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Scientific and practical Conference "Modern Trends in the Treatment of STEMI"

Scientific and practical Conference "Modern Trends in the Treatment of STEMI", timed to coincide with the 15th anniversary of Moscow City Center of Interventional Cardioangiology and the 90th anniversary of acclaimed Soviet-Russian cardiac surgeon and cardiologist, Academician Vladimir Bourakovsky is scheduled for **November 8–9, 2012**.

Well-known Russian and foreign specialists invited to attend the Conference, will present lectures and participate in the Round Table on the problems of STEMI treatment. The Conference will be held in Moscow World Trade Center (Krasnopresnenskaya embankment, 12).

Contents

Immediate and Long-Term Effects of Promus Drug-Eluting Stents with Everolimus Coating and Cypher Drug-Eluting Stents with Sirolimus Coating in CAD Patients with Coronary Atherosclerosis

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The effects of two coronary drug-eluting stents – Cypher coated with Sirolimus (SES) and Promus coated with Everolimus (EES) – in 206 CAD patients with stable angina pectoris are being analyzed. After 12 months of prospective follow-up, the incidence of adverse events (nonfatal myocardial infarction, recurrent angina, restenosis) was 10.8% and 14.2%, respectively, without significant difference. Percentage of stent restenosis was low (6.9% and 8.5%, $p > 0.05$), as well as the need for repeated coronary intervention in the target vessel (3.9% and 6.6%, $p > 0.05$). The frequency of late stent thrombosis was 0.9% for EES and 1.9% for SES ($p > 0.05$). It is concluded that main characteristics of the Promus stent are not worse than those of the Cypher stent, and the Promus stent can be widely used in CAD patients.

Key words: *percutaneous coronary intervention, Cypher and Promus drug-eluting stents, frequency of complications (restenosis, late thrombosis, recurrent angina), dual antiplatelet therapy.*

The main indications for myocardial revascularization in CAD patients are the persistence of angina symptoms despite optimal medication therapy and/or poor prognosis according to stress tests. Percutaneous coronary interventions (PCI) – angioplasty with stenting in patients with stable angina and suitable coronary artery anatomy – allows for dilation of one or more vessels with a high probability of recovering permeability and low risk (1, 2, 3). Restenosis development after stent implantation remains a major problem with PCI. In recent years, new models and various types of stents have been developed. They are widely used in interventional cardiology for the treatment of coronary atherosclerosis. Previously, the best results were obtained for Cypher stents coated with Rapamycin (Sirolimus). Similar results were obtained when using stents coated with Paclitaxel (Taxus stent) (4).

A new Promus stent (Xience V) has been recently developed. It is capable of releasing an antiproliferative agent Everolimus (limus family member). Technologies used in this stent development reduce the risk of early (thrombosis) and late (restenosis) complications. This stent has a thin polymer coating to keep the vessel lumen free, thus reducing the incidence of restenosis and subsequent revascularizations; this is its main advantage over standard stents (5). Considering the indicated features of the Promus stent and insufficient knowledge of it in the Russian Federation, it was topical to compare it with the Cypher stent representing the gold standard and being the most studied in current interventional cardiology. Currently, such studies are started in Europe and Russia, and special attention is drawn to them (6–8).

The objective of our work was to evaluate the effectiveness of the drug-eluting stent with Everolimus coating (Promus) in CAD patients with coronary atherosclerosis and its influence on the development of early and late (12 months) complications during prospective follow-up.

Material and methods

CAD patients with Functional Class (FC) II–IV exertional angina pectoris were sequentially included into the prospective study. These patients underwent PCI, as indicated, with

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implantation of the Promus stent coated with Everolimus (EES) (Boston Scientific, USA) or the Cypher stent coated with Sirolimus (SES) (Cordis Johnson & Johnson, USA) in the Laboratory of Vascular and Interventional Radiology of A.L. Myasnikov Cardiology Research Institute, Russian Cardiology Research-and-Production Complex, in 2007–2010.

The following inclusion criteria have been used: men and women aged 30–75 years with CAD, FC I–IV exertional angina according to the classification of the Canadian Cardiovascular Society (9). Coronary angiography showed >50% stenosis of the coronary artery diameter, and the diameter of the coronary artery intended for stent implantation was ⩾2.5 mm and <4 mm (during visual and computer assessment). The performance of PCI procedure required obligatory informed consent from the patients.

Patients were excluded from the study if they had one or more of the following: acute myocardial infarction (MI), unstable angina pectoris, infeasible percutaneous coronary intervention (PCI) with stent implantation, circulation failure of NYHA class III–IV, history of other stents implantation prior to the study, history of coronary bypass surgery, hemodynamically significant valvular heart disease, left ventricular ejection fraction <40% (according to the echocardiogram or ventriculography), renal insufficiency (creatinine >160 mcmol/L), impossibility of prescription and long-term application of Clopidogrel and Aspirin after PCI. In addition, the patients with bifurcation lesions and small vessels (<2.25 mm) lesions, with diffuse multiple lesions, chronic total occlusion of the coronary arteries and lesion of the left main coronary artery were excluded from the study.

The patients that were included into the study underwent a standard examination. It included a detailed interview of patients, a thorough analysis of the patients' complaints and characteristics of the disease (previous myocardial infarction, cardiac arrhythmias, cerebral stroke, symptoms of cardiac failure); the main risk factors were evaluated. Additional methods of examination included: ECG at rest, treadmill stress tests according to the Bruce protocol (1971), 24-hours ECG monitoring, biochemical blood tests (cholesterol, triglycerides, LDL, HDL, transaminases, troponins T and I, creatine phosphokinase, glucose, creatinine).

After discharge, the condition of patients was evaluated during outpatient examination, telephone interview or re-hospitalization, if necessary. Patient's complaints, angina FC, CAD clinical course and complications, medication therapy after PCI and its tolerability were evaluated. During the outpatient examination or hospitalization the following procedures were conducted: blood tests, ECG at rest or during stress (treadmill test), 24-hours ECG monitoring, repeated coronary angiography.

The following end-points were evaluated: death from any cause, death from cardiovascular disease, nonfatal myocardial infarction, and cerebrovascular accident. The frequency of repeat myocardial revascularization was also analyzed (i.e. PCI or coronary bypass surgery due to in-stent restenosis or stenosis development in other coronary arteries without previous PCI, in the area other then that of the previously implanted stent; development of late stent thrombosis, as defined by ARC (10), as well as combinations of indicated complications – endpoints).

Results

Clinical characteristics of patients are presented in Table 1. It can be seen that patients with implanted Promus and Cypher stents are comparable in terms of basic clinical characteristics. Prior to PCI, the vast majority of patients in both groups (85.1% and 88.5%) were middle-aged men (58.1 ± 10.1 and 58.5 ± 10.2 years, respectively). In both groups there was a high prevalence of major cardiovascular risk factors: tobacco smoking in 32.6% and 35.2%, hypertension – in 56.4% and 61.9%, hyperlipidemia – in 71% and 74%, diabetes mellitus type 2 – in 11.8% and 14.2%; history of MI – in 59.4% and 66.6% of patients, respectively.

Angiographic characteristics of patients are presented in table 2.

It is seen that the groups did not significantly differ in terms of baseline angiographic data (number of affected arteries, initial degree of narrowing and lesion morphology). During CAG, rates of 1-, 2-, 3-vascular lesions in the EES and SES groups were similar (62%, 28%, 11% in the EES group and 64%, 26%, 15% in the SES group). The frequency of LAD lesions was 48.5% in the EES group and 51.4% in the SES group. It should also be noted that in both groups more than 1/3 of the patients had severe coronary lesions of C type (EES – 33.6%, SES – 36.19%), thus indicating a high cardiovascular risk in patients included in the study. There were no significant differences in diameter and length of the implanted stents between groups. In both groups each patient had 1–3 drug-eluting stents implanted. On average, 1.6 stents

Table 1. Clinical characteristics of patients with stents coated with Everolimus (Promus) and Sirolimus (Cypher)

Parameter	Promus (n = 101)	Cypher (n = 105)	p
Mean age (years)	58.1 ± 10.1	58.5 ± 10.2	0.76
Males (%)	89 (88.1%)	93 (88.5 %)	0.87
Smokers (%)	33 (32.6%)	37 (35.2%)	0.76
Arterial hypertension (%)	57 (56.4%)	65 (61.9 %)	0.47
Diabetes mellitus type 2 (%)	12 (11.8%)	15 (14.2%)	0.68
FC I angina (%)	4 (4%)	5 (4.8%)	0.94
FC II angina (%)	62 (61%)	65 (62%)	0.94
FC III angina (%)	35 (35%)	35 (33%)	0.79
Postinfarction cardiosclerosis (%)	63 (62.5%)	0 (66.6%)	0.31
TC (mmol/l)	5.9 ± 0.8	6.0 ± 0.7	0.73
LDL-C (mmol/l)	3.9 ± 0.8	2.8 ± 0.9	0.62
HDL-C (ммоль/л)	1.4 ± 0.8	1.4 ± 0.6	0.94
TG (mmol/l)	2.4 ± 1.0	2.4 ± 0.9	0.23
Mean follow-up (months)	9.8 ± 6.4	10 ± 7.1	0.41

Notes: PCI – percutaneous coronary intervention (angioplasty with stenting). TC - total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TG – triglycerides. In parentheses – the percentage of patients. Differences between groups are insignificant.

Table 2. Angiographic characteristics of patients with Everolimus-eluting (n = 101) and Sirolimus-eluting (n = 105) stents

Parameters	EES n (%)	SES n (%)	p
1. Number of affected vessels, stenosis more than 50% (%):			
1 vessel	62 (61.39)	66 (62.86)	
2 vessels	28 (27.72)	24 (22.86)	0.61
3 vessels	11 (10.89)	15 (14.29)	
2. Stenosis localization (%):			
LAD (DB)	49 (48.51)	54 (51.43)	
CxA (OMB)	21 (20.79)	24 (22.86)	0.88
RCA (PDA, RPLA)	31 (30.69)	27 (25.71)	
3. Type of lesion (AHA/ACC classification (11), %):			
A	32 (31.68)	36 (34.29)	
B	35 (34.65)	31 (29.52)	0.72
C	34 (33.6)	38 (36.19)	
4. Average reference diameter of the vessel (mm)	2.91 ± 0.51	2.96 ± 0.49	0.06
5. Min. d. initially (mm)	0.9 (0.79–1.44)	0.8 (0.49–1.43)	0.51
6. Min. d. after stenting (mm)	2.8 (2.2–2.75)	2.9 (2.07–2.76)	0.21
7. Average stent length (mm)	20.5 ± 5.34	21.5 ± 4.27	0.21
8. Average number of stents per patient	1.6	1.7	0.53
9. Artery narrowing degree (%):			
before stenting	81.6 ± 9.7	79,6 ± 8,9	0.14
after stenting	10.0 ± 0.34	11,2 ± 0.38	0.11

Notes: LAD – left anterior descending artery, DB – diagonal branch of LAD, CxA – circumflex artery, OMB – obtuse marginal branch of CA, RCA – right coronary artery, LCA – left coronary artery, Min. d. – minimum diameter. There were no significant differences between the groups ($p > 0.05$).

were implanted per one patient during PCI in the EES group and 1.7 stents – in the SES group.

The analysis of the basic parameters of angiographic coronary artery lesions (artery reference diameter, minimum diameter of the artery, percentage of stenosis) did not show any significant differences between groups with EES and SES implants at baseline and immediately after the intervention. Average stent length in the EES group was 20.5 ± 5.34 mm, in the SES group – 21.5 ± 4.27 mm. Initially, minimum artery diameter in the affected area averaged 0.9 (0.79–1.44) mm, the percentage of stenosis before stenting was 81.6 ± 9.7% in the

Table 3. Clinical outcomes in patients with EES and SES after 12 months of prospective follow-up

Parameters	Promus (n = 101)	Cypher (n = 105)	p
Stent thrombosis:			
Late (up to 12 months)	1 (0.9%)	2 (1.9%)	0.58
Myocardial infarction:	4 (3.9%)	6 (5.7%)	0.58
Q-wave	2	2	
non-Q-wave	2	4	
Patients referred for CABG after PCI	1(0.9%)	0	–
Repeat target vessel revascularization (TLR)	4 (3.9%)	7 (6.6%)	0.53
Recurrence of angina	7 (6.9%)	9 (8.5%)	0.79
Repeated CAG:			
MI	4	6	
recurrence of angina	7	9	
other reasons	9	8	
Total:	20	23	0.88
Death	0	0	–
MACE (cardiac death + MI + TLR + stent thrombosis)	11 (10.8%)	15 (14.2%)	0.53

Note: CAG – coronary angiography; MACE – major adverse coronary events; TLR – need for repeat target vessel revascularization.

EES group; in the SES group, minimum diameter of the artery was 0.8 (0.49–1.43) mm, the percentage of stenosis before stenting 79.6 ± 8.9%. Immediately after the intervention, minimum artery diameter at the site of stent implantation was 2.8 (2.2–2.75) mm, residual stenosis after stenting was 10.0 ± 0.34% in the EES group; in the SES group, minimum artery diameter at the site of stent implantation was 2.9 (2.07–2.76) mm, residual stenosis after stenting was 11.2 ± 0.38%.

To analyze long-term results of coronary stenting, patients were evaluated at baseline and in 6 and 12 months after the intervention. Patients who underwent stenting without hospital complications were invited to return to the Institute for clinical control in 6 and 12 months. In case of recurrent angina and other cardiac complications (MI, serious cardiac arrhythmia, circulation failure), patients underwent control coronary angiography for ethiology of angina recurrence and possible stent restenosis. We monitored the patients for 12 months to assess mortality, MI frequency (non-*Q*-wave or *Q*-wave), frequency of CAG repeats, need for repeat target lesion revascularization (TLR), stent thrombosis frequency and frequency of the combined endpoint, so-called major adverse cardiac event (s), MACE, which included: mortality, MI, need for TLR, and stent thrombosis. Clinical outcomes in patients with implanted Promus and Cypher stents within 12 months are presented in Table 3.

By the end of 12-month follow-up, only 7 patients (of 101) had recurrent angina (3 patients within 4 months, 2 patients within 6 months, 1 patient within 9 months and 1 patient within 11 months) in the group with implanted Promus stents, with 5 (of 7) patients having symptoms of myocardial ischemia during treadmill stress test. In three cases, the relapse was caused by restenosis, which was confirmed by coronary angiography (two stenoses >75% in the left anterior descending artery, and one – in the circumflex artery). Stenoses were successfully eliminated by repeat PCI. In two cases, severe stenosis was found in coronary arteries not subjected to PCI. In 1 month, one of the patients successfully underwent coronary artery bypass grafting, another one (with a critical RCA stenosis) – successful PCI. In two patients with recurrent angina, stents were passable, and there were no other lesions of the coronary arteries during coronary angiography. Four patients (3.9%) from the Promus group had myocardial infarction (two of them had non-*Q*-wave MI). MI was confirmed by blood biochemistry (increased troponin T), typical changes in ECG and coronary angiography data.

In the group with implanted Cypher stents (105 persons), angina reccurred in 9 cases (after 3 months – in 3 patients, 5 months – in 3, 7 months – in 2 and after 10 months – in 1 patient). Symptoms of myocardial ischemia during treadmill test were detected in 6 of 9 patients. This suggests that angina recurrence, stress test results and restenosis are not always consistent. To predict restenosis, other up-to-date methods of diagnosis have to be used in addition to ECG stress test (12). For example,

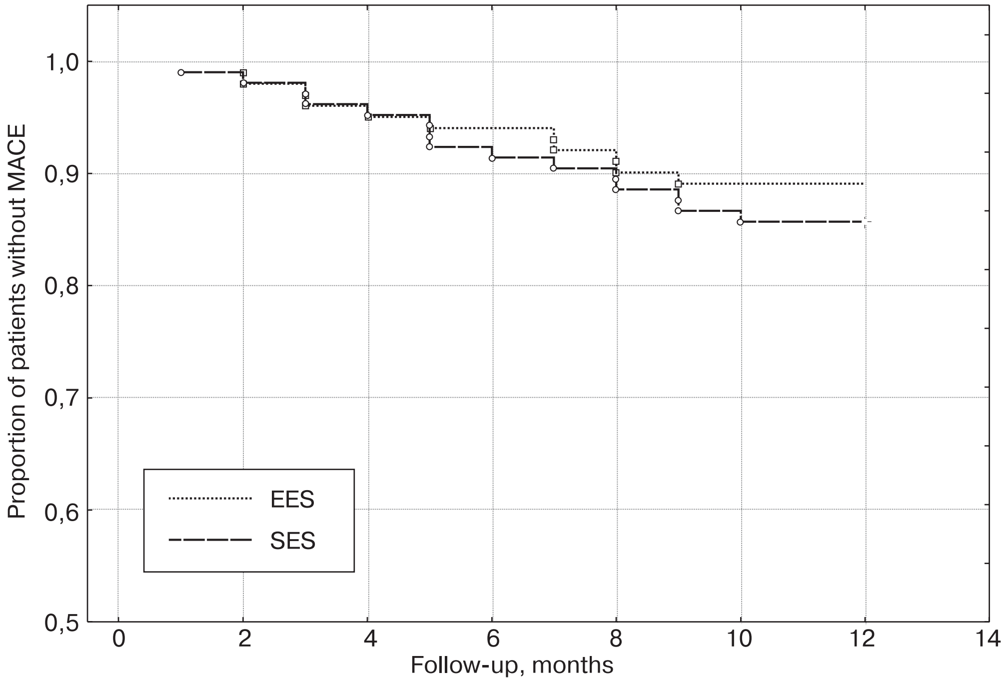

Figure 1. Primary endpoint: MACE (cardiac death, MI, diagnosed stent thrombosis, target vessel revascularization) for EES compared with SES. *Note:* $p > 0.01$.

radionuclide imaging techniques (stress myocardial scintigraphy) have a higher sensitivity, whereas techniques that evaluate contractile reserve (stress echocardiography) have a slightly lower sensitivity but higher specificity. The capability of these techniques to identify silent myocardial ischemia should also be considered. In 5 (of 9) patients with implanted Cypher stents, recurrent angina was due to restenosis, as confirmed by coronary angiography. These restenoses (3 in left anterior descending artery, two in circumflex artery) were successfully eliminated by repeat PCI. There were two cases of severe stenosis of the arteries previously not subjected to PCI (85% stenosis of RCA and 75% stenosis of CA), which were also successfully eliminated by repeated PCI.

Six of 105 patients (5.7%) from the Cypher group had MI during the study (non Q-wave MI in 4 of them), as confirmed by clinical data and the results of coronary angiography (3 occlusions of the previously implanted stents which were successfully eliminated by repeat PCI; and 2 other cases of stenosis in another coronary artery previously not subjected to PCI (occlusion of CA and LAD was observed), which were also successfully removed by PCI). It should be noted that in 2 cases recurrent angina was not associated with restenosis in coronary arteries or occurrence of new hemodynamically significant arterial lesions, and its recurrence was likely associated with the functional factors, including coronary artery spasm.

In our comparative 12-month study, the combined MACE endpoint (cardiac death, MI, diagnosed stent thrombosis, target vessel revascularization) was 10.8% for EES and 14.2% for SES (Figure 1).

Thus, during 12-month follow-up of 206 patients in both groups with implantation of drug-eluting stents, only 3.9% with EES and 6.6% with SES needed a repeated revascularization due to stent restenoses which were successfully eliminated by repeated PCI. Recurrent angina occurred in 6.9% and 8.5% of patients with EES and SES, respectively. The frequency of the combined MACE endpoint (cardiac death, MI, diagnosed stent thrombosis, target vessel revascularization) was 10.8% for EES and 14.2% for SES ($p > 0.01$). Stent thrombosis occurred in 0.9% of cases in patients with EES implantation and in 1.9% of cases (including 0.95% of subacute thrombosis) with SES implantation. These data confirm non-inferiority of the Promus stent as compared with the Cypher stent.

Discussion

An important achievement in interventional cardiology is the development of stents coated with medicines (drug-eluting stents) (13). Stenting of coronary arteries in CAD patients is currently the most commonly used method of myocardial revascularization. However, in-stent restenosis frequently occurs after stent implantation due to damage of the vessel endothelium and subsequent neointimal hyperplasia occurring mainly in the first 6 months after PCI. In-stent restenosis rate is 10–30%, depending on the lesion nature, patient's clinical status and type of intervention.

Drug-eluting stents (DES) consist of three components: metal base (so-called platform) and the polymer layer bearing the medicine or mixed with it. Drug substance and its pharmacokinetics largely determine the future properties of drug-eluting stents. The drug must ensure the inhibition of neointimal growth within the stent and at the same time should not be toxic if emitted in concentrations sufficient for the required degree of inhibition. The rate of drug release and its concentration in the relevant place have to be predictable and controllable. Development of a suitable polymer drug carrier is a very difficult task. On the one hand, it should provide controlled release of the drug, not enhancing the inflammatory reaction at the site of stent implantation and not being thrombogenic; on the other hand – it should be sufficiently strong to withstand sterilization and implantation. In this case the polymer acts as a container for the medicinal agent and provides its metered output. At various times different polymers were tested, such as phosphorylcholine, ceramic materials, biocompatible nondestructive, biodegradable and soluble coatings.

The practical application of coronary polymer-coated stents capable of releasing antiproliferative agents led to a significant reduction of the restenosis risk <10%. Even in CAD patients with diabetes mellitus and a typical high risk of restenosis after PCI, DES greatly reduced the need for subsequent revascularization of the target lesion site (approximately to 7–10%) depending on the extent of the lesion and the vessel diameter. DES with an established effectiveness have to be used by default in almost all the clinical situations and for almost all the categories of lesions, except cases with any concerns or contraindications to long-term DAPT (1). The main cause of subacute and late stent thrombosis consists in termination of antiplatelet therapy (even in 1 year after the intervention, when patients take only Aspirin).

In our study, all the patients after PCI were prescribed DAPT at standard doses (acetylsalicylic acid 100 mg + Clopidogrel 75 mg). After 6 months, 15% and 18.4% patients from the EES and SES groups, respectively, discontinued Clopidogrel therapy; after 12 months of follow-up, there were 29.2% and 33.1% of such patients in the EES and SES group, respectively. The reasons for drug withdrawal were as follows: drug intolerance due to the epigastric pain, dyspepsia, as well as financial difficulties (high cost of Clopidogrel). We did not observe any gastrointestinal bleedings.

Recurrent angina represents one of the numerous causes of chest pain. The most frequent coronary causes of chest pain syndrome after PCI are: acute, subacute and late in-stent thrombosis, incomplete revascularization, restenosis, atherosclerosis progression in other segments, pain associated with hyperextension of the stent, or combination of the above reasons. The main functional causes of angina recurrence after revascularization are: coronary microvascular dysfunction, spasm of epicardial coronary arteries and spasm of coronary arteries in the area adjacent to the stent (14, 15).

According to the ARTS study (16), 42% of patients suffered angina recurrence and / or became candidates for repeat revascularization within 5 years after PCI. Within one year, absolute risk of cardiovascular complications and extra invasive procedures was higher by 7% and 30.6%, respectively, in patients with incomplete revascularization after PCI and multivessel disease as compared with patients with complete revascularization (23.4%).

Restenosis is a result of excessive and uncontrolled proliferative response of cell elements to injury and implanted stent (17). Restenosis after PCI is a complex process characterized by a proliferative reaction in smooth muscle and intimal elements of the vessel wall in response to injury and foreign material. The development of restenosis was often observed during balloon angioplasty and bare stent installation. Restenosis and high rate of repeat revascularization are the main limitations of PCI with bare metal stent implantation in patients with multivessel coronary artery disease (18). Risk factors of restenosis are diabetes mellitus, extended stenosis, bifurcation stenosis, chronic occlusions, and a small (<2.5 mm) diameter of the vessel.

At the present work, patients included into the study have none of the above arterial lesions. Restenosis after implantation of Everolimus and Sirolimus-coated stents was 6.9% and 8.5%, respectively. Similar data were obtained in recent large studies (SORT OUT IV, BASKET-PROVE).

The randomized study SORT OUT IV (19) included more than 2,600 patients with varying degrees of severity of coronary artery lesions in routine clinical practice conditions, i.e. it was an “all-comers” study (all incoming patients with no exclusion criteria). The study was organized to test an assumption on non-inferiority of Xience V stent to the Cypher stent. Both stents showed better results than it was expected in terms of the MACE combined endpoint (4.9% for Xience V and 5.2% for Cypher). These data confirm that the Xience V stent is as good as the Cypher stent in terms of immediate and long-term effects. No significant differences in main safety parameters have been shown, including frequency of cardiac death (1.9% Xience V and 1.4% Cypher: p = 0.31), MI (1.1% and 1.4%, p = 0.48), and also a diagnosed or probable stent thrombosis (0.9% Xience V and 0.9% Cypher, p = 0.83). The study SORT OUT IV demonstrated excellent functional characteristics, high safety and effectiveness of both stents.

The prospective, randomized, comparative BASKET-PROVE (20) study was conducted to evaluate effects and safety of Cypher vs Xience V vs Vision bare metal stent (BMS) in 2,314 patients, in whom stents ⩾3.0 mm were implanted. The primary endpoint was a combined indicator (cardiac death and nonfatal MI) within 2 years of follow-up. According to this criterium, no significant differences between the three stents have been identified (2.3% Cypher, 3.2% Xience V and 4.8% BMS). There was also no difference in the incidence of late and very late stent thrombosis for the compared stents within 2 years. During this period, the frequency of nonfatal MI was lower in the Cypher stent group (0.9%) in comparison with groups of Xience V and Vision BMS (1.7%).

Recurrence of pain after PCI is not always associated with restenosis (14). Chest pain remaining after PCI may be associated with incomplete revascularization of the coronary arteries (21, 22).

Thus, Joelson et al. (23) found that the angina was most likely associated with incomplete myocardial revascularization in the group of 102 examined patients with angina recurrence after PCI. In these patients, relapse occurred within one month after the intervention. At the same time, pain occurred in 2–6 months after PCI is more typical for restenosis, and the pain recurrence in more than 6 months after the intervention is often associated with progression of atherosclerotic lesions in other arteries.

Due to widespread use of drug-eluting stents, the incidence of restenosis has significantly decreased. However, stent thrombosis can develop during the procedure and immediately after it. The incidence of subacute stent thrombosis (in the period from 24 h to 30 days since stent implantation) is 1.1%, and the rate of late stent thrombosis is 0.4% in patients with implanted stents coated with Sirolimus or Paclitaxel (24). All late in-stent thromboses occurred in patients that were receiving monotherapy with acetylsalicylic acid or not receiving antiplatelet therapy. One cannot exclude the possibility that at least some of the clinical benefits of drug-eluting stents may be due to prolonged dual antiplatelet therapy.

Two-component antiplatelet therapy for at least one year (Clopidogrel) and life-long acetylsalicylic acid should be prescribed in patients with implanted DES (25).

While before PCI all our patients received DAPT, after 6 months 85.0% of patients in the EES group and 81.6% in the SES group still received DAPT, and in 12 months there were 70.8% and 66.9% of such patients, respectively.

Martsevich et al. (26) have analyzed the database of CAD patients who underwent angioplasty with stent implantation. 239 patients were interviewed. According to current clinical guidelines, despite the need for dual antiplatelet therapy after coronary plasty, only 112 (47%) patients received Clopidogrel for 12 months.

The more time passes since the invasive procedures before angina occurrence, the more likely is that the return of symptoms is associated with the progression of the disease rather than with restenosis. It is important to note that DAPT cannot completely prevent the development of in-sent thrombosis.

