ISSN 1727-818X

International Journal of Interventional Cardioangiology

№40
2015

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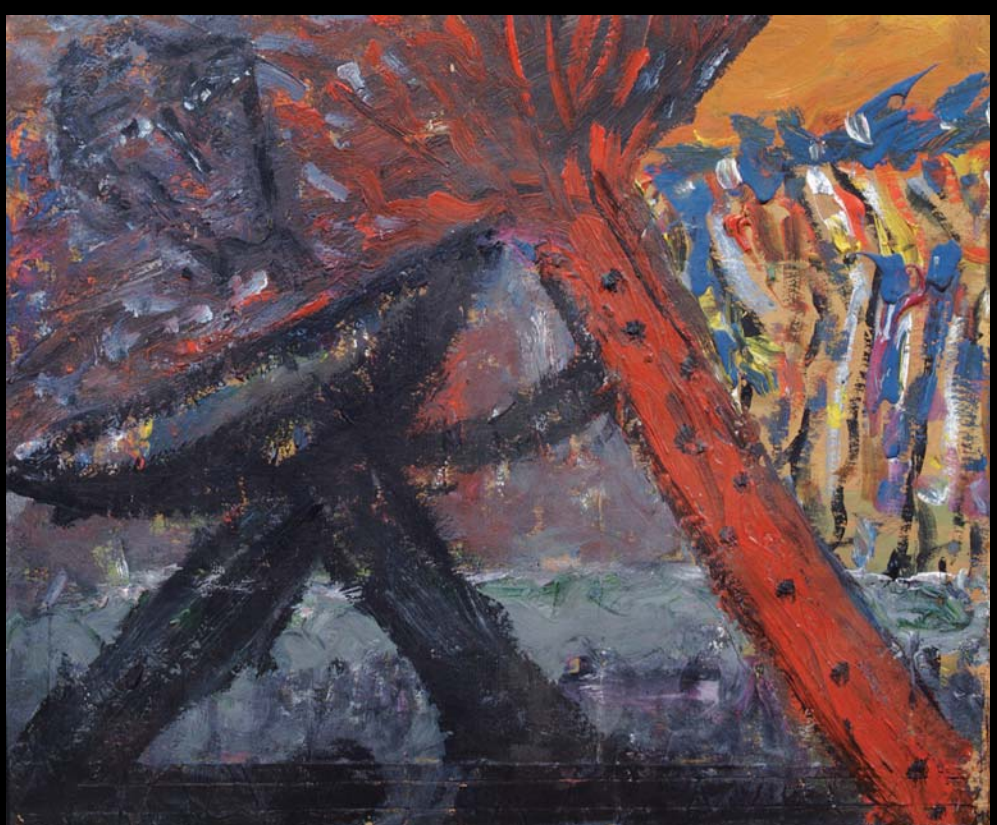

RUSSIAN SOCIETY OF INTERVENTIONAL CARDIOANGIOLOGY

ISSN 1727-818X

INTERNATIONAL JOURNAL OF INTERVENTIONAL CARDIOANGIOLOGY

№ 40-2015

"International Journal of Interventional Cardioangiology". peer-reviewed scientific and practical journal. Founded in 2002.

Website: www.ijic.ru

Address of the Editions:
101000, Moscow,
Sverchkov per., 5
Phone (+7 495) 624 96 36
Fax (+7 495) 624 67 33

Translation:
Translation bureau
MEDTRAN

Prepared by:
VIDAR Publishing House

Computer makeup:
Yu. Kushel

Corrector:
T. Lukovskaya

Special gratitude to
George Guiguineishvili,
doctor and artist,
for the offered opportunity
to put the photocopy
of his painting
"Interventional
Cardioangiology"
on the cover
of the magazine

ISSN 1727-818X
9 771727 818001

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Structure of the article: (1) Title page; **(2)** Condensed abstract and keywords; **(3)** Structured abstract; **(4)** List of abbreviations; **(5)** Text; **(6)** Acknowledgements (if applicable); **(7)** References; **(8)** Legends for figures; **(9)** Tables. The pagination should start from the title page.

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Contents

The Results of Elective Percutaneous Coronary Interventions during Bivalirudin or Heparin Infusions Depending on the Type of Vascular Access

M.A. Sinkov, A. A. Shilov, V.I. Ganyukov*

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The presented article evaluates the PCI results in patients with stable coronary heart disease during bivalirudin and heparin infusions depending on the type of vascular access. The following results were obtained: the immediate and long-term results of elective PCI performed via transradial access using anticoagulant support with unfractionated heparin and PCI performed via transfemoral access during bivalirudin therapy are comparable in terms of the number of postoperative hemorrhagic complications and the number of adverse cardiovascular events.

Ключевые слова: *bivalirudin, chronic coronary heart disease, hemorrhagic complications, transradial access, transfemoral access, long-term results.*

Abbreviations

PCI – percutaneous coronary intervention
UFH – unfractionated heparin
STEMI – *ST*-segment elevation myocardial infarction
NSTEMI – non-*ST*-segment elevation myocardial infarction
CHD – coronary heart disease
CA – coronary artery
ACS – acute coronary syndrome
APTT – activated partial thromboplastin time

Purpose of the study. To compare the immediate and long-term results of percutaneous coronary interventions in patients with stable coronary heart disease during bivalirudin and heparin infusions depending on the type of vascular access.

Background. It is currently proved that the bivalirudin instead of unfractionated heparin (UFH) during primary PCI reduces the number of hemorrhagic complications. At the same time, there is no conclusive evidence of bivalirudin clinical advantage over UFH during elective PCI.

Materials and methods. 127 patients with chronic CHD who underwent elective PCI were enrolled. The patients were simply randomized into two arms: Bivalirudin + Transfemoral access arm (n = 65) – the anticoagulant bivalirudin was used during intervention performed via transfemoral access and Heparin + Transradial access arm (n = 62). The arms were compatible in terms of clinical demographical parameters and risk factors for hemorrhagic complications (Mehran Score 14 ± 7 versus 13 ± 6, p = 0.451). The endpoints were: death, myocardial infarction, repeat myocardial revascularization, bleeding events during hospitalization and total number of adverse cardiovascular events during hospitalization and 1 year after randomization.

Results. The immediate (in-hospital) and long-term (up to 1 year) results were compared by both the number of deaths, myocardial infarctions, repeated myocardial revascularizations and hemorrhagic events, and the total number of adverse cardiovascular events.

Conclusions. The immediate and long-term results of elective PCI performed via transradial access during anticoagulant support with unfractionated heparin and PCI performed via transfemoral access during bivalirudin therapy are comparable both in the number of postoperative hemorrhagic complications, and the number of adverse cardiovascular events.

Introduction

Optimal anticoagulant therapy associated with PCI is still being searched. Possessing a whole spectrum of modern antithrombotic drugs, one should remember about the risk of

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The article was received on March 18, 2015.
Accepted for publication on April 22, 2015.

hemorrhagic complications, which usually elevates proportionally to antithrombotic effect of the drug (1).

It is currently proved that the hemorrhagic complications related to PCI are an independent predictor of adverse cardiovascular events, such as deaths and repeated myocardial infarctions (2). Therefore, it is especially difficult to find a balanced solution between the best antithrombotic background for PCI and risk of hemorrhagic complications in patients highly prone to cardiovascular complications including patients older than 75 years, female sex, diabetes mellitus, impaired renal function, prior anemia and reduced left ventricle ejection fraction (3). Thus, the main objective of up-to-date PCI medicinal support is a decrease in both thrombotic complications and bleedings.

Possible ways to reduce the number of hemorrhagic complications are use of an antithrombotic agent rapidly inactivated in the body and selection of a safe vascular access. Currently, a direct thrombin inhibitor - bivalirudin which is characterized with a very short half-life is a possible alternative to UFH (4). The clinical efficacy of bivalirudin is still not entirely clear. Thus, the randomized study HORIZINES-AMI showed that bivalirudin in patients with STEMI was safer in terms of hemorrhagic complications compared to UFH with a simultaneous significant reduction in the number of deaths (5, 6). However, controversial results were obtained from more recent studies. In HEAT-PPCI study, bivalirudin results were worse compared to unfractionated heparin therapy in terms of prevention of total mortality, cerebrovascular accidents, repeated myocardial infarctions, or non-elective revascularizations, with an equal incidence of bleeding (7). In contrast, the EUROMAX study demonstrated a bivalirudin-related significant decrease in the incidence of the composite endpoint compared with heparin treatment (both unfractionated heparin and enoxaparin), mainly due decreased incidence of massive bleedings (8), which resulted in reduction of the class recommendations for bivalirudin use from class I to class IIa for STEMI patients in 2014 (9, 10).

While there is some positive trend in reduction of adverse cardiovascular events when bivalirudin is used in STEMI patients, there is still no reliable evidence for NSTEMI patients or patients with stable CHD. The few studies which evaluated the results of elective PCI with bivalirudin (REPLACE-2 (11), ISAR-REACT-3 (12) and ARMYDA-BIVALVE (13)) included not only stable patients but a cohort of patients in whom endovascular intervention was performed for NSTEMI. In this context, the modern European guidelines for PCI in patients with chronic CHD and NSTEMI specify the bivalirudin use as IIa class recommendations (10).

Another approach to reduce the risk of hemorrhagic complications is selecting a safe vascular access for PCI. As the RIVAL study showed, the transradial access in patients with acute coronary syndrome (ACS) not only decreases hemorrhagic complications from the access site, but also reduces mortality; hence, the transradial access in ACS patients is assigned to the class IIa recommendations (14, 15). Although, to date there is no evidence regarding safety benefit of transradial access over transfemoral one in patients with chronic CHD.

Thus, currently there are two clinically effective approaches to reduce the number of ACS-related bleeding complications: use of bivalirudin or transradial access. However, efficacy of presented approaches to reduce hemorrhagic complications and their comparative benefits in patients with stable CHD remain an open question.

Purpose of the study

To compare the immediate and long-term results of percutaneous coronary interventions in patients with stable coronary heart disease during bivalirudin and heparin infusions depending on the type of vascular access.

Materials and methods

127 CHD patients with exertional angina, functional class II–IV, who underwent elective PCI were enrolled in this prospective randomized study.

The inclusion criteria were: men and women aged up to 75 years with CHD and FC II–IV exertional angina according to the classification of the Canadian Cardiovascular Society (16), with stenosis of the target CA >50% and a diameter from 2.5 mm. The confirmation of hemodynamic significance of stenosis 50–69% using the stress test was mandatory. The exclusion criteria were: acute coronary syndrome, history of coronary artery bypass grafting or thrombosis of previously implanted stents, chronic total occlusion of coronary artery and hemodynamically significant stenoses of the left main coronary artery or the impossibility of prescription and long-term administration of clopidogrel and aspirin.

Table 1. Primary characteristics of the enrolled patients

Parameter	Bivalirudin + Transfemoral access arm (n = 65)	Heparin + Transradial access arm (n = 62)	p
Mean age, years	60.7 ± 6.5	58.9 ± 7.1	0.199
Smokers, abs. (%)	52 (82.3 %)	59 (95.2%)	0.271
Arterial hypertension, abs. (%)	60 (97.1%)	58 (93.5%)	1.000
Type 2 diabetes mellitus, abs. (%)	10 (15.3%)	9 (14.5%)	0.967
Females, abs. (%)	35 (53.8 %)	28 (43.1 %)	0.897
Grade >2 obesity, abs. (%)	8 (12.3 %)	6 (9.7 %)	0.365
Risk of hemorrhagic complications according to Mehran Score	14 ± 7	13 ± 6	0.451

Depending on anticoagulant support (bivalirudin or heparin) and vascular access (transradial or transfemoral), the patients were simply randomized into two arms: Bivalirudin + Transfemoral access arm (n = 65) – the anticoagulant bivalirudin was used during intervention performed via transfemoral access and Heparin + Transradial access arm (n = 62) – the anticoagulant unfractionated heparin and transradial access were used.

PCI medicinal support: The loading dose of clopidogrel 600 mg was administered 12 hours prior to intervention and 75 mg in the morning on the day of intervention.

Bivalirudin regimen was as follows: 0.75 mg/kg bolus before intervention, and then at a dose of 1.75 mg/kg/h throughout the intervention. The drug administration was stopped immediately after PCI.

During PCI unfractionated heparin was administered at a dose of 100 U/kg and further, if necessary, heparin doses of 2500 Units were additionally injected to achieve APTT = 300–350 sec.

After stent implantation, all patients received dual antiplatelet therapy for 1–6 months depending on the type of implanted stent.

Immediate interventional results were evaluated during the patient's stay in the clinic since PCI until discharge.

The long-term results were evaluated 12 months after performed PCI via telephone.

The following parameters were analyzed: immediate interventional success (residual CA stenosis at the implantation site <10% with TIMI III antegrade flow and no adverse cardiovascular events), the immediate (in-hospital) and long-term results of PCI (all deaths, MIs, strokes, repeat revascularizations of the target artery), hemorrhagic events according to the BARC classification (17) during the follow-up.

The risk of hemorrhagic complications was assessed before PCI in all patients using Mehran score (17).

Hemostasis: When PCI was performed via transradial access, the sheath was removed immediately after the intervention. The hemostasis was achieved using TRBand (Terumo) or compression bandage. When transfemoral access was used, the sheath was removed 2–4 hours after completion of bivalirudin infusion and in case of heparin therapy — when APTT was <150 sec. To achieve hemostasis, the artery was pressured with fingers or FemoStop device, then compression bandage was applied for 8 hours with strict bed rest for 24 hours.

The study results were processed using the software package Statistica for Windows 6.0 (StatSoft Inc., USA). The discrete variables were presented as median, the continuous variables – as mean ± standard deviation. To evaluate the qualitative and quantitative variables, χ^2 test and Student's test were used, respectively. The differences were considered statistically significant at $p < 0.05$.

Results

When the study arms were compared, no significant differences in the primary clinical and demographic characteristics or risk factors of bleeding were observed (Table 1).

The patients in both groups had predominantly single-vessel coronary disease (Bivalirudin + Transfemoral access arm – 55.4%, Heparin + Transradial access arm – 51.6%; p = 0.804), mean SYNTAX scores were 19.4 ± 6.8 and 20.2 ± 6.1, respectively, p = 0.541. The drug-eluting stents were predominantly implanted in more than 75% of patients in both arms. For bifurcation stenting (21.5% of patients in the Bivalirudin + Transfemoral access arm and 25.8% in the Heparin + Transradial access arm (p = 0.905)), single stent techniques, such as provisional T-stenting were preferred (70% of cases of bifurcation interventions). Angiographic characteristics of patients enrolled in the study are presented in Table 2.

Table 2. Angiographic characteristics of the patients

Parameter	Bivalirudin + Transfemoral access arm (n = 65)	Heparin + Transradial access arm (n = 62)	p
Bifurcation stenting, abs. (%)	14 (21.5%)	16 (25.8%)	0.905
SYNTAX Score	19.4 ± 6.8	20.2 ± 6.1	0.541
Average number of stents per patient	1.15	1.2	–
Mean stent length, mm	21.6 ± 7.5	22.4 ± 7.5	0.599
Mean stent diameter, mm	3.3 ± 0.5	3.2 ± 0.5	0.306
Drug-eluting stents	54 (83.1%)	48 (77.5%)	0.334

Table 3. In-hospital PCI results in chronic CHD patients with bivalirudin or heparin therapy

Parameter	Bivalirudin + Transfemoral access arm (n = 65)	Heparin + Transradial access arm (n = 62)	p
Non-fatal MI, abs. (%)	2 (3.1%)	1 (1.6%)	0.899
Stroke, abs. (%)	–	–	–
Death, abs. (%)	–	–	–
Repeated target vessel revascularization, abs. (%)	1 (1.5%)	1 (1.6%)	0.998
Hemorrhagic complications (BARC type 1–2 bleeding or subcutaneous hematoma >5 cm)	3 (4.6%)	2 (3.2%)	0.899
Total number of adverse cardiovascular events, abs. (%)	6 (9.2%)	4 (6.4%)	0.675

Table 4. Long-term PCI results in chronic CHD patients with bivalirudin or heparin therapy

Parameter	Bivalirudin + Transfemoral access arm (n = 65)	Heparin + Transradial access arm (n = 62)	p
Non-fatal MI, abs. (%)	5 (7.7%)	4 (6.5%)	0.656
Stroke, abs. (%)	–	–	–
Death, abs. (%)	–	1 (1.6%)	0.946
Repeated target vessel revascularization, abs. (%)	5 (7.7%)	3 (4.8%)	0.785
Total number of adverse cardiovascular events, abs. (%)	10 (15.3%)	8 (11.3%)	0.677

The immediate interventional success was achieved in 98.4% (n = 64) of patients from the Bivalirudin + Transfemoral access arm and 100% (n = 62) of patients from the Heparin + Transradial access arm (p = 1.00). In one patient from the Bivalirudin + Transfemoral access arm during elective bifurcation stenting of the left anterior descending artery intraoperative myocardial infarction occurred due to occlusion of the diagonal artery. Totally, two cases (1.6%) of stent thrombosis were reported in both arms, one thrombosis was caused by the coronary artery dissection; the cause of second thrombosis was not identified.

During the in-hospital period, there were no such serious cardiovascular events as death and stroke. The total number of adverse cardiovascular events was 9.2% in the Bivalirudin + Transfemoral access arm and 6.4% in the Heparin + Transradial access arm (p = 0.675) (Table 3).

Hemorrhagic complications were reported in 4.6% (n = 3) of patients from the Bivalirudin + Transfemoral access arm and 3.2% (n = 2) of patients from the Heparin + Transradial access arm (p = 0.899). Mostly, they were subcutaneous hematomas (>5 cm in diameter) and bleedings from the arterial puncture site. All complications were BARC type 1 or 2. One pulsatile hematoma at the femoral artery puncture site was observed in the Heparin + Transradial access arm on Day 2 after PCI. The hematoma cavity was thrombosed on Days 3–4 with conservative treatment.

Based on the 12-month follow-up results, the total numbers of adverse events in both arms are comparable: 15.3% (n = 10) in the Bivalirudin + Transfemoral access arm and 11.3% (n = 8) in the Heparin + Transradial access arm, p = 0.677. The highest incidence of the adverse events was observed for repeated revascularization of the target vessel and relapsed myocardial infarction (Table 4).

Discussion

As the conducted study demonstrated, the immediate and long-term results of PCI in patients with chronic CHD were comparable between the bivalirudin and transradial access arms. The number of hemorrhagic complications in the bivalirudin and transfemoral access arm was comparable with the UFH and transradial access arm. It may be assumed that transradial access prevents the PCI-related hemorrhagic complications as effectively as the medicinal support with bivalirudin. This assumption is confirmed by the fact that, according to the literature data, more than 50% of hemorrhage events after endovascular interventions occur from the vascular access site (18).

As the HORIZINES-AMI study showed, the use of bivalirudin during primary PCI in STEMI patients may be accompanied with the increased number of stent thromboses on Day 1 after intervention (4). The reason is that bivalirudin inactivation in the body occurs before the loading dose of clopidogrel inhibits sufficiently the platelet function. The increase in the number of thrombotic complications on the first day after intervention was not documented in this study. One stent thrombosis (1.6%) caused by the coronary dissection was observed in the bivalirudin arm. This is likely related to the fact that all patients received a loading dose of clopidogrel at least 12 hours before stenting, and by the time of intervention the drug fully exerted its antiplatelet activity.

Thus, the use of bivalirudin in CHD patients during elective PCI is accompanied by a low number of adverse cardiovascular events. As the conducted study demonstrated, bivalirudin showed no advantages over transradial access in terms of reducing the number of hemorrhagic complications.

Conclusions

The immediate and long-term results of elective PCI performed via transradial access during anticoagulant support with unfractionated heparin and PCI performed via transfemoral access during bivalirudin therapy are comparable both in the number of postoperative hemorrhagic complications and adverse cardiovascular events.

References

1. Popma J.J., Berger P., Ohman E.M. et al. Antithrombotic therapy during percutaneous coronary intervention. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004, 126, 576–599.
2. Sumeet S., Bach R.G., Chen A.Y. et al. Baseline Risk of Major Bleeding in Non–*ST*- Segment–Elevation Myocardial Infarction The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009, 119, 1873–1882.
3. Mehran R., Pocock S., Nikolsky E. et al. A Risk Score to Predict Bleeding in Patients With Acute Coronary Syndromes. J. Am. Coll. Cardiol. 2010, 55, 2556–2566.
4. Stone G.W., Witzenbichler B., Guagliumi G. et al. Bivalirudin during Primary PCI in Acute Myocardial Infarction. N. Engl. J. Med. 2008, 358, 2218–2230.
5. Kastrati A., Neumann F.-J., Mehilli J. et al. Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention. N. Engl. J. Med. 2008, 359, 688–696.
6. Stone G.W., Witzenbichler B., Guagliumi G. et al. HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N. Engl. J. Med. 2008, 358, 2218–2230.
7. Shahzad A., Kemp I., Mars C. et al. On behalf of the HEAT-PPCI trial investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet. 2014, 7, 2541–2619.
8. Zeymer U., van 't Hof A., Adgey J. et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with *ST*-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. Eur. Heart J. 2014, 5, 2457–2602.
9. Wijns W., Kolh P., Danchin N. et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur. Heart. J. 2010, 31 (20), 2501–2555.
10. Kolh P., Windecker S., Alfonso F. et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur. J. Cardiothorac. Surg. 2014, 46 (4), 517–592.
11. Lincoff A.M., Bittl J.A., Harrington R.A. et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. J. Am. Med. Assoc. 2003, 289, 853–863.
12. Kastrati A., Neumann F.-J., Mehilli J. et al. ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N. Engl. J. Med. 2008, 359, 688–696.
13. Patti G., Pasceri V., D'Antonio L. et al. Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in high-risk patients undergoing percutaneous coronary intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin study). Am. J. Cardiol. 2012, 110 (4), 478–484.
14. Jolly S.S., Yusuf S. et al. Radial vs. femoral access for coronary angiography and intervention in patients with acute

coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet. 2011, 377 (9775), 1409–1420.
15. Hamon M., Pristipino C. et al. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. Eurointerventions. 2013, 8, 1242–1251.
16. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. Can. J. Cardiol. 2002, 18, 371–379.
17. Mehran R., Rao S.V., Bhatt D.L. et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academic Research Consortium. Circulation. 2011, 123, 2736–2747.
18. Jolly S.S., Amlani S., Hamon M., Yusuf S., Mehta S.R. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am. Heart J. 2009, 157, 132–140.

Original Minimally Invasive Retroperitoneal Approach for Transcatheter Aortic Valve Implantation

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Recently, transcatheter aortic valve implantation (TAVI) became a routine clinical practice for the treatment of severe aortic stenosis in non-operable patients or in patients at high risk for "open" surgery. At present, many surgeons performing TACI prefer transfemoral approach because of its minimal invasiveness. However in about one third of patients with calcified or small femoral arteries, it is necessary to use other, alternative approaches – transapical, transaortic or subclavian – each of them having its indications and contraindications. Meanwhile in some cases it is impossible to use anyone of these approaches. The search of solution for this problem led us to the performance of TAVI through a new minimally invasive retroperitoneal approach to the iliac arteries.
Key words: *aortic stenosis, transcatheter aortic valve implantation, retroperitoneal approach.*

Aortic valve operations are mostly performed in patients with calcified aortic stenosis. Surgical replacement is a method of choice with strictly defined indications (1) and low post-operative mortality (2). But surgical risk may be high in some patients, especially in senile and patients with severe comorbidities, and sometimes surgery is absolutely contraindicated (3, 4). Another option of treatment for high-risk patients appeared after introduction of transcatheter valve intervention (TAVI) (5). This procedure holds a firm place in the treatment of atherosclerotic aortic valve disease.

Nowadays many surgeons prefer trans-femoral approach. But in cases when femoral arteries are small or diseased, another access route can be used – trans-apical (Edwards Sapient XT valve), trans-aortic, or subclavian (CoreValve). Unfortunately, in some cases none of these approaches are available. In our opinion, minimally invasive retroperitoneal approach can be an alternative route to iliac arteries. There are no literature references about use of this route for TAVI.

The main retroperitoneal surgical access to aorta was described by C. Rob in 1961. It implies incision made from costal margin downward and medially with dissection of oblique muscles (6, 7) (Fig. 1) Disadvantage of

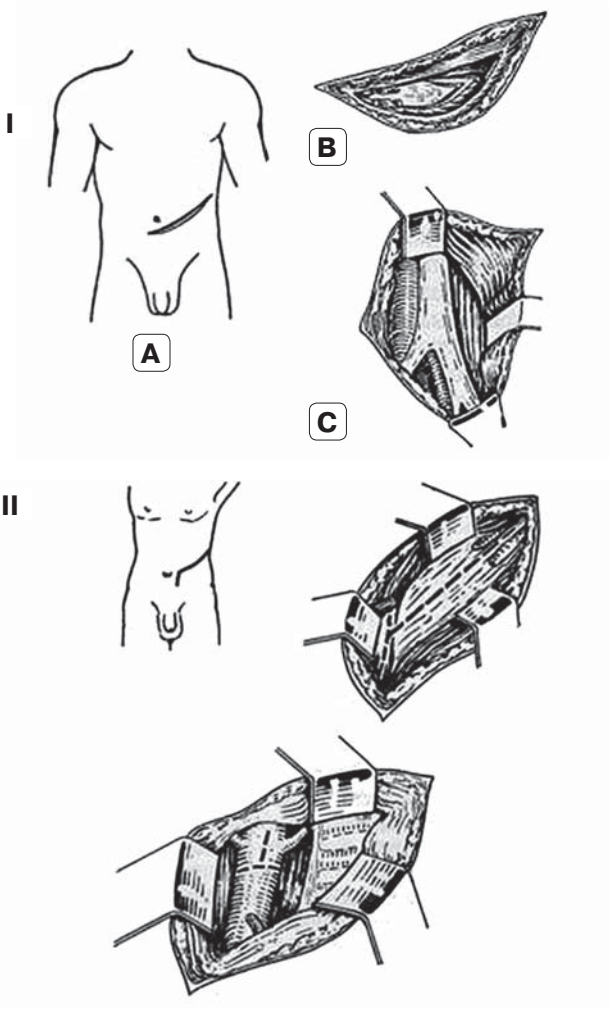

Fig. 1. Retroperitoneal access to terminal abdominal aorta.
I – according to Rob (1963): A – scheme of incision; B – external and internal oblique muscles are dissected, transverse muscle is divided, rectal muscle partially dissected; C – aorta, its bifurcation and common iliac arteries are exposed;
II – modified retroperitoneal access to supra- and subrenal abdominal aorta.

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Manuscript received on February 17, 2015.
Accepted for publication on March 12, 2015.

