ISSN 1727-818X

International Journal of Interventional Cardioangiology

№13
2007

Read in the journal:

RUSSIAN SOCIETY OF INTERVENTIONAL CARDIOANGIOLOGY

ISSN 1727-818X

INTERNATIONAL JOURNAL OF INTERVENTIONAL CARDIOANGIOLOGY

Quarterly Journal of the Russian Scientific Society of Interventional Cardioangiology

№ 13, 2007 г.

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

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Special gratitude to
George Gigineishvili,
doctor and artist, for the offered opportunity to put the photocopy of his painting
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ISSN 1727-818X
9 771727 818001

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Contents

Recommendations of Heart Editors Action Round Table (HEART Group) concerning the ethical principles of scientific publications

Ethics

Purpose is to ensure transparency and honesty in the scientific process that promotes ethical conduct in performance and publication of research

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Hospital and Long-Term Outcomes with the Use of Cypher Sirolimus-Eluting Coronary Stent

B. Tiryaki[1], I.V. Pershukov, I.V. Levitsky, V.V. Lopukhova, Sh.T. Jamgyrchiev, A.N. Samko, Yu.A. Karpov., A.L. Myasnikov

Research Institute of Cardiology, Russian Cardiological Scientific Production Complex of Ministry of Health and Social Development of Russian Federation, Moscow

Regional Clinical Hospital #1, Voronezh

SUMMARY

This study assessed the effect of Cypher Sirolimus -eluting coronary stents during 27 months after implantation in patients with coronary atherosclerosis without previous interventions. Stents were implanted to 703 affected coronary segments in 554 patients. Thirty-two percent of stenoses were complicated. Twenty-three percent of patients had 2 to 4 Cypher stents implanted. Immediate success was obtained in 100%, no cases of acute thrombosis were reported. The incidence of subacute thrombosis and non-Q wave myocardial infarction during in-patient period was 0.2%. All patients remained alive during the follow-up of subgroup consisting of 108 patients for 27 months after hospitalization. Mean follow-up period was 257±107 days. The percentage of surviving patients without restenosis, angina pectoris, myocardial infarction and repeated revascularization was 94% during this period. Restenosis rate was 5.6%. Successful repeated revascularizations were performed in 6 patients with in-stent restenoses.

Key Words: angina, thrombosis, stent, restenosis, revascularization.

INTRODUCTION

The 21st century in invasive cardiology started with clinical introduction of effective antiproliferative drug coating of coronary stents (1-3). First clinical study in new "age of drug-eluting stents" was First In Man (FIM) study, in which BX Velocity coronary stents (Cordis, USA) with polymer coating eluting antiproliferative agent Rapamycin/Sirolimus were implanted to 45 consecutive non-randomized patients (4). No patients had clinical signs of angina and angiographically significant restenosis at 6 months after stenting (5). Study results were impressive after 12 months follow-up as well (4). After completion of FIM study Sirolimus-eluting stent was named as Cypher (Cordis J&J, USA).

The subsequent project RAVEL – a randomized comparison of Sirolimus-eluting Cypher stent (Cordis, USA) with its analogue bare stent, BX Velocity, did not reveal any cases of significant restenosis in group of coated stents during first 6 months of follow up (6). However, in further studies of Cypher SIRIUS (7), E-SIRIUS (8), C-SIRIUS (9) stents, which were more representative of real populations of stented patients, restenosis in drug-eluting stent turned out to have place (3). P.W. Serruys and his co-workers in Netherlands made an attempt to assess the potentials of Cypher stent use in real routine clinical practice (10). They have analyzed register of all interventions with implantation of Cypher stent in their cardiological clinic in Rotterdam (calling it RESEARCH) (3, 10). Unfortunately there were no such studies in Russia; therefore we considered assessing of outcomes in the whole sample of patients under our observation who underwent implantation of Cypher stents to be relevant.

MATERIAL AND METHODS OF THE STUDY

Patient selection criteria

The present study included 554 patients hospitalized since 2002 until October, 2004, with stable exertional angina (II to IV functional class according to Canadian classification) or acute coronary syndrome (unstable angina, non-Q-wave or Q-wave myocardial infarction). One or more hemodynamically significant stenosis (>50% of vessel diameter) in one or more coronary arteries (CA) were revealed in them during coronary angiography.

Exclusion criteria for the present study were: any previous percutaneous coronary intervention (PCI) in stented CA; previous coronary artery bypass grafting. Moreover, patients with Aspirin or Clopidogrel intolerance were not included in study as well as patients with hemorrhagic stroke or gastrointestinal bleeding during the last 6 months before coronary stenting (CS).

Angiographic exclusion criteria for this study were stenosis of the left main CA trunk, vessel reference diameter (VRD) at the site of stenosis below 2.2 mm or above 4.5 mm, vessel kink greater than 60 located proximal to lesion or at the site of stenosis.

According to ethical protocol all patients included in study were informed about impending treatment and gave written informed consent.

Technique of stenting

Stenting was performed after ballon predilatation of stenosis or directly if there was possibility to implant the stent without prior dilatation of narrowed segment. Stent implantation lasted for 20-25 sec-

[1] Tiriaki B.
Regional Clinical Hospital #1
Voronezh, 394066, Moskovsky prospect, 151
Manuscript received on October 12, 2007
Accepted for publication on November 6, 2007

onds under nominal pressure of 10-11 atmospheres. Stent diameter to vessel reference diameter ratio of 1:1 was achieved with subsequent stent dilatations under pressure 12 to 20 barometric atmospheres.

Pharmacological support of stenting

Aspirin at a dose of 75 to 162 mg a day was administered to all patients from the moment of hospitalization. Patients received Clopidogrel (Plavix) at a dose of 75 mg 2 days before stenting or at a dose of 300 mg 6 hours before procedure, after implantation of Cypher – for 3 to 12 months at a daily dose of 75 mg.

Unfractionated heparin was administered to patients at a beginning of CS as a bolus (5000 IU) through cannula in aorta and was continued further up to 5000 IU every 60 minutes till CS ending. The efficacy of heparin therapy was assessed by activated coagulation time (ACT) which was increased up to more than 300 seconds. Nitroglycerin was administered intracoronary at a dose of 200 μg before and after stenting.

Follow-up

Analysis of stenting results included 3 endpoints.

The first one - immediate angiographic results (incidence of following events was estimated: death, occlusion of artery with subsequent MI, bleedings).

The second endpoint – clinical results before termination of hospitalization (incidence of death, MI, recurrence of angina and repeated revascularization of stented artery).

The third endpoint – clinical and angiographic results at up to 27 months follow-up after stenting. Clinical results were assessed according to number of fatal outcomes, subsequent PCI or CB surgery, MI and recurrent angina associated with stented segment. Angiographic results were defined during control coronary angiography. Binary restenosis (repeated narrowing of stented artery by 50% of diameter or more) rate was estimated.

Statistical considerations

Values are presented as mean ± standard deviation. Survival function was estimated using Kaplan-Meier method. “Statistica for Windows Release 6.0” (StatSoft Inc, USA) was used for analysis.

RESULTS

Most patients (78%) in present study were male. Patients age was 35 to 85 years with mean of 57±7 years. Every third patient (34%) had increased blood cholesterol level (more than 5.2 mmol/l). Every tenth patient (11%) suffered from diabetes mellitus and received specific therapy orally or insulin subcutaneously. Almost one third of patients (32%) have had myocardial infarction before stenting and 16% of patients had clinical picture of acute coronary syndrome at the moment of present hospitalization. Main clinical parameters of patients are shown in Table 1.

Table 1. Baseline clinical characteristics.

Main clinical characteristics (n=448 patients)	
Age (years); range	57±7; 35–85
Males/ Females	432/122
Diabetes mellitus	11%
Smokers	37%
Hypercholesterolemia > 5.2 mmol/L	34%
Prior MI	32%
Acute coronary syndrome	16%

Four hundred eleven patients underwent stress testing on cycle ergometer before coronary angiography and stenting. Sixty-eight percent of patients had positive cycle ergometry test, 25% had ambiguous test or diagnostic criteria were not achieved, and submaximal heart rate (HR) during test was obtained in 7% of patients and therefore test was negative. Maximal load ranged from 75 to 150 W, with mean of 97±18 W. Maximum achieved HR was 76 to 159 beats per minute with mean of 141±12 beats per minute.

Diagnostic coronary angiography was performed prior to stenting. In 84% of patients coronary stenting was performed in 1-9 days after coronary angiography and in 16% of patients, intervention was performed as integrated procedure along with coronary angiography. Twenty-six percent of patients had multivessel lesion, 23% underwent stenting in more than one segment (artery). Main baseline angiographic values are shown in Table 2.

Table 2. Baseline angiographic characteristics.

Main angiographic characteristics (n=703 affected segments)	
Vessel reference diameter (mm)	2.89±0.57
Vessel reference diameter < 3 mm	27%
Minimal vessel diameter (mm)	0.58±0.41
Diameter stenosis (%)	80±9
Stenosis length (mm)	16.9±7.5
Extended stenosis (>20 mm)	31%
Stenosis localization	
Anterior descending artery	45%
Circumflex artery	22%
Right coronary artery	33%
Stenosis type according to ACC/AHA classification	
Stenosis A	13%
Stenosis B	61%
Stenosis C	26%

Seven hundred three stents were implanted to 554 patients during interventions. Elective implantation of Cypher stent was performed in 96% of patients, stent was implanted after suboptimal result of balloon angioplasty in 3% of patients, and after unsuccessful balloon angioplasty – in 1%. Maximum pres-

sure in balloon during stent dilatation was 12 to 20 atmospheres with mean of 13.2±1.6 atmospheres. Optimal stent implantation required 2 to 4 dilatations with mean of 2.73±0.65 dilatations. Parameters of intervention are shown in Table 3. All of 703 Cypher stents were successfully implanted without dissections D-F, occlusions and "no reflow". Therefore, immediate success of stent implantation was 100%.

Table 3. Parameters of Cypher implantation of (n=703 segments).

Success of stenting	100.0%
Single stenting	77%
Multiple stenting (2 to 4 Cypher stents)	23%
Stent length (mm)	18.8±8.7
Vessel reference diameter after stenting (mm)	3.02±0.48
Minimal vessel diameter after stenting (mm)	2.77±0.45
Increase of vessel diameter (mm)	2.20±0.55

One patient (0.2%) developed acute coronary syndrome (with elevation of ST-segment, but without Q-wave) on 2nd day after stenting. The patient received platelet glycoprotein receptor blocker, thyrophyban, intravenously as a bolus, after which control coronary angiography was performed. The stented segment of coronary artery was patent on control angiograms, there were no signs of thrombosis. Distal blood flow in the stented artery was adequate (TIMI 3). Post-stenting in-hospital period in remaining 553 patients was uncomplicated, and all patients were discharged. Thus, incidence of subacute thrombosis and myocardial infarction after stent implantation during in patient period was 0.2%.

All patients were alive during subsequent follow-up of a subgroup consisting of 108 patients (Table 4) within 2 to 27 months (64 to 804 days, mean period = 257±107 days). Three patients (2.8% out of 108 patients) developed nonfatal infarction (1 – Q-wave, 2 – non-Q-wave). On repeated coronary angiography restenosis was revealed in 6 patients (5.6%) after MI or with recurrent angina. It was diffuse in-stent restenosis above 50% in 2 cases (1.9%), and restenosis in marginal stent segments was revealed in 4 cases (3.7%). Thus general incidence of restenosis and related events was 5.6% of number of re-examined patients. All 6 patients with restenosis revealed at control coronary angiography underwent successful repeated revascularization of the target vessel.

Table 4. Twenty-seven month follow up of 108 patients after stenting.

Mean follow-up (days)	257±107
Cumulative percentage of patients without complications	102 (94.2%)
Death	0
Myocardial infarction	3 (2.8%)
Recurrent angina	3 (2.8%)
Restenosis	6 (5.6%)
Repeated revascularization	6 (5.6%)

DISCUSSION

Several generations of coronary stents took turns during 20 years of clinical use (12). Initially, in first decade of stent use (end of 1980-s and early 1990-s) investigators proved that their use did not result in increase of acute and subacute complications compared with balloon angioplasty and other transluminal catheter methods (13). At that, the main long-term complication of coronary interventions – restenosis – appeared to decrease significantly during half a year from the moment of intervention (14). Search for optimal stent construction showed that in real practice coil stents had no significant advantages in comparison with other catheter methods concerning long-term adverse events (12). Main devices with proven advantages turned out to be matrix/tubular stents (14-7). In addition, ring stents, multi-design stents and "pioneers" of coronary endografting self-expanding stents were used and remain in clinical practice owing to their efficacy (12). However, in-stent restenosis could be decreased only, but no constructions could eliminate it at all. Real revolution in invasive cardiology took place in 2001 when first impressive results of implantation of stents with antiproliferative coating (drug-eluting stents) were presented (1, 3, 5). Boom of coated stents is noted worldwide during last 3 years (18). They are used in increasing frequency forcing out uncoated stents (3).

However, stent construction remains to be important issue which still is order of the day (19). Thus, on July 19, 2004, Boston Scientific, which had earlier performed 6 successful multicenter (including randomized) studies of Paclitaxel-coated TAXUS stent had to urgently recall 40000 coated TAXUS stents and approximately 60000 uncoated prototypes Express2 worldwide because of detected defect in stent delivery system. This defect did not allow to deflate balloon ("no deflation" effect) and remove it after stent implantation and resulted in complications in 43 patients and 3 fatal cases. These data were officially published on sites www.bostonscientific.com and www.taxus-stent.com.

It is very important to know stent characteristics and peculiarities to really predict possible thrombosis and neointimal hyperplasia at the site of implantation (16, 17, 21, 22). In present study, Cypher stent was implanted in stenoses of different complexity without acute thrombosis with record low rate of subacute thrombosis (0.2%). Stent restenosis rate amounted to 5.6% during 27 months follow up in subgroup of patients who returned for control. Such a value confirms long term stent stability regarding suppression of neointima proliferation and guarantees maximum safety for different groups of patients (15, 16, 21, 23). Considerable contribution to such a result of optimal Clopidogrel therapy for 3 to 12 months after intervention should be noted (3, 11, 23). We can suppose absence of angina recurrence and adverse events after stenting for the rest of patients who did not come to control

examination. Our suppositions regarding favorable long-term outcome in patients who did not come to control examination are indirectly confirmed by works where multicenter and single-center studies of coated stents were performed. Thus, in all previous projects of Cypher stent assessment (3, 5-9) overwhelming majority of patients without angina recurrence and adverse events had no restenosis at the site of stent placement during control examination.

CONCLUSIONS

1. Restoration of coronary blood flow (immediate success) following Cypher stent implantation in patients with atherosclerotic lesion of native coronary arteries was achieved in 100%.

2. The in-hospital rate of adverse coronary events following stenting was amounted to 0.2%. Prognosis during long-time follow-up (mean of 8 months) was favorable in 94% of patients.

References:

1. Batyraliev T.A., Pershukov I.V. Overview of clinical studies concerning coronary heart disease and its invasive treatment. Kardiologia, 2002,5,68-70.
2. Mahmud E., Keramati S. Highlights of the 2003 Transcatheter cardiovascular therapeutics annual meeting: Clinical implications. J. Am. Coll. Cardiol., 2004,43,684-90.
3. Pershukov I.V., Batyraliev T.A., Samko A.N. et al. Achievements of invasive cardiology. 2003. Part II. Kardiologia,2004,12, 66-74.
4. Sousa J.E., Costa M.A., Abizaid A. et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries. Circulation, 2001,103,192–5.
5. Rensing B.J., Vos J., Smits P.C. et al. Coronary restenosis elimination with a sirolimus eluting stent. First European human experience with 6-month angiographic and intravascular ultrasonic follow-up. Eur. Heart. J., 2001, 22, 2125–2130.
6. Morice M.C., Serruys P.W., Sousa J.E. et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N. Engl. J. Med., 2002,346,1773–80.
7. Moses J.W., Leon M.B., Popma J.J. et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N. Engl. J. Med., 2003,349,1315–23.
8. Schofer J., Schluter M., Gershlick A. et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomized controlled trial (E-SIRIUS). Lancet, 2003,362,1093–9.
9. Schampaert E., Cohen E.A., Schluter M. et al. The Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients With Long De Novo Lesions in Small Native Coronary Arteries (C-SIRIUS). J. Am. Coll. Cardiol., 2004,43,1110 –5.
10. Lemos P.A., Lee C.H., Degertekin M. et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital (RESEARCH) registry. J. Am. Coll. Cardiol., 2003,41,2093–9.
11. Smith S.C., Dove J.T., Jacobs A.K. et al. ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines). A Report of the ACC/AHA Task Force on Practice Guidelines. J. Am. Coll. Cardiol., 2001,37,2239i-lxvi.
12. Serruys P.W., Kutryk M.J.B. Handbook of coronary stents. Third edition. Martin Dunitz, 2000, p.424.
13. Sigwart U., Puel J., Mirkovitch V. et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N. Engl. J. Med., 1987,316,701–706.
14. Serruys P.W., de Jaegere P., Kiemeneij F. et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease: Benestent Study Group. N. Engl. J. Med., 1994,331,489–495.
15. Baim D.S., Levine M.J., Leon M.B. et al. Management of restenosis within the Palmaz-Schatz coronary stent: the U.S. multicenter experience – the U.S. Palmaz-Schatz Stent Investigators. Am. J. Cardiol., 1993,71,364–366.
16. Pershukov I., Batyraliev T., Samko A., et al. In-hospital, six- and eighteen month's results of Ephesos coronary stent implantation in patients with unstable or stable angina. Eur. J. General Med., 2004,1(1),19-25.
17. Boland J.L., Corbeij H.A.M., Van Der Giessen W. et al. Multicenter evaluation of the phosphorylcholinecoated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int. J. Cardiovasc. Intervent., 2000,3,215-25.
18. Belenkov Yu.N., Batyraliev T.A., Pershukov I.V., Samko A.N. Invasive cardiology – focus on restenosis. Part II. Kardiologia, 2002,11,68-72.
19. Zidar J.P., Fry E., Lambert C. et al. The VENUS trial: A multicenter registry of the Cordis BX Velocity stent. Am. J. Cardiol., 2000,86,suppl.8A:17i.
20. Rensing B.J., Vos J., Smits P.C. et al. Coronary restenosis elimination with a sirolimus eluting stent. First European human experience with 6-month angiographic and intravascular ultrasonic follow-up. Eur. Heart J., 2001, 22, 2125–2130.
21. Rogers C., Edelman E.R. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation, 1995, 91, 2995-3001.
22. Serruys P.W., van Hout B., Bonnier H. et al. Randomized comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet, 1998, 352, 673-81.
23. Karpov Yu.A., Sorokin E.V. Drug treatment of angina: Expectations and disappointments. Russkij Meditsinskij Zhurnal, 2002, vol. 10, №19, p. 43.

Thrombolytic Therapy for Elderly Patients with MI in Routine Clinical Practice

A.N. Sumin[1], N.G. Pervova, O.P. Khairedinova.
Federal Medical and Prophylactic Center
"Research and Clinical Center of Miners' Health", Leninsk-Kuznetsky

Abbreviations

TLT — thrombolytic therapy
ECG — electrocardiogram
CPK — creatine phosphokinase
BET — bicycle ergometry test
ECHOCG — echocardiography
ET — emergency team
HR — heart rate
BP — blood pressure
MI — myocardial infarction
ACE — angiotensin-converting enzyme
CI — catheter interventions
CAG — coronary angiography

Introduction

The proportion of elderly patients among all patient with MI has been increasingly high during the last years, reaching 60-70% from all treated patients (1-3). Treatment of this patient category is characterized by higher number of comorbidities, more severe clinical course of the myocardial infarction and worse prognosis as compared to younger patients (3). Despite this fact, till recently treatment of these patients has been associated with lower use of expensive and invasive procedures (4,5). This was due to poor availability of catheter-based procedures (5,6), was well as the safety and efficacy concerns of thrombolytic therapy in elderly groups (1,3-5,7,8). In large randomized studies the proportion of elderly patients was low and unrepresentative (4,9), therefore, the concepts of treatment strategy in these patients are based on single-center studies or registry data (5,10,11). Due to apparent geographical differences in the potential of cardiological care and treatment strategies (2,6,12) the results of international studies can not be extrapolated on the clinical practice in Russia. Thus, the purpose of our study was to evaluate safety and efficacy of thrombolytic therapy in elderly patients with MI in real clinical practice of a Noninvasive Cardiology Department.

Material and methods

This retrospective cohort studies included 658 consecutive patients with Q-wave MI, who were treated in the Coronary Care Unit of the Center of Miners' Health between May 1999 and December 2002. The diagnosis of MI was confirmed by typical chest pain, specific ECG changes and elevated level of CPK. Analysis of hospital records allowed to isolate 289 patients admitted within 6 hours after the MI onset. Thrombolytic therapy (TLT) was performed in 194 patients (66 women and 128 men). Indications to TLT were chest pain episodes lasting over 30 min and less than 6 h plus the characteristic ECG pattern (ST elevation 0.1 mV and higher in at least two standard leads or 0.2 mV and higher in at least two leads or recurrent left bundle branch hemiblock). TLT was rejected for the following reasons: active internal hemorrhage at the time of examination; history of hemorrhagic stroke (any longevity) or other types of cerebrovascular events within the last year; severe hypertension on admission; serious surgery within the last 3 weeks; severe coagulation disorders; hemorrhagic diathesis. The TLT schedule included IV bolus of a direct anticoagulant followed by IV infusion of 1.5 million U streptokinase during 30-60 min. Subsequently the IV infusion of a direct anticoagulant was continued and the dose was adjusted by APTT value. All patients took aspirin in the absence of contraindications. Indirect signs of coronary reperfusion were: decrease or complete reduction of chest pain; ECG changes including the decrease of total ST elevation by ≥50% of the baseline value; the occurrence of reperfusion-related rhythm disorders. To assess the extent of infarction area all patients underwent serial study of CPK (U/l) with measurement of its peak serum activity. On discharge all patients underwent additional testing – bicycle ergometry test and echocardiography with LVEF measurement. The following endpoints were used to assess the clinical course of the disease: recurrent myocardial infarctions, early postinfarction angina and death. Long-term results were recorded up to December 2003 (5 to 55 months, median 32 months), the endpoints were death and recurrent MI.

The results were analyzed on STATISTICA 6.0 software using the following statistical methods: single-factor analysis of variance for continuous variables, chi-square test and Kruscal-Wallace test for non-parametric values. The long-term results were assessed using Kaplan-Meyer survival curves.

Results

Clinical values of the study groups are listed in Table 1. Interestingly, TLT groups were characterized by higher rate of emergency team hospital admissions as compared to non-TLT groups (p=0.01), though there were no such differences in patients over 70

[1]Sumin Aleksey Nikolayevich,
3 Volzhsky pereulok str.,
Leninsk-Kuznetsky,
Kemerovo Region, Russia, 652509
Telephone (home): (38456) 2-31-03
e-mail: an_sumin@mail.ru
Received 9 February 2007.
Accepted for publication August 28, 2007

years of age. Nevertheless, the mean time between the onset of chest pain and hospital admission was similar between the groups (p=0.39). Other notable differences included more frequent lateral MI in TLT groups (p=0.01). There were no differences in BP and HR values (p=0.25 and p=0.16, respectively), however, the BP level was significantly lower in non-TLT groups (p=0.006). In non-TLT patients over 70 years the percent of diabetics was higher (21.2%; p=0.05). In addition, the non-TLT groups had higher numbers of patients with a history of stroke (p=0.001), which is not surprising, because this was one of the contraindications to TLT. Nevertheless, the incidence of cerebrovascular disease was comparable in TLT and non-TLT groups and significantly increased with age (p=0.001).

The TLT groups had higher incidence of ventricular extrasystoles (p=0,001), which can be explained by the development of reperfusion syndrome (Table 2). In non-TLT patients over 70 years of age the rate of atrial fibrillation was higher (21.2%; p=0.02), which can be due to more severe clinical course of MI in this category of patients. Following TLT the ST returned to isoline significantly more quickly (see Table 3) as compared to non-TLT groups (p=0.001), which is an indirect evidence of a more rapid formation of necrosis and increased rate of reparative processes in peri-infarction area after TLT.

The maximum CPK level in TLT groups was higher, than in non-TLT patients of similar age (p=0.002), suggesting larger extent of myocardial injury in these groups. Analysis of TLT complications (see Table 4) indicates, that there were no differences in their rate between various age groups. Most frequent event was the hypotension (29.4%; 31.5% and 30.4% of cases, respectively; p=0.16). Nausea and dizziness were less frequent and similar in all groups – 1.4-7.4% (p=0.12 and p=0.22). Gastrointestinal hemorrhage was found in 2 out of 194 patients aged below 60. The hemorrhage was treated medically and didn't require blood transfusion. In addition, there were 2 cerebrovascular accidents.

One of them occurred in a patient under 60 and resulted in death. The other one (subarachnoid hemorrhage) occurred in a patient aged 60-69, who was subsequently discharged. There were no such complications in patients over 70 years.

Echocardiography performed prior to discharge (see Table 3) showed higher rate of LV aneurysm in non-TLT groups (p=0.06) with comparable LVEF values (p=0.13). In patients under 60 years this rate was almost 4 times higher, in patients between 60 and 69 years – 3 times higher, and in patients over 70 – 2 times higher. Daily BET stress testing showed significant (p=0.001) age-proportional decrease of exercise tolerance in both TLT and non-TLT groups. The number of recurrent myo-

Table 1. Clinical values of MI patients in different age groups depending on TLT administration.

