were more severe in the EucaTAX group according to several parameters (Table 6). The results of our study are consistent with the data obtained from the previous trials with the Cypher (15,16,17,18). However, large trials with EucaTAX are not yet completed, and the comparison with studies using other paxlitaxel-eluting stents is inappropriate due to the absence of the camouflage glycocalyx coating.

Table 4. Angiographic parameters of coronary lesions during repeated CAG at 9 months.

Parameters	Cypher n=39	EucaTAX n=54	P
min d (mm)	1,66 (1,03-2,47)	1,65 (1,03-2,65)	0,43
Restenosis (%)	36 (25-60)	36 (26-68)	0,6
Late loss (mm)	0,6 (0,19-1,28)	0,9 (0,31-1,45)	0,32
Increase of stenosis (%)	23 (10-47)	34 (11-55)	0,45

min d – minimal diameter.

Table 5. 2-year clinical outcomes after the intervention.

Parameters	Cypher N=320	EucaTAX N=282	(p)
Mortality · Cardiac · Non-cardiac	0 0 0	3(1,1%) 2(0,7%) 1(0,4%)	0,064
Myocardial infarction · Q-wave · Non-Q-wave	2(0,6%) 0 2(0,6%)	2(0,7%) 2(0,7%) 0	0,89
Control CAG	75(23,4%)	80(28.4%)	0,17
TLR	20(6,25%)	46(16,3%)	0,0001
Stent thrombosis · Acute (<1 day) · Subacute (up to 1 month) · Late (1-12 months) · Very late (>12 months)	3(0,9%) 2(0,6%) 0 0 1(0,3%)	1(0,4%) 0 1(0,4%) 0 0	0,1
MACE(mortality/MI/TLR/thrombosis)	25(7,8%)	52(18,4%)	0,001

CAG – coronary angiography; MACE – major adverse coronary events; TLR – target lesion revascularization.

Table 6. Angiographic parameters of coronary lesions during repeated CAG 2 years after the intervention.

Parameters	Cypher n=75	EucaTAX n=80	(p)
min d (mm)	1,99 (1,34-2,49)	1,35 (0,98-1,95)	0,0002
Restenosis (%)	32 (19-50)	51 (27-69,5)	0,001
Late loss (mm)	0,5 (0,11-1,11)	0,99 (0,44-1,47)	0,0001
Increase of stenosis (%)	8 (6-39)	37,5 (18-54)	0,0003

min d – minimal diameter.

CONCLUSION

Thus, our experience in the use of paclitaxel-eluting EucaTAX stent versus sirolimus-eluting Cypher stent in the comparative study showed the superiority of Cypher in decreasing the rates of target lesion revascularization (TLR) and major adverse coronary events (MACE).

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Stent-Grafting of Pseudo- and Fusiform Brachiocephalic Aneurysms

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The standard endovascular techniques are associated with a high rate of complications and relapses in case of fusiform and pseudoaneurysms of the brachiocephalic arteries. Stent-grafting demonstrated its superior efficacy and safety over the other endovascular techniques in the treatment of the head and neck vessel aneurysms. Five cases of endovascular treatment of pseudo and fusiform aneurysms of the carotid and vertebral arteries in 5 patients using stent-grafts over the period from 2009 till 2010 were analyzed.
Stent-grafts were successfully implanted and aneurysms were excluded in all five patients. No deaths occurred during the follow-up. There was no evidence of neurological signs at the examination. Control examinations demonstrated the patency of all grafts; there were no signs of recanalization and/or increase in the aneurysm dimensions.

Keywords: *stent-graft, pseudoaneurysm, fusiform aneurysm.*

Objectives: to assess the efficacy and safety of endovascular treatment for pseudo- and fusiform aneurysms of the carotid and vertebral arteries using stent-grafts.

Background: endovascular treatment of fusiform and pseudo- aneurysms using stent-grafts demonstrated its efficacy and safety compared to other endovascular techniques including the treatment of the head and neck vessel aneurysms.

Methods: Five cases of endovascular treatment of pseudo- and fusiform aneurysms of the carotid and vertebral arteries in five patients using stent-grafts over the period from 2009 till 2010 were analyzed. Four patients were males, patients' age varied from 22 to 48 years. Three aneurysms were posttraumatic, and two were fusiform. Aneurysms' location was as follows: the cervical segment of ICA, petrous segment of ICA, intracranial part of the vertebral artery. Five stent-grafts were implanted in five patients. Treatment results were monitored by means of interview, ultrasound, and CT-angiography. The follow-up period varied from 3 to 8 months.

Results: stent-grafts were successfully implanted and aneurysms were excluded in all five patients. The aneurysms were not visualized and adjacent vessels were patent according to the control angiography. No deaths occurred during the follow-up. There was no evidence of neurological signs at the examination. Control examinations demonstrated the patency of all grafts; there were no signs of recanalization and/or increase in the aneurysm dimensions.

Conclusions: stent-grafting is an effective and safe treatment option for the carotid and vertebral artery aneurysms. Especially, this applies to such complex aneurysms as pseudo- and fusiform aneurysms where other endovascular techniques are associated with a high incidence of relapses and complications. The long-term patency of stent-grafts is unknown; immediate postoperative results suggest the optimistic conclusions, however.

Abbreviations:

ICA	– internal carotid artery
MCA	– middle cerebral artery
CT	– computed tomography
ECG	– electrocardiogram
HR	– heart rate
EchoCS	– echocardioscopy
TUS	– triplex ultrasound
TCDG	– transcranial dopplerography
PTFE	– polytetrafluoroethylene
VA	– vertebral artery

Advances in the endovascular surgery made it a worthy alternative to open surgery for the carotid and vertebral aneurysms. However, the standard endovascular techniques are associated with a high rate of complications and relapses in case of fusiform and pseudoaneurysms, which encourages the search for new treatment methods for this pathology. Over the last years stent-grafts demonstrated their superior efficacy and safety over other endovascular techniques in some individual clinical cases including treatment of the head and neck vessel aneurysms (1-4).

MATERIALS AND METHODS

Five cases of endovascular treatment of pseudo- and fusiform aneurysms of the carotid and vertebral

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arteries in five patients using stent-grafts were analyzed at the Regional Vascular Center of the State Institution of Healthcare Rostov Regional Clinical Hospital over the period from 2009 till 2010. Four patients out of them were males, patients' age varied from 22 to 48 years. Aneurysms location was as follows: pseudoaneurysm of the distal third of the cervical segment of the left ICA, pseudoaneurysm of the middle third of the cervical segment of the right ICA, pseudoaneurysm of the petrous segment of the left ICA, and two fusiform aneurysms of the intracranial part of the vertebral arteries. Two patients had previous subarachnoid hemorrhage 11 and 37 days before. In-hospital thromboembolism of the left MCA developed in one patient with the pseudoaneurysm of the left ICA. Three patients with pseudoaneurysms reported previous injury: random violence resulting in closed craniocerebral injury and traffic accidents 6, 8 and 17 months prior to thehospitalization, respectively.

All interventions were elective. The transfemoral approach was used in all cases. Five Jostent GraftMaster (Abbott Vascular) stent-grafts were implanted. No distal protection was used.

Three out of five patients received aspirin 100 mg once daily prior to the intervention; antiplatelet drugs were not prescribed to two patients before stent-grafting due to the previous subarachnoid hemorrhage. Following endovascular intervention all patients were given a loading dose of clopidogrel 600 mg and aspirin 300 mg followed by prolonged treatment with clopidogrel 75 mg/day and aspirin 300 mg/day. All patients were given I.V. heparin 5,000-10,000 IU during the intervention to maintain activated clotting time at the level of 2.0-2.5 x normal limit.

After the discharge the treatment results were monitored by means of interview, ultrasound, and CT-angiography. The follow-up period varied from 3 to 8 months.

RESULTS

Stent-grafts were successfully implanted and aneurysms were excluded in all five patients. The aneurysms were not visualized and adjacent vessels were patent according to control angiography.

After the discharge the follow-up period varied from 3 to 8 months. No deaths occurred during follow-up. There was no evidence of neurological signs at the examination. The follow-up ultrasound was performed in two patients with extracranial aneurysms in 3 and 6 months; CT-angiography was performed in patients with intracranial aneurysms in 3, 4, and 8 months. Control examinations demonstrated the patency of all grafts; there were no signs of recanalization and/or increase in the aneurysm dimensions.