In a prospective randomized ARMIDA-150 (27) study, effects of supportive treatment with standard and high doses of Clopidogrel on platelet aggregation, inflammation and endothelial function were compared in patients who underwent PCI. In a month after PCI (T-0), the patients were randomized into 2 groups: patients from one group received a standard maintenance dose of Clopidogrel (75 mg/day, n = 25) during 30 days (up to T-1), and patients from the second group received a higher Clopidogrel dose (150 mg/day, n = 25) during the same period. Then the first group of patients was swiched to high-dose Clopidogrel, and patients of the second group – to the standard dose. This treatment also lasted for 30 days (up to T-2). At time points T-0, T-1 and T-2, platelet reactivity, endothelial function (using flow-dependent vasodilatation with reactive hyperemia), and highly sensitive C-reactive protein were investigated in patients. It was found that in patients after PCI, Clopidogrel at a maintenance dose of 150 mg/day was associated with a stronger inhibition of platelet aggregation and decrease in number of patients with poor response, as well as significant improvement of endothelial function and more powerful anti-inflammatory effect than during treatment with currently recommended dose of 75 mg/day. This can support using a higher maintenance dose of Clopidogrel in this category of patients. However, the role of longer two-component antiplatelet therapy, despite the recommendations of several studies (13, 28, 29), is not fully supported in current literature and requires further investigations (25, 30, 31, 32).

In our work, after successful PCI, the patients have been recommended to comply with CAD secondary prevention activities which are proved to reduce the risk of coronary and cerebral complications and cardiovascular mortality (optimum body weight, control of blood sugar and lipids, keeping diet were recommended; patients with previous MI have been recommended to take beta-blockers and ACE inhibitors). During the follow-up, 1/3 of the patients stopped smoking (at baseline, 33% of patients smoked in the EES group and 35% – in the SES group; in 12 months – 20% and 25%, respectively). Concomitant hypertension was observed in 56% and 62% of patients, and after PCI – less than in 30% of patients. Diabetes before PCI was observed in 12% and 14% of patients, after 12 months of observations – in 10% and 11% of patients, respectively. These measures could favorably influence the incidence of complications in the group of patients under study.

Our results support eligibility, safety and effectiveness of drug-eluting stents with Everolimus coating (Promus) in cardiological practice in our country.

Conclusions

1. Promus and Cypher stents were 100% successful according to angiography data in 206 CAD patients who underwent PCI-coronary stenting during the hospital stage.

2. After implantation of the EES (101 persons) and SES (105 persons), the incidence of major adverse events (nonfatal myocardial infarction, recurrent angina, incidence of restenosis) in CAD patients was 10.8% and 14.2%, respectively, and did not significantly differ within 12 months of prospective follow-up.

3. Effects of EES and SES coronary stenting in both groups of CAD patients were as follows: a low percentage of stent restenosis (6.9% and 8.5%, $p > 0.05$) and the need for target coronary vessel re-intervention (3.9% and 6 6%, $p > 0.05$). The frequency of late stent thrombosis was as low as 0.9% for EES and 1.9% for SES ($p > 0.05$).

4. Adverse outcomes during 12 months of follow-up were not identified: the incidence of nonfatal myocardial infarction was 3.9% and 5.7%, respectively. Before the PCI procedure, all patients had angina pectoris; in 12 months after stenting angina was observed only in 27% of patients in the EES group and in 28% of patients in the SES group; there were no deaths.

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Experience with the Use of Retrograde Recanalization for Chronic Coronary Occlusions

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From May 2006, through December 2010, in two major clinics of Far-Eastern federal district, we have attempted 64 retrograde recanalizations of chronic coronary occlusions (CCO) in 64 patients. We have used the technique of kissing wires, landmark technique, CART and its modification, as well as "knuckle-wire technique". The damaged arterial lumen has been restored in 51 (79.7%) cases. The main causes of failure were the impossibility to advance the wire through the collaterals into the distal segment of the artery (46.1%) and the impossibility to cross the CCO (46.1%). Intraoperative life-threatening complications developed in 3 (4.7%) patients, hemodynamically insignificant hospital complications were noted in 5 (9.8%) cases. In 1 year of the follow-up clinically insignificant angiographic stenoses have been revealed in 14.5% of cases.
Key words: *chronic coronary occlusion, retrograde recanalization, wires.*

Chronic coronary occlusion (CCO) is considered the most complex challenge facing interventional cardiologists. The rate of CCO in patients with clinically significant coronary artery disease (CAD) undergoing coronary angiography is 30% to 50% (3, 7). It has been shown that successful recanalization in patients with viable myocardium leads to the decrease of angina class, the decrease of the probability of subsequent surgical interventions, contributes to the increased survival (14). The difficulties of recanalization of CCO are related to rather low frequency (50–70%) of successful tunneling of the occlusion (6, 9, 14), high rate of restenosis or reocclusion after successful balloon angioplasty or implantation of bare metal stents (6).

The development of new technologies and techniques has contributed to the increase of the rate of successful attempts of percutaneous recanalization of CCO as well as to the increase of long-term patency of the coronary arteries (4). One of the most promising and fast developing technique is the tunneling of the ocllusion through the distal segment of the diseased artery – the so-called "retrograde revascularization" of CCO (4).

The purpose of our work was to present our experience with CCO recanalization using retrograde approach.

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Material and methods

From May 2006, through December, 2010, on the base of Railroad Clinical Hospital at "Khabarovsk-I" station and The Primorye Territory Regional Clinical Hospital N1 (Vladivostok) the patients with CAD and with at least one CCO have been selected for the study. A lesion with totally absent antegrade blood flow and duration over 3 months was considered as chronic coronary occlusion. The duration of the occlusion was calculated from the date of preceding myocardial infarction or from the time of the first coronary angiography during which this occlusion had been revealed (1, 12, 14).

Functional status of the patients was evaluated using Canadian classification (CCS) for the determination of functional class (FC) of angina. All patients underwent EchoCG at rest with calculation of left ventricular ejection fraction by Simpson technique and stress-EchoCG. In order to specify the character of the occluded vessel lesion and the anatomy of collateral vessels all patients have been submitted to multi-view coronary angiography.

The detection of viable myocardium in the territory of the occluded vessel during stress-EchoCG served as indication for percutaneous procedure (13). Retrograde method of CCO recanalization was considered reasonable in the presence of one of the following conditions: prolonged occlusion (⩾15–20 mm), large distal segment of the occluded artery, complex anatomy (non-tapered proximal "stump", the presence of bridging collaterals, a side branch arising at the site of occlusion), failed earlier attempt of antegrade coronary angioplasty, non-stenotic / non-occluded vessel giving birth to the collaterals intended for the intervention (1 ,9, 10, 12).

CCO has been approached through epicardial or septal collateral vessels. The collaterals were passed using Whisper LS, Whisper MS (Abbott) wires and the wires from the Fielder (Asahi) family (13). The search of a septal canal was performed using coronary wire Fielder XT (13). In all cases the coronary wire was supported by an OTW balloon or a microcatheter (5, 12).

The wire Fielder FC was considered as the first choice wire for retrograde recanalization of CCO in our series (13). If necessary, it was replaced by a stiffer wire from Miracle or Cross-it families, and then (in order of increasing stiffeness): Pilot 200, Conquest 12 and Conquest Pro 12.

After successful advancement of a coronary wire and a supporting cathehter through the collaterals, the following techniques were used for recanalization of CCO:

1. Direct tunneling by a retrograde wire ("landmark technique"). With this technique a wire inserted by a retrograde way remains stationary and is used as a visual landmark for the manipulations with an antegradely inserted wire (5).

2. The technique with bidirectional touching wires ("kissing-wire technique"). With this technique the stiff antegrade wire and the retrograde wire are stepwisely advanced towards each other (5).

3. If it was impossible to place two coronary wires in the same lumen the preference was given to CART technique (Controlled Antegrade and Retrograde subintimal Tracking) or its modification (9, 10, 12). In such case the retrograde wire is inserted into the subadventitial layer of the vessel, then a false subadventitial space is formed using a catheter and a balloon. Then the proximal true lumen has to be connected with the false subadventitial lumen using an antegradely inserted wire.

4. The "knuckle-wire technique" (5) was applied after unsuccessful attempts of direct recanalization with retrograde wire when only a minimal calcification of the coronary arteries was present. In such case a large cavity is created in the subintimal space around the artery, then a contralateral coronary wire is inserted in this cavity.

After a retrograde coronary wire is successfully advanced through the occlusion, the artery is pre-dilated with a retrograde balloon catheter, and then an antegrade wire is advanced. If it proves impossible to advance the retrograde balloon catheter through the wire, a complete or incomplete coronary loop is created. An "incomplete coronary loop" is formed by squeezing the retrograde wire's tip in the antegrade catheter with a balloon on order to increase its fixation and facilitate the tunneling of CCO by the retrograde catheter with subsequent predilatation and advancement of the antegrade wire.

The "complete coronary loop" is created by seizing the tip of a retrograde coronary wire in the aorta with a loop-like snare GooseNeck (ev3), as well as by inserting the tip of the retrograde coronary wire in the antegrade catheter's ostium and leading it out of the Y-connector (1, 9, 12). After that antegrade balloon dilatation and sequential stenting of the occluded stenting of the occluded segment are performed (1, 10).

After antegrade insertion of the wire the coronary angioplasty has been performed using the generally adopted technique: balloon dilatation of the occluded segment using balloons of increasing diameter, then – sequential stenting of the whole dilated segment (1, 15). Only drug-eluting stents have been used.

The procedure was judged successful if after the intervention the diameter of stenosis was <30%, normal blood flow with complete perfusion has been restored and no major complications occurred (death, myocardial infarction, urgent coronary surgery).

Prior to the intervention all patients received Aspirin (100 mg/day) and Clopidogrel (75 mg/day). Right before the intervention the patients were administered 10,000 U of heparin with subsequent administration of 1000–2000 U/hour during the procedure in order to maintain APPT > 250 sec. After recanalization of CCO all patients were prescribed Aspirin (100 mg/day) for a long period of time and Clopidogrel (75 mg/day) for 12 months and more.

Within 6 to 12 months after the procedure the patients underwent repeated cardiological examination, presented subjective evaluation of their well-being (good, satisfactory, bad), had their CCS class of angina determined and underwent EchoCG, stress-testing and coronary angiography.

Statistical analysis

Qualitative values are presented as percentage of the total number of patients, quantitative data are presented as means ± SD. Qualitative values were compared using Fisher's exact test. The differences between the quantitative values were assessed using Mann-Whitney U-technique. $p < 0,05$ were considered statistically significant.

Results

The study comprised 64 patients with CAD aged from 44 to 71 years (mean age 57.2 ± 3.4 years). Clinical and demographical data of patients are presented in Table 1.

Retrograde recanalization of CCO has been attempted in all 64 patients (64 attempts). Antegrade recanalization of CCO has been attempted at first stage in 63 (98.4%) patients. One patient (1.6%) had the occlusion starting from the ostium of the right coronary artery, which made unfeasible the insertion of a guiding catheter, so the tactics of primary retrograde recanalization was choosen.

We have succeeded with the restoration of the lumen in 51 of 64 (79.7%) attempts of retrograde recanalization of CCO. Table 2 depicts the relation between the procedural success and the characteristics of occlusions and collateral vessels, as well as technical particularities of the intervention.

When the RCA was affected, the use of retrograde approach for CCO recanalization was reliably more effective (84.9%), then in cases with the CxB or the LAD involvement (54.6%, $p = 0.037$).

In 6 (9.4%) cases we could not advance the coronary wire through the collaterals. In 9 (14.1%) cases we could not advance the catheter after successful advancement of a coronary wire into the distal bed of the target artery. In these patients retrograde wire was used as a marker for antegrade recanalization using direct approach.

We have managed to advance the catheter into the distal part of the involved vessel in 49 (76.6%) cases. The attempts of wire and catheter advancement through septal collateral arteries were significantly more effective then through epicardial arteries (81.0% vs. 33.3%, $p = 0.023$).

Of 51 successful recanalizations of CCO, in 23 (45.1%) cases it was possible to advance the antegrade coronary wire into the true distal lumen, and in 28 (54.9%) cases – the retrograde coronary wire into the proximal segment of the occluded artery. The percentage of successful retrograde wire advancement was significantly higher than of the antegrade wire advancement (77.8% vs. 40.4%, $p = 0.012$).

As a result of performed procedures we have implanted 115 coronary stents, that is, on the average, 2.7 stents per 1 occluded vessel.

The attempts of CCO recanalization failed in 13 (20.3%) patients. The causes of failures are shown on Figure 1.

Table 1. Clinical and demographic characteristics of patients

Characteristics	Values (n = 64)
Age, years	57.2 ± 3.4
Women, n (%)	2 (3.2%)
Class, angina of effort, n (%)	
I class CCS*	38 (59.4%)
II class CCS	21 (32.8%)
III class CCS	5 (7.8%)
Left ventricular ejection fraction, %	47 ± 9,3
History of MI, n (%)	63 (98.4%)
Risk factors, n (%)	
Smoking	28 (43.8%)
Hyperlipidemia	31 (48.4%)
Arterial hypertension	51 (79.7%)
Diabetes mellitus, type II	19 (29.7%)
Affected arteries, n (%)	
1	31 (48.4%)
2	22 (34.4%)
3	11 (17.2%)
Stenting of non-target vessel, n (%)	23 (35.9%)

* Canadian Cardiovascular Society

In 3 (23.1%) of 13 patients we had to stop recanalization of CCO because of life-threatening complications. The RCA that gave approach to the collaterals, has been deeply intubated by a guiding catheter during catheter positioning in the occlusion, and an occluding dissection has developed. Emergency stenting of the dissected segment led to the occlusion of a major side branch and the development of marked clinical and ECG signs of antero-septal myocardial infarction. For this reson we had to stop the procedure of recanalization of the RCA.

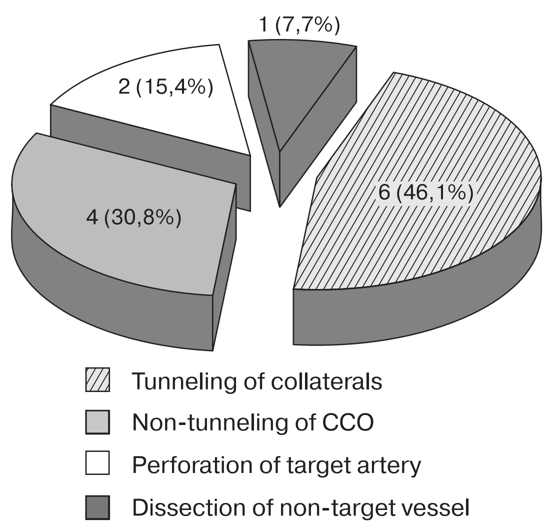

Figure 1. Caused of failed CCO recanalization.

Table 2. Results of PCI depending on the characteristics of occlusion and collaterals, technical particularities of the procedure

Characteristics	Attempts (n = 64)	Successful attempts (%)
Location of CCO *		
RCA	53	45 (84.9)[1]
LAD or CxB	11	6 (54.6)[1]
Wire advancement through the collaterals		
Septal	58	47 (81.0)[2]
Epicardial	6	2 (33.3)[2]
Technique of CCO tunneling		
Direct technique	57	18 (31.6)
Kissing wires	40	7 (17.5)
CART	33	22 (66.7)
"Knuckled wire"	8	4 (50.0)
Advancement of antegrade balloon in the true distal lumen	57	23 (40.4)[3]
Advancement of retrograde balloon in the true proximal lumen	36	28 (77.8)[3]

[1,2,3] the differences between the groups are statistically significant: p=0.037, 0.023 и 0,012, respectively;
* RCA – right coronary artery, LAD – left anterior descending artery, CxB – circumflex branch.

Retrograde recanalization of the RCA using CART and reverse CART techniques led to the development of Elis type III perforation of the coronary artery (5). Emergency puncture and drainage of the pericardial cavity have been performed. In 1 case the volume of hemopericardium did not exceed 400 ml, the bleeding stopped spontaneously. In another patient a massive bleeding into the pericardial cavity developed after the creation of subintimal cavity by antegrade balloon catheter (reverse CART). In order to eliminate this complication we have proceeded with the intubation of the RCA's stump with JR 6F catheter and lipid embolization of the source of bleeding.

In another 4 (30.8%) patients the procedure of recanalization was stopped after numerous unsuccessful attempts to pass the CCO, when total duration of the procedure has exceeded 180 minutes and/or total volume of the contrast agent has amounted to 600 ml (1, 5 ,9 ,10).

Early postoperative period

Early postoperative complications developed in 5 (9.8%) patients after successful recanalization of CCO. Atrial fibrillation requiring two days of Cordaron therapy has been registered in 2 (3.9%) patients. Both patients recovered sinus rhythm. Control coronary angiography has revealed hematoma of interventricular septum, which did not affect hemodynamics, in 3 (5.9%) patients; all these patients were discharged in due time.

Early after successful recanalization of CCO 45 (88.2%) patients noted improved well-being, 6 (11.8%) did not note any change. FC of angina has decreased in 17(33.3%) patients.

The increasing FC of angina requiring enhancement of conservative therapy has been noted in 3 patients with intraoperative complications. CABG has been performed without complications in 5 patients (4 with occlusion of the LAD and 1 with occlusion of the RCA).

Long-term follow-up after revascularization

The results of intervention have been followed in 48 (94.1%) patients for 6–18 months (10.2 ± 4.3 months) after successful recanalization of CCO. Cardiological examination has revealed the development of class II angina in 13 patients (27.0%); 11 (22.9%) of them had manifested ischemic changes during bicycle ergometry at 75–100 Wt. The remaining 35 (72.9 %) patients subjectively judged their well-being as "good", had an active life and did not restrict physical load. EchoCG with the measurement of left ventricular ejection fraction has been performed in the long-term in all patients. The comparison with preoperative values did not reveal significant difference.

In total, the restenosis of the recanalized coronary artery has been documented in the long-term in 7 (14.5%) patients; in 5 (10.4%) cases restenosis involved the sites around the stent, in 2 (4.2%) cases it was in-stent restenosis. All 7 patients underwent repeated endovascular procedure with correction of this pathology (stenting).

Discussion

The background of method of retrograde recanalization of CCO is that the distal part of CCO capsula can be softer, thinner or even absent, which can significantly facilitate the tunneling of the occlusion by coronary guidewire (9). Recent studies have shown the rate of successful percutaneous interventions for CCO revascularization using retrograde approach increasing up to 57–79% and even more (10, 11).

We present our results of using retrograde approach to recanalization of CCO. The effectiveness of this technique in our group of patients was 79.7% (51 of 64 cases). This is comparable with other authors' results. Thus, Biondi-Zoccai et al. (2) had a 71% success with the use of retrograde approach to recanalization of CCO in 17 patients; the effectiveness of retrograde approach in the group of 31 patients with CCO presented by Chung et al. (3) was 78,8%.

In a major study by Kimura et al. (8) retrograde approach to recanalization of CCO has been successful in 90.6% of 224 attempts – this is somewhat higher than in our work. The differences can be attributed to the particularities of patients' selection and technical characteristics of the interventions. Thus, in the series of Kimura et al. all patients underwent revascularization of CCO using CART technique and its modifications, while in our series this technique has been used only in one half of cases (33 of 64), and has demonstrated the highest effectiveness among all the techniques that have been used (66.7%) (8).

The success rate with the approach to the distal bed of the involved artery in our series was significantly higher when septal collaterals have been used, than with the use of epicardial vessels (81.0% vs. 33.3%, $p = 0.023$). It is considered that septal collaterals have certain advantages: epicardial canals often has a complex anatomy and can be tortuous (9), have a tendency for more common rupture, and when they rupture, there is a risk of hemopericardium and cardiac tamponade (12). Moreover, septal canals, as a rule, are shorter than epicardial ones. However, the use of septal canals is associated with higher risk of small-focal myocardial infarction. Some authors advice to take into account the character of the vessel's course, its tortuosity, and not the diameter of its lumen (9, 13).

In our series CCO were most commonly located in the RCA (53 of 64, 82.8%); the highest percentage of successful attempts of retrograde recanalization also was seen when this artery was involved (45 of 53, 84.5%). High incidence of CCO in the RCA has been described by other authors. Thus, in the series of Biondi-Zoccai et al. (2) the occlusion was located in the RCA in 65% of cases, and in the series of Kimura et al. (8) – in 69.8% of cases. Chung et al. (3) found CCO in the RCA in somewhat lower percentage of patients (45.2%). Unfortunately, anyone of these authors does not mention the percentage of successful attempts of retrograde recanalization of CCO depending on the artery involved.

Failed recanalization of CCO in our series has been due to the impossibility to advance the wire through the collaterals into the distal bed of the target vessel (46.1%) and the difficulties during the tunneling of CCO itself (46.1%, including 15.4% – perforation of the vascular wall). The wire and catheter advancement through CCO already has been described as the most technically challenging stage of recanalization (2, 8). High rate of difficulties encountered during wire advancement into the collaterals can be related to specific selection of patients with complex anatomy of the collateral bed.

The intraoperative complications in our series included the perforation of the involved artery (3.1%) and the dissection of non-target vessel, that led to the development of myocardial infarction despite emergency stenting (1.6%). The incidence of perforation in the work of Kimura et al. (8) is similar to our data (3.1%), while the dissection of non-target (donor) vessel developed in 0.4% of cases – in 1 patient. As Kimura et al. have analyzed the results of recanalization of numerous CCO, they have met other complications: death – in 0.4% of cases, Q-wave MI – in 0.9% and non Q-wave MI – in 3.6% of cases.

In our series significant angiographic restenosis of a successfully recanalized artery developed in the long-term in 14.5% of cases, which does not reliably differ from the literature data on CCO recanalization using entegrade approach and DES. Thus, according to the data of a large study by Valenti et al. (14), in 1 year after the procedure repeated percutaneous intervention was necessary in 12% of patients (40 of 344).

Conclusions

1) The effectiveness of retrograde approach to recanalization was 79.7% (51 of 64). The highest effectiveness was achieved with reca-

nalization of CCO in the RCA (45 of 53; 84.9%) and with the approach to the distal bed of the involved artery through septal collaterals (47 of 58; 81.0%).

2) The failure was often caused by the impossibility to advance the wire to the distal bed through the collaterals (6 of 13; 46.1%) and the difficulties during the tunneling of CCO itself (6 of 13; 46.1%).

3) The incidence of life-threatening intraoperative complications was 4.7% (3 of 64), among them – the perforation of the involved artery and the dissection of non-target vessel, leading to myocardial infarction. Minor in-hospital hemodynamic complications occurred in 9.8% of patients (5 of 51), among them – atrial fibrillation (2 of 51; 3.9%) and hematoma of interventricular septum (3 of 51; 5.9%).

4) The results of successful recanalization of CCO has been followed in the long-term (mean, 10.2 months) in 48 (94.1%) patients: 13 (27.0%) patients had Class II exertional angina, 35 (72.9%) patients had Class I angina or had no symptoms of angina at all. Angiographic restenosis of the recanalizaed artery has been revealed in 14.5% (7 of 48) patients.

Thus, high percentage of successful retrograde recanalization of CCO and the comparability of our results with the data of literature allow us to recommend this algorithm of the choice of methods and techniques of procedure for broad use in the departments of interventional cardiology.

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A Case of Bioresorbable Scaffold Implantation in a Young Woman with 10-Years Coronary History

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We present a case of myocardial re-infarction in a young woman, who underwent implantation of a bioresorbable scaffold, which is unique for Russia. The patient had several risk factors of AMI; the main factor was heavy smoking during many years. Besides, the development of AMI has been influenced by the presence of infectious agents (Chlamydia pneumoniae and Helicobacter pylori), genital factors predisposing to coronary pathology – several medical abortions, menstrual disorders, uterine myoma; exogenital factors – hormonal disorders, blood clotting disturbances and excessive emotional stress of triggering significance. A certain pathogenetic role has been played by endothelial dysfunction, pediatric history and multiorgan pathology.
The patient had a long history of CAD with slow progressing of chronic heart failure and atherosclerosis. However the ensemble of risk factors in the absence of congenital and genetic anomalies has provoked not only two acute myocardial infarctions in young age (<35 years), but also led to the development of multivessel coronary disease (by 44 years) with the risk of a new cardiovascular accident within the next 10 years according to Framingham scale (at least 4%) with high risk of formation of clear indications for cardiovascular surgery within the next 5 years. The use of modern coronary imaging techniques and of a new generation of stents – bioresorbabale platforms – allowed us to prevent a new episode of AMI in the settings of asymptomatic CAD, to restore the architecture of the major vessels as well as to create a potential for timely prevention of eventual threat within the next few years. Obviously, bioresorbable scaffolds are one of the most promising trends in the development of interventional cardiology.
Key words: *myocardial infarction, scaffold, bioresorbable scaffold, female.*

Cardiologists tend to underestimate the prevalence of acute myocardial infarction (AMI) in women. Herewith the most unfavorable recent trend for "youthification" of coronary artery disease (CAD) is of special concern (1–9).

Sex-related particularities of the diagnosis, treatment and rehabilitation of patients with AMI have been recognized a long time ago (2–4). Etiopathogenesis of CAD in women, especially in young women, represents a special problem. AMI in young patients can be due to: early atherosclerosis of the coronary arteries (responsible for up to 89.9% of AMI), significant physical and emotional stresses (3.4%) (5, 6), unknown causes (2.2%), dislipoproteidemia (0.9%), hormonal balance disturbances (0.6%) (2) and other reasons (3%) (3–9).

The cases of AMI in young women are rare and of a great clinical interest. We have faced one such case. This case is singular, as in the late rehabilitation period the patient received a bioresorbable scaffold – this device was already named "the fourth revolution" in interventional cardiology, however up to now it is virtually not used in broad clinical practice in Russia.

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Case report

The patient T,. a 46-years old woman, working as operator at a gas-fillng station from the age of 25 (occupational hazard – gasoline vapor).

In history: chronic bronchitis (from the age of 2) and frequent acute respiratory diseases (ARD). The patient has no family history of CAD; no genetic anomalies or congenital diseases have been revealed. She had been pregnant 10 times and gave birth to 1 child (after the first pregnancy, at the age of 18, without any pathology).

Her living conditions are satisfactory. Social history is unfavorable due to negative psychological microclimate in the family and low income. The patient smokes from the age of 18 (1 pack per day). She admits alcohol abuse, however not more than 1–2 liters of spirits per week.

In the first weeks of January 2000 (at the age of 33) the patient has felt severe girdle pain in the upper one-third of the abdomen while eating spicy meals; she did not apply for medical care. As the pain persisted for one day, she has called for emergency team and has been brought to a village hospital; acute pancreatitis has been diagnosed. After a course of treatment her well-being improved, however in several days she had noted dyspnea, dizziness, weakness and heart palpitation while walking. The ECG has revealed the signs of acute injury of the anterolateral left ventricular wall. For this reason on January 25th, that is, in 55 hours after the onset of MI, the patient has been urgently transferred to Ural Institute of Cardiology.

At admission her condition was moderately severe. The auscultation revealed muffled rhythmic heart sounds, moderate tachycardia (HR = 110 bpm). Her blood pressure was 120/80 mm Hg.

ECG (25.01.00): non-paroxysmal supraventricular tachycardia, 100 bpm, QS in leads V_2–V_3, qR in leads V_4–V_6, ST elevation in leads V_2–V_6, negative T wave in leads I, aVL, V_2–V_6, ST depression in leads III, aVF.