Parameters	TLT			Non-TLT			F	P
	Group 1 Under 60 years (n=68)	Group 2 60-69 years (n=57)	Group 3 Over 70 years (n=69)	Group 4 Under 60 years (n=31)	Group 5 60-69 years (n=31)	Group 6 Over 70 years (n=33)		
Men	56 (82.9%)	38 (67.3%)	34 (49.3%)	25 (80.6%)	24 (77.4%)	16 (48.5%)	H=26.97	0.001
Emergency team admission	59 (86.4%)	46 (90.9%)	59 (85.5%)	22 (71.4%)	21 (67.7%)	28 (84.5%)	H=3.05	0.01
MI localization								
Anterior	36 (52.9%)	31 (54.3%)	29 (42.1%)	14 (45.1%)	13 (41.9%)	19 (57.6%)	H=4.63	0.46
Posterior	43 (63.2%)	25 (43.8%)	33 (47.8%)	15 (48.3%)	16 (51.6%)	15 (45.5%)	H=3.29	0.65
Lateral	27 (39.7%)	28 (49.1%)	32 (46.3%)#	12 (38.7%)	7 (22.6%)	7 (21.2%)	H=14.2	0.01
Apical	4 (5.8%)	6 (10.5%)	5 (7.3%)	9 (3.2%)	2 (6.4%)	3 (9%)	H=6.47	0.26
Time AE (min)	135.1±8.1	157.5±9.2	140.7±8.3	185±21.2	158.7±14.8	153.9±19.2	1.64	0.39
Duration AE (min)	159.3±7.5	182.7±9.3	171.9±8.7	194±18.5	172.3±17.1	186.1±22.6	0.85	0.37
SBP, mm Hg	139.0±2.8	136.7±2.9	134.3±3.8	130.2±5.5	123.9±6.1	131.4±7.5	1.32	0.25
DBP, mm Hg	87.9±1.6	84.9±1.8	84.7±1.4	82.1±2.4	77.4±3.4*$	76.5±5.0*$	3.33	0.006
HR, bpm	70.8±1.9*	77.5±2.5	78.6±1.7	75.3±3.0	74.6±2.9	74.1±5.3	1.59	0.16
Comorbidities								
HT	41 (60.3%)	21 (36.8%)	44 (63.8%)	18 (58%)	18 (58%)	25 (75.8%)	H=7.73	0.17
DM	2 (2.9%)	5 (8.8%)	7 (10.2%)	10 (3.2%)	10 (3.2%)	7 (21.2%)$	H=11.09	0.05
CVD	8 (11.8%)	14 (24.6%)	39 (56.5%)	3 (9.6%)	6 (19.4%)	14 (42.4%)	H=47.16	0.001
CVA	–	1 (1.8%)	2 (2.8%)	3 (9.6%)$	3 (9.6%)	6 (18.1%)$*	H=19.63	0.001
PICS	12 (17.6%)	16 (28.1%)	13 (18.8%)	12 (38.7%)	9 (29%)	12 (36.4%)	H=8.34	0.15

Note: * - p<0.05 as compared to Group 2, $-p<0.05 as compared to Group 1, #-p<0.05 as compared to Group 6, MI – myocardial infarction, Emergency team admission – patients were transported with emergency team, time AE – time between the onset of angina episode and the onset of treatment, Duration AE – the duration of angina episode (from the onset of pain to complete reduction of pain), SBP – systolic blood pressure on admission, DBP – diastolic blood pressure on admission, HR – heart rate on admission, HT - hypertension, DM – diabetes mellitus, CVD – cerebrovascular disease, CVA – history of a cerebrovascular accident, PICS – postinfarction cardiosclerosis

Table 2. Rhythm and conduction disorders in MI patients of different age groups depending on TLT administration.

Parameters	TLT			Non-TLT			H	P
	Group 1 Under 60 years (n=68)	Group 2 60-69 years (n=57)	Group 3 Over 70 years (n=69)	Group 4 Under 60 years (n=31)	Group 5 60-69 years (n=31)	Group 6 Over 70 years (n=33)		
VE	21 (30.8%)	29 (50.9%)#$	31 (44.9%)#	4 (12.9%)$	8 (25.8%)	6 (18.1%)	23.39	0.001
VT	7(10.3%)	4 (7%)	8(11.6%)	3 (9%)	3(9%)	4(11.5%)	8.42	0.13
AE	3 (4.4%)	3 (5.3%)	4 (5.8%)	2(6.4%)	2 (6.4%)	3 (9%)	2.98	0.7
VF	(0.5%)	(2.3%)#	(3.4%)#	2(6.4%)$	2 (6.4%)$	3 (9%)$	15.23	0.09
AF	2 (3 %)#	3 (5.3%)#	9 (13 %)$	1 (3%)#	3 (9%)	7(21.2%)	13.11	0.02
SVE	2 (3%)	–	3 (4.3%)	1 (2%)	1 (2%)	2 (4.3%)	5.92	0.31
AVB 1-2	5 (7.4%)	3 (5.3%)	3 (4.3%)	–	1 (3%)	3 (9%)	5.24	0.39
AVB 3	5 (7.4%)	1 (1.7%)	1 (1.5%)	–	3 (9%)	3 (9%)	8.54	0.13

Note: * - p<0.05 as compared to Group 2, $-p<0.05 as compared to Group 1, #-p<0.05 as compared to Group 6, VE – ventricular extrasystoles, VT – ventricular tachycardia, AE – atrial extrasystoles, VF – ventricular fibrillation, AF – atrial fibrillation, SVE – supraventricular extrasystoles, AVB 1-2 and AVB 3 – grade 1-2 and 3 atrioventricular block.

Table 3. Particularities of in-hospital period of MI patients of different age depending on TLT administration.

Parameters	TLT			Non-TLT				P
	Group 1 Under 60 years (n=68)	Group 2 60-69 years (n=57)	Group 3 Over 70 years (n=69)	Group 4 Under 60 years (n=31)	Group 5 60-69 years (n=31)	Group 6 Over 70 years (n=33)		
CPKmax (g/l)	2103.9±176.3*	2711.8±283.4	1880.0±187.1*	1838.6±176.6*	1551.2±291.2*	1439.7±216.0*	F=3.83	0.002
ST decrease (h)	6.5±4.1	7.0±1.7	7.5±2.7	11.2±8.9	12.2±11.1	14.2±6.8	F=27.55	0.001
BET ET (Wt)	82.5±4.1	65.4±6.2	43.1±6.9$	80±8.5	58.3±5.9$	32.1±7.1$	F=6.78	0.001
LVEF (%)	48.9±1.1	44.7±1.2	45.8±1.5	45.6±1.8	47.3±1.8	48.9±1.6	F=1.73	0.13
LV aneurysm	3 (4.3%)	3 (5.5%)	8 (11.8%)	5 (16.1%)	6 (19.4%)*	8 (23%)	H=10.55	0.06
EPA	3 (4.4%)	4 (7%)	7 (10.1%)	1 (3%)	5 (16%)	6 (18%)	H=9.04	0.11
Recurrent MI	1 (1.4%)	1 (1.7%)	1 (1.4%)	1 (3%)	3 (9%)	4 (12%)	H=7.31	0.19
Killip score	1.24±0.07	1.72±0.1	1.75±0.09	1.58±0.18	2.06±0.17	2.25±0.2	F=17.57	0.001
Mortality	4 (5.8%)#	8 (14.5%)#	10 (15.9%)#	11 (12.9%)	7 (22.6%)	13 (39.3%)	H=19.9	0.001
Hospital stay (days)	18.3±0.4	18.2±0.6	19.9±0.5	17.8±0.61	19.2±0.9	19.3±0.81	F=1.84	0.006

Note: * - p<0.05 as compared to Group 2, $-p<0.05 as compared to Group 1, #-p<0.05 as compared to Group 6, max CPK-maximum level of creatine phosphokinase, ST decrease – time of ST decrease on ECG, BET ET – exercise tolerance measured during bicycle ergometry test, LVEF – left ventricular ejection fraction, EPA – early postinfarction angina, Killip score – chronic heart failure grade according to Killip scale, HF – heart failure.

cardial infarctions was similar between the TLT groups (see Table 3) – 1 case in each group, which accounted for 1.4%, 1.7% and 1.4% of cases, whereas in non-TLT groups the number of recurrent myocardial infarctions increased to 3%, 9% and 12%, respectively (p=0.19). Early postinfarction angina was most frequent in the third group of TLT patients (4.4%, 7.0% and 10.1% of cases), however, in non-TLT groups this percent was slightly higher - 3%, 16% and 18%, respectively (p=0.11). In patients treated with TLT (regardless of the age) the Killip score was significantly lower (1.24±0.07, 1.72±0.1 and 1.75±0.09; and 1.58±0.18, 2.06±0.17 and 2.25±0.2; respectively, p=0.001). Hospital mortality rate in TLT groups was substantially lower as compared to non-TLT patients of similar age, with over 2-fold difference for patients under 60 and over 70 years, and a 1.5-fold difference for patients aged 60 to 69 (p=0.001). Mean mortality rate was 11% in TLT groups vs 24.9% in non-TLT groups. This differences can not be explained by different concomitant agents, as the treatment schedules included similar proportions of

Table 4. Complications of thrombolytic therapy.

	Group 1 Under 60 years (n=68)	Group 2 60-69 years (n=57)	Group 3 Over 70 years (n=69)	H	P
ST	1 (1,4%)	1 (1,8%)	–	3,31	0,19
GIH	2 (2,9%)	–	–	3,33	0,19
Dizziness	5 (7,4%)	2 (3,5%)	1 (1,4%)	3,07	0,22
Nausea	4 (5,9%)	3 (5,3%)	3 (4,4%)	4,19	0,12
Decreased BP	20 (29,4%)	18 (31,5%)	21 (30,4%)	1,80	0,16

Note: ST – stroke, GIH – gastrointestinal hemorrhage, BP – blood pressure.

beta-blockers, direct anticoagulants and aspirin (see Table 5). More frequent use of ACE inhibitors, vasopressors, antiarrhythmic agents in elderly groups may be due to more severe heart failure in these patients. Other highly effective agents (clopidogrel, low-molecular weight heparin) and coronary interventions, unfortunately, were equally unavailable to patients from all age groups irrespective of the TLT administration.

Table 5. Medical therapy in MI patients from different age groups depending on TLT administration.

Parameters	TLT			Non-TLT			H	P
	Group 1 Under 60 years (n=68)	Group 2 60-69 years (n=57)	Group 3 Over 70 years (n=69)	Group 4 Under 60 years (n=31)	Group 5 60-69 years (n=31)	Group 6 Over 70 years (n=33)		
Heparin (n, %)	68 (100%)	57 (100%)	69 (100%)	31 (100%)	31 (100%)	33 (100%)	0.0	1.0
BAB (n, %)	55 (81.4%)	43 (78.2%)	54 (78.3%)	19 (61.3%)	25 (80.6%)	24 (72.7%)	5.71	0.33
Aspirin (n, %)	67 (98.6%)	56 (98.2%)	67 (97.1%)	30 (96.8%)	28 (90.3%)	31 (94%)	5.61	0.35
ACEI (n, %)	30 (44.3%)	30 (52.7%)	45 (65.2%)	16 (51.6%)	17 (54.8%)	23 (69.7%)	9.23	0.1
Diuretics (n, %)	6 (8.5%)	10 (18.1%)	12 (17.3%)#	11 (35.5%)$	9 (29%)$	14 (42.4%)*$	21.14	0.001
Kordaron (n, %)	1 (1.4%)	9 (16.4%)$	16 (23.2%)$	8 (25.8%)$	10 (32.3%)$	4 (12.1%)	21.59	0.001
Dopmin (n, %)	2 (2.8%)	11 (20%)$	9 (13%)#	7 (22.5%)$	8 (25.8%)$	13 (40.6%)$	25.54	0.001
Hormones (n, %)	3 (4.2%)	9 (16.4%)	10 (14.5%)#	5 (16.1%)	7 (22.5%)*$	13 (39.4%)$	21.33	0.001

Note: * - p<0.05 as compared to Group 2, $-p<0.05 as compared to Group 1, #-p<0.05 as compared to Group 6, TLT – thrombolytic therapy, BAB – beta-adreno-blockers, ACEI– angiotensin-converting enzyme inhibitors.

The highest number of in-hospital deaths was detected in non-TLT groups regardless of the age (see Figure 1). Further prospective follow-up also revealed age-related differences in mortality rate (2=29.4; p=0.0001). The highest survival rates were observed in patients under 60 irrespective of the treatment method: total survival rate was 89.1% in TLT group (2 deaths – one occurring at 18 months, the other – at 36 months time point) vs 87.1% in non-TLT group (no deaths among 20 discharged patients). Among patients aged 60 to 69 the total survival rate was 80.2% in TLT groups (2 deaths – one occurring at 24 months, the other – at 36 months time point) vs 67.5% in non-TLT group (2 deaths at 12 months). The lowest long-term survival was observed in patients over 70 with total survival rate of 74.4% in TLT group (5 deaths) vs 51.1% in non-TLT group (2 deaths).

Recurrent myocardial infarctions during follow-up also occurred in non-TLT groups ($\chi 2$ =10.49; p=0.063). These differences were minimal in patients over 70 years with recurrent MI rate of 14.7% in TLT group vs 15.8% in non-TLT group. In younger patients the differences in the rate of recurrent MI were more pronounced: among patients under 60 this rate was 7.6% and 22.2%, among patients aged 60 to 69 – 4.2% and 21.7%, respectively.

Discussion

The primary conclusion is that nonselective use of TLT in elderly patients with MI is safe, provides the decrease of hospital mortality rate and improvement of the long-term prognosis. Nevertheless, we failed to achieve the low mortality rate, comparable to those seen in leading Russian centers of interventional cardiology (13-15). What could be the reasons for it?

One of such reasons is the ***age distribution*** of our patients – people over 60 years prevailed among the treated patients (65.7% from all cases). This was due to the fact, that the study didn't utilize any prehospital patient selection strategy – all MI patients in the population of 200 thousand people were treated in our department. In various European registries the age distribution was very similar to our situation (considering slightly lower mean lifetime in Russia and earlier retirement). Thus, approximately one third of all MI patients (20 to 43%) are over 75 years of age (5,10,16,17). Similar age distribution was reported by one of the Municipal hospitals of Moscow: 30.7% of patients under 60, 26% of patients aged 61 to 70 years and 43.3% of patients over 70 (18). Lower mortality rate was achieved in multicenter or single-center trials with age-related inclusion limits (typically, they included very low proportion of patients over 70-75 years) (4,15).

If we consider only elderly patients, the ***hospital mortality rate*** revealed in our study will be comparable to other registries. Thus, among Norwegian patients aged over 75 years the hospital mortality rate due to MI was 26.4% (17). However, the efficacy of TLT in elderly patients was not confirmed in all studies. In MI patients aged 65-75 years, TLT contributed to the decrease of hospital mortality rate from 9.8% to 6.8%, whereas in patients over 75 this index increased from 15.4 to 18% (7). Among 2045 MI patients from ACOS registry the hospital mortality rate was 23.4% for medical therapy vs 25.4% for TLT (19). According to Berlin registry there was almost 3-fold difference in mortality rate between patients over 75 and under 75: 23.7% vs 7.3% (5). In Spanish patients aged over 75 (according to TRIANA registry) the hospital mortality rate didn't decrease after TLT (performed in 35%) or angioplasty (performed in 22% of patients), reaching 26.7%; 21.2% and 23.9%, respectively. Patients after TLT had lower rate of death due to cardiogenic shock, however, they had higher rate of hemorrhagic events (possibly due to the treatment with combination of tenekteplase and low-molecular weight heparin) (8). Therefore, all Russian studies failed to demonstrate the efficacy of TLT (20), though this study showed, that the hospital mortality rate approximated 6.6% in MI patients aged 60-74 with reperfusion of the infarction-related artery. However, for all TLT patients this value was

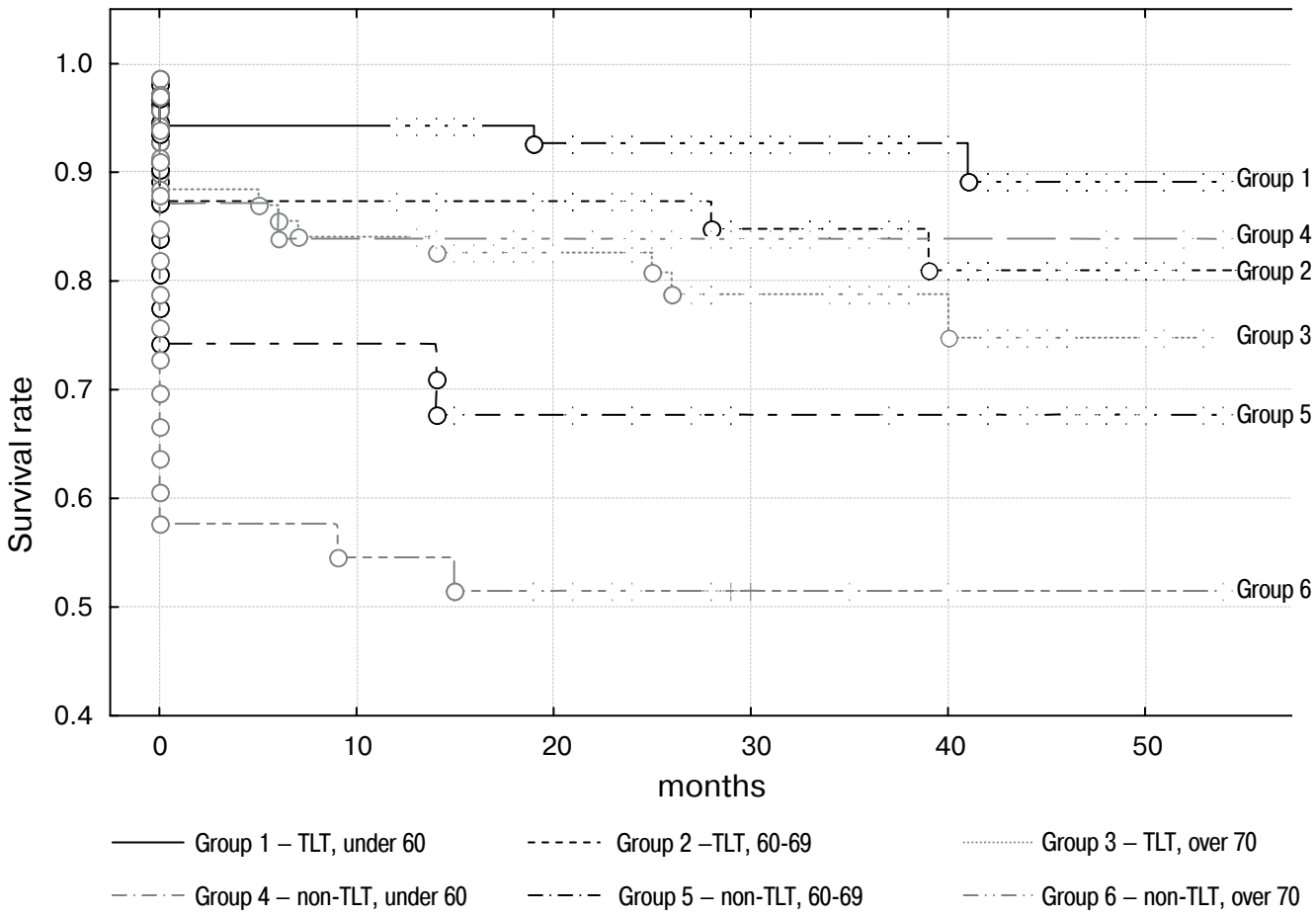

Figure 1. Comparison of survival rates in MI patients from different age groups depending on TLT administration.

similar to control (16.2% for TLT vs 17.2% for non-TLT patients aged 60 to 75; 23.3% vs 24.3% - in patients aged over 75, respectively). In this instance the possible reason for apparent inefficacy of TLT was the time of its beginning – up to 12 h after the onset of the disease, when the TLT efficacy declines (in our study the reperfusion was performed within the first 6 h after the onset of chest pain). In foreign studies (when TLT failed to decrease the hospital mortality rate) this effect was due to the increased number of hemorrhagic complications related to novel antiplatelet agents (8,9,21). Thus, according to ASSENT-3 and ASSENT-3 PLUS studies conducted in MI patients aged over 65 using the combination of tenekteplase with enoxaparin or abciximab, the risk of hemorrhagic events was higher as compared to monotherapy with nonfractioned heparin (21). In Spanish registry the hemorrhagic events were more frequently associated with combination of tenekteplase and low-molecular weight heparins (8). In the treatment of MI patients over 75 the nonfractioned heparin is more indicated for TLT, because the combination of low-molecular weight heparin with TLT increases the risk of hemorrhagic stroke (9). Available data confirm the fact, that the use of combined fibrin-specific agent and GPIIb/IIIa inhibitors in patients over 75 years increased the risk of intracranial hemorrhage (4). As a number of other publications (20,22), our study showed, that the risk of hemorrhagic complications was low in elderly patients and didn't differ from that in MI patients aged under 60.

The long-term results of TLT in elderly patients with MI are also rather promising – the majority of observation studies demonstrated the improved early survival rate (4,20,23,24). Among patients over 75 in ACOS registry the total 1-year mortality rate was 52.4% for conventional therapy vs 41.3% for TLT (19). Importantly, the total 1-year mortality rate in our patients was substantially lower after TLT in all age groups. Nevertheless, we can not deny, that the total hospital mortality rate in elderly patients with MI (even with the use of TLT and small number of hemorrhagic events) is still high ranging from 14 to 16%.

Subsequent decrease of this value might be ensured by the use of ***catheter interventions (CI)***, however, the investigation of morphological changes occurring in vessels of MI patients aged 80 showed more pronounced calcification and longer lesions (25). This can be the reason why CI can not decrease the hospital mortality rate in all cases with elderly patients – e.g., in patients with MI and cardiogenic shock in SHOCK study (26). On the other hand, the use of angioplasty in MI patients aged over 75 (86% coverage) was associated with total mortality rate of 20.5% (10), whereas in MI patients over 80 (80% coverage) the hospital mortality rate was 43% (27). The possible reason can be the higher number

of hemorrhagic events after CI in MI patients over 75 compared to younger patients (13.0% vs 3.5%, p<0.05), which was associated with increased hospital mortality rate (19.6% vs 4.5%; p<0.001) (28).

However, increasing number of studies suggest, that the mortality in elderly patients with MI can be decreased using CI (4,6,19,29-31), though the results are rather conflicting: one study showed significant decrease of the hospital mortality rate - 2% vs 15.4% in medical therapy group (29), whereas in another study this value was decreased to 12% after CI in MI patients aged 80 years (the patients with cardiogenic shock being excluded from the analysis) (31). In ACOS registry 30% of patients underwent CI providing over 2-fold decrease of hospital mortality rate (to 10.2%) compared to other types of therapy (19). Finally, this resulted in the long-term increase of the number of elderly patients surviving the MI. Thus, CI provides the decrease of 1-year mortality rate in patient over 75 up to 8.5% (vs 19% in patients receiving conventional therapy) (29). In MI patients over 75 the CAG (which was followed by revascularization in 67% of cases) resulted in the decrease of 1-year mortality rate down to 21% vs 37.3% in patients without CAG (p<0.0001) (30). Among 2045 MI patients age over 75 years in ACOS registry 51% received medical therapy, 19% - TLT and 30% - primary CI with total 1-year mortality rate being 52.4%, 41.3% and 19.3%, respectively (19). Analysis of the 7-year survival in elderly patients with MI revealed the 6.2% difference between regions with large amount of interventional centers and regions with poor availability of the interventional options (6). Recent review also demonstrated, that many clinical trials and registries indicated improved survival and low risk of stroke after CI as compared to TLT in elderly patients with STEMI (4).

Clinical practice includes another problem – the low activity of therapy in elderly patients and poor availability of treatment with proven efficacy. Thus, according to Berlin Myocardial Infarction Registry, the recommended therapy was less commonly provided to MI patients over 75 as compared to younger patients (reperfusion therapy –39.8 vs 71.7%, beta-blockers– 62.8 vs 78.3%, statins – 26.5 vs 45.5%), the same applied to TLT (19.9% vs 38.9%, p<0.001) (5). Beta-blocker were under-administered in 59% MI patients over 60 and only in 41% MI patients under 60 (p=0.11) (32). The proportion of CI patients decreased with age in RICO registry (from 21% in patients under 70 to 11% in patients over 80) (11). Nevertheless, our study didn't show such age-related discrimination, however, the modern expensive treatment options were equally unavailable to patients of all age groups.

Unfortunately, in Russian practice (as demonstrated by recent International multicenter studies) (12,13) the reperfusion interventions are substantially less common as compared to well-developed countries. During the last years (4) the approach to these methods in patients over 65 is similar to that in younger patients, particularly, if there is a possibility for quick arrival, as well as in certain clinical situations (cardiogenic shock, contraindications to TLT), catheter interventions are recommended. So far, the long distances and remoteness of many sites from the Centers of Interventional Cardiology make TLT the only available method of reperfusion for MI (4,34). In many Russian centers this is far more important. We hope, that our successful experience with TLT in elderly patients will help clinicians to use this method in their routine practice.

Conclusion

1. Among 658 patients treated in the Coronary Care Unit, 289 (43.8%) were admitted within 6 h after the onset of MI, thrombolytic therapy was performed in 67.4% of cases. There were 34.3% of patients aged under 60, 30.4% of patients aged 60-69 and 35.5% of patients aged over 70. The use of thrombolytic therapy, beta-blockers, ACE inhibitors, aspirin and direct anticoagulants was similar between various age groups.

2. The use of trombolytic therapy provided substantial decrease of the hospital mortality rate in all aged groups, including patients aged 60-69 years (from 22.6% to 14.5%) and patients aged over 70 years (from 39.3% to 15.9%). The improved survival of patients in TLT groups was also demonstrated by prospective follow-up during 32 months (mean).

3. The number of hemorrhagic complications was similar between the groups; in MI patients over 70 there were no cases of hemorrhagic stroke or serious hemorrhage.

4. When an emergency catheter intervention is unavailable, the thrombolytic therapy is an effective and sage reperfusion method in elderly patients with MI.

References:

1. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation. 2004, 110(9), e82-292.

2. White H.D., Aylward P.E., Huang Z., et al.; VALIANT Investigators. Mortality and morbidity remain high despite Captopril and/or Valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Circulation. 2005,112(22), 3391-9.

3. Rich M.W. Epidemiology, clinical features, and prognosis of acute myocardial infarction in the elderly. Am. J. Geriatr. Cardiol., 2006, 15(1), 7-11

4. Mehta R.H., Granger C.B., Alexander K.P., et al. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. JACC, 2005, 45(4), 471-8.

5. Schuler J., Maier B., Behrens S., Thimme W. Present treatment of acute myocardial infarction in patients over 75 years : Data from the Berlin Myocardial Infarction Registry (BHIR). Clin. Res. Cardiol., 2006, 95(7), 360-7.