Two clinical cases of successful endovascular intervention for pseudo- and fusiform aneurysms using stent-grafts are presented in this paper.

Patient B., 24 years, suffered the head injury with cerebrovascular accident manifesting as speech disorder and the right limbs weakness due to act of random violence on June 17, 2009. He was hospitalized via ambulance at the Department of Neurology at the place of residence, where he was treated with positive changes: the increase in the strength of the right limbs and speech recovery. The ultrasound examination revealed the posttraumatic aneurysm of the left ICA.

On November 23, 2009 the patient was referred to the Department of Vascular Surgery of the Regional Vascular Center of Rostov Regional Clinical Hospital, Rostov-on-Don, for the intervention. At the admission he reported episodic headaches and dizziness. There was palpable pulsation over the common carotid arteries on the both sides. Weak systolic murmur over the left internal carotid artery was heard on auscultation. ECG showed sinus rhythm, HR = 64 bpm. EchoCS showed grade 1 mitral valve prolapse, grade 0-1 mitral valve insufficiency, heart cavities are not dilated, there is no evidence of myocardial hypertrophy, the left ventricle systolic and diastolic parameters are normal. Provisional diagnosis of "posttraumatic aneurysm of the left internal carotid artery" was confirmed by brachiocephalic TUS performed in hospital; parietal concentric thrombus was revealed in the aneurysm cavity. Brain CT showed signs of previous cerebrovascular accident in the territory of the left MCA. Pseudoaneurysm of the distal third of the cervical segment of the left ICA measured 23x10 mm was revealed by the brachiocephalic angiography (Fig. 1)

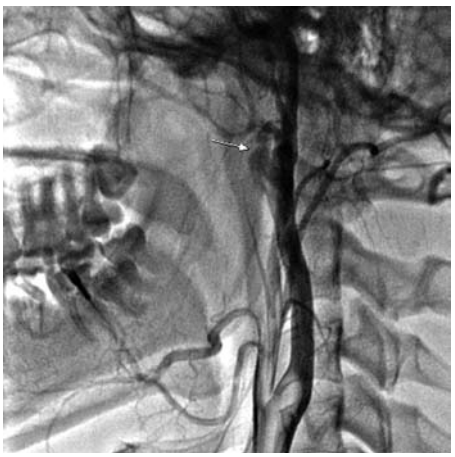

Figure. 1. Pseudoaneurysm (arrow) of the cervical segment of the left ICA.

The patient was given aspirin 100 mg once daily from the time of admission.

Weakness of the right limbs and speech disorder developed dramatically on Day 3 of the hospitalization. Brain CT revealed no signs of acute pathology. Brain TCDG showed decrease in the linear blood flow velocity in the left MCA. Ischemic cerebrovascular accident in the territory of the left MCA was diagnosed. Thrombolytic therapy was decided to be started: Actilyse 50 mg (1 mg/ml), 7 mg out of them was administered as an intravenous push over 1 minute, and the remaining 43 mg – via iv infusion pump

over 1 hour. The clinical status improved significantly while on treatment (recovery of the strength of the right limbs and speech).

Taking into account a high possibility of repeated thromboembolism and the patient's status, the risk, and the complexity of open surgery in this anatomical area, the decision to perform the endovascular intervention – stenting of the left ICA – was made.

On November 27, 2009 endovascular intervention was performed via the right transfemoral approach under local anesthesia. Intravenous heparin 5,000 IU was previously administered. The guide-catheter 7 Fr was placed into the left common carotid artery; cerebral vessel angiography was performed. The transend guidewire (Boston Scientific) measured 0,014 in x 205 cm was placed into the intracranial part of the left ICA; Jostent GraftMaster stent graft (Abbott Vascular) measured 5.0x26 mm was advanced over the guidewire at the aneurysm area and implanted at 16 atm. Insignificant opacification of the aneurysm cavity was observed at the control angiography. To remove residual aneurysm opacification the balloon catheter was repeatedly placed in the stent-graft and dilated for 40 seconds. The control angiography showed no blood flow in the aneurysm, and preserved patency of the left ICA and its branches (Fig. 2). To prevent stent-graft thrombosis, the patient received single doses of clopidogrel 600 mg and aspirin 300 mg immediately after the intervention and then clopidogrel 75 mg and aspirin 300 mg once daily.

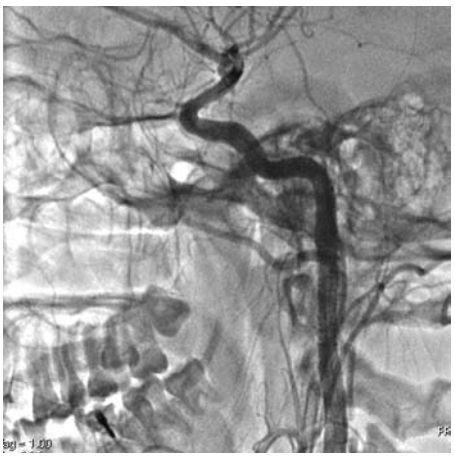

Figure. 2. No opacification of the cavity of ICA pseudoaneurysm after the stent-grafting.

Condition at the discharge was fair. There were obvious positive changes in the neurological status: no cerebral symptoms, the face is symmetric, tongue is located at midline, tendon reflexes are vivid, D=S, the limb strength score is 5 on the both sides, Romberg and finger-to-nose tests are unremarkable, there are no sensitivity disorders.

The ultrasound examination of the neck vessels 3 months later showed the patency of the stent-graft; there were no signs of recanalization and/or the aneurysm growth. There is no evidence of neurological signs.

Patient V., 48 *years*, admitted to the Department of Cerebrovascular Accident of the Regional Vascular Center of the State Institution of Healthcare Rostov Regional Clinical Hospital with complaints on a headache in the front and occipital areas, photophobia, and increased BP up to 170 and 100 mmHg. He suffered subarachnoid hemorrhage 11 days prior to the hospitalization. At the examination: level of consciousness - grade 1 stupor; meningeal signs - photophobia, positive Kernig's sign, neck rigidity. The patient had a history of an epileptic seizure. Preliminary diagnosis: Spontaneous subarachnoid hemorrhage, Hunt and Hess grade 3, meningeal syndrome. In-hospital CT angiography showed fusiform aneurysm of the right vertebral artery. Selective brachiocephalic angiography showed fusiform aneurysm of the intracranial part of the right vertebral artery measured 12 mm in diameter (Fig. 3).

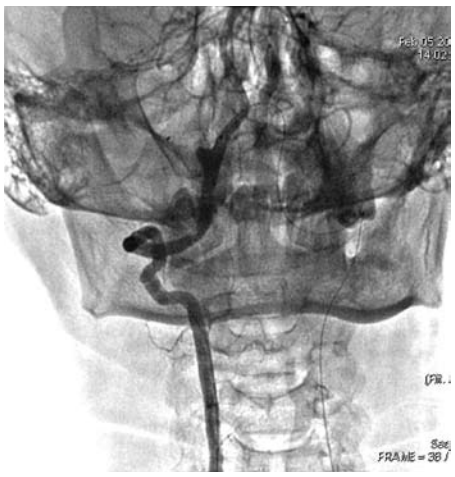

Figure 3. Fusiform aneurysm of the intracranial part of the right vertebral artery.

Taking into account the risk of repeated subarachnoid hemorrhage and the patient's status, the risk, and the complexity of open surgery in this anatomical area, the decision to perform the endovascular intervention – stenting of the intracranial part of the right vertebral artery – was made.

Endovascular intervention was performed via right transfemoral approach under local anesthesia. I.V. heparin 5,000 IU was previously administered. The guide catheter 7 Fr was placed into the right vertebral artery. The transend guidewire (Boston Scientific) measured 0,014 in x 205 cm was placed into the intracranial part of the left VA via the right VA. An attempt to place the stent-graft in the intracranial part of the right VA failed due to significant VA tortuosity. The guide catheter 7 Fr was placed into the left vertebral artery. The transend guidewire (Boston Scientific) measured 0,014 in x 205 cm was placed into the intracranial part of the right VA via the left VA; Jostent GraftMaster (Abbott Vascular) measured 3.0x26 mm stent-graft was advanced over the guidewire in the spindle-shaped area of the dilated right VA and implanted at 16 atm. successfully. Control

angiography: the aneurysm is not contrasted, vertebral and basilar arteries and their branches are patent by (Fig. 4).