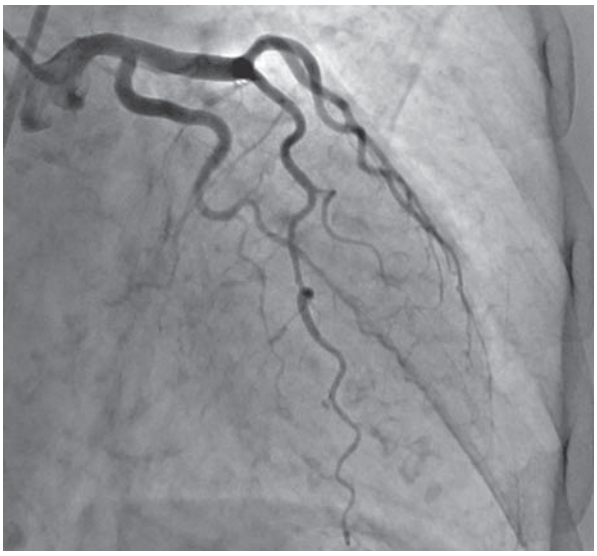


Fig. 2. Angiogram of the left coronary artery (LCA).

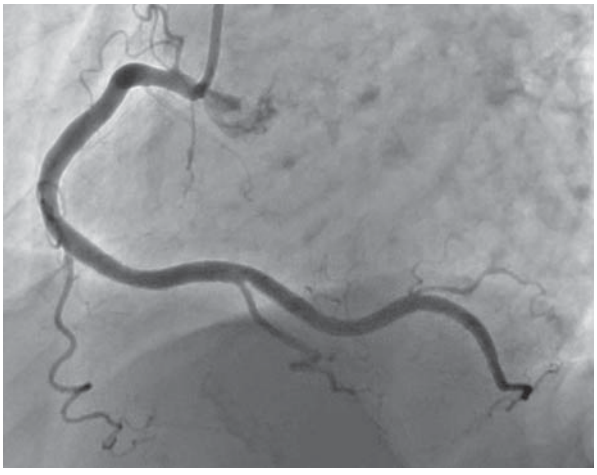


Fig. 3. Angiogram of the right coronary artery (RCA).

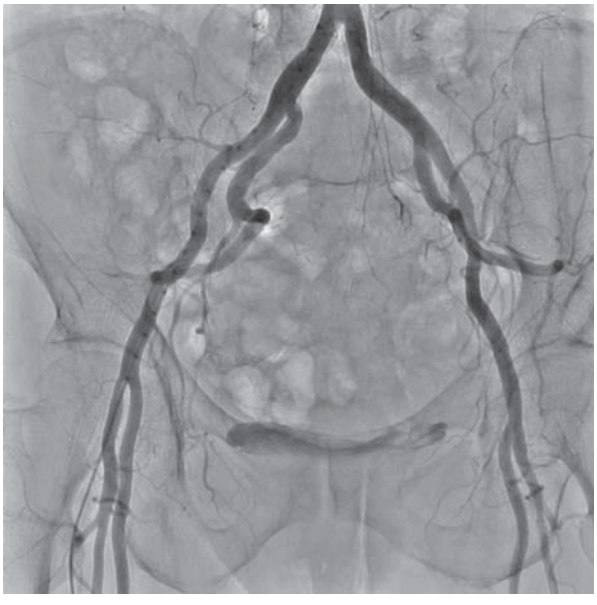


Fig. 4. Angiogram of the iliac and the femoral arteries.

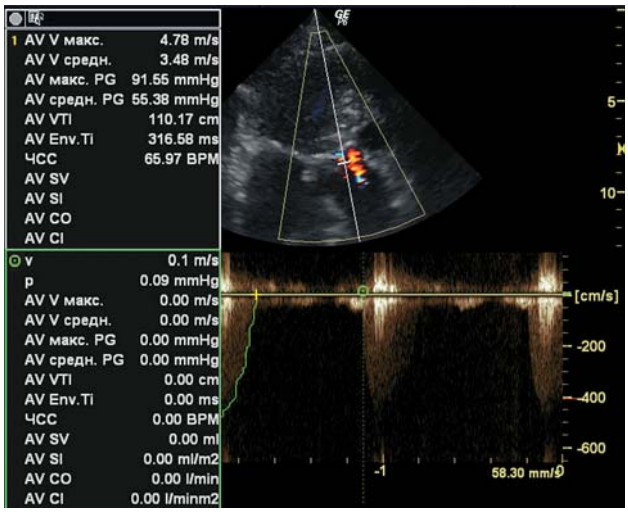


Fig. 5. Transthoracic echocardiography (before TAVI). Continuous wave Doppler echocardiography, apical position. Systolic pressure gradient measurement. Peak pressure gradient is 91 mm Hg, mean pressure gradient is 55 mm Hg.

this access is eventual injury of vessels, nerves and muscle structures, leading to neuralgias, trophic disorders and disorders of innervation. According to Honig M. et al., anterior abdominal wall relaxation occurs in 23%, pain syndrome in 37% (8).

Search for optimal and less traumatic surgical manipulations led to development of minimally invasive methods. They emerged as an alternative to traditional aortofemoral reconstructive operations performed via wide trans- or retroperitoneal access (9, 10, 11). Minimal access surgery (MAS) in infrarenal aortic reconstruction are used in Russia since 2001, nevertheless only few articles are dedicated to this problem (12, 13).

We present the first case of transcatheter aortic valve implantation (CoreValve, Medtronic) in a patient with critical aortic stenosis and high surgical risk via innovative retroperitoneal minimally invasive access. Standard access routes in this patients are unavailable.

A 77 years old female patient was admitted to Moscow City Center of Interventional Cardiology with dyspnea on moderate exertion.

She has arterial hypertension since 2005, maximal BP 170/100. Her usual BP after receiving medical treatment is 120/80 mm Hg. She notes exertion dyspnea for about 2 years. Echocardiography performed in spring 2004, revealed severe aortic stenosis. No history of previous rheumatism or tonsillitis was reported. At the admission to the Center the patient underwent complete examination, including coronary angiography that showed mild

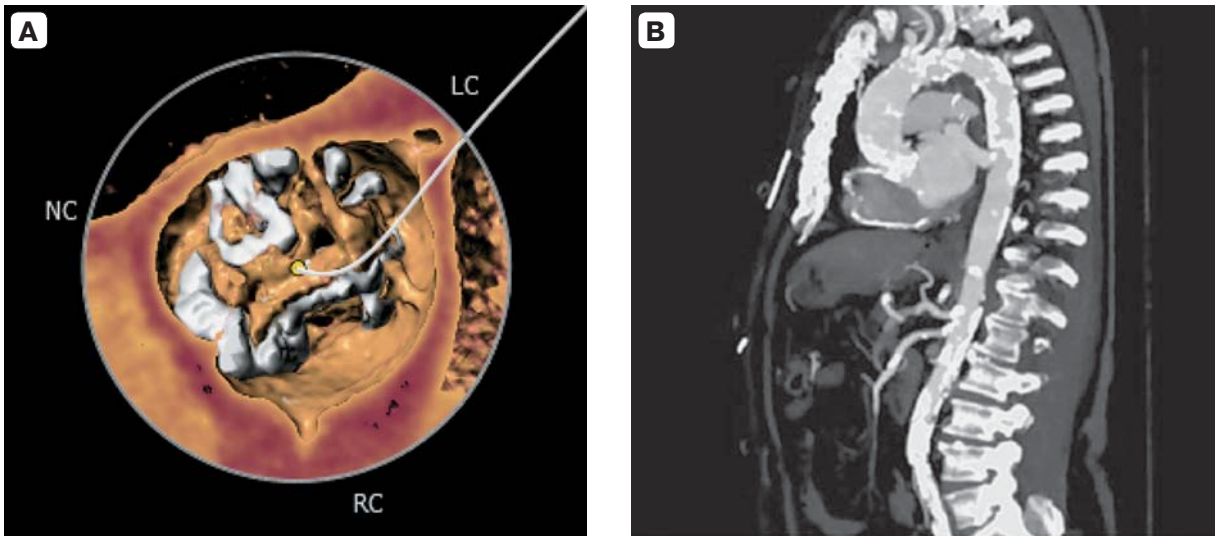


Fig. 6. Multispiral CT. A – 3D-reconstruction, VRT. Aortic valve annulus, axial view. Marked calcification of the leaflets; B – atherosclerotic disease of the thoracic and the abdominal aorta.

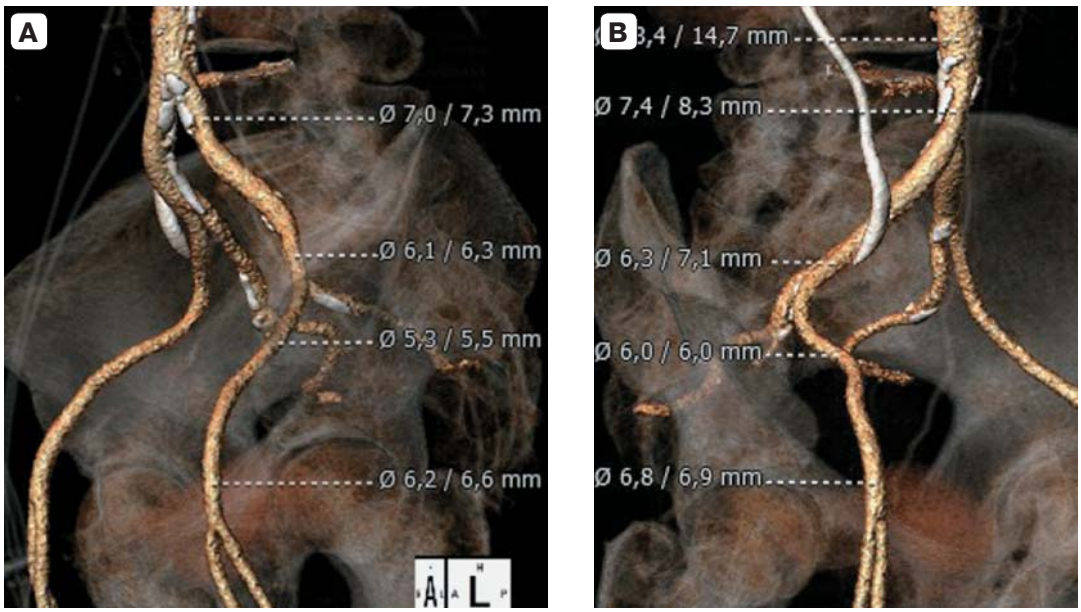


Fig. 7. Multispiral CT of the pelvic arteries. A – 3D-reconstruction of the left iliac and the femoral arteries; B – 3D-reconstruction of the right iliac and the femoral arteries.

diffuse disease with no hemodinamically significant lesions, SYNTAX score =0 (Fig. 2–4).

Echocardiography showed dilated left atrium (LA area 19 cm^2, anteroposterior dimension 35 mm) and symmetric left ventricular hypertrophy. Left ventricular function was satisfactory with LVEF 75%, end-diastolic size (from parasternal position) 4.3 cm, end-systolic size (from parasternal position) 2.4 cm, end-diastolic volume 83 cm3, end-systolic volume 20 cm^3. The diastolic thickness of the interventricular septum was 13 mm (up to 18 mm in basal part), posterior wall diastolic thickness was 13 mm. Ascending aorta diameter was 36 mm, sinotubular junction diameter 25 mm, sinus diameter 31 mm, aortic annulus diameter 20–21 mm, right ventricular outflow tract diameter 18 mm, sinus height 16 mm, aortic valve leaflets were calcified. Doppler echocardiography showed second degree of aortic regurgitation, aortic jet velocity 4.8 m/sec, peak systolic gradient 92 mm Hg, mean systolic gradient 55 mm Hg, aortic valve area 0.54 cm^2. Mitral valve presented with discordant leaflets movement, mean diastolic gradient 0.9 mm Hg and mild regurgitation. Mean pulmonary artery pressure 37 mm Hg (Fig. 5).

Contrast-enhanced multispiral CT confirmed atherosclerotic disease of thoracic and abdominal aorta and total calcification of aortic valve. Aortic annulus diameter 19 × 25 mm, sinus diameter 31 × 32 mm, sinotubular junction diameter 29 mm, sinus height 15.6 mm, left ventricular outflow tract diameter

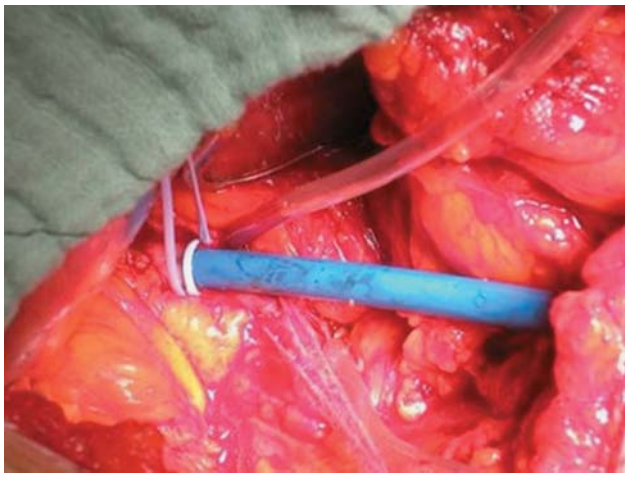


Fig. 8. 18 Fr introducer fixed in the right common iliac artery.

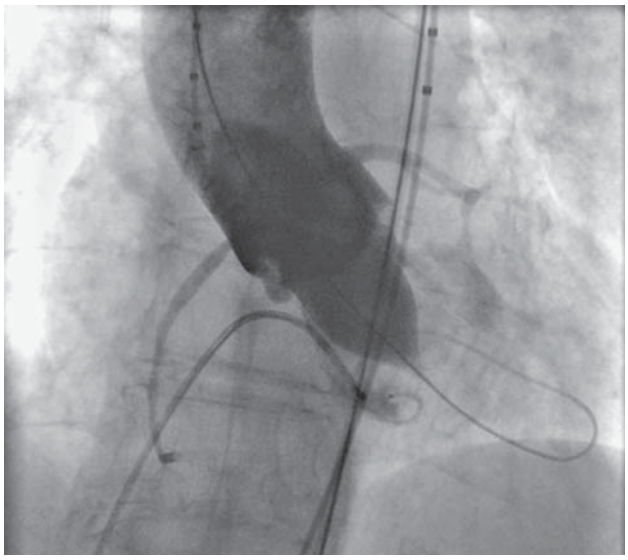


Fig. 9. Aortic balloon valvuloplasty by Nucleus 20/40 mm and simultaneous aortography.

29 mm, aortic angle 38°, LCA ostium height 15 mm, RCA ostium height 13 mm. Right subclavian artery was 6.2 mm, with C-shaped tortuosity of the proximal segment. The aortic arch and the descending aorta were calcified. Infrarenal aorta diameter 13.4 × 14.7 mm. Right common iliac artery 7.4 × 8.3 mm, left common iliac artery 7.0 × 7.3 mm. Right external iliac artery 6.3 × 7.1 mm, left external iliac artery 5.3 × 5.5 mm. Right superficial femoral artery 6.8 × 8.9 mm, left superficial femoral artery 6.2 × 6.6 mm (Fig. 6–7).

Electrocardiography showed sinus rhythm with HR of 72 beats per minute and signs of left ventricular hypertrophy.

24-hours ECG monitoring showed sinus rhythm with HR of 48–136 beats per minute (mean, 71 bpm). Ventricular (2770) and supraventricular (81) extrasystoles were seen. No ST deviation was marked.

Her blood count revealed decreased level of hemoglobin (104 g/l)

Taking into consideration severe aortic stenosis, severe comorbidities, high risk of surgery (Euroscore 23%), the heart team, consisting of endovascular surgeon, cardiac surgeon, cardiologist and anesthesiologist, decided to perform transcatheter implantation of CoreValve valve. Required device size was estimated as 26 mm.

Since patient had marked calcification of aorta, and the diameters of iliac and subclavian arteries were less than 6.5 mm (compared to 18 Fr CoreValve delivery catheter), transfemoral, subclavian and transaortic routes were considered unavailable. Transapical route is unavailable for CoreValve too. Thus, a decision was made to perform TAVI via retroperitoneal minimally invasive route.

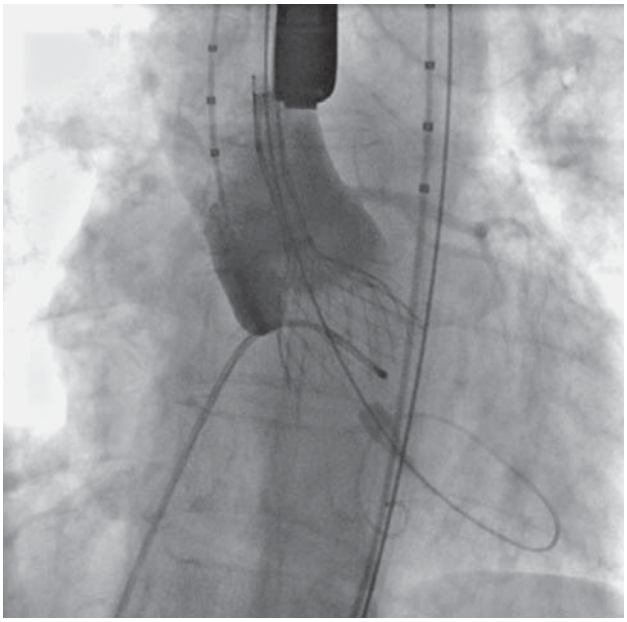
Procedure

Retrograde catheterization of the aorta and antegrade catheterization of the inferior vena cava were performed under local anesthesia, 7Fr and 6 Fr sheaths, respectively, were inserted. Temporary pacing electrode was introduced into the right ventricle.

Surgical access to terminal aorta and common iliac artery (CIA). Oblique incision 10–12 cm long was made from the costal margin to the point 2 cm under the umbilicus. The aponeuroses of the external oblique, the internal oblique and the transverse muscles, as well as the transverse fascia were dissected. The peritoneum was shifted medially to gain exposure of terminal aorta and CIA. Aortic and iliac artery walls were soft with some solitary calcification sites. A 8 mm Gore-Tex explant was implanted into the terminal aorta. A18 Fr introducer was inserted into the explant and fixed. (Fig. 8)

Two pigtail catheters were introduced into the non-coronary sinus and the left ventricle via the left transfemoral route using Ingwire guidewires and pressure gradient was measured. Peak pressure gradient was estimated as 70 mm Hg. Balloon catheter Nucleus 20/40 mm was introduced and balloon dilatation was performed during pacing at 180 bpm and carotid artery compression with simultaneous aortography (Fig. 9). Hemodynamics were stable. A 26 mm Corevalve was introduced and positioned using Amplatz Super Stiff guidewire. Aorography was performed and valve was implanted (Fig. 10). Hemodynamics remained stable. Control angiography showed excellent results with perfect positioning of the valve, no paravalvular regurgitation and good visualization of the coronary arteries. Mean pressure gradient decreased to 8 mm Hg.

Transesophageal echocardiography showed minimal aortic regurgitation and satisfactory function of prosthesis. Peak pressure gradient was 11.4 mm Hg. No signs of hydropericardium were seen (Fig. 11–12).



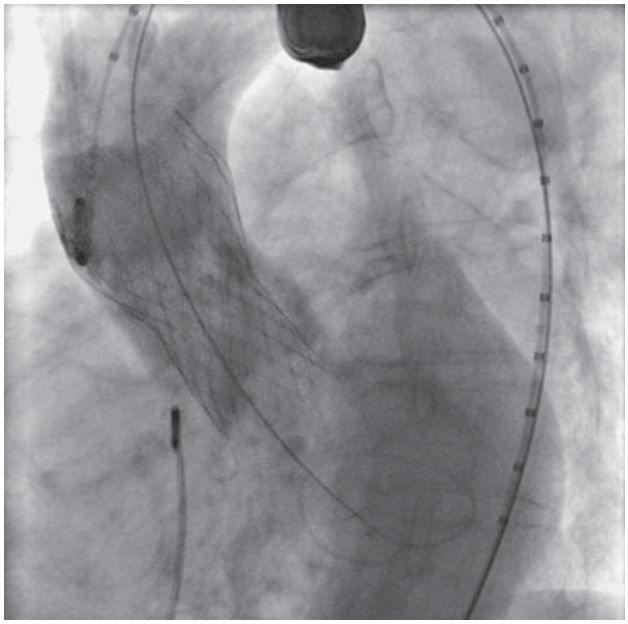


Fig. 10. Implantation of CoreValve System 26 mm.

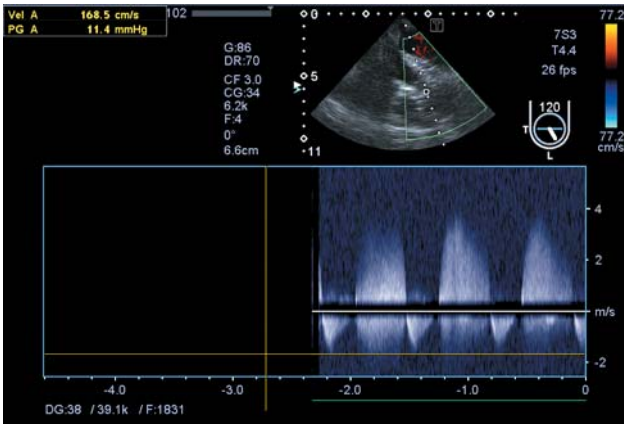


Fig. 11. Transesophageal echocardiography (intraoperationally). Continuous wave Doppler echocardiography. Measurement of systolic pressure gradient. Peak systolic pressure gradient is 11.4 mm Hg.

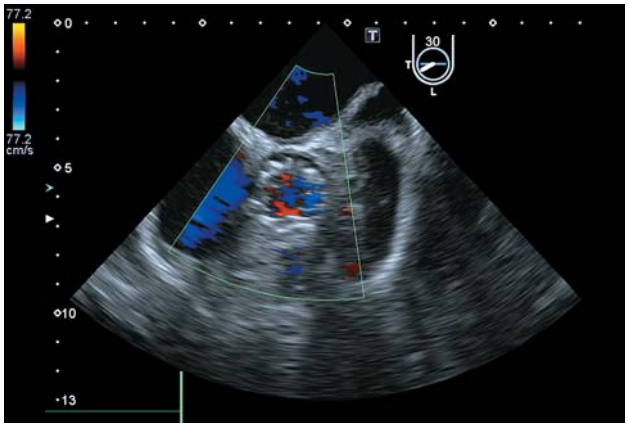


Рис. 12. Transesophageal echocardiography (intraoperationally). Continuous wave Doppler echocardiography. The prosthesis is seen. Aortic regurgitation is minimal.

Delivery catheter was withdrawn and explant was ligated and cut off. The pulses on the iliac arteries were good. Surgical wound was closed with intracutaneous suture. Procedure duration was 94 minutes, the exposure duration was 17 minutes and 300 ml of contrast medium were used.

Clinical diagnosis. Acquired valvular disease. Severe calcified aortic stenosis. Heart failure stage 1, NYHA class II. Arterial hypertension stage 2. Transcatheter implantation of CoreValve prosthesis 27.10.2014.

Concurrent diagnosis. Discirculatory encephalopathy 2 grade. Chronic iron-deficiency anemia.

Thus, transcatheter aortic valve implantation via retroperitoneal route appears to be safe and feasible. The main advantage of this access route consists in decreased aggressiveness of the operation and good exposure of the aorta and the common iliac arteries. The use of this method allowed to extend indications for TAVI and can be an option when no other surgical access is available.

References

1. Bonow R., Carabello B., Chatterjee K. et al. 2008 focused update incorporated into the acc/aha 2006 guidelines for the management of patients with valvular heart disease: A report of the american college of cardiology/American heart association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease): Endorsed by the society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, and society of thoracic surgeons. Circulation. 2008, 118 (15), e523–e661.

2. Brown J., O'Brien S., Wu C. et al. Isolated aortic valve replacement in north america comprising 108,687 patients in 10 years: Changes in risks, valve types, and outcomes in the society of thoracic surgeons national database. J. Thorac. Cardiovasc. Surg. 2009, 137 (1), 82–90.
3. Dewey T.M., Brown D.L., Herbert M.A. et al. Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. Ann. Thorac. Surg. 2010, 89 (3), 758–767.
4. Dimarakis I., Rehman S.M., Grant S.W. et al. Conventional aortic valve replacement for high-risk aortic stenosis patient not suitable for transcatheter aortic valva implantation: feasibility and outcomes. Eur. J. Cardiothorac. Surg. 2011, 40 (30), 743–748.
5. Conradi L., Seiffert M., Franzen O. et al. First experience with transcatheter aortic valve implantation and concomitant percutaneous coronary intervention. Clin. Res. Cardiol. 2011, 100 (40), 311–316.
6. Rob C. Extraperitoneal approach to the abdominal aorta. Surgery. 1963, 53, 87–89.
7. Dolinin V.A., Lebedev L.V., Peregudob I.G. et al. Technique of surgical interventions on the vessels. St. Petersburg., Hippocrate, 2004, 171. (In Russian)
8. Honig M., Mason R., Giron F. et al. Wound complications of the retroperitoneal approach to the aorta and iliac vessels. J. Vasc. Surg. 1992, 15, 28–34.
9. Weber G., Geza J., Kalmar N. K. et al. Aorto-bifemoral bypass through retroperitoneal "mini"-incision (preliminary report). Orv. Hetil. Review. Hungarian. 1994, 135 (37), 2035–2038.
10. Dion Y.M., Katkhouda N., Rouleau C. et al. Laparoscopy-assisted aortobifemoral bypass. Surg. Laparosc. Endosc. 1993, 3 (5), 425–429.
11. Klokocovnik T., Mirkovic T., Pintar T. et al. Minilaparotomy for aortoiliac occlusive disease: preliminary results. Tex. Heart Inst. J. 2002, 29 (4), 316–318.
12. Khamitov F.F., Vertkina N.V., Belov Yu.V. et al. Minimally invasive technologies in the surgery of abdominal aortic aneurysms in elderly patients. Khirurgia, 2008, 6, 78-81. (In Russian).
13. Fadin B.V., Prudkov M.I, Kuznetsov A.A. First experience with aortofemoral bypass grafting with the use of mini-laparotomy approach in critical lower limb ischemia in patients with multifocal atherosclerosis. Endoskopicheskaya khirurgia, 2002, 5, 12–16. (In Russian)

The Immediate and Long-term Results of the Graft Interventions

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Despite satisfactory immediate results of coronary artery bypass grafting (CABG), the risk of major cardiovascular events in patients remains high. Repeat CABG leads to a higher incidence of deaths and major cardiovascular events, therefore percutaneous coronary interventions (PCIs) are the option of choice for patients with post-CABG angina. The study focuses on the immediate and long-term graft stenting results. The study results show that when using the study algorithm, the graft stenting leads to the favorable immediate and long-term outcomes.