6. Stukel T.A., Lucas F.L., Wennberg D.E. Long-term outcomes of regional variations in intensity of invasive vs medical management of Medicare Patients with acute myocardial infarction. JAMA, 2005, 293(11), 1329-37.
7. Thiemann D.R., Coresh J., Schulman S.P., et al. Lack of Benefit for Intravenous Thrombolysis in Patients With Myocardial Infarction Who Are Older Than 75 Years. Circulation, 2000, 101, 2239-2246.
8. Bardaji A., Bueno H., Fernandez-Ortiz A., et al. Type of treatment and short-term outcome in elderly patients with acute myocardial infarction admitted to hospitals with a primary coronary angioplasty facility. The TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) Registry. Rev. Esp. Cardiol., 2005, 58(4), 351-8.
9. La Manna A., Goktekin O., Fiscella D., et al. Which strategy should be used for acute ST-elevation myocardial infarction in patients aged more than 75 years? J. Cardiovasc. Med. (Hagerstown), 2006, 7(6), 388-96.
10. Dangelser G., Gottwalles Y., Huk M., et al. Acute ST-elevation myocardial infarction in the elderly (>75 years). Results from a regional multicenter study. Presse Med., 2005, 34(14), 983-9.
11. Popitean L., Barthez O., Rioufol G., et al. RICO Survey Working Group. Factors affecting the management of outcome in elderly patients with acute myocardial infarction particularly with regard to reperfusion. Data from the French regional RICO survey. Gerontology, 2005, 51(6), 409-15.
12. Domanski M., Antman E.M., McKinlay S., et al. Geographic variability in patient characteristics, treatment and outcome in an International Trial of Magnesium in acute myocardial infarction. Control. Clin. Trials., 2004, 25(6), 553-62.
13. Iosseliani D.G., Kostianov I.Yu., Chernysheva I.Ye. et al. The decrease of hospital mortality rate in patients with acute myocardial infarction. International Journal of Interventional Cardiology, 2003, 3, 21-25.
14. Ruda M.Ya. Medical therapy for acute myocardial infarction. International Journal of Interventional Cardiology, 2006, 10, 66-70.
15. Zavolozhin S.A., Mirolyubova O.A., Golyshev S.V., Zavolozhin A.S. The effect of delayed coronary angioplasty after thrombolytic therapy on the outcome of an acute myocardial infarction. Kardiologia, 2006, 10, 8-12.
16. Maier B., Balzi D., Tiia A., et al. Hospital care of patients with ST-elevation myocardial infarction in four different European regions: Data from regional myocardial infarction registries in Berlin, Dijon, Florence, Tartu. Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz., 2005, 48(10), 1176–1183
17. Jortveit J., Brunvand H. Elderly patients with acute myocardial infarction receive less medical therapy. Tidsskr. Nor. Laegeforen., 2006, 126(15), 1921-4.
18. GLezer M.G., Sementsov D.P., Sobolev K.E. The treatment of patients with acute myocardial infarction in typical clinical settings. Kardiologia, 2005, 1, 9-13.
19. Zeymer U., Gitt A., Winkler R., et al. Mortality of patients who are older than 75 years after ST elevation myocardial infarction in clinical practice. Dtsch. Med. Wochenschr., 2005, 130(12), 633-6.
20. Repin A.P., Syrkina A.G., Markov V.A. Systemic thrombolysis for acute myocardial infarction in elderly and senile patients. Clinical medicine, 2006, 84(3), 39-43.
21. Sinnaeve P.R., Huang Y., Bogaerts K., et al.; ASSENT-3 and ASSENT-3 PLUS investigators. Age, outcomes, and treatment effects of fibrinolytic and antithrombotic combinations: findings from Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 and ASSENT-3 PLUS. Am. Heart J., 2006, 152(4), 684, e1-9.
22. Vaisanen O., Makijarvi M., Silfvast T. Quality of life of elderly patients after prehospital thrombolytic therapy. Resuscitation, 2005, 66(2), 183-8.
23. Berger A.K., Radford M.J., Wang Y., et al. Thrombolytic therapy in older patients. JACC, 2000, 36, 366 –74.
24. Stenestrand U., Wallentin L., for the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKSHIA). Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction: one-year follow-up for large prospective cohort. Arch. Intern. Med., 2003, 163, 965–71.
25. Hassani S.E., Mintz G.S., Fong H.S., et al. Negative remodeling and calcified plaque in octogenarians with acute myocardial infarction: an intravascular ultrasound analysis. JACC, 2006, 47(12), 2413-9.
26. Dzavik V., Sleeper L.A., Picard M.H., et al.; SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK Investigators. Outcome of patients aged >or=75 years in the SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK (SHOCK) trial: do elderly patients with acute myocardial infarction complicated by cardiogenic shock respond differently to emergent revascularization? Am. Heart J., 2005, 149(6), 1128-34.
27. Wang Y.C., Hwang J.J., Hung C.S., et al. Outcome of Primary Percutaneous Coronary Intervention in Octogenarians with Acute Myocardial Infarction. J. Formos. Med. Assoc., 2006, 105(6), 451–458
28. Feliciano J., Fiarresga A.J., Timoteo A.T., et al. Primary coronary angioplasty in the elderly. Rev. Port. Cardiol., 2005, 24(2), 205-14.
29. Zhang Q., Zhang R.Y., Zhang J.S., et al. Outcomes of primary percutaneous coronary intervention for acute ST-elevation myocardial infarction in patients aged over 75 years. Chin. Med. J., 2006, 119(14), 1151-1156
30. Harpaz D., Rozenman Y., Behar S., et al. Israeli Working Group on Intensive Cardiac Care, Israel Heart Society. Coronary angiography in the elderly with acute myocardial infarction. Int. J. Cardiol., 2006, (Epub ahead of print)
31. Kornowski R., Teplitsky I., Brosh D. et al. Primary angioplasty for acute myocardial infarction in octogenarian patients. Harefuah., 2006, 145(5), 334-7.
32. Vega D.D., Dolan K.L., Pollack M.L. Beta-blocker use in elderly ED patients with acute myocardial infarction. Am. J. Emerg. Med., 2006, 24(4), 435-9.
33. Reed S.D., McMurray J.J., Velazquez E.J., et al.; VALIANT Committees and Investigators. Geographic variation in the treatment of acute myocardial infarction in the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial . Am. Heart J., 2006, 152(3), 500-8.
34. Orso F., Maggioni A.P. What is the optimal reperfusion strategy for elderly patients with acute MI? Am. J. Geriatr. Cardiol., 2006 15(1), 14-8.

Femoral Access with Application of Hemostatic Devices Versus Radial Access in Coronary Angioplasty

Yu.V.Artamonova, Z.A.Kavteladze[1], A.M.Babunashvili, D.P.Dundua, D.S.Kartashov, G.J.Travin, V.E.Glagolev
Center of Endosurgery and Lithotripsy (CELT), Moscow

"The big incision shows the big surgeon".
Popular wisdom.

"The cut should be as long as necessary,
and as short, as much it possible"
Theodore Kocher
"Aphorisms and Quotations for the Surgeon" M.Schein

The puncture for angiography and endovascular surgery is the smallest incision in surgery. So, who are we, the "smallest" surgeons? But, if at least some dozens of diseases could be treated from a single puncture ... Who is the "small" surgeon, and what other incision would allow it?

Introduction

The puncture for angiography and endovascular surgery is the smallest incision used in surgery. But how many possibilities it offers...

The principal criteria for the choice of such access are convenience, comfort and functionality, prevention of complications such as bleeding from the puncture site, subcutaneous or intracavitary hematoma, false aneurysm, arterio-venous fistula, arterial thrombosis, spasm, nerve disruption, infection or inflammatory process.

Due to the vast clinical experience and the modern armaments for retrograde femoral access the rate of all major and minor complications doesn't exceed 10%.

Axillar, translumbar, femoral arteriotomy, popliteal, femoral, carotid, ulnar approaches were offered as alternative access at various periods of angiography and endovascular surgery. These sites provide different possibilities but have higher rate of by traumatic and vascular complications. Nevertheless, many of them remain in the surgeon's arsenal and are used in some medical situations.

In the 1990-s years the radial artery access was introduced. It didn't require prolonged digital compression or strict bed rest. In many clinics coronary angioplasty is performed only through radial approach.

Almost at the same time the medical industry has offered new technologies for closure of the puncture site on the common femoral artery. The closure or suture devices were to replace the conventional manual hemostasis in endovascular interventions, when in addition to prolonged manual compression, the patient commonly has to stay in bed for 6 or more hours. Today there are more than ten commercially available devices, which can be divided into two groups:

1) suture devices, such as Perclose ProGlide (Abbott), Closer, Prostar, Techstar and Duett (Vascular Solutions), Staplers (Medtronic angiolink EVS), StarClose (Abbott), Syvek patch (Marine Polimer Technologies), Chito-seal (Abbott), Closur-Pad and AngioLink (Medtronic), Stasys (St. Jude Medical), Neptun (TZ), Superstitch (Satura), X-Site (Datascope);

2) closure devices - Angio-Seal (St. Jude Medical), On-Site, VasoSeal (Datascope), Biodisc (used only in Europe), Boomerang Closurewire (Cardiva Medical), SoundSeal (Therus Corporation), Cardiodex (Tirat-Hacarmel), AccessClosure (Mountain View), Eclipse (Ensure Medical).

Background

The hemostatic devices substantially decrease the rate of the so-called local vascular complications after the femoral artery puncture. The devices are being improved and become more easy to use.

Medical industry has actively participated the development and introduction of closure devices. The estimated annual market of closure devices amounts to 800 million dollars. Recently various comparative studies of different technologies for radial and femoral access were started.

In 2000 Agostoni et. al. (18) analyzed 12 randomized studies enrolling 3224 patients with radial or femoral accesses for coronary angiography and coronary angioplasty. The incidence of cardiovascular complications was similar between the two

[1]Z.A. Kavteladze
Department of Cardiovascular Surgery
Center of Endosurgery and Lithotripsy,
111 123, Moscow, Shosse Entuziastov, 62
Tel. +7 495 305 34 04
Fax +7 495 305 69 35
e-mail: zaza@celt.tu
Manuscript received on September 23, 2007.
Accepted for publication on October 31, 2007.

groups (CI 0.57-1.48, p=0.7). Radial access had higher rate of local complications as compared to femoral access (CI 0.09-0.42, p <0.0001), but also higher frequency of failures (transition to other artery, impossibility of a radial artery puncture) (CI 1.63-6.71) due to the absence of technical skills. Radial artery occlusions occurred in 5 % of patients. This had no clinical significance because hand perfusion is performed through radial and ulnar arteries with extensive collateral communication between them. However some patients have incomplete palmar arch which, in case of radial artery occlusion, can reduce collateral perfusion and cause palmar ischemia. Allen's test is used for adequate assessment of collateral palmar perfusion. In December 2005 Greenwood et. al (19) assessed the accuracy of Allen's test in patients with transradial coronary angiography. The study included 55 patients: Allen's test was negative in 20 patients (normalization of palmar skin color within 10 seconds), intermediate in 15 patients and positive in 20 patients. Three patients with positive Allen's test were excluded due to the absence of the collateral blood supply through the palmar arch. All patients with positive Allen's test were men and had bigger radial arteries (3.4 vs 2.8 mm, p <0.001) and smaller diameter of the ulnar artery (1.9 vs 2.5 mm, p <0.001) compared to patients with normal Allen's test. Patients with positive test had significantly reduced pollex perfusion 30 min after radial artery occlusion (3.2 vs 7.7 cm/s, p <0.001) compared to patients with normal (negative) Allen's test (7.7 vs 21.4 cm/s, p <0.001).

Additional anesthesia is often necessary in radial access due to severe pain. Femoral access with closure devices can compete with radial access.

There are some alternative approaches securing hemostasis such as manual compression, compressive bandage or closure/suture devices.

In 1998 Pracyk et al (1) performed a randomized study of manual hemostasis vs. hemostasis with closure/suture devices. The study included 778 patients with coronary interventions. 390 patients were followed for 8 months after the procedure. Compared to manual hemostatis, closure devices decreased the rate of complications, such as femoral artery thrombosis, hematoma, pseudoaneurysm, arteriovenous fistula by 63 % (p=0.041). However the use of the hemostasis closure/suture devices required skilled medical staff. Application of the devices was preferable for patients, in whom prolonged hemostasis time was expected (large introducer, double antiaggregation and anticoagulation therapy). Closure and suture devices decreased the hemostasis time and the bed rest period.

In 1998 Ward et al (2) studied the efficacy and safety of Angio-Seal device (AS) vs manual hemostasis (MH) after coronary angiography. The study included 304 patients, 202 with application Angio-Seal and 1 h reambulation time, and 102 patients with manual hemostasis and 4-6 h reambulation time after introducer removal.

The AS group was characterized by shorter hemostasis time (0.9±3 vs 17.0±8 min, p=0.0001) and hospital stay (5.0±4 vs 7.7±4 h, p=0.0001). Hemorrhage and vascular complications were observed in 19 patients (9%) in AS group vs. 6 patients (6%) in MG group (p=0.397).

In 2002 Geary and et al (9) assessed the risk of infectious complications associated with closure devices. The rate of infections was increased in patients with closure devices. Infectious or inflammatory process at the femoral artery puncture site necessitating open surgery occurred in 5 patients treated with Perclose device.

Another study (Cherr et al (20), 2001) enrolled 1807 patients. The puncture aperture in the right femoral artery was closed with Percutaneous device. The infectious complications which demanded surgical treatment were found in 5 patients (3%).

The risk of infectious complications is highest in patients with diabetes, obesity, chronic renal failure, history of heart valve grafting, patients with joint prostheses, patients with long-term hospitalization or infectious diseases.

Other complications included large and small hematoma, paravasal or intracavitary hematoma, pulsative hematoma, artery thrombosis, spasm, distal embolism, arteriovenous fistula, nerve disruption, infectious and inflammatory process. Social complications such as loss of the important functions due to weakness of limbs, impaired motion accuracy, influence of the psychological factor can also occur.

Surgery is not required in patients with subcutaneous hematoma.

If femoral artery puncture was performed above the inguinal ligament the hematoma could extend to the retroperitoneum and cause pain, hemorrhage and hypotension. The diagnosis may be confirmed by ultrasound study. If there're no signs of continuing hemorrhage medical therapy (bed rest and blood transfusion) is performed. Continuing hemorrhage requires open surgery.

The arteriovenous fistula develops when continuing hemorrhage from the puncture site of reduces pressure in adjacent venous vessels leading to formation of arterio-venous fistula. The patient may have painful sensations and systolic murmur over the puncture site. Surgical treatment is usually necessary, because the fistula tends to enlarge.

Pulsative hematoma of the artery puncture site with systolic murmur suggests the diagnosis of pseudoaneurysm. The primary risk factors are short period of manual compression or puncture of superficial artery instead of common femoral artery. In 1995 Katzenschlager et al (13) performed a study entitled "Incidence of Pseudoaneurysm after Diagnostic and Therapeutic Angiography". This study included 565 patients, who underwent 581 procedures. Pseudoaneurysms occurred in 14 % of the first 300 procedures with standard manual hemostasis time vs 1.1 % of subsequent 281 procedures with manual hemostasis time exceeding 5 min. Other

risk factors are the large diameter of introducer, massive anticoagulation and antithrombotic therapy during the intervention.

If the size of a pseudoaneurysms exceeds 2 cm or in patients with growing hematoma, compressive bandage or surgical therapy is recommended. In some clinics local injection of thrombin or collagen into the pseudoaneurysm cavity is applied. If the diameter of a pseudoaneurysm is less than 2 cm medical therapy is indicated.

Arterial thrombosis requires thrombectomy.

Since 1998 more than 30 studies were performed in Europe in 37066 patients (7) to assess the risk of vascular complications after manual hemostasis vs. closure devices. The most important endpoints were the efficiency of closure device, complexity of its delivery, complications and cost. The closure was effective in 95% of cases and depended on the surgical skills. The complexity of delivery system was similar for various devices. There were no significant differences in vascular complications risk in patients with manual hemostasis vs. closure/suture devices. Meta-analysis of randomized studies has shown that the risk of complications depended on the device used and on subsequent coronary angioplasty. In studies with coronary angiography as the only diagnostic option there were no differences between manual hemostasis and closure device hemostasis, except for an insignificant trend towards lower frequency of complications in patients with closure devices. The cost of such devices has been decreasing.

Results of our own studies

Following modern trend, in the late 1990-s we began active use of radial access in the Department of Cardiovascular Surgery of the Center of Endosurgery and Lithotripsy,, Moscow. To date up to 85-90% of PTCA procedures are performed through radial approach. Between January and March 2004 we studied 100 patients operated through radial access. A total of 52 PTCAs and 48 diagnostic procedures were carried out via the right-hand radial access. We used 5, 6 and 7 F introducers. Elective interventions were performed in 87 patients. Additional approach through contralateral radial artery was required in 6 patients (4 cases were successful). Femoral access was required in 3 patients. The number of patients with additional approach was 7 (5 women). The radial artery thrombosis occurred in 20% of patients.

The difficulties with the passage through brachiocephalic trunk were encountered in 8 patients. Repeated punctures were required in 4 cases. In spite of insignificant quantity of complications the technique demanded additional anesthesia due to severe pain.

High rate of radial artery thrombosis was an alarming sign. Therefore we increased out requirements to the selection of instruments and their quality standards. Depending on the test objective (coronary angiography or PTCA) and the risk of conversion to open surgery we have made the selection of instruments more meticulous to avoid the change of introducer (and additional arterial injury). We prefer to use short (11 cm) hydrophilic introducers. We routinely used intraarterial verapamil and nitroglycerine injection to prevent spasm. Injection of 5000 U heparin through the introducer is performed in all cases. These measures dramatically reduced the rate of radial artery thrombosis due to radial access (NMT 3%).

The first closure device appeared in Russia several years ago. Active use of such devices in the Center of Endosurgery and Lithotripsy led us to the idea of a randomized study aimed at the comparison of radial and femoral approaches with hemostatic devices for coronary angioplasty.

Study objective:

Comparison of femoral access with active hemostasis to radial access for coronary angioplasty.

The exclusion criteria were previous use of suture devices, positive Allen's test, absent pulse over radial and femoral artery, expected hemodynamic disorders during coronary angioplasty requiring intraaortic balloon counterpulsation, expected need for a pacemaker, cardiogenic shock, history of coronary artery bypass grafting. The endpoints were reduction of hemoglobin to less than 100 mg/l, >50% residual artery stenosis, death, myocardial infarction. Active hemostasis was secured using Perclose (9; 14 %) and Starclose (6 patients; 10 %) Abbott Vascular Ltd, Vasoseal (16 patients; 25 %) and On-Site (2 patients) Datascop Ltd (3 %), Cook Vascular Closur Device (31 patients; 48 %) devices.

Material and methods:

The study included 128 patients (64 patients in each group). Radial access group included 50 men and 14 women, femoral access group – 48 men and 16 women. Mean age in radial access group was 60 years vs. 57 years in femoral access group. Diabetes was found in 21 patients in radial access group vs. 31 patients in femoral access group. Hyperlipidemia was revealed in 57.6% of patients in radial access group and in 63.1% of patients in femoral access group. In radial access group 46.3% of patients were smokers vs. 47.8 % in femoral access group. The acute coronary syndrome was observed in 28% of the patients in radial access group and 34% in femoral access group.

Angiographic endpoints included puncture time (s), introducer size (F), introducer insertion time (s), need for introducer replacement (s), selective catheterization time (s), general procedure time (min), radioscopy time (min), total radiation dose (mGy/cm2), contrast substance volume (ml) without ventriculography. There were no substantial differences between the groups.

A mixture of verapamil + nitroglycerine + heparin was injected intraarterially to prevent radial artery

spasm. GP IIb/IIIa receptor inhibitor was used in 1 patient in femoral access group.

Statistical data analysis was performed using SPSS-PC software package.

Results

Paracatheter hematoma occurred in 23 patients in radial access group vs. 10 patients in femoral access group (significant difference).

The introducer was replaced in 29 patients with radial access vs. 8 patients with femoral access. The volumes of contrast media used in both groups were no significantly different (radial access 165 ml, femoral access 150 ml). Fluoroscopy time was 23.2 min in radial access group vs. 17.5 min in femoral access group (significant difference). There were significant differences in procedure time (min) and total radiation dose (mGy/cm2). Bifurcational stent was used in 23.6 % of patients in radial access group vs. 23.8% of patients in femoral access group, direct stent implantation - in 70% and in 73%, respectively. There were no significant differences in the quantity of stents. TIMI III flow was achieved in 100 % of cases in both groups. Reambulation time was 2.6 h in radial access group and 3.2 h in femoral access group (significant difference).

Complications

The most frequent complications during the first 3 days following coronary angioplasty in radial access group were arterial spasm in 58% of cases, hypodermic hematoma in 39% (Fig. 1), arterial occlusion in 12% (Fig. 2), extremity weakness in 23% of cases. Rare complications included dissection in 9% of cases, nerve disruption in 4% of cases.

In femoral access group the hypodermic hematoma was observed in 10 % of cases, arterial spasm in 2% of cases, bleeding in 1% of cases, nerve disruption in 3% of cases, arterio-venous fistula in 4% of cases, inflammatory process in 4% of cases, extremity weakness in 2% of cases.

Long-term results

The long-term follow-up included 64 patients (50%) assessed at 6 months. Arterial thrombosis was found in 6 patients in radial access group, artery stenosis - in 7 patients in radial access group.

Discussion

Summarizing the published data and our own material we established the following assessment criteria of radial and femoral access (Table 1).

Since recently the incidence of repeated endovascular procedures have been increasing. Typical consequences of repeated punctures are pain at the puncture site of the common femoral artery and fibrous tissue formation. After three or more interventions in some patients the vascular access through the right femoral artery becomes more and more problematic. In such cases it is necessary to pass to the left common femoral artery or radial

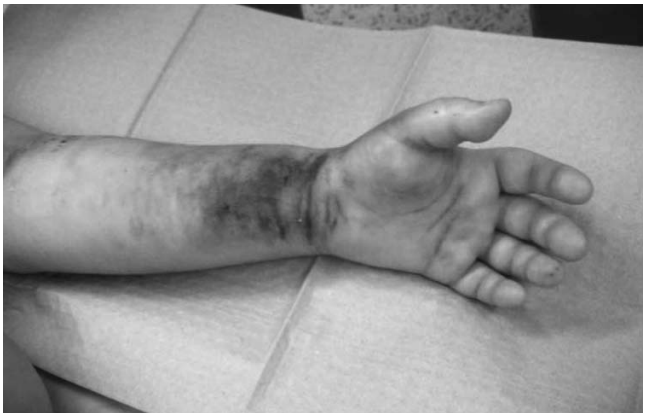

Figure 1. Extensive hypodermic hematoma of the left forearm.

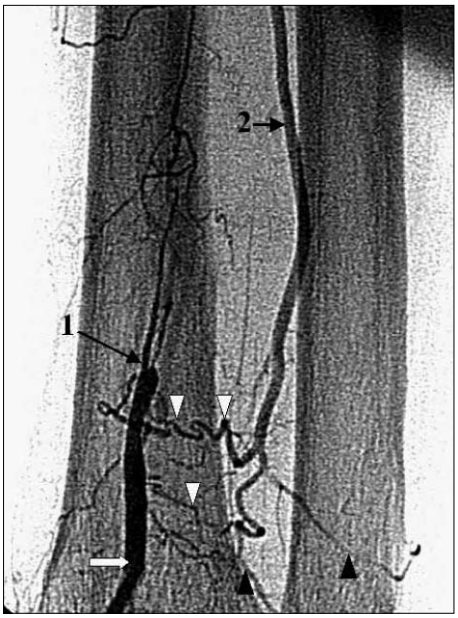

Figure 2. Radial artery occlusion
1. Radial artery stump
2. Interosseous artery
3. Ulnar artery

Table 1. RADIAL VS. FEMORAL ACCESS.

Criteria	Radial	Femoral
Feasibility of repeated puncture	++	+++
Arterial spasm	+++	+++
Possible use of a > 7F introducer	+	+++
Convenience for the operator right / left arteries	+++ / +	+++ / +++
Subcutaneous hematomas Intracavitary hematomas	+++ – +	+ + +
Nerve disruption	+	+++
Puncture apertures hemorrhage (> 300ml)	+	++
Arterio-venous fistula	+	+++
False aneurysms formation	–	+
Compressive hemostasis	+++	+
Patient comfort (no pain, fast reambulation)	++	+
Cost of instruments for puncture and hemostasis	+	++
Early reambulation of patients	+++	++
Reduction of hospital stay	+++	++

Note: +, ++, +++ increasing level of the criterion

arteries. Therefore it is crucial to find the methods implying the use of manual hemostasis or an "active" hemostasis with closure devices, which produce only minor vascular injury and prevent deformation of the artery and fibrous tissue formation. Thanks to the introduction of active hemostasis devices it is now possible to overcome «the Achilles' heel» of all endovascular procedures and decrease the rate of complications associated with access site. However surgical clips, sutures and haemostatic sponge left in the artery wall after closure make the repeated puncture more difficult.

Conclusions

There were no significant differences between radial and transfemoral approaches in the rate of complications such as dissection, haemorrhage, pseudoaneurysm formation. Both methods have similar functionality, injury rate and convenience.

In radial access group the most frequent complications were arterial spasm, occlusion and subcutaneous hematoma.

The advantage of closure devices over manual hemostasis are unclear. In addition, the actual limiting factor for our country is the cost of the closure device.

Finally, the access choice remains with the surgeon.