EchoCG (25.01.00): akynesia of interventricular septum (IVS) in the apical region. 1st degree mitral regurgitation. Left ventricular ejection fraction (LVEF) – 42%.

Biochemical blood count (25.01.00) has shown: high level of blood glucose – 11.9 mmol/l (norm – 3.6–6.1 mmol/l), GOT – 79 IU (norm – 15–46 IU), GPT – 82 IU (norm – 11–66 IU), creatine phosphokinase – 534 U/l (norm – 30–135 U/l), creatine phosphokinase-MB – 268 U/l (norm – <16 U/l). Coagulogram: significant platelet hyperagregation on inductors, hypercoagulation – 1st degree syndrome of disseminated intravascular coagulation, inhibited fibrinolysis.

Lipid spectrum (25.01.00): total cholesterol – 4.2 mmol/l (norm – <5.2 mmol/l), HDL cholesterol – 1.7 mmol/l (norm – >0.91 mmol/l), LDL cholesterol – 1.57 mmol/l (norm – <3.53 mmol/l), triglycerides – 2.04 mmol/l (norm – <2.26 mmol/l), atherogenicity index (HDL cholesterol /total cholesterol) – 0.4 (norm – >0.25). Conclusion: lipid spectrum is normal.

The diagnosis of AMI has been confirmed in our clinic on the base of WHO criteria (typical clinical presentation, ECG changes, significant increase of cardiospecific enzymes).

Thrombolytic therapy was not applied because of late hospitalization. In the settings of therapy with desagregants, β-blockers, nitrates, ACE inhibitors, diuretics and metabolic agents, angina attacks did not recur, the signs of heart failure regressed.

Taking into account clinical presentation, young age of patient and normal lipid spectrum, we have decided to perform coronary angiography (CAG) in order to reveal the causes of AMI (figure 1). On February 7th, 2000, selective CAG and left ventriculography have been performed. Angiography of the right and left coronary arteries revealed the occlusion of the middle segment of the LAD and of the posterior interventricular artery. The peripheral bed did not opacify (Figure 1). Left type of coronary circulation. Left ventriculography has shown akynesia of the apical region. LVEF – 57%. SYNTAX score 15.5. Stenting was not performed in view of lacking technical capabilities.

The definite clinical diagnosis was: CAD, primary acute Q-wave infarction of the left ventricular anterior wall (anteroseptal, apical, lateral LV walls) on 23.01.2000. Complications: non-paroxysmal supraventricular tachycardia (25.01.2000). NYHA class I. Rehabilitation has been conducted in accordance with the IV functional class (Classiciation of Scientific Center of Cardiology of the Academy of Medical Sciences of the USSR, 1983).

On April 9th, 2002, (at the age of 35), at 8:00 a.m., at rest, the patient felt intense pain in arms and shoulder joints; the pain has lasted for approximately two hours and was accompanied by abundant cold sweat. The emergency team was called in 2.5 hours after the onset of pain and the patient was urgently brought to the hospital with the diagnosis of acute myocardial reinfarction.

As the contraindications were absent, at 10:35 a.m. thrombolytic therapy (TLT) with intravenous Streptase (1.5 mln.IU, in dropped infusion) was started. Blood clotting time (BCT) – up to 5 minutes. In 10 minutes after the start of thrombolysis ventricular fibrillation developed. Defibrillation (300 J) with the necessary amount of cardiopulmonary resuscitation were carried out. After that hemodynamics remained stable, angina pain did not recur, BCT – up to 60 min. Repeated CAG was not performed.

EchoCG (09.04.02): global left ventricular contractility within normal limits. Akynesia of the apical segments of the IVS, lateral wall and apex of the left ventricle. LVEF – 62%.

24-hours ECG monitoring: during 24 hours (15-16.04.02) – sinus rhythm with variations at daytime from 55 to 78–98–115–122 beats per minute, at nighttime – from 50 to 58–78–115 beats per minute. No changes of ST segment in comparison with the baseline were seen.

Bicycle ergometry (BEM) (15.04.02): negative, low physical tolerance. Double product – 143 kg/min (functional class IV).

The definite clinical diagnosis was: CAD, repeated acute Q-wave infarction of left ventricular anterior wall (anteroseptal, superior, lateral LV walls) on 09.04.2002. Postinfarction cardiosclerosis (with scars on the LV anterior wall dated 2000). Comorbidities: chronic bronchitis, chronic pancreatitis, chronic hypochromic anemia. Complications: heart rhythm disturbances – ventricular fibrillation (09.04.2002), non-paroxysmal supraventricular tachycardia (09.04.2002). Circulatory insufficiency NYHA class I.

Rehabilitation was carried out in accordance with functional class IV. On April 30th, 2002, the patient has been discharged under the care of the rehabilitation department of Ural Institute of Cardiology (see

ECG tracings in figure 1). During May–June, 2002, in the settings of medical therapy (Aspirin, Egilok, Renitek, Preductal, Fenuls) the patient was free of angina attacks, there were no clinical signs of heart failure. In June, 2002, the patient started complaining of general weakness and chest discomfort, dyspnea of effort, periodical headaches and dizziness.

On September 20th, the patient underwent perfusion single-photon tomography of the myocardium with ^{99m}Tc-MIBI at rest and with VEM-probe (figure 1). Conclusion: the study revealed transmural myocardial scars in the area of heart apex and in apical segments of the anteroseptal and lateral LV walls. Stress-induced ischemia (risk area) was registered in anterolateral and posterolateral apical segments. According to scintigraphy data, the area of unviable myocardium was limited by 2–3 segments.

On February 21st, 2003 (at the age of 36) endothelial dysfunction (ED) has been studied (17, 18). During reactive hyperemia test relative dilatation of the brachial artery was 2.4%, besides, severe degree of ED was confirmed by vasoconstrictor reaction.

From March, 2003, through January, 2009 (at the age of 42), the patient did not appeal for medical care. In her words, during this period her dyspnea progressed (manifestations of chronic heart failure within the limits of NYHA class II) and the frequency of palpitations attacks during effort increased. The patient denied episodes of chest pain. In 2007–2009, she suffered from progressive chronic bronchitis (respiratory failure class 2), had 3 medical abortions and did not take any medications. In January 2009, while spending her holiday in Netherlands, she lost consciousness in the hotel, and the emergency team brought her to Erasmus University Medical Center (EUMC). At admission the patient refused medical care for financial reasons. Her arterial blood pressure was 90/60 mm Hg, ECG revealed the signs of scars on the anterior and posterior LV walls, without ischemic changes and rhythm disturbances, EchoCG showed LV EF of 51%, total cholesterol was 7.7 mmol/l. The patient attributed this episode of syncope (in her words, the second in her life) with alcohol intake and bathing in the morning. Taking into account the history of hypotension, this could provoke hemodynamic instability with marked fall of blood pressure and collapse-like condition.

At the insistence of the friends, in February 2009, the patient was readmitted to EUMC in planned order for additional examination and a series of visual studies of the coronary arteries. On February 10th, 2009, she underwent coronary angiography with blood flow visualization using CT-system HeartFlow (multislice CT), a series of images was obtained with IVUS (including with virtual histology of the arteries) (Volcano corporation), optical coherent tomography (OCT) with 3D regimen (LightLab Imaging) and near-infrared spectroscopy (InfraRedX) (figures 2–6). Performed studies have revealed a significant stenosis of the second segment of the LAD, of the circumflex branch and of the distal portions of the right coronary artery with the involvement of the 3rd, 7th and 11th segments (SYNTAX score 21.5). In view of significant stenosis of the above-mentioned vessels we have decided to use bioresorbable Everolimus-eluting stents 3 × 12 mm (Abbott Vascular, Santa Clara, CA, USA) in both segments (for complete information see figures 7 and 8). In both cases post-stenting angiography has shown the absence of residual stenosis and TIMI III blood flow restoration. On February 14th the patient was discharged from the EUMC in a satisfactory condition (without negative ECG dynamics and any complications) with the recommendations to come back for control in 6 and 24 months. Upon her return to Russia the patient has been given the recommendations concerning the changes in her lifestyle, a complex therapy for prevention and treatment of chronic heart failure and CAD has been prescribed. However the patient refused continuous follow-up in rehabilitation center of UIC.

In October 2011, the patient has applied to UIC with the results of complex investigation from EUMC. According to these data and the results of coronary arteries imaging, both scaffolds have degraded in about 12–24 months after the implantation. The comparison of the cross-section surface area (CSA) immediately and in 6 and 24 months after scaffold implantation revealed the following changes in the vascular wall (figures 2–6): the average CSA of the vessel increased from 13.8 to 15.1 mm^2, the average CSA of the scaffold – from 6.3 to 7.0 mm^2, the minimal CSA of the scaffold – from 5.6 to 5.5 mm^2, neointimal hyperplasia was 0.3 mm^2, the minimal CSA of the lumen increased from 5.7 to 6.0 mm^2, the total CSA of the plaque increased from 7.2 to 8.2 mm^2. The results of virtual intravascular ultrasonic histology were suggestive of degradation of the plaques' necrotic nucleus and the increase of the amount of fibrous tissue in the site of scaffold implantation (figure 3). Our results can be considered successful with total restoration of the arterial lumen (figure 4) and without signs of pathological remodeling of the vessels, as well as without such complications as restenosis or late atherothrombosis in the site of scaffold implantation. We have also revealed in this patient two cases of tissue arch formation at the site of scaffold implantation after its degradation that can be interesting from the viewpoint of interventional cardiology (figures 4–6). In all probability, these arches were of complex connec-

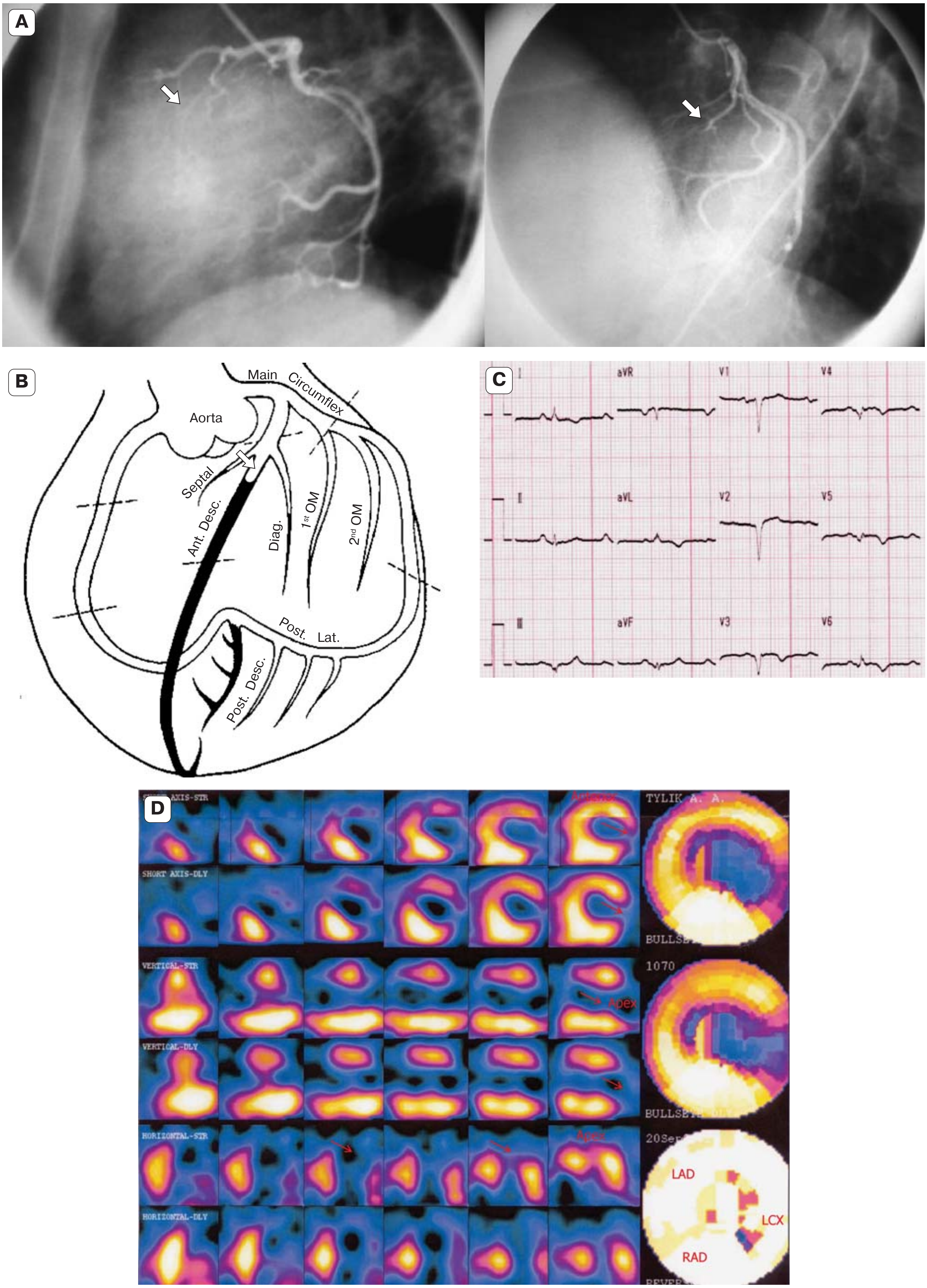

Figure 1. Results of coronary angiography (CAG), ECG and myocardial scintigraphy. **A, B** – CAG in AP + cranial and LAO + caudal views. **C** – 12-leads ECG. **D** – results of myocardial scintigraphy in 3 views, as well as comparative analysis of changes at rest and during exercise.

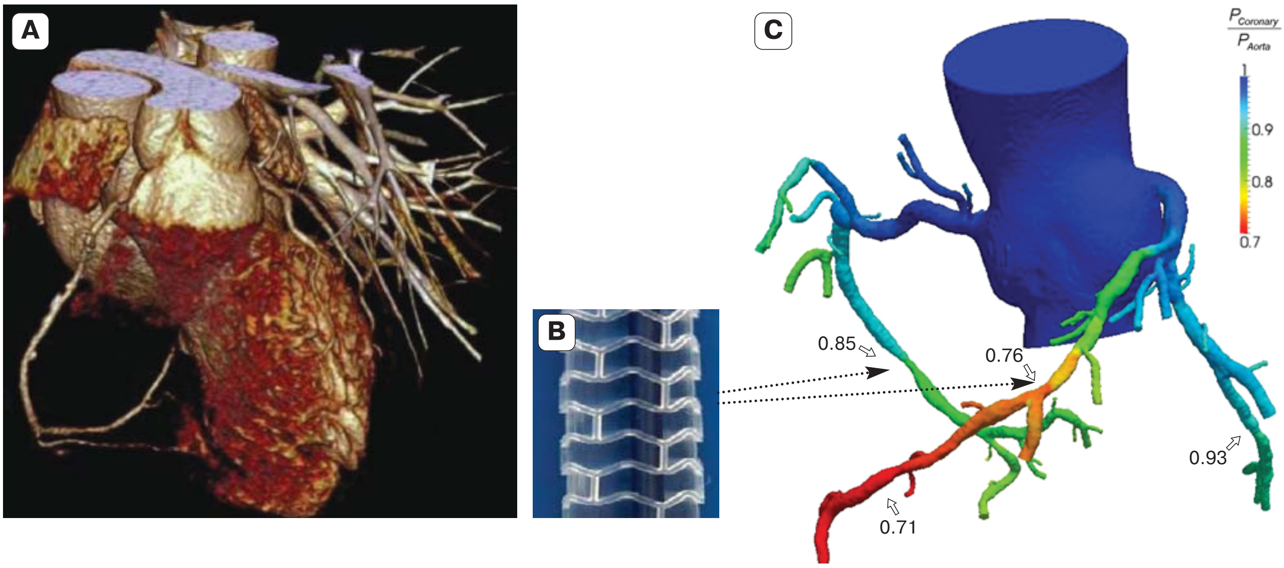

Figure 2. Computed tomography. **A** – multislice CT (MSCT). **B** – exterior appearance of a bioresorbable scaffold (Abbott Vascular). **C**– the image of coronary blood flow processed with the HeartFlow system. Blue segment of the scale – normal blood flow, red segment – significantly decreased blood flow. The figures mark the blood flow's intensity: "1" – maximally intense blood flow, "0" – totally absent blood flow.

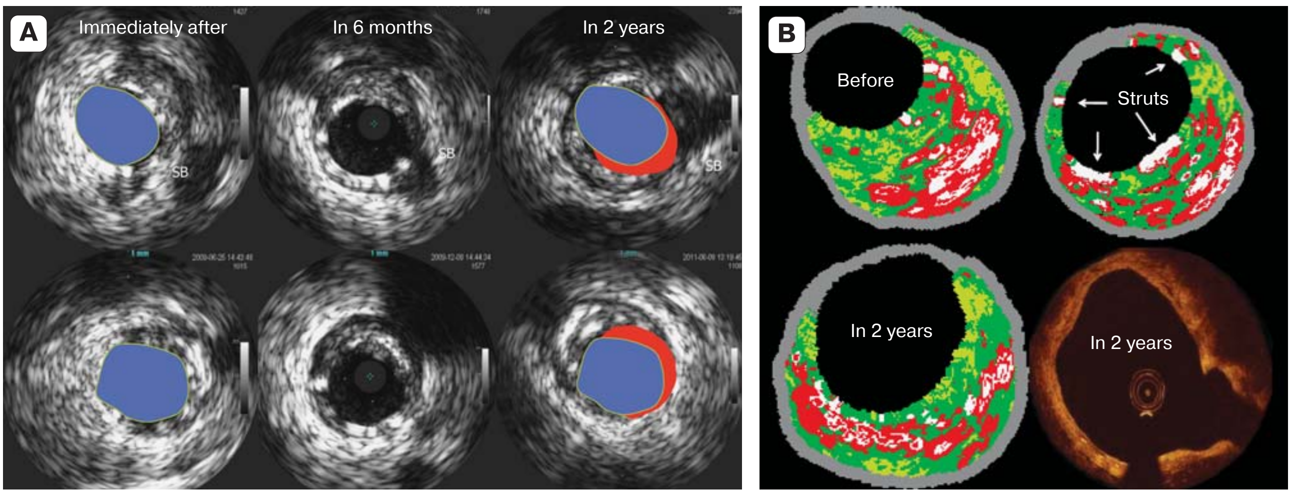

Figure 3. Intravascular ultrasonic (IVUS) scanning of the coronary arteries, including in the regimen of virtual histology (VH). **A** – the changes of vessels' segments in IVUS regimen immediately after scaffold implantation, in 6 and 24 months after the intervention. Blue color marks vascular lumen, red color – the changes of the lumen, in particular, visible increase of the lumen after total degradation of the scaffold. **B** – comparative results of vascular wall imaging using IVUS in VH regimen. Upper part of the fragment – the changes before and after scaffold implantation, lower part – the changes of vascular architecture in 2 years after the intervention. Red color – the areas of vascular tissue necrosis and calcification, white color – areas of calcification and scaffold, light green and yellow – fibro-lipid tissues, dark green – fibrous tissue. The lower right panel – the results of optical coherent tomography (OCT) of the same vessel in 2 years after scaffold implantation.

tive tissue-neointimal nature and resulted from thrombus organization and fibrin deposition. Figure 5 displays the cavity remaining in the vessel after plaque rupture (the episode of unstable plaque rupture, for example, with angiographic signs of no-reflow and clinical evidence of ischemia, was not registered, but in all probability the plaque has ruptured during scaffold implantation). The vulnerability of this arterial segment from the viewpoint of the presence of an unstable plaque has been confirmed by near-infrared spectroscopy just prior to scaffold implantation. The analysis of bioresorbable scaffold implantation during two years is shown in figures 8 and 9. The main advantage of bioresorbable scaffold in comparison with metal stent consists in complete restoration of the arterial lumen and scaffold disappearance within 12–24 months without signs of pathological remodeling of the vessel and, what is the most important, with the evidence of atherosclerosis regression at the site of scaffold implantation. The main disadvantage of the scaffold are its large struts (comparable to those of the first-generation DES –

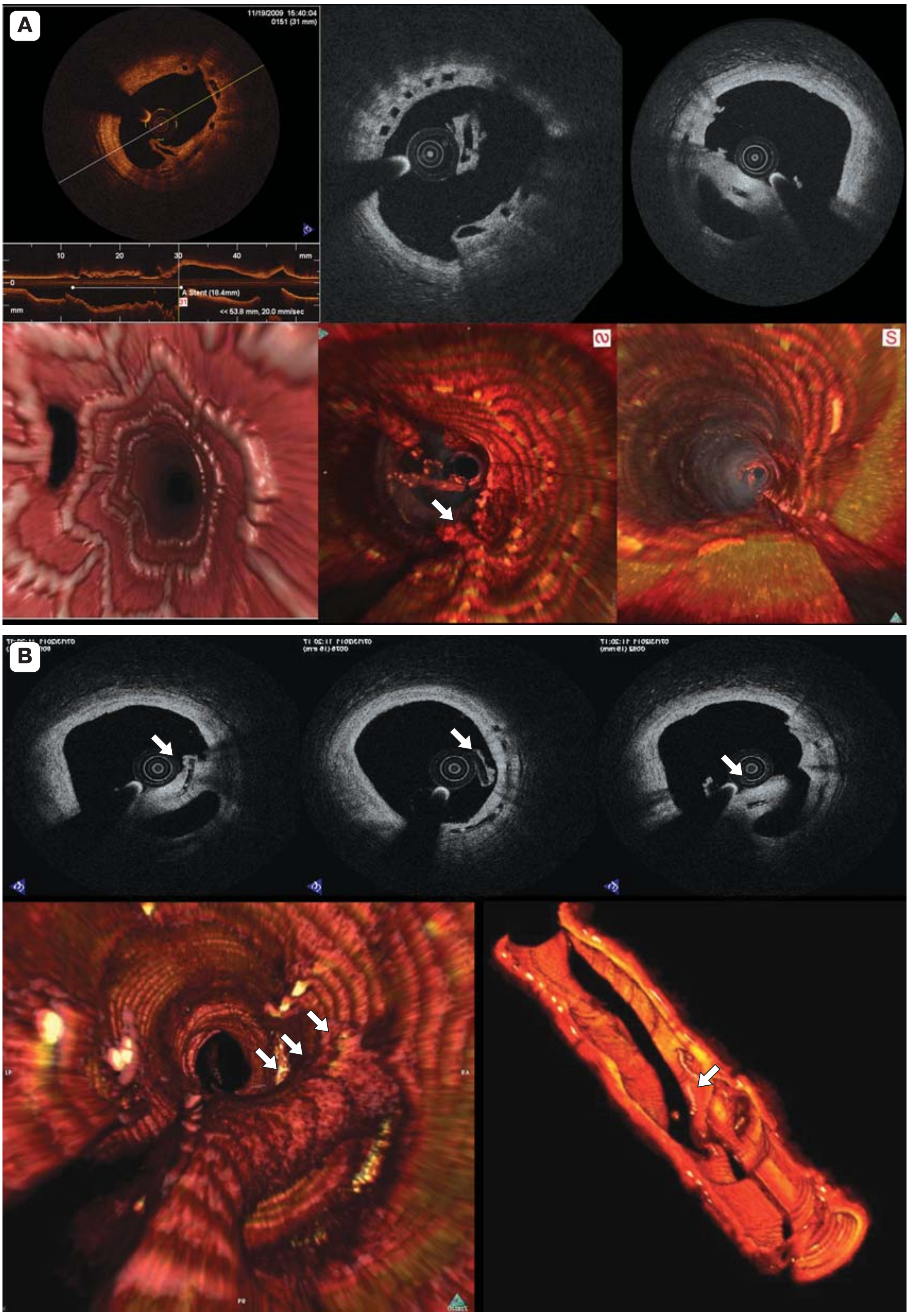

Figure 4. Optical coherent tomography (OCT) of the segments of coronary arteries after the intervention, with the demonstration of a case of tissue arch formation at the site of scaffold degradation. **A** – OCT of the vessels: immediately after scaffold implantation, in 6 and 24 months after the implantation. Lower panel – three-dimensional restoration of the vessel image: the shadow of the scaffold's struts can be seen. **B** – formation of tissue arch of a complex connective tissue-neointimal nature at the site of scaffold degradation(the history of scaffold damage with OCT-catheter) . The black line seen on the images is an artefact.

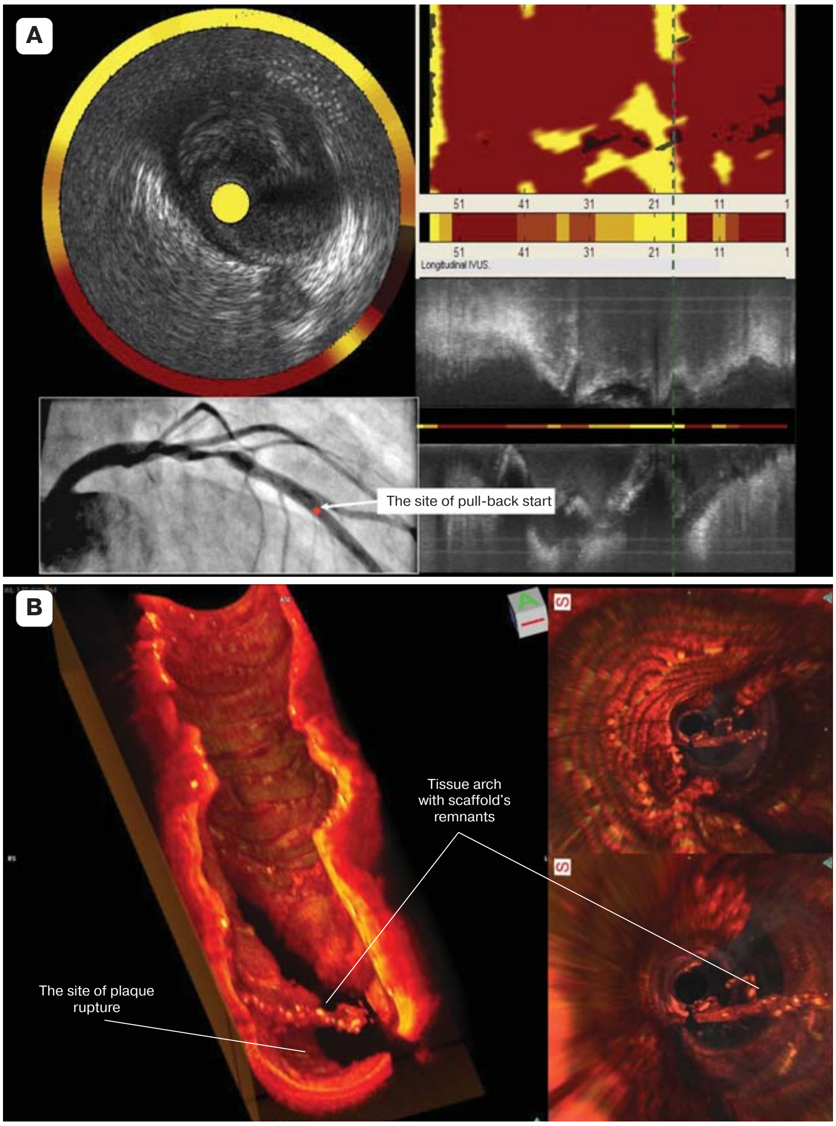

Figure 5. Visualization of a tissue arch at the site of damaged scaffold after OCT-imaging of the coronary arteries. **A** – transcatheter scanning of the coronary artery wall at the site of intended implantation of a bioresorbable scaffold. Yellow color – the lipid-rich sites. **B** – three-dimensional OCT of the same segment in 6 months after scaffold implantation.