Key words: *coronary graft stenting, graft lesions, graft occlusions, algorithm of lesion selection for graft stenting.*

List of abbreviations

BA – balloon angioplasty
ITA – internal thoracic artery
BMS – bare-metal stent
MI – myocardial infarction
CABG – coronary artery bypass grafting
ACS – acute coronary syndrome
DES – drug-eluting stent
MS – myocardial scintigraphy
FFR – fractional flow reserve
PCI – percutaneous coronary intervention

The study objective is: to analyze the immediate and long-term graft stenting results in patients with post-CABG angina using the proposed algorithm.

Background. Currently, the venous graft interventions amount to 5–10% of all PCIs. However, to date, there is no clear algorithm for endovascular treatment of patients with post-CABG angina.

Methods. The study included 88 patients who underwent graft stenting according to the study algorithm. The elderly males were predominant (95.45%). There were patients with FC III and IV stable exertional angina (62.5% and 33%, respectively). The chronic occlusions of native coronary arteries were diagnosed in 76.14% of cases; diffuse lesions of the native arteries were diagnosed in 87.5% of cases; the incidences of calcifications, diffuse graft lesions, and graft occlusions were 56.82%, 12.5%, and 4.5%, respectively.

Results. The immediate interventional results were satisfactory in 98.86% of cases. The survival was 100%. One patient developed intramural MI. The clinical signs of angina pectoris diminished by at least two functional classes in 100% of patients.

Mean follow-up period was 21 (14–27) months. The long-term rates of MI and target lesion revascularization were 2.3% and 11.36%, respectively. The angina relapsed in 23 (26.14%) patients in the remote period. The angina relapses were caused by in-stent restenosis and progression of marginal stenosis or formation of new lesions in 8 (9.09%) patients each. There was a trend to reduction of the long-term PCI rates (14.63% DES versus 25.53% BMS) and target lesion PCI rates (9.76% DES versus 12.76% BMS) when DES was used.

Conclusions. When the native arteries and grafts are equally affected, the revascularization of the native arteries should be preferred, but in case of more complex lesions of the native arteries, the graft stenting should be chosen.

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Manuscript received on April 10, 2015
Accepted for publication on April 17, 2015

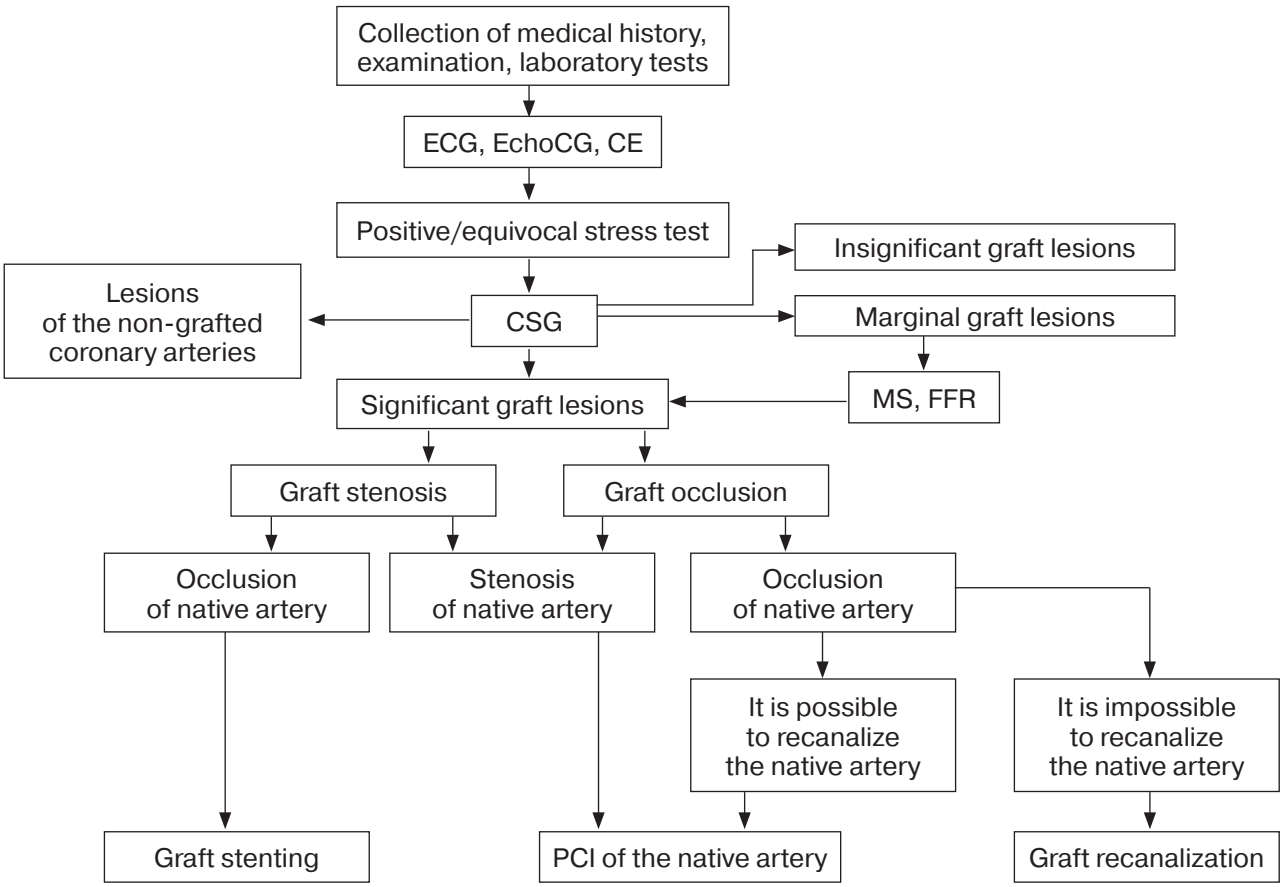

Figure 1. The algorithm of lesion selection for stenting.

Currently, more than 300,000 coronary artery bypass graftings are performed annually (14). After CABG, 10–15% of venous grafts close during the first year, and up to 50% of grafts are occluded within 10 years (2, 3). The SOS (Stenting of Saphenous vein grafts) trial demonstrated that, on average, 39% of marginal venous grafts stenoses (30–60% of the graft angiographic diameter) progressed to significant stenoses (>70%) within 35-month follow-up (4).

In the opinion of cardiologists and cardiac surgeons, the repeat CABG for graft lesions is not the surgery of choice due to higher mortality compared to the primary coronary artery bypass grafting. 5-year and 10-year survival rates after re-CABG are 75–90% and 55–75%, respectively (5).

The endovascular intervention is the option of choice in the treatment of graft lesions (6, 7, 8).

Currently, the venous graft interventions comprise 5–10% of all PCIs. The graft stenting is associated with higher rates of intraoperative complications, major cardiovascular events due to distal embolism, “no-reflow” phenomenon, and restenosis compared with coronary arteries stenting (9, 10, 11).

The study objective is: to analyze the immediate and long-term graft stenting results in patients with post-CABG angina using the proposed algorithm.

Materials and methods

The study was conducted in A.A. Vishnevsky 3rd Central Military Clinical Hospital of the Ministry of Defence of the Russian Federation. The algorithm of graft lesions selection for stenting is presented in Figure 1. The study included the patients with significant graft lesions (⩾70% graft stenosis) based on the coronarography and shuntography (CSG) and/or positive stress test in the area supplied with this graft (cycle ergometry (CEM), myocardial scintigraphy (MS) or fractional flow reserve (FFR)), FC II–IV stable angina. The patients with ACS, FC I angina, lesions in the non-grafted arteries were excluded from the study.

According to the above criteria and algorithm presented in the chart, 88 patients were included in the study and underwent graft stenting; 4 (4.5%) patients out of them underwent graft recanalization.

Prior to CABG, all patients had laboratory tests, ECG and EchoCG, stress tests; the optimal

Table 1. Clinical characteristics of patients

Parameter	n = 88
Age, years	58 (53–62)
Males	95.45%
Angina	88 (100%)
FC III	55 (62.5%)
FC IV	29 (33%)
Body mass index (kg/m^2)	27.3 (25–31.5)
Arterial hypertension	78 (88.63%)
Hypercholesterolemia	65 (73.86%)
Mean total cholesterol, mM	5.7 (5.0–6.3)
Mean LDL cholesterol, mM	4.1 (3.9–4.3)
Smoking	53 (60.23%)
Previous myocardial infarction	62 (70.45%)
Chronic heart failure	81 (92%)
FC I	22 (25%)
FC II	56 (63.6%)
FC III	3 (3.4%)
FC IV	0 (0%)
LVEF, %	57 (48–60)
Diabetes mellitus	16 (18.18%)
History of CVA	6 (6.82%)
Peripheral artery lesion	37 (42.05%)
Renal failure	4 (4.5%)
Chronic obstructive pulmonary disease (COPD)	22 (25.00%)

Table 2. Angiographic characteristics of patients

Angiographic parameter	n = 88
Number of affected arteries	3 (2–3)
Total number of grafts	3 (3)
Number of patent grafts	2 (1–2)
Degree of coronary artery stenosis	100 (100)
Degree of graft stenosis	80 (80–90)
Bifurcation stenting	0 (0)
Main LCA lesion	6 (6.82%)
Proximal LAD lesion	36 (40.91%)
Chronic occlusion	67 (76.14%)
Diffuse lesion of the native coronary arteries	77 (87.5)%
Calcified arterial lesion	50 (56.82%)
Diffuse graft lesion	11 (12.5%)
Total stent length, mm	27 (22–30.5)
Mean stent diameter, mm	3.5 (3.0–3.5)

Table 3. Localization of graft lesions

Affected segment	Arm II
Proximal segment	20 (22.73%)
Middle segment	36 (40.91%)
Distal segment	32 (36.36%)

medicinal therapy was selected. 4 days before PCI, all patients were prescribed dual desegregate therapy (acetylsalicylic acid 100 mg/day + clopidogrel 75 mg/day).

The complete elimination of graft stenosis was considered as satisfactory technical results of PCI. Graft stenting was defined as PCI of one graft with obligatory implantation of drug-eluting stent (DES) or bare metal stent (BMS).

The following immediate interventional results were assessed during the in-hospital period: mortality, acute MI, repeat myocardial revascularization (PCI or CABG), major cardiovascular events.

The interventional results were considered to be satisfactory if angiographic results were obtained and angina severity was diminished by at least two functional classes, or clinical signs of angina completely resolved and there were no major adverse cardiovascular events.

The **in-hospital** major adverse cardiovascular events were as follows: death, MI and emergency interventions (PCI or CABG), however, the patients who had in-hospital major cardiovascular events were not excluded from the study, as their long-term results were of interest.

The following endpoints were evaluated in the **follow-up period**: incidences of lethal outcomes, acute MI, recurrent angina, all PCIs, repeat revascularizations of the target lesion and major adverse cardiovascular events.

The major adverse cardiovascular events in the follow-up period included death, myocardial infarction, and all PCI.

The angina relapse in the follow-up period was defined as development of the angina pectoris symptoms (if there were no signs after PCI) or its progression by at least one functional class among patients with persistent angina symptoms.

Repeat revascularizations of the target vessel were performed in case of in-stent restenosis (thrombosis).

The lesion formation in previously unchanged coronary artery or graft as well as progression of stenotic atherosclerotic process, and symptoms reoccurrence due to this process were not considered to be complications.

Restenosis was defined as stenosis > 50% inside a stent or at the stent edges.

The tabulated data are presented as percentages, mean value and standard deviation, median and interquartile interval depending on the variables distribution.

The primary clinical characteristics of the enrolled patients are presented in Table 1.

General angiographic characteristics of the enrolled patients are presented in Table 2. The graft lesions by localization are presented in Table 3.

RCA was the most common symptom-related artery; LAD placed second. Morphology of the graft lesions is presented in Figure 2.

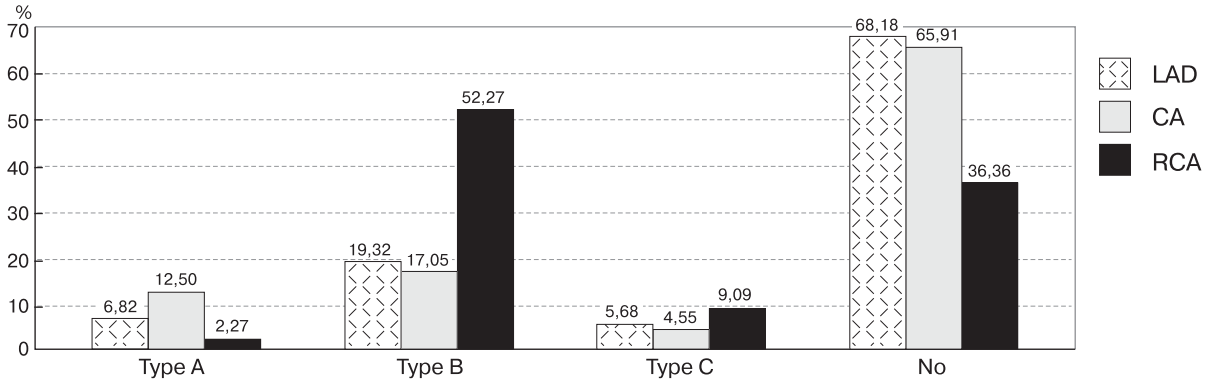

Figure 2. Morphology of the graft lesions.

The lesions of grafts to RCA were most commonly observed. The lesions of grafts to LAD were the rarest ones (if any, commonly type B).

Results

The implantation rates of DES (46.6%) and BMS (50%) were comparable. DES and BMS were implanted into one graft in 3 (3.4%) patients.

On Day 1 after PCI, increased troponin T level was observed in 8 patients. The increased troponin T level was negligible in 7 patients and not accompanied with negative changes in the ECG. One patient developed embolism of obtuse marginal branch (OM) when a Wall carotis stent was implanted in the large arteriovenous graft. On Day 1 after PCI, a significantly increased troponin T level was observed in this patient, however, the ischemical dynamics on ECG resolved. Mean troponin T level is presented in Table 4.

The in-hospital survival was 100%. One patient developed intramural MI (Table 5).

Therefore, the clinical signs of angina pectoris diminished by at least two functional classes in 100% of patients (Fig. 3).

The immediate interventional results were satisfactory in 98.86% of cases.

The long-term results were obtained from all patients over 3–36 months (mean follow-up was 21 (14–27) months).

There were no deaths in the follow-up period.

2 patients (2.3%) had MI in the follow-up period: 19 and 28 months after PCI. The direct MI cause in all cases was confirmed late DES thrombosis.

The incidence of revascularization procedures (PCIs) was 20.45%, and the rate of target lesion revascularization was 11.36%.

The angina relapsed in 23 (26.14%) patients in the follow-up period (Table 7). The timing of angina relapse ranged from 11 to 36 months. The angina relapses were caused by in-stent restenosis and progression of marginal stenosis or formation of new lesions in 8 patients (9.09%) each. 6 (6.8%) patients had BMS restenosis, thus, DESs were implanted to them.

Table 4. Mean cardiotropic enzyme level on Day 1 after intervention

Enzyme	n = 88	p
Troponin T (N=0.0 ng/mL)	0,033 ± 0,145	0,000004

Table 5. The Immediate (in-hospital) results

Parameter	n = 88
Mortality	0(0%)
Myocardial infarction	1(1.14%)
Stent thrombosis	0(0%)
Urgent cardiovascular intervention	0(0%)
Major cardiovascular events	1(1.14%)
TIMI III flow	87(98.86%)
Immediate clinical success	87(98.86%)

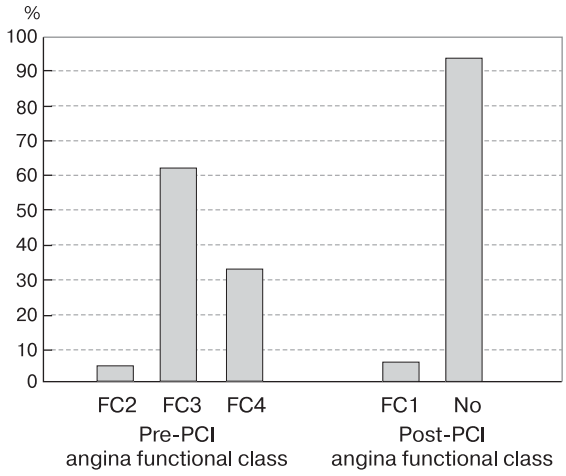

Figure 3. Dynamics of angina functional classes in the enrolled patients.

Table 6. Long-term results

Parameter	n = 88
Mortality	0 (0%)
Myocardial infarction	2 (2.27%)
CABG in the follow-up period	26 (29.55%)
PCI in the follow-up period	18 (20.45%)
PCI of the target lesion	10 (11.36%)
Major cardiovascular events	18 (20.45%)

Table 7. Causes of angina relapses based on CSG results

Parameter	n = 88
In-stent restenosis	8 (9.09%)
Late stent thrombosis	2 (2.27%)
Progression of stenotic atherosclerosis	9 (10.23%)

One patient (1.14%) had restenosis within the previously implanted DES (Xience V), and one patient (1.14%) had marginal DES restenosis (Cypher). In both cases, restenosis BA was performed using a drug-eluting balloon. The angina-free period varied from 11 to 28 months and from 13 to 32 months for BMS and DES, respectively.

The major cardiovascular event-free Kaplan-Meier survival curve is presented in Figure 4.

There was a trend to reduced rates of angina relapses (DES 21.95% versus BMS 29.79%), follow-up PCI (DES 14.63% versus BMS 25.53%) and PCI of target lesion (DES 9.76% versus BMS 12.76%) when DES was compared to BMS, although the differences were not statistically significant.

Discussion

The enrolled patients underwent CABG and had numerous risk factors for development and progression of CHD and variety of co-morbidities. All patients included in the study had a high risk for open heart surgery based on EuroSCORE scale. In general, the clinical characteristics of patients were similar to those of subjects included in a number of other studies designed for graft stenting (12–18). Some risk factors for CHD (smoking, hypertension), and co-morbidities (chronic heart failure, prior myocardial infarction, chronic obstructive pulmonary disease) were more common in patients included in our study, however, type 2 diabetes mellitus was observed more rarely.

The angiographic characteristics of the grafts lesions largely coincide with the literature data (12–18). However, higher incidence of calcification of the native arteries was noted in our study.

The in-hospital survival was 100%; the incidence of myocardial infarction was 1.14%; the frequency of major adverse cardiovascular events was 1.14%. The immediate interventional results were satisfactory in 98.86% of patients. The main predictors of technical failures were diffuse degeneration of the venous graft and large volume of atherosclerotic plaque.

The immediate results were slightly better than those from large studies of graft stenting. According to the literature data, the incidence

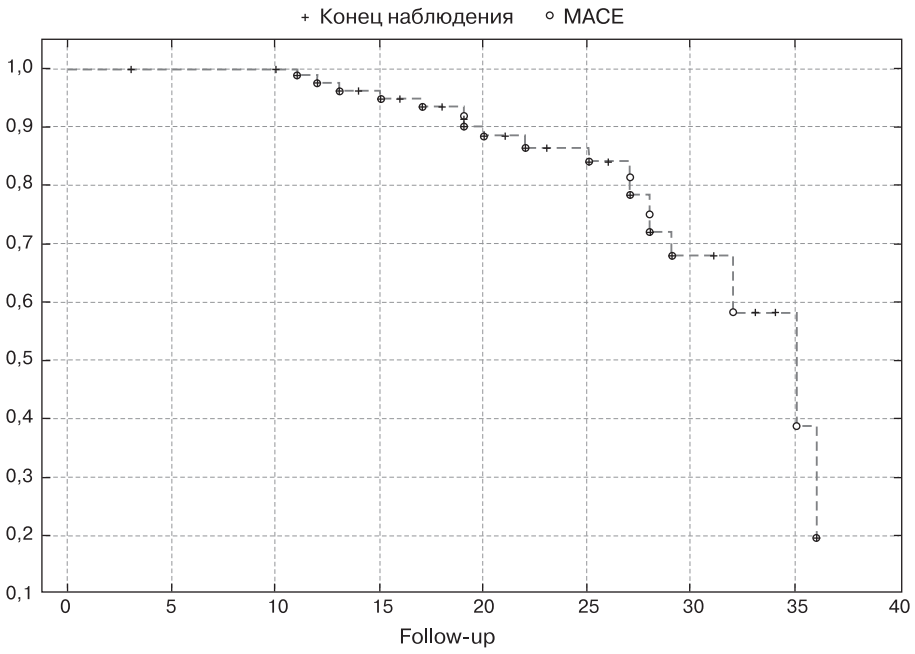

Figure 4. Dynamics of MACE-free survival.

of MI varied from 2 to 5% (12–18), the frequency of TIMI 3 blood flow was 90-93%, and the rate of major adverse cardiovascular events ranged from 2.6 to 6% (12–18). These results can be partly explained by the fact that not all types of graft lesions were stented in our study compared to the listed studies. The graft lesions were selected based on the algorithm. Additionally, recanalization of occluded grafts was minimized in our study and amounted to 4.5% only because the literature data showed adverse outcomes of these interventions. According to the published data, successful recanalization of chronic occlusion of grafts ranges from 32% to 79%, while restenosis is up to 61%, even with DES (19–21).

Analysis of the endovascular treatment results identified risk factors of the major adverse cardiovascular events during the in-hospital stay. The clinical factors were: previous MI, COPD, smoking, diabetes mellitus, multifocal atherosclerosis, and hypercholesterolemia. The angiographic factors were: diffuse graft lesion, calcified lesion, affected main LCA, and chronic occlusions.

The long-term results were evaluated in patients during the follow-up period from 3 to 36 months.

According to the literature data, the follow-up mortality after graft revascularization ranges from 1% to 5.2% (12, 14, 17, 18). There were no deaths during the follow-up in the study arm.

The MI incidence based on the published data ranges from 4.2% to 6% (3, 12, 14, 15, 17–19, 22, 23). A lower incidence of myocardial infarction in our study can be explained by graft stenting according to the algorithm, almost complete refusal from recanalization of occluded grafts, and high patients' adherence to lipid-lowering therapy, which significantly reduces the incidence of major adverse cardiovascular events in the follow-up period (17, 24, 25).

In our study, the late stent thromboses were observed in follow-up years 2 and 3, and their rate was higher compared with the literature data (26, 27). The reasons for these very late stent thromboses are still poorly understood.

Follow-up revascularization and target lesion revascularization rates were 20.45% and 11.36%, respectively. In the published literature on graft stenting, follow-up revascularization rates vary from 11.5% to 22% depending on lesion complexity and types of stents (3, 12, 14, 15, 17–19, 22, 23, 28), but in most of the above studies, the endpoints were target vessel revascularization and/or target lesion revascularization. In our study, follow-up PCI frequency included all PCIs. The frequency of target lesion revascularization was defined separately and comparable with the literature data (7.2–13.1%) (3, 12, 14, 15, 17–19, 22, 23, 28).

The in-DES restenoses are partly explained by the fact that they were implanted in the internal thoracic artery (ITA) graft and when the ITA grafts are stented, restenoses increase significantly (30, 31). Nevertheless, restenosis rates do not exceed the literature data (6.8–15%) (3, 12, 14, 15, 17–19, 22, 23, 28).

Cumulative rate of major cardiovascular events is comparable with most studies designed for graft revascularization. According to the literature data, mean value is approximately 15.4–26% (3, 12, 14, 15, 17–19, 22, 23, 28). However, it should be noted that in some studies it reached 30–68%, especially in case of diffusely affected or occluded grafts (19, 20). In our study, this parameter included all cases of follow-up revascularization regardless of whether they were the target lesion revascularizations or not.

There was a trend to reduced incidences of angina relapses (DES 21.95% versus BMS 29.79%), follow-up PCI (DES 14.63% versus BMS 25.53%) and PCI of target lesion (DES 9.76% versus BMS 12.76%) when DES was compared to BMS, although the differences were not statistically significant. However, they were comparable with the literature results for graft stenting: repeat target lesion revascularizations range from 7.2% to 15% when DES is used and from 13.1% to 26% when BMS is used (3, 12, 14, 15, 17–19, 22, 23, 28), if not taking into account the results from studies of grafts occlusion and arterial grafts where this value was much higher (19, 20).

The statistical analysis using a Cox regression model identified the clinical and angiographic relative risk factors for the major adverse cardiovascular events. The independent clinical predictors were: elderly age (relative risk = 1.033; 95% CI: 0.984–1.08), type 2 diabetes mellitus (relative risk = 2.85; 95% CI: 1.13–7.17), previous MI (relative risk = 1.54; 95% CI: 0.65–3.64), and grade 2–3 obesity (relative risk = 1.045; 95% CI: 0.95–1.15). These factors are mentioned to a greater or lesser extent in different revascularization studies as predictors of major cardiovascular events (3, 12, 14, 15,

17–19, 22, 23, 28). The independent angiographic predictors were type C lesion of the graft to the LAD (relative risk = 1.27; 95% CI: 0.75–2.15) and type C lesion of the graft to the RCA (relative risk = 1.027; 95% CI: 0.99–1.06). These 2 factors are not mentioned in the published data, since few investigators apply this classification to determine the morphology of the grafts lesions, although these factors coincide indirectly with the risk factors observed in other studies: multivessel coronary disease (relative risk = 5.32; 95% CI: 1.03–27.56) and small stents diameter (relative risk = 1.042; 95% CI: 0.99–1.087). These risk factors are confirmed by numerous studies and listed in almost all the literature data.

Conclusions

1. If the proposed algorithm is followed, the grafts stenting gives favorable immediate and long-term results.

2. When the native arteries and grafts are equally affected, revascularization of the native arteries should be preferred, but in case of more complex lesions of the native arteries, the graft stenting should be chosen.

3. The graft occlusion interventions are characterized by a low rate of technical success and also increased risk of major adverse cardiovascular events; therefore, they are justified only when any other revascularization methods fail.

4. It is appropriate to consider re-CABG in case of multiple grafts occlusions, unfeasible revascularization of native arteries, and medicinal therapy failure.