References:

1. Pracyk J.B. Wall T.C., Longabaugh J.P. et al. A randomized trial of vascular hemostasis techniques to reduce femoral vascular complications after coronary intervention. Cardiology, 1998, 15, 81(8), 970-6.
2. Ward S.R., Casale P., Raymond R. et al. Efficacy and safety of a hemostatic puncture closure device with early ambulation after coronary angiography. Angio-Seal Investigators. Cardiology, 1998, 1, 81(5), 569-72.
3. Kapadia S.R., Raymond R., Knopf W. et al. The 6Fr Angio-Seal arterial closure device: results from a multimember prospective registry. Cardiology, 2001, 15, 87(6), 789-91, A8.
4. Silber S., Gershony G., Schon B. et al. A novel vascular sealing device for closure of percutaneous arterial access sites. Cardiology, 1999, 15, 83(8), 248-52.
5. Silber S., Tofte A.J., Kjellevand T.O. et al. Final report of the European multi-center registry using the Duett vascular sealing device. Herz, 1999, 24(8), 620-3.
6. Baim D.S., Knopf W.D., Hinohara T. et al. Suture-mediated closure of the femoral access site after cardiac catheterization: results of the suture to ambulate and discharge (STAND I and STAND II) trials. Cardiology, 2000, 1, 85(7), 864-9
7. Koreny M., Riedmuller E., Nikfardjam M. et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. JAMA, 2004, 21, 291(3), 350-7.
8. Nikolsky E., Mehran R., Halkin A. et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. Coll. Cardiol., 2004, 15, 44(6), 1200-9
9. Geary K., Landers J.T., Fiore W., Riggs P. Management of infected femoral closure devices. Cardiovasc. Surg., 2002, 10(2), 161-3
10. El-Jack S.S., Ruygrok P.N., Webster M.W. et al. Effectiveness of manual pressure hemostasis following transfemoral coronary angiography in patients on therapeutic warfarin anticoagulation. Cardiology. 2006, 15, 97(4), 485-8. Epub 2006 Jan 4.
12. Krueger K., Zaehringer M., Strohe D. et al. Postcatheterization Pseudoaneurysm: Results of US-guided Percutaneous Thrombin Injection in 240 Patients. Radiology, 2005, 236(3), 1104-10. Epub 2005 Jul 29.
13. Katzenschlager R., Ugurluoglu A., Ahmadi A. et al. Incidence of pseudoaneurysm after diagnostic and therapeutic angiography. Radiology, 1995, 195(2), 463-6
14. Muller D.W., Shamir K.J., Ellis S.G., Topol E.J. Peripheral vascular complications after conventional and complex percutaneous coronary interventional procedures.
Cardiology, 1992, 1, 69(1), 63-8.
15. Krueger K., Zaehringer M., Strohe D. et al. Postcatheterization Pseudoaneurysm: Results of US-guided Percutaneous Thrombin Injection in 240 Patients. Radiology, 2005, 236(3), 1104-10. Epub 2005 Jul 29
16. Paulson E.K., Sheafor D.H., Kliewer M.A. et al. Treatment of iatrogenic femoral arterial pseudoaneurysms: comparison of US-guided thrombin injection with compression repair. Radiology, 2000, 215(2), 403-8.
17. La Perna L., Olin J.W., Goines D. et al. Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. Circulation, 2000, 7, 102(19), 2391-5.
18. Agostoni P., Biondi-Zoccai G.G., de Benedictis M.L. et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; Systematic overview and meta-analysis of randomized trials. Coll. Cardiol., 2004, 21, 44(2), 349-56.
19. Greenwood M.J., Della-Siega A.J., Fretz E.B. et al. Vascular Communications of the Hand in Patients Being Considered for Transradial Coronary Angiography: Is the Allen's Test Accurate? Coll. Cardiol., 2005, 6, 46(11), 2013-7. Epub 2005 Nov 9.
20. Cherr G.S., Travis J.A., Ligush J., Jr et al. Infection is an unusual but serious complication of a femoral artery catheterization site closure device. Ann. Vasc. Surg., 2001, 15(5), 567-70.
21. Hamraoui K., Ernst S.M., van Dessel P.F. et al. Efficacy and safety of percutaneous treatment of iatrogenic femoral artery pseudoaneurysm by biodegradable collagen injection. Coll. Cardiol., 2002, 17, 39(8), 1297-304.
22. Barbeau G.R., Arsenault F., Dugas L. et al. Evaluation of the ulnopalmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen's test in 1010 patients. Heart J., 2004, 147(3), 489-93.
23. Benit E., Vranckx P., Jaspers L. et al. Frequency of a positive modified Allen's test in 1,000 consecutive patients undergoing cardiac catheterization. Cathet. Cardiovasc. Diagn., 1996, 38(4), 352-4.

Contrast-Induced Nephropathy. Literature Review and Preliminary Data of Clinical Study

D.P. Dundua , Z.A. Kavteladze, A.M. Babunashvili, D.S. Kartashov, G.Yu. Travin, Yu.V. Artamonova, S.A. Drozdov, K.V. Bylov

Center of Endosurgery and Lithotripsy (CELT), Moscow, Russia

Cardiovascular diseases are the leading cause of mortality in industrial countries. High-quality and accurate cardiovascular visualization is essential for adequate assessment, treatment and prevention of cardiovascular diseases. Vessels usually could not be visualized under X-ray examination because they are radiolucent. Intravenous or intra-arterial administration of radiographic contrast medium (or simply contrast agents) makes vessels "visible", permits to reveal the character and precise localization of lesions. Contemporary treatment would be really impossible without that. Selective and computer angiography with administration of contrast substances is used increasingly in medical practice.

Radiographic Contrast Agents and Contrast-Induced Nephropathy

Ionic or nonionic iodine-containing contrast agents (CA) which are used for angiography and computer tomography differ not only in chemical structure and molecular weight but in their physicochemical properties. CA are organic compounds containing benzene ring and iodine atoms. CA differ in their chemical structure, number of iodine atoms, presence of ionized or unionized iodine. Differences in chemical structure determine different physicochemical properties of CA such as osmolarity and viscosity as well. It is known that osmolarity of solution is determined by the number of all particles dissolved in it – electrolytes. Osmolarity of CA is determined by the number of iodine atoms and active particles, therefore, ionic CA has significantly higher osmolarity than nonionic ones. As for solution viscosity, it is governed by property of fluid bodies to resist movement of one of their part against another one. Correspondingly dimeric CA (molecule of which contains two benzene rings) are more viscous than monomeric CA.

Ionic CA of first generation such as methyl glucamine diartrizoat (Urografin, Shering, Germany) contained benzene ring with three iodine atoms and were remarkable for higher osmolarity relative to plasma (1400-1800 μosmol/kg) (1-5). Ionic CA may have a significant influence on potassium and sodium exchange within cardiac myocyte, and when administered intracoronary cause rhythm and conduction disturbances, and inhibit myocardial contractility.

CA are administered in bloodstream quickly and in sufficiently large amounts for high-quality visualization and that affects significantly physicochemical properties of plasma. Plasma osmolarity which is rather constant value under common condition increases quickly. Hyperosmolar plasma influences kidneys function and quite often causes transient acute renal dysfunction which is called contrast-induced nephropathy (CIN).

First-generation high-osmolar CA often produced nephropathy. Osmolarity of second-generation nonionic CA, such as Iohexol (Omnipaque, GE Healthcare, USA), Iopromide (Ultravist, Shering, Germany), Ioversol (Tyco Healthcare Group AG, Switzerland), is significantly lower (500-850 μosmol/kg). Low-osmolar CA causes CIN far rarer than high-osmolar first-generation CA. Proceeding from this considerations CA with still lower osmolarity should be still less nephrotoxic. This served as a background for development of isoosmolar CA with an osmolarity equal to that of plasma. Iodixanol (Visipaque, Nicomed, Norway) with osmolarity of 290 μosmol/kg represents such an agent. However, due to dimeric structure of Iodixanol molecule (two benzene rings) its viscosity is higher than that of other CAs. Nowadays least viscosity inheres in low-osmolar ionic CA Iopramide (Ultravist, Shering, Germany).

The effect of nephrotoxicity is dose-dependent.. The higher is the dose of administered CA, the higher would be the risk of nephropathy. Kidney toxicity is more pronounced with ionic high-osmolar and more viscous CAs (2, 3, 4). Correspondingly, ideal contrast agent would be isoosmolar nonionic with low viscosity.

Although clinical consequences of CA use are well known many things in pathogenesis of CIN are still unclear. Particularly, mechanisms of CIN pathogenesis are not entirely elucidated, the problems concerning the efficacy of different ways of its prevention and comparative nephrotoxicity of different iodine-containing CAs are not adequately studied. Wide spreading of radiographic contrast methods of diagnostics and treatment results in the increase of CIN incidence.

Pathogenesis

Acute renal failure in response to administration of CAs develops due to renal tubules necrosis, although exact cause of tubules necrosis is not entirely ascertained. Necrosis is considered to be developed

[1]D.P. Dundua,
Department of Cardiovascular Surgery
Center of Endosurgery and Lithotripsy,
111 123, Moscow, Shosse Entuziastov, 62
Tel. +7 495 305 34 04
Fax +7 495 305 69 35
e-mail: david.doundoua@gmail.com
Manuscript received on September 23, 2007.
Accepted for publication on October 31, 2007.

because of ischemia of cortical layer, resulting from a decrease of blood flow due to the spasm of afferent arteriole. Direct nephrotoxic effect of CAs plays definite role as well.

Animal (6) and histological studies of renal tissue samples revealed vacuolization of renal tubular cells (7). Hyperosmolar CA also increase diuresis and sodium urinary excretion which results in decrease of glomerular filtration due to tubule glomerular feedback. Isoosmolar dimeric CA affect diuresis to a lesser degree. On the other hand, nonionic dimers may increase urine viscosity thus producing an increase of pressure in tubules and a decrease of glomerular filtration. Moreover, increase of blood plasma viscosity may be accompanied by erythrocyte aggregation in microvessels which may result in ischemia of tissues and organs (11). Angiospasm induced by CA appears in response to administration of radiographic contrast agents due to high viscosity and stimulation of adenosine and endothelin (21-24). Although spasm of cortical layer arterioles may be the leading mechanism of experimental CIN development, nonselective endothelin blocker did not prevent CIN in clinical practice (25).

Diabetes mellitus and congestive heart failure increase risk of CIN development. Synthesis of nitric oxide, powerful endogenous vasodilatator, is known to be disturbed under such conditions.

Other possible mechanism of CIN development is renal tubules damage caused by direct toxic effect of free radicals which appears after administration of CA (8, 9, 14, 26). Experimental data suggest that protective antioxidative enzymes are inactivated under hypovolemia. Obvious favorable protective effect of acetylcholine for prevention of CIN is an indirect evidence of the role of free radicals.

Damage of renal tubules is significantly more pronounced under vasoconstriction. It has been shown that the use of low-osmolar CA produced a decrease of creatinine clearance. Simultaneous administration of theophyllin, the agonist of adenosine receptors, prevented renal dysfunction. Theophyllin was significantly less effective in group where high-osmolar CA was used.

CIN pathogenesis is intricate, many things are not entirely clear. All mentioned above mechanisms are likely to take part in CIN development concurrently.

Incidence

CIN incidence varies significantly depending on studied population. This fact may explain significant scatter of CIN incidence values (from 0 to 50%) reported in different clinical studies. It is also important that there is no common definition of CIN nowadays. It is known that nephropathy may develop due to other causes (for example due to renal embolism with atheromatous mass during angiography, nephrotoxic drugs effect etc.). It is hard to tell how strong this factors influence nephropathy development in every specific case, thus, it is more correct to speak not about contrast-induced nephropathy but about nephropathy associated with contrast agent. However, the expression “contrast-induced nephropathy” is widely spread and we will use it as well.

According to data from prospective trials, slight increase of serum creatinine level (0.2 mg/dl or 18 μmol/l on the average) is quite common following contrast administration (3). An increase of serum creatinine level by more than 50% from baseline or by more than 1 mg/dl (88 μmol/l) is observed relatively rarely, mainly in presence of several risk factors (2, 9). On the whole, CIN develops significantly more often when renal dysfunction exists. For example, with normal baseline creatinine level there is no significant decrease of renal function after administration of CA (1, 2). In cases of moderately increased serum creatinine level – from 1.5 to 4.0 mmol/l (132 352 μmol/l) – CIN incidence is 4-11% (1, 2, 4, 27). However nephropathy develops in more than half of cases with initially high creatinine level (6, 27, 28, 29). Risk of CIN development increases significantly in the presence of combination of renal failure and several risk factors such as diabetes mellitus, hypovolemia, heart failure or anemia (1-5).

Percutaneous coronary interventions (PCI) are also associated with increased risk of CIN development because they are often carried out in patients with atherosclerosis and severe concomitant diseases (30-33). The analysis of 7500 patients after PCI has shown that the increase of creatinine level by 0.5 mg/dl (44 μmol/l) in 3.3% of patients, and 25% of them had baseline creatinine level over 2.0 mg/dl (177 μmol/l). In-hospital and 5-year mortality increased significantly in patients developing acute renal failure. Another two studies (31,32) revealed that post-PCI renal failure is associated with poor prognosis; however these studies did not specify the cause of acute renal failure, which could also be provoked by atheroembolism or hypoperfusion due to hypotension.

Risk Factors

Decrease of glomerular filtration rate is observed in renal failure. An increase of creatinine level more than 1.5 mg/l or 132 μmol/l, diabetic nephropathy, pronounced heart failure, hypovolemia, PCI, use of large amounts of CA (1-6, 9, 30-33) are well known risk factors for CIN. CIN risk is dose-dependent, which was clearly shown in many clinical studies. Risk of CIN is minimal with CA doses of 1 ml/kg and not more than 70 ml. Risk is relatively slight with the doses less than 5 ml/kg (but not more than 300 ml in total). However, the association of risk factors and renal failure (creatinine level above 5 mg/dl or 440 μmol/l) can lead to nephropathy progression even after the administration of 20-30 ml of CA . CA type influence renal function as well. Previously, risk of CIN development was high when high-osmolar ionic CA were used. With the development of modern nonionic low-osmolar CA this risk decreased significantly. Risk of CIN is expected to be still lower with isoosmo-

lar CA (with osmolarity equal to that of plasma) (12). However, this issue is not ultimately solved because not all the studies have confirmed the advantages of dimeric isoosmolar CA over low osmolar monomeric CA (38). Some data suggest lower toxicity of CA with lesser viscosity as compared to isoosmolar CA with increased viscosity (39).

Clinical presentations and diagnostics

Acute renal dysfunction manifests within 12-24 hours after contrast examination. In overwhelming majority of cases, oliguria does not occur, renal dysfunction is transient and normalization takes place within 3-5 days (8). However, in small percentage of patients creatinine level increases up to over 5 mg/dl (440 μmol/l) and sometimes hemodialysis becomes necessary. CIN resulting in chronic renal failure is more commong in patients with initially impaired renal function, especially in the presence of diabetes mellitus (8, 29).

Necessity of dialysis in CIN is well studied in patients after PCI. Usually this contingent is characterized by poor somatic status and high mortality rate. Depending on initial renal function, the severity and character of concomitant diseases, 1 to 12% out of these patients need hemodialysis (31, 36). The observation of 1800 patients after PCI revealed that 14.4% of them developed acute renal failure with necessity of hemodialysis in 0.8% (31). In-hospital mortality among patients who required dialysis reached 36%, while mortality did not exceeded 1% in patients without renal dysfunction, and two-year survival rate in patients with dialysis after PCI was 19%.

CIN is diagnosed on the basis of serial determination of creatinine concentration after diagnostic or therapeutic intervention. Renal failure should be distinguished from ischemic lesion of kidneys, interstitial necrosis and atheroembolism. First two conditions develop under hypotonia, shock or sepsis. Skin manifestations on shin and foot, so called livedo reticularis, are more typical for atheroembolism as well. With this, renal failure develops gradually, after days and weeks, usually without normalization of renal function or with progressive renal failure.

CIN prevention

Renal dysfunction is much more amenable to prevention than to treatment. Thus, it is necessary to ascertain if there are any risk factors of CIN development and to consider all indications and contraindications for X-ray contrast examination or intervention once more before carrying out the procedure. The study of case history and physical examination are sufficient for revealing a potential for renal dysfunction development. Some risk factors of CIN such as dehydration can be easily eliminated before administration of contrast agent (CA). If multiple risk factors are combined the threat of CIN development increases significantly (10-44). A numerical score for assessment of CIN risk prior to percutaneous coronary intervention has been suggested (33).

Serum creatinine concentration, patient's height and weight should be determined before administration of CA. Serum creatinine level should be determined at 24 72 hours after intervention as well. Risk of CIN development is higher in patients with low body weight. In order to assess renal function more exactly creatinine clearance may be calculated using Cockcroft-Gault formula (45). Risk of CIN development after intervention is shown to be more predictable with the calculation of correlation between administered CA volume and creatinine clearance (46).

There is real threat of lactoacidosis development in patients with diabetes mellitus and initial renal dysfunction taking metformin. Therefore, it is reasonable to withdraw metformin 48 hours before and after contrast examination.

Hydration is a common measure for CIN prevention. However, optimal way of fluids administration and doses are not ultimately determined (9-12). There are data about greater efficacy concerning CIN prevention of intravenous administration of normal saline as compared to water ingestion (47, 48). One study comparing intravenous fluid administration 12 hours before contrast examination and oral water administration along with single bolus dosing of isotonic saline, revealed that under intravenous hydration decrease of glomerular function was less marked than under water intake (50). Carrying out of hydration with 0.45% solution of sodium chloride was suggested for decreasing of renal salt load before contrast examination. However, hydration with hypotonic solution was found to be less effective for CIN prevention than use of isotonic solution of sodium chloride (51).

Urine alkalization may neutralize free radicals in renal tubules. It was the background for the study comparing hydration with sodium bicarbonate and hydration with sodium chloride. Although it was shown that bicarbonate was more effective for CIN prevention the study was early terminated because there were less endpoints in sodium bicarbonate group than it was expected. Confidence level at reached stage was less than it would be required for definite conclusions (52).

N-acetylcysteine (ACC) having antioxidant and vasodilatory action decreases risk of CIN development (53-57). First clinical study of ACC impact on the risk of CIN development showed that the increase of creatinine concentration by more than 0.5 mg/kg from baseline was observed in 2% of patients receiving ACC as compared to 21% in control group (53). In subsequent studies, role of ACC in CIN prevention after percutaneous coronary interventions in patients with renal dysfunction was studied (54-59). Results of these studies are somewhat contradictory, however, summarizing all the data one might assume about possible protective role of ACC in CIN prevention (58).

Kay et al. suggest that vasodilatory action of ACC influenced the improvement of renal hemodynamics within certain limits which is part of the reason for the decrease of serum creatinine level and the increase of creatinine clearance in patients receiving ACC (59). It has been suggested that ACC altered the results of serum creatinine investigation,contributed to the increase of creatinine clearance in renal tubules or to the decrease of endogenous creatinine production. If at least one of mentioned above hypotheses is correct, then calculation of creatinine clearance based on forecasting formula which takes into consideration serum creatinine level or results of 24-hours serum creatinine test in urine may result in acquisition of false data on the improvement of renal function. ACC is known not to influence on less mediated methods of measurement of glomerular filtration such as iothalamath, inulin or cystatin C clearance.

There are data suggesting greater efficacy of high doses of ACC as compared to that used in previously conducted randomized studies (1800 mg per day). As a whole, significant decrease of CIN incidence was observed in clinical studies with high total doses of ACC (>4000 per day) (60).

Ascorbic acid was also studied as agent for CIN prevention due to its antioxidant effect. In recent randomized study of 231 patients with mild renal failure referred for heart catheterization, the decrease of CIN incidence was observed among those who received ascorbic acid (5 g) before and after procedure. CIN incidence in the group of ascorbic acid was 9% vs. 20% in placebo group (60). Results are encouraging but subsequent studies are needed for confirmation of these data. It should be noted that high doses of ascorbic acid may result in supersaturation with oxalates.

Many other methods for CIN prevention were suggested but no convincing data which prove their efficacy are obtained.

Theophyllin and aminophylline were also used in order to decrease the risk of CIN. Meta-analysis of trials concerning this issue showed that antagonists of adenosine receptors decrease risk of CIN as compared to placebo (63). However, it is hard to interpret unambiguously these data due to heterogeneity of groups included in different trials and because of the fact that none of agents showed clinically significant efficacy in prevention of CIN as well (64, 65).

Forcing diuresis with furosemide, mannitol, dopamine or their combination did not influence or increase CIN frequency as compared to standard hydration (66, 67). Vasodilators such as dopamine, phenoldopame, atrial natriuretic factor, calcium antagonists and prostaglandins do not have any superiority over hydration therapy (68 70).

Hemofiltration and hemodialysis. No influence of hemodialysis on CIN prevention was revealed. As to hemofiltration which is performed before and after X-ray contrast examination, it was effective as compared to hydration in patients with chronic renal failure (CIN frequency was 5% in hemofiltration group vs. 50% in group of standard hydration therapy). In-hospital mortality was also significantly lower in group of hemofiltration (71, 72). It is too early to make ultimate conclusion concerning hemofiltration since procedure affects plasma creatinine concentration and correspondingly it is hard to evaluate its influence on nephropathy while procedure influence on mortality is hard-to-explain. Taking into consideration the cost of procedure, hemofiltration can not be recommended for routine use and should be reserved for the sickest patients (73, 74).

The type of X-ray contrast agent also may affect the renal function. Previously, risk of CIN development was high when high-osmolar ionic CA were used. With the development of modern nonionic low-osmolar CAs this risk decreased significantly. According to integrated data of comparison of high-osmolar CA with low-osmolar ones, the latter contributed to the decrease of CIN risk.

Isoosmolar CA with osmolarity equal to that of plasma are possibly even less nephrotoxic. One multicenter trial comparing low-osmolar CA and isoosmolar CA revealed that an increase of creatinine level by more than 0.5 mg/dl was observed significantly rarely in group where isoosmolar agent Iodexanol was used as compared to low-osmolar CA Iohexinol (75). However, it should be noted that groups were not homogenous, patients who received low-osmolar CA had diabetes mellitus of greater duration, higher baseline creatinine level and they significantly more often underwent percutaneous coronary interventions. Possibly, it were these differences that become the cause of extraordinary high CIN incidence (increase of creatinine concentration by 0.5 mg/dl in 26% of patients!) observed in the group of low osmolar CA Iohexanol. Another trial comparing Iohexanol and Iohexol during peripheral angiography showed that an increase of creatinine level by 25% from baseline was seen more rarely in the group of isoosmolar CA (3.7% vs. 10%). However, the protocol of this trial did not include blood samples collection in strictly determined time, which could influence the results (76). Other trials, on the contrary, failed to prove superiority of isoosmolar Iohexanol over low-osmolar CA in terms of reduction of hospitalization time or CIN prevention (76, 77). There are data about lower toxicity of CA with lesser viscosity as compared to isoosmolar CA with increased viscosity (77).

Conclusion

There is no unequivocal opinion concerning the role of CA in CIN prevention. The most reasonable methods for CIN prevention are as follows: continuous intravenous hydration with isotonic solution and possibly with sodium bicarbonate and use of high dose ACC (78).

One could say for certain that the use of large volume of CA (more than 5 ml per kg of body weight) contributes to a significant increase of CIN risk irrespective of CA type. Risk of CIN is significantly increased

in the presence of initial renal failure combined with diabetes mellitus, heart failure, hypovolemia.

In spite of that, the amount of contrast agent administered in practice during endovascular interventions is often significantly more than "permissible". Concomitant diseases are not always taken into consideration. Intervention is quite often performed in emergency manner and there is no time for adequate examination of patient and for the realization CIN prevention procedures. Interventions often happen to be performed repeatedly during few days. Sometimes we deal with several unfavorable factors. There are still not enough data allowing for the recommendation of one CA type as the safest one for prevention of CIN.

Preliminary results of the clinical trial

A uniform protocol for CIN prevention is accepted in the Department of cardiovascular surgery of the CELT clinic. Plasma creatinine level is determined in all patients before endovascular intervention and than twice, 24 and 48 hours after endovascular intervention.

Active hydration of patients is implemented after physical examination. It implies unlimited fluid intake before administration of CA and i/v infusion of physiological saline at a rate of 1 ml/kg/h from the beginning of intervention and within 24 hours. Hydration is implemented at a rate of 0.5 ml/kg/h in patients with low ejection fraction (below 40%) and congestive heart failure. In patients with initially increased creatinine level i/v administration of fluids is started 2-12 hours before the intervention and continues for 48 hours. Acethylcystein is administered to such patients additionally for 2 days intravenously or orally at a dose of 1200 mg x 4 daily.

Patients were randomized into 4 groups in order to investigate influence of different CAs on renal function during endovascular interventions.

Group 1: endovascular interventions performed using Iodixanol (Visipaque);

Group 2: endovascular interventions performed using Iohexol (Omnipaque);

Group 3: endovascular interventions performed using Ioversol (Optiray);

Group 4: endovascular interventions performed using Iopromide (Ultravist).

Study objective was to assess the influence of different contrast agents on serum creatinine level during percutaneous endovascular interventions;

The design of the study was open-labeled, randomized. Four hundred patients are planned to be included to study by blind randomization, each group will comprise 100 patients.

Clinical endpoints:

— Increase of plasma creatinine level during in-hospital stay by 25% from baseline;

— Progression of renal failure within 1 year after intervention.

Secondary clinical endpoints:

— Survival rate within 1 year after intervention;

— Survival rate, repeated hospitalizations and interventions within 1 year after primary intervention.

Material and methods

One hundred and twenty nine patients were randomized in the period from March 15 to September 18, 2007. One hundred and twenty three patients were included in the study. Patients who underwent contrast examination or intervention twice during 24 hours (n=6) were excluded from this analysis. Preliminary report presents data from 102 patients who were followed for 30 days after the discharge.

Definition of CIN: increase of serum creatinine level by more than 25% from baseline at 24 or 48 hours after endovascular intervention. Data collection was made by means of Microsoft Office Excel 2003. Statistical data proceeding was performed using computer program SPSS-PC (version 9).

Mean age of patients was 58.9±12 years. Most of them (80, or 78,5%) were males. Distribution of groups by sex and age is shown in Table. 1. Groups did not differ significantly by number of severe concomitant diseases such as diabetes mellitus, arterial hypertension and by frequency of renal dysfunction before the intervention. Body weight index was higher in group of Iohexol as compared to other groups.

Table 1. Distribution of patients by groups.

Groups	1 Iodixanol (Visipaque)	2 Iohexol (Omnipaque)	3 Ioversol (Optiray)	4 Iopromide (Ultravist)
Number of patients	21	37	34	10
Age	60.2+10	58.3+13	55.9+11	55.3+14
Female	4 (19%)	7 (19%)	9 (26%)	2 (20%)
BMI*	29.4	35.0	31.0	31.6
Diabetes	4 (19%)	15 (40%)	5 (18%)	3 (30%)
AH	10 (45%)	14 (38%)	12 (35%)	4 (40%)
Initial CRF	2 (10%)	3 (8%)	3 (10%)	1(10%)

* Body weight index (kg/sq.m) was significantly higher in 2nd group.

Results

Mean volume of administered CA per patient was slightly lower in groups of Iodixanol and Iopromide (289 and 291 ml respectively) than in groups of Iohexol and Ioversol, however, the difference was not statistically significant. Mean calculated amount of CA per patient was highest in Iohexol group (319 ml); however, patients with body weight index above 25 prevailed in this group as well (mean group BWI 35.0) which did not reveal significant difference during correlation analysis. Groups did not differ by creatinine clearance level calculated using Cockcroft-Gault formula (46).

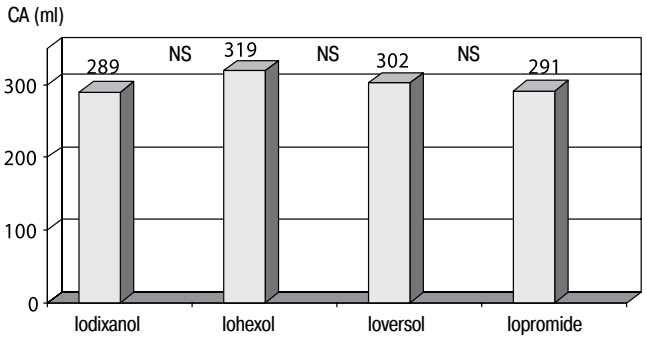

Figure 1. Mean amount of contrast agent (ml) in compared groups.