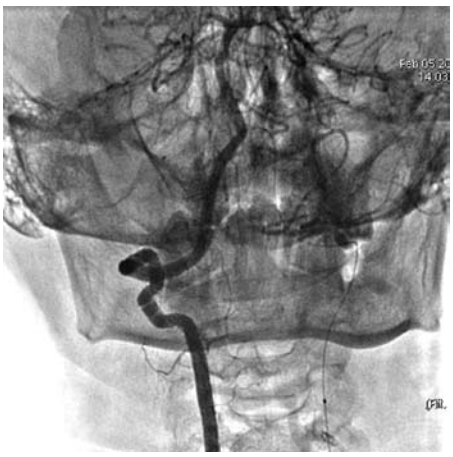

Figure 4. Angiogram of the right vertebral artery after stent-grafting.

In order to prevent stent-graft thrombosis, the patient received single doses of clopidogrel 600 mg and aspirin 300 mg immediately after intervention and then clopidogrel 75 mg and aspirin 300 mg once daily.

Condition at the discharge was fair. Neurological status demonstrated obvious positive changes.

CT angiography performed 4 months later showed the patency of the stent-graft; there were no signs of recanalization and/or the aneurysm growth. There is no evidence of neurological signs.

DISCUSSION

The incidence of intracranial fusiform aneurysms is less than 0.1% (5, 7). In spite of this, this is a very dangerous condition with a 5-year mortality of up to 80% (5-7). Pseudoaneurysms of the head and neck vessels are characterized with a high rate of neurological complications and mortality achieving 80% and 40%, respectively (8).

Endovascular techniques for pseudo- and fusiform aneurysms include parent vessel occlusion, coiling with or without stent (balloon) support, bare metal stenting or stent-grafting (9-15).

The destructive methods for fusiform and pseudoaneurysms, particularly parent vessel occlusion, were widely used in the past (7, 9, 16-19). This method is risky per se; a thorough preoperative examination including balloon occlusion test is required (7). In case of inadequate collateral blood flow additional bypass grafting may be required (7). However, 5-22% of patients who had positive balloon occlusion test develop ischemic complications including stroke (20-22). Moreover, cases of aneurysm formation and/or aneurysm growth after carotid occlusion were reported in literature (23-25).

The stent introduction in the practice and the evolving of interventional techniques led to a new more physiological concept of the "endovascular reconstruction", which allows to preserve the patency of the parent vessel and exclude the aneurysm (7). However, stenting is insufficient to reduce the blood flow in the aneurysm cavity and to occlude it due to the cellular stent structure and the need for anticoagulants and antiplatelet drugs to reduce the risk of thromboembolism and stent thrombosis (26, 27). Stenting may be combined successfully with coiling for more stable occlusion of the aneurysm cavity (3, 27-31). In this case a stent serves as a rigid support to prevent coil sagging in the vascular lumen and as a matrix for endothelial growth as well (32). This method demonstrated good results, but has disadvantages, as it is quite difficult to achieve the complete occlusion of wide-necked or irregular-shaped aneurysms (3, 28, 32). Even in combined use of stenting and coiling in the treatment of complex aneurysms, the rate of recanalization is up to 20% (3, 28, 32).

Stent-grafting became an effective promising alternative to open surgery and some endovascular techniques. It is used successfully in the treatment of aneurysms of the thoracic and abdominal aorta as well as in aneurysms, ruptures, dissections, and arteriovenous fistulas of the peripheral arteries (3, 19, 33). Clinical observations demonstrate the efficacy of stent-grafting for aneurysms located in the skull base, ruptures of the extracranial parts of the carotid arteries, iatrogenic lesions of the cavernous segments of ICA, and petrous carotid fistulas (34-40). These observations suggest that stent-grafting may be the simplest, fastest, and most effective option to preserve a parent artery.

Over the last years, the use of stent-grafting for brain aneurysms was reported (3, 19, 26, 33, 41-43). Stent-grafts have many potential advantages for the intracranial use (41). Stent-grafting permits to exclude quickly the aneurysm and to preserve the patency of the parent artery (41). The stent-grafting has lower incidence of aneurysm relapses than that with coiling or embolization using liquid substances (41). This technique allows to avoid manipulations in the aneurysm cavity, which reduces the risk of rupture (41). Additionally, stent-grafting has lower mass effect than coiling or Onyx embolization for large and giant aneurysms (41).

Different coating materials are used in the stent-grafts. PTFE grafts demonstrated acceptably low complication rate including acute and subacute stent thrombosis (in case of optimal deployment) (45). Moreover, PTFE layer showed a low rate of in-stent intimal hyperplasia and stenosis due to inhibition of inflammatory cells migration and cytokine diffusion (3, 4, 33, 34, 40, 45, 46). Laboratory studies of PTFE grafts also confirm the clinical data (40). Dacron or silicon containing grafts have lower incidence of the patency of the parent artery at the implantation site due to acute inflammation and excessive fibrosis (4, 33, 40, 47, 48).

Limited flexibility is a disadvantage of stent-grafts; which precludes their passing through the kinks of the cerebral arteries and may cause a spasm or dissection (3, 4, 19, 32, 33, 41, 42). Moreover, grafts

may only be used at the vessel portions without any major branches; the occlusion of which may result neurological disorders (3, 19, 32, 41). These portions include the cervical, petrous, and cavernous segments of ICA, extracranial and intracranial segments of the vertebral artery up to the origin of the posterior inferior cerebellar artery, and then - up to the confluence of the both vertebral arteries (19, 33, 41). Moreover, Saatci reported stent-grafting at the site of the ophthalmic artery origin without any symptoms, which was attributed by authors to blood flow restoration via collaterals from the external carotid artery territory (3). In the presence of the parietal thrombus in the spindle-shaped dilated segment of the vertebral or basilar artery its branches become non-functional, thus, making stent-grafting possible (49).

There are no data on the long-term patency of stent-grafts in the worldwide literature. However, available data allow to expect the positive results on preservation of blood flow in a parent artery (3, 4, 19).

CONCLUSIONS

Stent-grafting is an effective and safe treatment option for the carotid and vertebral aneurysms. Especially, this applies to such complex aneurysms as pseudo- and fusiform aneurysms where other endovascular options are associated with a high incidence of relapses and complications. The long-term patency of stent-grafts is unknown; however, immediate postoperative results suggest the optimistic conclusions.

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Hereditary Factors in the Origin of Stress-Induced Transformation of the Athlete's Heart

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The article presents the results of the investigation of the influence of hereditary factors: angiotensin converting enzyme (ACE), regulatory genes PPAR and NFAT, calcineurin (CNB) and endothelial growth factor (VEGFA) gene polymorphisms on morphological and functional features of the athlete's heart. The alleles of susceptibility to the abnormal transformation in the heart were revealed. The recommendations to identify the cardiac risk groups among athletes based on the results of molecular genetic screening were made.

Keywords: *abnormal transformation of the athlete's heart, gene polymorphism, molecular genetic screening, susceptibility genes for cardiac diseases in athletes.*

Active implementation of molecular genetic assessments in the medicine and in the cardiology resulted in expanded horizons of the understanding of the role of interaction between hereditary and environmental factors in the development of various abnormal conditions, including those in athletes (7-12). According to the demographic data, within the last 20 years a critical growth of specific cardiac diseases was reported in athletes. Those diseases are considered one of the main reasons of depressed functional status, premature ending of sport career and even of athletes' deaths (4-5, 31). In a number of the West European countries the cardiovascular mortality in athletes is 2.5-fold as large as the average value in non-sportsmen (22, 33). The main reason of this adverse situation consists in the abnormal transformation of the "athlete's heart", typical for 30% to 75% of different athletes according to the majority of foreign authors (26, 31-32). According to B. Maron (1995), one of the leading experts in heart diseases in athletes, this complex condition is characterized by the clinical and functional polymorphism and is predominantly familial (26).

For more than hundred years, the specialists in the sports medicine and cardiology tried to understand the features of the physiological athlete's heart and the reasons of its abnormal transformation. At the present day it has been established that the physiological and pathological changes of the athlete's heart are based on the reorganization of the heart architecture (remodelling) (31). This process primarily includes the hypertrophic and dilatational changes in the configuration of ventricular myocardium and in spatial relations of the cardiomyocytes, accompanied by immune shifts and cytochemical changes (5, 34). The idea is that the nature of these changes varies and depends on the individual response of the athlete's organism to professional risk factors (sports discipline, duration and intensity of the exercises and adequacy of training) (5-12). Summarizing all the above mentioned facts, one could suggest that the physiological and pathological transformation of the athlete's heart are based on the uniform hereditary molecular biological mechanisms, which determine the process of physiological remodelling in the context of appropriate physical exertion, while in case of physical overstress they trigger the life-threatening conditions.