References

1. Epstein A.J., Polsky D., Yang F. et al. Coronary revascularization trends in the United States, 2001–2008. JAMA, 2011, 305, 1769–1776.
2. Bockeria L.A., Alekyan B.G. The guidance on the roentgenologic-endovascular surgery of the heart and vessels. Moscow. Publisher NCSSH im. A.N. Bakuleva RAMN. 2008. Vol.3, p. 592. (In Russian)
3. Harskamp R.E., Lopes R.D., Baisden C.E. et al. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. Ann. Surg. 2013, 257 (5), 824–833.
4. Abdel-Karim A.R., Da Silva M., Lichtenwalter C. Prevalence and outcomes of intermediate saphenous vein graft lesions: findings from the stenting of saphenous vein grafts randomized-controlled trial. Int. J. Cardiol., 2013, 168 (3), 2468–2473. Epub 2013 Apr 3.
5. Stamou S.C., Pfister A.J., Dullum M.K. et al. Late outcome of reoperative coronary revascularization on the beating heart. Heart Surg. Forum. 2001, 4, 69–73.
6. Brilakis E.S., Wang T.Y., Rao S.V. et al. Frequency and predictors of drug-eluting stent use in saphenous vein bypass graft percutaneous coronary interventions: a report from the American College of Cardiology National Cardiovascular Data CathPCI registry. JACC Cardiovasc. Interv. 2010, 3, 1068–1073.
7. Brodie B.R., Wilson H., Stuckey T. et al. Outcomes with drug-eluting versus bare-metal stents in saphenous vein graft intervention results from the STENT (strategic transcatheter evaluation of new therapies) group. JACC Cardiovasc. Interv. 2009, 2, 1105–1112.
8. Morrison D.A., Sethi G., Sacks J. et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. J. Am. Coll. Cardiol. 2002, 40, 1951–1954.
9. Al S.J., Velianou J.L., Berger P.B. et al. Primary percutaneous coronary interventions in patients with acute myocardial infarction and prior coronary artery bypass grafting. Am. Heart J. 2001, 142, 452–459.
10. Brodie B.R., Versteeg D.S., Brodie M.M. et al. Poor long-term patient and graft survival after primary percutaneous coronary intervention for acute myocardial infarction due to saphenous vein graft occlusion. Catheter. Cardiovasc. Interv. 2005, 65, 504–509.
11. Stone G.W., Brodie B.R., Griffin J.J. et al. Clinical and angiographic outcomes in patients with previous coronary artery bypass graft surgery treated with primary balloon angioplasty for acute myocardial infarction. Second Primary Angioplasty in Myocardial Infarction Trial (PAMI-2) Investigators. J. Am. Coll. Cardiol. 2000, 35, 605–611.
12. Hakeem A., Helmy T., Munsif S. et al. Safety and efficacy of drug eluting stents compared with bare metal stents for saphenous vein graft interventions: a comprehensive meta-analysis of randomized trials and observational studies comprising 7,994 patients. Catheter. Cardiovasc. Interv. 2011, 77, 343–355.
13. Lee M.S., Hu P.P., Aragon J. et al. Comparison of sirolimus-eluting stents with paclitaxel-eluting stents in saphenous vein graft intervention (from a multicenter Southern California Registry). Am. J. Cardiol. 2010, 106, 337–341.
14. Lee M.S., Yang T., Kandzari D.E. et al. Comparison by meta-analysis of drug-eluting stents and bare metal stents for saphenous vein graft intervention. Am. J. Cardiol. 2010, 105, 1076–1082.
15. Mehilli J., Pache J., Abdel-Wahab M. et al. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. Lancet. 2011, 378, 1071–1078.
16. Meier P., Brilakis E.S., Corti R., et al. Drug-eluting versus bare-metal stent for treatment of saphenous vein grafts: a meta-analysis. PLoS One. 2010, 5, e11040.
17. Testa L., Agostoni P., Vermeersch P. et al. Drug eluting stents versus bare metal stents in the treatment of saphenous vein graft disease: a systematic review and meta-analysis. EuroIntervention. 2010, 6, 527–536.
18. Wiisanen M.E., bdel-Latif A., Mukherjee D., Ziada K.M. Drug-eluting stents versus bare-metal stents in saphenous vein graft interventions: a systematic review and meta-analysis. JACC Cardiovasc. Interv. 2010, 3, 1262–1273.
19. Al-Lamee R., Ielasi A., Latib A. et al. Clinical and angiographic outcomes after percutaneous recanalization of

chronic total saphenous vein graft occlusion using modern techniques. Am. J. Cardiol. 2010, 106 (12), 1721–1727.
20. Garg N., Hakeem A., Gobal F., Uretsky B.F. Outcomes of percutaneous coronary intervention of chronic total saphenous vein graft occlusions in the contemporary era. Catheter. Cardiovasc. Interv. 2014, 83 (7), 1025–1032.
21. Levine G.N., Bates E.R., Blankenship J.C. et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J. Am. Coll. Cardiol. 2011, 58 (24): e44–e122.
22. Brilakis E.S., Lichtenwalter C., de Lemos J.A. et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. J. Am. Coll. Cardiol. 2009, 53, 919–928.
23. Kitabata H., Loh J.P., Pendyala L.K. et al. Two-year follow-up of outcomes of second-generation everolimus-eluting stents versus first-generation drug-eluting stents for stenosis of saphenous vein grafts used as aortocoronary conduits. Am. J. Cardiol. 2013, 112 (1), 61–67.
24. Shah S.J., Waters D.D., Barter P. et al. Intensive lipid-lowering with atorvastatin for secondaryprevention in patients after coronary artery bypass surgery. J. Am. Coll. Cardiol. 2008, 51, 1938–1943.
25. Zhou Q., Liao J.K. Statins and cardiovascular diseases: from cholesterol lowering to pleiotropy. Curr. Pharm. Des. 2009, 15, 467–478.
26. Babunashvili A.M., Ivanov V.A. Coronary Chronic Total Occlusion: anatomy, pathophysiology, endovascular treatment: Monograph. Moscow, ACB Publisher, 2012, pp.487–509. (In Russian).
27. Iakovou I., Schmidt T., Bonizzoni E. et al. Incidence, predictors and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005, 293, 2126–2130.
28. Hougaard M., Thayssen P., Kaltoft A. et al. Long-term outcome following percutaneous coronary intervention with drug-eluting stents compared with bare-metal stents in saphenous vein graft lesions: from Western Denmark heart registry. Catheter. Cardiovasc. Interv. 2014, 83 (7), 1035–1042.
29. Ybarra L.F., Ribeiro H.B., Pozetti A.H. et al. Long-term follow-up of drug eluting versus bare metal stents in the treatment of saphenous vein graft lesions. Catheter. Cardiovasc. Interv. 2013, 82 (7): E856–E863.
30. Ijsselmuiden A.J.J., Ezechiels J.P., Westendorp I.C.D. et al. Complete versus culprit vessel percutaneous coronary intervention in multivessel disease: A randomized comparison. Am. Heart J. 2004, 148, 467–474.
31. Jones J.M., O'kane H., Gladstone D.J. et al. Repeat heart valve surgery: risk factors for operative mortality. J. Thorac. Cardiovasc. Surg. 2001, 122, 913–918.

Fractional Flow Reserve as a Reliable Method of Identifying the Syndrome-Related Artery in Patients with Stable Coronary Artery Disease (Literature Review)

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To date, invasive coronary angiography is a routine method for the evaluation of the state of cardiac vessels. However, in their everyday practice, invasive cardiologists face the difficulties in the evaluation of coronary blood flow in the presence of clear clinical picture and the data of instrumental method of study. Wide-spread use of the methods of intravascular visualization facuilitate accurate determination of the tactics of treatment in many cases, however all these methods are just an addition to coronary angiography and cannot assess functional state of the coronary arteries. The method of invasive evaluation of the state of coronary blood flow based on the measurement of trans-stenotic gradient got general recognition and became a regular clinical practice. Unfortunately, the method of evaluation of fractional flow reserve has its advantages and drawbacks, which should be always taken into account in questionable situations. This article is an attempt of a review and an analysis of the existing literature with the aim to give an objective assessment of this methods role in everyday clinical practice.

Key words: *fractional flow reserve, coronary artery disease, PCI.*

Recent advances in endovascular surgery comprise not only the field of complex cases treatment, but also high-precision assessment of functional state of coronary blood flow. Angiography remains the "Gold Standard" for coronary vessels visualization. But this technique is limited due to two-dimensional view of vessel and does not always provide accurate information regarding degree of stenosis (1). Besides, coronary angiography provides only limited data about functional and physiological state of coronary blood flow, particularly in borderline stenosis (2).

In real life cardiologist sometimes faces considerable discrepancy between the results of stress tests and coronary angiography. Therefore routine use of functional intravascular methods provides optimal choice of treatment. The purpose of this literature review is to provide an excursion into the existing research base on fractional flow reserve assessment and to define the advantages and the disadvantages of this method.

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Manuscript received on December 10, 2014.
Accepted for publication in January 13, 2015

It is known that FFR reflects correlation between intracoronary blood pressure and degree of stenosis under conditions of altered blood flow. These two parameters must be measured during the maximal pharmacological hyperemia. FFR less than 0.75 indicates hemodynamically significant stenosis (3). E.g. DEFER study, performed in 2001 to evaluate FFR measurement significance in treating borderline stenosis, included 325 patients who had no documented myocardial ischemia in previous 2 month. All of them had stenosis over 50% in arteries over 2.5 mm in diameter. Patients were divided into 3 groups according to the results of coronary angiography. The first group included patients with FFR over 0.75 and no PCI performed (91 patients), the second group (90 patients) included patients with same FFR and PCI performed, and the third group (144 patients) with FFR less than 0.75, all of whom received PCI. Late outcomes were assessed in 12 months in 325 patients (100%), in 24 months – in 317 (98%) and in 5 years – in 286 patients. No significant difference in MACE-free survival was found between the first and the second groups (80% and 73%, respectively; p = 0.52), whereas it was significantly less in the third group (63%; p = 0.03). 5-years outcome after delayed PCI in borderline stenosis estimated as FFR over 0.75 was excellent. Risk of cardiac death and myocardial

infarction was less than 1% yearly and was not less after PCI performed. (4).

Since description of technical details of FFR measurement is not the goal of this article, it would be interesting to provide an excursion into the existing research base of FFR measurement, to define the advantages and the disadvantages of this method and the correlation between FFR and both coronary angiography data and the results of stress tests.

Results of FFR measurement usually correlate with the results of stress tests and have well defined borderline value of 0.75. It was demonstrated by De Bruyne (5, 6), Pijls (7, 8), Chamuleau (9). The lowest ischemia-free value of FFR was estimated by comparison of FFR results with the results of stress tests. De Brunye et al. (5) showed that among 60 patients with single-vessel disease and normal LV function, FFR of 0.72 was the lowest and stress ECG was normal. Same authors (7) investigated FFR in 60 patients with single-vessel disease and positive stress test before and after PCI. 56 patients had pre-PCI FFR less than 0.74 and post-PCI FFR over 0.75. These data are suggestive of a high grade of correlation between FFR measurement and stress test results.

FFR also correlates well with the results of stress-echo with dobutamine. 75 patients with single-vessel disease underwent stress-echo and FFR assessment (10). 20 patients had FFR over 0.75 and negative stress-echo, while 41 out of 54 had FFR less than 0.75 and positive stress-echo. Some studies compared FFR to the results of stress-scintigraphy (9, 2, 13). All these studies performed independently by Abe, Fearon and Chamuleau, have shown a high grade of correlation between FFR and non-invasive tests.

It was also established that FFR < 0.75 is 100% specific for stress-induced ischemia, whereas FFR >0.80 is highly sensitive (over 0.90) to the absence of stress-induced ischemia (6, 7, 8). A so-called “grey zone” between 0.75 and 0.80 is not associated with high incidence of late cardiovascular events according to T.P. van Hoef et al. (14)

Sometimes it can be very challenging to define stenosis degree or syndrome-related artery in patients who did not receive stress-test prior to coronary angiography. Results can be controversial or nonconfirming (11, 4). Some controversy can also be seen in cases when two stenoses are located in the same artery. It is evident that each of them can influence coronary blood flow. Distal stenosis can lower pressure gradient in proximal stenosis, thus increasing FFR value. FFR measurement in distal stenosis gives an idea of summated complex influence of both stenoses, however is unable to distinguish the lesion that significantly impacts the blood flow. (15). Some authors tried to develop charts and equations to determine FFR values in case of multiple lesions (16). They managed to find strict correlations between predicted and actual FFR value, measured after PCI, but only in 32 patients (15, 16). It is evident that these data do not have any practical value. In real-time clinical practice only total influence of all lesions in an artery can be assessed by measuring FFR distally to the most distal stenosis. E.g. in case of FFR <0.75, PCI can be performed for the most angiographically severe stenosis. After successful PCI, FFR can be measured again to estimate other stenoses. (17).

Similar problems may occur in patients with multivessel disease. The presence and the degree of ischemia in each vessel must be assessed individually. A large-scaled study by Beller et al. (18) included 12000 patients and showed that treatment of MVD using only PCI or only CABG makes little sense.

Since non-invasive tests are not accurate in identification of syndrome-related lesion in MVD, the usefulness of FFR in these cases is evident (19). FFR measurement is especially useful for determining the most appropriate method of treatment.

De Bruyne (20) showed that in case of total diffuse coronary atherosclerosis with absent visual signs of significant stenoses, FFR can be less than 0.75. The diameter gradient and the pathologic vascular resistance can lead to abnormal FFR measurement in these vessels.

Coronary vasospasm in intact vessel accompanied by positive stress test results is a well known clinical paradox and presents one more “weak spot” of FFR measurement. Vasospasm will not be angiographically documented due to hyperemic protocol performed and FFR value will be normal. The same can be seen when collateral blood flow is well-developed, according to Pijls et al. (21, 22)

RESOLVE study (23) performed by Jeremias et al. showed that pressure gradient can be seen without pharmacological hyperemia if it is high enough. Pressure gradients were assessed in two groups of patients with and without pharmacological hyperemia. According to the authors, this is enough to determine whether

revascularization is needed immediately or it can be safely delayed. Christian Bietau et al. reports that no significant difference was seen between intracoronary and intravenous administration of hyperemic agent. 114 patients with borderline stenoses (50–75%) were randomized into two groups: with intracoronary administration (40 μg for RCA, 80 μg for LCA) and intravenous continuous infusion (140 μg/kg/min in two minutes) of adenosine. FFR values determined by both techniques in both groups demonstrate a high degree of correlation ($r = 0.99$, $p < 0.001$), whereas intracoronary bolus takes less time and is much more comfortable for patient. (24)

Another evidence of aforementioned information can be found in numerous studies that assessed FFR during multi-slice CT imaging. Evidently these studies were performed without selective hyperemia. Bjarne L. et al. found high degree of correlation between non-invasive and invasive FFR measurements in 254 patients. (25) Sara Gaur et al. also reported high reliability of non-invasive FFR compared to invasive FFR ($p = 0.60$) (26).

Some interesting studies compared FFR and intravascular imaging. A. Takagi et al. (27) studied 51 patients using IVUS and FFR. They showed correlation between minimal lumen area and FFR measurement results. C. Briguori et al. (28) made the same in 53 patients. They found no correlation between atherosclerotic plaque area measured by IVUS and FFR, thus demonstrating that FFR correlates with narrowing of arterial lumen, not with prevalence or size of atherosclerotic plaques.

The main purpose of modern optical coherence tomography, as well as of IVUS, is the assessment of arterial wall. Sun-Joo Jang et al. studied 42 patients with borderline stenoses before PCI using OCT and FFR. They showed that FFR and OCT correlate well in the assessment of borderline stenoses in small samples, and are also highly sensitive (67–75%) and specific (92–100%) if FFR is less than 0.80. The above studies convincingly demonstrates the relevance of FFR and OCT data. The advantages and the disadvantages of each method are still a matter to discuss and need further investigation.

Thus, FFR measurement is a major breakthrough in using intracoronary pressure gradient for coronary arteries assessment. FFR binds intracoronary pressure measurement and evaluation of stenosis significance. The advantages of FFR compared to routine coronary angiography are evident. For example, coronary angiography is unreliable when dealing with ostial lesions whereas FFR shows that most of them are not significant. In cases of multivessel disease FFR can prevent unnecessary and complex coronary interventions and thus avoid complications and unsatisfactory long-term results. FFR can be an invaluable tool in anatomically complex cases, allowing to reveal syndrome-related stenosis and avoid senseless full revascularization. The fact that only one-third of lesions over 75% are significant, can give a stimulus for further interpretation of the concept of revascularization volume. But in real-life clinical practice FFR is seldom needed and its routine use is limited by technical complexity, the need of pharmacological support, the length of the procedure and patient's discomfort.

References

1. Prati F., Regar E., Mintz G.S. et al. Imaging of atherosclerosis: optical coherence tomography (OCT). Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur. Heart J. 2010, 31, 401–415.
2. Folland E., Vogel R., Hartigan P. et al. Relation between coronary artery stenosis assessed by visual, caliper and computer methods and exercise capacity in patients with single-vessel coronary artery disease. Circulation. 1994, 89, 2005–2014.
3. Escaned J., Alfonso F., Botas J. Pressure wire: technical considerations. Basic principles of fractional flow reserve. Intracoronary diagnostic techniques. McGraw-Hill/Interamericana, Madrid, 2003, 337.
4. Pijls N., van Schaardenburgh P., Manoharan G. et al. Percutaneous coronary intervention of funtionally nonsignificant stenosis. 5-Year follow-up of the DEFER Study. J. Am. Coll. Cardiol. 2007, 49, 2105–2111.
5. De Bruyne B., Bartunek J., Sys S.U. et al. Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. Circulation, 1995, 92, 3183–3193.
6. De Bruyne B., Pijls N., Bartunek J., et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation, 2001, 104, 157–162.
7. Pijls N., van Gelder B., van der Voort P. et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995, 92, 3183–3193.
8. Pijls N., de Bruyne B., Peels K. et al. Measurement of myocardial fractional flow reserve to assess the functional severity of coronary artery stenosis. N. Engl. J. Med. 1996, 334, 1703–1708.
9. Chamuleau S.A.J., Meuwissen M., van Eck-Smit B.L.F. et al. Fractional flow reserve, absolute and relative coronary blood flow velocity reserve in relation to the results of

technetium-99m sestamibi single-photon emission computed tomography in patients with two-vessel coronary artery disease. J. Am. Coll. Cardiol. 2001, 37,1316–1322.
10. Bartunek J., Marwick T.H. Rodrigues A.C.T. et al. Dobutamine-induced wall motion abnormalities: Correlation with fractional flow reserve and quantitative coronary angiography. J. Am. Coll. Cardiol. 1996, 27, 1429–1436.
11. Topol E.J., Ellis S.G., Cosgrove D.M. et al. Analysis of coronary angioplasty practice in the United States with an insurance-claims data base. Circulation. 1993, 87, 1489–1498.
12. Abe M., Tomiyama H., Yoshida H. et al. Diastolic fractional flow reserve to assess the functional severity of moderate coronary artery stenoses in comparison with fractional flow reserve and coronary flow velocity reserve. Circulation. 2000, 102, 2356–2370.
13. Meuwissen M., Chamuleau S.A.J., Siebes M. et al. Role of variability in microvascular resistance of fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. Circulation. 2001, 103, 184–187.
14. van de Hoef T. P., van Lavieren M.A., Damman P. et al. Prognostic value of fractional flow reserve after deferral of revascularization using the 0,75 Defer or 0,80 fame OR 0.80 FAME fractional flow reserve cut-off value: clinical implications of the 0,75-0,80 fractional flow reserve grey zone. J. Am. Coll. Cardiol. 2014, 63. doi: 10.1016/S0735-1097(14) 61786-1.
15. Pijls N., de Bruyne B., Bech G.J.W. et al. Coronary pressure measurement to assess the gemodynamic significance of serial stenoses within one coronary artery. Validation in humans. Circulation. 2000, 102, 2371–2372.
16. De Bruyne B., Pijls N., Heyndrickx G.R. et al. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and validation. Circulation. 2000, 101, 1840–1847.
17. Pijls N., De Bruyne B. Fractional flow reserve in some specific pathologic conditions. In: Coronary Pressure. Second Edition. Dordrecht: Kluwer Academic Publishers. 2000, 255–267.
18. Beller G.A., Zaret B.L. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation. 2000, 101, 1465–1478.
19. Botman C.J., Bech G.J.W., De Bruyne B. et al. PTCA versus bypass surgery in patients with multivessel disease: a tailored approach based on coronary pressure measurement. J. Am. Coll. Cardiol. 2001, 37,55A.
20. De Bruyne B., Hersbach F., Pijls N. et al. Abdominal epicardial coronary resistance in patients with diffuse atherosclerosis but “normal” coronary angiography. Circulation. 2001, 104, 2401–2406.
21. Van Liebergen R., Piek J.J., Koch K.T. et al. Quantification of collateral flow in humans a comparison of angiographic, electrocardiographic and hemodynamic variables. J. Am. Coll. Cardiol. 1999, 33, 670–677.
22. Pijls N., De Bruyne B., eds. Coronary pressure. Dordrecht, Kluwer Academic Publishers. 1997, 60–68.
23. Klocke F.J. Resting Versus Vasodilated Pressure Gradients in Assessing Stenosis Severity. J. Am. Coll. Cardiol. 2014, 63 (13), 1262–1263.
24. Bietau C., Schlundt C., Klinghammer L., Achenbach S. Comparison of intravenous and intracocronary adenosine for determination of pressure-derived fractional flow reserve. J. Am. Coll. Cardiol. 2014, 63 (12_S), 1016–1097.
25. Nørgaard B.L., Jonathon L., Gaur S. Diagnostic Performance of Noninvasive Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography in Suspected Coronary Artery Disease The NXT Trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J. Am. Coll. Cardiol. 2014, 63(12), 1145–1155.
26. Gaur S., Bezerra H.G., Evald H. Reproducibility of invasively measured and non-invasively computed fractional flow reserve. J. Am. Coll. Cardiol. 2014, 63 (12_S), 1016–1097.
27. Takagi A., Tsurumi Y., Ishii Y. et al. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis. Relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. Circulation. 1999, 100, 250–255.
28. Briguori C., Anzuini A., Airoldi F. et al. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and correlation with fractional flow reserve. Am. J. Cardiol. 2001, 87, 136–141.
29. Sun-Joo Jang, Jung-Min Ahn, Seung-Jung Park, Wang-Yuhl Oh. Derivation and validation of optical coherence tomography-derived fractional flow reserve for the assessment of intermediate coronary lesions. J. Am. Coll. Cardiol. 2014, 63, 1016–1097.

Reperfusion Peak during Primary Angioplasty in Patients with STEMI: Incidence, Predictors, and Impact on Outcome

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The study is designed to assess the ST changes during primary PCI in patients with STEMI using continuous 12-lead ECG monitoring. The reperfusion peak is described, its incidence is evaluated; and its predictors are identified.
Key words: *reperfusion, STEMI, PCI, ECG monitoring.*

Background and objective. The blood flow restoration in the infarct-related artery (IRA) is the main strategy for *STEMI* treatment. ECG analysis demonstrated that *ST* depression while the effective reperfusion therapy is being performed may be preceded by short peak of exacerbated *ST* elevation. The aim of this study was to investigate the incidence and predictors of reperfusion peak during primary percutaneous coronary intervention (PCI) in patients with *STEMI*.

Methods. Continuous 12-lead ECG monitoring from the admission to the hospital, lasting during PCI was performed in 70 subjects, mean age was 56 ± 13 years; and 86% out of them were males. To identify predictors of reperfusion peak, the clinical, angiographic and electrocardiographic characteristics were assessed in a regression model.

Results. Reperfusion peak, an instant increase in *ST* elevation immediately after the IRA lumen restoration by 117 ± 101% with fast inverse changes was registered in 38.6% of cases. Its occurrence was associated with (when univariate analysis was used): complete occlusion of the IRA (OR 10.18; 95% CI: 2.00–51.9; p = 0.005), *ST* elevation in a lead with its maximum magnitude > 400 μV (OR 13.75; 95% CI: 2.57–73.46; p = 0.002) and the total *ST* displacement > 1500 μV (OR 18.4; 95% CI: 4.27–79.34; p < 0.001). Complete occlusion of the IRA and total displacement retained independent predictive values based on the multivariate analysis (OR 12.06; 95% CI: 1.50–96.94; p = 0.019 and OR 22.75; 95% CI: 4.02–128.75; p < 0.001, respectively).

Conclusions. The reperfusion peak is observed in slightly more than one-third of patients during primary PCI for *STEMI*. The complete occlusion of the IRA and significant *ST* elevation before reperfusion are predictors for its occurrence.

The blood flow restoration in the infarct-related artery is the main strategy in the treatment of acute myocardial infarction (AMI) with *ST*-elevation (1, 2). Evaluation of ECG changes is the leading method to evaluate the efficacy of thrombolytic therapy and fades into the background when percutaneous interventions (PCIs) with direct control of the blood flow restoration in the infarct-related artery are performed. However, the restoration of epicardial perfusion during primary angioplasty does not exclude abnormal microvasculare perfusion (3). It is known that the *ST*-segment recovery correlates with the microcirculatory blood restoration (4, 5) and ECG monitoring after the PCI completion is a routine method in clinical practice.

Continuous ECG monitoring gives additional information on the reperfusion period. In particular, it is shown that in some cases the *ST* depression with the reperfusion therapy demonstrates no monotonic pattern, and the *ST* depression is preceded by a short peak of an exacerbated *ST* elevation referred to as reperfusion peak (6, 7). To date, the pathophysiological

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The article was received on January 22, 2015
Accepted for publication on March 04, 2015

mechanisms of reperfusion peak and its predictors are not investigated enough; there is no consensus on its impact on outcomes.

The objective of this study was to evaluate the *ST* changes during primary angioplasty in AMI patients, to investigate the incidence and predictors of reperfusion peak and its influence on the outcomes in patients.

Material and methods

The study included patients with *STEMI* admitted for primary angioplasty in the clinic of V.A. Almazov Federal Center for Heart, Blood, and Endocrinology and clinic of Mechnikov Saint Petersburg State Medical Academy, Saint Petersburg from 2010 to 2013. The diagnosis of *STEMI* was confirmed based on the standard criteria: new-onset or presumably new-onset *ST* elevation >100 μV in two adjacent leads out of V_4–V_6, II, III, AVF and > 200 μV (>250 for males younger than 40 years) in leads V_1–V_3 (8). The patients with implanted permanent pacemakers, complete left or right bundle branch block, severe scar changes making difficult ECG interpretation were excluded. The patients who had cardiogenic shock, indications for temporary pacemaker implantation were also excluded.

The coronary angiography was performed using GE Innova 3100 (GE Healthcare); the epicardial blood flow was assessed according to the TIMI scale (9). Echocardiography (EchoCG) was performed using Acuson Cypress (Siemens) and Vivid-7 (GE Healthcare), the left ventricle ejection fraction (LVEF) was measured using the modified Simpson algorithm from apical 4- and 2-dimensional sections (10). All patients received standard therapy: dual antiplatelet therapy, heparin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins.

After admission all enrolled patients had continuous 12-lead ECG monitoring using cardiorecorders Kardiotechnika-3M, (Incart, Saint Petersburg). X-ray-negative cable MAC LAB (USA) made it possible to monitor 12-lead ECG in a setting of X-ray operating room with no disturbances for visualization of coronary arteries during PCI. The leads were placed according to the Mason-Likar diagram (11) except for neutral lead which was placed in the right axillary area symmetrically to the V6 lead.