CIN was observed in patients with initial renal dysfunction in overwhelming majority of cases (in 5 out of 8 patients). CIN incidence differed and was 4.7% (1 case) in Iodixanol group, 6.5% in Iohexol group (in 4 patients), 10% in Ioversol group (2 cases) and 10% in Iopromide group (1 case). As evident from Figure 2, CIN was significantly less common in group 1 and in group 3. However, in one patient out of 2 with CIN from group 3 (Ioversol), we revealed CRF progression which ultimately necessitating chronic dialysis. Thus, it is hard to say about significant difference in CIN severity between groups 2, 3 and 4.

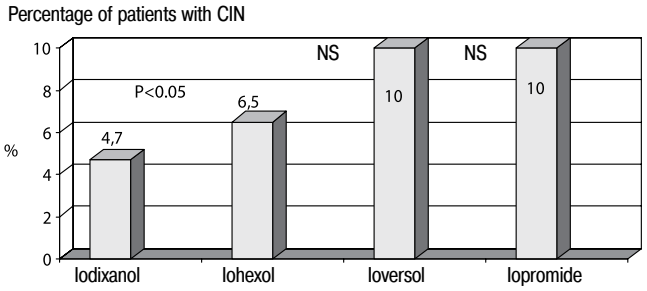

Figure 2. CIN frequency (in per cent) in compared groups.

Our results are generally consistent with the results of other trials concerning CIN. We also noted low incidence of renal dysfunction after use of isoosmolar CA. Relatively low incidence of CIN development in our cases is explained by the fact that the number of patients with baseline renal dysfunction was not too large in all compared groups. Maintenance of CIN prevention measures also seemed to play important role in prevention of renal dysfunction.

However, one should remember that the number of observations does not allow to draw more categorical conclusions at the moment. Study is not completed yet, only its preliminary results are presented.

Based on the mentioned above, on this stage we may conclude that modern low-osmolar and isoosmolar CA are well tolerated by patients, complications associated with their use are rare. Simple prophylaxis measures permit to prevent CIN development in the majority of cases.

References:

1. Parfrey P.S., Griffiths S.M., Barrett B.J. et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N. Engl. J. Med., 1989, 320,143.
2. Rudnick M.R., Goldfarb S., Wexler L. et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. Kidney Int., 1995, 47,254.
3. Davidson C.J., Hlatky M., Morris K.G. et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann. Intern. Med., 1989, 110,119.
4. Schwab S.J., Hlatky M.A., Pieper K.S. et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. N. Engl. J. Med., 1989, 320,149.
5. Cigarroa R.G., Lange R.A., Williams R.H., Hillis L.D. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am. J. Med., 1989, 86,649.
6. Lautin E.M., Freeman N.J., Schoenfeld A.H. et al. Radiocontrast-associated renal dysfunction: Incidence and risk factors. Am. J. Roentgenol., 1991, 157, 49.
7. Lautin E.M., Freeman N.J., Schoenfeld A.H. et al. Radiocontrast-associated renal dysfunction: A comparison of lower-osmolality and conventional high-osmolality contrast media. Am. J. Roentgenol., 1991, 157,59.
8. Rudnick M.R., Berns J.S., Cohen R.M., Goldfarb S. Nephrotoxic risks of renal angiography: Contrast-media associated nephrotoxicity and atheroembolism. A critical review. Am. J. Kidney Dis., 1994, 24,713.
9. Barrett, B.J. Contrast nephrotoxicity. J. Am. Soc. Nephrol., 1994, 5,125.
10. Solomon R. Contrast-medium-induced acute renal failure. Kidney Int., 1998, 53,230.
11. Weisbord S.D., Palevsky P.M. Radiocontrast-induced acute renal failure. J. Intensive Care Med., 2005, 20, 63.
12. Aspelin P., Aubry P., Fransson S.G. et al. Nephrotoxic effects in high-risk patients undergoing angiography. N. Engl. J. Med., 2003, 348, 491.
13. Sandler C.M. Contrast-agent-induced acute renal dysfunction--is iodixanol the answer?. N. Engl. J. Med., 2003, 348, 551.
14. Yoshioka T., Fogo A., Beckman J.K. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. Kidney Int, 1992, 41,1008.
15. Agmon Y., Peleg H., Greenfield Z. et al. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. J. Clin. Invest., 1994, 94,1069.
16. Weisberg L.S., Kurnik P.B., Kurnik B.R. Radiocontrast-induced nephropathy in humans. Role of renal vasoconstriction. Kidney Int., 1992, 41,1408.
17. Kramer B.K., Kammerl M., Schweda F., Schreiber M. A primer in radiocontrast-induced nephropathy. Nephrol. Dial. Transplant., 1999, 14, 2830.
18. Heyman S.N., Rosen S. Dye-induced nephropathy. Semin. Nephrol., 2003, 23,477.
19. Detrenis S., Meschi M., Musini S., Savazzi G. Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art. Nephrol. Dial. Transplant., 2005, 20,1542.
20. Persson P.B., Hansell P., Liss P. Pathophysiology of contrast medium-induced nephropathy. Kidney Int., 2005, 68,14.
21. Cantley L.G., Clark B.A. et al. Role of endothelin and prostaglandins in radiocontrast-induced renal artery constriction. Kidney Int., 1993, 44,1217.

22. Katholi R.E., Taylor G.J., McCann W.P. et al. Nephrotoxicity from contrast media: Attenuation with theophylline. Radiology, 1995, 195,17.
23. Russo D., Minutolo R., Cianciaruso B. et al. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. J. Am. Soc. Nephrol., 1995, 6,1451.
24. Pflueger A., Larson T.S., Nath K.A. et al. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. Mayo Clin. Proc., 2000, 75,1275.
25. Wang A., Holcslaw T., Bashore T.M. et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. Kidney Int., 2000, 57,1675.
26. Heinrich M.C., Kuhlmann M.K., Grgic A. et al. Cytotoxic effects of ionic high-osmolar, nonionic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells in vitro. Radiology, 2005, 235,843.
27. Barrett B.J., Parfrey P.S., Vavasour H.M. et al. Contrast nephropathy in patients with impaired renal function: High versus low osmolar media. Kidney Int, 1992, 41,1274.
28. Manske C.L., Sprafka J.M., Strong J.H., Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am. J. Med., 1990, 89, 615.
29. Weinrauch L.A., Healy R.W., Leland O.S. et al. Coronary angiography and acute renal failure in diabetic nephropathy. Ann. Intern. Med., 1977, 86,56.
30. Rihal C.S., Textor S.C., Grill D.E. et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation, 2002, 105,2259.
31. McCullough P.A., Wolyn R., Rocher L.L. et al. Acute renal failure after coronary intervention: Incidence, risk factors, and relationship to mortality. Am. J. Med., 1997, 103,368.
32. Nikolsky E., Mehran R., Lasic Z., et al. Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. Kidney Int, 2005, 67,706.
33. Mehran R., Aymong E.D., Nikolsky E. et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J. Am. Coll. Cardiol., 2004, 44,1393.
34. McCarthy C.S., Becker J.A. Multiple myeloma and contrast media. Radiology, 1992, 183,519.
35. Holland M.D., Galla J.H., Sanders P.W., Luke R.G. Effect of urinary pH and diatrizoate on Bence Jones protein nephrotoxicity in the rat. Kidney Int., 1985, 27,46.
36. Gruberg L., Mintz G., Mehran R., et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J. Am. Coll. Cardiol., 2000, 36,1542.
37. Morcos S.K., El-Nahas A.M., Brown P., Haylor J. Effect of iodinated water soluble contrast media on urinary protein assays. Brit.Med. J., 1992, 305(6844), 29
38. Liss P. et al. Renal failure in 57925 patients undergoing coronary procedures using iso-osmolar or low osmolar contrast media. Kidney Int., 2006,70(10),1811-1817.
39. Pungh N.D. et al. Iodixanol in femoral angiography (phase III): A comparative double-blind parallel trial between iodixanol and iopromide. Clinical Radiology, 1993,47(2), 96-99.
40. Dangas G., Iakovou I., Nikolsky E. et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and he-modynamic variables. Am. J. Cardiol., 2005, 95, 13-9.
41. Abizaid A.S., Clark C.E., Mintz G.S. et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insuffciency. Am. J. Cardiol., 1999, 83, 260-3.
42. Messana J.M., Cieslinski D.A., Humes H.D. Comparison of toxicity of radiocontrast agents to renal tubule cells in vitro. Ren. Fail., 1990,12,75-82.
43. Katholi R.E., Woods W.T. Jr., Taylor G.L. et al. Oxygen free radicals and contrast nephropathy. Am. J. Kidney Dis., 1998,32,64-71.
44. Heyman S.N., Reichman J., Brezis M. Pathophysiology of radiocontrast nephrop-athy: a role for medullary hypoxia. Invest. Radiol., 1999,34,685-91.
45. Cockcroft D.W., Gault M.H. Prediction of creatinine clearance from serum cre-atinine. Nephron, 1976,16,31-41.
46. Laskey W.K., Jenkins Ch., Selzer F. et al. Volume to creatinine ratio. Am. J. Cardiol., 2007, 50, 584-90
47. Bader B.D., Berger E.D., Heede M.B. et al. What is the best hydration regimen to prevent contrast media-induced nephro¬toxicity? Clin. Nephrol. 2004,,62,1-7.
48. Trivedi H.S., Moore H., Nasr S. et al. A randomized prospective trial to assess the role of saline hydration on the devel¬opment of contrast nephrotoxicity. Neph¬ron Clin. Pract., 2003,93,C29-C34.
49. Thomsen H.S., Morcos S.K., Members of the Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). In which patients should serum creatinine be measured before iodinated contrast medium administration? Eur. Ra-diol., 2005,15,749-54.
50. Taylor A.J., Hotchkiss D., Morse R.W., McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a ran¬domized trial on inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunc¬tion. Chest, 1998,114,1570-4.
51. Mueller C., Buerkle G., Buettner H.J. et al. Prevention of contrast media-associat¬ed nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch. Intern. Med., 2002,162,329-36.
52. Merten G.J., Burgess W.P., Gray L.V. et al. Prevention of contrast-induced nephropa¬thy with sodium bicarbonate: a random¬ized controlled trial. JAMA, 2004, 291, 2328-34.
53. Fishbane S., Durham J.H., Marzo K., Rudnick M. N-acetylcysteine in the pre¬vention of radiocontrast-induced nephropathy. J. Am. Soc. Nephrol., 2004,15,251-60.
54. Tepel M., van der Giet M., Schwarzfeld C. et al. Prevention of radiographic-contrast-agent–induced reductions in renal function by acetylcysteine. N. Engl. J. Med., 2000, 343,180-4.
55. Kshirsagar A.V., Poole C., Mottl A. et al. N-acetylcysteine for the prevention of ra-diocontrast induced nephropathy: a meta-analysis of prospective controlled trials. J. Am. Soc. Nephrol., 2004,15,761-9.
56. Pannu N., Manns B., Lee H., Tonelli M. Systematic review of the impact of N-ace-tylcysteine on contrast nephropathy. Kidney Int., 2004, 65, 1366-74.
57. Bagshaw S.M., Ghali W.A. Acetylcysteine for prevention of contrast-induced ne-phropathy after intravascular angiography: a systematic review and meta-analysis. BMC Med., 2004,2, 38. (Also available at http://www.biomedcentral.com/1741-7015/ 2/38.)
58. Nallamothu B.K., Shojania K.G., Saint S. et al. Is acetylcysteine effective in prevent¬ing contrast-related nephropathy? A meta-analysis. Am. J. Med., 2004,117,938-47.

59. Kay J., Chow W.H., Chan T.M, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA, 2003, 289,553.
60. Marenzi G., Assanelli E., M.D., Marana I., et al. N-Acetylcysteine and Contrast-Induced nephropathy in primary angioplasty. N. Engl. J. Med., 2006,354,2773-82.
61. Spargias K., Alexopoulos E., Kyrzopoulos S. et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation, 2004,110(18),2837-42.
62. Canavese C., Petrarulo M., Massarenti P. et al. Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. Am.J. Kidney. Dis., 2005,,45(3),540-9.
63. Bagshaw S.M., Ghali W.A. Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Arch. Intern. Med., 2005, 165(10),1087-93.
64. Erley C.M., Duda S.H., Rehfuss D. et al. Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol. Dial. Transplant., 1999, 14(5), 1146-9.
65. Ix J.H., McCulloch C.E., Chertow G.M. Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis. Nephrol. Dial. Transplant., 2004, 19(11), 2747-53.
66. Solomon R., Werner C., Mann D. et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N. Engl. J. Med., 1994,331(21),1416-20.
67. Weinstein J.M., Heyman S., Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. Nephron, 1992,62(4),413-5.
68. Chertow G.M., Sayegh M.H., Allgren R.L., Lazarus J.M. Is the administration of dopamine associated with adverse or favorable outcomes in acute renal failure? Auriculin Anaritide Acute Renal Failure Study Group. Am. J. Med., 1996,101(1),49-53.
69. Bakris G.L., Lass N.A., Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: A role for dopamine-1 receptors. Kidney Int., 1999,56(1),206-10.
70. Tumlin J.A., Wang A., Murray P.T., Mathur V.S. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am. Heart J., 2002,143(5),894-903.
71. Marenzi G., Marana I., Lauri G., Assanelli E. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N. Engl. J. Med., 2003, 349,1333.
72. Marenzi G., Lauri G., Campodonico J, et al. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. Am. J. Med., 2006, 119, 155.
73. Klarenbach S.W., Pannu N., Tonelli M.A., Manns B.J. Cost-effectiveness of hemofiltration to prevent contrast nephropathy in patients with chronic kidney disease. Crit. Care Med., 2006, 34, 1044.
74. Cruz D.N., Perazella M.A., Bellomo R, et al. Extracorporeal blood purification therapies for prevention of radiocontrast-induced nephropathy: a systematic review. Am. J. Kidney Dis., 2006, 48,361
75. Aspelin P., Aubry P., Fransson S.G, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N. Engl. J. Med., 2003, 348,491.
76. Carraro M., Malalan F., Antonione R., et al. Effects of a dimeric vs. a monomeric nonionic nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur. Radiol., 1998,8(1),144-7.
77. Barrett B.J., Katzberg R.W., Thomsen H.S. Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease Undergoing Computed Tomography: A Double-Blind Comparison of Iodixanol and Iopamidol. Invest. Radiol., 2006, Nov., 41(11), 815-821.
78. Karmazanovsky G.G., Polyaev Yu.A., Yudin A.L., Shilmanovsky N.L. Modern X-ray contrast agents and nephropathy: how to decrease risk of renal failure development? Meditzinskaya Vizualizacia, 2007, 1, 135-144.

Stenting in Acute and Chronic Occlusion of Coronary Arteries (A Review)

A. L. Krylov[1]

Research Institute of Cardiology under Tomsk Research Center of the Russian Academy of Medical Sciences, Tomsk, Russia

Abbreviations:

MI — myocardial infarction;
PES — paclitaxel-eluting stent;
IR — in-stent restenosis;
SES — sirolimus-eluting stent;
CADILLAC — Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications;
STEMI — ST-elevation myocardial infarction.

Studies performed in the 1990-s by Grines C.L. et al. (1993); Zijlstra F. et al. (1993); de Boer M.J. et al. (1994b); Berger P.B. et al. (1999a; 1999b; and others) had made the advantage of endovascular repair in myocardial infarction versus thrombolysis quite obvious. Coronary angioplasty (balloon dilatation and stenting of the infarct-related artery) became generally adopted for the treatment of myocardial infarction (MI). Further studies were aimed at the search of the most effective method of revascularization in myocardial infarction (MI). It was important to decide whether MI should be treated with stenting, or balloon dilatation of the coronary artery would be enough.

In 2001 H. Suryapranata et al. published the results of their study, which included 112 patients (group I) with stent implantation into the infarct-related artery and 115 patients (group II) with PTCA alone (Suryapranata H. et al., 2001). The patients were followed-up for 1 year postoperatively. The rate of unfavorable outcomes (death or recurrent MI) was 4% in group I vs. 11% in group II (p=0.04). The 1-year rate of repeated revascularization was 13% group I vs. 34% in group II (p < 0,001). Restenosis was revealed on angiography in 12% of patients with stents vs. 34% of patients with balloon dilatation (p < 0.001) (Suryapranata Het al., 2001). In 2002 the results of CADILLAC multicenter study (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications), which included 2082 patients with the MI, were published (Stone G.W. et al., 2002). Patients were divided into four groups: (1) balloon dilatation of coronary arteries (n=518); (2) balloon dilatation of coronary arteries + abciximab (n=528); (3) stent implantation (n=512); (4) stent implantation + abciximab (n=524). During the six-month follow-up the rate of unfavorable outcomes (death, recurrent myocardial infarction, stroke, repeated hospitalization) was maximal in group 1 (20%) and minimal in group 4 (stenting + abciximab) (10.2%). Therefore, the rate of unfavorable events was two times lower (p<0.001) in patients with stent implantation + abciximab versus patients with balloon dilatation of coronary arteries. There were no significant differences between the groups as regards to the frequency of repeated MI, stroke and death; although the rate of repeated revascularization was lower in patients with stenting (Stown G.W. et al., 2002). Similar conclusions were made in the STEMI study (ST-elevation myocardial infarction), which included 849 patients with stent implantation and 834 patients with balloon angioplasty (Suryapranata H.. et al., 2005). In 2003 the results of further follow-up obtained in these 2082 MI patients were published (CADILLAC study) (Cox D.A. et al., 2003). Analysis of the clinical data suggested, that the rate of repeated PTCA during the first 30 days following primary procedure was 5.1% in patients with balloon dilatation vs. 2.3% in patients with bare metallic stents (p<0.007). The 1-year follow-up showed, that the frequency of unfavorable outcomes in patients with balloon dilatation was 21.9% vs. 13.8% in patients after stenting (p<0.001) (Cox D.A. et al., 2003).

Thus, the independent randomized trials showed that stenting is a more effective method of myocardial revascularization as compared to balloon dilatation of coronary arteries, because the development of restenosis after stent implantation is slower resulting in less need for repeated revascularization.

The above information concerned the use of bare stents for myocardial revascularization. The results of clinical approbation of sirolimus-eluting stents (SES) were published in 2003 (Saia F. et al., 2003). The study included 96 patients with acute coronary artery occlusion (myocardial infarction); 46 had multi-vessel disease and 12 were in cardiogenic shock (Saia F. et al., 2003). The patients were followed up for 6 months following hospitalization. Unfavorable outcomes (death, repeated myocardial infarction, repeated revascularization) during this period were observed in 8.4% of all patients (Saia F. et al., 2003) compared to the frequency of unfavorable outcomes after the implantation of bare stents – 10.2% (Stone G.W. et al., 2002). The differences between sirolimus-eluting stents and the bare stents may seem insignificant. However, nearly all unfavorable outcomes associated with sirolimus-eluting stents occurred during hospital stay (only one patient died after discharge from the hospital) (Saia F. et al.,

[1]A.L. Krylov
634034, Tomsk, Kievskaya str., 111.
Telephone (business hours): (3822) 26-21-74
Email: maslov@cardio.tsu.ru
Manuscript received on August 20, 2007
Accepted for publication on September 13, 2007

2003). The 6-month rate of repeated revascularization was 5.7% in patients with bare stents (Stone G.W. et al., 2002), whereas only one patient had an unfavorable event after unsuccessful implantation of a drug-eluting stent (Saia F. et al., 2003). Implantation of bare stents was associated with 22% rate of restenosis and 5.7% rate of reocclusion (Stone G.W. et al., 2002). There were no cases of restenosis or reocclusion during the 6-month follow-up after the implantation of sirolimus-eluting stents (Saia F. et al., 2003). These facts brought the authors to the conclusion that the use of sirolimus (rapamycin)-eluting stents in acute myocardial infarction was safe and effective (Saia F. et al., 2003). In 2007 J. Daemen et. al. published the results of the 3-year follow-up in MI patients after the implantation of SES (n=186), PES (n=136) or bare stents (n=183). The mortality rate was 13.3% in patients with bare stents, 11.5% in patients with SES and 12.4% in patients with PES. These differences were insignificant. The rate of repeated revascularization was 12% in patients with bare stents, 8% in patients with SES and 7.7% in patients with PES. These differences were insignificant as well. The 3-year cumulative rate of unfavorable outcomes (death, myocardial infarction, repeated revascularization) was 25.5% in patients with bare stents, 17.9% in patients with SES and 20.6% in patients with PES. Again, the differences were insignificant (Daemen J. et al., 2007c). The group of L.S. Diaz de la Llera (L.S. Diaz de la Llera et al., 2007) studied 60 MI patients after implantation of bare stents and 60 MI patients after implantation of sirolimus-eluting stents. All variables were similar between the study groups during 1-year follow-up. Works by J. Daemen et. al. (2007c) and L.S. Diaz de la Llera et. al. (2007) are the only that failed to reveal significant differences between the coated and bare stents in acute coronary occlusions. In a Japanese study (Gochi T. et al., 2006) that enrolled 200 patients with MI, half of the patients underwent implantation of SES and another half was treated with bare stents. During 9 months following MI the rate of in-stent restenosis (ISR) was 4% in SES group vs. 19% in patients with bare stents ($p < 0.001$). The rate of repeated revascularization was 4% in SES group vs. 10% in patients with bare stents, however, the difference was insignificant (p=0.149). During 9 months following MI the rate of unfavorable outcomes was 6% in SES group vs. 17% in patients with bare stents (r=0.038) (Gochi T. et al., 2006). The results of a multi-centre randomized study performed in France were published in 2006 (Spaulding C. et al., 2006). The study enrolled 712 patients with MI and ST elevation. The duration of follow-up was 1 year after primary angioplasty with SES and bare stents. During this period the unfavorable events occurred in 7.3% of patients in SES group vs. 14.3% of patients with bare stents (r=0.004). The reduced rate of unfavorable outcomes was due to the decrease of repeated revascularization frequency from 13.4% in patients with bare stents to 5.6% in SES group (r=0.001). There were no significant differences between the groups in the rate of death, myocardial infarction and stent thrombosis (Spaulding C. et al., 2006). In 2006 Percoco G. et al. published the results of an Italian study performed in 205 MI patients with implantation of SES and 1177 MI patients with bare stents (Percoco G. et al., 2006). One year after AMI the rate of unfavorable outcomes (death, myocardial infarction, repeated revascularization) was significantly lower in SES group (p=0.03); repeated revascularization was also less common in patients with sirolimus-eluting stents (p=0.01). The same year Newell M.C. et al. published the results of an American study performed in 306 patients with MI, 156 of which underwent SES implantation and 150 – implantation of bare stents (Newell M.c. et al., 2006). Hospital mortality rate was 0.6% in SES group compared to 5.3% in patients with bare stents (p=0.015). The 6-month mortality rate was 1.9% in SES group vs. 10.1% in patients with bare stents (p=0.003). The 6-month rate of repeated revascularization was 1.3% for sirolimus-eluting stents vs. 8.1% for bare stents (p=0.005). The 6-month rate of unfavorable outcomes (death, MI, repeated revascularization) was 3.2% in SES group vs. 16.1% in patients with bare stents (p=0.0001). Hence, sirolimus-eluting stents in patients after MI reduced the rate of repeated revascularizations and the risk of death. Italian cardiologists studied the long-term outcome (8 to 12 months following stent implantation) of primary angioplasty of the infarct-related artery (Pasceri V. et al. 2007). The study enrolled 2357 patients with MI, 1177 of which underwent implantation of stents with antiproliferative coating, while another 1180 underwent implantation of bare stents. The rate of death or MI was similar between the groups: 5.8% in patients with drug-eluting stents vs. 6.9% in patients with bare stents. The rate of repeated revascularization in patients with bare stents was 2.5 times higher (12%) as compared to stents with antiproliferative coating (Pasceri V. et al. 2007). The rate of in-stent thrombosis was similar between the groups (Pasceri V. et al. 2007). In the study performed in Shanghai, which included 225 patients with MI, 123 patients underwent implantation of bare stents, while 102 patients were treated with SES (Zhang F.et al. 2007). The 300-day rate of unfavorable events was 7.8% in SES group vs. 22.8% in patients with bare stents (p=0.005) (Zhang F.et al. 2007). Higher rate of unfavorable outcomes in patients with bare stents was due to higher rate of repeated revascularization (17.1%) as compared to SES group (1%) ($p< 0.001$). Similar results were obtained in another independent Chinese study (Gao H. et al., 2007), which included 101 MI patients, who underwent implantation of a “Firebird“ SES, and 55 MI patients, who underwent implantation of bare stents. The 6-month rate of death, repeated revascularization, unfavorable events in SES group was 2.0%, 6.9% and 9.9%, respectively, compared to 3.6%, 30.9% and 36.4% in patients with bare stents ($p < 0.05$) (Gao H. et al., 2007). In 2007 Menichelli et

al. published the results of an Italian randomized study (Menichelli M. et al., 2007). The study enrolled 320 patients STEMI (ST-elevation myocardial infarction), half of which underwent SES implantation, while another half underwent implantation of bare stents. Follow-up coronary angiography was performed 1 year following the procedure. The 1-year rate of in-stent restenosis was 9.3% in SES group vs. 21.3% in patients with bare stents (p=0.032). The 1-year rate of repeated revascularization was 5% in SES group vs. 13.1% in patients with bare stents (p=0.015), the rate of cardiac unfavorable events was 6.8% in SES group vs. 16.8% in patients with bare stents (p=0.005). The rate of target vessel failure was 8.7% in SES group vs. 18.7% in patients with bare stents (p=0.007) (Menichelli M. et al., 2007). Therefore, according to Menichelli M. et al., primary PTCA with SES decreased the rate of restenosis by 56%, the rate of repeated revascularization – by 62%, the rate of unfavorable cardiac events – by 59% and increased the efficacy of coronary reperfusion by 53%. Consequently, there is a strong evidence that stents with antiproliferative coating are more favorable in MI as compared to the bare stents as regards to the rate of IR, the need for repeated revascularization and the frequency of unfavorable outcomes.

The above information concerned the acute coronary occlusion which usually result in life-threatening myocardial infarction. However, chronic coronary occlusions are equally life-threatening. Annual mortality rate among patients with such occlusions, undergoing conservative treatment, is 19% (Stone G.W. et al., 2005b).