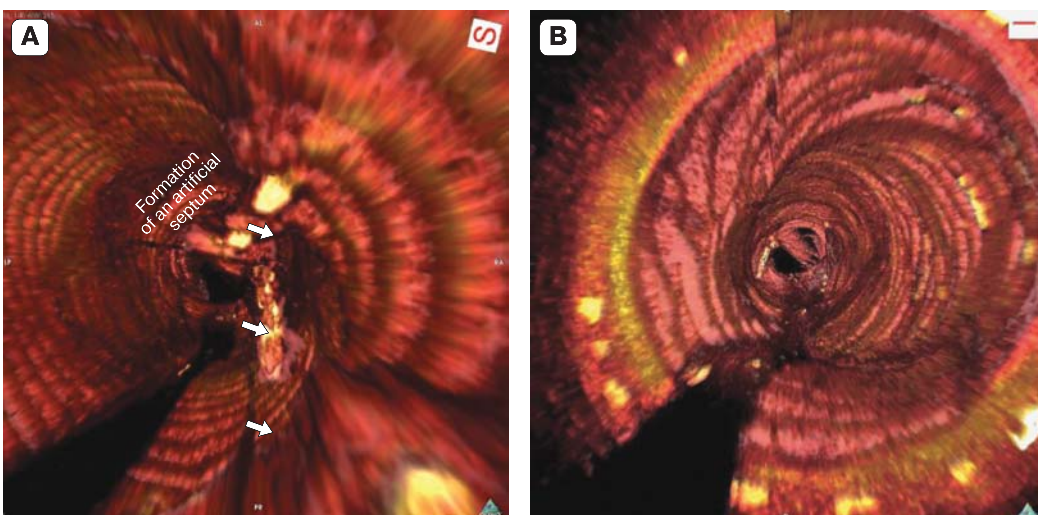

Figure 6. Three-dimensional optical coherent tomography of the vessels: a new tissue is seen as a septum at the site of scaffold degradation. **A** – the presence of arch-like new tissue at the site of scaffold malapposition. The gap between the scaffold and the arterial wall is patent, without signs of fibrin depositions. **B** – normal vascular lumen in 2 years after scaffold implantation. One can see the debris of an almost totally biodegraded scaffold.

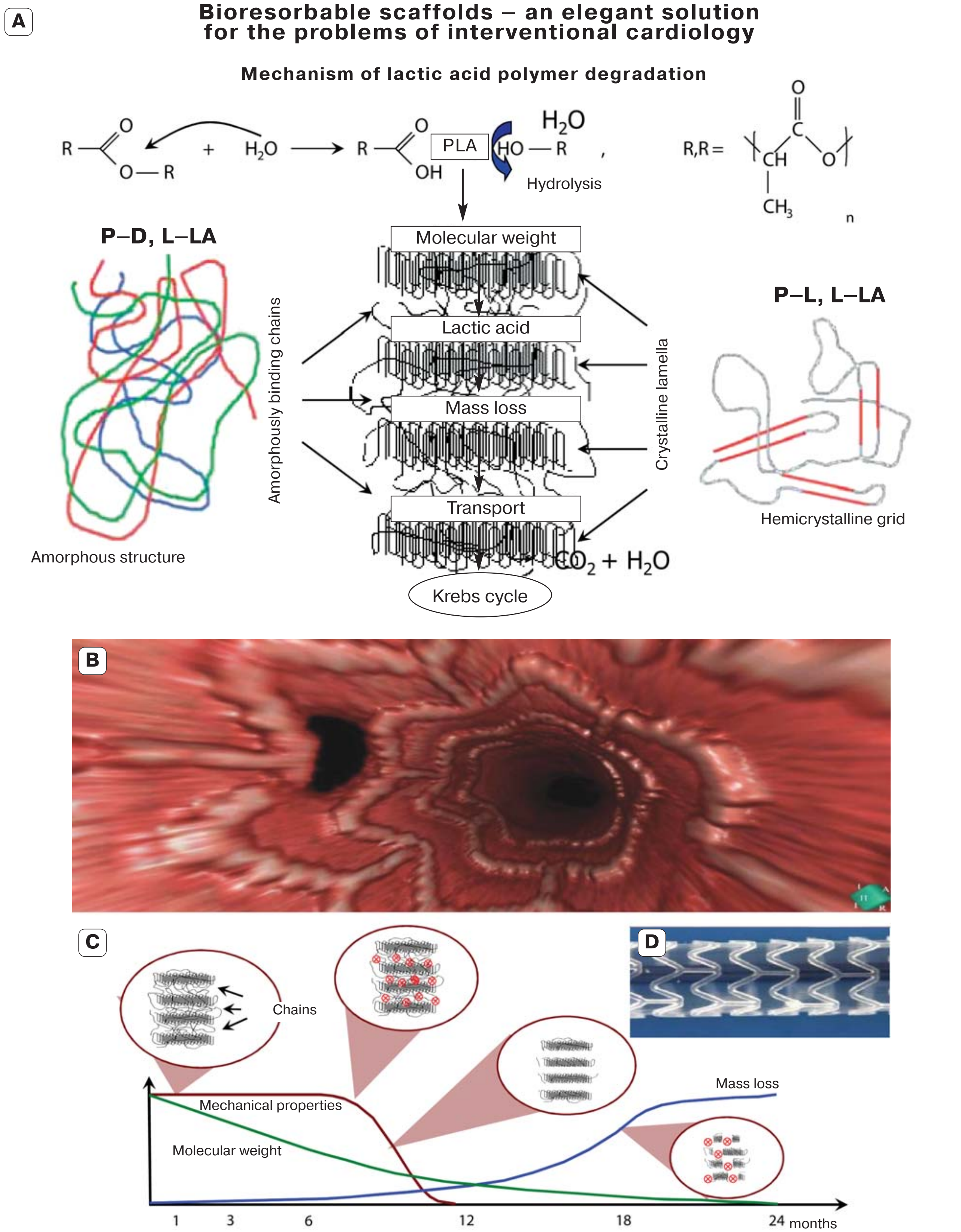

Figure 7. Polymer nature of bioresorbable scaffolds.
The picture shows the main information on polymer structure of a bioresorbable scaffold BVS ABSORB (version 1.0, produced by Abbott Vascular, Santa Clara, CA, USA). **A** – mechanism of polymer degradation to oligomers and monomers with the involvement of end products into Krebs cycle. **B** – the appearance of the artery immediately after the implantation of a bioresorbable scaffold obtained with the use of three-dimensional optical coherent tomography. **C** – duration of the main effects and biodegradation of the scaffold. The scaffold totally preserves its mechanical properties within the first 9-12 months. The mass loss reaches its critical point in about 18 months after the implantation, and total biodegradation occurs in 24 months. **D** – exterior appearance of the bioresorbabal scaffold.

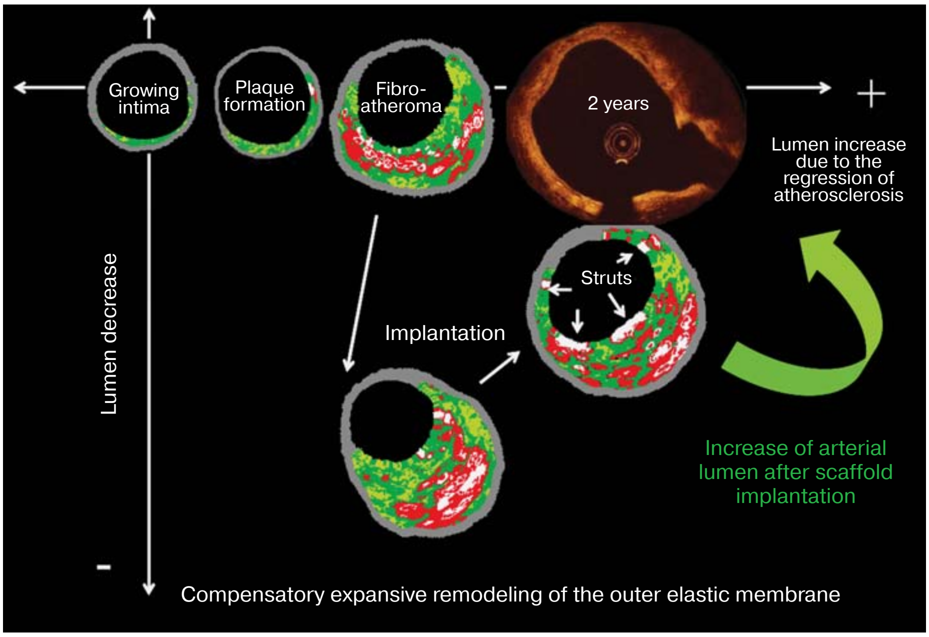

Figure 8. Natural remodeling of the vessel after the implantation of a bioresorbable scaffold.
The image obtained with the use of intravascular ultrasonic scanning: with the progressing of atherosclerosis the plaques increases in volume. The lower panel – a big eccentric, but mature plaque with marked necrotic nucleus and at least 170 μm-thick fibrous layer, "touching" the necrotic nucleus of the intima and vascular lumen, with eventual calcification of this area. The upper panel – a significant increase of vascular lumen with the signs of total plaque degradation in 2 years after the intervention.

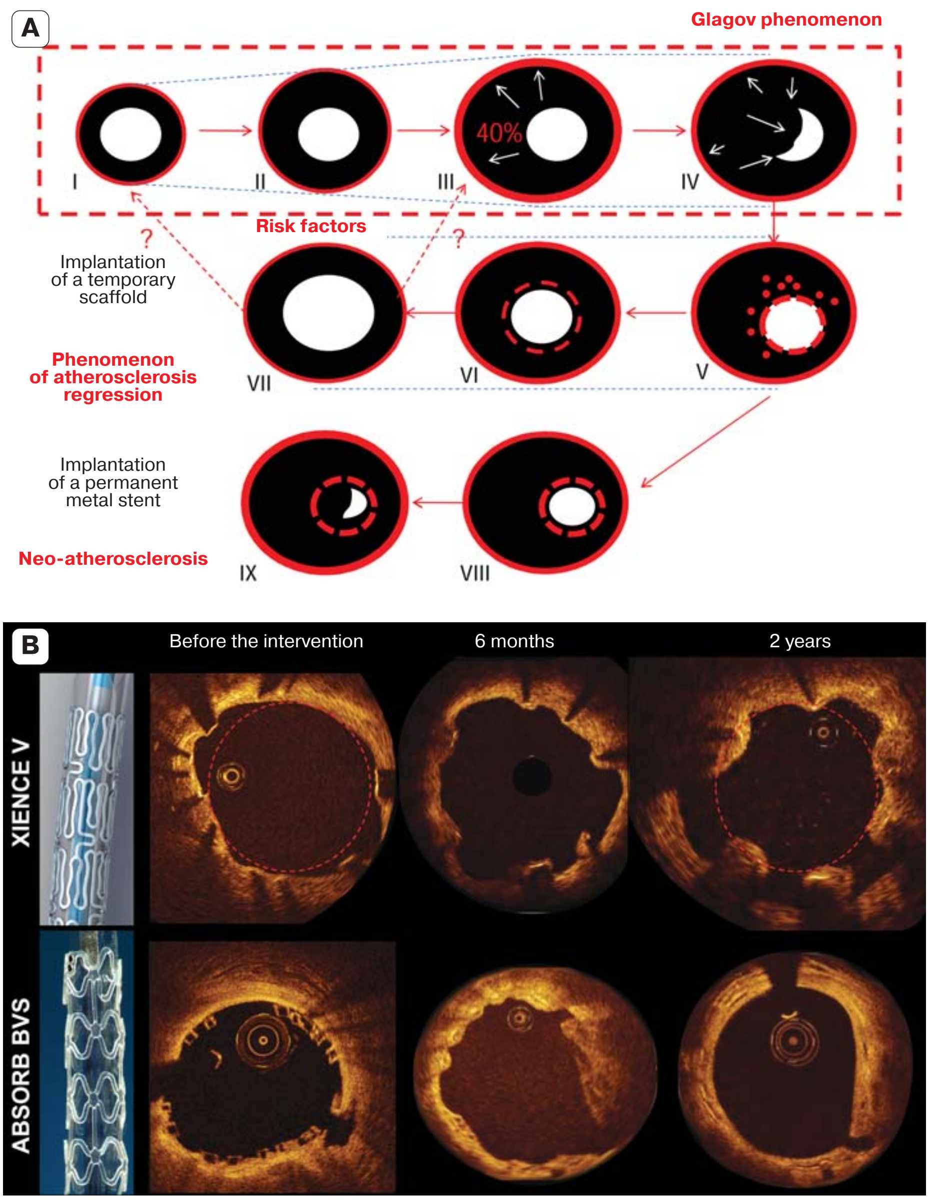

Figure 9. Remodeling of the vessel after implantation of a metal stent or a bioresorbable scaffold, according the paradigm of Glagov phenomenon. **A** – schematic interpretation of the processes of vascular remodeling during natural atherogenesis, as well as after implantation of a metal stent or a bioresorbable scaffold. **B** – comparative schedule of optical coherent tomography of the vessels after the intervention with an everolimus-coated metal stent and with an everolimus-coated bioresorbable scaffold. After the implantation of XIENCE V stent (2 years of the procedure) the processes of neointimal hyperplasia are absent, one can see the "cauliflower" phenomenon – arterial walls deformation with the development of invaginations.

150 μm in comparison with 88,6 μm in XIENCE V stent) and less impressive mechanical properties (the scaffold's radial force does not exceed 883 mm Hg in comparison with minimal force of 991 mm Hg in metal stents).

The patient repeatedly refused from regular follow-up in the rehabilitation center of UIC. During the last visit she has been given the recommendations for correcting her lifestyle (primarily, to stop smoking and alcohol abuse, as well as to prevent undesirable pregnancy and to change the place of work). The therapy for the correction of chronic heart failure of functional class I–II (ejection fraction 50–51%), chronic obstructive pulmonary disease and CAD has been prescribed.

Comments

The development and the course of CAD in young women have their particularities, distinguishing this group of patients from men and elder women. There are no doubts, that the development of CAD in women is influenced by the same factors as in men. However the influence of exo- and endogenous causes of CAD in young women is offset due to the protective effect of estrogens (1–9).

Thus, in our case one can determine several factors leading to the development of CAD: obviously, the main risk factor was heavy smoking of many years duration. Besides, the development of AMI was influenced by the presence of infective agents (*Chlamydia pneumoniae* and *Helicobacter pylori*); genital factors – medical abortions, menstrual disorders, uterine myoma – predisposing to coronary pathology; exogenital factors – hormonal balance disorders, blood clotting disorders and excessive emotional stresses of triggering significance. A certain pathogenetic role has been played by endothelial dysfunction, pediatric history and multiorgan pathology.

The course of CAD in our patient was prolonged, with slow progressing chronic heart failure and atherosclerosis. However the ensemble of risk factors in the absence of congenital and genetic anomalies has provoked not only two AMI in young age (below 35 years), but also the formation of multivessel coronary lesion. By the age of 44 years her SYNTAX score was already 21.5, with at least 4% risk of a new cardiovascular accident within the next 10 years by Framingham scale and a high risk of formation of clear indications for cardiovascular surgery within the next 5 years. The use of up-to-date methods of coronary imaging and of a new generation of stents – bioresorbable scaffolds (10, 11) – has allowed us to prevent a new episode of AMI in the presence of an asymptomatic CAD, to restore the architecture of major vessels, as well as to create the potential for timely prevention of eventual threat within the years to come. Obviously, bioresorbable scaffolds are one of the most promising trends in the development of interventional cardiology.

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Successful Removal of a Rare "Giant" Left Atrial Spherical Thrombus, that has been Diagnozed as Myxoma Prior to the Operation

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Only few cases of spherical thrombi of the left atrium have been described in the world literature. We present a case of successful surgical treatment of spherical thrombus of the left atrium attached to the interatrial septum. Prior to the operation it has been thought to be a left atrial myxoma, because of the similiarity of ultrasound presentation of these two entities. It is especially interesting, that the thrombus has formed in a female patient without history of cardiac arrhythmia, valvular or endocardial pathology.

Key words: *spherical thrombus of the left atrium, myxoma diagnostics, surgical treatment of the heart neoplasms.*

According to the literature, most common left atrial neoplasms are thrombi (1) and primary heart tumors (8). As a rule, left atrial thrombi develop as a result of disturbed intracardiac hemodynamics in this heart chamber due to mitral valve defects or coronary artery disease (1–5). In most cases the formation of thrombi (in absence of evident infection) is preceded by atrial fibrillation and the enlargement of left atrial cavity. Due to certain anatomical and hemodynamical reasons, a thrombus is initially formed in the left atrial appendage (1).

According to autopsy data, primary heart tumors are revealed in 0.0017–0.19% of cases (6, 7). About half of them are myxomas. They are more common in women aged 35–55 years. In 80–90% of cases myxomas are localized in the left atrium (LA), significantly less frequently in the right atrium and even more rarely in the ventricles (8). LA myxomas in most cases originate from the region of fossa ovalis of the interatrial septum (IAS).

We present a case of diverging clinical, intraoperative and pathological diagnosis of a left atrial mass. During clinical and laboratory examination a large spherical mobile neoplasm of the left atrium fixed to the interatrial septum (IAS) was diagnosed as a left atrial myxoma. However, after histological analysis the diagnosis was changed to "giant" spherical thrombus.

A 62-years-old woman was admitted to the Department of Cardiovascular Surgery of Moscow City Center of Interventional Cardioangiology on May 3, 2010 with the diagnosis: left atrium neoplasm (myxoma?).

The patient had a history of essential hypertension, III stage. During several years she had periodical pain in the left side of the chest not related to exercise and a slight dyspnea on exertion. In view of these complaints the patient has applied at her local out-patient service. EchoCG performed in district out-patient department revealed a left atrial mass, and the patient has been referred to our Center. On EchoCG performed in consultative department of the Center (April 1, 2010), cardiac cavities were not enlarged, the left ventricle contractility was satisfactory, ejection fraction = 64%, the left ventricular wall kinetics without significant disturbances. There were signs of diastolic dysfunction (hypertrophic type). End-diastolic and end-systolic diameter in the parasternal position were 4.6 and 3.0 cm, respectively. Diastolic thickness of the interatrial septum was 11 mm. The left atrium was not enlarged (3.8 cm). A mobile (amplitude of movement 1.5 cm) echonegative spherical mass, sized 31.2×37.5 mm was seen in the left atrium. It originated from the middle third of the interatrial septum (IAS), had no contact with the mitral valve cusps, and did not prolapse into the left ventricle (Fig. 1). The left atrial appendage was free of any masses. Transmitral blood flow was not disturbed. There were insignificant fibrotic changes and thickening of the mitral valve. Insignificant age-related changes were revealed in

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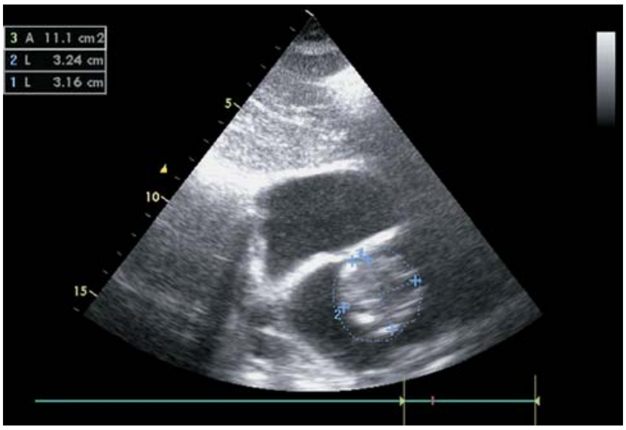

Figure 1. EchoCG – Thrombus in the left atrium.

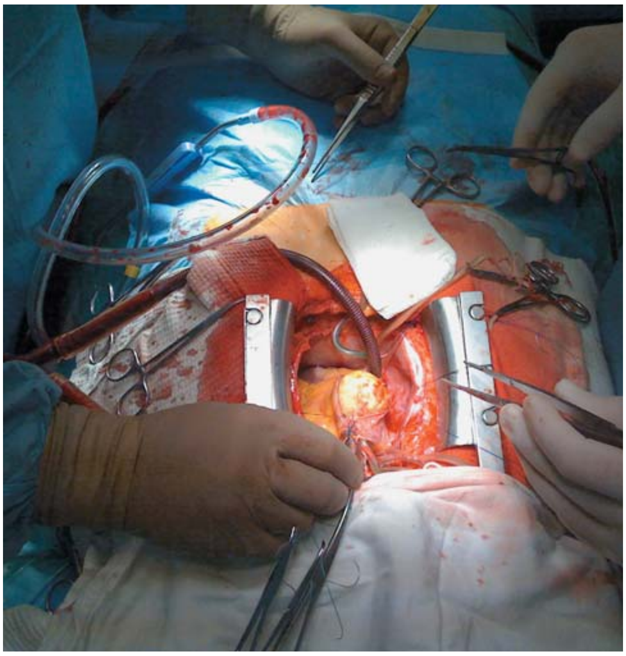

Figure 2. Access through the right atrium.

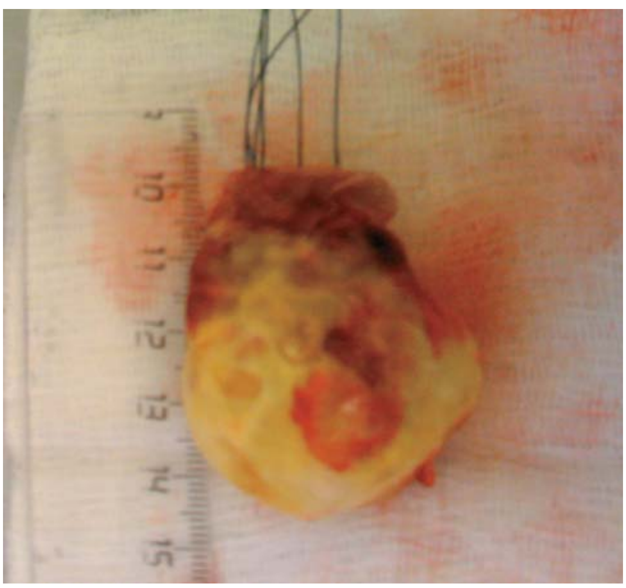

Figure 3. Removed thrombus (4 × 3 cm).

the aortic valve and aortic root. Inferior vena cava was of normal size, with more than 50% collapse on inspiration. Transesophageal EchoCG showed: V max on the aortic valve – 1.2 m/sec. Estimated systolic pulmonary arterial pressure was 25 mm Hg. Mitral regurgitation (degree 1) was present. X-ray and other clinical and laboratory investigations did not reveal any concomitant pathology. The coagulogram was normal. So, left atrium neoplasm (myxoma?) has been diagnosed, and surgical treatment was recommended.

The operation was performed on May 4, 2010, under normothermic cardiopulmonary bypass (separate cannulation of the venae cava and aorta) and hypothermic cardioplegia (Custodiol). The excision of a neoplasm in the left atrium, with partial resection of IAS and IAS reconstruction using synthetic Gortex patch (3 × 2 cm) was performed through the right atrial approach. After opening the right atrial wall we have seen patent foramen ovale in the upper part of fossa ovalis (4 mm). The IAS was dissected along the whole length from the upper pole downwards. A neoplasm has been found in the left atrium. It was attached to the middle third of the IAS and had a basis measuring approximately 5–7 mm (Fig. 2). The posterior edge of the basis was closely adjacent to the posterior wall of the left atrium. After preliminary application of the traction sutures, the basis of the neoplasm was excised, leaving 5 mm edges, and the neoplasm was removed through the right atrium. It was of whitish-yellow color, dense and measuring about 4 × 3 cm. The examination of the left atrium did not reveal any additional neoplasms. Left heart cavities were rinsed. The endocardial surface was smooth. A iatrogenic ASD was closed by 3 × 2 cm Gortex patch (Prolen 3/0). The right atrium was closed with padded sutures. After removing the clamp from the aorta, the heart activity restored spontaneously. ECG showed sinus rhythm. The duration of the aortic cross-clamping was 44 minutes, the duration of the cardiopulmonary bypass – 70 minutes. The patient was extubated 4 hours after the operation. She had sinus rhythm, with stable hemodynamics. The postoperative period was unremarkable. Repeated EchoCG revealed satisfactory contractility of LV myocardium, cardiac cavities were not enlarged, interatrial septum was continuous throughout, there was no shunt at the atrial level. Any additional mass was not seen in the LA cavity. On the 12th day after surgery the patient was discharged in satisfactory condition. In 6 months at control examination she did not present any complaint, her EchoCG was normal.

Removed material was sent for the histological investigation to Sklifosovsky Research Institute of Emergency Medicine. Macroscopic investigation performed on 05.05.2010 revealed: a spherical dense mass measuring 3.5 × 3.5 cm, with haemorrhages on the smooth whitish surface, with vast loci of calcinosis (Fig. 3). The section presented with yellow, laminated tissue. Histological analysis showed dense packed layers of fibrin, few-celled, with loci of calcium concretions in the thin connective-tissue capsule. According to definite conclusion, this was an incapsulated thrombus of indeterminate age. There were no signs of myxoma.

This case is of interest for the practical cardiac surgery due to the following reasons:

1. Single reports on spherical thrombi of the left atrium can be found in the literature (9–11);

2. Meanwhile, we did not find in the available literature the information on spherical thrombi of the left atrium merged with interatrial septum in patients with sinus rhythm without blood flow disorders at the level of mitral valve, without any pathology of the left atrial endocardium, and in the presence of normal parameters of blood clotting system.

3. The study of this patient's history did not reveal episodes suggestive of thromboembollic events in the brain vessels or other major arteries. The absence of history of thromboembolism with such location of the thrombus, with its impending stepwise formation – that is, mandatory succession of sates from the soft to the organized and incapsulated one, is hardly explainable from the point of view of practical medicine (10).

4. Considering the thrombus parameters – volume (almost 40 cm^3) and weight (more than 40 g), the pedicle measuring 5–7 mm, mobility (amplitude 1.5 cm), cohesion with the IAS (as opposed to growing from it, as is usual for myxomas), and the absence of mitral stenosis as a potential barrier (9), it is hard to understand why the thrombus did not tear off and dislocate to the systemic circulation.

In conclusion, it should be repeated once again that one has to be very careful when removing a neoplasm from the heart cavity. Particularly, as it can be a thrombus attached to the IAS, and its destruction can lead to the severest consequences.

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Post-Revascularization Dynamics of Brain Natriuretic Peptide Level in Patients with Acute Coronary Syndrome

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The purpose of the study consisted in the evaluation of the dynamics of brain natiruretic peptide level in patients with ACS + ST. According to the authors, the concentration of BNP in patients with ACS depends on the location of the lesion and correlates with the decrease of LV systolic function and the degree of cardiac failure. After reperfusion therapy of ACS maximal concentration of BNP is seen on day 3, followed by a decrease below the baseline value. The inclusion of Corvitin in the scheme of patients' management contributes to systematic progressive decrease of BNP concentration in patients with ACS + ST and disappearance of peak activity on day 3.

***Key words:** acute coronary syndrome, reperfusion therapy, brain natriuretic peptide, Corvitin.*

List of abbreviations

ACS + *ST* – acute coronary syndrome with *ST* elevation
BNP – brain natriuretic peptide
CF – heart failure
LV – left ventricle

Purpose of study consisted in the evaluation of the dynamics of brain natriuretic peptide (BNP) level in patients with acute coronary syndrome with ST elevation (ACS + *ST*) after revascularization.