This assumption is closely related to breakthroughs in ecogenetics – science of the environmental influence on manifestation of the hereditary characteristics of the body and on the role of genetic polymorphisms in this process. Gene polymorphisms represent neutral mutations, which define the intraspecies variability and the ranges of individual intraspecies variability (23). The issues of the ecogenetic pathology and of genetic polymorphism were most completely investigated in the research projects of well-known American experts L. Cavalli-Sforza, K. Olden and K. Busher. The first project (Human Genome Diversity Project) worked out the basic problems related to human origin, formation of races, ethnogenesis, anthropology etc. (23). The second project (Environmental Genome Project) included the investigation of the genetic basis of individual susceptibility or resistance to the adverse exogenous factors (16). In the course of the studies the idea of the existence of susceptibility genes arose – the alleles of polymorphous genes consistent with the birth and with the life, which contribute to the formation of various ecogenetic diseases under certain

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conditions. As a rule, such abnormal conditions are multifactorial: as opposed to the monogenetic diseases resulting from the gene mutations, the ecogenetic diseases require the presence of both susceptibility genes and the adverse environmental factors as a pre-requisite. Depending on the trigger factor features, the susceptibility genes belong either to the environmental genes or to the trigger genes, which initiale the pathologic process (16).

In this context, the studies initiated in 1995 under the leadership of K. Busher and focused on the search of specific gene-determinants of sports successes are of special interest for the sports medicine (17). In this project, more than 130 "sports polymorphisms" highly widespread in athletes and related to the development of certain athletic characteristics (velocity, endurance, strength) were studied (15). However, according to the clinical medicine, some *"sports polymorphisms" (gene of angiotensin converting enzyme [ACE], regulatory gene of lipid metabolism [PPAR], regulatory genes of myocardial hypertrophy [CnB and NFAT] and regulatory genes of vascular endothelial growth [VEGF])* represent the susceptibility genes for a range of serious ecogenetic diseases. Those include the hypertensive and coronary heart disease, heart arrhythmia, type 2 diabetes mellitus and obesity (18-19, 21-22). Probably, specific combinations of these genetic factors not only affect the growth of sports results but cause the abnormal transformation of the athlete's heart due to the sports overexertion. The search of the answer to this question appeared to be rather difficult, as besides the investigation of the clinical functional and biochemical mechanisms of abnormal changes, the individual environmental factors were to be considered, such as conditions and character of training and competitions, which contribute to the pathologic gene effects.

During the last 5 years the Laboratory of Functional Diagnostics at the Russian State University of Physical Education, Sports, Youth and Tourism together with the Moscow Scientific and Practical Centre of Sports Medicine (Head – Z.G. Ordzhonikidze) and Saint-Petersburg Research Institute of Physical Education have been performing the studies focused on identification of the new "sports polymorphisms" and their association with the morphologic and functional characteristics of the athlete's heart. In this period, the laboratory performed complex clinical, functional and genetic assessment of more than 30 high-skilled athletes (Masters of Sports, Masters of Sports of International Level, Honoured Masters of Sports) engaged in cyclic sports (rowing, allround speed skating), velocity and strength sports (single fight), complex coordination (artistic gymnastics), competitive sports (tennis) and complex technical sports (motor racing, motor bicycle racing). In the course of the investigation the special attention was paid to the study of hereditary factors related to physiological and pathological transformation of the athlete's heart. As was said, the main feature of the athlete's heart consists in the slight myocardial hypertrophy, which must not exceed 13 mm, according to the authorities in sports cardiology (26, 33). The second feature of the physiological athlete's heart, which is at least equally important, includes the slight increase in the left ventricular end-diastolic dimension (LVEDD) (up to 55 mm), not exceeding the critical value of 60 mm (26). In our study the physiological (up to 13 mm) increase in the left ventricular posterior wall thickness (LVPWT) was observed in 25% of athletes. In 75% of the subjects LVPWT increased to 13 17 mm. The left ventricular diameter ranged from to 46 to 58 mm, thus not exceeding the critical range typical for documented heart pathology. In the course of the study we pointed out the discrepancy between the echocardiography data and the electrocardiography results, which revealed the ECG signs of the left ventricular myocardial hypertrophy in only 7% of athletes. This dissonance could be explained by the fact that, according to multiple assessments, the formation of the physiological athlete's heart is accompanied by the hypertrophy of both left and right heart (Table 1).

Table 1. Differential diagnosis of the physiological and pathological athlete's heart (26).

Features	Physiological athlete's heart	Pathological athlete's heart
Hypertrophy	Symmetric up to 13 mm	Asymmetric more than 13 mm
LV diastolic diameter	⩽ 60 mm	⩾ 60 mm
LV diastolic filling	Normal	Abnormal
Left atrium diameter	⩽ 40 mm	⩾ 40 mm
LV wall thickness	Decreases after the discontinuation of exercises	Constant

As a rule, the symmetric hypertrophy manifests itself by the absence of clinically significant ECG changes and by virtually normal ECG pattern. The presence of electrocardiography signs of myocardial hypertrophy in athletes without echocardiography signs of asymmetric hypertrophy may indicate the premorphologic involvement of the right or left heart and predict the formation of the pathologic athlete's heart (32). In our case the subgroup with ECG signs of myocardial hyperthrophy included solely males with high sports skill category (3 World-Class athletes and 2 Honoured Masters of Sports), members of the Russian picked teams in rowing (4) and speed skating (1).

The assessment of the influence of hereditary factors on specific morphological and functional features of the cardiovascular system in athletes included several stages. The first step was focused on the determination of gene polymorphisms common in athletes and probably significant in the process of abnormal transformation of the athlete's heart. The candidate genes included: angiotensin converting enzyme gene (ACE), regulatory genes PPAR and NFAT, calcineurin gene (CNB) and vascular endothelial growth factor gene (VEGFA) (Table 2).

Table 2. The range of functional activity of the polymorphisms in the (G/C) PPARA, (T/C) PPARD, (G/A) NFATC4, (I/D) ACE, (5I/5D) CNB, (G/C) VEGFA genes

Gene	Coded protein	Gene function	Class of polymorphism
PPARA	(refSNP)	Regulates activity of the genes responsible for carbohydrate and lipid metabolism in the myocardium	rs4253778 G
PPARD	PPARδ	Regulates activity of the genes responsible for metabolism of cholesterol, fatty acids oxydation	rs2016520
NFATC4	Nuclear factor of active T-lymphocytes	Regulates expression of many genes, including cytokines genes (TNF- , IL 1,4,5)	rs2229309
ACE	Angiotensin converting enzyme	Catalyses the conversion of angiotensin I into angiotensin II, regulating vascular tone	rs4340
VEGFA	Vascular endothelial growth factor	Stimulates the growth of vascular endothelium, prevents the apoptosis of myocytes	rs2010963
CNB	Calmodulin dependent protein phosphatase	Plays a key role in the transformation of hypertrophy signals	+5/-5 promotorr

Thereafter, the relation between these genes polymorphism and the myocardial hypertrophy over 13 mm was studied. In the course of this study, the involvement of the alleles of polymorph genes of PAAC system (D-ACE) (7, 13), of the alleles of regulatory genes of lipid metabolism (C – PPARA; C - PPARD) (1,8-9), of regulatory genes of hypertrophic response (D-CNB) (2, 10-12) and NFAT (Ala160 NFATC4) (3, 10) and of G allele of regulatory gene of vascular endothelial growth factor (G-VEGFA) (10-12) in the formation of inappropriate hypertrophic response in various athletes was revealed.

These results confirm the opinion of E. Chin (2000) about the involvement of multiple signal pathways in the triggering of abnormal myocardial hypertrophy (19-20). Probably, the stress-induced changes of gene regulatory programs result in the activated expression of a wide range of genes, including the skeletal muscles and myocardium sarcomer proteins genes, several signal systems, ion channels and other genes, including a series of mytochondrial genes, which induce the remodelling of the athlete's heart (25, 27, 29). The results of the study lead to a suggestion that calcineurin-dependent signal pathway takes part in the mechanism of stress-induced myocardial remodelling in athletes. Molkentin et al. (1998) demonstrated that active calcineurin and its down-stream effector *NFATC4* can induce the hypertrophic growth of cardiomyocytes in vitro (27). In transgenic mice the cardiac expression of active calcineurin results in progressive myocardial hypertrophy with subsequent heart dilation, cardiac failure and death (27-28, 36). The previously reported interaction between *NFATC4* gene and physical activities (2) and the increased prevalence of A1a allele of NFATC4 in high-skilled athletes with myocardial hypertrophy exceeding 13 mm, demonstrated in our study (10), suggest the involvement of the above gene factors in the abnormal transformation of the athlete's heart. This suggestion confirms the involvement of the immune system, previously reported in the experiments, in the process of abnormal stress-induced remodelling of oxygen transfer system in athletes under conditions of inappropriate exercises (4, 6).