In 2004 the International Congress of Interventional Cardiologists defined chronic occlusion as an occlusion lasting over 3 months (Stone G.W. et al., 2005b). Chronic occlussion is a common type of coronary perfusion impairment. Chronic oclussion of the right coronary artery occurs most commonly (45% of cases), the LAD is involved in 28% of cases, and the occlusion of the circumflex branch of the LAD occurs in 27% of cases (Stone G.W. et al., 2005a). Poor effect of balloon dilatation in chronic coronary occlusion is well established. Thus, according to M.R. Bell et al. (1992), the immediate success rate was only 66% in patients with total chronic coronary occlusion. For comparison, balloon dilatation of coronary stenosis provides reperfusion in 84% patients (Meier B., 1989). In addition, insufficient effect of balloon dilatation in coronary occlusion is largely due to the high rate of reocclusion following balloon dilatation (Violaris A.G. et al., 1995). The 6-month rate of restenosis was 5.7% in patients with occlusion vs. 34% in patients with coronary stenosis (Violaris A.G. et al., 1995). Today angioplasty is thought to ensure the highest effect in coronary occlusions existing for less than 3 months, provided that the occlusion is short, not adjacent to a side branch and the plaque is not calcified (Stone G.W. et al., 2005a). The "age" of occlusion is most crucial for successful recanalization of the obstructed artery. Thus, G.W. Stone et. al. reported the results obtained in 116 patients, in whom the mean "age" of occlusion was 22 months (Stone G.W. et al., 2005a). Only in 54% of these patients the recanalization of occluded vessel proved effective (Stone G.W. et al., 2005a). Average rate of successful PTCA for chronic occlusions varies, according to various medical centers, from 74% to 77% (Stone G.W. et al., 2005b).

Introduction of stents into the clinical practice allowed to improve the results of coronary artery recanalization. The 1-year rate of restenosis decreased from 62% with balloon dilatation to 38% with stenting (p<0.0001); the rate of re-occlusion – from 20% with balloon dilatation to 8% with stenting (p<0.0001), and the rate of repeated revascularization – from 31% to 15% (p < 0.0001) (Stone G.W. et al., 2005a). In spite of the apparent improvement of the outcomes of endovascular interventions, the rate of restenosis and re-occlusion after bare stent implantation remained high. Treatment of chronic occlusions is still associated with high rate of unfavorable outcomes during hospital stay (3.8%), including the mortality rate of 1.3% (Stone G.W. et al., 2005a). J. Schofer et. al. (1999) showed that 6-months rate of angiographic restenosis after stenting was 33% in patients with coronary occlusion vs. 28% in patients with coronary stenosis. A particularly high rate of the restenosis (44% during 6-month follow-up) was found in cases when the occlusion was over 18 mm in length (Schofer J. et al., 1999). The clinical introduction of laser and mechanic atherectomy provided immediate success rate of 91% in total coronary occlusion (Serruys P.W. et al., 2000b). Unfortunately, atherectomy had no influence on the 6-months rate of in-stent restenosis, which was 40% in these patients (Serruys P.W. et al., 2000b). The 1-year rate of angina recurrence was 70% (Serruys P.W. et al., 2000b).The introduction of stents with antiproliferative coating into the clinical practice gave hope for the improvement of PTCA results. The first report concerning the use of coated stents was published in 2004 (Hoye A. et al., 2004). The study included 84 patients with chronic coronary occlusion, 56 of them underwent implantation of sirolimus-eluting stents, another 28 patients were treated with bare stents. The 1-year rate of unfavorable outcomes was 3.6% in SES group vs. 27.3% patients with bare stents (p<0.05) (Hoye A. et al., 2004). These large differences failed to reach statistical significance because of small sample size. Reocclusion was reported only in 1 patient 6 months following SES implantation; the 6-month rate of binary restenosis (over 50% lumen reduction) was 9% in SES group (Hoye A. et al., 2004). These results were substantially better as compared to bare stents (Stone G.W. et al., 2005a), but apparently inferior to that after SES implantation in focal stenosis, where the 6-month rate of IRS was only 1% (Serruys P.W. et al., 2002a). However, some authors report lower rates of restenosis after

implantation of SES for chronic occlusion – 3.4% during 6 months (Stone G.w. et al., 2005a), which is still 3.4-times higher than in focal stenosis. The low efficacy of stenting in occlusion was probably due to imperfection of the equipment and the technique of stent implantation used in such procedures. Organized thrombus was commonly found in patients with coronary occlusion (Stone G.W. et al., 2005a). Considering these findings, F.J. Zidar et. al. (1996) studied 60 patients with unsuccessful recanalization of the occluded artery. These patients received 8-h intracoronary infusion of urokinase. Following the infusion the rate of successful recanalization was over 50%. Unfortunately, due to its complex nature, this approach to coronary reperfusion hasn't become widely adopted. In 2006, G. Melzi et al. reported successful application of a new device («CROSSER CTO Recanalization System») in patients with chronic occlusion (mean "age" of occlusion was 9 months), which, due to vibration of the catheter, could reestablish the blood flow in the obstructed artery. This endovascular intervention was called "vibration angioplasty" (Stone G.W. et al., 2005a). Unfortunately, the sample was small (n=28) and the follow-up duration was only 30 days. Therefore, it is still unclear whether the above-mentioned device is able to solve the problem of chronic occlusion. In 2007, E. Meliga et. al. reported successful application of SES in chronic occlusion of aortocoronary grafts.

Does the recanalization of coronary artery occlusion provide any benefit? The suitability of PTCA in patients with chronic occlusion is demonstrated by the mortality rate (Stone G.w. et al., 2005b). The 1- year mortality rate after successful reperfusion of an occluded artery was 10% vs. 19% in patients with unsuccessful reperfusion ($p<0.001$). The 10-year mortality rate following successful recanalization is 26% vs. 35% in case of unsuccessful recanalization ($p=0.001$) (Stone G.W. et al., 2005b). These findings showed that PTCA could significantly reduce the mortality rate in patients with chronic coronary occlusion (Stone G.W. et al., 2005b). However, these data pertain only to balloon dilatation and implantation of bare stents. Unfortunately, we can not provide similar findings for stents with antiproliferative coating, because such studies haven't been published yet.

Thus, PTCA with implantation of antiproliferative stents should be preferred for the treatment of acute coronary occlusion (myocardial infarction), as the rate of restenosis and, consequently, the rate of repeated revascularization, is lower following implantation of these stents as compared to bare stents. Some authors (Newell M.c. et al., 2006; Gao H. et al., 2007) reported lower mortality rate in patients with coated stents vs. patients with bare stents. Stenting should be the preferred in PTCA of chronic occlusions, as stenting provides lower rate of restenosis, reocclusion and repeated revascularization as compared to balloon dilatation. The benefit of coated stents over bare stents requires further investigation.

References:

1. Grines C.L., Browne K.F., Marco J. et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N. Engl. J. Med., 1993, 328(10), 673-679.
2. Zijlstra F., de Boer M.J., Hoorntje J.C. et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N. Engl. J. Med., 1993, 328(10), 680-684.
3. de Boer M.J., Hoorntje J.C., Ottervanger J.P. et al. Immediate coronary angioplasty versus intravenous streptokinase in acute myocardial infarction: left ventricular ejection fraction, hospital mortality and reinfarction. J. Am. Coll. Cardiol., 1994b, 23(5), 1004-1008.
4. Berger P.B., Ellis S.G., Holmes D.R. et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Circulation, 1999a, 100(1), 14-20.
5. Berger P.B., Tuttle R.H., Holmes D.R. et al. One-year survival among patients with acute myocardial infarction complicated by cardiogenic shock, and its relation to early revascularization: results from the GUSTO-I trial. Circulation, 1999b, 99(7), 873-878.
6. Suryapranata H., De Luca G., van 't Hof A.W. et al. Is routine stenting for acute myocardial infarction superior to balloon angioplasty? A randomised comparison in a large cohort of unselected patients. Heart, 2005, 91(5), 641-645.
7. Stone G.W., Grines C.L., Cox D.A. et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N. Engl. J. Med., 2002, 346(13), 957-966.
8. Cox D.A., Stone G.W., Grines C.L. et al. Outcomes of optimal or "stent-like" balloon angioplasty in acutemyocardial infarction: the CADILLAC trial. J. Am. Coll. Cardiol., 2003, 42(6), 971-977.
9. Saia F., Lemos P.A., Lee C.H. et al. Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction: a clinical and angiographic study. Circulation, 2003, 108(16), 1927-1929.
10. Daemen J., Tanimoto S., García-García H.M. et al. Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction (from the RESEARCH and T-SEARCH Registries). Am. J. Cardiol., 2007c, 99(8), 1027-1032.
11. Díaz de la Llera L.S., Ballesteros S. et al. Sirolimus-eluting stents compared with standard stents in the treatment of patients with primary angioplasty. Am. Heart J., 2007, 154(1), 164.e1-164.e6.
12. Gochi T., Umeda H., Yoshida N. et al. Promising efficacy of the sirolimus-eluting stent in patients with acute myocardial infarction J. Cardiol., 2006, 48(5), 253-261.
13. Spaulding C., Henry P., Teiger E. et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N. Engl. J. Med., 2006, 355(11), 1093-1104.
14. Percoco G., Manari A., Guastaroba P. et al. Safety and long-term efficacy of sirolimus eluting stent in ST-elevation acute myocardial infarction: the REAL (Registro REgionale AngiopLastiche Emilia-Romagna) registry. Cardiovasc. Drugs Ther., 2006, 20(1), 63-68.

15. Newell M.C., Henry C.R., Sigakis C.J. et al. Comparison of safety and efficacy of sirolimus-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction. Am. J. Cardiol., 2006, 97(9), 1299-1302.
16. Pasceri V., Patti G., Speciale G. et al. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. Am. Heart J., 2007, 153(5), 749-754.
17. Zhang F., Ge J., Qian J. et al. Sirolimus-eluting stents in real-world patients with ST-segment elevation acute myocardial infarction. Int. Heart J., 2007, 48(3), 303-311.
18. Gao H., Yan H.B., Zhu X.L. et al. Firebird sirolimus eluting stent versus bare mental stent in patients with ST-segment elevation myocardial infarction. Chin. Med. J., 2007, 120(10), 863-867.
19. Menichelli M., Parma A., Pucci E. et al. Randomized trial of sirolimus-eluting stent versus bare-metal stent in acute myocardialiInfarction (SESAMI). J. Am. Coll. Cardiol., 2007, 49(19), 1924-1930.
20. Stone G.W., Kandzari D.E., Mehran R. et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation, 2005b, 112(15), 2364-2372.
21. Stone G.W., Colombo A., Teirstein P.S. et al. Percutaneous recanalization of chronically occluded coronary arteries: Procedural techniques, devices, and results. Catheter. Cardiovasc. Interv., 2005a, 66(2), 217-236.
22. Bell M.R., Berger P.B., Bresnahan J.F. et al. Initial and long-term outcome of 354 patients after coronary balloon angioplasty of total coronary artery occlusions. Circulation, 1992, 85(3), 1003-1011.
23. Meier B. Coronary Angioplasty. Grune & Stratton Inc., Orlando, USA, 1989, 279 p.
24. Violaris A.G., Melkert R., Serruys P.W. Long-term luminal renarrowing after successful elective coronary angioplasty of total occlusions. A quantitative angiographic analysis. Circulation, 1995, 91(8), 2140-2150.
25. Schofer J., Rau T., Schluter M., Mathey D.G. Restenosis after stenting of matched occluded and non-occluded coronary arteries. Should there be a difference? Eur. Heart J., 1999, 20(16), 1175-1181.
26. Serruys P.W., Hamburger J.N., Koolen J.J. et al. Total occlusion trial with angioplasty by using laser guidewire. The TOTAL trial. Eur. Heart J., 2000b, 21(21), 1797-1805.
27. Hoye A., Tanabe K., Lemos P.A. et al. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. J. Am. Coll. Cardiol., 2004, 43(11), 1954-1958.
28. Serruys P.W., Degertekin M., Tanabe K. Et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation, 2002a, 106(7), 798-803.
29. Zidar F.J., Kaplan B.M., O'Neill W.W. et al. Prospective randomized trial of prolonged intracoronary urokinase infusion for chronic total occlusion in native coronary arteries. J. Am. Coll. Cardiol., 1996, 27, 1406-1412.
30. Melzi G., Cosgrave J., Biondi-Zoccai G.L. et al. A novel approach to chronic total occlusions: the crosser system. Catheter Cardiovasc. Interv., 2006, 68(1), 29-35.
31. Meliga E., García-García H.M., Kukreja N. et al. Chronic total occlusion treatment in post-CABG patients: Saphenous vein graft versus native vessel recanalization-Long-term follow-up in the drug-eluting stent era. Catheter Cardiovasc. Interv., 2007, 70(1), 21-25.

Risk Factors Effect on the Inflammation Reaction Course and the Atherosclerosis Development

I.I. Chukayeva, N.V. Orlova, V.A. Aleshkin, D.G. Gromov, A.L. Pukhalsky, E.G. Alekseyeva
Department of Out-Patient Therapy of the Moscow Faculty of the State Educational Institution of Higher Professional Education, «Russian State Medical University of Roszdrav»;
N. G. Gabrichevsky Moscow Scientific Research Institute of Epidemiology and Microbiology;
Moscow City Center of Interventional Cardioangiology; Medicogenetic Research Center of the Russian Academy of Medical Sciences, Moscow.

Key words: atherosclerosis, obesity, diabetes mellitus, inflammatory reactions, cytokines, insulin resistance.

The understanding of atherosclerosis pathogenesis has substantially extended in recent years. A great role in the coronary artery lesion is given not only to the impact of cholesterol, lipids, coagulation disbalance, but also to the role in the development of the atherosclerotic plague of inflammation mechanisms involving inflammation cells – phagocytes and T-lymphocytes (14, 29). The first link in the chain of processes leading to the development of pathologic changes and inflammation in the vascular wall is sedimentation of antigen-antibody complex on vascular surface (13). Galloping inflammation relapses result in thickening of the intima (inner vascular layer) (8). Inflammation episodes are accompanied by the middle vascular layer (media) necrosis, segmental intima and media proliferation, lipids and calcium deposits, thrombi formation at the pathologically changed artery segment. Antigen properties can be acquired by metabolites (paraproteins, paraglycoproteins) and sometimes even by an insulin protein molecule (1). Study of the atherosclerotic plague development stages revealed the plague instability to be of great importance to atherosclerosis progression and CHD (Coronary Heart Disease) complications. Inflammatory theory of the atherogenesis is confirmed by raised concentrations of inflammatory response markers in the blood of patients with cardiovascular diseases (CHD) (8).

A great role in the atherogenesis belongs to risk factors, such as obesity and type II diabetes. Obesity often precedes numerous diseases. A close connection of the obesity with type II diabetes, hypertension, CHD and ischemic stroke is noted. As the metabolism of triglycerides is considered to be the primary function of the adipose tissue, the dislipidemia (dislipoproteinemia) was regarded as the main pathogenetic effect on the coronary arteries (5). The latest studies prove adipose tissue to be not only a fat depot but active agent in the energy homeostasis. The term "adipocytokine" was chosen to mark bioactive factors secreted by adipose tissue and influencing other body tissue function. Lately there has been a growing body of evidence introducing generalized and abdominal obesity as the state accompanied by a slight inflammation (19).

One of the main risk factors of CHD is diabetes mellitus. Vascular lesion in diabetes mellitus has lately been considered as one of the manifestations and not a complication of the underlying disease. Vessel changes can occur both in manifest diabetes and glucose tolerance disorder. Basic pathologic processes in vessels are revealed at the basement membrane level. Various factors are examined in angiopathy pathogenesis: protein, lipid and carbohydrate metabolism disturbances; tissue hypoxia; coagulation disbalance and increased hemostatic activity of the blood; role of a genetic factor and immune system factors (3, 9). In recent years studies show the impact on the inflammation processes of the metabolic syndrome including dislipidemia, obesity, insulin resistance, arterial hypertension (25, 26). There is, however, no consensus on mechanisms and degree of each metabolic factor impact on coronary vessels lesion till recent times.

The objective of our research was to study the relationship between coronary vessel lesion and presence of associated risk factors with inflammation intensity in CHD patients.

MATERIAL AND METHODS

The study is based on observation of coronary heart disease (CHD) patients who underwent an in-patient treatment at the Moscow City Center of Interventional Cardioangiology (director – Professor D. G. Iosseliani). We observed 160 patients with verified diagnosis of CHD, exertional angina pectoris, who were divided into 4 groups. The first group included 42 patients with a verified diagnosis of CHD without concomitant diseases. Thirty five patients had CHD accompanied with obesity (2nd group), 38 patients were diagnosed CHD with accompanying type II diabetes (3rd group) and 38 patients had a CHD with both accompanying obesity and type II diabetes (4th group).

Patient age averaged 60.8+3.4 years. Four study groups were comparable regarding gender and age.

[1]I.I. Chukaeva
e-mail: vrach315@yandex.ru
Manuscript received on June 25, 2007
Accepted for publication on September 17, 2007

The diagnosis of CHD was based on typical pain attacks, case history, ECG examination, veloergometry and coronarography. Diagnosis of type II diabetes was based on the case history, clinical picture, fasting glucose level above 7 mmol/L in the repeated glucose tolerance test. Diagnosis of obesity was based on the body mass index (BMI) measurements above 30 kg/m2.

Patients with acute myocardial infarction and instable angina pectoris were excluded from the study. We excluded also patients with accompanying diseases which could affect parameters under investigation: malignant tumors, systemic diseases; exacerbation of gastrointestinal, lung and kidney diseases.

On admission to the hospital the patients received conventional CHD therapy: beta-blockers, antiaggregants, ACE (angiotensin-converting enzyme) inhibitors; nitrates for pain syndrome.

Dynamic control of an electrocardiogram (ECG), blood pressure (BP), heart rate (HR), biochemical parameters (CK, MB-CK, ALAT, ASAT, LDH, glucose, urea, creatinine, bilirubin), blood electrolytes, blood and urine analysis was performed in all patients.

All patients underwent coronary angiography in the X-ray-operating-room via «Siemens» angiography system (Germany) using Judkins technique. Under local anesthesia with Novocain solution, common femoral artery tapping was done, then one by one the left ventricle and coronary artery orifices were catheterized through the installed introducer of 7-8 French in diameter. We used Omnipac 300, Omnipac 350, Ultravist as contrast agents. Left coronary artery angiography was performed at least in two right and left oblique projections with caudal and cranial angulations; right coronary artery – in one frontal, right and left oblique views with cranial angulation. LCA was injected with 6-10 ml of contrast agent, RCA — 5–6 ml at the rate of 2–4 ml/sec. A shooting rate was 12.5 fps. Images were stored at the hard drives of the Hicor system of Siemens Corporation (Germany). Coronary angiogram analysis was performed through the program at the same computer.

Cytokines (IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ) were assessed through the enzyme-linked immunosorbent assay. Blood for the analysis was collected before coronary angiography. In the study we used «Proteinovy kontur» Company (St. Petersburg) reagent sets for enzyme immunoassay of human cytokines (IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ).

Set operation principle: sandwich protocols of enzyme-linked immunosorbent assay were used in the sets. According to the protocol we used two monoclonal antibodies with different epitope specificity to the studied interleukin. One of the antibodies was immobilized on solid phase (inner surface of the sockets) and the other one was conjugated with biotin. At the first stage of the analysis the interleukin contained in the calibration and analyzed samples binds with antibodies immobilized on the inner surface of the sockets. At the second stage of the analysis the immobilized interleukin reacts with the second antibody-biotin conjugate. The bound conjugate amount is in direct proportion to the interleukin amount in the analyzed sample. At the final stage of the analysis avidin-peroxidase is brought into the sockets. During incubation with the substrate mixture the coloring of a solution in the sockets takes place. Coloration degree is in direct proportion to the amount of bound labeled antibodies. After measuring the optical density of the solution in the sockets via the calibration curve, the IL concentrations in the analyzed samples are estimated.

The obtained data was processed at the Intel Celeron based PC in the Microsoft Excel environment using the installed Analysis Pack, specially intended for solving statistical problems. Mean values were compared using standard methods of variation statistics of the biomedical profile.

The study was held according to the Helsinki declaration.

RESULTS AND DISCUSSION:

During analysis of the obtained data four groups of coronary artery lesion intensity were identified. Vascular index (VI) suggested by Gensini et al. and Sullivan et al. (1990) was calculated according to the number of coronary arteries with hemodynamically significant stenosis (over 50% of the vessel lumen). VI ranged from 0 to 3. The first group included patients with insignificant hemodynamic changes in the coronary arteries, the second – with stenosis of over 50% of one artery lumen, the third – with stenosis of two arteries and the fourth – with stenosis of more than two arteries. During analysis groups with VI of 1-3 were compared. We analyzed the correlation of coronary artery lesion degree with the accompanying obesity and type II diabetes. The following results were obtained: among patients with the coronary angiography findings of 1 artery stenosis the patients without accompanying risk factors – obesity and type II diabetes — prevailed (51%). Yet presence of carbohydrate and lipid metabolism disturbances in patients was accompanied mainly by atherosclerotic lesion of more than 2 coronary arteries. The results are presented in Table 1.

Table 1. Relationship between coronary vessel lesion and accompanying obesity and type II diabetes mellitus.

Coronarography findings / Risk factors	Lesion of 1 vessel (%)	Lesion of 2 vessels (%)	Lesion of 3 or more vessels (%)
No concurrent diseases	52 % (n=13)	28 % (n=7)	20 % (n=5)
Obesity	24 % (n=5)	43 % (n=9)	33 % (n=7)
Type II diabetes	19 % (n=5)	33 % (n=9)	48 % (n=13)
Obesity and type II diabetes	26 % (n=7)	33 % (n=9)	41% (n=11)

Our data coincide with the studies sustaining the impact of accompanying risk factors on the atherosclerosis development. CHD risk factors include diabetes mellitus, obesity, hyperlipidemia, arterial hypertension, smoking, etc. In patients with accompanying risk factors the prognosis is worse – rapid CHD progression, development of complications, including early myocardial infarction (6, 11). Until recent times a pathogenetic role of the CHD risk factors has been considered to determine lipids disbalance, endothelium function disturbance and nitric oxide oxidative inactivation (4, 9, 17, 18). But the reasons of rapid development of the atherosclerotic vascular lesion in a given patient population and the degree of risk factor effect on inflammation mechanisms in pathologic processes have still not been completely discovered.

The following results were obtained during the evaluation of blood serum cytokine activity in patients with variable atherosclerosis intensity. TNF-α level in examined patients' blood serum was below the lower limit of activity quantification.

Proinflammatory cytokine (IFN-γ, IL-6, IL-8) levels correlated with the number of stenosed coronary arteries. The least cytokine activity values were observed in patients without significant vascular lesion. Proinflammatory cytokine levels elevated accordingly with increasing of the stenosed coronary arteries number. The highest values of IFN-γ, IL-6 and IL-8 corresponded to the lesion of more than two coronary arteries.

Antiinflammatory cytokine values (IL-4, IL-10) depended inversely. With increasing of the number of stenosed coronary arteries the patient IL-4 and IL-10 activity values diminished. The least cytokine values were determined in patients with more than two coronary arteries affected.

Table 2. Cytokine values depending on the extent of coronary arteries lesion and the signs of atherosclerotic plaque disruption.

Coronarography findings / Cytokines	Without significant lesion of vessels	Lesion of 1 vessel	Lesion of 2 vessels	Lesion of 3 and more vessels
IFN-γ (pg/ml)	13.43±2.13	34.22±3.15	32.61±3.64	55.77±5.64*
IL-4 (pg/ml)	1.8±0.32	1.32±0.24	1.44±0.32	1.37±0.25
IL-6 (pg/ml)	2.84±0.46	7.17±0.64	6.02±0.46	12.97±2.43*
IL-8 (pg/ml)	51.04±4.63	45.96±3.37	75.7±6.44*	147.83±8.54*
IL-10 (pg/ml)	1.61±0.37	1.77±0.54	1.18±0.32	0.97±0.17*

* p< 0.05 versus control

Our data confirm the importance of inflammation factors in the development of the coronary artery atherosclerotic lesion. Elevated levels of proinflammatory cytokines known to initiate inflammatory reactions show their active role in the vascular endothelium injury and atherosclerotic plague formation (27, 28). IL-6 may play the key role in the development of the coronary diseases through metabolic, procoagulatory and endothelial mechanisms (29). Vascular wall lesion results in the rupture of endothelium cells and the impact upon vascular smooth muscles cells. Endothelium and smooth muscle cells produce IL-6 which is found in human atherosclerosis lesions. Prognostic value of IL-6, C-reactive protein and other acute inflammation proteins in the future development of myocardial infarction and vascular diseases mortality is acknowledged by many researchers. The leading role in the development of chronic inflammation belongs to interferons (IFN) and interleukins, which are secreted by T-helpers and phagocytes, respectively. Interferon affects phagocytes, thus intensifying the expression of type-II MCH molecules, cytokine production. IL-1 in its turn activates T-helpers and their IFN-γ secretion. IFN-γ induces the expression of intercellular adhesion molecules which contribute to the accumulation of T-lymphocytes in different locations. Activated phagocytes at the same time cause numerous injuries of the nearby tissues, especially vessels (22, 28). Comparison of the obtained data on the prevalence of the patients with accompanying type II diabetes and obesity among the multiple coronary artery stenosis population and, at the same time, more apparent cytokine activity in this population suggests the influence of the risk factors on the inflammation processes in atherosclerosis.

Comparing proinflammatory cytokines IL-6, IL-8, INF-γ levels in obese patients with corresponding parameters in patients without accompanying risk factors, higher levels of the studied cytokines were identified. Antiinflammatory cytokine levels had the opposite tendency – IL-4 level decrease compared to the first group was noted. The results are provided in the Table 3.

Table 3. Cytokine levels in CHD patients by accompanying type II diabetes and obesity.