When the monitoring data were analyzed to assess changes in the ventricular repolarization, only supraventricular complexes were used. When the magnitude of *ST* segment was estimated, the isoelectric line was considered to be mean signal level in the area proceeding to the QRS beginning by 40–20 msec. *ST* displacement was measured in each recorded lead, and then total *ST* displacement was calculated as the sum of *ST* elevations in the leads with direct signs of myocardial infarction and reciprocal *ST* depression. *ST* changes were analyzed in all 12 standard leads. To assess the ischemia based on Sklarovskiy-Birnbaum algorithm, presence or absence of *S* wave in leads with *rS* pattern was taken into account and *J/R* ratio in leads with *qR* pattern was determined (12).

After discharge the patients were followed in the FMIC on the outpatient basis. The study protocol was approved by the Local Ethics Committee at V.A. Almazov FMIC.

In the case of normal distribution, the data were presented as mean ± standard deviation, in the case of non-normal distribution, the median and interquartile ranges were presented. The Student t-test was used to compare the quantitative variables with normal distribution; if distribution was non-normal, the non-parametric tests were used (Mann–Whitney test). The differences between groups in incidences of the variables were determined using two-sided exact χ^2 test. The result was considered statistically significant at $p < 0.05$. To identify the clinical factors associated with the reperfusion peak, the univariate and multivariate regression analysis mathematical models were used. At the first step, clinically relevant parameters were compared between the groups. The variables significantly differed between the groups were then included in the univariate regression analysis model and the odds ratio was calculated (13). To identify the independent predictors, the factors with significant association revealed in the univariate analysis, were included in the multivariate model.

The statistical analysis was performed using the SPSS 19.0 statistical package (SPSS Inc., Chicago, Il, USA).

Results

The study included 70 subjects; mean age was 56 ± 13 (28–82) years; and 86% out of them were males. The reperfusion peaks (Figures 1–3) were recorded during primary angioplasty in 38.6% of cases. The *ST* elevation started increasing immediately after lumen restoration of the infarct-related artery and reached its maximum in 5.3 ± 3.2 minutes. The magnitude of *ST* elevation measured in one lead with the most pronounced *ST* elevation, increased at the peak on average by 117 ± 101%

(40–335%). Peak *ST* elevation was maximal in the same lead as at baseline (before PCI). In cases when reciprocal *ST* depression was recorded prior to reperfusion, its magnitude was also significantly increased at the time of reperfusion (Figures 1–3). The total *ST* displacement in all leads with *ST* elevation and reciprocal *ST* depression increased at the reperfusion peak by 148 ± 159% (32–560%) compared to pre-peak baseline value. Reaching its maximum at the peak, *ST* elevation started to decline gradually reaching pre-peak values in 9.3 ± 5.6 minutes, and declined further till full *ST* recovery and stabilization. Time to *ST* stabilization was 120 (IQ 77) minutes in the reperfusion peak group, and did not differ significantly from the non-reperfusion peak group: 97 (IQ 118) minutes, p = 0.22.

The patients with reperfusion peak most commonly (93%) had complete occlusion of the infarct-related artery (IRA) and no blood flow (TIMI 0), while the patients without reperfusion peak had complete occlusion of the IRA and TIMI 0 only in 49% of cases, p = 0.002 (Table 1); the remaining patients had preserved residual blood flow (TIMI I). The most pronounced magnitude of pre-PCI *ST* elevation in the reperfusion peak group was 492 ± 261 μV compared to 254 ± 153 μV in the non-reperfusion peak group (p = 0.002). The proportion of patients in whom the *ST* elevation in a single lead exceed 400 μV was 52% in the reperfusion peak group compared to 6.9% in the non-reperfusion peak group (p = 0.001). Similarly, the total *ST* displacements in the elevated and reciprocally depressed leads were

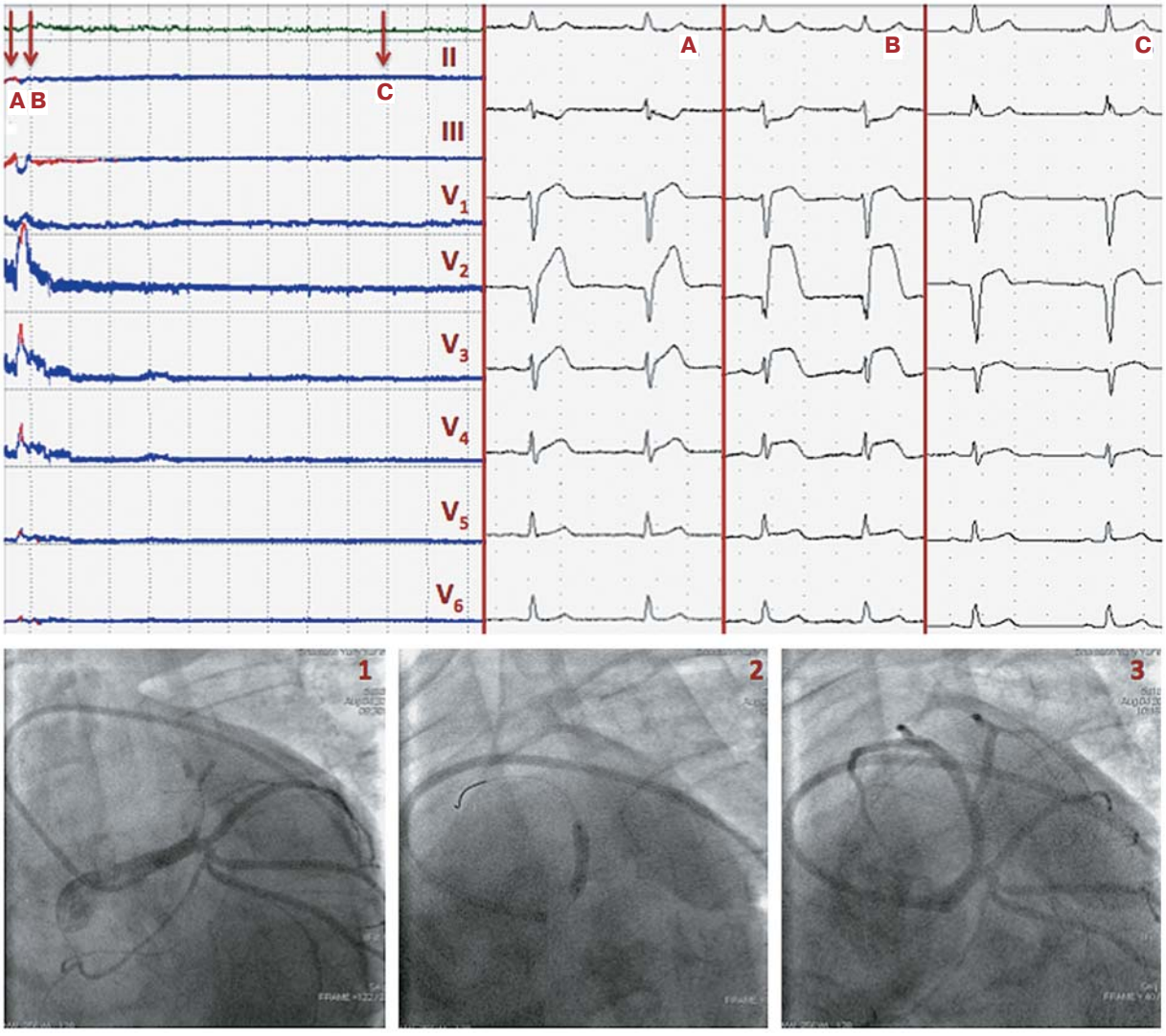

Figure 1. ST changes during primary angioplasty in a male patient Sh., 41 y.o. with anterior STEMI. The increase in ST elevation immediately after blood flow restoration in the infarct-related artery – reperfusion peak followed by its rapid decline. A – ECG before reperfusion; B – ECG at reperfusion peak; C – ECG after ST decline (pointed with arrows). Angiograms: 1 – LAD occlusion; 2 – balloon inflation in the infarct-related artery (LAD); 3 – blood flow restoration in the LAD (TIMI III).

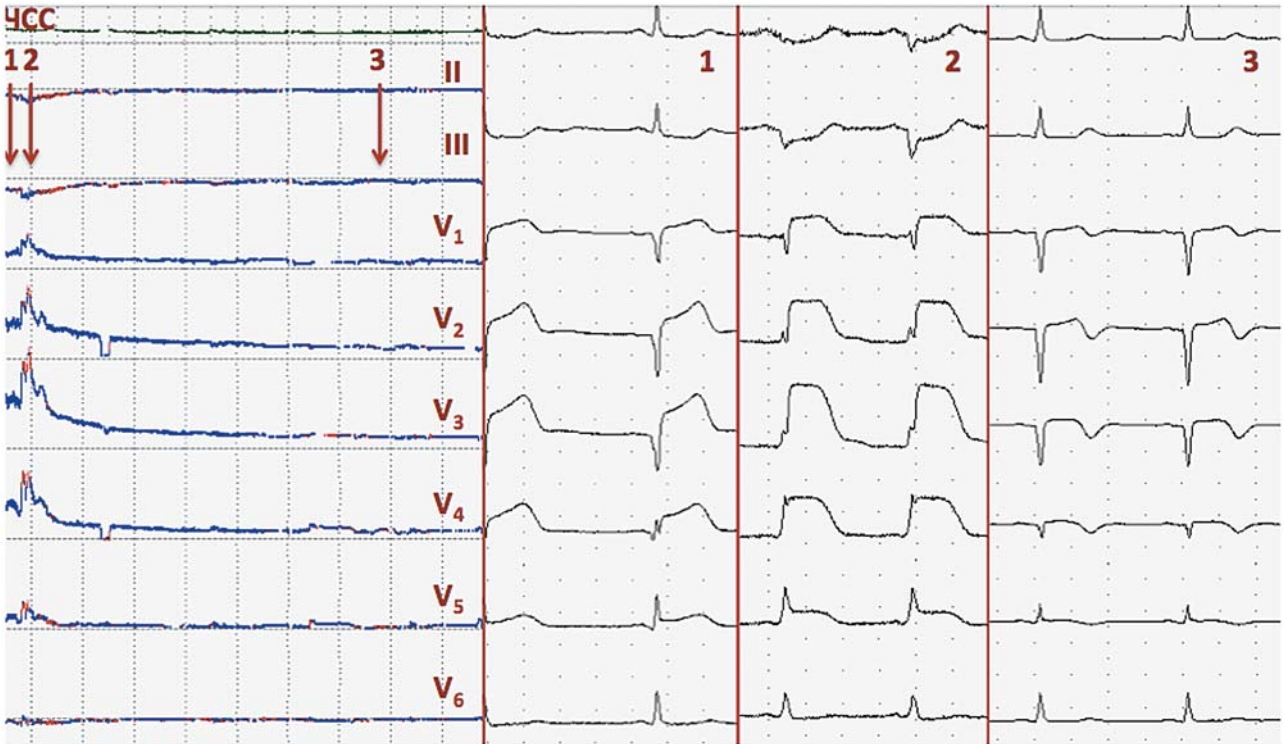

Figure 2. ST changes during primary angioplasty in a male patient K., 64 y.o. with anterior STEMI. The increase in ST elevation immediately after blood flow restoration in the infarct-related artery – reperfusion peak followed by its rapid decline. 1 – ECG before reperfusion; 2 – ECG at reperfusion peak; 3 – ECG after ST decline (pointed with arrows).

1990 ± 1098 μV versus 1062 ± 843 μV in the reperfusion peak group and non-reperfusion peak group, respectively (p = 0.001). The proportions of patients with the total *ST* displacements >1500 μV were 78% versus 14% in the reperfusion peak and non-reperfusion peak, respectively, p < 0.001.

The groups did not differ by age, sex, prevalence of hypertension or diabetes mellitus. The proportion of patients with previous AMI and unstable angina prior to this AMI did not differ between the groups. The groups did not differ by multivessel coronary disease, LAD as the infarct-related artery, AMI localization,

Table 1. Clinical, angiographic and ECG characteristics of patients with STEMI depending on the presence or absence of reperfusion peak during primary angioplasty

Characteristics	Reperfusion peak, n = 27	No reperfusion peak, n = 43	p
Age	59 ± 12	55 ± 13	0.10
Sex (males)	23 (86%)	37 (86%)	1.00
Previous MI	2 (7.4%)	7 (16.2%)	0.62
EH	20 (74%)	29 (67%)	1.00
Diabetes	2 (7.4%)	3 (7.0%)	1.00
Unstable angina prior to AMI	13 (48%)	18 (42%)	0.72
Localization (anterior AMI)	16 (59%)	24 (56%)	1.00
Time “signs onset-to-PCI”, min	492 ± 261	254 ± 152	0.72
Multivessel disease	16 (59%)	24 (56%)	1.00
IRA (LAD)	16 (59%)	24 (56%)	1.00
Total occlusion of the IRA, TIMI 0	**25 (93%)**	**21 (49%)**	**0.002**
Pre-PCI ST elevation in single lead, μV	**492 ± 261**	**254 ± 153**	**0.002**
Pre-PCI ST elevation in single lead >400 μV	**14 (52%)**	**3 (6.9%)**	**0.001**
Pre-PCI ST elevation, lead sum, μV	**1990 ± 1098**	**1062 ± 843**	**0.001**
Pre-PCI ST elevation, lead sum, >1500 μV	**21 (78%)**	**6 (14%)**	**<0.001**
3-rd grade ischemia (Birnbaum)	7 (26%)	4 (9.3%)	0.12

OAMI – acute myocardial infarction; EH – essential hypertension; PCI – percutaneous coronary intervention; IRA – infarct-related artery

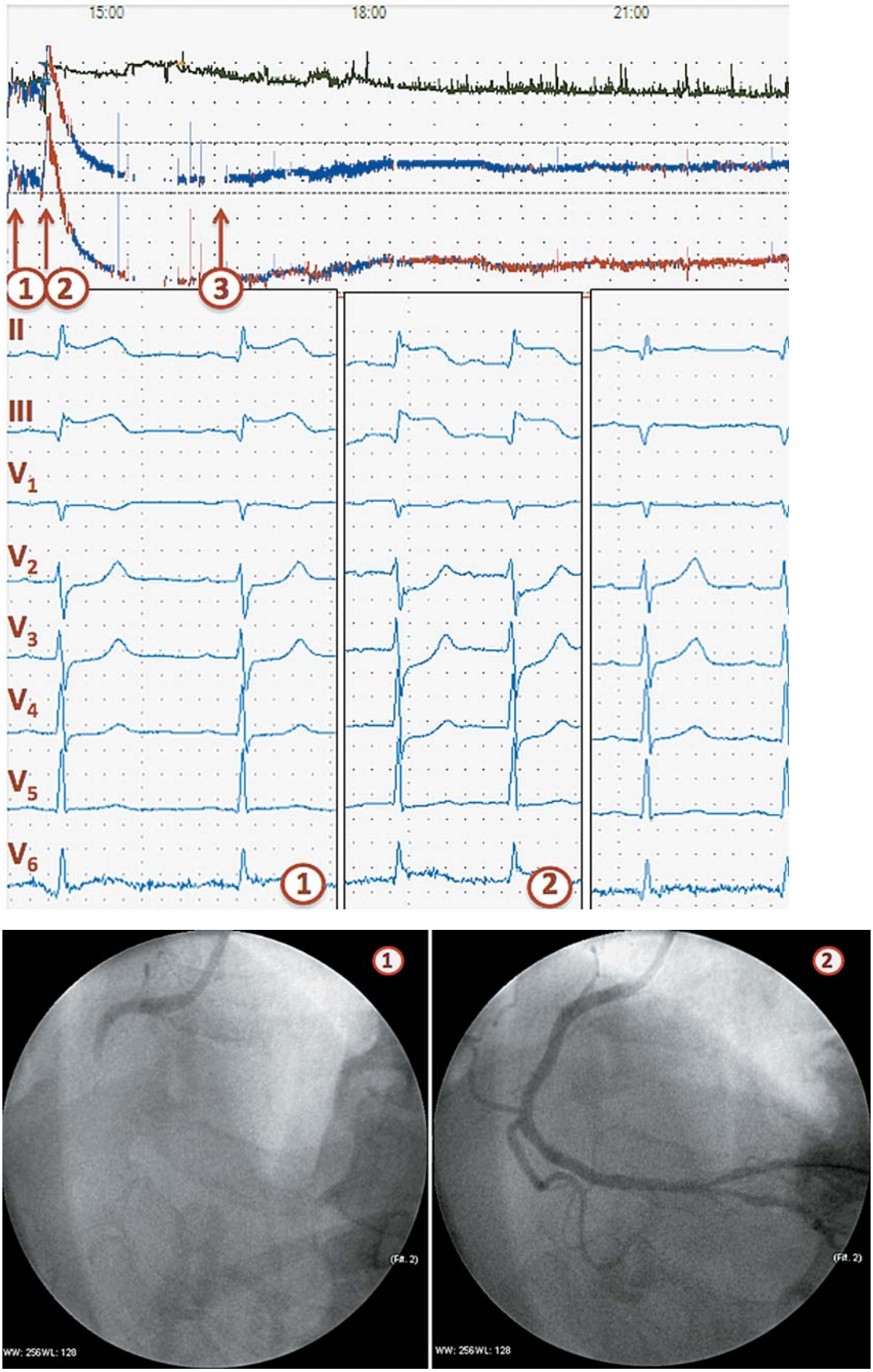

Figure 3. ST changes during primary angioplasty in a male patient Sh., 67 y.o. with inferior STEMI. The increase in ST elevation immediately after blood flow restoration in the infarct-related artery – reperfusion peak followed by its rapid decline. 1 – ECG before reperfusion; 2 – ECG at reperfusion peak; 3 – ECG after ST decline (pointed with arrows). Below: 1 – angiogram prior to reperfusion (proximal occlusion of the RCA), 2 – complete blood flow restoration in the infarct related artery.

Table 2. Factors related to the reperfusion peak occurrence during the blood flow restoration

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95%CI	p	OR	95%CI	p
Total occlusion of the IRA	10.18	2.00–51.90	0.005	12.06	1.50–96.94	0.019
ST elevation > 400 μV	13.75	2.57–73.46	0.002	–	–	–
Total ST displacement >1500 μV	18.4	4.27–79.34	<0.001	22.75	4.02–128.75	<0.001

Table 3. Some baseline and follow-up clinical and echocardiographic parameters in the reperfusion peak and non-reperfusion peak groups

Parameter	Reperfusion peak group	Non-reperfusion peak group	p
LVEF on Day 1,%	50 ± 8	51 ± 9	0.80
LVEF at Month 12,%	49 ± 9	50 ± 7	0.75
ΔLVEF at Month 12	-1.1 ± 9.5	1.1 ± 5.4	0.58
Proportion of patients with reduced EF at Month 12 ⩾10	1 (4.1%)	0	0.69
HF III NYHA at Month 12	3 (12.6%)	1 (2.3%)	0.08
HF progression in the follow-up, %	7 (29.0%)	2 (5.7%)	0.07

LVEF – left ventricle ejection fraction; ΔФВ ЛЖ – LVEF change from acute period to Month 12; HF – heart failure.

time window “signs onset-to-PCI”, and proportion of patients with grade 3 ischemia according to the Sklarovskiy-Birnbaum method.

Univariate analysis revealed that the complete occlusion of the IRA (OR 10.18; 95% CI: 2.00–51.9; p = 0.005), *ST* elevation in a lead with its maximum magnitude > 400 μV (OR 13.75; 95% CI: 2.57–73.46; p = 0.002) and the total *ST* displacement > 1500 μV (OR 18.4; 95% CI: 4.27–79.34; p < 0.001) were associated with the reperfusion peak occurrence at the moment of blood flow restoration (Table 2). Complete occlusion of the IRA and total displacement retained independent predictive values based on the multivariate analysis (OR 12.06; 95% CI: 1.50–96.94; p = 0.019 and OR 22.75; 95% CI: 4.02–128.75; p < 0.001, respectively).

The majority of enrolled patients had intact or slightly reduced global systolic function. Based on the EchoCG results obtained on Day 1 of AMI, the ejection fraction was 51 ± 9%, without significant difference between the groups depending on the presence or absence of reperfusion peak (Table 3). During in-hospital treatment, 4 patients died and 2 out of them were from the reperfusion peak group. After discharge, 7 patients were lost for follow-up for various reasons; the remaining subjects were under a prospective dynamic follow-up with mean duration of 23 ± 19 months. There were no deaths among discharged patients during the follow-up. Based on the 12-month EchoCG data, the groups did not differ by the ejection fraction. After 12 months, there was a trend to greater incidence of HF progression and greater proportion of patients with higher HF classes in the reperfusion peak group (Table 3).

Discussion

In this study, the reperfusion peak was observed in 38.6% of subjects which is consistent with the previously published data on the incidence of this ECG phenomenon during primary angioplasty (23–63%) (14–16) and systemic thrombolysis (68–75%) (7, 17). It is shown that after experimental myocardial infarction caused by complete mechanical occlusion of the LAD by inflating the balloon followed by an equally rapid subsequent simultaneous reperfusion, the reperfusion peak occurs during the blood flow restoration in 100% of cases (18). Thus, the reperfusion peak pattern observed in this study while the primary angioplasty is performed, does not differ visually from the pattern observed in the experiment (18) and in real practice when systemic thrombolytic therapy is conducted (17). The reason for rarer occurrence of this ECG phenomenon in real practice should be most probably sought in the particularities of the pathophysiological mechanisms of “ischemia-reperfusion” in AMI. The *STEMI* progression is caused by thrombotic occlusion resulting from pro-inflammatory and coagulation pathways, often associated with complete or partial spontaneous lysis of thrombus, distal embolization and vasospasm (19). These factors can lead to intermittent obstruction of the infarct-related artery, partial restoration of blood flow, and as a consequence, initiation of the pre – and post-conditioning mechanisms, in their

turn affecting the *ST* changes during reperfusion. For example, in this study, the reperfusion peak at the time of blood flow restoration was associated with complete occlusion of the IRA according to coronary angiography data, while the presence of non-occlusive thrombosis significantly reduced the probability of this phenomenon. Another predictor of reperfusion peak was *ST* displacement immediately before reperfusion characterizing the severity of ischemic injury, which is consistent with the data from another recently published study (20). Collateral blood flow to the territory of the occluded artery may have a certain value in terms of the probability of reperfusion peak occurrence, but its role in acute occlusions is not very high, and quantification is difficult (21). We did not confirm the data on the lower incidence of reperfusion peak in patients with unstable angina prior to this AMI, which could be associated with the myocardial preconditioning (20). According to our data, the probability of reperfusion peak occurrence was also not associated with the previous AMI. We did not reveal the dependence between the presence or absence of a peak and time period "signs onset-to-PCI" which is consistent with the published data (16).

At present, the data on the pathophysiological mechanisms underlying the "reperfusion peak" and its prognostic value are controversial. There is an opinion that reperfusion peak is an electrophysiological phenomenon caused by diselectrolytic changes related to reperfusion (22–24). At the same time, it is demonstrated that the patients with reperfusion peak have higher maximum troponin level (15, 16, 25), lower left ventricle ejection fraction (15), and larger final area of myocardial necrosis (16, 20). Thus, the reperfusion peak is associated with a greater severity of myocardial injury. However, it is not quite clear whether it's associated with a larger pre-reperfusion injury or reperfusion injury itself (26). Some studies show that reperfusion peak is associated with more pronounced baseline *ST* elevation before reperfusion (20, 27), that is also confirmed in our study, as well as poorer collateral blood flow and larger myocardial area involved in the "ischemia-reperfusion" process (27). According to other authors, the peak reflects reperfusion injury, contributing to the final necrotic area (28) and is caused by distal embolization with thrombus fragments and leukocyte aggregates, microcirculatory spasm and edema (29, 30). In our study, no-reflow phenomenon was not observed, the patients with reperfusion peak had angiographically verified complete restoration of blood flow in the infarct-related artery and the peak of exacerbated *ST* elevation was followed by rapid normalization. Apparently, the further investigations directly assessing the risk area and final necrotic area are required to determine the nature of reperfusion peak. The pilot experimental study demonstrated the relationship between the magnitude of reperfusion peak and necrotic area size but not the area of myocardium at risk (18).

The currently available data on the prognostic value of reperfusion peak are controversial. According to Näslund data (7), 1-year mortality in patients with reperfusion peak was lower than in patients from the non-reperfusion peak group, 5-year mortality rates did not differ. The prospective observation for more than 2 years demonstrated that all-cause mortality and cardiac mortality rates were significantly higher in the reperfusion peak group (20). The small sample size and small number of endpoints in our study preclude from definite conclusions on prognostic value of the reperfusion peak, and further investigations should be conducted.

Conclusions

1. The reperfusion peak is observed in slightly more than one-third of *STEMI* patients during primary angioplasty; it is rarer than in experimental AMI model with total occlusion and subsequent simultaneous IRA reperfusion.

2. The predictor for this ECG phenomenon is complete occlusion of the IRA before reperfusion and significant *ST* elevation as manifestations of the severity of pre-reperfusion myocardial ischemia.