Basement. Today the study of neurohormonal activation and of the role of BNP in early diagnosis of heart failure and determination of prognosis in patients with ACS + *ST* is in the focus of interest.

Material and methods. The study comprised 68 patients with ACS + *ST*, who have been divided into the groups depending on their lesion's location, the method of reperfusion therapy (systemic thrombolythic therapy, transluminal balloon angioplasty), the use of Corvitin.

Results of study. The comparison of patients on the base of the class of acute heart failure (Killip) has demonstrated the increase of BNP concentration from class I to class III–IV. Thus, in patients with Killip class I, BNP level was 984.20 ± 123.79 pg/ml, with Killip class II – 1347.50 ± 112.15 pg/ml, and in patients with Killip class III + IV – 1432.67 ± 162.71 pg/ml. The difference between the groups with Killip classes I and II, Killip classes I and III–IV was statistically significant ($p < 0.05$). There were no statistically significant difference between the groups with Killip classes II and III–IV.

Irrespective of the method of reperfusion therapy (thrombolythic therapy or balloon angioplasty), the concentration of BNP increased by the day 3 of the follow-up. By the day 5, the concentration of BNP decreased in both groups.

At days 3 and 5 of the follow-up, the concentration of BNP in the group of patients receiving Corvitin was significantly lower than in the group of patients who got only traditional therapy ($p < 0.001$).

Conclusions. The concentration of BNP in patients with ACS depends on the location of the lesion (it is higher with anterior LV wall lesion) and correlates with the decrease of regional and local systolic LV function, increase of LVEDV and the degree of heart failure. After reperfusion therapy for ACS, mainly – after primary angioplasty, maximal BNP concentration is seen on day 3, with subsequent decreasing below the baseline level. The inclusion of antioxidant agent – Corvitin – in the scheme of therapy contributes to systematic progressive decrease of concentration of BNP in patients with ACS, as well as to the absence of peak activity at day 3.

Currently, the study of neurohormonal activity and the role of brain natriuretic peptide (BNP) in early diagnosis of heart failure and determination of prognosis in patients with ACS generates the worldwide interest. High level of BNP is associated with the extension of infarction area (5, 10). The concentration of BNP in the blood of such patients increases in direct proportion with the degree of LV dysfunction,

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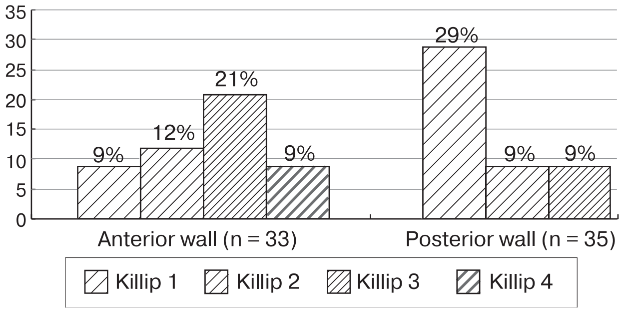

Figure 1. Prevalence of different classes of acute left ventricular failure (Killip score) depending on the location of the lesion ($\chi^2 < 0.05$).

along with the Killip class of heart failure (4, 7) and the level of pulmonary capillary pressure, and, in general, reflects the total score of individual cardiovascular risk (3, 4). High concentration of BNP is an independent predictor of repeated cardiovascular events and mortality in patients with ACS with ST elevation within the first 30 days (6, 11), as well as in 10 months after the onset of acute ischemia (9).

This study was aimed at the evaluation of the dynamics of BNP concentration in patients with acute coronary syndrome (ACS) with ST elevation depending on the lesion's location, the applied methods of therapy and the Killip class of heart failure.

Material and methods of study

The study comprised 68 patients with ACS with ST elevation on ECG, admitted to the department of emergency cardiology of the Republican Scientific Center of Emergency Medicine within 6 hours after the onset of angina attack. Mean age of patients was 57.62 ± 4.64 years, and 52 of them (76.5%) were males.

The verification of the diagnosis was based on clinical and electrocardiographic symptoms. The patients with myocardial reinfarctions and marked comorbidities requiring medical treatment were not included in the study. *ST* elevation in the anterior leads (AW) was noted in 33 (48.5%) patients, in posterior leads (PW) – in 35 (51%). All patients underwent reperfusion procedures. Systemic thrombolythic therapy with IV administration of Streptokinase (1.5 mln IE in 100 ml of 0,9% sodium chloride solution for 60 minutes) was applied in 30 patients (TLT group). Thirty-eight patients (PTCA group) underwent transluminal balloon angioplasty of the infarct-related artery. Baseline therapy in all cases included antiagregants, anticoagulant agent (under the control of aPPT), β-adrenoblockers, ACE inhibitors and statins. Additionally, 14 patients from the TLT group and 17 patients form the PTCA group received IV infusions of Corvitin (0.5 g in 50 ml of isotonic sodium chloride solution) immediately after hospitalization, in 2 and in 12 hours; then 0.5 g twice per day 12 hours apart for 2–3 days; then at days 4–5 – 0.25 g in 50 ml of isotonic solution once per day.

The concentration (pg/ml) of brain natriuretic peptide has been measured using immunoenzymometry technique (Cobas 232 Roche CARDIAC, Germany) in all patients at baseline, at days 3 and 5. The dynamics of BNP level was determined in relation to ECG-signs of ischemic injury, the reperfusion therapy applied and the use of Corvitin in the management strategy.

All data were entered in the summary tables. The following values have been calculated: for parametric indices – mean and SD, for non-parametric indices – frequency distribution. The significance of intergroup differences was estimated using Student's criterion for paired parametric indices and χ^2 criterion for the differentiation of frequency distribution of the characteristics.

Results of study

Clinical evaluation of the severity of hemodynamic lesions using Killip score revealed higher prevalence of classes 3 (21%) and 4 (9%) and lower prevalence of class 1 (9%) in patients with ACS with ST elevation in the anterior leads in comparison with the patients with posterior wall injury [class 3 – 9%, class 4 – 0%, class 1 – 29% (fig. 1), p for χ^2 frequency distribution <0.05]. During the follow-up an aneurysm of the LV wall developed in 5 patients (15%) with the anterior wall lesion, in patients with posterior lesion no LV aneurysms were revealed. Baseline BNP concentration in patients with anterior wall lesion was significantly higher than in patients with posterior wall lesion. Further increase of BNP concentration was noted in both groups of patients by the 3rd day of treatment; then, by the day 5, the concentration decreased; however relative dynamics was not significantly different between the groups. Thus, during the whole period of the follow-up the concentration of BNP in the group with anterior location of the lesion was higher than in group with posterior location ($p < 0.001$) (Table 1).

The distribution of patients depending on the heart failure class has demonstrated the increased concentration of BNP with a higher degree of hemodynamic disturbances (BNP in patients with Killip class I – 984.20 ± 123.79 pg/ml, Killip II – 1347.50 ± 112.15 pg/ml, Killip II I+ IV – 1432.67 ± 162.71 pg/ml), the difference between the groups with Killip I and II and Killip I and III+IV was significant ($p < 0.05$). During the follow-up the relative dynamics of BNP were similar in patients with different Killip score, except for the patients who has BNP concentration >3000 pg/ml, without decreasing tendency.

The concentration of BNP rose by the 3rd day of the follow-up irrespective of the method of reperfusion. By the day 5, the concentration of BNP decreased in both groups, and it has been noted that angioplasty has contributed to the significantly more pronounced decrease of this index (54.74%,vs. 32.71% in the group of TLT; $p < 0.01$), which led to reliably lower concentration of BNP in the end of the follow-up period in patients who underwent angioplasty ($p < 0.01$) (Table. 1).

The relation of dynamics of BNP concentration in patients with ACS to the inclusion of Corvitin into the therapy is of special interest. In the settings of traditional therapy the concentration of BNP increased significantly (by 52.78%) by the day 3 of the follow-up, with subsequent decrease by 32.29% from the baseline level. Meanwhile in patients who received additional Corvitin, the concentration of BNP did not peak by the day 3. On the contrary, it decreased progressively by 23.52% and 60.21%, respectively by the days 3 and 5 (the differences in the dynamics of BNP concentration during the whole period of the follow-up – $p < 0.001$). As a result, at the day 3, as well as at the day 5, the concentration of BNP in patients receiving Corvitin was significantly lower than in patients who received only traditional therapy ($p < 0.001$ for the days 3 and 5 of the follow-up).

As during the study we have revealed various regularities in the changes of values depending on the methods of treatment, we proceeded with conditional division of all patients into the following groups: AW/TLT/C+; AW/TLT/C–; AW/AP/C+; AW/AP/C–; PW/TLT/C+; PW/TLT/C–; PW/AP/C+; PW/AP/C– (fig. 2). While such distribution did not reveal significant intergroup differences (which was probably related to small number of patients in the groups), it allowed us to disclose the following regularities: the concentration of BNP in the groups with anterior lesion during the whole period of the follow-up was higher, than in the groups with posterior location of the process. The concentration of BNP in the groups of patients who received Corvitin decreased progressively during the whole period of the follow-up, while in the groups of traditional therapy peak concentration has been marked at day 3 with subsequent decrease below the baseline level. The changes (the increase, as well as the decrease of BNP concentration) were significantly more apparent in patients who underwent AP.

Discussion

We have found a high concentration of BNP in patients with ACS and ST segment elevation on ECG, at that patients with AW lesion had higher BNP concentration. There was a correlation between BNP concentration and Killip class of heart failure. These results comport with other authors' data on the role of ischemia and hemodynamic disturbances in the secretion of BNP by cardiomyocytes (8, 10, 12). The peak of BNP concentration at day 3, probably, is related to reperfusion injury and is pathogenetically caused by activation of peroxidation of lipids and damage of cardiocytes' membranes by free oxygen radicals (1). This phenomenon can explain higher peak concentration in patients after primary coronary angioplasty in comparison with the patients who received systemic TLT, as AP provides more pronounced reperfusion effect (96%, vs. 60% after TLT) (3). The use of antioxidant agent

Table 1. BNP concentration in patients with ACS depending on the location of lesion and the applied therapy

	Location		Reperfusion therapy		Corvitin	
	AW (n = 33)	PW (n = 35)	AP (n = 38)	TLT (n = 30)	C– (n = 37)	C+ (n = 31)
BNP	1817.45 ± 58.77	740.60 ± 50.78***	1251.58 ± 102.72	1277.90 ± 115.30	1259.11 ± 104.32	1268.06 ± 113.19
BNP 3	1833.06 ± 99.80	815.91 ± 69.65***	1353.95 ± 127.55	1253.27 ± 111.52	1636.81 ± 109.06	918.90 ± 100.15***
BNP 5	894.67 ± 82.48	378.60 ± 41.58***	497.55 ± 61.94	795.60 ± 88.95**	793.54 ± 81.57	432.71 ± 53.95***
BNP 3%	4.24 ± 6.36	30.97 ± 15.12	22.63 ± 13.08	12.14 ± 9.85	52.78 ± 12.19	–23.52 ± 5.76***
BNP 5%	–48.47 ± 5.36	–41.77 ± 6.36	–54.74 ± 5.53	–32.71 ± 5.68**	–32.29 ± 5.20	–60.21 ± 5.68***

AW – anterior wall, PW – posterior wall, AP – angioplasty, TLT – thrombolytic therapy, C– – no Corvitin added, C+ – Corvitin added to standard therapy.
Significance of intergroup differences: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$

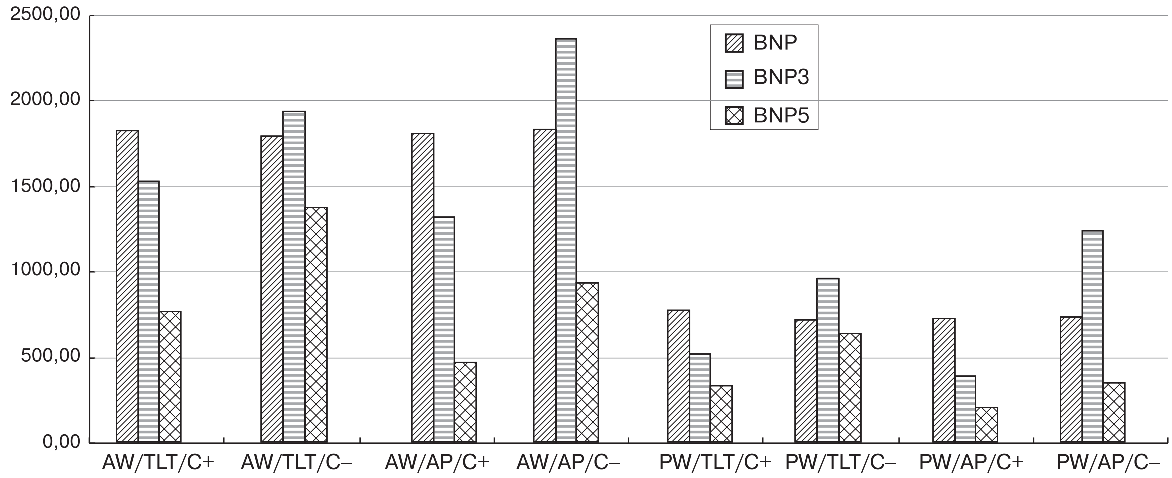

Figure 2. Absolute dynamics of BNP concentration in patients with ACS depending on the location of lesion and method of treatment (pg/ml).

Corvitin, blocking 5-lipoxygenase pathway of arachidonic acid metabolism, permits to reduce reperfusion injury. This is manifested clinically by a decreased frequency of arrhythmic events during reperfusion (2), and in our study resulted in the absence of BNP peak concentration already by the 3rd day. In whole, after successful reperfusion, already by the day 5 of therapy, BNP concentration significantly decreased. This effect was more marked in patients after AP, due to more effective reperfusion, and was confirmed by more evident improvement of hemodynamic status, and the use of Corvitin contributed to the enhancement of this effect.

Conclusions

1. BNP concentration in patients with ACS depends on the location of the lesion and correlates with the degree of heart failure.

2. In the settings of reperfusion therapy for ACS, mainly – after primary AP, maximal increase of BNP concentration is seen on day 3, with subsequent decrease below the baseline level.

3. The inclusion of antioxidant agent Corvitin in the scheme of treatment contributes to regular progressive decrease of BNP concentration in patients with ACS and disappearance of the peak at day 3.

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Inflammation Factors Influencing the Prognosis in Patients with *ST* Segment Elevation Myocardial Infarction After Percutaneous Coronary Interventions

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It is known that coronary stent implantation provokes local and systemic inflammatory responses, and restenosis is one of the manifestations of inflammatory reaction.
We examined 225 STEMI patients who underwent successful primary PCI and had their blood concentrations of subclinical inflammation markers determined on the 10th–14th day from the disease onset. In one year, prognosis was assessed in 180 (80.0%) patients. Stepwise logistic regression analysis has showed that the odds ratio for adverse one-year prognosis was significant in patients with a high Killip class (II–IV) of acute heart failure on admission and with high blood concentrations of IL-12 (more than 110.01 pg/mL). The authors concluded that inflammation markers are the factors determining a high risk of repeated coronary accidents in MI patients who underwent PCI during the acute period of the disease.
Key words: *myocardial infarction, percutaneous coronary intervention, non-specific subclinical inflammation.*

List of abbreviations:

CAD – coronary artery disease
IL – interleukin
MI – myocardial infarction
CA – coronary artery
NP – neopterin
ACS – acute coronary syndrome
CVA – cerebrovascular accident
TLT – thrombolytic therapy
CRP – C-reactive protein
CHF – chronic heart failure
PCI – percutaneous coronary intervention
TNF-α – tumor necrosis factor-a
sEsel – sE-selectin
sPsel – sP-selectin
sCD40L – proinflammatory CD40 ligand
STEMI – ST elevation myocardial infarction

Purpose of study. To reveal and assess factors that influence the adverse long-term prognosis in STEMI patients after successful PCI.

Background. Despite the significant achievements in CAD prevention and treatment, the problem of restenosis after endovascular interventions comes to the forefront. It is known that coronary stent implantation provokes local and systemic inflammatory response, and restenosis is one of the manifestations of inflammatory reaction.

Material and methods. 225 STEMI patients, who were admitted to the hospital within one calendar year and underwent successful primary PCI, have been included in the study. The concentration of subclinical inflammation markers in the blood was determined on the 10th–14th day from the disease onset. In one year, prognosis was assessed in 180 (80.0%) patients. In order to detect independent predictors of unfavorable outcomes, the direct stepwise algorithm of linear logistic regression has been chosen.

Results. According to the results of stepwise logistic regression analysis, the odds ratio for adverse one-year prognosis was significant in patients with a high Killip class (II–IV) of acute heart failure on admission and with high blood concentrations of IL-12 (more than 110.01 pg/mL); the logistic regression model included factors related, based on results of univariate analysis, to the risk of adverse prognosis (sex, MI history, angina, CHF (chronic heart failure), posterior MI by electrocardiography data, high blood concentrations of TNF-α, IL-12, CRP and neopterin on the 10th–14th day from the MI

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onset). Quality of the model has been verified using C-statistics (0.81, 95% CI 0.71–0.91, $p < 0.001$).

Conclusions. Inflammation markers are the factors determining a high risk of repeated coronary accidents in MI patients who underwent PCI during the acute period of the disease. Higher activity of intravascular non-specific inflammation is one of the responsible mechanisms.

A tendency to prefer endovascular methods of treatment even for the severe forms of coronary artery disease (CAD) over the coronary artery bypass grafting has been observed for the last 10 years (1, 2). However, despite the significant achievements in CAD prevention and treatment, the problem of restenosis after endovascular interventions comes to the forefront (3). Recent studies have demonstrated that coronary stent implantation provokes local and systemic inflammatory syndrome (4, 5), and restenosis is one of the manifestations of inflammatory reaction.

From the viewpoint of pathophysiology, atherosclerosis is considered to be a form of chronic inflammation in the vessel wall with activation of the immune system cells at different stages of chronic inflammation. A lot of evidence has been obtained confirming that inflammation in the vessel wall intima plays a leading role at all stages of atherogenesis, from formation of atherosclerotic plaque until its destruction (6, 7). However, there are still disputes about what markers and on what disease stages indicate activity/stabilization of atherosclerotic process. Results of some prospective population studies have demonstrated a relationship between increased blood levels of an early marker of acute inflammation [C-reactive protein (CRP)] and the risk of cardiovascular morbidity (8–11). It has also been demonstrated that tumor necrosis factor-α (TNF-α), interleukins (IL-1b, IL-6, IL-18) are the markers of inflammatory process' activity and independent predictors of acute coronary syndrome (ACS), myocardial infarction (MI) and coronary death in patients with atherosclerosis of the coronary arteries (CA) (12, 13).

As stents are usually deployed in the affected CA segments with typical marked inflammation (14), stenting can potentiate the inflammatory process, which, in turn, determines the risk of subsequent restenosis.

The objective of this study was to reveal and assess factors which influence the adverse long-term prognosis in patients with *ST*-elevation MI (STEMI) who underwent successful percutaneous coronary intervention (PCI).

Material and methods

Study protocol has been approved by the Local Ethics Committee. Prior to the study all patients signed an informed consent for participation in the study.

Inclusion criteria: ST-elevation MI (STEMI) which developed within 24 hours prior to admission; successful percutaneous coronary intervention in a symptom-related artery. Exclusion criteria: myocardial infarction as a complication of PCI or coronary artery bypass grafting, terminal renal failure, documented cancer, exacerbation of chronic visceral diseases, as well as other diseases which significantly shorten the life span and are themselves capable of changing the inflammation markers.

During in-hospital period, patients were treated in conformity with SCRF (the Society of Cardiology of the Russian Federation) guidelines (2007) on diagnostics and treatment of patients with acute STEMI. When possible, the method of myocardial reperfusion was chosen for all patients as soon as possible; these methods included balloon angioplasty, stenting of a symptom-related coronary artery or intracoronary thrombolytic therapy (TLT).

The study included 225 STEMI patients (56 women and 169 men), who were admitted to the hospital and underwent successful primary PCI within one calendar year. Clinical and historical characteristics of patients are presented in Table 1.

Concentrations of the following subclinical inflammation markers in the blood were determined on the 10^{th}–14^{th} day after the disease onset by enzyme immunoassay: interleukin-12 (IL, pg/mL), IL-10 (pg/mL), IL-8 (pg/mL), IL-6 (pg/mL), tumor necrosis factor-a (TNF-α, pg/mL), fibrinogen (g/L), C-reactive protein (CRP, mg/L), neopterin (NP, nmol/L), sE-selectin (sEsel, ng/mL), sP-selectin (sPsel, ng/mL) and proinflammatory CD40 ligand (sCD40L, ng/mL).

Mean values of analyzed inflammation markers (Table 2) in STEMI patients were significantly higher than in patients of comparable age with stable CAD assigned to the control group (16 patients with I–II functional class of angina without the history of MI).

Follow-up period lasted for 1 year. On the base of one-year follow-up results, the following endpoints were assessed: repeated non-fatal MI, cerebrovascular accidents (CVA), cardiac

Table 1. Clinical and historical data of patients

Characteristics	Value
Men, n (%)	169 (75.11)
Women, n (%)	56 (24.89)
Age, years (95% CI)	57.52 (56.31–58.72)
Smoking, n (%)	168 (54.67)
Arterial hypertension, n (%)	200 (88.89)
Diabetes mellitus, n (%)	35 (15.56)
History of myocardial infarction, n (%)	37 (16.44)
History of angina, n (%)	93 (41.33)
History of acute cerebrovascular accident, n (%)	12 (5.33)
History of chronic heart failure, n (%)	10 (4.44)
Multifocal atherosclerosis, n (%)	49 (21.78)
Obesity (BMI > 25), n (%)	154 (68.44)
Anterior MI, n (%)	102 (45.33)
Posterior MI, n (%)	123 (54.67)
Left ventricular ejection fraction, % (95% Ci)	51.0 (50.11–52.49)
Left ventricular ejection fraction (<46%), n (%)	46 (20.44)
Acute heart failure, Killip class at admission (II-IV), n (%)	32 (14.22)
Mean TIMI score (severity of MI)	2.0 (2.59–3.09)
In-hospital recurrence of MI, n (%)	9 (4.0)
Reperfusion, n (%):	
– bare metal stent	192 (85.33)
– drug-eluting stent	8 (3.56)
Balloon angioplasty	11 (4.89)
Intracoronary TLT	14 (6.22)
In-hospital drug therapy, n (%):	
– Aspirin	214 (95.11)
– Clopidogrel	207 (92.0)
– β-blockers	219 (97.33)
– ACE inhibitors	196 (87.11)
– Diuretics	58 (25.78)
– Statins	45 (20.0)
– CA antagonists	170 (75.56)

Table 2. Comparative results of blood serum analysis in patients with STEMI and stable CAD (mean with 95% CI)

Indices	STEMI	Stable CAD	p
TNF-α, pg/ml	10.21 (9.30–11.13)	2.42 (2.56–7.41)	0.0001
IL-12, pg/ml	94.32 (82.72–105.92)	54.73 (47.54–61.92)	0.003
IL-10, pg/ml	2.15 (1.83–2.47)	0.33 (0.26–0.40)	0.0001
IL-8, pg/ml	4.48 (3.46–5.49)	2.14 (1.98–2.39)	0.0001
IL-6, pg/ml	4.88 (3.15–6.61)	0.74 (0.27–1.22)	0.0001
CRP, mg/l	13.45 (12.08–14.81)	2.73 (0.49–5.95)	0.0001
Neopterin, nmol/l	13.25 (9.47–30.62)	6.84 (4.40–9.94)	0.004
sE-selectin, ng/ml	72.30 (48.50–150.05)	29.70 (20.02–44.75)	0.01
sCD40L, ng/ml	6.11 (3.16–14.38)	3.69 (2.28–10.71)	0.03
Fibrinogen, g/l	5.30 (2.90–7.02)	3.14 (2.70–4.25)	0.02

death, repeated hospitalizations for unstable angina and cardiac decompensation.

Statistical processing of the study results was performed using SPSS statistical program (version 19.0, USA). Values are provided as percentage ratios for relative parameters and as arithmetic means and 95% confidence intervals (CI) for quantitative parameters. Two independent groups were compared by the quantitative parameter using Mann-Whitney U-test.

In order to detect independent predictors of unfavorable outcomes, the direct stepwise algorithm of linear logistic regression has been used. χ^2 and the area under ROC-curve (C-statistics), which determine the diagnostic value of the studied method, were further calculated. The value of this parameter exceeding 0.70 is diagnostically significant. Differences between compared groups were considered significant when the p-value was less than 0.05 (two-sided test of significance).

Table 3. Factors associated with unfavorable prognosis

Factor	Odds ratio	95% CI	p
Women vs. men	4.68	2.23–9.81	<0.001
Age >70 years vs. age <79 years	2.01	0.81–4.97	0.12
History of myocardial infarction	1.97	0.94–4.15	0.06
History of angina	2.80	1.50–5.24	<0.001
History of chronic heart failure	5.85	1.16–29.35	0.01
History of acute cerebrovascular accident	0.64	0.16–2,55	0.52
Multifocal atherosclerosis	2.13	1.05–4,29	0.03
Smoking vs. non-smoking	0.79	0.43–1.45	0.45
Obesity	1.0	0.94–1.06	0.83
Diabetes mellitus	1.11	0.46–2.67	0.81
History of arterial hypertension	0.97	0.36–2.58	0.95
Killip II–IV vs. Killip I	2.88	1.21–6.81	0.01
LVEF <46%	1.64	0.80–3.33	1.16
Posterior MI vs. anterior MI	0.55	0.30–1.02	0.05
In-hospital recurrence of MI	4.05	0.75–21.74	0.08
TNF-α concentration > 14.12 pg/ml	3.83	1.37–10.64	0.009
IL-12 concentration >110.01 pg/ml	8.57	2.56–28.66	<0.001
IL-10 concentration >3.03 pg/ml	1.79	0.61–5.24	0.27
IL-8 concentration >17.15 pg/ml	6.26	0.59–65.71	0.12
IL-6 concentration >8.05 pg/ml	2.66	1.0–7.05	0.04
CRP concentration >14.21 mg/l	1.04	0.99–1.09	0.04
sEsel concentration >60.14 ng/ml	1.83	0.81–4.10	0.13
sCD40L concentration >5.05 ng/ml	1.78	0.79–4.0	0.15
Neopterin concentration >8.34 nmol/l	2.55	1.08–6.02	0.02
Fibrinogen concentration >4.02 g/l	0.88	0.67–1.14	0.31

Table 4. Multifactor correlates of unfavorable prognosis

Index	Odds ratio	95% CI	p
Killip class (II–IV) of acute heart failure vs. Killip class I	7.83	2.27–26.95	<0.001
IL-12 concentration > 110.01 pg/ml	3.69	0.68–19.81	0.03

Results

In one year, prognosis was assessed in 180 (80.0%) patients; 45 (20.0%) patients were not available for contacts. The following end-points have been revealed in 71 (31.56%) patients: death – 22 (9.77%), hospitalization for reinfarction – 21 (9.33%), hospitalization for unstable angina – 21 (9.33%), hospitalization for CVA – 2 (0.88%), hospitalization for decompensation of chronic heart failure (CHF) – 5 (2.22%).