Parameter	Group 1 (CHD without risk factors)	Group 2 (CHD + obesity)	Group 3 (CHD + DM)	Group 4 (CHD + obesity + DM)
INF_{γ} pg/ml	13.43±2.11	18.74±3.42	47.06±2.43*	65.91±6.73*
IL-4 pg/ml	1.8±0.5	1.55±0.21	1.43±0.32	1.05±0.2*
IL-6 pg/ml	2.84±0.32	4.03 +0.41	7.83±0.34	18.14±0.61*
IL-8 pg/ml	51.04±3.21	64.63±4.8*	92.82±5.3*	145.49±11.2*
IL-10 pg/ml	1.61±0.34	1.6±0.23	1.34±0.23	0.71±0.24*
C-RP pg/ml	5.56±0.45	8.31±0.75*	8.62±0.64*	11.48±2.4*

* p< 0.05 versus control

Assessing individual cytokine activity values in obese patients other researchers revealed the adipose tissue activity in their production. During non-inflammatory states in humans IL-6 secretion by the adipose tissue was noted. Meanwhile, the omental adipose tissue secretes 3 times more IL-6 than subcutaneous adipose tissue (21). Dynamic studies in humans showed simultaneous postprandial increase of the IL-6 concentration and glucose and insulin levels in the interstitial fluid of the subcutaneous adipose tissue (29). IL-6 inhibits adipocyte activity and leads to an increase

of triglyceride secretion in rats (20, 27). In humans IL-6 results in elevated fasting free fatty acid (26) and triglyceride concentrations. Fatty acids in food modulate cytokine release. The production of IL-1, TNF-α and IL-6 by granulocytes and macrophage colony-stimulating factor by the peripheral mononuclear cells diminishes after the addition of polyunsaturated fatty acids to meals in women. On the contrary, high consumption of hydrogenised fats with meals elevates the TNF-α and IL-6 production. Therefore, meal fatty acid profile substantially affects cytokine production.

An important factor in the pathophysiology of the abdominal obesity is the leptin production which directly relates to the body fat distribution. Furthermore, although the first description of leptin dealt with its role in the modulation of food intake and energy inputs, at present there is evidence on its participation in the body immune processes. It's confirmed by leptin ability for enhancing cytokine production and macrophage phagocytosis (16). Indeed, leptin higher concentrations correlate with increased concentrations of inflammation markers in individuals with pathologic obesity (27).

The analysis of proinflammatory cytokines IL-6, IL-8 and INF-γ in CHD patients with the accompanying type II diabetes showed their substantial increase in comparison with the control group and excess over corresponding parameters in the obesity group. Antiinflammatory cytokines IL-4 and IL-10 levels were lower in the group of type II diabetes patients. In the group of the patients with two accompanying risk factors (obesity and type II diabetes) synergistic parameter changes were noted: increase of proinflammatory cytokines and decrease of antiinflammatory cytokines in comparison with 2nd and 3rd groups (Table 3).

Taking into account the abdominal obesity and carbohydrate metabolism disturbances to be the main criteria of the metabolic syndrome, underlying significant role of insulin resistance is being discussed. Observed changes of the studied cytokines can thus be directly attributed to this factor.

Insulin resistance and accompanying hyperinsulinemia is suggested to underlie accelerated atherogenesis in patients with type II diabetes. There is extended clinical evidence on the hyperinsulinemia to be an independent CHD development risk factor in diabetes-free individuals (1, 25). In recent years studies show the direct atherogenic effect of insulin upon vascular wall causing proliferation and migration of smooth muscle cells, lipids production in the smooth muscle cells and fibroblast proliferation (10, 14).

Insulin resistance and lipid metabolism disturbances can have certain parallel mechanism of action. In the acute phase of inflammation, cytokines cause reactions in the plasma and tissues leading to changes in lipoproteins. Induced hyperlipidemia can represent non-specific immune reaction which is in different ways aimed to harmful biological and chemical agent reduction and serves for the redistribution of the nutrient intake by the cells (15).

After the acute infections insulin resistance is identified even after the clinical convalescence when carbohydrate metabolism is still slightly diminished. Both IL-6 effect and acute infections are characterized with insulin-stimulating glucose assimilation deficiency in spite of normal oxidation of carbohydrates. A possibility of chronic or subclinical infection to simultaneously facilitate both IL-6 level increase and insulin resistance cannot be ruled out (7, 10). It should be mentioned, that higher leukocyte amount in peripheral blood was connected with insulin resistance. Further studies demonstrated that the amount of neutrophils and lymphocytes correlates positively with some components of the insulin resistance syndrome and the plasma insulin concentration specifically relates to the amount of lymphocytes and monocytes (23).

C-reactive protein (CRP) level was also higher in CHD patients with two risk factors. CRP represents simultaneously some acute-phase protein groups: mediators, transport proteins and immunoregulators. This protein was found to regulate the immunocompetent cell functions. CRP activates monocytes, regulates neutrophil function through their potential cytotoxicity controlling, increases phagocytosis of neutrophil debris. In early stages of inflammation CRP acts as a component of macrophage activation mechanism inducing chemotaxis and superoxide production. CRP performs protective function by blocking inflammation mediator production through binding the membrane phospholipids. Higher CRP levels revealed in patients with accompanying obesity and type II diabetes confirm the inflammation processes hyperactivity in coronary patients in the presence of risk factors. At the same time, CRP level increase in cardiovascular patients is often associated with the development of complications: myocardial infarction, CHD destabilization, lethal outcome. Inflammation course seems to determine the prognosis to a large extent.

CONCLUSIONS:

1. Direct relationship of proinflammatory cytokines IFN-γ, IL-6 and IL-8 levels and an amount of stenosed coronary arteries was revealed in CHD patients, suggesting the active role of inflammation factors in the atherosclerosis development.

2. Inverse relationship of the antiinflammatory cytokines IL-4 and IL-10 levels with a stenosed coronary arteries amount is noted in CHD patients.

3. In CHD patients with accompanying obesity and type II diabetes more coronary arteries have atherosclerotic lesions compared to patients free of risk factors.

4. CHD patients with accompanying obesity have higher values of proinflammatory and lesser values of antiinflammatory cytokines which can indicate pathogenetical influence of the obesity on the atherosclerosis development through the inflammation mechanisms.

5. The most evident changes of the cytokine activity are noted in patients with two risk factors being metabolic syndrome criteria. This finding may result from insulin resistance and reflect its impact on the inflammation and atherosclerosis development.

References:

1. Ametov A. S. Insulin secretion and insulin resistance: two sides of a medal. Problemy Endocrinologii, 2002,48,33.
2. Ametov A. S., Smirnova O. M., Shestakova M. V. Beta-cell: normal and pathological insulin secretion. Moscow,2005.
3. Balobolkin M. I. Diabetology. Moscow, 2000.
4. Golikov P. P., Golikov A. P. Role of nitric oxide in pathology. TOP-meditsina, 1999, 5, 24–27.
5. «CHD: inflammation and lipids», TOP-Meditsina, 2000, 9, 3.
6. Irgashev S. B. Peculiarities of protein synthesis in the heart and liver in experimental myocardial infarction. In: Topical problems of cardiology. Tashkent, 1980, 34–35.
7. Lipson V. V. Pharmacological correction of insulin resistance. Khimichesky farmakologichesky Zhurnal, 1999, 33, 7.
8. Mayansky A. N. Modern evolution of I. I. Mechnikov's idea of intravascular inflammation. Immunologia, 1995, 4, 8-14.
9. Mazovetsky A. G., Belikov V. K. Diabetes mellitus. M. 1987.
10. Nazarov P. G. Reactants of the acute inflammation phase. SPb, Nauka,2001.
11. Orlova N. V. Role of the acute phase proteins and immunological parameters in myocardial infarction diagnostics and prognosis.Dissertation of the Candidate of Medical Sciences, 1989.
12. Potapnev M. P. Significance of the immune regulatory cytokines in the formation of the inflammatory reaction. Zdravookhranenie,1996, 11,50-54.
13. Terekhova-Uvarova N. A. Autoallergic reactions of the myocardium. 1982.
14. Chazov I. E., Mychka V. B. Metabolic syndrome and the arterial hypertension.Arterialnaya Guipertenzia, 2002, 8, 1.
15. Chopyak V. V. Cytokines and their role in the inflammation processes. Meditsynskiye
Novosti,1997,9.
16. Chan J.C., Cheung J.C., Stehouwer C.O. et al. The central roles of obesity-associated dyslipidiamia, endothelial activation and cytokines in the metabolic syndrome – an analysis by structural equation modeling. Int. J. Obes. Relat. Metab. Disord.,2002, 26, 994-1008.
17. Facchini F., Hollenbeck C.B., Chen Y.N.et al.Demonstration of a relationship between white blood cell count, insulin resistance, and several risk factors for coronary heart disease in women.J. Intern. Med.,1992,232, 267-272.
18. Femandez-Real J.M., Lainez B., Vendrell J.et al.Shedding of tumor necrosis factor- α receptors, blood pressure and insulin sensitivity in type 2 diabetes mellitus. Am. J. Physiol. Endocrinol. Metab.,2002, 282, 952-959.
19. Greenberg A.S., Nordan R.P., McIntosh J.et. al. Interleukin-6 reduces lipoprotein lipase activity in adipose tissues ofmice in vivo and in 3T3-LI adipocytes: a possible role for interleukin-6 in cancer cachexia.Cancer. Res. 1992,52, 4113- 4116.
20. Grunfeld C., Feingold K.R.Regulation of lipid metabolism by cytokines during host defense. Nutrition, 1996, 12 (Suppl. I), 524-526.
21. Harris T.B., Ferrucci L., Tracy R.P. et al.Associations of elevated interleukin-6 and C-reactive protein levels with morta1ity in the elderly.Am. J. Med.,1999, 106, 506-512.
22. Jaffe E. A. Inflamation. Basic. Principles and Clinical Correlates.J .I.Gallian,.I M. Goldstein, R. Snyderman eds. New York, 1988,9,559-576.
23. Kirchgessner T.G., Uysal K.T., Wiesbrock S.M. et al.Tumor necrosis factor-α contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. J. Clin. Invest., 1997, 100, 2777-2782.
24. Leinonen E., Hurt-Camejo E., Wiklund O. et al. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2
diabetes. Atherosclerosis,2003, 166, 387-394.
25. Lopes-Virella M., Virella G.Cytokines, modified lipoproteins, and arteriosclerosis in diabetes. Diabetes, 1996,45.(suppl. 3), 540-544.
26. Nophar Y., Kemper O., Brakebusch C.et al.Soluble forms of tumor necrosis factors (TNP-RБ). The cDNA for the type 1 TNF-R, cloned using amino acid sequence data of its soluble form, encodes both the cell surface and a soluble form of the receptor.EMBO J., 1990, 9, 3269-3278.
27. Sarraf P., Frederich R.C., Tumer E.M. et al.Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J. Exp. Med.,1997, 185, 171-175.
28. Wilson A.G., Symons J.A., Mc.Dowell T.L. et al.Effects of a polymorphism in the human tumour necrosis factor a promoter on transcriptional activation. Proc. Natl. Acad. Sci USA , 1997, 94, 3195-3199.
29. Woods A., Brull D.J., Humphries S.E., Montgomery H.E.Genetics of inflammation and risk of coronary artery disease: the central role of interleukin 6.Eur. Heart. J. 2000, 21, 1574-1583.
30. Zissel G.,Schlaak J.,Schlaak M., Mueller-Quernheim J.Regulation of cytokine release by alveolar macrophages treated with interleukin-4, interleukin-10, or transforming growth factor beta. Eur. CytokineNetw.,1996, 7,1,59-66.

Angiographic Diagnosis and Endovascular Treatment of Gastrointestinal Bleeding

A.Krajina[1], M. Lojik, J. Raupach, V. Chovanec, S. Rejchrt, P. Vyroubal.
Department of Radiology and Medicine, Teaching Hospital Hradec Kralove, Charles University in Prague.

Acute gastrointestinal (GI) bleeding encompasses a wide spectrum of symptoms ranging from scant hematochezia, which can safely be evaluated in the outpatient setting, to massive hemorrhage resulting in shock. There are three possible categories of patients who can be referred for visceral angiography, when patients with minor bleeding are excluded.

The first category is comprised of patients with chronic intermittent bleeding resulting in sideropenic anemia. Angiography is indicated to reveal vascular pathology but never extravazation. These patients have the greatest benefit from endoscopy alone.

The second category includes patients with severe, life threatening bleeding which suddenly stops and the patient becomes hemodynamically stable and then occurs another episode of hemorrhage. The intensity of bleeding can vary even from minute to minute. Angiography in these patients should be targeted by positive nuclear medicine scanning or by repeating identical angiograms within a few minutes. In extreme cases provocative bleeding studies with intraarterial vasodilators, heparin or thrombolytics can be useful to identify the site of bleeding and decrease the number of negative angiograms.

The third category comprises patients with continual active bleeding. These patients become shocked very soon and are best managed by urgent angiography with transcatheter bleeding control.

A clinical distinction must be made between upper GI and lower GI bleeding. Up to 90 % of all these severe GI bleedings are from a lesion proximal to the ligament of Treitz which is borderline between upper and lower GI bleeding. Endoscopy is crucial both for excluding bleeding from gastroesphageal varices, and for diagnosis of transpapillary bleeding (hemobilia and hemosuccus pancreaticus).

The causes of bleeding from the upper GI tract referred for endovascular treatment were duodenal ulcer (51 %), gastric ulcer (12 %), postsurgical bleeding (11 %), tumor (11 %), inflammatory condition (8 %), gastritis (3 %), postendoscopic sphincterotomy (3 %) and trauma (3 %). This group of patients with adequate treatment had mortality rate as high as 25 to 30 %. Reports of angiographic accuracy have ranged from 60 % to 86 %.

[1]Prof. Antonin Krajina M.D.
Dept. Radiology University Hospital
500 05, Hradec Kralove, Czech Republic
Email: krajina@fnhk.cz
Manuscript received on February 09, 2007
Accepted for publication on August 27, 2007

Patients with lower GI bleeding tend to be more elderly than those with gastric and duodenal lesions. Angiographic accuracy is only 40-48 %. Localization of a bleeding site is of paramount importance, because limiting the extent of emergency bowel resection can drop operative mortality in cases when bleeding control cannot be performed by embolization. Diverticular disease is found in 2/3 of patients older than 80 years. Diverticula are formed at the site where vasa recta penetrates the muscular wall of the colon. Bleeding occurs from ruptured vasa recta at the lesion neck or when fecalith erodes a vessel over the apex of diverticulum. While diverticula are found in the left colon more frequently, right-sided diverticula appear to have a higher incidence of bleeding.

So called angiodysplasia is characterized by multiple arteriovenous shunts and predominates in the right colon and cecum. There is high tendency for recurrent hemorrhage. Both benign adenomatous polyps and adenocarcinoma may cause life-threatening bleeding. The colonoscopy is strictly recommended even after successful transcatheter treatment. Iatrogenic bleeding after colonoscopic polypectomy may also occur and present even in up to 14 days after the intervention.

History

For extravasation to be detectable, bleeding must exceed 0.5 ml/min. Since its introduction in 1963, selective arteriography has transformed from purely diagnostic technique to a therapeutic method of bleeding control. First the selective arterial infusion of vasoconstringent agents through the same catheter used to identify the bleeding site and then transcatheter embolization was utilized to stop bleeding in the upper GI tract. Embolisation proximal to the mesenteric border of the colon using 4-5F catheters led to the bowel infarction in up to 33 %.

Finally the advent of the microcatheters led to renewed interest in embolization in the lower GI tract in the 1990's.

Technique of the superselective catheterization has increased possibilites of targeted embolization. While it potentially increased reliability of selective arterial occlusion by closer embolic agent delivery to the bleeding site, more reliable but also more aggressive embolic agents (nonresorbable particles, acrylic glue) could not do so much of collateral ischemia when they were delivered much more selectively.

Embolotherapy is now considered by many interventional radiologists a primary option for treating upper but also lower GI bleeding. Embolotherapy

has several advantages over local vasoconstrinctive therapy, including quicker completion of therapy and decreased likelihood of systemic complications. Superselective embolotherapy is more technicaly demanding and probably more expensive because of used microcatheters, microwires and dedicated embolic agents.

Angiographic diagnosis

The use of the meticulous technique is crucial to reveal extravasation in angiographic studies for gastrointestinal bleeding. Opacification of the celiac trunk and superior mesenteric artery followed by selective arteriography of the left gastric, gastroduodenal and splenic arteries is necessary for evaluation of upper GI bleeding. In patients with lower GI bleeding the inferior mesenteric artery should be injected first so that the rectosigmoid can be seen free of the bladder. This injection should be done in a slight right anterior oblique projection to separate the loops of the sigmoid colon. The operator must be sure that the whole anatomical area has been properly screened. Two injections with different centralization in both superior and inferior mesenteric arteries are usually required in adults when 40 cm image intensifier is used for digital subtraction angiography (DSA). Large volume of injected contrast agent and long filming is mandatory to increase chance of extravasation detection.

The butylscopolamine (20 mg i.v.) or glucagon (0.2-0.5 mg i.v.) may be administered after endoscopy when intensive bowel peristalsis interferes with digital subtraction images. In patients with artificial respiration temporary breathing disconnection may be helpful to eliminate respiratory artefacts on digital subtraction angiograms. When extravasation of contrast medium is demonstrated at angiography, embolic therapy is performed as selectively as possible, with microcatheter coaxially inserted into a 5F catheter.

The use of carbon dioxide in diagnosis of extravasation

CO_2 gas reduces the attenuation of the blood vessel and its low viscosity allows it to pass through tiny arteries and small arterial tears. When CO_2 enters the bowel it rapidly expands giving an angiographic sign of enlarging bubble. Even nonselective CO_2 angiography can reveal extravasation which is not seen on conventional angiography.

Image quality of CO_2 angiograms is limited due to the low contrast of CO_2 gas and nonbleeding vascular abnormalities cannot be detected. Therefore CO_2 angiography should be used as a complementary angiographic technique to the conventional angiography.

Hand injection of CO_2 is very easy and using 60 ml syringe even large vessels can be opacified. CO_2 must never be delivered direct from the high pressure cylinder as potentially dangerous volume could be injected. The syringe should be filled through pressure reducing valve in a passive way and not using aspiration to avoid air contamination. The filled syringe is disconnected from the cylinder and simply attached to the diagnostic catheter. The catheter is purged of saline prior to injection. This manoeuvre ensures smooth rapid injection rather than explosive delivery which breaks up the gas bolus.

The angiographer must be aware of potential hazards of CO_2 angiography such as neurotoxicity of CO_2 and transient ischemia. The latter is caused by trapped CO_2 gas interfering with normal blood flow. This, so called vapor lock, has been reported in the mesenteric arteries. Its clinical presentation was self-flimiting hemorrhagic diarrhoea.

Pitfalls, tips and tricks in the angiographic diagnosis of bleeding

The intermittent course of bleeding can result in a negative angiographic examination if during the injection the bleeding has decreased or ceased. We usually repeat injection in 10 minutes, or inject vasodilatators intraarterially, if we are sure to evaluate the proper vessel.

Endoscopy-directed blind embolization could be successfull when technique of microcathers is used. There was found no difference of clinical outcome between upper GI bleeders who underwent so called blind embolization and those who underwent embolization after a bleeding site had been demonstrated angiographically. Angiographic examination of the stomach and duodenum should also be carried out if a negative superior and inferior mesenteric angiogram is obtained in a patient presenting with lower GI bleeding. A prepyloric ulcer that is actively bleeding can mimic a duodenal location of extravasation as a duodenal bleeding from the inferior pancreaticoduodenal artery may seem to originate in the transverse colon. This problems can be resolved by repeating the injection in a right anterior oblique position.

The normal parenchymal blushes can be confused with extravasation. They can be the superimposed left adrenal gland on the gastric fundus, and corpora cavernosa on the rectum. The hyperemic appearance of the gastric wall can be caused by gastritis which is frequently present in patients bleeding from other causes such as duodenal ulcers or Mallory-Weiss tears. We should always look for bleeding from the colonic diverticle even if we have found angiodysplasia at first.

The bleeding segment of the small bowel can be opacified by methylene blue via selectively placed microcatheter into the bleeding superior mesenteric branch. The pathologic segment of the small bowel can be easily detected after the laparotomy.

Embolization

Possible mechanisms of embolization in a bleeding vessel includes decreased artrial perfusion pressure to the bleeding site, local vasospasm the patient's ability to form clot and effect of delivered embolic agent. The microcatheter-microwire locally induced vasospasm or local infusion of platelets were reported to be effective in selected patients to stop GI bleeding even without embolization. Generally,

correction of preexisting coagulopathy is the most important factor for a durable outcome.

The angiogram documenting extravasation is used as a road-map to navigate a 3F microcatheter which is inserted coaxially through the 5F diagnostic catheter. This occasionally requires oblique views, more selective and stable position of the guiding catheter and use of zoom-technique for angiography.

Selection of the embolic agent depends on location of a bleeding site (upper or lower GI bleeding), selectivity of a microcatheter position in relation to bleeding site and also on personal experience of the angiographer. The n-butyl-2-cyanoacrylate (Histoacryl Blue, Braun, Germany) is the most efficient embolic agent used in large upper GI bleeding. Its injection requires special skills because its dilution with oily contrast medium (Lipiodol Ultrafluide, Guerbet, France) changes dramatically time of its solidifying in bloodstream. Ideally the glue passes the bleeding site, gets outside of the artery and fills also the proximal part of the bleeding vessel. The microcatheter is removed immediately after injection of the glue. A new microcatheter is necessary if extravasation persists.

Embolization with microcoils and polyvinylalcohol microparticles is performed step by step and the microcatheter can be used for selective injections to follow bleeding range. This technique is utilized in the lower GI tract since complete devascularization is undesirable in the bowel. The microcatheter is ideally placed into the vasa rectae or to the border of the colon (the marginal artery) to control bleeding and limit risk of ischemia. The used microparticles of the PVA should be larger than 250 μm. The microcoils are in size ranged from 2 to 20 mm. Embolization should be continued until arterial extravasation is arrested. The completion angiogram performed through the guiding catheter must be carefully assessed to exclude filling of bleeding site via collaterals.

CO_2 extravasation can persists after sufficient embolization therefore iodinated contrast medium is preferred. Repeat angiogram should be performed 10 to 15 min after embolization to confirm stable occlusion and exclude extravasation..

Results

Embolotherapy using microcatheters in patients with upper GI bleeding from peptic ulcers is used when endoscopic therapy failed. Embolization brings 29 % risk of recurrent bleeding, 16 % rate of additional surgery and 25,8 % risk of death in a group of patients with mean age 75 years, with higher (i.e. 67 %) incidence of heart disease and previous anticoagulation medication in 25 % of cases. These numbers are well comparable with surgical results despite the surgical patients were significantly younger (average difference 12 years), had lower incidence of heart disease and lower rate of anticoagulation treatment. Preexisting coagulopathy and the use of coils as the only embolic agent were found to be associated with a higher risk of rebleeding.

In patients with persistent extravasation at superior mesenteric arteriography after embolization of the gastroduodenal artery synchronous embolization of the inferior pancreaticoduodenal artery can be an effective therapy. This procedure has the risk of pancreatic and duodenal necrosis.

Embolotherapy in lower GI bleeding is not used so frequently as in upper GI bleeding. This is because of ten times lower frequency of bleeding in comparison to the upper part of GI tract. Second reason is more difficult microcatheter navigation in the both mesenteric arteries which requires certain level of skills and last reason is risk of the bowel ischemia. More than 170 patients treated by the embolization technique described above were reviewed in literature. This metaanalysis revealed clinical success rate ranging from 76 % to 91 %, and risk of major ischemic complications ranged from 0 % to 6 % when microcoils and or microparticles were used. The only exception was 22 % rate of major bowel ischemia when liquid embolic agent was used for embolization. Diverticular bleeding responds best to embolization. Bleeding from angiodysplasia and bleeding from the cecum can have reported rebleeding rate up to 75 %. High rate of rebleeding after cecal embolization is explained by higher rate of angiodysplasia and rich collateral network.

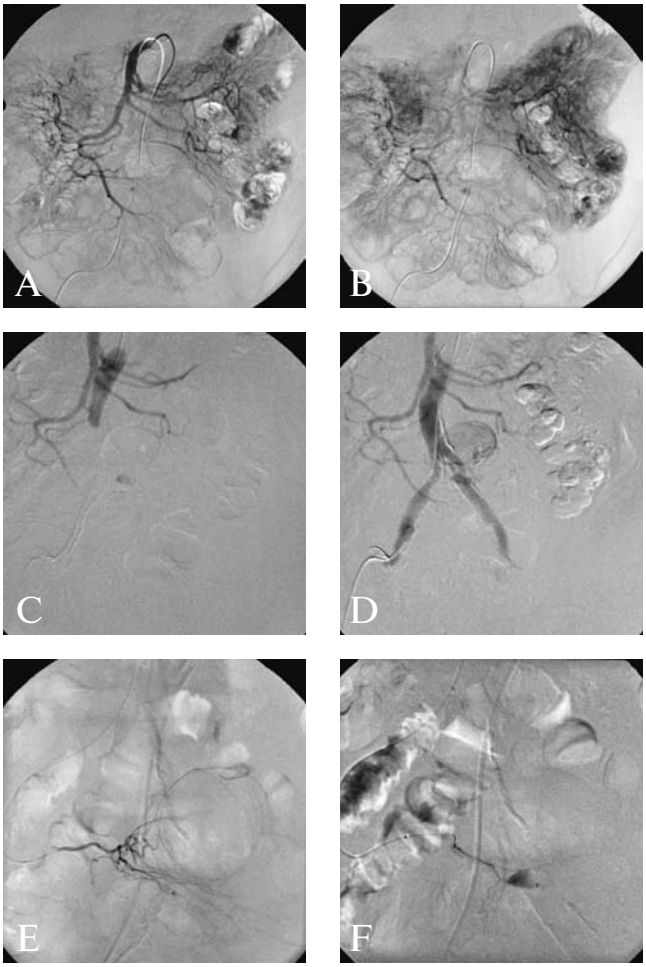

Figure. 1. 75-year old male with lower GI bleeding. A, B. Superior mesenteric angiogram revealed extravasation. C, D. Extravasation was confirmed by CO2 angiography. E. The bleeding artery was catheterized by a microcatheter. F. The microcatheter injection revealed extravasation and bleeding was stopped by embolization using 300 μm microparticles of the polyvinylalcohol.

Conclusion

Coaxial microcatheter embolization has proven to have its stable place in therapeutic algorithm in the therapy of GI bleeding. Embolization is now considered a primary option for this treatment. Infusion of vasoconstrictors (i.e. vasopressin) is still preferable for diffusely bleeding lesions and cases in which superselective catheterization is not possible. Its main disadvantage over endoscopy and surgery is limited availability outside of centers. Embolotherapy and endoscopic treatment of arterial GI bleeding appear to be complementary. Patients with heavy arterial bleeding should be first evaluated with angiography with the intent to be embolized while patients with intermittent bleeding should undergo endoscopy first, and in case of lower GI bleeding with previous bowel preparation.