References

1. Steg P.G., James S.K. et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with *ST*-segment elevation. Eur. Heart J. 2012, 33 (20), 2569–2619. Epub 2012/08/28.
2. O'Gara P.T., Kushner F.G., Ascheim D.D. et al. 2013 ACCF/AHA guideline for the management of *ST*-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013, 127 (4), e362–e425. Epub 2012/12/19.
3. Tanaka A., Kawarabayashi. T, Nishibori Y. et al. No-reflow phenomenon and lesion morphology in patients with acute myocardial infarction. Circulation. 2002, 105 (18), 2148–2152. Epub 2002/05/08.
4. Nijveldt R., Beek A.M., Hirsch A. et al. Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular

magnetic resonance measures of microvascular injury. J. Am. Coll. Cardiol. 2008, 52 (3), 181–189. Epub 2008/07/12.
5. van 't Hof A.W., Liem A., de Boer M.J., Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle Myocardial infarction Study Group. Lancet. 1997, 350 (9078), 615–619. Epub 1997/08/30.
6. Demidova M.M., Tichonenko V.M., Burova N.N. Types of *ST*-segment resolution during thrombolytic therapy in patients with acute coronary syndrome. Int. J. Interventional Cardioangiol. 2008, 16, 16–21.
7. Nilsson J.B., Jensen S., Ottander P., Näslund U. The electrocardiographic reperfusion peak in patients with *ST*-elevation myocardial infarction. Scand. Cardiovasc. J. 2007, 41 (1), 25–31. Epub 2007/03/17.
8. Thygesen K., Alpert J.S., Jaffe A.S. et al. Third universal definition of myocardial infarction. Eur. Heart J. 2012, 33 (20), 2551–2567. Epub 2012/08/28.
9. Sheehan F.H., Braunwald E., Canner P. et al. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI Phase I) trial. Circulation. 1987, 75 (4), 817–829. Epub 1987/04/01.
10. Lang R.M., Bierig M., Devereux R.B. et al. Recommendations for chamber quantification. European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology. 2006, 7 (2), 79–108. Epub 2006/02/07.
11. Mason R.E., Likar I. A new system of multiple-lead exercise electrocardiography. Am. Heart J. 1966, 71 (2), 196–205. Epub 1966/02/01.
12. Birnbaum Y., Drew B.J. The electrocardiogram in *ST* elevation acute myocardial infarction: correlation with coronary anatomy and prognosis. Postgrad. Med. J. 2003, 79 (935), 490–504. Epub 2003/09/19.
13. Bland J.M., Altman D.G. Statistics notes. The odds ratio. Br. Med. J. 2000, 320 (7247), 1468. Epub 2000/05/29.
14. Nilsson J.B., Eriksson A., Naslund U. Transient Increase in *ST*-segment Changes at Time of Reperfusion in Acute Myocardial Infarction Treated by Coronary Angioplasty. J. Invasive Cardiol. 1998, 10 (5), 246–250. Epub 2000/04/14.
15. Terkelsen C.J., Norgaard B.L., Lassen J.F. et al. Potential significance of spontaneous and interventional *ST*-changes in patients transferred for primary percutaneous coronary intervention: observations from the *ST*-MONitoring in Acute Myocardial Infarction study (The MONAMI study). Eur. Heart J. 2006, 27 (3), 267–275. Epub 2005/10/18.
16. Terkelsen C.J., Kaltoft A.K., Norgaard B.L. et al. *ST* changes before and during primary percutaneous coronary intervention predict final infarct size in patients with *ST* elevation myocardial infarction. J. Electrocardiol. 2009, 42 (1), 64–72. Epub 2008/11/06.
17. Demidova M.M., Tikhonenko V.M., Burova NN. Assessment of the state of a patient with acute coronary syndrome during thrombolytic therapy with the use of multichannel ECG-monitoring. Kardiologiya. 2009, 49 (7–8), 25–31. Epub 2009/08/07.
18. Demidova M.M., van der Pals J., Ubachs J.F. et al. *ST*-segment dynamics during reperfusion period and the size of myocardial injury in experimental myocardial infarction. J. Electrocardiol. 2011, 44 (1), 74–81. Epub 2010/12/21.
19. Van de Werf F., Bax J., Betriu A. et al. Management of acute myocardial infarction in patients presenting with persistent *ST*-segment elevation: the Task Force on the Management of *ST*-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur. Heart J. 2008, 29 (23), 2909–2945. Epub 2008/11/14.
20. Lonborg J., Kelbaek H., Holmvang L. et al. *ST* peak during primary percutaneous coronary intervention predicts final infarct size, left ventricular function, and clinical outcome. J. Electrocardiol., 2012, 45 (6), 708–716. Epub 2012/07/27.
21. Khand A., Fisher M., Jones J. et al. The collateral circulation of the heart in coronary total arterial occlusions in man: systematic review of assessment and pathophysiology. Am. Heart J. 2013, 166 (6), 941–952. Epub 2013/11/26.
22. Coronel R., Wilms-Schopman F.J., Opthof T. et al. Reperfusion arrhythmias in isolated perfused pig hearts. Inhomogeneities in extracellular potassium, *ST* and *TQ* potentials, and transmembrane action potentials. Circ. Res. 1992, 71 (5), 1131–1142. Epub 1992/11/01.
23. Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. Physiol. Rev. 1999, 79 (3), 917–1017. Epub 1999/07/03.
24. Van Emous J.G., Schreur J.H., Ruigrok T.J., Van Echteld C.J. Both Na+-K+ ATPase and Na +-H+ exchanger are immediately active upon post-ischemic reperfusion in isolated rat hearts. J. Mol. Cell. Cardiol. 1998, 30 (2), 337–348. Epub 1998/05/30.
25. Johanson P., Jernberg T., Gunnarsson G. et al. Prognostic value of *ST*-segment resolution-when and what to measure. Eur. Heart J. 2003, 24 (4), 337–345. Epub 2003/02/13.
26. Terkelsen C.J. The reperfusion *ST*-peak in acute myocardial infarction. J. Electrocardiol. 2011, 44 (1), 82–83. Epub 2010/12/21.
27. Miida T., Oda H., Toeda T., Higuma N. Additional *ST*-segment elevation immediately after reperfusion and its effect on myocardial salvage in anterior wall acute myocardial infarction. Am. J. Cardiol. 1994, 73 (12), 851–855. Epub 1994/05/01.
28. Monassier J.P. Reperfusion injury in acute myocardial infarction: from bench to cath lab. Part II: Clinical issues and therapeutic options. Arch. Cardiovasc. Dis. 2008, 101 (9), 565–575. Epub 2008/12/02.
29. Xu Y., Huo Y., Toufektsian M.C. et al. Activated platelets contribute importantly to myocardial reperfusion injury. Am. J. Physiol. Heart Circ. Physiol. 2006, 290 (2), H692- H6929. Epub 2005/10/04.
30. Engler R.L., Schmid-Schonbein G.W., Pavelec R.S. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. Am. J. Pathol. 1983, 111 (1), 98–111. Epub 1983/04/01.

Thrombosis of Non-Stenotic Coronary Arteries

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The treatment results of 4 patients with thrombosis of non-stenotic coronary arteries are reviewed. The conservative therapy was effective in all cases.

Ключевые слова: *non-stenotic coronary arteries, coronary thrombosis, acute myocardial infarction.*

Abbreviations

IVUS – intravascular ultrasound
CA – coronary artery
CAG – coronarography
LV – left ventricle
LCX – left circumflex artery
AMI – acute myocardial infarction
RCA – right coronary artery
LAD – left anterior descending artery
LMCA – left main coronary artery

Introduction

Acute myocardial infarction (AMI) in patients without atherosclerotic lesions of the coronary arteries (CAs) and hemodynamically significant stenoses is a relatively rare condition (1–15). The aetiology and pathogenesis of such AMI are still not fully clarified; the possible causes are coronary spasm, thrombosis, inflammation, embolization, endothelial dysfunction, hypercoagulation, myocarditis, aortic dissection, poisoning with some medicinal and narcotic drugs.

Objective: to analyze the cases and treatment principles in patients with CA thrombosis without hemodynamically significant stenoses.

Materials and methods

Four AMI patients aged from 32 to 50 y.o. were examined during 4 years (2009–2012) (0.06% out of 7002 patients). There were 3 males (all were smokers – at least 1 pack of cigarettes per day) and 1 female, in whom coronary angiography (CAG) revealed thrombi in the non-stenotic CAs.

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Manuscript received on September 15, 2014.
Accepted for publication on April 15, 2015.

Results

Three patients were admitted within 2.5 hr to 4 hr 20 min from angina onset in severe and very severe condition with typical clinical manifestations: chest pain and retrosternal pain. At admission, the female patient had clinical signs of cardiogenic shock. ECG demonstrated signs of peracute phase of AMI.

Clinical cases

A 45 years old female. She was admitted in a very severe condition with signs of cardiogenic shock. At 6 a.m. she experienced intensive pressing pain behind her breastbone. The ECG performed by medical emergency team demonstrated peracute phase of the anterior advanced myocardial infarction. At pre-hospital stage she received morphine, dopamine, clexane, aspirin; 1.5 hours after angina onset systemic thrombolysis using tissue plasminogen activator Actilyse was started. She was admitted 2.5 hours after angina onset in severe condition due to AMI complicated with cardiogenic shock. HR was 34 bpm. BP was 82/65 mm Hg. Peripheral pulse was absent. There was tachypnoe – 26–28 respirations per minutes. ECG on admission showed sinus rhythm, complete AV block with a substitute rhythm from AV connection. There was a peracute phase of transmural antero-septal myocardial infarction involving the lateral wall of the LV. Temporary pacemaker was placed; dopamine 12 μg/kg/min was infused. CAG results (Fig. 1): the coronary blood flow of the right type, the unchanged left main coronary artery (LMCA), left anterior descending artery (LAD) with a blood clot in the proximal part narrowing the lumen by 70%, the ostium of the left circumflex artery (LCX) stenosed by 50%, right coronary artery (RCA) not changed. Intra-aortic balloon pumping was started (1 : 1). With inotropic support, intra-aortic balloon pumping and temporary pacing the patient's condition was stabilized. Temporary pacing was stopped on Day 2, the intra-aortic balloon pump was removed on Day 4. The therapy was given (including heparin, Zyllt 75 mg, Thrombo ASS 100 mg, and then Cardiomagnyl

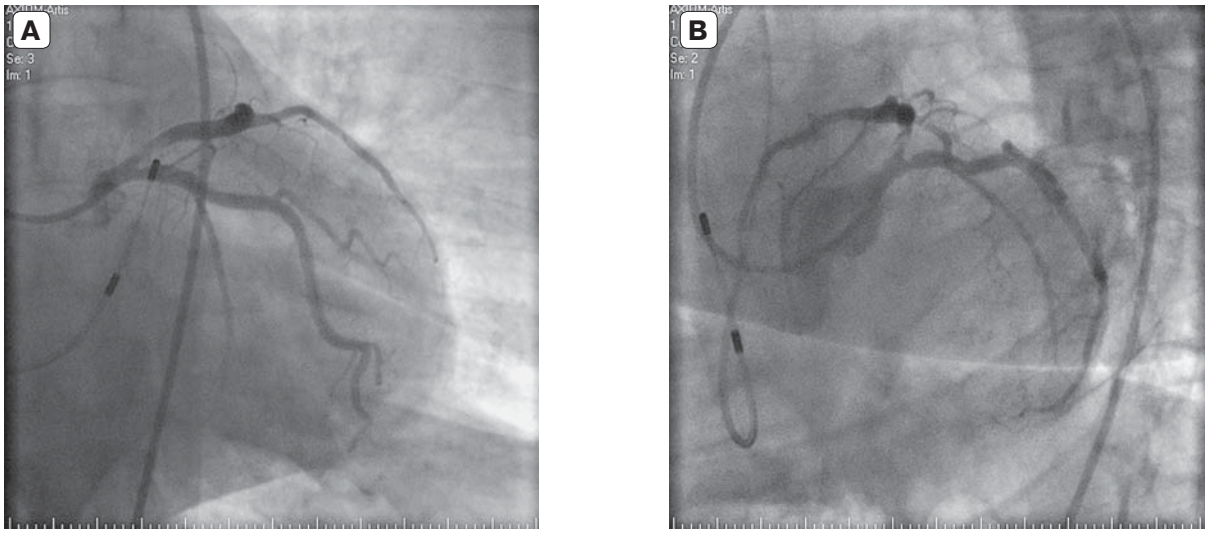

Figure 1. Coronarograms. Thrombus in the proximal segment of the LAD narrowing the lumen by 70%. The ostium of the LCX is stenosed by 50%.

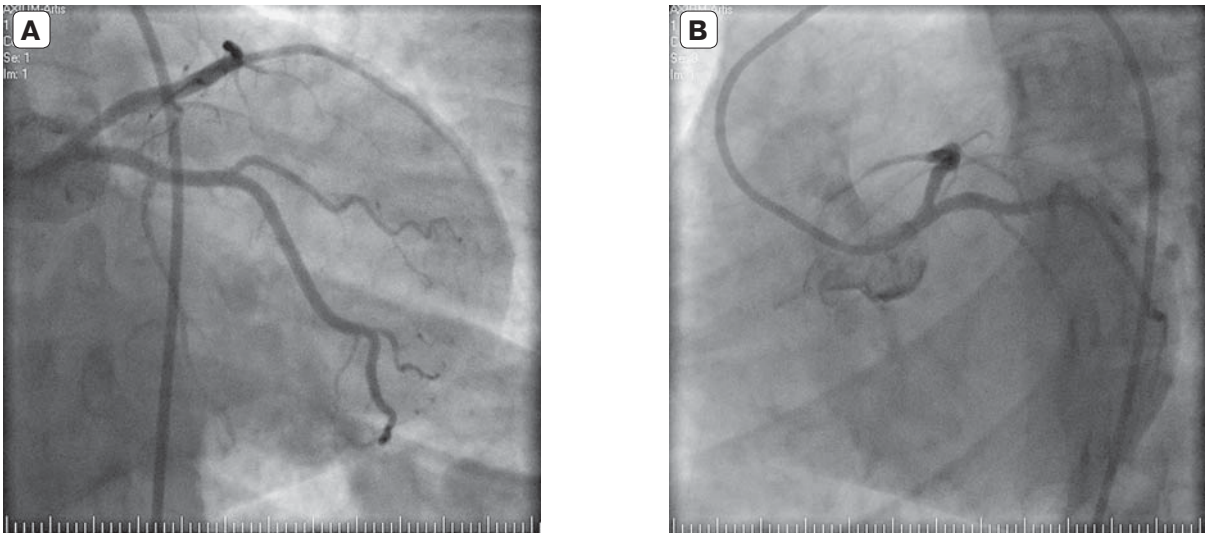

Figure 2. Coronarograms at Week 3. Coronary arteries are not changed, complete lysis of the thrombus.

75 mg), there were no cardiac pain, rhythm disturbances or heart failure signs. ECG revealed the evolution of transmural anterior advanced myocardial infarction. EchoCG demonstrated impaired LV contractility in the septal, anterio-septal, apical areas (7 segments, dyskinesis of the inferior and septal-apical segments with wall thinning and aneurysm formation, mural thrombus in the aneurysm cavity 13 × 8 mm). Follow-up CAG (Fig. 2) at Week 3: No LAD thrombosis, LAD and LCX without hemodynamically significant stenoses. She was discharged in a fair condition.

In the remaining 3 cases, CAG revealed LAD thrombosis.

A 50 years old male. CAG: non-occlusive oval thrombus with uneven, blurred contours and small fluctuating movements in the distal part of LMCA expanding to the bifurcation. No other CA changes. The treatment included: heparin 25,000 Units IV as a drop infusion then 5000 Units SC 4 times a day; Plavix 300 mg, then 75 mg/day, with subsequent replacement with Zyllt 75 mg, Arixtra 2.5 mg SC; aspirin 125 mg/day. CAG on Day 14: CAs unchanged, no blood clots.

A 40 years old male. CAG: Non-occlusive oval thrombus in the middle segment of the LAD, blood flow TIMI 3. There were no significant coronary stenoses. Integrilin 180 μg/kg was infused intravenously as a bolus, then as continuous infusion 2 μg/kg/min for 24 hours. The treatment included: Plagril 75 mg/day, Thrombo ASS 100 mg/day. He was discharged on Day 3 for personal reasons without follow-up CAG.

A 32 years old male. Typical pain developed one month ago, was not treated, the patient was admitted

with thrombosis of arteries of lower extremities. After collection of medical history, the examination was performed. The ECG demonstrated focal changes in the anterior wall of the left ventricle (LV). The EchoCG showed signs of local changes of myocardial contractility in the anterior-lateral and septal walls of the LV, hypokinesia of the apical segments; troponin 0.276 ng/ml). On the base of these data, an antero-septal AMI involving the the apex and side wall of the LV was suspected. CAG: 65% stenosis of the proximal segment of the LAD, distally there is an oval opacification defect with well-defined smooth contours with fluctuating movements, the remaining arteries without significant changes. The treatment included: warfarin 5 mg and heparin 2500 Units 6 times a day. CAG on Day 9: no changes in the LAD. The thrombotic masses formed in the coronary arteries can be friable and loose, they can be lyzed and fragmented both spontaneously and under therapy. First CAG was performed one month after thrombus formation at the time when the patient did not receive treatment, the parietal part of thrombus simulating the narrowing and separate floating fragment – the former "core" of the thrombus still were preserved. Therapy significantly accelerated the lysis and on Day 9 while therapy was given, there was a complete lysis of both parietal thrombotic masses and free thrombotic fragment.

Discussion

As a rule, the reports on thrombosis of the unchanged CAs deals with single cases. Only Poyet R. et al. (11) examined 17 patients and Roule V. et al. (12) reported on 16 patients and found 36 similar cases caused by several etiological factors, primarily spasm and prothrombotic coagulopathy. Almost all reports were based on CAG data of thrombosis of angiographic unchanged CAs, some of them had minimal changes.

Poyet R. et al. (11) examined 17 AMI patients with or without ST-elevation using intravascular ultrasound (IVUS). On the base of CAG, the coronary vessels were assessed as normal or almost normal with the thrombi. IVUS revealed discrete lesions in all patients with angio-graphically normal arteries and identified short, single, small, eccentric, hypoechoic lesions.

Some patients with angiographically normal arteries may have minimal changes that predispose to thrombosis.

A number of investigators (8, 12, 15) believe that, beside smoking, such patients have other, rather typical, cardiovascular risk factors, however the primary role is played by spasm and coagulopathy.

Kadowaki K. et al. (8) consider that AMI associated with angiographically normal arteries can be caused by combination of spasm and CAs thrombosis. Suzuki N. et al. (15) introduced acetylcholine 50 μg intracoronary, which caused a spasm in a patient with simultaneous thrombosis of the RCA and LAD after therapy, during follow-up CAG, which showed complete disappearance of the thrombi. According to the authors, spasm preceded and caused the CA thrombosis.

In our case, CAG revealed not only LAD thrombosis but an ostial stenosis of the left circumflex artery (LCX) by 50%. Post-treatment follow-up CAG revealed neither thrombus nor stenosis. This case confirms the important role played by the spasm combined with thrombosis in unchanged CAs.

Thrombosis of unchanged CAs is possible in thrombophilia and hypercoagulopathy caused by genetic factors (6, 13). The examined 32-year-old patient had already repeated thrombosis of the peripheral arteries suggesting thrombophilia.

Some investigators believe that the coronary thrombosis is typical for young patients (2, 8, 13, 14). In our cases, CA thrombosis occurred in young and middle-aged patients (32–50 y.o.).

AMI with unchanged CA thrombosis was observed in drug addicts (1, 5).

Simultaneous thrombosis of several CAs is possible (3,14,15). Thus, Serrano C.V.Jr. et al. (14) observed non-occlusive thrombosis of the LAD and RCA in 32-year-old patient. After thrombolysis the blood clots were completely lyzed and angiographic pattern presented normal CAs. Suzuki N. et al. (15) revealed during CAG a blood clot in the middle part of the RCA and complete occlusion of the distal part of the LAD. Chong F. et al. (3) described a case of thrombosis of the distal part of LMCA, LAD and intermediate artery.

The primary treatment principles. Roule V. et al. (12) treated 16 patients – glycoprotein IIb/IIIa inhibitor was administered in 75% of cases.

Germing A. et al. (7) reported a patient with a large thrombus of LMCA subtotally narrowing the lumen of the LCX and LAD, with glycoprotein IIb/IIIa inhibitor (Abciximab). The next day, the blood clot did not disappear; the treatment was continued for several days and on Day 6 CAG revealed no thrombus. Ozeren A. et al. (10) successfully used a glycoprotein IIb/IIIa inhibitor Tirofiban for massive thrombus which almost completely occluded the distal part of the LCX.

Dagdelen S. et al. (4) found no signs of atherosclerosis and a blood clot in the LAD (22 mm in length and 1.9 mm in diameter)in AMI patient during CAG. The treatment consisted of administration of Tirofiban firstly as a bolus over 30 minutes and then for 24 hours as IV infusion, acetylsalicylic acid, nitroglycerine and warfarin. The follow-up at Month 2 showed complete disappearance of the thrombus in the unchanged CAs.

Chong F. et al. (3) performed thrombus aspiration, administered a glycoprotein IIb/IIIa inhibitor and performed intra-aortic balloon pumping to stabilize hemodynamics. According to the authors, in such cases, thrombus aspiration without stenting can lead to good results.

Karanasos A. et al. (9) suspected thrombosis of the RCA ostium during CAG and optical coherence tomography, which showed no atherosclerotic changes of the vessel wall. The treatment consisted in the thrombus aspiration and stenting of the RCA ostium.

The patients with AMI caused by non-occlusive thrombosis in angiographically normal CAs, have good long-term outcome after acute phase if treatment strategy is correctly selected (12).

Thus, the primary treatment option is administration of a glycoprotein IIb/IIIa inhibitor and double antiplatelet therapy. Thrombus aspiration is used less frequently and only one report (9) described the combined use of thrombus aspiration and stenting.

In all our 4 cases, there was LAD thrombosis and no CA stenoses. In 3 AMI cases, thrombus produced a significant obstacle within the CA lumen, but the blood flow was preserved (TIMI 3), therefore, conservative therapy (which was effective) was chosen rather than thrombus aspiration. No thrombus aspiration was required in a male patient with 1-month AMI: the thrombus was partially lyzed within a month even in the absence of treatment, but parietal part of the thrombus and its non-lysed "core" located distally and floating in the lumen remained. Conservative therapy was effective in this case.

Conclusions

1. In rare cases, acute myocardial infarction caused by thrombosis of non-stenotic coronary arteries is possible.

2. Conservative therapy is effective in thrombosis of unchanged coronary arteries and blood flow TIMI 3.

References

1. Apostolakis E., Tsigkas G., Baikoussis N.G. et al. Acute left main coronary artery thrombosis due to cocaine use. J. Cardiothorac. Surg. 2010, 19 (5), 65.
2. Bouabdallaoui N., Mouquet F., Ennezat P.V. Acute myocardial infarction with normal coronary arteries associated with subclinical Graves disease. Am. J. Emerg. Med. 2013, 31 (12), 1721.e1–e2.
3. Chong F., Cox N., Lim Y. Thrombus aspiration alone: a potential strategy in ST elevation myocardial infarction intervention. Heart Lung Circ. 2011, 20 (11), 724–725.
4. Dagdelen S., Soydine S., Ergelen M., Caglar N. Resolution of a spontaneous coronary artery thrombus with a new antiplatelet agent. Int. Angiol. 2001, 20 (3), 244–247.
5. Duchene C., Olindo S., Chausson N. etc. Infarctus cerebral et myocardique apres consommation de cannabis chez une femme jeune. Rev. Neurol. (Paris). 2010, 166 (4), 438–442.
6. Gaspar J., Benchimol C., Gadelha T., Penna G.L. Arterial thrombosis and acute myocardial infarction with angiographically normal coronary arteries in a woman heterozygous for both factor V Leiden and prothrombin mutation. Rev. Port. Cardiol. 2011, 30 (9), 727–729.
7. Germing A., Mugge A., Lindstaedt M. Recurrent myocardial ischemia due to riding left main coronary artery bifurcation thrombus-noninterventional therapy with glycoprotein blocker and thrombolysis. Cardiovasc. Revasc. Med. 2006, 7 (2), 76–80.
8. Kadowaki K., Sato T., Abe Y. et al. A case of acute myocardial infarction following intracoronary thrombi caused by coronary artery spasm. Kokyu To Junkan. 1992, 40 (7), 705–708.
9. Karanasos A., Tsiamis E., Stefanadis C. Myocardial infarction caused by ostial right coronary artery thrombus in the absence of atheromatosis. J. Invasive Cardiol. 2012, 24 (9), 188–189.
10. Ozeren A., Aydin M., Ozkökeli M. et al. Treatment of intracoronary thrombus using tirofiban in a patient with normal coronary arteries. Jpn. Heart J. 2004, 45 (2), 343–346.
11. Poyet R., Cuisset T., Bali L. et al. Coronary wall characteristics after myocardial infarction without significant coronary angiographic lesion: an intravascular ultrasound study. Acta Cardiol. 2010, 65 (6), 627–630.
12. Roule V., Sabatier R., Lognoné T. et al. Thrombus in normal coronary arteries: retrospective study and review of case reports. Arch. Cardiovasc. Dis. 2011, 104 (4), 216–226.
13. Sayin M.R., Akpinar I., Karabag T. et al. Left main coronary artery thrombus resulting from combined protein C and S deficiency. Intern. Med. 2012, 51 (21), 3041–3044.
14. Serrano C.V.Jr., Ramires J.A., Gebara O.C. et al. Acute myocardial infarction after simultaneous thrombosis in normal right and left coronary arteries. Clin. Cardiol. 1991, 14 (15), 436–438.
15. Suzuki N., Hiasa Y., Miyazaki S. et al. Acute myocardial infarction caused by simultaneous occlusion of the right coronary artery and the left anterior descending coronary artery probably due to coronary spasm: a case report. J. Cardiol. 2005, 45 (5), 213–217.

A Case of Successful Closure of Coronary-pulmonary Fistula with a Stent Graft

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Coronary-pulmonary fistula leading to pulmonary hypertension can have a severe negative effect of the condition of patients. The authors suggest the use of stent-grafts for such fistulae closure.

Key words: *coronary-pulmonary fistula, pulmonary hypertension, stent-graft.*

Adult patients seeking medical care most often suffer from shortness of breath, chest pain on exertion, and heart irregularity. These sings are the indications for coronary angiography. A coronary-pulmonary fistula revealed during the diagnostic procedure is associated with coronary atherosclerosis only in single cases.

The patent arterial passage (fistula) is the main issue in the differential diagnosis of coronary-pulmonary fistula, but other congenital arteriovenous communications should also be excluded. While two-dimensional echocardiography helps to diagnose various arteriovenous communications, coronary angiography is the main diagnostic method to determine the coronary anatomy. Computed tomography gives a presentation on the relationship between coronary-pulmonary fistula and the cardiac cavities. Accurate diagnostics and effective surgical correction of the heart defect give positive postoperative results and reduce the complications risk.

Surgical treatment is a traditional approach to eliminate coronary-pulmonary fistulas. However, currently the endovascular technique is often used (1–9).

Surgical treatment of the heart defect is indicated for patients who have hemodynamically significant coronary fistulas. The procedure should be aimed at closing the abnormal communication via catheter embolization, either by suturing in the cardiac chamber or great vessel under visual control during open heart surgery as well as correction of concomitant cardiac pathology.

A 66 y.o. mail was admitted to the department for elective coronary angiography with complaints of periodic pressing retrosternal pain and shortness of breath, resolving after nitroglycerin intake. The patient had a history of two myocardial infarctions. In January 2013, his status deteriorated, namely his exercise tolerance reduced. He underwent elective coronary angiography, which revealed extensive LAD narrowing in the middle third up to 80%, two coronary-pulmonary fistulas arising from the LAD proximal segment; the circumflex artery originated from the right coronary artery (Fig 1). The estimated right ventricle pressure at rest was 37 mm Hg based on EchoCG results. The decision was made to perform IVUS, stent the LAD middle segment and

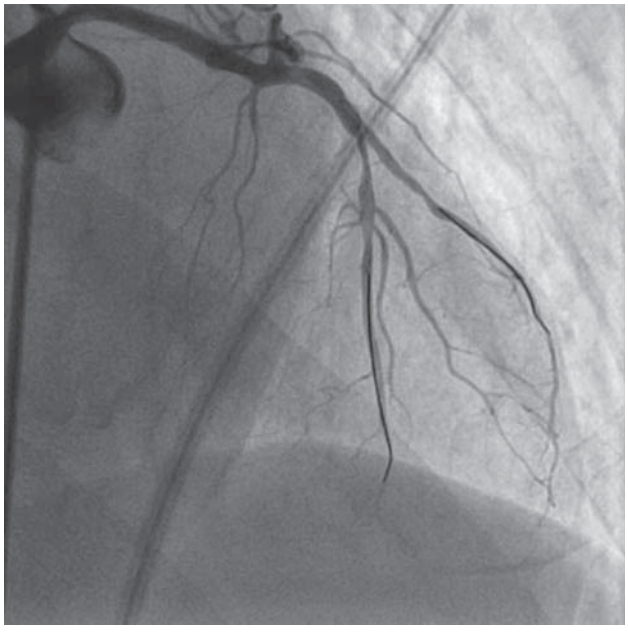

Fig. 1. Patient F., Coronary angiogram: extensive LAD narrowing in the middle third up to 80%, two coronary-pulmonary fistulas arising from the proximal segment of the LAD; the circumflex artery arising from the right coronary artery.