On the other hand, the abnormal myocardial hypertrophy in athletes is based on the modified energy metabolism, with increased glucose uptake and decreased oxydation of fatty acids due to the reduced mRNA level, which codes the oxydative enzymes. The experimental evidences of this fact include the formation of myocardial hypertrophy in animal models with gene defect of mytochondrial enzymes and depressed uptake of fatty acids (25).

In the course of the study, the main attention was paid to the interaction between D allele of ACE gene and the structural features of the athlete's heart. The excessive activity of angiotensin converting enzyme is known to contribute to the proliferation of myocardial connective tissue (type I collagen) with subsequent decrease of myocardial elasticity (37). Besides the correlation of D allele with myocardial hypertrophy over 13 mm in athletes, revealed in the study (29, 7), it is considered in the clinical cardiology as the factor of hereditary susceptibility to myocardial infarction (18) and sudden cardiac death risk (SCD). It should be noted, that in persons with ID genotype SCD risk is 1.8-fold higher, and in persons with DD genotype it is more than 2.2-fold higher. Zee et al. demonstrated that the carriership of DD polymorphism decreases significantly with the increase of years. This fact leads to a suggestion about the influence of this allele on the risk of fatal heart diseases (37). K. Nakai (1994) demonstrated the association between DD genotype and the increased number of affected vessels in patients with coronary heart disease; Amant et al. (1997) reported the correlation between this genotype and the incidence of stenosis and restenosis following coronary angioplasty (22, 30). In the context of confirmed stress-induced pattern of abnormal cardiovascular changes in athletes, one could suggest that the overactive ACE enzyme due to D allele carriership leads to the impaired myocardial relaxation with subsequent left ventricle hypertension, and finally to the decompensation of hypertrophy, abnormal dilation of the athlete's heart with decreased functional activities. Thus, D allele (ACE) is probably a trigger of stress-induced cardiac diseases in athletes, while the carriership of its homozygote combination represents an adverse factor for sports. In our study, the adverse homozygote combination DD (ACE) was observed in 25% of speed skaters, in 18% of rowers, in 20% of shooters, in 30% of divers and in 21% of unarmed self-defence athletes. In the course of the study, the comparison of functional parameters of single-fight athletes with adverse homozygote combination DD (ACE) was performed. In this subgroup of athletes, the significant decrease in physical performance, inappropriate increase in blood pressure and heart rate on exertion and progressive depression of ST segment

during the exertion at the level of marginal anaerobic metabolism were observed (7).

These results lead to a suggestion that the susceptibility genes could contribute to both physiological and pathological transformation of the athlete's heart, realizing their abnormal effects in the context of certain adverse ecologic conditions (for instance, under conditions of repeated psychofunctional physical overexertion). In turn, the abnormal stress-induced transformation of the athlete's heart belongs to the ecogenetic disease, and their manifestiation is closely related both to the athletes exposure to the professional risk factors and to the presence of adverse polymorph susceptibility alleles in the athlete's genotype: PAAC system *(D-ACE))* (7,17), regulators of lipid metabolism (C – *PPARA; C - PPARD*) (1,7-11), of hypertrophic response *D-CNB*) (2) and NFAT (Ala160 *NFATC4*) (2) and vascular endothelial growth regulator (*G-VEGFA*). In order to support this suggestion the detailed assessment of molecular genetic mechanisms of abnormal transformation of the athlete's heart in various athletes is required, which is only possible using the multidisciplinary approach and combined efforts of the experts specialized in the fundamental study methods, as well as of clinical and sports cardiologists. The most significant practical result of comprehensible assessment of cellular and molecular bases of pathological athlete's heart formation should be the development of new gene-specific methods of heart protection in the sports, which could decrease the risk of specific ecogenetic disease in athletes and result in their sports longevity.

PRACTICAL RECOMMENDATIONS

Since the susceptibility genes of stress-induced transformation of the athlete's heart, revealed in our studies, became the subject of investigation in the sports genetics and are used for the selection and determination of the sports profession, we strongly recommend to reveal timely homozygote and certain heterozygote forms of the above polymorphisms in the genotype of young athletes. The presence of 5 or more risk alleles (*PPARA C, PPARD C, CNB D, NFATC4 Ala160 and VEGFA G*) in the genotype of young athletes may be used for the identification of the cardiac risk group for the purposes of individual scheduling of training and limitation of cyclic sports. The presence of homozygote combination (DD polymorphism) of ACE gene, which is the susceptibility gene of life-threatening conditions and an adverse factor for professional sports, in the genotype of both young and high-skilled athletes is an indication for limitation of physical exertions. Athletes, who exercise the velocity and strength skills, demand the most attention, because the incidence of D allele of ACE is significantly higher in this population (V.A. Rogozkin, 2000).

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Endovascular Correction of the Right Uterine Artery Pseudoaneurysm. A Clinical Case

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Uterine artery pseudoaneurysm is a rare but potentially life-threatening complication of gynecological surgery. A 39-years-old female patient diagnosed with uterine arteriovenous shunt was admitted to the Gynecology Department at Irkutsk Regional Clinical Hospital in January, 2010, three months after elective myomectomy (with enucleation of three myoma nodes) for interstitial subserous myoma of the uterus. The diagnosis of the right uterine artery pseudoaneurysm was confirmed by CT scanning and angiography. No arteriovenous shunt was revealed. The reduction of blood flow in the uterine arteries was performed using the radio-endovascular technique to prevent the contralateral anastomoses formation and potential uterine bleeding. The endovascular uterine artery embolization is an effective and minimally invasive technique for the treatment of the uterine artery pseudoaneurysm.

Keywords: *uterine artery pseudoaneurysm, endovascular embolization.*

List of abbreviations:
IRCH – Irkutsk Regional Clinical Hospital
UAE – uterine artery embolization

Introduction:

A pseudoaneurysm is a cavity filled with blood which communicates with the true artery lumen. A pseudoaneurysm is surrounded with adjacent tissues outside the arterial wall (1,2). The vascular wall damage as a cause of false aneurysm development results from inflammation, vessel injury or iatrogenic damage during surgical intervention, tissue biopsy or drainage (2).

A uterine artery pseudoaneurysm is a rare but serious complication of the hysterectomy (3,4), myomectomy (5,6), caesarean section (7), and curettage (8). The incidence of false aneurysm formation after myomectomy is 0.63% (9). Without timely US, CT and angiographic diagnosis and appropriate treatment, pseudoaneurysms tend to predictable rupture resulting in life-threatening bleeding (3,4,6).

The exact mechanism of false aneurysm development after myomectomy is unknown. It is possible that the uterine artery damage is caused by the enucleation of a deep intramyometrial node. There are only single reports describing pseudoaneurysm after myomectomy, which is probably due to the asymptomatic nature of this complication (5,6). Therefore some authors recommend performing US scan of the uterus in all patients following myomectomy (3).

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We describe a case of the right uterine artery pseudoaneurysm detected on US scan 2 months after myomectomy, which was successfully eliminated by the transcatheter uterine artery embolization (UAE) with PVA particles.

Clinical case:

A 39-years-old female patient diagnosed with uterine arteriovenous shunt was admitted to the Gynecology Department at Irkutsk Regional Clinical Hospital in January, 2010 three months after elective myomectomy (with enucleation of three myoma nodes) for interstitial subserous myoma of the uterus. The postoperative course was unremarkable. The patient was discharged for the ambulatory follow-up at the maternity welfare center where the control US scan revealed a fluid containing cavity measured 26x22x25 mm located in the right lateral uterine wall, and a high-velocity arteriovenous shunt in the uterine wall, probably at the site of enucleation of one of the myoma nodes. The pseudoaneurysm was diagnosed by multispiral CT angiography (Fig. 4).