Univariate analysis was conducted in order to detect factors associated with the adverse one-year prognosis (Table 3). It has been revealed that women, as well as patients with post-infarction cardiosclerosis (PICS), a history of angina, CHF, multifocal atherosclerosis, recurrent MI during hospitalization period, posterior MI, II–IV Killip class acute heart failure and higher blood concentrations of inflammation markers (such as TNF-α, IL-12, CRP and NP) were more likely to have an adverse one-year prognosis.

In order to assess factors which independently influence the possibility of the adverse prognosis, we have included into the stepwise logistic regression analysis the factors demonstrating a relationship with the risk of adverse prognosis according to the results of univariate analysis. These factors were: sex, a history of MI, angina, CHF, high Killip class of acute heart failure, posterior MI according to ECG data, high blood concentrations of inflammation markers (TNF-α, IL-12, CRP and NP) on the 10^{th}–14^{th} day after MI onset. Prognostically unfavorable level of inflammation markers has been determined at the best sensitivity/specificity ratio.

The odds ratio for adverse one-year prognosis was significant in patients with a high Killip class of acute hear failure on admission and with high blood concentrations of IL-12 (Table 4).

Quality of the model has been verified using C-statistics (0.81, 95% CI 0.71–0.91, $p < 0.001$).

Discussion

When discussing these results, it is worth noting that recent data suggest the association of increased blood content of some non-specific inflammation markers with an increased risk of CAD development, and, in case of already existing disease – with adverse prognosis (15). However, there is no unequivocal opinion regarding the prognostic value even of such a parameter as CRP concentration. Some trials have shown prognostic value of CRP only in healthy subjects, as well as in patients with minimal (initial) manifestations of CAD (16, 17). According to other authors, the level of CRP determined in ACS patients at discharge from the hospital had higher prognostic value than the same parameter at admission. In authors' opinion, CRP at discharge is apparently an important marker of slow stabilization of atherosclerotic plaque. It has been shown that high levels of CRP (>10 mg/L) are associated with lower survival after the primary or rescue PCI in ACS patients (18). Even the lower baseline CRP (2.37 mg/L) turned out to be a predictor of an adverse 30-day prognosis in patients who underwent primary PCI within the first 6 hours after the acute MI onset (19). Recent studies have revealed that stent deployment is accompanied by an increase of CRP level. Increased CRP level is a highly sensitive marker of systemic inflammation indicating an increased risk of plaque rupture and adverse coronary events (4, 5). Bhatt et al. have showed an association between stenting results, CRP, mortality and, to a lesser extent, MI (20). Correlation between a high CRP level and incidence of adverse coronary events in patients after stenting was detected in another study (5). Our results confirm the prognostic value of high plasma CRP in the course of post-infarction period after endovascular intervention.

In the present study, of all the interleukins studied, IL-12 played an important role as a predictor of adverse cardiovascular events in STEMI patients who underwent PCI. There is limited evidence for IL-12 as an inflammation marker of atherosclerosis, with most of the studies being experimental. It has been proved that IL-12 in combination with IL-18 are powerful inductors of synthesis of proinflammatory cytokine interferon-gamma (IFN-γ) (21), which accelerates progressing of atherosclerosis (22). Immunohystochemistry studies show an increased content of IL-12 in human atherosclerotic plaques compared with the normal arteries (23). Our earlier study proved a high significance of IL-12 in predicting vascular accidents in STEMI patients during 12 months of follow-up (24). For patients examined within the scope of this study, this marker is important in predicting the course of post-infarction period after PCI. Thus, IL-12 may be an independent marker of atherosclerosis progression.

According to available data, an increased TNF-α level is associated with repeated coronary accidents in CAD patients (25). The CARE study has shown that Increased expression of TNF-α in 9 months after MI predicts high risk of coronary morbidity in patients during 5-year follow-up (26). Novarro-Lopez et al. (27) have shown that plasma concentrations of TNF-α and IL-6 significantly increase after PCI and remain high for 6 months. Although this variable was excluded from the prognostic model during the stepwise regression analysis in our study, the univariate analysis showed that high TNF-α concentrations unfavorably influence the long-term prognosis in MI patients after endovascular interventions.

The processes being reflected by increased blood sCD40L are subject of an active discussion. Platelets were proved to be the main source of this molecule (95%). However, sCD40L is expressed by smooth muscle endothelial cells, fibroblasts, B-lymphocytes, i.e. cells playing an important role in atherogenesis. According to Bavendiek et al., a level of this marker in patients with acute MI depends on platelet activity rather than reflects the proinflammatory status; meanwhile, in patients with chronic CAD (stable angina), and, to a greater extent, in healthy subjects, sCD40L level correlates with activity of inflammatory process, in particular with plasma concentrations of IL-6 (28).

Our results failed to show the role of this marker in predicting unfavorable outcomes in MI patients after PCI. However, a small prospective study has shown that high sCD40L level may predict restenosis after coronary angioplasty (29). The authors of the study demonstrated an important role of CD40L both in the intimal hyperplasia and in constrictor arterial remodeling; these underlie the formation of restenosis after angioplasty and stenting of the coronary arteries. It has been established that CD40L can stimulate expression of intercellular adhesion molecules and increase the release of monocyte chemoattractant protein from endothelial cells. This is an important signal for accumulation of the inflammatory cells after the vessel damage, which inhibits endothelial migration essential for re-endothelization of the damaged vessel. However, not all the investigators share the above opinion on important role played by sCD40L in predicting the course of acute and chronic CAD (28, 30).

One more biomarker, neopterin, presented in this study, may be used for identification of a group at high risk of new vascular accidents within 1 year among MI patients after invasive reperfusion in the acute period of the disease. Increased serum NP concentrations were detected in atherosclerotic lesions of the coronary arteries (31), especially in ACS (32). Its level correlates with atherosclerosis extension, degree of arterial stenosis, concentrations of homocystein, fibrinogen and uric acid. Thus, Zourdidakis a. Avanzas (33) have shown that the risk of accelerated CAD development increases 5-fold at the NP level >7.5 nmol/L. NP is significantly higher in ACS patients prior to treatment as compared with chronic CAD patients as well as with healthy subjects (34).

NP and CRP participate in body defense responses to myocardial damage in ACS patients, and their levels are associated with the development of complications in this category of patients. Increased NP and CRP serum activity in ACS patients is an independent predictor of morbidity (35). The present study has shown that high activity of both NP and CRP plays an important role in the development of repeated cardiovascular events within one year after acute MI.

Thus, the results of our study demonstrate that inflammation markers are the factors determining a high risk of repeated coronary accidents in MI patients who underwent invasive reperfusion during the acute period of the disease. Higher activity of intravascular nonspecific inflammation is one of the responsible mechanisms.

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Atherosclerosis in Ancient Egyptian Mummies: The Horus Study

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Objective: *To determine whether ancient Egyptians had atherosclerosis.*
Methods: *We performed whole body, multislice CT scanning on 52 ancient Egyptian mummies from a variety of eras, specifically looking for cardiovascular structures and arterial calcifications. Images were interpreted by a consensus of 7 imaging physicians and historical data of the individual mummies were collected from museum and other records. Age at the time of death was determined from CT evaluation of the bones and joints.*
Results: *Of the 52 mummies, 44 had identifiable cardiovascular (CV) structures and 20 of these had either definite atherosclerosis (defined as calcification within the wall of an identifiable artery, n = 12) or probable atherosclerosis (defined as calcifications along the expected course of an artery, n = 8). Calcifications were found in the aorta as well as the coronary, carotid, iliac, femoral and peripheral arteries. The 20 mummies with definite or probable atherosclerosis were older at time of death (mean 45.1 ± 9.2 y) than the mummies with CV tissue but no atherosclerosis (34.5 ± 11.8 y), (p < 0.002). Two mummies had evidence of severe arterial atherosclerosis with calcifications in virtually every arterial bed. Definite coronary atherosclerosis was present in two mummies, including a princess who lived between 1550–1580 BCE. This finding represents the earliest documentation of coronary atherosclerosis in a human. Definite or probable atherosclerosis was present in mummies who lived during virtually every era of ancient Egypt represented in this study, a time span of 1800 years. Intact hearts were also found in almost all eras and were present in 16 mummies. Two mummies had heavy mitral annular calcifications.*
Conclusions: *Atherosclerosis was commonplace in mummified ancient Egyptians.*
Key words: *Atherosclerosis, arterial calcifications, coronary artery disease, mummies, coronary calcification.*

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Introduction

Cardiovascular diseases are the world's largest killers, claiming more than 17 million lives in 2010. Our 21st century epidemic of cardiovascular disease continues to spread from wealthy, developed areas of the world to poorer, developing countries as their economic conditions improve (1). Death from cardiovascular diseases, primarily due to an increase in the prevalence of atherosclerosis, is projected to affect more than 23 million people per year by 2030 (2). As the diet, lifestyle, and environmental risk factors for the development of atherosclerosis spread from "modern," wealthy nations to the rest of the world, cardiovascular disease follows. It is tempting to conclude that atherosclerotic cardiovascular disease is exclusively a disease of modern society and did not affect our ancient ancestors. We herein provide evidence to the contrary.

Seminal work performed in Egypt by Sir Marc Armond Ruffer, 100 years ago, identified histologic evidence of atherosclerosis in the aorta and other large arteries on autopsies performed on multiple 3000 year old Egyptian mummies (3). In 1852, Johann Nepomuk Czermak found calcified aortic atherosclerosis in a single elderly Egyptian mummy (4). In 1909, S.G. Shattock found atheromatous deposits in the aorta of the Pharaoh Menephtah, believed in some traditions to be the Pharaoh of the Exodus (5). In 1931, Allen Long examined the heart of Lady Teye, a mummy in the collection of the Metropolitan Museum in New York, who lived during the 21st dynasty (1070–945 BCE), finding histologic evidence of coronary atherosclerosis, with intimal thickening and calcification in the epicardial coronary arteries, as well as areas of fibrosis in the myocardium consistent with prior myocardial infarction (6) Autopsies of Egyptian mummies were commonly performed a century ago, but have rarely been performed in recent years given the destructive nature of the process.

We know that the genesis of our ongoing epidemic of atherosclerotic cardiovascular disease is multifactorial and that atherosclerosis arises through a complex interaction of genetic and environmental influences (7–9). As part of a comprehensive, multidisciplinary approach to this contemporary problem, the study of ancient Egyptian mummies may provide unique insights into the ancestral origins of atherosclerosis.

We (11, 12) and others (13–18) have begun to use modern x-ray computed tomography (CT) to examine these ancient humans in a nondestructive fashion. We report here our findings using CT to systematically search for evidence of arterial calcification as a marker for cardiovascular disease in 52 ancient Egyptian mummies.

Methods

Study Population. We performed whole body six-slice CT using a Siemens Emotion 6 (Florsheim, Germany), on 45 mummies housed in, or in the case of two of these mummies, brought to, the Egyptian National Museum of Antiquities in Cairo. Mummies were selected for scanning from multiple historical eras based on their good state of preservation and the likelihood that intact vascular tissue would be present. An attempt was made to scan both males and females of varying ages, but the mummies studied were not randomly selected. Forty-two mummies underwent CT scanning specifically for this study in February, 2009 and in May, 2010. Three other mummies housed in the Egyptian National Museum of Antiquities underwent CT scanning on this machine. They were included in this study because cardiovascular tissue was known to be present in two and one was the subject of a postgraduate thesis of one of the authors (IB).

Demographic information was obtained by an extensive search of museum and other resources by a team of experienced Egyptologists and experts in mummy restoration (IB, GAM, AHN). Gender was determined by biological anthropologic assessment of the genital/reproductive organs and morphology of the pelvis, femur and skull. Age was estimated by a biologic anthropologist (MATS) by assessment of auricular surface metamorphosis of the pelvis, the morphologic changes of the pubic symphysis, scores of the cranial suture closures and architectural changes in the clavicle, humerus and femur (19, 20).

The study design was approved and permission to image the mummies was granted by formal votes of the Supreme Council of Antiquities, Egypt. Clinical informed consent was obtained from the contemporary human patients whose CT images were used for comparison.

CT Imaging. Using the Siemens Emotion 6 scanner, imaging was performed of the thorax, abdomen, pelvis and extremities at 130 kv with 1.25 mm collimation and 50% overlap. The head and neck were imaged at 130 kv with 0.6 mm collimation and 50% overlap. In addition, CT scans were performed using a similar technique with GE LightSpeed scanners (Pewaukee, WI) on five Egyptian mummies at the Bowers

Museum in Santa Ana, CA and another Egyptian mummy currently housed at the Nelson-Atkins Museum in Kansas City, MO. Five of these were imaged using a GE LightSpeed-Plus four-slice scanner in 2005 and one using a GE Light-Speed Ultra 8-slice scanner in 2002. The resultant group imaged thus totaled 52.

Image interpretation. Images were interpreted by a consensus of seven experienced cardiovascular imaging physicians (AHA, MIM, JDS, MLS, GST, RCT, LSW) focusing on identification of cardiovascular tissue and the presence or absence of calcification in the vessel walls and heart. Image reformatting and measurements of the thickness and x-ray attenuation (Hounsfield units) of various structures were made using a Siemens multi-modality imaging workstation. The Apple platform OsiriX DICOM viewing software (version 3.81, Geneva, Switzerland) was also utilized to facilitate consensus image review. Vascular tissue and the heart were identified by their anatomic position in the body and relationship to contiguous structures enhanced by the use of 3D MPR and MIP reconstructions. The presence of calcification in the vessel wall was defined qualitatively by comparing multiple regions within visualized cardiac and vascular tissue to one another. Non-contrast CT images obtained in two contemporary patients with known vascular disease were included for comparison and illustration and to help identify anatomic landmarks.

As described previously (11), calcification in the vessel wall of a clearly identifiable artery was considered diagnostic of atherosclerosis. Calcification along the expected course of an artery was considered to be probable atherosclerosis.

Vascular regions were divided into the five distinct beds modified from the method of Allison et al. (21) the carotid; coronary; aortic; iliac; and femoral/popliteal/tibial (termed peripheral) vascular beds). The vascular bed findings of mummies 1–22 have been reported in brief previously (11).

In the current publication, the cardiovascular findings of these mummies, as well as the additional 30 mummies, are described in greater detail after comprehensive review of the 52 mummies.

Statistical analysis. Statistical analysis was performed using SPSS software (version 16 for Mac, Cary, North Carolina). A p value of <0.05 was considered significant. We investigated possible gender differences in age at death, and atherosclerosis status, using t and χ^2 tests, respectively. We also used individual binary logistic regressions to determine whether the odds of having atherosclerosis would increase with advancing age and be greater in later chronological eras. We used χ^2 to test the potential (22) that priests/priestesses would be more likely to have atherosclerosis than nonclergy. Lastly, among the subset of mummies who had atherosclerosis, we tested the hypothesis that older mummies would have a more severe form of the disease (as defined by greater number of vascular beds affected) using χ^2. For this analysis, we divided the sample into those younger versus older than 40 years, as this age threshold is consistent with an accepted risk factor for CAD and was roughly equivalent to the mean age of death in the present sample (mean, SD).

Results

Sample characteristics. The demographics and cardiovascular findings of the 52 ancient Egyptian mummies are found in Figs. 1, 10. They lived between 1981 BCE and 364 CE.

Mean estimated age at death was 38.1 ± 12.0 years (ranging from 10 to 60+ years. Gender could be determined for all except for the youngest two mummies who were prepubescent. The mean age at death did not differ by gender (40.0 ± 10.2 and 37.6 ± 12.4 for the 33 men and 17 women, respectively, p = 0.26). The identity or social position was determined for 25, and each of these was of high socioeconomic status. While the identities of the remaining 27 are unknown, the financial costs of mummification suggest that they too were of high socioeconomic status. The place of excavation is known for 43 mummies. Each of these was excavated either near the Nile River or at an oasis in Upper Egypt, an area that is now the southern part of modern Egypt.

CT images demonstrated identifiable aortic or peripheral vascular tissue in 43 mummies An intact heart or heart remnants could be identified in 31 mummies. One mummy had an intact heart without vessels present, yielding 44 mummies with cardiovascular (CV) tissue who could be evaluated for atherosclerosis (27M/16F/1U). The estimated mean age at death of these 44 mummies was 39.3 ± 11.8 (SD) years. The mean age at death did not differ by gender (40.9 ± 10.4 vs. 38.2 ± 12.5 y for men and women, respectively, p = 0.45).

Predictors of atherosclerosis. Definite or probable atherosclerosis was seen in 20 (45%) of the 44 mummies in whom cardiovascular tis-

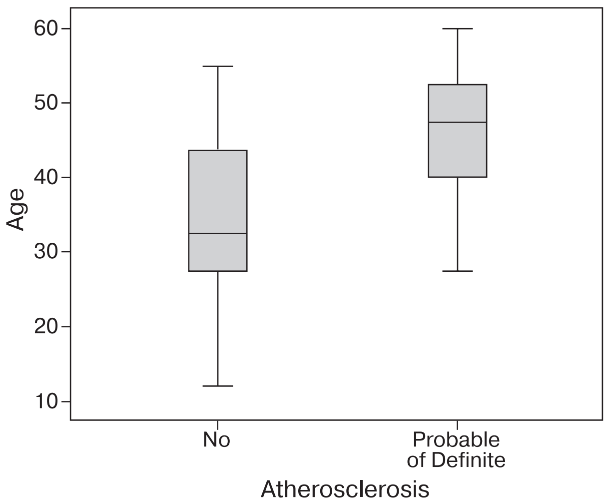

Fig. 1. Age at Death of Mummies With and Without Athersoclerosis. Median age at death (line) ± 25th percentile (shaded box) and range (brackets) of the mummies with vascular tissue but no atherosclerosis and mummies with probable or definite atherosclerosis. The mummies with atherosclerosis were significantly older ($p < 0.002$).

sue was present. Of these 20, 12 mummies had definite atherosclerosis and 8 had probable atherosclerosis.

The 20 mummies with definite or probable atherosclerosis were older (mean 45.1 ± 9.2 y) than the mummies with CV tissue but no atherosclerosis (34.5 ±11.8 y, $p < 0.002$) (Figure 1). With each year of advancing age, the probability of having atherosclerosis increased by 9.6% (OR = 1.096, p = 0.006).

The frequency of atherosclerosis did not differ between genders (p = 0.38). Of the 20 with atherosclerosis, 11 (55%) were male and 9 (45%) were female.

In those with definite or probable atherosclerosis, the average number of vascular beds involved was 2.2 ± 1.3. Those with atherosclerotic involvement of >3 beds were significantly more like to be >40 years in comparison to those with involvement of one or two beds (p = 0.02). In fact, all mummies with involvement of >3 beds were >40 years old.

Atherosclerosis was most common in the aorta in 14/44 (32%), followed by the peripheral vessels (13/44, 30%), carotids (8/43, 18%), iliacs (6/44, 14%) and coronaries (3/44, 7%). An example of a mummy with atherosclerosis in each vascular bed is a princess who lived during the Second Intermediate Period (1580–1550 BCE) and died in her early 40's (mummy 35, Figure 3, A). An image from a CT scan of the abdominal aorta from a modern patient is shown for comparison (Figure 3, B). Figure 4 shows severe atherosclerotic calcifications in the arteries of the upper leg in a male scribe who lived during the 18th Egyptian dynasty. Video 3 represents a female mummy recently excavated from Fayoum of an unknown historic period who died in her late 40's also with atherosclerosis of multiple vascular territories. Of note, we were unable to definitively determine the cause of death for any of the 52 mummies. Representative examples of mummies with carotid, aortic and peripheral vascular atherosclerosis are shown in Figures 2–6.

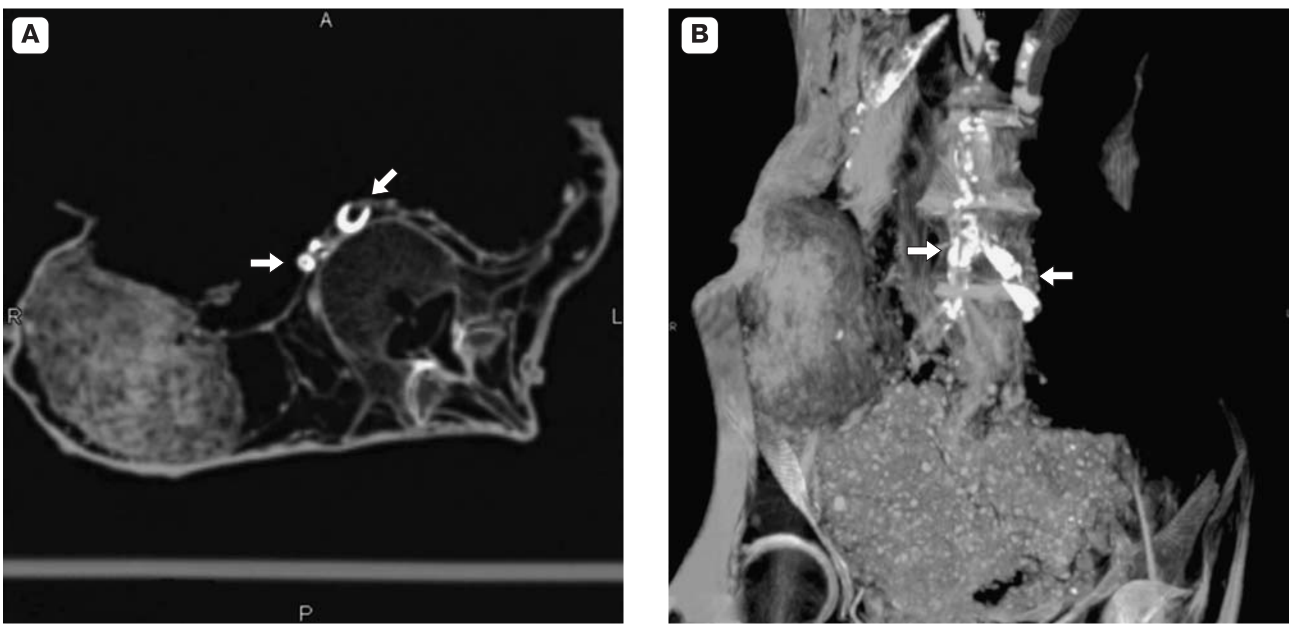

Fig. 2. Atherosclerosis in the Common Iliac Arteries. Computed tomography maximum intensity projection showing heavy calcification (arrows) in the common iliac arteries on (**A**) axial and (**B**) coronal projections in the mummy of a princess who lived during the Second Intermediate Period.

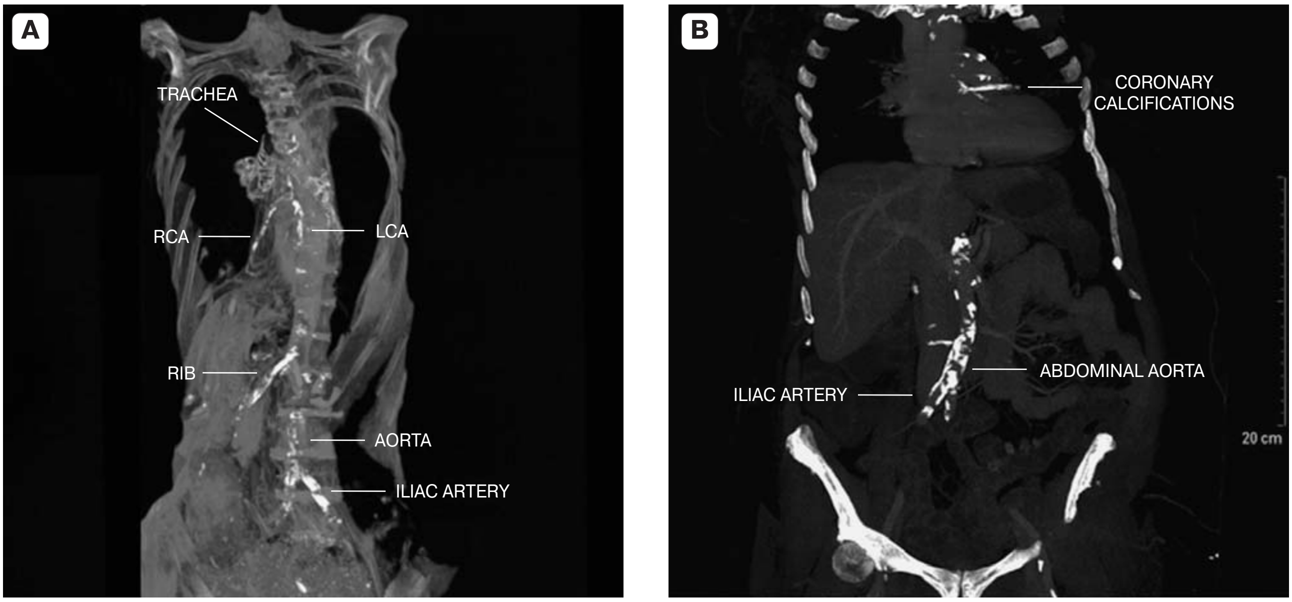

Fig. 3. Atherosclerosis in the Coronary, Aortic and Iliac Arteries (**A**) Reoriented coronal thick slab 3-dimensional multiplanar reconstruction window adjusted for vascular calcification, computed tomography image of the mummy of a princess who lived during the Second Intermediate Period shows calcifications in the coronary and iliac arteries, indicating the person had diffuse atherosclerosis. The posterior descending and posterolateral branches of the right coronary artery can be discerned distal to calcifications of the proximal and mid right coronary. (**B**) Computed tomography scan from a modern Egyptian patient showing similar calcifications in the coronary and iliac arteries. LCA – left coronary artery, RCA – right coronary artery.

Fig. 4. Atherosclerosis in the Superficial Femoral Arteries. Computed tomography maximum intensity projection of the upper legs showing extensive calcifications along the course of the superficial femoral arteries in the mummy of a man who lived during the 18th Dynasty.

Cardiac findings. Of the 31 with hearts present, an intact heart was present in 16 (31%), and heart remnants in 15 (29%) of the 52 mummies imaged. Hearts could be identified in mummies of all historic periods. Two of those with intact hearts had definite coronary atherosclerosis and one had probable coronary atherosclerosis. Figure 6 demonstrates carotid arteries. Examples of coronary artery calcifications are seen in Figures 7, 8. The mean age of those with coronary atherosclerosis was 48.3 ± 6.3 y. This is qualitatively greater than the mean age for the entire sample, although small sample size precluded us from performing inferential statistics.

Mitral annular calcification was present in 2 (6%) of the 31 mummies with intact or remnant hearts (Figure 9).

Socioeconomic status and atherosclerosis. Among the 25 for whom social position could be determined, 10 were priests or priestesses. Atherosclerosis was less common in priests than in non-priests (p = 0.012).

The historical era in which the individuals lived was known for 41 of the 44 mummies with cardiovascular tissue present. At least one mummy with atherosclerosis was found in all eras except the Middle Kingdom in which only one mummy was available for scanning who did not have vascular tissue (Figure 10). In a logistic regression, historical era was not predictive of atherosclerosis status (p = 0.23). Thus, atherosclerosis was not more prevalent in later historic periods than in earlier ones (OR = 0.74, p = 0.24).

Discussion

This study describes the incidence and distribution of arterial wall calcification in ancient Egyptian mummies. We used non-invasive x-ray computed tomography in a manner similar to its use in contemporary humans (23) to search for calcified atherosclerotic plaque in the remains of 52 ancient Egyptians.