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The article was received on January 27, 2015
Accepted for publication on January 30, 2015

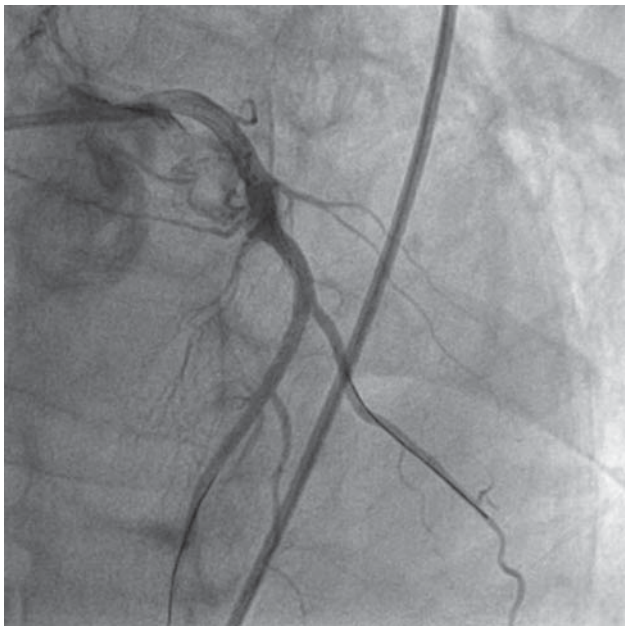

Fig. 2. Stenting of the middle segment of the LAD.

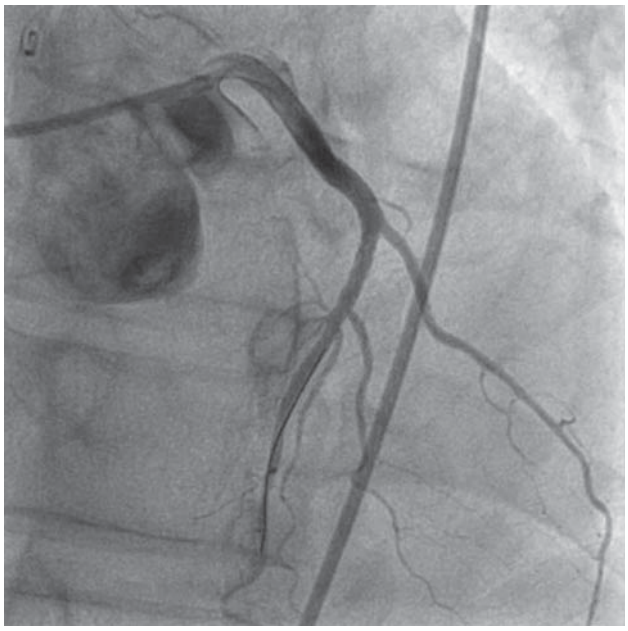

Fig. 3. Second step of the procedure – stent-graft implantation (4,0 × 19 mm).

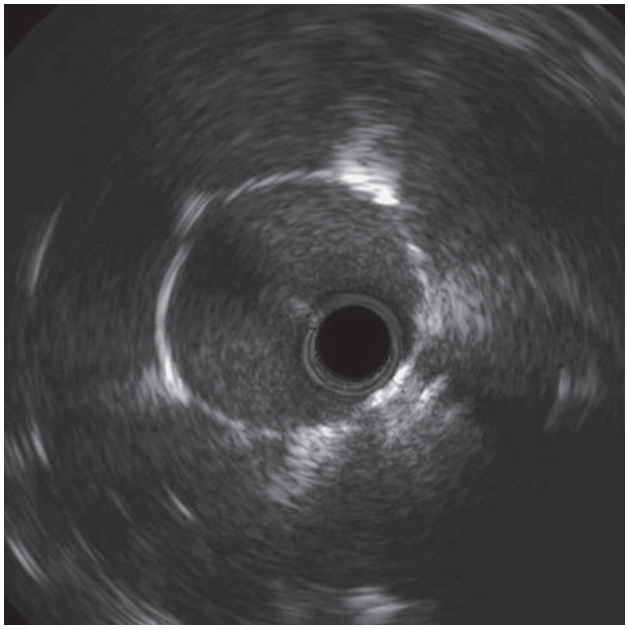

Fig. 4. Control IVUS.

close coronary-pulmonary fistula. The possible closure of coronary-pulmonary fistula with coils and coronary stent graft was considered. Given the technical complexity associated with fistula embolization and high risk of embolic complications, it was decided to implant a coronary graft GRAFTMASTER 4.0 × 19 mm. The first step was stenting of the LAD middle segment (Fig. 2). The second step was implantation of stent graft 4.0 × 19 mm (Fig. 3). A small shunt of contrast medium into the coronary-pulmonary fistula territory was observed after stent graft implantation. Follow-up LCA angiography performed in 2 minutes revealed no shunt. Follow-up IVUS was performed (Fig. 4). After intervention, the patient noted improvement: no pain and shortness of breath on exertion. 6-month follow-up EchoCG revealed the estimated right ventricle pressure of 28 mm Hg. The patient notes the lack of pressing retrosternal pain and increased exercise tolerance.

Conclusion:

In case of significant coronary-pulmonary fistulas causing grade 1–2 pulmonary hypertension, closure of coronary-pulmonary fistulas can decrease the pressure in the pulmonary circulation and improve the symptoms.

In this clinical case, the coronary graft GRAFTMASTER 4.0 x 19 mm showed favorable angiographic, ultrasound and clinical results at 6-month follow-up.

References

1. Burakovsky V.I., Bockeria L.A. Cardiovascular Surgery. M., Meditsina, 1996, 340–348, 359–362. (In Russian)
2. Wanes C.A., Williams R.G., Bashore T.M. et al. ACC/AHA 2008. Guidelines for the Management of adult with Congenital Heart Disease: report of the American College of Cardiology/American Heart Association Task Forse on Practice Guidelines (writing committee to develop guidelines on the management of adult with congenital heart disease). Circulation. 2008, 118 (23): 714–833.
3. Valente A.M., Lock J.E., Gauvreau K. Predictors of long-term adverse outcomes in patient with congenital coronary artery fistulae. Circulation: cardiovascular interventions. 2010, 3 (2), 134–139.
4. Chirantan V. Mangukia. Coronary artery fistula. Ann. Thorac. Surg. 2012, 93, 2084–2092.

5. Said S.M., Burkhart H.M., Schaff H.V. Late outcome of repair of congenital coronary artery fistulas – a word of caution. J. Thorac. Cardiovasc. Surg. 2013, 145, 455–460.
6. Bauer H.H., Allmendinger P.D., Flaherty J., Owlia D. et al. Congenital coronary arteriovenous fistula: spontaneous rupture and cardiac tamponade. Ann. Thorac. Surg. 1996, 62, 1521–1523.
7. Dimitrakakis G., Wheeler R., Von Oppell U. et al. Surgical management of a double coronary cameral fistula associated with mitral and tricuspid regurgitation, patent foramen ovale, and chronic atrial fibrillation. Heart Surg. Forum. 2008, 11, 209–212.
8. Bockeria L.A., Podzolkov V.P., Alekyan B.G., Makhachev O.A. ICVT on-line discussion. A coronary artery fistulae: history and surgical experience. Interact. CardioVasc. Thorac. Surg. 2007, 6, 414–415.
9. Bockeria L.A., Mironenko V.A., Bockeria O.L. et al. The combination of the correction of multiple arteriovenous malformations and coronary-right ventricular fistulas with cryoablation of arrhythmogenic areas of the right ventricle outflow tract. Thorac. and CardioVasc. Surg. 2009, 1, 61–66. (In Russian)

Chronic Heart Failure in Patients with Type 2 Diabetes Mellitus

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We present a literature review of prevalence, pathogenesis, and prognosis of chronic heart failure (CHF) in patients with type 2 diabetes mellitus (T2DM). Diabetes and CHF acquire the status of the epidemic of the XXI century and require health care costs for prevention and treatment of these diseases. Application of modern pharmacological preparations and instrumental treatment of cardiovascular diseases (CVDs) increases life expectancy and significantly improves the quality of life of patients with CHF both with normal carbohydrate metabolism (CM) and with T2DM. However, the risk of cardiovascular mortality (CVM) in patients with T2DM compared to those with normal CM remains unchanged. The rapidly growing population of patients with T2DM will soon change a recently established idea of better CVD treatment outcomes. Violation of myocardial remodelling in T2DM is caused by a combination of factors associated with diabetic cardiomyopathy, reduction of the metabolic activity of cardiomyocytes, insufficient glucose transport into cells, endothelial dysfunction, diabetic macro- and microangiopathy myocardial fibrosis leading to disruption of filling the left ventricle and the development of CHF. Insulin resistance (IR) and compensatory hyperinsulinemia (HI) play a key role in the pathogenesis of T2DM. To improve the results of treatment aimed at risk reduction of CHF development in patients with T2DM and impaired glucose tolerance (IGT), it is necessary to achieve the traditional primary objective, i.e. glycemic control. Since IR and compensatory HI play a key role in the T2DM pathogenesis and are closely associated with the risk of arterial hypertension (AH) and CVDs due to atherosclerosis, the treatment of patients with T2DM and IGT and CHF should involve the drugs affecting IR.

Key words: *type 2 diabetes mellitus, chronic heart failure, cardiovascular mortality, hyperglycemia, glycated hemoglobin, insulin resistance, hyperinsulinemia.*

The relevance of chronic heart failure (CHF) in patients with type 2 diabetes mellitus (T2DM) is determined by a high incidence of these diseases, as well as T2DM-associated increased risk of CHF. The number of these patients increases annually (1). One-year mortality in patients with severe CHF reaches 12%, even in specialized hospitals. Up to 612,000 CHF patients annually die in the Russian Federation (RF) (2). Studies conducted in the USA, have demonstrated a continuous increase in the number of CHF patients with preserved systolic function (PSF), which poses a problem of CHF with PSF (CHF-PSF) as one of the non-infectious epidemics of the XXI century (3). This CHF population primarily includes older women with poorly managed arterial hypertension (AH) and/or T2DM, the CHF-PSF incidence in whom achieves 68% (2, 4). The prevalence of CHF in Russia is steadily increasing and reaches 7.9 million people (7%). Functional class (FC) II–IV chronic heart failure (NYHA) is observed in 4.5% of the population (5.1 million people), of which high FCs (III–IV) amount to 2.1% (2.4 million people) (5). In 2011, at 71st meeting of the American Diabetes Association (ADA) it was stated that one in three persons born after the year 2000, during his/her life develops diabetes (ADA, 2011) (6). In the Russian Federation, as of January 01, 2013, the number of DM patients was 3,778,000 and 325,000 and 3,452,000 out of them have T1DM and T2DM, respectively (7). The rapidly growing population of T2DM patients in a short time will change the modern view of the improved prognosis for treatment of cardiovascular diseases (CVDs). Thus T2DM and CHF acquire the status of the epidemic of the XXI century and require health care costs for the treatment and prevention of these diseases.

Among the main causes of CHF, T2DM ranks 4th after chronic obstructive pulmonary disease (COPD), AH and coronary heart disease (CHD) (8).Given the economic growth and advances in medical science, the life expectancy of the organized population increases; therefore, an issue of treating patients with multiple diseases, i.e. co-morbidities becomes topical in clinical practice. In elderly and geriatric patients (9,10)

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The article received on March 23, 2015.
Accepted for publication April 20, 2015.

the severity of the CHF clinical pattern depends on comorbidities (11, 12), while extracardiac comorbidities may prevail over the cardiac ones (13), thus significantly limiting prescription of a number of glucose-lowering drugs (14).

Study of CHF prevalence, prognosis and treatment strategy in T2DM patients is an important issue. The Framingham study was the first epidemiological study to prove an increased CHF risk in T2DM patients (15). The analysis of the OASIS registry (Observational Assessment of Safety in Seroquel) to investigate T2DM influence on CHD long-term outcomes showed that CHF risk in T2DM patients was 3.43 times higher compared with those with normal carbohydrate metabolism (CM) (16). The incidences of heart failure in men and women with T2DM were 4 and 8 times higher, respectively, compared with patients with normal CM (15). The population studies proved that in elderly patients, T2DM is a risk factor for CHF, and the risk increases with growing severity of T2DM (17, 18). At the same time, it was revealed that 15–26% of CHF patients have T2DM (19). According to other authors, CHF in patients with T2DM was detected in 78.3% and 83.3% men and women, respectively, admitted in the endocrinology hospital and, respectively, in 87.0% and 81.0% of DM patients from the city registry (20). Based on the EPOHA-HSN results (2003–2005) it was concluded that in the Russian Federation the DM prevalence in CHF patients was 11.9% (21). Thus, the literature discusses the prevalence of obvious T2DM in CHF patients, and impaired glucose tolerance (IGT) continues to be a significant but under-investigated problem.

The patients with systolic chronic heart failure (S-CHF) not receiving hypoglycemic treatment and with glycated hemoglobin (HbA1c) >6.7%, have a risk of one-year mortality almost 2 times higher compared with patients with HbA1c level ⩽6.7% (22). In this case, T2DM plays an important role as a factor for development of myocardial fibrosis and impaired filling of the left ventricle (LV) with subsequent formation of S-CHF and typical LV dilatation and reduced contractility. The patients with S-CHF are younger and predominantly males (9, 23).The main reason determining the clinical pattern and severity in S-CHF patients is previous myocardial infarction (MI) (85.2%), while one-third of patients have repeated MI. S-CHF patients predominantly suffer from CHD, are mostly males and some of them have a history of significant physical loads (10).

Diastolic CHF (D-CHF) is the predominant cause of CHF (24, 25, 26), as among older subjects there is a high proportion of patients with increased myocardial rigidity (27) due to AH (28), CHD (29) and T2DM, as well as their combination (30, 31).The D-CHF is characterized with normal or reduced LV sizes and preserved contractility in contrast to S-CHF, in which the primary criterion of unfavorable outcome is the reduced ejection fraction (EF) (32). Solomon SD et al. demonstrated that at Year 2 after MI, the LV sizes increase less and CHF is observed 2 times more frequently in T2DM patients compared to those without T2DM (33).In patients with D-CHF, the primary factors defining features of myocardial injury, CHF clinical pattern and severity are AH (76.7%), overweight and obesity (39.5% and 33.7%), T2DM or IGT (29.1% and 12.8%) (34). The combination of CHD and T2DM is the determining factor for high mortality in CHF patients (35).

CHF in T2DM patients develops due to combination of CHD and diabetic microangiopathy reducing the coronary blood flow reserve as well as diastolic LV dysfunction (36) and diabetic autonomic cardiac dysfunction of the LV described in 1984 by D. Ewing (37). Diabetic autonomic cardioneuropahy (DACN) is one of the T2DM complications significantly affecting CVD clinical pattern and outcomes (38). DACN is observed in patients with a long lasting T2DM, which worsens the quality of life and is associated with high mortality (39, 40, 41). In patients with CHF and T2DM the risk of MI is higher in the presence of DACN (42). A meta-analysis of 15 longitudinal studies (43) which included a total of 2900 patients followed for 1–16 years showed that the presence of DACN results in higher mortality. The most dangerous manifestation of DACN is an asymptomatic myocardial ischemia. When 1468 T2DM patients were followed, there were only 10% of patients without DACN, and asymptomatic ischemia was detected in 20% of DACN patients (44, 45).

Metabolic ischemia typical for T2DM and manifesting as abnormal contractility of cardiomyocytes plays an important role. In hyperglycaemia settings, final glycation products and their precursors are overproduced, which changes blood protein structure and extracellular matrix and leads to dysfunction of the nerve fibres. The levels of all previous intermediate products of glycolysis are elevated and alternative pathways are activated: glyceraldehyde-3-phosphate, glycerol and methylglyoxal come in

the pathway of protein kinase C and final glycation products, fructose-6-phosphate enters hexosamine pathway, and glucose itself enters the polyol pathway. All the above pathological pathways of glucose and its metabolites utilization are responsible for DM complications affecting nerve tissue (neuropathy) and vascular wall (angiopathy) (46, 47). Thus, there is a T2DM specific atherosclerotic lesion of the proximal and distal parts of coronary arteries (48) combined with the metabolic ischemia of myocardiocytes (49, 50) and DACN (51).

There is a variety of mechanisms of CHF progression associated with T2DM. They include diabetic nephropathy (52) and cardiovascular autonomic neuropathy (53), insulin resistance (IR) and endothelial dysfunction (54), hemostasis disorders (55) and overexpression of pro-inflammatory cytokines (56). The combination of morphological and biochemical changes in the myocardium specific to T2DM patients, which is called diabetic cardio-myopathy, leads both to disturbance of diastolic processes and impaired myocardial contractility (57). Therefore, patients with CHF and T2DM have lower exercise tolerance compared to CHF patients without T2DM (58). Thus, the presence of T2DM compared with CHF patients with normal CM predetermines more severe functional class of CHF and, consequently, poor outcome.

According to the results from population and clinical studies, the mortality risk in CHF patients is increased 1.29-3.19-fold in the presence of T2DM (58). According to the study DIABHYCAR (type 2 DIABetes Hypertension Cardiovascular Events and Ramipril), the mortality in T2DM patients with CHF was 12 times higher than in T2DM patients without CHF (58, 59). The number of hospitalizations and length of hospital stay for decompensated CHF in T2DM patients are significantly higher than in those with normal CM which is confirmed by the large studies: BEST (Dutch acronym for Behandel-Strategieen - therapeutic strategies), RESOLVD (the Randomized Evaluation of Strategies for Left Ventricular Dysfunction), MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) (58, 60). The heart failure was the most common cause of death and accounted for 66% of 1-year overall mortality in the study DIGAMI (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction) in patients with acute myocardial infarction (AMI) and T2DM (61). In patients with T2DM, AMI is complicated by acute left ventricular failure 3 times more frequently compared to the subjects with normal CM (62).

According to the registry of the A.L. Myasnikov Scientific Research Institute of Cardiology, in patients with II–IV FC CHF (NYHA) the presence of T2DM significantly worsens outcomes in females and patients with EF <38%, and when systolic blood pressure (sBP) is <120 mm Hg. In the subgroups of patients with EF <30% and hypotension (sBP < 90 mm Hg) the severity of outcome was determined by the severity of CHF (63).

Up to 55% of patients with T2DM die within 5 years after AMI compared with 30% among patients with normal CM, and the incidence of repeated MI in patients with T2DM is 60%higher compared to patients without T2DM (64). The results from the prospective Quebec Cardiovascular Study published in January 2009 further demonstrated that the risk of cardiovascular mortality (CVM) in T2DM patients is 3 times higher and 4.5 times higher when T2DM is combined with CVDs than in patients with normal CM (65). The modern pharmacological drugs and interventional methods of CVD treatment increase life expectancy and significantly improve quality of life of patients both with normal CM and T2DM. However, the risk of CVDs in patients with T2DM compared with subjects with normal CM remains unchanged.

A role of T2DM in the formation of non-ischemic CHF is discussed, i.e. when the CM disturbances cause myocardial fibrosis leading to S-CHF (66, 67). Cardiac fibrosis is the leading morphological sign in T2DM patients. Increased collagen level and altered diastolic function are observed in the myocardium (68).The increase in the number of CHF cases in T2DM patients cannot be attributed only to more advanced or severe MI. The reasons for increased incidence of CHF in T2DM patients after AMI are not clearly understood and require further investigation (69). It is difficult to identify CHF directly related to T2DM, because co-morbidities of T2DM can independently disturb the myocardial function. In our opinion, these data cannot be discussed without analysis of the hyperglycemia role in the pathological process. In T2DM, cardiovascular dysfunction is caused by specific vessel injuries depending on vessel diameters – diabetic macro- and microangiopathy. Both vascular disorders play a role in the pathogenesis of ischemic myocardial damage in patients with T2DM.

The leading role in the development of coronary obstruction belongs to diabetic macroangiopathy (70); it is manifested as aggressive coronary atherosclerosis with higher incidence of multivessel coronary lesions (71). The patients with T2DM have abnormal formation of collateral vessels in response to ischemia, which may lead to CHF and poor outcome after MI (72). The features of lipid profile in T2DM are characterized by a "lipid triad", which includes increased triglycerides, reduced high density lipoproteins (HDL) cholesterol (Ch) and predominance of atherogenic fraction – low density lipoproteins (LDL) (73,74). T2DM is characterized by activation of platelet-vascular and coagulation hemostasis due to increased procoagulants concentrations, inhibition of fibrinolytic system, reduction in vascular wall athrombogenicity and decrease in activity of endogenous anticoagulants (75,76). When assessing significance of hyperglycemia pathogenetic role, one should consider its mandatory association with dyslipidemia, hyperinsulinaemia (HI), impaired vascular reactivity, which are of independent value for the coronary disorders (77). This means that cardiac complications of T2DM are not limited to hyperglycaemia only (78). Thus, the main pathogenetic mechanisms of the cardiovascular diseases in patients with T2DM are hyperglycemia (79), endothelial dysfunction, impaired blood rheological properties and lipid metabolism (80), HI, IR, genetic factors, AH, smoking and others (81). Hyperglycemia plays a critical role in the primary damage of the vascular wall and creates conditions for further development and progression of both atherosclerotic process (82) and disorders of cardiomyocytes metabolism.

One of the mechanisms determining the significance of T2DM as a risk factor for CHD is the damaging effect of hyperglycemia on the cellular function and metabolism, particularly endothelial cells and cardiomyocytes, due to so-called "glucose toxicity effect", with ultimate cell apoptosis (83,84). The increased blood glucose level is combined with endothelial dysfunction (85) as the glucose is able to activate the transcription factor NF-kB with cyclooxygenase (COX-2) overexpression, enhanced production of prostaglandin E2, activation of caspase-3 and apoptosis of endothelial cells (86). Endothelial dysfunction is observed in healthy descendants of T2DM patients suggesting hereditary genesis of this disease (87). A large number of genes involved in the risk of CVDs, T2DM and CHF are currently under study. The meta-analysis published in 2011, suggests that the allele A carriers have 1.5 times higher risk of CVDs compared with the GG genotype carriers (88). The issue regarding polymorphism of genes involved in the formation of predisposition and development of CHF in T2DM patients is topical, but currently it is still early to make practical conclusions.

It is known that chronic hyperglycemia increases the risk of CHF. The increase of HbA1c in the blood by 1% is associated with CHF risk increase by 16% (89). In patients with CHD associated with T2DM without CHF signs, the initial increase in HbA1c level by 1% was accompanied with increased risk of CHF by 36% within 4-year follow-up (90). Study CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), detected increased risk of cardiovascular death and hospitalizations for CHF in case of HbA1c increase (91). HbA1c level decrease $\geqslant$1% during the year in T2DM patients with initially poor glycemic control slows CHF progression (92). However, further studies of patients with CHF combined with T2DM revealed U-shaped pattern of the relationship between HbA1c and mortality. This means that not only T2DM patients with pronounced HbA1c increase (>9.5%) but also with HbA1c <6.5% have a poor outcome (93, 94). These studies show that glycemic control can reduce the incidence of CHF but the target HbA1c levels should be at the lower limit of normal.

It is known that the impairment of normal insulin secretion starts long before diagnosis of T2DM. At the stage of IGT, the incidence of coronary atherosclerosis is significantly higher than in subjects with normoglycemia (95). The Euro Heart Survey on Diabetes and the Heart (EHS) study detected IGT in 36% of CHD patients and newly diagnosed T2DM was observed in 22% of CHD patients. Thus, the overall proportion of patients with abnormal CM among AMI subjects reached 45–53% (96, 97). According to the Moscow acute coronary syndrome (ACS) registry (2012), the abnormal CM in ACS patients was observed in 36% of cases, and 20.7% and 15.3% out of them had a history of and newly diagnosed abnormal CM, respectively (98).

Postprandial hyperglycemia compared with an increased fasting glucose blood level is associated with the risk of CHD significantly more often (99,100). The study involving healthy

individuals and T2DM patients demonstrated that the steady increase in the glucose level up to 15 mM over 24 h was accompanied with development of oxidative stress and endothelial dysfunction with reduced endothelium-dependent relaxation (EDR) of the brachial artery. However, glucose level fluctuations within 5-15 mM every 6 h over 24 h caused significantly more severe disorders than stable hyperglycemia within 10–15 mM. These effects were eliminated by the administration of vitamin C, suggesting the leading role of activated peroxidation processes in their development. Therefore, when treating T2DM patients not only blood glucose levels should be normalized, but normal glucose tolerance should be also restored (101)

A key factor for T2DM development is IR which increases with CHF progression (102). Hyperglycemia in the absence of HI was not combined with increased oxidative activity of the aortic tissue. The increased mitochondrial production of superoxide radical (SOR) in the heart and aorta with chronic glucose load may result from both glucose and insulin activity; the latter was increasingly released in the hyperglycemia settings (103). This can be explained by the fact that the pathogenic effect of hyperglycemia is defined not only by its direct effect, but is largely mediated by its influence as a component of the IR syndrome. Hyperinsulinemia and IR are powerful atherogenic factors (104) leading to increased proliferation of endothelial cells (105).

The mechanisms underlying the IR have not been finally determined. The results of the analysis of interactions between insulin and target cells show three groups of mechanisms responsible for the IR development: pre-receptor, receptor and post-receptor ones. In most cases, IR is caused by defects in the insulin signaling at the post-receptor stage due to structural and functional disorders of proteins involved in the signaling determination. To maintain the concentration of blood glucose at a normal level, compensatory HI occurs. Then, IGT develops leading to metabolic syndrome (106). Compensatory HI and IR play a key role in the pathogenesis of CM disorders (107). It should be noted that the results from XXth century studies of CHD and CHF in T2DM patients were based on the investigation of the CM compensation when sulfonylureas (SMs) and insulin not affecting HI and IR were used. Currently, investigation of the course and the prognosis of CHD and CHF in T2DM patients treated with drugs affecting HI and IR is of great practical interest.