The patient underwent angiography of the vascular territory of the both internal iliac arteries via the right femoral artery puncture by Seldinger's technique using a 5F introducer and ventricular catheter. The superselective contrast medium injection through the Roberts catheter was performed sequentially into the both uterine arteries. Signs typical of fibromyoma (highly tortuous and hyperplastic vessels) were revealed in the vascular territory of the left uterine artery. The embolization with the two doses of PVA particles (500-700 μm) was performed until sustained stasis of the contrasted blood in the artery was achieved (Fig. 1,2).

The contrast enhancement of the right uterine artery revealed a false aneurysm (35x30 mm) with turbulent flow, regular contours and retention of the contrasted blood. No arteriovenous shunt was

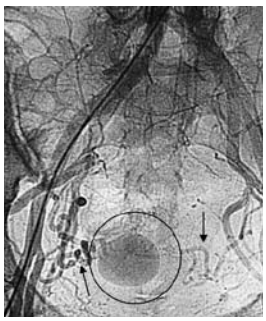

Figure. 1.

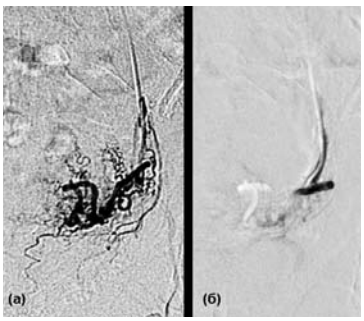

Figure. 2.

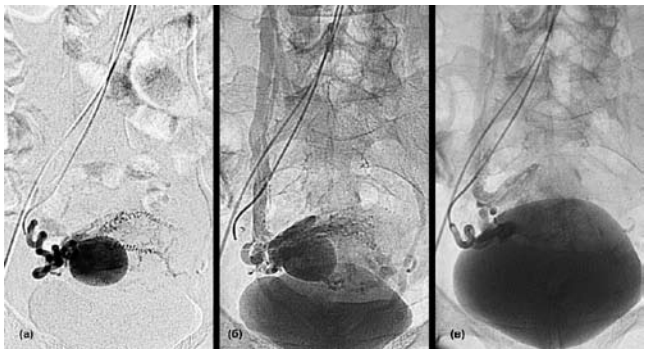

Figure. 3.

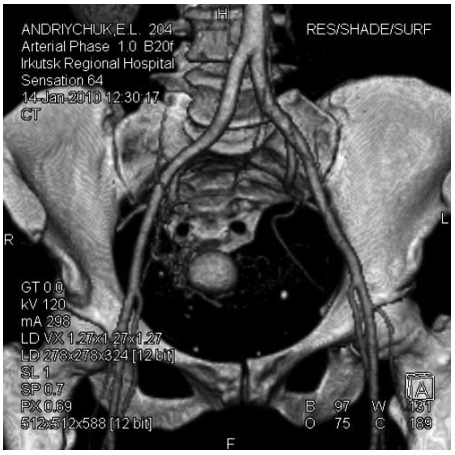

Figure. 4.

revealed. The venous phase occurred timely. The right uterine artery was embolized with three doses of PVA particles (500-700 μm) until sustained stasis of the contrasted blood in the artery was achieved and the pseudoaneurysm was no longer visualized (Fig. 3).

During the postoperative period the patient's condition was fair: body temperature - 36.6 C; complaints on mild pulling pain in the lower abdomen. No vaginal discharge was observed.

The control US scan performed 5 days after UAE revealed a cavity measured 21x17x20 mm with the signs of organizing hematoma located along the anterior wall of the right tubal angle.

The patient was discharged in fair condition for the follow-up at the maternal welfare center at her place of residence.

Conclusion:

The endovascular uterine artery embolization is a minimally invasive technique for the treatment of uterine fibromyomatosis and uterine bleeding of various etiology. UAE has been used for the treatment of uterine myoma since 1995 (10), however, as early as 1979, the uterine artery embolization was used for hemostasis in postpartum and postoperative bleeding (11,12,13). The efficacy of UAE as a method to achieve sustained hemostasis in traumatic pelvic bleeding, gynecological diseases, and pelvic cancer exceeds 97% (12).

In the management of pseudoaneurysms, UAE is superior to conventional surgery, which requires intracavitary intervention. It is quite difficult to identify and ligate a vessel nourishing the aneurism intraoperatively, while an attempt to evacuate a hematoma often leads to secondary bleeding due to reduction of the hematoma tamponade effect. UAE allows the exact visualization and superselective closure of the nourishing vessel. The embolization of the distal microvascular bed of the artery can be achieved as well, which is impossible with conventional ligation.

When performing UAE to eliminate a false aneurysm, it is important to close both the nourishing and contralateral uterine artery to prevent interarterial collateral formation.

UAE is a safe, effective and minimally invasive method to prevent acute bleeding events in uterine artery pseudoaneurysm.

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Vulnerable Atherosclerotic Plaque: New Prospects of Intracoronary Imaging

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This paper presents the current approaches to evaluate the features of atherosclerotic plaques using invasive methods of the coronary artery imaging. The histological features of so-called "vulnerable" atheromas are briefly addressed as well. The factors limiting the gray scale IVUS potentialities for evaluating such plaques are described. The need for differentiated assessment of atheroma components – lipid, fibrous, and calcium, as well as of the thickness of fibrous cap is highlighted. The potentialities of IVUS with mathematical processing of backscatter signal for virtual histological assessment of atheroma components are described in detail. The characteristics of the optical coherence tomography technique for measuring the vulnerable plaque fibrous cap thickness are also addressed.

Keywords: *IVUS, vulnerable plaque, atherosclerosis, imaging*

The recent years have been marked by significant improvements in the prevention and treatment of cardiovascular diseases worldwide. Nevertheless, despite advances in modern cardiology, acute coronary syndrome continues to be the leading cause of death in general population. Current methods for acute coronary syndrome prevention are intended to reduce systemic risk factors using modern medical therapy including antiplatelet drugs, statins, ACE inhibitors, and β-blockers. However, despite continued active therapy, acute coronary events still occur. Several large clinical studies showed that patients treated with high-dose statins and achieving optimal LDL levels still experience acute cardiovascular events. Thus, additional methods for prevention of acute coronary events are to be searched, and the prevention of atherosclerotic plaque complications is one of such measures.

The identification of atherosclerotic plaques at high risk of complications, so-called vulnerable plaques, and utilizing local and systemic therapeutic approaches may additionally reduce the potential cardiovascular risk. Searching the location of potential plaque rupture leading to myocardial infarction is a promising strategy of cardiovascular examinations allowing to determinate indications for coronary revascularization more clearly.

Thrombosis is one of the main factors causing an acute coronary event. The atherosclerotic plaque rupture or erosion are important in this process. These two events are different: in endothelial erosion, a thrombus develops on the surface of a plaque, whereas in rupture, it forms within the plaque. To date, both plaque rupture and erosion are considered to be the consequence of inflammation, especially of macrophage activation in response to intimal infiltration by oxidized lipoproteins. The autopsy findings suggest that the occlusive thrombus is caused more often by the plaque fibrous cap rupture than by endothelial erosion on its surface.

A fibrous cap rupture is a complication related to the large lipid core formation (1,2). The data from many studies suggest that a thin cap of fibroatheroma (TCFA) covering a large lipid core with poor vascularization and cellular composition seems to be more prone to rupture (3-5). Some authors showed that TCFA rupture causes 60% of acute coronary events; moreover, other not yet ruptured TCFAs are found in 70% of patients.

Histological examinations have identified the morphological features of high-risk plaques prone to rupture:

- large plaque volume;
- positive coronary artery remodeling leading to its dilation at the site of atheroma;
- large lipid core (more than 40% of the plaque volume) containing cholesterol esters and clefts, and oxidized lipids;
- fibrous cap and adventitial infiltration by inflammatory cells (mainly macrophages, activated T-cells, and mast cells;
- thin fibrous cap (less than 65 μm) depleted of collagen and smooth muscle cells;
- increased adventitial and intimal neovascularization.

The probability of acute coronary syndrome development depends strongly on the presence of unstable plaques in the coronary circulation. The main objective of atherosclerosis imaging is the identification of a vulnerable plaque before ACS develops. A number of pathology studies have shown that the artery lumen is not necessarily narrowed in atherosclerosis; therefore, the coronarography does not

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reveal coronary artery lesion until a hemodynamically significant stenosis develops. The retrospective and prospective angiographic examinations showed that only 2/3 of ACS patients who underwent coronarography several weeks or months prior to an acute coronary event had hemodynamically significant luminal narrowing (6). Thus, it was found that myocardial infarction is often caused by atherosclerotic plaques moderately narrowing the lumen of the coronary artery.