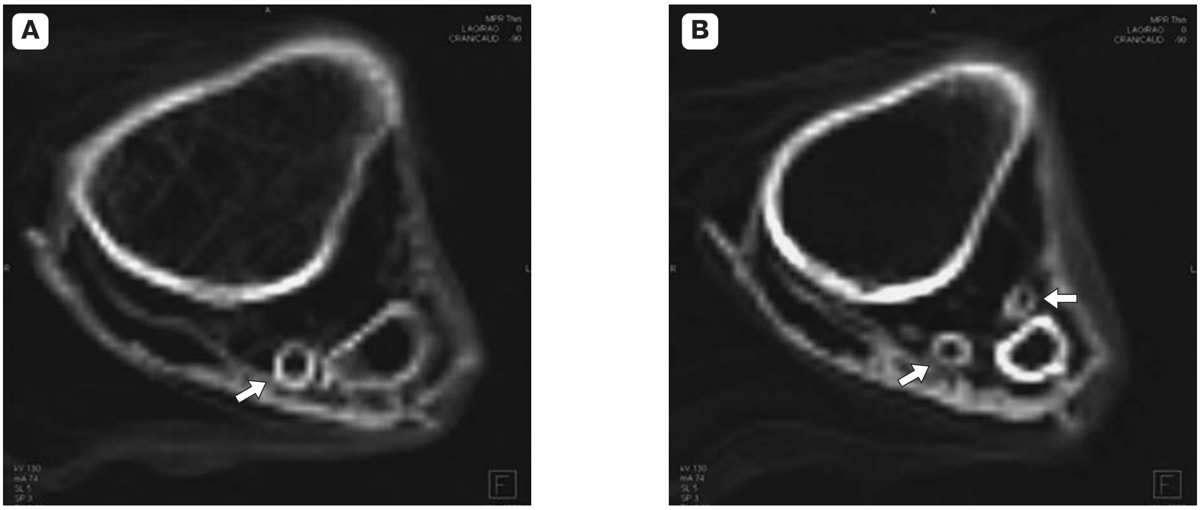

Fig. 5. Atherosclerosis in the Popliteal and Tibial Arteries.
Axial computed tomography images of the left leg distal to the knee showing (**A**) calcifications in the popliteal artery (arrow), and (**B**) in a slightly distal position, showing calcifications in the peroneal artery and the anterior tibial artery (arrows) in the mummy of a woman who lived during the Ptolemaic Period.

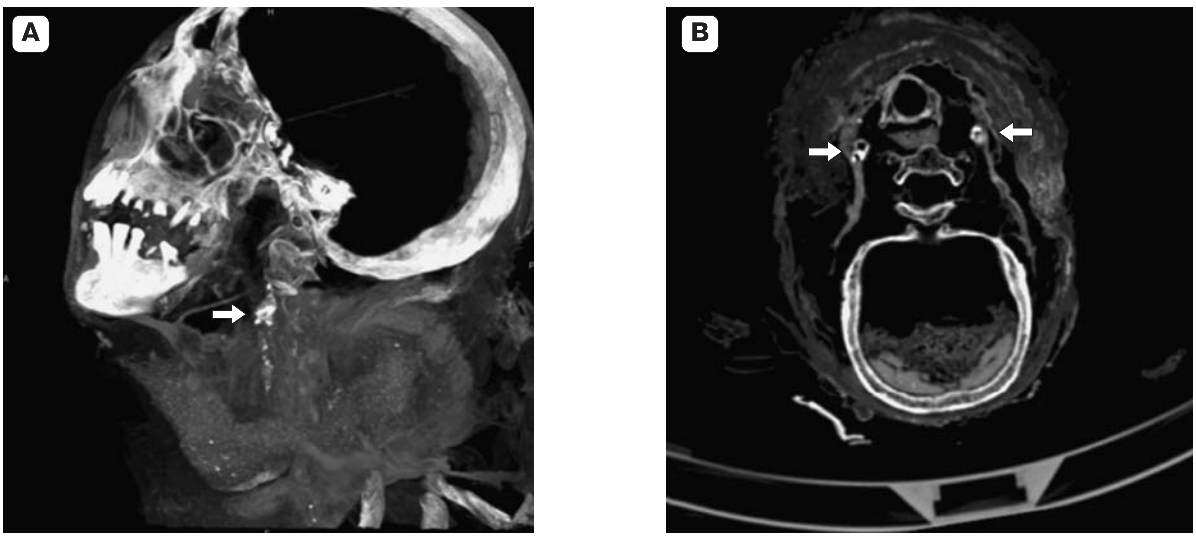

Fig. 6. Atherosclerosis in the Carotid Arteries.
Computed tomography maximum intensity projection sagittal view (**A**) showing heavy calcifications in the region of the left carotid artery at the carotid bulb (arrow), and (**B**) axial view showing heavy calcifications in the region of both the right and left carotid bulbs (arrows) in the mummy of a man who lived during the 18th Dynasty.

Of the 44 mummies in whom we could identify vascular tissue, 45% had vascular calcification. While the number of subjects we were able to examine is small in comparison to modern epidemiologic studies, we conclude that atherosclerosis was common in ancient Egypt. We saw evidence of calcification in the aorta (32%), peripheral vessels (30%), carotids (18%), iliacs (14%) and coronary arteries (7%). Due to varying and incomplete preservation of the mummies, not all of these vascular beds could be imaged in each mummy. However, it is apparent that vascular calcification affected arteries in many regions of the body in ancient Egyptians, just as it does in contemporary humans. Similar to modern demographics, arterial calcification in these mummies was more common as the age at death increased. The incidence of vascular calcification was similar in men and women.

Our finding of extensive coronary calcification in mummy 35, a princess living in the 17th dynasty (1580–1550 BCE) of the Second Intermediate Period represents, to our knowledge, the earliest documentation of a human with coronary artery disease ever recorded. As well, our finding of carotid disease in ancient

Egyptian mummies is also apparently novel, not having previously been reported in our review of histologic or imaging investigations to

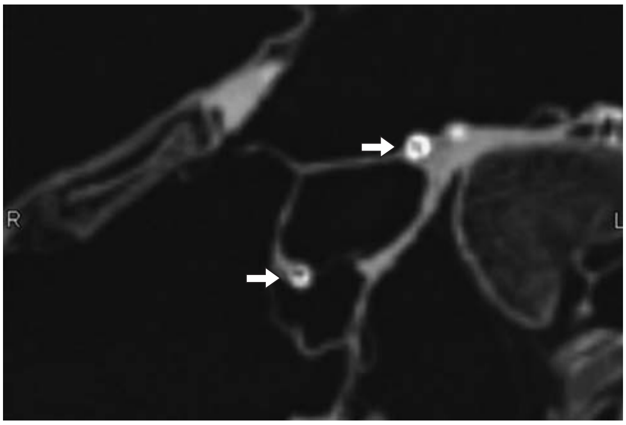

Fig. 7. Atherosclerosis in the Left and Right Coronary Arteries.
Maximum intensity projection computed tomography image showing calcifications in the left and right coronary arteries (arrows) in the mummy of a princess who lived during the Second Intermediate Period.

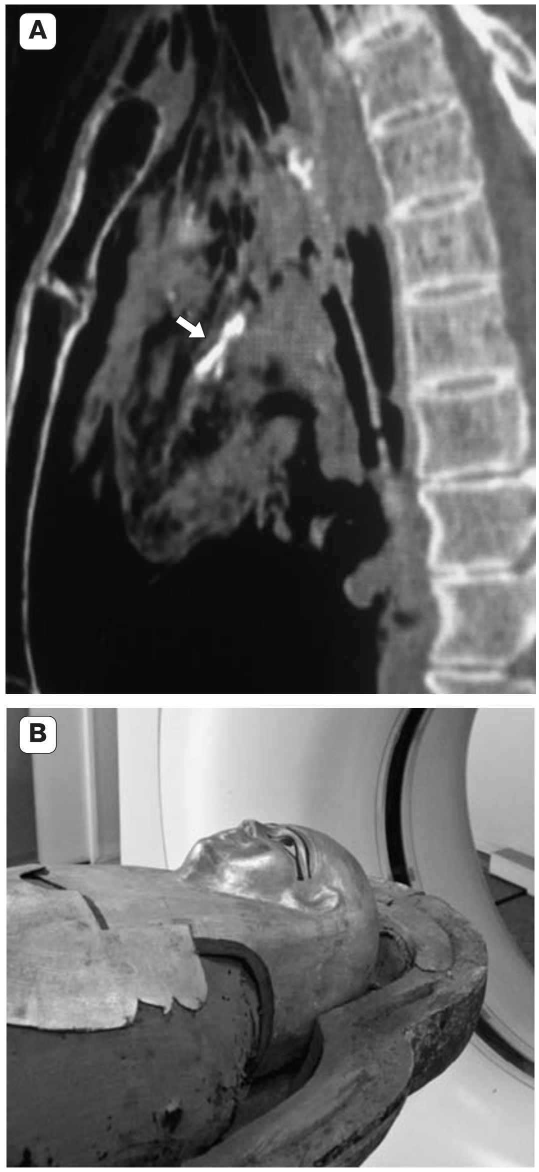

Fig. 8. Atherosclerosis in the Left Coronary Artery.
(**A**) Maximum intensity projection computed tomography image showing calcifications of the left coronary artery (arrow). (**B**) Anthropoid mask of the same mummy, a man who lived during the Ptolemaic Period.

date. Our relatively large sample size of mummies undergoing CT imaging extends the investigations of Ruffer (3), Long (6) and earlier investigators (4, 5) who documented atherosclerosis in single or small case studies of autopsied ancient Egyptian mummies. Our larger sample size, spanning two millennia, allowed us to explore the relative frequency of atherosclerosis rather than simply its existence.

We used CT findings of arterial calcification as a surrogate for the presence of atherosclerosis. Vascular calcification is generally regarded as a highly specific, late stage manifestation of atherosclerosis. The earliest pathologic manifestations of atherosclerosis include intimal thickening and "fatty streaks". Complex changes occur as the disease progresses, with structural remodeling of the vessel, cellular infiltrates, lipid accumulation, thrombosis, fibrosis and calcification involving the media as well as the adventitia. 24 Atherosclerosis is a systemic disease, usually affecting various arterial beds to a different degree and producing a myriad of clinical manifestations, ranging from myocardial infarction to stroke to limb gangrene in different individuals.

Many of the mummies we studied had arterial calcification in the pelvis and legs, areas that were relatively better preserved in these ancient humans than other vascular beds. It has been shown that an increasing degree of tibial artery calcification as measured by CT identifies increasing severity of peripheral arterial disease and identifies patients with a higher risk for amputation, independent of traditional risk factors (25). Calcification of the lower extremity arteries, more common in diabetics and patients with renal failure, is a strong predictor of an adverse outcome due to associated coronary heart disease (26–28). Arterial calcification was also seen in the aortas and carotid arteries of these mummies. Many studies have shown an association between aortic and coronary atherosclerosis and with aortic aneurysm, renal failure and stroke, all of which share common risk factors (29).

We identified calcification of the mitral annulus in two mummies, but were unable to visualize the aortic valve leaflets well enough to comment on the presence or absence of valvular calcification, both of which are highly associated with risk factors for atherosclerosis and systemic calcified atherosclerosis (30–31).

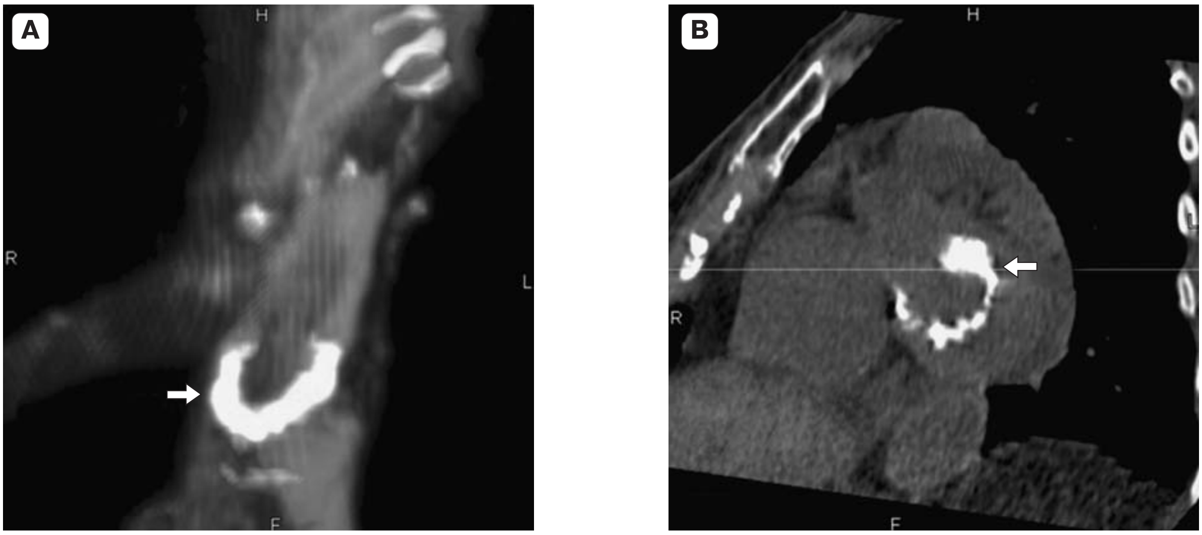

Fig. 9. Mitral Annular Calcifications.
(**A**) Heavy calcifications in the region of the mitral valve annulus (arrow) in the heart of a mummy of a woman who lived in ancient Egypt. (**B**) Similar appearance of heavy mitral annular calcification (arrow) in a noncontrast computed tomography scan performed in a modern patient.

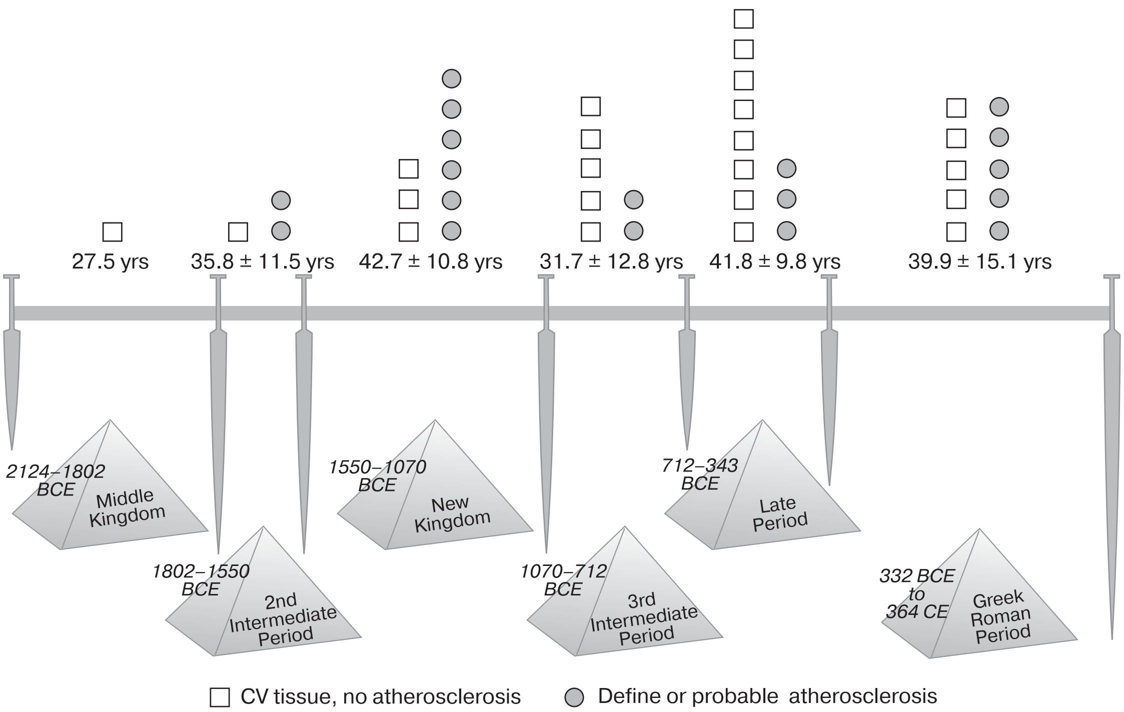

Fig. 10. Historical Time Distribution of Atherosclerosis in the Mummies.
The presence of identifiable cardiovascular tissue and atherosclerosis found in the mummies is shown in relation to the ancient Egyptian eras in which they lived. Atherosclerosis was found in virtually all time periods represented in the study. Open boxes indicate cardiovascular (CV) tissue, no atherosclerosis, solid circles represent definite or probable atherosclerosis.

We detected evidence of atherosclerosis in almost all of the dynastic eras of ancient Egypt, a time span of 1800 years. However, we do not have specific data regarding potential risk factors for atherosclerosis in our study subjects, such as diabetes, hypertension, sedentary life style and obesity. Tobacco was not available in ancient Egypt.

David (22) and others have speculated that the ancient Egyptian diet may have been atherogenic, as hieroglyphic inscriptions on Egyptian temple walls indicate that beef, wildfowl, bread, cake and beer were regularly consumed. Significant differences may have existed between the food consumed by royalty, priests and other elites and that eaten by common farmers and laborers (32). The elite were presumably more likely to be mummified after death. Caution must be exercised in attempting to generalize our results to the entire ancient Egyptian population. There is no doubt, however, that ancient Egyptians were not hunter-gatherers.

Profound changes began to occur in human lifestyle and diet about 10,000 years ago with the introduction of agriculture and animal husbandry. Egyptians had formed an organized agricultural society along the Nile that long predated the mummies that we studied. It is plausible that the composition of their diet was conducive to the development of atherosclerotic cardiovascular disease (32).

As civilization advanced, humans including the ancient Egyptians survived to older ages. Prior to the modern era, infectious disease, trauma and famine were the most common causes of death. Perhaps genetic adaptation favoring a beneficial inflammatory response to infection had a pleiotropic effect promoting the development of atherosclerosis (33, 34). The genes that mediate infection, inflammation and nutrition may also influence vascular disease, and specifically the calcification of atherosclerotic plaque. We now recognize that inflammation plays an important role in atherosclerosis (34–37) and advancing age (37–38).

We used a six slice scanner to acquire thin CT axial images of the mummies, reconstructing images in multiple two and three dimensional planes. Due to absence of vessel integrity, intravascular iodinated contrast could not be used, a major disadvantage when comparing mummy CT images to clinical images now routinely acquired in living patients. Recently developed CT canners with larger detector arrays for wider coverage per rotation and employing strategies for better temporal resolution offer little advantage for imaging of the motionless mummies. However, newer machines with improved spatial resolution and machines employing multiple x-ray energies might improve characterization of plaque. Dual energy CT might be useful in differentiating calcium hydroxyapatite associated with atherosclerotic plaque from natron, a salt used in the mummification process.

We have no independent pathologic verification that areas of arterial calcification which we identified by expert consensus interpretation of these non-contrast CT images actually represent atherosclerotic plaque. Our interpretations are based on our knowledge of arterial anatomy, the similarity of the appearance of vascular calcification in modern patients and in the mummies, the increasing incidence with age in the mummies imaged as is seen in contemporary humans and the fact that histologic studies showing arterial calcification in a similar distribution have been previously reported (3–6).

While we believe our study conclusively documents the presence of arterial calcification, we have no documentation that any of the mummies we examined actually had overt signs and symptoms of cardiovascular disease. The estimated mean age at the time of death of the mummies we studied was 38.1 ± 12.0 years, a relatively old age 3000 years ago. Several mummies had such diffuse generalized atherosclerosis that clinical symptoms would seem to have been likely. Ancient Egyptian hieroglyphic texts mention symptoms consistent with angina, acute myocardial infarction and congestive heart failure (39). For example, an ancient Egyptian papyrus text for physicians comments, “If thou examinist a man for illness in his cardia, and he has pains in his arms, in his breasts and on one side of his cardia...it is death threatening him” (40). Relief sculptures found in ancient Egyptian tombs have been interpreted as showing sudden death, with a nobleman collapsing in the presence of his servants (41).

Our findings of frequent arterial calcification support the hypothesis that atherosclerotic cardiovascular disease was clinically extant in ancient Egypt.

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Modern Approaches to the Treatment of Patients with Multivessel Coronary Disease (Review of Literature)

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Myocardial revascularization is a modern generally accepted standard of treating the patients with multivessel coronary disease and clinical signs of angina. Earlier conducted multiple randomized studies have revealed the advantage of coronary artery bypass grafting over the percutaneous coronary interventions regarding the decreased incidence of repeated myocardial revascularization at identical parameters of mortality and myocardial infarction incidence. Implementation of drug-eluting stents into the clinical practice has revealed new treatment options for this severe category of patients and reduced the incidence of repeated myocardial revascularization. Evolution of endovascular methods of treating the patients with multivessel coronary disease has been showed in this article, and the results from current randomized studies of this problem have also been provided.

Key words: *coronary heart disease, multivessel coronary disease, drug-eluting stent.*

Abbreviations

CAD – coronary artery disease
PCI – percutaneous coronary intervention
CABG – coronary artery bypass graft
CAG — coronary angiography
LCA – left coronary artery
MI – myocardial infarction
PTCA – percutaneous transluminal (balloon) coronary angioplasty
BMS – bare-metal stent
DES – drug-eluting stent

Introduction

Currently, coronary artery disease (CAD) is the most common cardiovascular disease in economically developed countries worldwide that causes the highest rate of death, disability, and expenses compared with any other disease (1).

Multivessel coronary disease occurs more frequently than a single-vessel lesion among CAD patients. According to the statistics, from 40% to 60% of endovascular interventions are performed on patients with multivessel coronary disease (2). As a rule, this group is represented by patients with complex, morphologically unfavorable lesions of the coronary arteries and also with severe concurrent pathology, which significantly influences the choice of treatment method for such category of patients. Besides, the results of randomized studies are of great importance when determining treatment approaches in patients in the age of evidence-based medicine.

Currently, there are three main methods of treating patients with multivessel coronary disease: drug therapy, surgical myocardial revascularization [coronary artery bypass graft (CABG) surgery], and endovascular myocardial revascularization [percutaneous coronary intervention (PCI)]. Each of these treatment methods is continuously developing and has its advantages and disadvantages.

Comparative analysis and results of drug therapy, CABG and PCI

Three large multicenter randomized studies (VACS, ECSS, CASS) started soon after implementation of CABG surgery into the clinical practice, have been aimed at the analysis of the results of surgical myocardial revascularization and drug treatment in patients with stable exertional angina. The majority of patients (91.1%) included in these studies, according to coronary angiography (CAG) data, had multivessel coronary disease or the left main coronary artery (LCA) lesion. Meta-analysis of these studies' results has showed that the larger the ischemic myocardium area is, the better is

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prognosis for patients who underwent CABG. Mortality among patients who underwent CABG was significantly lower after 5 years (10.2% and 15.8%, $p = 0.0001$) and after 10 years (26.4% and 30.5%, $p = 0.03$) compared with patients treated pharmaceutically. At the same time, the incidence of myocardial infarction (MI) was comparable between the groups. CABG was the most efficacious in patients with severe coronary artery lesions: LCA lesion, three-vessel lesion and two-vessel lesion involving the left anterior descending artery (3).

There are a few randomized studies (ACME, MASS, ACIP) comparing the efficacy of transluminal balloon coronary angioplasty (PTCA) and drug therapy in patients with exertional angina. Patients with one or two coronary artery lesions were enrolled in each of these studies. Results of these studies are indicative of comparable incidence of lethal outcomes and MI between the study groups during the long-term follow-up. Meanwhile, PTCA promoted significant reduction in the severity of angina's clinical presentation compared with the drug therapy (4–6).

Taking into account the results of described studies, it is necessary to consider that treatment options for the patients with multivessel coronary disease have significantly extended since the moment they were published. ACE inhibitors, β-adrenoblockers and hypolipidemic drugs (statins) are widely used in drug therapy of CAD, and their effectiveness was confirmed in the later works (7–9). At the same time, coronary stents and double disaggregant therapy (aspirin and clopidogrel) are widely spread in the interventional cardiology, and this fact has also significantly increased the effectiveness of PCI (10, 11).

Interesting results of COURAGE study aimed at the comparison of the long-term outcomes of PCI and drug therapy in patients with stable exertional angina have been published in 2007. About 70% of patients enrolled in this study had multivessel coronary disease. Bare-metal stents (BMS) were implanted in 94% of patients who underwent PCI. Combined incidence of lethal outcomes and MI did not significantly differ in the long-term period between the groups (19% and 18.5%, $p > 0.05$). At the same time, significantly decreased severity of angina's clinical presentation and reduced need of repeated myocardial revascularization (21.1% and 32.6%, $p < 0.001$) was observed in PCI group. However, the results of this study should be interpreted with caution due to some peculiarities of its design. In particular, the patients have been enrolled into the study on the base of CAG data analysis, thus high-risk patients were excluded. It should also be noted that 43% of patients at randomization stage had no clinical angina. Moreover, a high adherence of patients to drug treatment (intake of aspirin, statins and β-blockers after 5 years of follow-up was 94%, 93% and 86%, respectively) is of note, which is hardly achieved in practice. All of this reduces representativeness of sampling in this study and lowers its prognostic value (12).

Thus, the results of presented studies suggest that myocardial revascularization in patients with multivessel coronary disease is highly beneficial. Hence, it is of great interest to compare the results of PCI and CABG in this category of patients.

Comparative analysis of the results of CABG and PCI

PTCA was performed for the first time by A. Gruentzig on September 16, 1977. During the first stage of its development, PTCA was performed only in 5% of patients with CAD who had a single-vessel local coronary lesion. Meanwhile, multivessel lesion was an absolute contraindication for performing PTCA.

Indications for PTCA significantly extended with accumulation of experience and improvement of techniques and instruments. Survey studies that combined the large number of patients confirmed PTCA to be an effective procedure for CAD treatment, and the incidence of major adverse events (death, MI, urgent CABG) does not exceed 5%.

As a result of increasing interest to actively developing interventional radiology methods of coronary pathology treatment, as well as the lack of randomized studies comparing two alternative methods of myocardial revascularization for multivessel coronary disease, several large randomized studies were conducted already by the middle 90s of the 20th century to compare efficacy of PTCA and CABG surgery (Table 1).

The incidence of repeated myocardial revascularization in these studies was significantly higher after PTCA and varied depending on the duration of follow-up from 32% to 56.7% vs. 3.2–13.6% in CABG group ($p < 0.001$) (13–18).

Thus, the results of randomized studies comparing the efficacy of PTCA and CABG in patients with multivessel coronary disease did not reveal differences in survival when using these two methods of treatment. Duration of hospitalization after PTCA procedure was on average 3 times shorter than after CABG. At the

Table 1. Results of randomized studies comparing PTCA and CABG for multivessel coronary disease

Study	In-hospital period			Follow-up		
	PTCA, %	CABG, %	p	PTCA, %	CABG, %	p
Mortality						
CABRI (13)	1.3	1.3	>0.05	10.9	7.4	>0.05
EAST (14)	1.0	1.0	>0.05	7.1	6.2	>0.05
ERACI (15)	1.5	4.6	>0.05	4.8	4.7	>0.05
GABI (16)	1.1	2.5	>0.05	2.6	6.5	>0.05
RITA (17)	0.7	1.2	>0.05	3.1	3.6	>0.05
BARI (18)	1.1	1.3	>0.05	10.7	13.7	>0.05
Myocardial infarction						
CABRI		no data		4.9	3.5	>0.05
EAST	3.5	10	0.004	14.6	19.6	>0.05
ERACI	6.3	6.2	>0.05	7.9	6.3	>0.05
GABI	2.3	8.1	0.022	4.5	9.4	>0.05
RITA	3.5	2.4	>0.05	6.7	5.2	>0.05
BARI	2.1	4.6	>0.05	10.9	11.7	>0.05

Table 2. Results of non-randomized studies of stenting for multivessel coronary disease

Investigator	Urgent CABG surgery, %	Success rate of intervention, %	Repeated myocardial revascularization, %	Major cardiovascular complications, %
Moussa et al.	2	97	30	34
Laham et al.	0	97	17	20
Mathew et al.	0	98.3	18.3	20.2
De Servi et al.	1.3	91.7	10.8	28
Kornowsky et al.	0.5	96	21	22

same time, CABG had significant advantage over PTCA procedures in terms of decreased incidence of repeated myocardial revascularization and reduction of angina functional class. PTCA results in patients with diabetes mellitus were considered unsatisfactory as compared with CABG procedures. Therefore, it has been postulated that CABG is a method of choice for myocardial revascularization in patients with diabetes mellitus who suffer from multivessel coronary disease. Also, it should be noted that according to inclusion criteria of these randomized studies, the risk of possible complications during PTCA was considered as low (13–18).