Conclusion

In conclusion, T2DM and CHF acquire the status of the epidemic of the XXI century and require health care costs for the treatment and prevention of these diseases. The modern medications and interventional methods of CVD treatment increases life expectancy and significantly improve the quality of life of CHF patients both with normal CM and with T2DM. However, the risk of CVDs in T2DM patients compared with subjects with normal CM remains unchanged. Disturbance of myocardial remodeling in T2DM is caused by the combination of factors associated with diabetic cardiomyopathy, decreased metabolic activity of cardiomyocytes, inadequate transport of glucose into cells, endothelial dysfunction, diabetic macro- and microangiopathy, myocardial fibrosis leading to impaired filling of the LV and development of CHF. The pathogenic effect of hyperglycemia is defined not only by its direct effect, but largely mediated by its influence as a component of the IR syndrome. A key factor for T2DM development is IR which increases with CHF progression. Hyperinsulinemia and IR are powerful atherogenic factors leading to increased proliferation of endothelial cells.The rapidly growing population of T2DM patients in a short time will change a recently established idea of improved outcomes of CVD treatment. To improve the results of treatment aimed at the reduction of CHF risk in T2DM patients it is necessary to achieve the traditional primary objective, i.e. control over glycemia. Since IR and compensatory HI play a key role in the pathogenesis of T2DM and are closely associated with the risk of AH and CVDs caused by atherosclerosis, the treatment of patients with T2DM and IGT with CHF should primarily involve drugs affecting the IR.

References

1. Bauters C., Lamblin N., Mc Fadden E.P. et al. Influence of diabetes mellitus on heart failure risk and outcome. Cardiovasc. Diabetol. 2003, 2, 1.
2. Danielyan M.O. Outcome and treatment of the chronic heart failure (20-year follow-up data). Avtoreferat (author's thesis abstract), PhD in Medicine, Moscow, 2001. (In Russian)
3. Owan T.E., Hodge D.O., Herges R.M. et al. Trends in prevalence and outcome of heartfailure with preserved ejection fraction. N. Engl. J. Med. 2006, 355 (3), 251–259.
4. Mareev V.Yu., Danielyan M.O., Belenkov Yu.N. On behalf of EPOHA–O–HSN working group. Comparative characteris-

tics of CHF patients depending on EF results from the Russian multicenter study EPOHA–O–HSN. Serdechnaya nedostatochnost (Cardiac Failure), 2006, 7 (4), 164–171. (In Russian)
5. National recommendations of the Russian Scientific Society of Cardiology and Society of Experts on Cardiac Failure on diagnostics and treatment of CHF (third revision). Serdechnaya nedostatochnost (Cardiac Failure), 2010, 11, 1 (57), 3–62. (In Russian)
6. Mayorov A.Yu. 71st Annual Meeting of American Diabetology Association (ADA), Sakharniy diabet (Diabetes mellitus), 2011, 3, 120–121. (In Russian)
7. Dedov I.I. Innovational technologies in treatment and prevention of the diabetes mellitus and its complications. Sakharniy diabet (Diabetes mellitus), 2013, 3, 2–10. (In Russian)
8. Mareev V.Yu., Ageev F.T., Arutyunov G.P. et al.National recommendations of the Russian Scientific Society of Cardiology and Society of Experts on Cardiac Failure on diagnostics and treatment of CHF (third revision) (approved at the Society of Experts on Cardiac Failure meeting on December 15, 2009). Serdechnaya nedostatochnost (Cardiac Failure), 2010, 11, 1, 3–62. (In Russian)
9. Gray L.K., Smyth K.A., Palmer R.M. et al. Heterogeneity in older people: examining physiologic failure, age, and comorbidity. J. Am. Geriatr. Soc. 2002, 50 (12), 1955–1961.
10. Bayliss E.A., Bayliss M.S., Ware J.E., Jr., Steiner J.F. Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list. Health Qual. Life Outcomes. 2004, 2, 47.
11. Wolff J.L., Starfield B., Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch. Intern. Med. 2002,162 (20), 2269–2276.
12. Lien C.T., Gillespie N.D., Struthers A.D., McMurdo M.E. Heart failure in frail elderly patients: diagnostic difficulties, co-morbidities, polypharmacy and treatment dilemmas. Eur. J. Heart Fail. 2002, 4 (1), 91–98.
13. van der Wel M.C., Jansen R.W., Bakx J.C. et al. Non-cardiovascular co-morbidity in elderly patients with heart failure outnumbers cardiovascular comorbidity. Eur. J. Heart Fail. 2007, 9 (6–7), 709–715.
14. Standi E. Aetiology and consenquences of the metabolic syndrome. Eur. Heart J. 2005, 7, 10–13.
15. Clark C., Perry R. Type 2 diabetes and macrovascular disease: epidemiology and etiology. Am. Heart J. 1999, 138, 330–333.
16. Malmberg K., Yusuf S., Gerstein H.C. et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000, 102 (9), 1014–1019.
17. Ryden L., Armstrong P., Cleland J., Horowitz J. et al. Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. Eur. Heart J. 2000, 21, 1967–1978.
18. Panova E.I. Myocardial infarction and type 2 diabetes mellitus; some features of the combined pathology. Nizhegorodskiy Meditsinskiy Zhurnal (Medical Journal of Nizhny Novgorod), 2008, 1, 10–14. (In Russian)
19. Bauters C., Lamblin N., Fadden E.R. et al. Influence of diabetes mellitus in heart failure risk an outcome. Cardiovasc. Diabetol. 2003, 2, 1.
20. Litaeva T.Yu. Chronic heart failure in patients with type 2 diabetes mellitus: prevalence, diagnostics and treatment features. Avtoreferat (author's thesis abstract), PhD in Medicine, Orenburg, 2011, p. 26. (In Russian)
21. Fomin I.V., Mareev V.Yu., Ageev F.T. et al. Diabetes mellitus as an etiological cause of CHF in the European part of the Russian Federation (EPOHA–HSN trial, in-hospital stage). Serdechnaya nedostatochnost (Cardiac Failure), 2012, 13, 1 (69), 3–9. (In Russian)
22. Goode K.M., John J., Rigby A.S. et al. Elevated glycated haemoglobin is a strong predictor of mortality in patients with left ventricular systolic dysfunction who are not receiving treatment for diabetes mellitus. Heart. 2009, 95 (11), 917–923. Epub 2009 Feb 19.
23. Cleland J.G., Swedberg K., Follath F. et al. The EuroHeart Failure survey programme a survey on the quality of care among patients with heart failure in Europe. Part 1: patients characteristics and diagnosis. Eur. Heart J. 2003, 24 (5), 442–463.
24. Lindsay M.M., Maxwell P., Dunn F.G. TIMP-1: a marker of left ventricular diastolic dysfunction and fibrosis in hypertension. Hypertension. 2002, 40, 136–141.
25. Ageev F.T. Diastolic heart failure: 10-year presentation. Serdechnaya nedostatochnost (Cardiac Failure), 2010, 11, 1 (57), 69–76. (In Russian)
26. Wu A.H., Smith A., Wieczorek S. et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. Am. J. Cardiol. 2003, 92, 628–631.
27. Ageev F.T., Danielyan M.O., Mareev V.Yu. et al. Patients with chronic heart failure in the Russian out-patient settings: features of population, diagnostics, and treatment (based on the EPOHA-O-HSN results). Serdechnaya nedostatochnost (Cardiac Failure), 2004, 5 (1), 4–7. (In Russian)
28. Fomin I.V. Arterial hypertension in the Russian Federation over the past 10 years. What is next? Serdtse (Heart), 2007, 6, 3 (35), 120–122.
29. Fomin I.V. Epidemiology of the chronic heart failure in the European part of the Russian Federation. Chronic heart failure. Moscow, GEOTAR – Media, 2010, 5–18. (In Russian)
30. Jessup M., Brozena S. Heart failure. N. Engl. J. Med. 2003, 348 (20), 2007–2018.
31. Redfield M.M., Jacobsen S.J., Burnett J.C. et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003, 289 (2), 194–202.
32. Tschope C., Kasner M., Westermann D. et al. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur. Heart J. 2005, 26 (21), 2277–2284.
33. Solomon S.D., St. John Sutton M., Lamas G.A. et al. Ventricular remodeling does not accompany the development of heart failure in diabetic patients after myocardial infarction. Circulation. 2002, 106, 1251.
34. Solomakhina N.I. Cardiac and extracardiac co-morbidity in elderly and geriatric patients with systolic and diastolic CHF. Serdechnaya nedostatochnost (Cardiac Failure), 2009, 6, 298–303. (In Russian).
35. De Groote P., Lamblin N., Mouquet F. et al. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. Eur. Heart J. 2004, 25 (8), 656–662.

36. Detry J. The pathophysiology of myocardial ischaemia. Eur. Heart J. 1996, 17 (I), 48–52.
37. Ewing D. Cardiac autonomic neuropathy. In: Jarret R., ed. Diabetes and heart disease. Amsterdam: Elsevier, 1984, 99–132.
38. Schonauer M., Thomas A., Morbach S., Niebauer J. et al. Cardiac autonomic diabetic neuropathy. Diabetes Vasc. Dis. Res. 2008, 5, 336–344.
39. Vertkin A.L. Diabetic autonomic neuropathy: diagnostics and treatment. Klinich. farmakologia I farmakoterapia (Clinical pharmacology and pharmacotherapy), 2004, 6, 4, 14–16. (In Russian)
40. Vinik A., Freeman R., Erbas T. Diabetic autonomic neuropathy. Semin. Neurol. 2003, 23, 365–372.
41. Vinik A., Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007, 115, 387–397.
42. Botova S.N. Diagnostic and prognostic significance of cardiovascular autonomic neuropathy in patients with type 2 diabetes mellitus combined with chronic heart failure. Nizhny Novgorod, 2009. (In Russian)
43. Spallone V., Ziegler D., Freeman R. et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes / Metabolism Research and Reviews. 2011, 27 (7), 639–653.
44. Vinik A., Maser R., Mitchell B., Freeman R. Diabetic Autonomic Neuropathy. Diabetes Care. 2003, 26 (5), 1553–1579.
45. Young L., Wackers F., Chyun D. et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA. 2009, 301, 1547–1555.
46. Podachina S.V. From classical therapy of diabetic neuropathy to solving the problem of hyperglycemic memory. Effective pharmacotherapy. Endocrinology, 2012, 1. 48–52. (In Russian)
47. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005, 54 (6), 1615–1625.
48. Barzilay J.I., Kronmal R.A., Bittner V. et al. Coronary artery disease and coronary artery bypass grafting in diabetic patients aged >65 years (Report from the coronary artery surgery study (CASS) registry). Am. J. Cardiol. 1994, 74 (4), 334–339.
49. Dedov I.I., Aleksandrov An.A. Problems of acute myocardial infarction in patients with diabetes mellitus: Munich echo. Sakharniy diabet (Diabetes mellitus), 2008, 1, 4–10. (In Russian)
50. Valensi P., Pariès J., Brulport-Cerisier V. et al. Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. Diabetes Care. 2005, 28 (11), 2722–2727.
51. Sima A.A., Thomas P.K., Ishii D., Vinik A. Diabetic neuropathies. Diabetologia. 1997, 40, Suppl. 3, B74–B77.
52. Strongin L.G., Pochinka I.G., Aleynik D.Ya., Charykova I.N. Survival predictors in patients with chronic heart failure and type 2 diabetes mellitus. Sakharniy diabet (Diabetes mellitus), 2004, (4), 14–18. (In Russian)
53. Strongin L.G., Botova S.N., Pochinka I.G. Prognostic value of cardiovascular autonomic neuropathy in patients with type 2 diabetes mellitus combined with chronic heart failure. Kardiologija (Cardiology), 2010, (2), 26–29. (In Russian)
54. Fonseca V., Desouza C., Asnani S., Jialal I. Nontraditional Risk Factors for Cardiovascular Disease in Diabetes. Endocr. Rev. 2004, 25 (1), 153–175.
55. Severina A.S., Shestakova M.V. Hemostasis disturbances in patients with diabetes mellitus. Sakharniy diabet (Diabetes mellitus), 2004, (1), 62–67. (In Russian)
56. Pochinka I.G. Peculiarities of tumour necrosis factor production in patients with chronic heart failure and type 2 diabetes mellitus. Collection of articles of X interregional cardiology forum. Nizhny Novgorod, 2006, 135–138. (In Russian)
57. Fang Z.Y., Prins J.B., Marwick T.H. Diabetic Cardiomyopathy: Evidence, Mechanisms, and Therapeutic Implications. Endocr. Rev. 2004, 25 (4), 543–567.
58. MacDonald M.R., Petrie M.C., Hawkins N.M. et al. Diabetes, left ventricular systolic dysfunction and chronic heart failure. Eur. Heart J. 2008, 29 (10), 1224–1240. Epub 2008 Apr 18.
59. Vaur L., Gueret P., Lievre M. et al. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the Diabhycar (type 2 DIABetes Hypertension Cardiovascular Events and Ramipril) study. Diabetes care. 2003, 26, 855–860.
60. MacDonald M.R., Petrie M.C., Hawkins N. et al. Diabetes, left ventricular systolic disfunction and chronic heart failure. Eur. Heart J. 2008, 29, 1224–1240.
61. Nichols G., Hillier T.A., Erbey J.R. et al. Congestive heart failure in type 2 diabetes: prevalence, incidence and risk factors. Diabetes Care. 2001, 24, 1614–1619.
62. Kakorin S.V., Sangar K.A., Bochkov P.A. Acute coronary syndrome complicated with acute heart failure in patients with carbohydrate metabolism disorders. Abstracts of the V All-Russian Forum “Emergency Cardiology Issues – 2012”. November 28–29, 2012, Moscow, 19. (In Russian)
63. Belenkov Yu.N., Mareev V.Yu., Ageev F.T. Danielyan M.O. Registry of A.L. Myasnikov Scientific Research Institute of Cardiology, 2002. (In Russian)
64. Aleksandrov A.A., Bondarenko I.Z., Kukharenko S.S. et al., Diabetes mellitus and coronary heart disease:solving research. Sakharniy diabet (Diabetes mellitus), 2005, 3, 34–38. (In Russian)
65, Bilchenko A.V. Diabetes mellitus and cardiovascular diseases, Zhurnal Liki Ukraini (Ukranian Drugs), 2009, 4 (130), 78–81 (In Russian)
66. Dries D.L., Sweitzer N.K., Drazner M.H. et al. Prognostic impact of diabetes mellitus in patients with heart failure according to the aetiology of left ventricular systolic dysfunction. J. Am. Coll. Cardiol. 2001, 38 (2), 421–428.
67. Kamalesh M., Subramanian U., Sawada S. et al. Decreased survival in diabetic paients with heart failure due to systolic dysfunction. Eur. J. Heart Fail. 2006, 8 (4), 404–408.
68. Picano E. Diabetic cardiomyopathy. The importance of being earliest. J. Am. Coll. Cardiol. 42, 454, 2003.
69. Standl E., Schnell O. A new look at the heart in diabetes mellitus: From ailing to failing. Diabetologia. 2000, 43, 1455.
70. Balabolkin M.I. Endocrinology. M., Universum Publishing, 1994. (In Russian)
71. Superko H.R., Krauss R.M., DiRicco C. Effect of fluvastatin on low-density lipoprotein peak particle diameter. Am. J. Cardiol. 1997, 80 (1), 78–81.
72. Sasso F.C., Torella D., Carbonara O. et al. Increased vascular endothelial growth factor expression but impaired vascular endothelial growth factor receptor signaling in the myocardium of type 2 diabetic patients with chronic coronal disease. J. Am. Coll. Cardiol. 2005, 46, 827.
73. Mazzone T., Chait A., Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic stud-

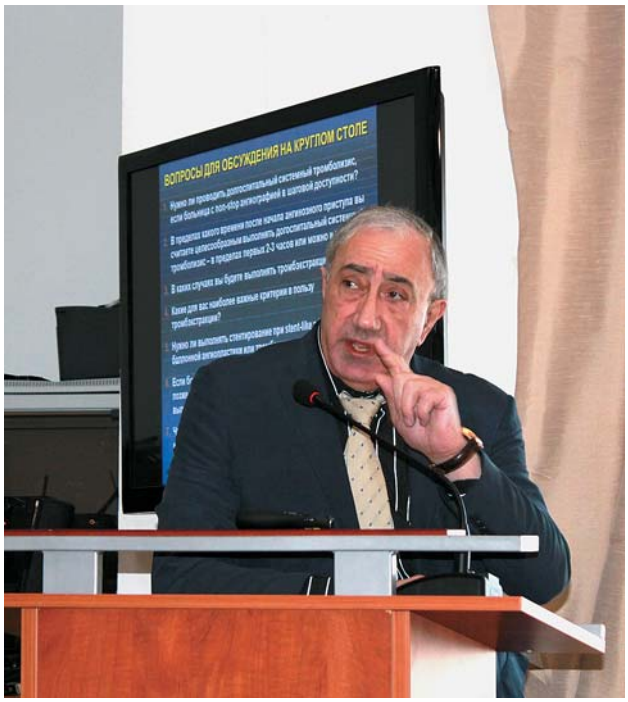
ies. Lancet. 2008, May 24, 371 (9626):1800–1809. doi: 10.1016/ S0140-6736(08)60768-0.
74. Jialal I., Amess W., Kaur M. Management of hypertriglyceridemia in the diabetic patient. Curr. Diab. Rep. 2010, 10 (4), 316–320. doi: 10.1007/s11892-010-0124-4.
75. Grant P.J. Diabetes mellitus as a prothrombotic condition. J. Intern. Med. 2007, 262 (2), 157–172.
76. Lemkes B.A., Hermanides J., Devries J.H. et al. Hyperglycemia: a prothrombotic factor? J. Thromb. Haemost. 2010, 8 (8), 1663–1669. doi: 10.1111/j.1538-7836.2010.03910.x.
77. Raitakari M., Ilvonen T., Ahotupa M. et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler. Thromb. Vasc. Biol. 2004, 24, 124–131.
78. Werner A., Travaglini M. A review of rosiglitazone in type 2 diabetes mellitus. Pharmacotherapy. 2001, 21 (9), 1082–1099.
79. Bartnik M., Ryden L., Ferrari R. et al. Euro Heart Survey Investigators. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. Eur. Heart J. 2004, 25, 1880–1890.
80. Kowalska I., Prokop J., Bachorzewska-Gajewska H. et al. Disturbances of glucose metabolism in men referred for coronary angiography. Diabet. Care. 2001, 24, 897–901.
81. Anselminoa M., Bartnikb M., Malmbergb K., Rydénb L. Management of coronary artery disease in patients with and without diabetes mellitus. Acute management reasonable but secondary prevention unacceptably poor: a report from the Euro Heart Survey on Diabetes and the Heart. Eur. J. Cardiovasc. Prev. Rehabil. 2007, 14, 28–36.
82. Severina A.S., Galitsina N.A., Parfenova E.V. et al. Role of endothelial dysfunction in diabetic macroangiopathies. M., 2007. (In Russian)
83. Favaro E., Miceli I., Bussolati B., Schimitt-Ney M. Hyperglycemia Induces Apoptosis of Human Pancreatic Islet Endothelial Cells . Am. J. Pathol. 2008, 173 (2), 442–450.
84. Dandona P., Chaudhuri A., Ghanim H. Acute Myocardial Infarction, Hyperglycemia, and Insulin. J. Am. Coll. Cardiol. 2009, 53, 1437–1439.
85. Hong Z., GuoLiang L., QiuYue W. et al. Effect of ghrelin on human endothelial cells apoptosis induced by high glucose. Biochem. Biophys. Res. Comm. 2007, 362, 677–681.
86. Sheu M., Ho F., Yang R. et al. High glucose induces human endothelial cell apoptosis through a phosphoinositide 3-kinase-regulated cyclooxygenase-2 pathway. Arterioscler. Throm. Vasc. Biol. 2005, 25, 539–547.
87. Goldfine A.B., Beckman J.A., Betensky R.A. et al. Family history of diabetes is a major determinant of endothelial function. J. Am. Coll. Cardiol. 2006, 47, 2456.
88. Zhang H.-F., Xie S.-L., Wang J.-F. et al. Tumor necrosis factor-alpha G-308A gene polymorphism and coronary heart disease susceptibility: An updated meta-analysis. Thromb. Res. 2011, 127 (5), 400–405.
89. Nichols G., Gullion C., Koro C. et al. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004, 27, 1879–1884.
90. van Melle J.P., Bot M., de Jonge P. et al. Diabetes, Glycemic Control, and New-Onset Heart Failure in Patients With Stable Coronary Artery Disease. Diabetes Care. 2010, 33 (9), 2084–2089.
91. Gerstein H.C., Swedberg K., Carlsson J. et al. CHARM Program Investigators. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch. Intern. Med. 2008, 168 (15), 1699–1704.
92. Strongin L.G., Pochinka I.G., Konysheva M.S., Glycemic control and course of chronic heart failure in patients with type 2 diabetes mellitus, Sakharniy diabet (Diabetes mellitus) 2012, 2, 17–21. (In Russian)
93. Aguilar D., Bozkurt B., Ramasubbu K., Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. J. Am. Coll. Cardiol. 2009, 54 (5), 422–428.
94. Strongin L.G., Pochinka I.G., Aleynik D.Ya., Charykova I.N. Survival predictors in patients with chronic heart failure and type 2 diabetes mellitus. Sakharniy diabet (Diabetes mellitus), 2004, 4, 14–18. (In Russian)
95. Saely C.H., Drexel H., Sourij H. et al. Key role of postchallenge hyperglycemia for the presence and extent of coronary atherosclerosis: An angiographic Study. Atherosclerosis. 2008, 199 (2), 317–322. Epub 2008 Jan 9.
96. Bartnik M., Ryden L., Ferrari R. et al. Euro Heart Survey Investigators. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. Eur. Heart J. 2004, 25, 1880–1890.
97. Bartnik M. Glucose regulation and coronary artery disease: Studies on prevalence recognition and prognostic implication. Karolinska Institutet, Stockholm, 2005.
98. Kakorin S.V., Erlikh A.D., Kalinkina A.A. Decompensation level of carbohydrate metabolism in patients with acute coronary syndrome and obvious/newly diagnosed type 2 diabetes mellitus (Moscow acute coronary syndrome registry). Abstracts of the VI All-Russian Forum “Emergency Cardiology - 2013”. Modern treatment approaches of acute coronary syndrome. November 28-29, 2013, Moscow, 2013, 22. (In Russian)
99. Smith N.L., Barzilay J.K., Shaffer D. et al. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. Arch. Intern. Med. 2002, 162, 209–216.
100. Temelkova-Kurktschiev T., Henkel E., Koehler C. et al. Subclinical inflammation in newly detected type II diabetes and impaired glucose tolerance. Diabetologia. 2002, 45, 151–156.
101. Ceriello A., Esposito K., Piconi L. et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes. 2008, 57, 1349–1354.
102. van Melle J.P., Bot M., de Jonge P. et al. Diabetes, Glycemic Control, and New-Onset Heart Failure in Patients With Stable Coronary Artery Disease. Diabetes Care. 2010, 33 (9), 2084–2089.
103. Midaoui A., Champlain J. Effects of glucose and insulin on the development of oxidative stress and hypertension in animal models of type 1 and type 2 diabetes. Hypertension. 2005, 23, 3, 581–588.
104. Aguilar D., Bozkurt B., Ramasubbu K., Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. J. Am. Coll. Cardiol. 2009, 54 (5), 422–428.
105. Lexis C.P.H., Rahel B.M., Meeder J.G. et al. Cardiovascular Diabetology. 2009, 8, 41. doi:10.1186/1475-2840-8-41.

The Rebirth of Traditions or The 1st Russian School of young specialists in endovascular diagnosis and treatment. The course: "BASICS OF INTERVENTIONAL CARDIOANGIOLOGY"

The Orders of the Ministry of Healthcare and Social Development of Russia № № 210n and 415n of the year 2009, have introduced into the nomenclature a new speciality – "Endovascular methods of diagnosis and treatment" – and have adopted the appropriate qualification criteria for the preparation of specialists of this profile. The chairs and the clinical sites aimed at the education of well-skilled specialists have been formed in many medical universities on the base of the faculties of post-graduate education. The unique character of this discipline is obvious and consists in its high "invasiveness"! Transcatheter technologies are being actively introduced in all clinical specialities, and in most cases hold the top positions. The opposite side of such "width of views" of the new speciality is a huge diversity of the basic level and the profile of specialists preparation. Cardiologists, neurologists, radiologists, general and cardiovascular surgeons, neurosurgeons, oncologists and representatives of many other profession are now coming into the specialtiy... Such multiplicity poses new tasks for the search of additional methods of education, able to unify the young specialists and to form the community of their professional philosophy.

The idea of the rebirth of the "school of young specialists" and of its conduction in a historical pearl of our country – the town of Suzdal – belongs to Professor David Iosseliani, the Director of Moscow City Center of Interventional cardioangiology, the founder and the Vice-President of Russian Society of Interventional cardioangiology (RSICA). The present President of RSICA, professor Alexander Osiev met this idea with enthusiasm. The event was held under his guidance, on March 25–27, 2915, in the hotel resort

The audience of the "School of young specialists"



Corr. Member of Russian Academy of Sciences
David Iosseliani

Corr. Member of Russian Academy of Sciences
Leonid Kokov

"Pushkarskaya Sloboda". The conduction of this School opened a new page in the history of our profession. Professors Alexander Osiev, Victor Demin and Serguey Semitko were the Co-Directors of the School. Fifty leading experts in the field of interventional cardioangiology formed the Organizing Committee. During two days, 26 lecturers have presented 40 lectures and discourses dedicated to the history of the profession, the basic principles of catheterization of the heart and vessels, the basics of methodology and the safety, and the perspective trends of research. Among the invited lecturers, the leading Russian experts in cardiac surgery and interventional cardioangiology – Academician Yuri Belov, Corresponding

Professor Victor Demin, Professor Alexander Osiev, Professor Serguey Semitko – Co-Directors of the "School"

Academician Yuri Belov

Members of the Russian Academy of Sciences David Iosseliani and Leonid Kokov – have found the opportunity to come and to speak before the audience of the "School".

The geography of participants (in total, 146 attendees have been registered) is really impressive: the young physicians came from 44 Russian cities, from Petrozavodsk to Vladivostok, and also from Kazakhstan (Astana) and Uzbekistan (Tashkent). All scientific and methodological materials of the "School" are available at the website of RSICA: http://www.rnoik.ru/ru/?idx=869

On behalf of the Organizing Committee and all the participants of the "School" we would like to express our gratitude to our partners – 14 companies that provided financial support necessary for the organization of the event. These are our general sponsors – Cardiomedics, Medtronic and GE Nycomed, main sponsors – Abbott Vascular/Exten Medical and Terumo/Daksmed, sponsors – Bayer, Biotronic, Vlaant, EGAMedical, Procardio, Raymed, Siemens. Let us thank the staff of the hotel resort "Pushkarskaya sloboda" for their hospitality and high level of service. The organizers of the event hope, that this year's "School of young specialists" will be the first step on the way of rebirth of a tradition, will contribute to the reinforcement of friendship, active professional communications between the specialists and also help them to get acquainted with the history of our country.

Sincerely,
Organizing Committee