The plaque vulnerability was determined to be dependent more on the artery's morphological characteristics and remodeling than on the degree of arterial stenosis (7). Arterial wall is not a static structure, it undergoes remodeling via the increase of the external diameter, while accommodating to the growing plaque to prevent arterial narrowing.

The atherosclerotic plaque imaging became possible with the use of intravascular ultrasound (IVUS) – an evaluation method used to assess the degree of atherosclerotic lesion detected by coronary angiography (9). An ultrasound transducer attached to the tip of IVUS-catheter generates US pulses and detects echo-signals from tissue. A real-time 2D image is produced in gray scale. This image allows assessing the vessel diameter and lumen, and the extent and morphological features of atherosclerotic plaque as well as the degree of arterial stenosis. The gray scale IVUS enables detecting the low echogenicity, positive remodeling and spotty calcifications, which are predominant in unstable patients compared to stable patients (14,15).

The positive arterial remodeling (defined as an increase in the external elastic membrane diameter at the site of atheroma) is a feature of a vulnerable plaque (10,18). The gray scale IVUS showed positive arterial remodeling at the site of an infarct-related plaque in ACS patients. A large lipid core and decreased fibrous tissue content are observed in these plaques compared to plaques without remodeling or with negative vascular remodeling (11,12).

The video-densitometric analysis of gray scale images allows to assess certain components of an atherosclerotic plaque; however, this technique is unable to determine exactly all its structures. This is due to the features of the gray scale (resolution of 300 μm) used for image creation. It is hence a suboptimal method for accurate and reproducible assessment of plaque composition. A so-called IVUS-derived TCFA is a large volume plaque containing confluent core of low echogenicity accounting for 10-20% of the overall plaque volume and non-visualized fibrous cap (i.e. fibrous cap thickness is below the resolution of IVUS (16)). The amount of calcium is variable; more than 10% are presented as spotty inclusions (17).

Some investigators attempted to overcome the limitations of gray scale IVUS ability to determine the atherosclerotic plaque components. The emergence of IVUS method using radiofrequency analysis of echo signal allows to distinguish the different histological structures of an atheroma: lipid, fibrous, and calcium. The method is based on the mathematical analysis of ultrasound backscatter signals. The mathematical processing of backscatter provides a color-coded map of an atheroma reflecting its different histological structures. The resolving power of IVUS is of 110-150 μm (19,20).

Investigators use IVUS radiofrequency data analysis to determine a TCFA surrogate called IVUS-derived TCFA, which is defined as a plaque with necrotic area (more than 10% of the total plaque volume) protruding into the vessel lumen and associated with artery lumen stenosis of 40% and more. It was determined that such plaques are often found in ACS and are most commonly revealed in the proxi-

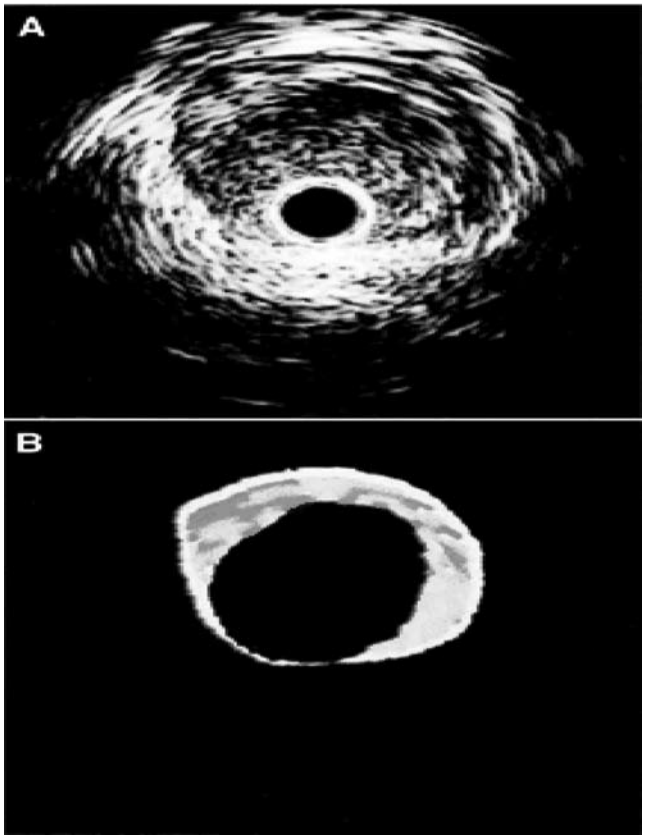

Figure. 1. IVUS characterization of the atherosclerotic plaque: gray scale image compared to virtual histology image (adapted from Rodriguez-Granillo G.A., et al, 2005).

A – gray scale image.

B – virtual histology image. White color – calcification; green color – fibrous tissue; red color – lipid (necrotic) core.

mal coronary segments.

There are three different ways of the mathematical processing of backscattered radiofrequency signal:

1. Autoregressive modeling – so-called virtual histology (IVUS-VH).

2. Fast Fourier transform (Integrated Backscatter (IB-IVUS)).

3. Wavelet analysis.

IVUS virtual histology, an autoregressive modeling of backscattered ultrasound signal, allows to identify four different structures within an atherosclerotic plaque, which are coded by different colors. 1

- fibrous/green, 2 - fibrolipid/light green, 3 – necrotic area/red, calcifications/white (20). The radiofrequency analysis of backscatter signal is a stepwise process. Firstly, the backscatter radiofrequency signal is received from the studied coronary segment, and then acquired images are displayed as sectors and a region of interest is selected. Homogenous regions of interest are identified for each of the four plaque components, which are identical to its histological structures and are analyzed by autoregressive modeling. The mathematical processing using the autoregressive modeling converts the obtained radiofrequency signal into the spectral data, which are represented as a linear regression plot reflecting the spectral frequencies and the corresponding radiofrequency ultrasound signal (21). The mathematically processed radiofrequency ultrasound signal from the four plaque components is color-coded which provides a color image of the virtual histological map of a plaque.

1 – fibrous plaque containing a large amount of dense collagen;

2 – fibrolipid plaque consisting of collagen and lipid inclusions;

3 – calcified necrotic plaque containing cholesterol clefts, foam cells and micro-calcifications in a necrotic area;

4 – calcified plaque without necrosis.

Comparison of the virtual histology data with the histological data showed the sensitivity and specificity of 80-92% in identification of the abovementioned four plaque components (20). The predictive value was 87% for fibrous component, 87% for fibrolipid component, 88% for necrotic area, and 97% for calcification.

The integrated backscatter intravascular ultrasound (IB-IVUS) method utilizes the mathematical processing of the backscattered radiofrequency ultrasound signal using the fast Fourier transform. The analysis is a stepwise process. Initially, the signal is decomposed into different frequency components using the fast Fourier transform algorithm. The integrated backscatter (IB) is calculated as the average power of the signal reflected from the small volume tissues. IB values for different plaque components are then coded by different colors providing the color map of a plaque. Comparison of IB values with the histological data of the coronary arteries showed the method sensitivity of 100% for calcifications, 94% for fibrosis, and 84% for lipids (23).