Comparative analysis of the results of the use of bare-metal stents and CABG

Results of the first non-randomized studies on stenting in multivessel coronary disease have also demonstrated the high level of intervention's direct angiographic success, the low level of complications during the stenting and the low incidence of common cardiovascular complications (Table 2). In comparison with the studies on balloon angioplasty, the need for urgent CABG was low (0% vs. 6–10%). The incidence of repeated myocardial revascularization after stenting (10.8–30%) was also significantly lower than after PTCA (35–55%) (16). However, as no randomization was performed during these studies, it was difficult to make final conclusions on the advantage of stenting over PTCA.

Hence, comparative assessment of the effectiveness of stenting and CABG in patients with multivessel coronary disease is of great interest. Up to now, 5 large randomized studies on this problem have been conducted.

ERACI II was the first randomized study assessing the effectiveness of stenting and CABG in patients with multivessel coronary disease. Combined incidence of death, Q-wave MI, stroke and need for repeated myocardial revascularization on Day 30 of observation was 3.6% in stenting group, that is, significantly lower than in CABG group (12.3%) ($p = 0.002$). Mortality on Day 30 after the intervention was lower in stenting group (0.9%) compared with CABG group (5.7%), $p < 0.013$. Survival on Day 900 of the study was also higher in stenting group (96.9% and 92.5%, respectively, $p < 0.017$). Meanwhile, the incidence of repeated revascularizations was 16.8% in stenting group and 4.8% in CABG group, $p < 0.002$.

Results of 5-year follow-up have showed that patients in the studied groups had similar survival rate (92.8% and 88.4%, respectively, $p = 0.16$) and MI incidence (97.3% and 94%, respectively, $p = 0.16$). The need for repeated myocardial revascularization was significantly higher in patients after stenting than in patients after CABG (28.5% and 7.6%, $p = 0.0002$). However, after 5 years of follow-up the same number of patients in both groups had no clinical signs of angina (19).

Single-center randomized MASS-II study compared the efficacy of PCI, CABG and drug therapy in patients with multivessel coronary disease. Mortality (CABG group – 4.0%, PCI group – 4.5% and drug therapy group – 1.5%) and stroke incidence (1.5%, 1.0% and 1.5%, respectively) after 1 year of follow-up were comparable in the studied groups ($p > 0.05$). MI incidence was 2.0%, 8.0% and 3.0%, respectively ($p = 0.01$); meanwhile, angina was absent in 88% of CABG group patients, 79% of PCI group patients and in 46% of patients from drug treatment group ($p < 0.0001$). While 12.3% of patients from PCI group and 8.0% of patients from drug treatment group underwent myocardial revascularization, the need for repeated revascularizations in CABG group was only 0.5% ($p = 0.008$).

After 10 years of the follow-up there was no statistically significant difference in the survival rate between the groups (75.1%, 74.9% and 69.0%, respectively, $p > 0.05$). MI (10.3%, 13.2% and 20.7%, respectively, $p = 0.016$) and repeated myocardial revascularization (7.4%, 41.5% and 39.4%, respectively, $p < 0.05$) were significantly less common in CABG group (20).

SoS study was conducted in 53 medical centers of Europe and Canada and included 988 patients with multivessel coronary disease and clinical signs of angina. After 1 year of the follow-up, mortality was lower in CABG group as compared with stenting group (0.5% and 2.5%, $p = 0.05$). After 2 years of the follow-up, this difference became more significant (1.2% and 4.1%, respectively, $p = 0.007$). However, these results were mostly associated with the fact that non-cardiovascular deaths, were more common in stenting group, and extremely low mortality was observed in CABG group compared with the previous randomized studies. After 2 years of follow-up, combined incidence of death and Q-wave MI was similar in both groups: 9.3% and 9.6%, respectively, $p > 0.05$. The incidence of repeated myocardial revascularization after 1 year of follow-up was higher in stenting group (13% and 4.8%) and persisted after 2 years (21.0% and 6.0%, $p = 0.0001$) (21).

Randomized ARTS study was conducted in 67 European clinics and included 1205 patients (600 in PCI group and 605 in CABG group) with multivessel coronary disease. After 1 year of the follow-up, the incidence of death (2.8% and 2.5%), MI (5.3% and 4.3%) and stroke (1.7% and 2.1%) did not significantly differ between CABG and PCI groups. However, the incidence of repeated CABG (0.5% and 4.7%, $p < 0.001$), repeated PCIs (3.5% and 16.8%, $p < 0.001$) and angina recurrence (10% and 21%) was significantly lower in patients after CABG. The study analyzed economic expenses depending on the method of myocardial revascularization which showed that immediate PCI, on average, was 4212$ cheaper than CABG. However, in 1 year of the follow-up this difference changed to 2973$ which can be attributed to higher incidence of repeated myocardial revascularization in PCI group.

In 5 years after the start of the study, the incidence of death was comparable: 8.0% in PCI group, 7.6% in CABG group, $p = 0.83$. Meanwhile, in the subgroup of patients with diabetes mellitus mortality was higher after PCI (13.4% and 8.3%, respectively, $p = 0.27$). The cumulative incidence of death, stroke and MI was not significantly different between groups (18.2% and 14.9%, respectively, $p = 0.14$). Repeated revascularizations were significantly more common in PCI group (30.3% and 8.8%, respectively, $p < 0.001$) (22).

AWESOME study was conducted in 16 veteran hospitals and included patients at high risk of open heart surgery and with unstable angina refractory to drug therapy. The immediate study results in this severe category of patients were satisfactory, 30-day survival was 95% in CABG group and 97% in stenting group. Mortality in 6 months after the operation was 10% and 6%, respectively.

There were also no significant differences in survival after 3 years of follow-up (79% and 80%, respectively, $p = 0.46$). As in the previous studies, the need for repeated myocardial revascularization was significantly higher in stenting group. However, 61% of patients from CABG group and 48% of patients from stenting group after 3 years of follow-up had no marked angina signs and did not require repeated myocardial revascularization ($p = 0.001$). Total treatment costs in stenting group after 5 years was 20% lower than in CABG group (23).

Thus, summarizing the results of provided studies, it can be concluded that stenting and CABG have comparable incidence of death and myocardial infarction during immediate and long-term follow-up. The patients with diabetes mellitus are an exception. Despite considerably greater number of complex coronary artery lesions submitted to PCI in the studies with BMS, the incidence of repeated revascularization procedures after stenting is significantly lower than in PTCA studies. However, CABG has an advantage over the stenting in terms of reduced incidence of recurrent angina and repeated myocardial revascularization.

Comparative analysis of the results of stenting with drug-eluting stents and CABG

Restenosis is the main factor limiting the effectiveness of stenting and leading to recurrence of clinical signs of angina. Implementation of DES, specially designed for decreasing the in-stent stenosis, into the clinical practice at the beginning of the 21st century has revealed new treatment options for patients with atherosclerotic lesions of the coronary arteries and decreased the incidence of repeated myocardial revascularization (11).

Already the first results of stenting with DES implantation in patients with multivessel coronary disease have demonstrated significant decrease of the incidence of repeated myocardial revascularization compared with BMS (11). The results of few multicenter randomized studies assessing the efficacy of DES in patients with multivessel coronary disease have been published so far.

ERACI III study represents the registry of patients with multivessel coronary disease. The study involved 225 patients after DES implantation. Later, their results were compared with the data from ERACI II study where the patients received BMS or underwent CABG surgery.

The incidence of major cardiovascular adverse events after 30 days of follow-up was comparable between the groups of patients who received DES (4.4%) or BMS (3.6%), $p = 0.81$. At the same time, after 1 year of the follow-up the incidence of major cardiovascular complications after DES implantation was lower (12%, $p = 0.038$) compared with the other groups of patients (22.2% in BMS group and 19.6% in CABG group). These results were attributed to the lower incidence of repeated myocardial revascularization (8.9% and 16.9%, respectively, $p = 0.02$) compared with patients who received BMS and to the lower incidence of death (3.1% and 7.6%, respectively, $p > 0.05$) and MI (2.7% and 6.2%, respectively, $p > 0.05$) compared with CABG group.

After 3 years of the follow-up, the studied groups were comparable in the incidence of death (5.7% in DES group, 4.8% in BMS group and in CABG group, $p > 0.05$) and MI (6.2%, 2.7% and 6.2%, respectively, $p > 0.05$). However, DES implantation contributed to the decrease of the incidence of major cardiovascular complications (22.7% and 29.8%, $p = 0.016$), primarily due to the lower need for repeated myocardial revascularization (14.2% and 24.4%, respectively, $p = 0.008$) compared with the patients implanted with BMS. At the same time, significant difference in the incidence of major cardiovascular complications among patients of CABG (22.7%) and DES group, observed after 1 year of the follow-up, was no longer observed after 3 years of the study. These results were attributed to increased number of repeated myocardial revascularizations after 1 year among patients with DES (5.2% and 0.9%, respectively). The incidence of major cardiovascular complications among patients with diabetes mellitus implanted with DES was higher than among diabetes-free patients (36.2% and 19.1%, $p = 0.018$) (24).

The main objective of the randomized CARDia study was to compare the efficacy of stenting and CABG in patients with diabetes mellitus and multivessel coronary disease. 510 patients were enrolled in the study.

After one year of the follow-up, combined incidence of death (3.2% and 3.2%, $p = 0.97$), MI (5.7% and 9.8%, $p = 0.08$) and stroke (2.8% and 0.4%, $p = 0.06$) was comparable between CABG (10.5%) and stenting (13.0%) groups ($p = 0.63$). Repeated myocardial revascularization procedures, as predicted, were more frequently performed after stenting (11.8% and 2.0%, respectively). A subgroup of patients (179 persons) implanted with sirolimus-eluting stents was pointed out of the stenting group. Combined incidence of death, MI and stroke in this subgroup of patients was 10.1%, which was comparable with CABG group; at the same time, repeated myocardial revascularization procedures were performed significantly more often (7.3%), $p = 0.013$. The authors have concluded that stenting was as efficacious as CABG; however, it was accompanied by more frequent need for repeated myocardial revascularization (25).

Multicenter ARTS-II study assessed the results of DES (sirolimus) implantation in

Table 3. Results of randomized SYNTAX study (4 years of follow-up)

Variable	1st year PCI	1st year CABG	2nd year PCI	2nd year CABG	3rd year PCI	3rd year CABG	4th year PCI	4th year CABG	Result PCI	Result CABG
Major cardiovascular complications	17.8%	12.4%	8.3%	5.7%	6.7%	4.8%	7.9%	4.2%	33.5%	23.6%
	p = 0.002		p = 0.03		p > 0.05		p = 0.002		p < 0.001	
Death	4.4%	3.5%	1.9%	1.5%	2.6%	1,9%	3,2%	2,2%	11,7%	8,8%
	p > 0.05		p > 0.05		p > 0.05		p > 0.05		p = 0.048	
MI	4.8%	3.3%	1.2%	0.1%	1.2%	0.3%	1.5%	0.3%	8.3%	3.8%
	p > 0.05		p = 0.008		p = 0.03		p = 0.01		p < 0.001	
Stroke	0.6%	2.2%	0.7%	0.6%	0.6%	0.5%	0.2%	0.4%	2.3%	3.7%
	p = 0.003		p > 0.05		p > 0.05		p > 0.05		p = 0.06	
Repeated myocardial revascularization	13.5%	5.9%	5.6%	3.7%	3.4%	2.5%	4.2%	1.6%	23%	11.9%
	p = 0.001		p > 0.05		p > 0.05		p = 0.002		p < 0.001	

patients with multivessel coronary disease. Patients participating in the earlier conducted ARTS-I study who underwent CABG or stenting with BMS were used as control groups. Therefore, inclusion criteria for ARTS-II and ARTS-I studies were similar.

The incidence of major cardiovascular complications in 1 year of the follow-up was comparable between DES group and CABG group (10.4% and 11.6%, $p > 0.05$). However, in DES group, the incidence of death (1.0% and 2.7%, $p > 0.05$), MI (1.2% and 3.5%, $p > 0.05$) and stroke (0.8% and 1.8%, $p > 0.05$) was lower, while the incidence of repeated myocardial revascularization (7.4% and 3.7%, $p > 0.05$) was higher than in CABG group.

The incidence of major cardiovascular complications (19.3% and 16.1%, $p > 0.05$) after 3 years of the follow-up was comparable between DES group and CABG group, and it was significantly higher in BMS group (34%, $p < 0.001$). The lowest incidence of death, MI and stroke was seen in patients after DES implantation. The need for repeated revascularization in patients from DES group (11%) was lower than after BMS placement (21.2%), but higher than after CABG (5.3%).

Diabetes mellitus turned out to be the most significant factor influencing the incidence of major cardiovascular complications among patients enrolled to ARTS-II study, primarily due to the higher need for repeated myocardial revascularization (26).

Prospective randomized SYNTAX study so far is the most significant study comparing the efficacy of CABG and PCI procedures with DES implantation (TAXUS, paclitaxel). 1800 patients with three-vessel coronary disease or the left main coronary artery stenosis are included in the study (897 in CABG group and 903 in stenting group). In order to determine the risk of endovascular intervention depending on the coronary lesion severity, a SYNTAX scale was developed: 0–22 points – low risk; 23–32 points – intermediate risk; more than 33 points – high PCI risk (27, 28).

Four-year results of SYNTAX study have showed that PCI with DES implantation results in major cardiovascular complications more often than CABG (Table 3). The main reason is a need for repeated myocardial revascularization. Despite the fact that two-, three- and four-year study results are generally similar to the first year results, there are some differences. The number of MI, comparable between two groups during the first year of follow-up, has significantly increased during the following three years in PCI group and, as a result, it was significantly higher in PCI group by the end of the fourth year of the follow-up. At the same time, the need for repeated myocardial revascularization, which significantly differed during the first year of the study, did not significantly differ between the groups during the next two years. Nevertheless, the need for repeated myocardial revascularization was significantly higher in PCI group again in the fourth year of follow-up. By the end of the fourth year of the follow-up, cardiovascular mortality was significantly higher in PCI group (7.6% and 4.3%, respectively, $p = 0.004$). The number of strokes suffered during the first year of the follow-up was significantly higher in CABG group, which was related to higher incidence of intraoperative strokes. At the same time, during the period from the second through the

Table 4. Study results in patients with the main LCA lesion depending on PCI risk by SYNTAX scale

Variable	PCI risk by SYNTAX score								
	Low			Intermediate			High		
	PCI, %	CABG, %	p	PCI, %	CABG, %	p	PCI, %	CABG, %	p
Major cardiovascular complications	26	28.4	>0.05	29.5	29.7	>0.05	42.6	26.3	<0.003
Death	7.1	9.2	>0.05	8	14.7	>0.05	17.9	10.5	>0.05
MI	4.3	3.1	>0.05	6	4.6	>0.05	10.9	6.1	>0.05
Stroke	1.8	4.1	>0.05	1	3.6	>0.05	1.6	4.9	>0.05
Repeated myocardial revascularization	18.2	16.8	>0.05	20.2	17	>0.05	31.3	11.8	<0.001

Table 5. Study results in patients with three-vessel lesion depending on PCI risk by SYNTAX scale

Variable	PCI risk by SYNTAX score								
	Low			Intermediate			High		
	PCI, %	CABG, %	p	PCI, %	CABG, %	p	PCI, %	CABG, %	p
Major cardiovascular complications	30.4	24.7	>0.05	33.3	17.9	<0.001	37.9	21.2	<0.001
Death	9	8.7	>0.05	18.6	12.4	0.04	14.5	6.5	0.02
MI	8.2	4.9	>0.05	10.5	3.1	0.004	7.9	1.9	0.01
Stroke	1.2	3.9	>0.05	2.5	3.6	>0.05	5.1	2.6	>0.05
Repeated myocardial revascularization	21.2	11.6	0.02	21	8.3	<0.001	26.7	11.2	<0.001

fourth year of the follow-up the incidence of strokes did not significantly differ between the groups. It should be also noted that clinical outcomes in patients with diabetes mellitus were significantly worse than in diabetes-free patients.

The incidence of major cardiovascular complications (4 years of the follow-up) was separately analyzed in this study depending on PCI risk, as assessed by SYNTAX score, and on the localization of coronary lesions: the main LCA (Table 4) or three-vessel lesion (Table 5).

On the base of the obtained data it was concluded that in cases with main LCA lesions, PCI is a good alternative to CABG in patients with low and intermediate PCI risk as assessed by SYNTAX score. At the same time, CABG is a method of choice in patients with higher PCI risk as assessed by SYNTAX score.

Analysis of the study results in patients with three-vessel coronary disease and low PCI risk as assessed by SYNTAX score indicates a comparable incidence of major cardiovascular complications in PCI and CABG groups. Nevertheless, CABG in patients with medium and high PCI risk as assessed by SYNTAX score has substantial advantage over PCI, manifested in a significant decrease of the rate of death, MI, repeated myocardial revascularization and major cardiovascular complications.

Thus, presented studies completely prove the efficacy and safety of DES which significantly improve long-term results of endovascular treatment of multivessel coronary disease. SYNTAX score is an effective way to determine a method of choice for myocardial revascularization in patients with multivessel coronary disease. Patients with low (SYNTAX score 0–22) PCI risk have comparable intervention results regardless of the chosen method of myocardial revascularization. Patients with intermediate (SYNTAX score 23–32) PCI risk and with the main LCA lesion have comparable intervention results regardless of the chosen method of myocardial revascularization, while CABG should be preferred in patients with three-vessel lesion of the coronary arteries. A high PCI risk according to the SYNTAX score is characterized by increased incidence of death, MI and major cardiovascular complications during endovascular interventions. The above-mentioned suggest that CABG is an optimal method of revascularization in patients with high SYNTAX score (⩾33).

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Alexander Osiev

On April 6th, 2012, the acclaimed physician, scientist and teacher Alexander Osiev turned 50.

After finishing cum laude the therapeutic faculty of Tiumen State medical institute and residency in Tiumen regional clinical hospital in 1986, Alexander Osiev has started his career in Tiumen branch of All-Union Center of Cardiology. While working in this center he had performed over 300 coronaroangiographic studies and up to 250 angioplasties per year. From 2002, he works in Academician E.N. Meshalkin Research Institute of Circulation Pathology, where a Center of endovascular surgery and X-ray diagnosis has been created under his guidance. During these years he has performed over 6000 endovascular interventions.

Dr. Osiev is an active researcher. In 2004, he has defended his Doctor thesis, and in 2010, has been awarded the title of Professor. He is the author and co-author of over 100 scientific papers, three monographs, the holder of 7 patents and 3 filing receipts for his inventions. Three medical technologies developed by Dr. Osiev have been approved by Federal Agency for the Oversight in the field of healthcare and social development.

Professor Osiev is perfectly familiar with advanced methods and technologies of endovascular surgery, he actively assimilates and inculcates the newest achievements into the clinical practice. He is one of the leading Russian specialists in such fields as transcoronary septal ablation in patients with obstructive form of hypertrophic cardiomiopathy, retrograde recanalization of chronic occlusions of the coronary arteries, endovascular closure of intracardiac defects, stent-grafting of the aorta and TAVI.

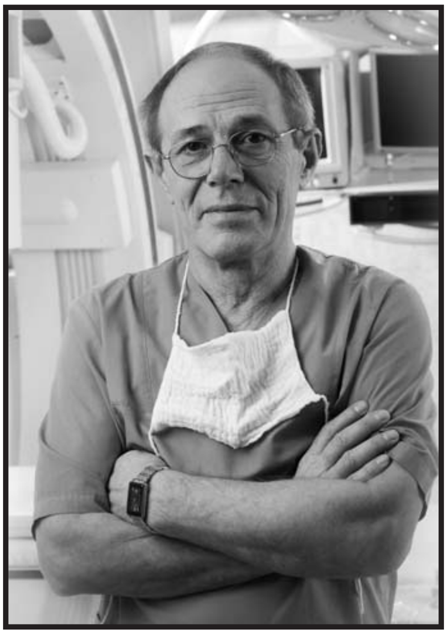
Along with clinical and scientific activities, Alexander Osiev attaches a great importance to the training of young specialists. He has guided the defense of 11 Candidate and 1 Doctor theses. He is conducting learning cycles in medical institutions of other Russian regions, master-classes on endovascular treatment of heart diseases, chronic coronary occlusions and other vascular pathologies in leading medical institutions of Russia, CIS countries and abroad.

Professor Osiev is member of Editorial Boards and Councils of the journals “Circulation Pathology and Cardiac Surgery”, “Diagnostic and Interventional Radiology”, “International Journal of Interventional Cardioangiology”, one of the founders of Siberian Association of Interventional Cardioangiology, member of the board of Russian Society of Interventional Cardioangiology, member of the board of Russian Society of Cardiovascular Surgeons, Honorary member of Russian Society of Interventional Radiology and Endovascular Surgery. He has been awarded the prize of Academician Meshalkin for a remarkable contribution in the development of cardiovascular surgery, the elaboration of new methods of diagnosis and treatment of cardiovascular diseases, as well as a Honorary diploma for his great contribution in the development of cardiac surgery in Siberia and the Far East.

Alexander Osiev is a regular participant of the biggest Russian and International scientific forums, he presents lectures and participates in trainings.

The friends, the colleagues and the Editorial Board of “International Journal of Interventional Cardioangiology” cordially congratulate Professor Alexander Osiev on his jubilee and wish him good health, happiness, a long and prosperous life and further successes in his active and fruitful scientific and practical work!

Viacheslav Buzaev



Honored Physician of Bashkortostan Republic, Chief Freelance endovascular surgeon of the Ministry of Healthcare of Bashkortostan Republic, Board member of Russian Society of Interventional Cardioangiology, Member of the Editorial Council of “International Journal of Interventional Cardioangiology”, doctor Viacheslav Buzaev has passed away on April 12th, 2012.

V. Buzaev was born on January 22nd, 1948, in Ufa. In 1974, he has graduated cum laude from the pediatric faculty of Bashkiria State Medical Institute and in 1977, has finished post-graduate education as cardiovascular surgeon in Bakoulev Institute for Cardiovascular Surgery in Moscow.

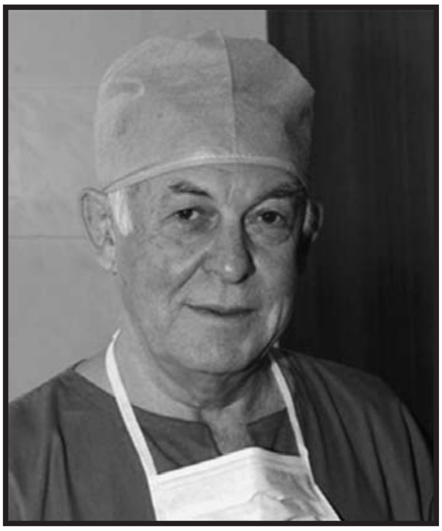
From that time professional activities of Dr. Buzaev has been inseparable from cardiology and cardiac surgery. In 1991, he has been invited to Ufa and appointed head of the unique Service of surgical treatment of heart arrhythmia, X-ray investigations and endovascular surgery in Bashkiria (in 2001, this Service has been transferred to Republican cardiological dispensary). In 1995, Viacheslav Buzaev has performed the first coronary angiography in Bashkiria, and in 1998 – the first coronary balloon angioplasty and the first coronary stenting. In 1999, he got the title of Honored Physician of Bashkortostan Republic.

In 2003, Dr. Buzaev has performed the first emergency artery restoration in acute myocardial infarction in Bashkortostan. The introduction of minimally invasive procedures of occluder closure of atrial and ventricular septal defects, as well as of patent ductus arteriosus, into the practice of Republican cardiological dispensary has started in 2004.

In 2008, Viacheslav Buzaev has defended his Doctor thesis “Hemodynamic criteria in the prediction of cardiac surgery in patients with venous congestion in pulmonary circulation”. In 2009, he was appointed Chief Freelance endovascular surgeon of the Ministry of Healthcare of Bashkortostan Republic. To the end of his life he remained practical surgeon in Republican cardiological dispensary – during the last 3 years he has performed about 800 operations and 1500 diagnostic procedures.

The Editorial Board of “International Journal of Interventional Cardioangiology” deeply mourns the death of a wonderful person and great specialist, Doctor Viacheslav Buzaev, and offers condolences to his family, friends and colleagues.

Anatoly Malashenkov



On March 29th, 2012, a wonderful person, an acclaimed surgeon and scientist, one of the founders of Russian cardiovascular surgery, Corresponding member of Russian Academy of Medical Sciences, the State Prize laureate, Professor Anatoly Malashenkov passed away after a long and severe disease.

For over 40 years professional activities of Professor Malashenkov have been connected with Bakoulev Institute for Cardiovascular Surgery. He came there as a young man and has worked his way from the residency up to the position of the Director of the Institute Coronary and Vascular Surgery and Deputy Director of the Center for Cardiovascular Surgery.

Anatoly Malashenkov is rightfully considered one of the pioneers of surgery for acquired heart diseases in our country. His works on the method of intraoperative myocardial protection using cardioplegia and on the problem of reconstructive surgery for valvular pathology are an enormous contribution in the development of this field of medicine. He was the founder of a new trend in Russian cardiovascular surgery – surgical treatment of ascending aortic and aortic arch aneurysms. He has guided the elaboration of the tactics of surgery for acute ascending aortic dissection and has taken an active part in the research work.

A unique surgeon, Anatoly Malashenkov has performed the most complex operations in patients with valvular pathology. He did the first operations for ascending aorta replacement with a xenopericardial conduit and simultaneous replacement of the ascending aorta with the resection of aortic coarctation in our country. He was one of the first Russian surgeons to develop and inculcate into practice the operations of multivalvular replacement and combined correction of acquired and ischemic heart diseases. He has been the leading Russian specialist in the field of treatment of cardiac tumors.

The work of Professor Malashenkov has been highly appreciated by the government and the medical community of Russia. He has been awarded the high title of “Honored Scientist of Russian Federation”, the State Prize of RF and a professional prize of Academician Bakoulev. He has been decorated with the “Order of Merits for the Fatherland” of 4th degree, the “Order of Honor” and the Order of N.I. Pirogov.

All those who were lucky to know Anatoly Malashenkov and to work with him will cherish his memory forever.

The Editorial Board of “International Journal of Interventional Cardioangiology” enters into the sorrow of the family, friends and colleagues of Professor Anatoly Malashenkov and offers them the most sincere condolences.