A wavelet analysis utilizes a waveform of limited duration with zero average amplitude. This method extracts a local wave pattern within obtained radiofrequency ultrasound signal and computes wavelet coefficients by the amplitude and the location of wavelets. Theoretically, different values of wavelet coefficients correspond to specific plaque components, which allows for plaque structure characterization. The ability of the method to assess the lipid plaque component was evaluated in a small study: the sensitivity of 81% and specificity of 85% were

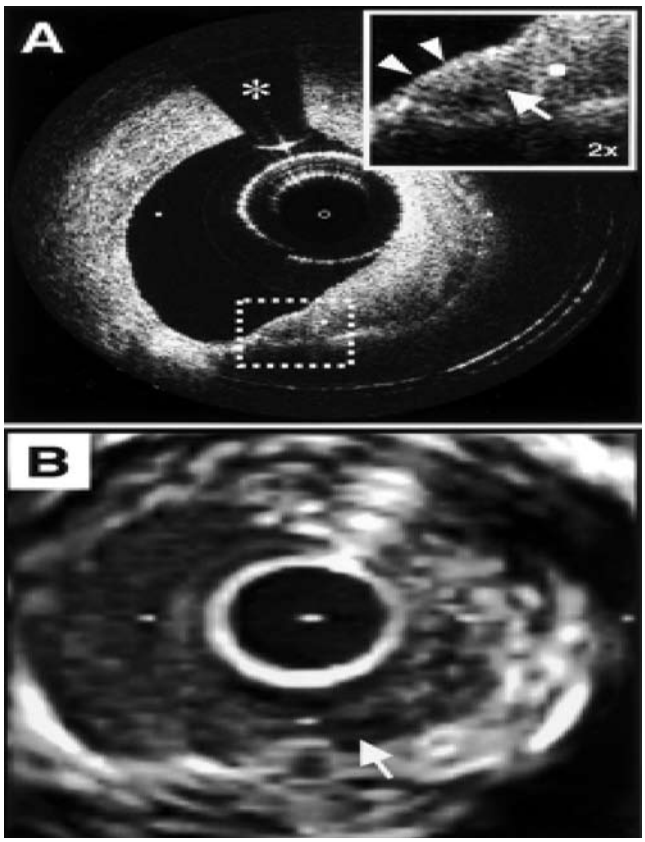

Figure. 2. Vulnerable atherosclerotic plaque imaging with OCT (A) and IVUS (B).

A – OCT shows the area of minimal fibrous cap thickness (20±3 μm) at the plaque shoulder – anticipated vulnerable site (shown at 2-fold magnification). B –the fibrous cap thickness is not visualized with IVUS.

demonstrated (24).

There are certain limitations of the use of IVUS radiofrequency data analysis. The data for radiofrequency analysis are derived from an ultrasound beam with a wavelength of more than 300 μm. As a consequence, it is impossible to detect plaque components extending beyond the resolving power of ultrasound (25). A potential limitation of this technique is the axial resolution, which is 150 μm for IVUS-VH, whereas the histologically determined fibrous cap thickness for vulnerable plaque is less then this value (26). Moreover, this method cannot assess the degree of the fibrous cap infiltration by macrophages and T-cells, which both are signs of TCFA.

The atherosclerotic plaque fibrous cap thickness is considered to be the most important factor of its instability. A cap with a thickness of less than 65 μm is considered to be vulnerable (27). However, in some studies a plaque was considered to be vulnerable if its cap thickness was of 260 μm, and stable with cap thickness of 360 μm (28). Until recently, there was no consensus among clinicians and pathologists regarding the critical threshold for cap thickness that if exceeded would lead to rupture. The clinicians based their opinion on the observations of the tissue shrinking during its fixation for histopathological examination. Moreover, so far there were no valid techniques to provide an accurate cap assessment in vivo.

Optical coherence tomography (OCT) has changed the existing situation. OCT is the optical analogue to IVUS, which can directly visualize a thin fibrous cap. The intracoronary OCT systems work with a resolution of 10 to 15 μm, which allows to accurately visualize thin fibrous cap thickness (30).

The principle of image acquisition with OCT is similar to that with IVUS and is based on measuring the beams generated by intravascular transducer and reflected from the vessel wall. The difference of the method is that OCT uses a probe generating light waves, while IVUS uses ultrasound. The light wavelength is much more shorter than ultrasound wavelength, therefore the resolving ability of OCT is higher. With OCT, ultra short light pulses are generated by intravascular probe (30). The use of light allows implementing various methods of coding acquired plaque image: polarization spectroscopy, absorption spectroscopy, elastography, OCT Doppler, and dispersion analysis. Furthermore, the resolution as high as 4 μm can be achieved technically mainly with modification of the intravascular catheter (31). There are experimental works in which optical coherent tomography was used for plaque optical biopsy (32). Importantly, OCT systems are compact and portable.

Kubo T. et al (36) showed that OCT was obviously superior to angioscopy and gray scale IVUS in detecting the superficial structures of an atherosclerotic plaque (Table 1).

Table 1. Comparison of OCT, coronary angioscopy (CAS) and IVUS.

FC status	OCT (n = 30)	CAS (n=30)	IVUS (n=30)	P
FC rupture	22 (73)	14 (47)	12 (40)	0,021
FC erosion	7 (23)	1 (3)	0 (0)	0,003
Thrombus	30 (100)	30 (100)	10 (33)	< 0,001

P < 0,05, OCT/CAS
P < 0,01, OCT/IVUS
P < 0,01, CAS/IVUS

The main limitation of OCT use is the scattering of generated light by blood cells. There are some methods for preventing light scattering in OCT: catheter tip flashing with saline, balloon inflation during imaging. A second potential limitation of OCT is the low penetration of light through the arterial wall (2-3 mm), therefore the size of necrotic area cannot always be determined (35). Such approaches to increase the penetration of optical beam into the vessel wall as spectral radar are being discussed. As water absorption peak exists approximately at 1,380 nm, some investigators are using light beams with median wavelengths of 1,250- 300 nm to increase penetration.

Coherence interferometry is used to obtain image with OCT: the echo delay time is used as a function of length, and the intensity of backreflection is plotted as a function of depth. The high resolution, which is more than 10-fold higher than that of IVUS, allows using OCT for imaging superficial structural components of an atherosclerotic plaque: vessel intimal thickness, fibrous cap thickness, and the portion of the lipid pool adjacent to a fibrous cap (35). The imaging of these structures of an atherosclerotic plaque may allow detecting potentially vulnerable plaques and additional cardiovascular risk stratification.

Both OCT and IVUS radiofrequency data analysis are gold standard for direct evaluation of morphological features of an atherosclerotic plaque in vivo (33,34). The axial resolution of OCT is 16± 1 μm, the value for radiofrequency IVUS is 110±7 μm. The deep structures of an atherosclerotic plaque and vessel remodeling features are better determined with virtual histology technique, as the penetration of ultrasound waves is higher. OCT is preferable for evaluation of an atheroma fibrous cap and vessel intima. Therefore, in some studies both techniques are used to obtain full information of an atherosclerotic plaque structure: OCT for superficial structures imaging, and virtual histology IVUS for assessing the structure balance through the entire plaque volume and the nature of artery remodeling.

As OCT has higher resolution than that of methods used so far and allows identifying thin cap fibroatheroma (TCFA), further studies are needed to evaluate the role of OCT in cardiovascular risk stratification. Several studies showed that ACS is a consequence of TCFA rupture, but it is unknown if the presence of TCFA always leads to ACS (37-40). Thus, ACS risk is to be evaluated in patients with TCFA. For instance, one study showed that the ruptured TCFAs were revealed in the coronary arteries in 8% of patients died from non-cardiac causes (40). In another study IVUS revealed plaque rupture in 80 (66%) of ACS patients and in 31 (27%) of patients with stable angina. Multiple plaque ruptures were revealed in 21 (17%) of ACS patients and in 6 (5%) of patients with stable angina (41).

It is also important that OCT can assess the degree of a fibrous cap infiltration by inflammatory cells (42,43). This component of the examination could potentially be critical for determination of TCFA rupture risk. To date, only sufficiently large inflammatory cell accumulations (more than 30 μm in diameter) can be revealed with OCT.

Polarization-sensitive OCT (PS-OCT) provides an additional option for an atherosclerotic plaque imaging, which allows for assessing the collagen content in a plaque (38,44). Strong correlation was noted between the collagen content measured by OCT and as assessed by histological examination (the positive predictive value of 0.889, and the negative predictive value of 0.929). OCT-elastography used for evaluating the elastic properties of the area of plaque location is another promising technique. Experimental data indicate its potential of quantifying the mechanical strength of TCFA (46,47). One more option of using optical coherence tomography is to assess plaque angiogenesis. For this purpose OCT Doppler or dispersion analysis is used (48).

Angiogenesis – formation of thin-walled vessels prone to rupture – is one of the factors of plaque destabilization. OCT Doppler may be used to identify blood flow in the newly developed capillaries of a fibroatheroma (49,50).

The coronary angiography has been the standard of CHD diagnostics for many years. The coronary artery stenosis progression was supposed to lead to complete occlusion an myocardial infarction. Many patients with severe stenosis according to coronary angiography underwent myocardial revascularization surgery. However, the obtained data suggest that myocardial revascularization does not prevent the development of ACS despite the reduction of CHD symptoms (47). The development of new methods for atherosclerotic plaque imaging allows detecting vulnerable plaques in coronary circulation and using various therapies for their stabilization – systemic lipid lowering therapy and local intervention in the area of potential instability.

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