References:

1. Aina R., Oliva V.L., Therasse E., et al. Arterial embolotherapy for upper gastrointestinal hemorrhage: outcome assessment. J. Vasc. Interv. Radiol., 2001, 12, 195-200.
2. Bell S.D., Lau K.Y., Sniderman K.W. Synchronous embolization of the gastroduodenal artery and the inferior pancreaticoduodenal artery in patients with massive duodenal hemorrhage. J. Vasc. Interv. Radiol., 1995, 6, 531-536.
3. Bloomfeld R.S., Rockey D.C. Diagnosis and management of lower gastrointestinal bleeding. Current Opinion in Gastroenterology 2000, 16, 89-97.
4. Bui J.T., West D.L., Pai R., Owens C.H.A. Use of a hydrogel-coated self-expandable coil to salvage a failed transcatheter embolization of a mesenteric hemorrhage. Cardiovasc. Intervent. Radiol., 2006, 29, 1121-1124.
5. Darcy M. Treatment of lower gastrointestinal bleeding: vasopressin infusion versus embolization. J. Vasc. Interv. Radiol., 2003, 14, 535-543.
6. Defreyne L., Vanlangenhove P., De Vos M. et al. Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage. Radiology 2001, 218, 739-748.
7. d´Othée B.J., Surapaneni P., Rabkin D., et al. Microcoil embolization for acute lower gastrointestinal bleeding. Cardiovasc. Intervent. Radiol., 2006, 29, 49-58.
8. Funaki B. Microcatheter embolization of lower gastrointestinal hemorrhage: an old idea whose time has come. Cardiovasc. Intervent. Radiol., 2004, 27, 591-599.
9. Karkos C.H.D., Vlachou P.A., Hayes P.D. et al. Temporary endovascular control of a bleeding aortoenteric fistula by transcatheter coil embolization. J. Vasc. Interv. Radiol., 2005, 16, 867-871.
10. Kobak J., Gandras E.J., Fleury L. et al. Embolization for treatment of gastrointestinal hemorrhage secondary to recurrent renal cell carcinoma. Cardiovasc. Intervent. Radiol., 2006, 29, 1117-1120.
11. Kuo W.T., Lee D.E., Saad W.E.A.,et al. Superselective microcoil embolization for the treatment of lower gastrointestinal hemorrhage. J. Vasc. Interv. Radiol., 2003, 14, 1503-1509.
12. Lang E.V., Picus D., Marx M.V., Hicks M.E. Massive arterial hemorrhage from the stomach and lower esophagus: impact of embolotherapy on survival. Radiology, 1990, 177, 249-252.
13. Lang E.V., Picus D., Marx M.V. et al. Massive upper gastrointestinal hemorrhage with normal findings on arteriography: value of prophylactic embolization of the left gastric artery. Am. J. Roentgenol., 1992, 158, 547-549.
14. Ripoll C., Banares R., Beceiro I. et al. Comparison of trancatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. J. Vasc. Interv. Radiol., 2004, 15, 447-450.
15. Rösch J., Dotter C.H.T., Brown M.J. Selective arterial embolization. A new method for control of acute gastrointestinal bleeding. Radiology, 1972, 102, 303-306.
16. Ryan J.M., Key S.M., Dumbleton S.A., Smith T.P. Nonlocalized lower gastrointestinal bleeding: provocative bleeding sutdies with intraarterial tPA, Heparin, and Tolazoline. J. Vasc. Interv. Radiol., 2001, 12, 1273-1277.
17. Schenker M.P., Duszak R., Jr., Soulen M.C. et al. Upper gastrointestinal hemorrhage and transcatheter embolotherapy: clinical and technical factors impacting success and survival. J. Vasc. Interv. Radiol., 2001, 12, 1263-1271.
18. Sos T.A., Lee J.G., Wixson D., Sniderman K.W. Intermittent bleeding from minute to minute in acute massive gastrointestinal hemorrhage: arteriographic demonstration. Am. J. Roentgenol., 1978, 131, 1015-1017.
19. Spinosa D.J., Matsumoto A.H., Angle J.F., et al. Transient mesenteric ischemia: a complication of carbon dioxide angiography. J. Vasc. Interv. Radiol., 1998, 9, 561-564.
20. Yoon W., Jeong Y.Y., Shin S.S. et al. Acute massive gastrointestinal bleeding: detection and localization with arterial phase multi-detector row helical CT. Radiology, 2006, 239, 160-167.

The Role of Hereditary Factors in Left Ventricular Myocardial Hypertrophy in Highly Skilled Athletes

E.V. Linde[1], I.I. Akhmetov[2], I.V. Astratenkova[2], A.G. Fedotova[3]
[1]Russian State University of Physical Training, Sports and Tourism.
[2] St.-Petersburg Research Institute of Physical Training
[3]Department of basic medicine, Moscow State University

Aspects of genetically determined physiological limits of left ventricular hypertrophy in highly skilled athletes are most important in today's sports medicine. Intensification of training and competitive process, on the one hand, and genetically determined limits of oxygen supply system functional reserve on the other hand, both cause decompensation of functions, which include left ventricular hypertrophy acting as a risk marker of cardiovascular events, early atherosclerosis, increased mortality rate (2-4, 13, 36, 41, 44).

The term "remodeling" (meaning the process of structural and functional changes of the heart in response to pressure or volume overload) is used to designate the structural and functional features of the "athlete's heart" (17, 33-35).

In sports medicine the term "physiological remodeling" is used to describe cardiovascular changes resulting in effective and energy-saving supply of the regular training and competitive stress (33).

The term "pathological remodeling" is used to describe the morphological and functional changes occurring due to excessive physical and psychological sports exercise (34-35). Approaches to differentiation of the "athlete's heart" pathological transformation are ambiguous (8-12). B. Maron, one of the leading specialists in cardiac changes caused by sports, indicates that this complex condition is characterized by clinical and functional polymorphism, diastolic dysfunction and, in some instances, is hereditary in nature (34). One of the symptoms of pathological remodeling is the non-effective myocardial hypertrophy accompanied by a decrease of physical performance of athletes (20, 25, 31-32).

It has been established, that the energy-saving mode of action of the athlete's heart is associated to the increased activity of sympathoadrenal and adenylate cyclase systems, as well as the increased number of adrenergic fibers per myocardial mass unit (8). As a result, the myocardial adrenoreactivity and the possibility of its acute adaptation become higher. Simultaneously, there is an increase in the number of H-chains in myosin heads, which carry ATPase activity causing increased speed and amplitude of heart contraction (41). This is followed by an increase of calcium channels activity and, as a result, of the speed and the extent of diastolic relaxation (42). These myocardial changes are paralleled by an increase of the coronary capillaries, myoglobin concentration and the activity of mitochondrial complex enzymes responsible for oxidation of the fatty acids (9-10). Such changes lead to the increased resistance of heart to fatigue and hypoxemia (21). Due to the increased number of mitochondria the growth of body aerobic power is accompanied by higher potential of muscles to utilize pyruvate, which is produced in large volumes during exercise. This prevents the increase of serum lactate in adapted persons (1, 10, 12, 21). Therefore, an optimal variant of myocardial adaptation develops in subjects with highest power of oxidative ATP resynthesis and is characterized by the combination of higher functional results of adaptation with moderate cellular hypertrophy, i.e. at the expense of minimal structural changes.

An important factor underlying the pathological myocardial remodeling in athletes is the hormone regulation rearrangement similar to stress reaction with increased activity of the renin-angiotensin-aldosterone system (RAAS) (18-19). There's an opinion, that hemodynamic stress caused by RAAS hyperactivation facilitates the proliferation of myocardial connective-tissue elements (type I collagen) followed by decreased elasticity (46). Perhaps, relaxation disorders accompanied by left ventricular hypertension underlie the ineffective hypertrophy and pathological dilatation of the athlete's heart and the decrease of its functional activity. On the other hand, the basis for ineffective myocardial hypertrophy in athletes can be the change of its energy metabolism accompanied by enhanced glucose utilization and decreased oxidation of fatty acids due to lower level of mRNA encoding their oxidative enzymes. An experimental demonstration of this fact was the development of myocardial hypertrophy in model animals with genetically determined defect in mitochondrial enzymes structure and the resulting inhibition of fatty acids metabolization (21).

Among the genetic determinants directly affecting the morphological and functional characteristics of the cardiovascular system and, possibly, participating in the development of ineffective hypertrophy of the athlete's heart, the RAAS (rennin-angiotensin-aldosteron system) and PPAR (peroxis α prolifer-

[1]Linde E.V.
105122, Moscow, Sirenevy blvd., 4
Russian State University of Physical Culture, Sport and Tourism.
Tel. + 7(495) 166 76 81
Mobile +7 916 319 27 96
e-mail: elena.linde@gmail.ru
Manuscript received on Fenruary 25, 2007
Accepted for publication on August 26, 2007.

ators-activated receptors) genes are of particular interest (6, 9-10,14-16, 22-24, 39-40).

One of the key RAAS enzymes – the angiotensin-converting enzyme (ACE) – catalyzes the formation of angiotensin II, the major vasoconstrictor peptide, and degradation of bradykinin, an important vasodilating factors. ACE is encoded by the ACE gene located in 17q23 locus. Analysis of the ACE gene polymorphism has showed that the presence or absence of the insertion composed of 287 nucleotide pairs in intron 16 substantially changes the enzyme activity. The presence of this insertion in ACE genes (allele I) decreases the enzyme activity, whereas the absence of the insertion (allele D) increases the enzyme activity (26, 28, 39). The increased activity of angiotensin II results in inadequate rise of the peripheral vascular resistance in response to exercise, thus causing the increase of left ventricular mass. According to the distribution of I and D alleles there exist three genetic polymorphism variants: II, ID and DD. The association between I/D ACE polymorphism and the development of left ventricular hypertrophy was convincingly demonstrated in a study by Montgomery group. Following 10 weeks of power training the left ventricular mass the subjects increased by 20.0 g in subjects with II genotype, by 38.5 g in subjects with ID genotype and by 42.3 g in subjects with DD genotype as confirmed by echocardiography (37).

The PPARα gene encoding the peroxis α proliferators-activated receptor (PPARα) is located in human chromosome 22. It is a regulator gene modulating the activity of several dozens of genes involved in the fatty acids and glucose metabolism and expressed in tissues with increased catabolism of fat – the slow-acting muscular fibers, liver, heart and brown adipose tissue; interestingly, the expression of PPARα in muscular tissues is 7 times that in fat tissue (12). In case of low expression the tissue potential to effective β-oxidation of fatty acids is decreased and the metabolism is switched to glycolytic energy synthesis. The G/C polymorphism of PPARα intron 7 is known to be related to the prevalence of metabolism of fatty acids and glucose (16). In G allele carriers the fatty acids oxidation is much more intense, than in C allele carriers. The insufficient oxidation of fatty acids in the latter is compensated by an increased glucose utilization. Jamshidi Y. et al. (2002) demonstrated the effect of PPARα intron 7 G/C polymorphism on the left ventricular mass changes during exercise and in response to exercise. It was established, that the left ventricular myocardial mass in volunteers after 10-week intensive training program increased by 8.6±1.2 g ($P<0.0001$). This increase significantly correlated with intron 7 genotypes ($P=0.009$); for GG genotype the increase was 6.7±1.5 g, significantly higher increase was observed in GC heterozygotes (11.8±1.9 g) and 3 times higher change – in CC homozygotes (19.4±4.2 г). Subjects with II-GG genotype combination showed least increase of the LV myocardial mass, whereas carriers of DD-CC combination had the highest increase (16).

A study of the above molecular and genetic markers of myocardial hypertrophy is crucial for high-level sports. Multicenter population studies have provided convincing evidence, that the left ventricular myocardial hypertrophy is an independent risk factor of cardiovascular events. Severe myocardial hypertrophy was most common (26 to 72% of cases) in athletes practicing cyclic sports predominantly developing endurance (3, 25, 27, 33-34).

Purpose of our study was to evaluate the morphological and functional characteristics of myocardium in athletes practicing cyclic sports with predominant development of endurance at various stages of their career and comparison of these findings to ACE and PPARA genes polymorphism, as well as the basic parameters of energy metabolism.

The genetic polymorphism study enrolled 79 athletes: 51 boat racers (23 girls and 28 young men) and 28 all-rounder skaters (12 girls and 16 young men). In 74 of these (49 boat racers and 25 all-round skaters) we compared the genetic polymorphism data to the morphological and functional characteristics of the myocardium. All athletes were members of the national team or the primary reserve team in boat racing and skating, had won (or were awarded) in many Russian and international competitions and had high professional grades: master of sports (MS), international master of sports (IMS) and honored master of sports (HMS). For sample comparison we used polymorphism data in control group composed of 842 subjects (not athletes, 290 men, 552 women, aged 16±2.3 years). To compare the functional testing results we used data acquired from 16 students of the Russian State University of Physical Training (aged 20±2.1 years), who didn't have continuous training in sports.

During the study all athletes were apparently healthy (see Table 1).

Table 1. Summary of the athletes study group.

Grade	Skating (M -57%; W- 43%)			Boat racing (M 58%; W- 42%)		
	Age (M±SD)	Total experience (M±SD)	Total experience within the grade (M±SD)	Age (M±SD)	Total experience (M±SD)	Total experience within the grade (M±SD)
MSC	16±4.1	2.0±0.5	2.0±0	18.3±0.5	3.9±0.5	2.5±0.5
MS	18±5.8	5.7±1.0	2.2±1.2	21.0±1.1	7.0±1.1	3.1±1.0
IMS	23.4±4.5	13.8±2.1	5.1±1.3	23.0±3.6	9.0±2.1	1.2±1.1
HMS	30±2.6	19.5±2.0	6.5±1.0	29.2±2.0	15.3±2.1	4.3±0.5

Study method: Echocardiographic assessment of the morphology and function of myocardial remodeling was performed using Aloka-3500 ultrasonography unit with phase 3.5 MHz probe. The myocardium, valves and subvalvular structures were assessed in M- and B-modes. Basic measurements were performed in M-mode along the longitudinal image of the left ventricle acquired with parasternal probe position. Electrocardiographic assessment of the myocardial function was performed using Alton-03 12-lead digital ECG unit with automatic measurement

of basic cardiac cycle values. The assessment of maximum cardiorespiratory system potential (Vmax, MOC, ПАНО???) in athletes was performed in muscular physiology lab of the State Research Center of the Medical and Biological Problems Institute and headed by O.L. Vinogradova, doctor of biological sciences. Testing of skaters was performed using stepwise stress increase "to the maximum" on Ergoline 900 bicycle ergometer (USA. The first step was 180 Wt for young men and 120 Wt for girls, the power was increased every 2 minutes by 30 Wt, the number of rotations was 60-70 rpm. Values describing the aerobic endurance of boat racers were obtained using stepwise stress increase on Concept II paddle ergometer between 150 Wt and 400 Wt power, step height 50 Wt, 3-min work cycle with 20 s rest. Serum lactate was measured electrochemically (Super GL easy, Germany), capillary blood test was performed at the end of each step. During the test blood gases and HR were continuously assessed (MetaMax 3B gas analyzer, Germany). Biological material sampling for further genetic screening was performed using oral lavage with normal saline to obtain buccal cells or scraping the cells with a disposable probe. The DNA was isolated using alkaline extraction or sorbent method. Genetic polymorphism was assessed with polymerase chain reaction (PCR) according to procedures described earlier (16, 39).

Statistical analysis was performed using general statistic methods. The chi-square and t-tests were used to detect significant difference between the groups. The following abbreviations were used: IVSD (cm) diastolic thickness of the interventricular septum; LVIDd (cm) – diastolic internal LV diameter; LVPWd (cm) – posterior LV wall thickness; LVIDs (cm) – systolic internal LV diameter; EDV (ml) – end-diastolic LV volume; ESV (ml) – end-systolic LV volume; SV (ml) – stroke volume; CO (l/m) – circulation minute volume; LVM/m2 (г/m2) –LV myocardium mass index; P – P-wave duration; PQ – PQ-interval duration; QRS – QRS interval duration; QT – QT interval duration; Wmax – maximum power achieved during the test; MOC/kg – ratio between the maximum oxygen consumption to the athlete's body mass.

1. Measurement of morphological and functional myocardial characteristics and maximum aerobic performance in athletes of various grades.

Mean values of the basic cardiac cycle intervals in skilled (MSC, MS) and highly skilled (IMS, HMS) skaters and boat racers didn't differ from the mean values in general population. Slightly higher values were obtained in subgroups of highly skilled athletes (see Table 2).

The left ventricular myocardium mass index (LVM/m^2), the interventricular septum thickness (IVSD) and LV posterior wall thickness (LVPWd) were above the control in all study groups. These findings coincide with the opinion of the leading sports cardiologists on the development of work hypertrophy during physiological remodeling of the myocardium in athletes (3, 30, 33-34). Comparison of the echocardiography

Table 2. Basic electrocardiographic values in skaters and boat racers (M±SD).

Sports	Skating (n=25)		Boat racing (n=49)		Control (n=16)
grade	MSC MS	MCMK 3MC	KMC MC	MCMK 3MC	
P (cm/s)	0.09	0.10	0.09	0.10	0.06±0.0
PQ (cm/s)	0.17	0.17	0.17	0.17	0.18±0.03
QRS (cm/s)	0.08	0.09	0.09	0.10	0.07±0.01
QT (cm/s)	0.39	0.42	0.39	0.40	0.40±0.02

* - values were significantly different with $p<0.05$ (t-test)

Table 3. Comparison between the echocardiographic data obtained at maximum power during stepwise test in all-rounder skaters and boat racers.

Sports	Skating (n=25)		Boat racing (n=49)		Control (n=16)
grade	MSC MS n=17	IMS HMS n=8	MSC MS n=42	IMS HMS n=7	
IVSD (cm)	1.23±0.18	1.31±0.18	1.27±0.21	1.41±0.23	0.8±0.31*
LVIDd (cm)	4.69±0.34	5.00±0.40	4.83±0.41	5.11±0.32	4.6±0.20
LVPWd (cm)	1.21±0.19	1.33±0.21	1.31±0.23	1.31±0.14	1.1 ±0.21*
LVIDs (cm)	3.05±0.34	3.20±0.40	3.23±0.50	3.41±0.34	3.1±0.13
EDV (ml)	105.5±21.89	127.33±27.77	114.64±29.31	135.0±24.12	73±0.22
ESV (ml)	29.30±9.13	33.78±11.97	36.11±17.52	40.43±10.94	45±0.23
SV (ml)	76.06±17.16	93.44±12.84	78.33±19.24	94.43±18.07	60 ±20.0
LVM/m^2 (g/m^2)	132.9±12.31	161.2±13.02	144.0±13.24	153.7±13.61	89±11.0*
MOC/kg	54.06±7.00	59.75±7.25	54.21±6.13	58.43±4.21	52.0±4.20
$W_{макс}$	344.59±26.42	419.76±27.98	390.76±38.21	546.11±36.23	250.8±32.1

* - values were significantly different with $p<0.05$ (t-test)

data with maximum aerobic test results (W max and MOC/kg) confirmed the higher values of physical performance in highly skilled athletes with higher LV myocardium mass index. Values of the internal systolic and diastolic LV diameter and volume in all subgroups were within the mean population range with the internal diastolic diameter approximating the higher limit of the mean population values, whereas the internal systolic diameter was at the lower limit. This situation creates favorable conditions for an adequate cardiac output and the effective supply for maximum load. Higher values of MOC/kg and W max were obtained in highly skilled athletes with significantly higher LV myocardium mass index (see Table 3). There were no significant correlation between the basic parameters of cardiac cycle, including Sokolov index (R5+S2 > 4.5 cm), and the values of LV myocardium hypertrophy (posterior LV wall thickness and the IVS thickness), which confirms low informativity of ECG for the diagnosis of LV hypertrophy in athletes (see Tables 2-3).

2. Analysis of ACE and PPARA genotype distribution in all-rounder skaters and boat racers.

As shown by ACE and PPARA genotype testing, the most common genotypes in both all-rounder skaters and boat racers were ID ACE (53.6 and 57.1%) and GG PPARA (53.6 and 79.6%). Comparison between

the distributions of genotypes in the two groups showed statistically significant difference in PPARA gene prevalence (P=0.0273), mainly due to the increased prevalence of GC genotype in all-rounder skaters. This particular feature of the skaters possibly favors their sport activity, for we had previously found an association between GC genotype and the speed-force parameters of the athletes (9). The prevalence of genotypes was similar to control in both study groups (see Table 4).

Table 4. Distribution of ACE and PPARA genotypes in all-rounder skaters (n=28), boat racers (n=49) and control group (n=842).

Genotypes	Skating, n (%)	Boat racing, n (%)	Control, n (%)
ACE II	7 (25.0)	12 (24.5)	199 (23.6)
ACE ID	15 (53.6)	28 (57.1)	420 (49.9)
ACE DD	6 (21.4)	9 (18.4)	223 (26.5)
PPARα GG	15 (53.6)	39 (79.6)	592 (70.3)
PPARα GC	13 (46.4)*	9 (18.4)*	224 (26.6)
PPARα CC	0	1 (2)	26 (3.1)

* - values were significantly different with p<0.05 (t-test)

Analysis of the genotype distribution in subgroups of all-rounder skaters with different skill level (see Table 5) showed 2-fold decrease of the ID ACE prevalence from 64.7 to 36.4% (P>0.05) and GG prevalence (PPARα) from 70.6 to 27.3% (P=0.0248) in the subgroup of highly skilled athletes. It can be assumed, that higher prevalence of aerobic potential genotypes (ID and GC) in the subgroup of highly skilled all-rounder skaters as compared to les skilled athletes was due to natural selection in sports. In addition, statistically significant difference in GC genotype prevalence were also found when comparing data in highly skilled all-rounder skaters to that of the control group (P=0.003). As compared to the subgroup of "MSC, MS", highly skilled boat racers had an increase of prevalence of ID (ACE) genotype from 54.8 to 71.4% (P>0.05) and GC (PPARA) genotype from 14.3 to 43 %, as well as a decrease in the prevalence of GG (PPARα) genotype from 83 to 57 % (P>0.05).

Table 5. Distribution of ACE and PPARA genotypes in all-rounder skaters (n=28), boat racers (n=49) with different skills and the control group (n=842).

Genotypes	Skating		Boat racing		Control group
	MSC MS n=17	IMS HMS n=11	MSC MS n=42	IMS HMS n=7	
ACE II	4 (23.5)	3 (27.3)	11 (26.2)	1 (14.3)	199 (23,6)
ACE ID	11 (64.7)	4 (36.4)	23 (54.8)	5 (71.4)	420 (49,9)
ACE DD	2 (11.8)	4 (36.4)	8 (19.0)	1 (14.3)	223 (26,5)
PPARα GG	12 (70.6)	3 (27.3)	35 (83.3)	4 (57.0)	592 (70,3)
PPARα GC	5 (29.4)	8 (72.7)*	6 (14.3)	3 (43.0)	224 (26,6)
PPARα CC	0	0	1 (2.4)	0	26 (3,1)

* - values were significantly different with p<0.05 (t-test)

The combined analysis of associations between several genes and the physical performance utilized combination approach, which showed more frequent combination of ID-GG polymorphisms both in all-rounder skaters and boat racers (50 and 48%, respectively) (see Fig. 1). In control group this combination was found more frequently as compared to other combinations (35.4%).

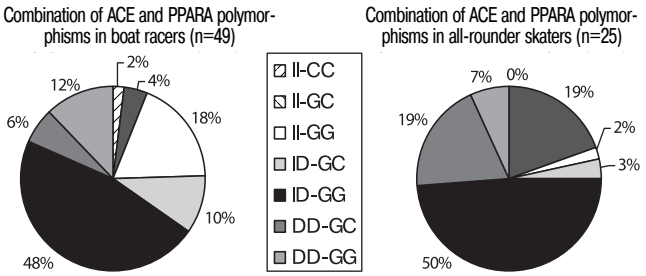

Figure 1. Combination of ACE and PPARA polymorphisms in all-rounder skaters and boat racers.

All highly skilled athletes were men and developed LV posterior wall (PWLV) and interventricular septum (IVS) hypertrophy from 1.3 to 1.8 cm. Combination of ACE and PPARα polymorphism in subgroups with myocardial hypertrophy had the following distribution: DD-ID/GC (24 - 19%); ID-II/GG (45 - 12%) – in all-rounder skaters and ID-DD/GG; II-GC (55%; 24%; 21%) – in boat racers (see Figure 2).

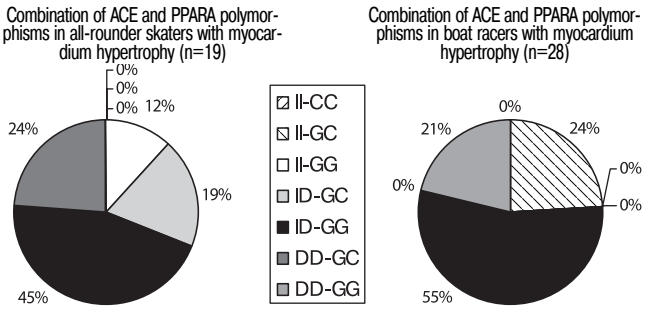

Figure 2. Combination of ACE and PPARA polymorphisms in all-rounder skaters and boat racers with myocardial hypertrophy.

Comparison between the predominant combinations of genotypes with basic morphological and functional myocardial values in highly skilled male skaters with a 7 to 12 years of experience showed, that higher values of LVPWd and maximum aerobic performance (MOC/kg and W/kg max) were detected in carriers of DD-GC combination genotype. In boat racers higher values of PWLV, IVS and maximum aerobic performance were found in athletes with ID-GG combination genotype (see Table 6).

Therefore, the most effective combination for the all-rounder skaters was the DD-GC combination (24%), which was significantly different from the prevalence of the same combination in control group (8.3%, P=0.001); whereas in boat racers this prevalence was ID-GG (55%); in control group the prevalence of this combination was 35.4%

Conclusion

Adaptive cardiovascular changes in athletes are

Table 6. Basic echocardiographic and egrospirometric values in males with various ACE and PPARA genotype combinations.

Parameters	Skating (n=13)		Boat racing (n=28)		
	DD-GC (24%)	ID-GG (12%)	ID-GG (55%)	II-GC (24%)	DD-GG (21%)
Mean experience in sports (years)	11.3	11.1	8.5	9.0	8.0
IVSD (cm)	1.5*	1.3	1.5*	1.3	1.4
LVIDd (cm)	5.0	4.8	4.9	5.1	5.0
LVPWd (cm)	1.3	1.3	1.6	1.5	1.3
LVIDs (cm)	3.1	3.4	3.3	3.4	3.3
EDV (ml)	125.0	122.8	125.0	122.9	126.0
ESV (ml)	41.0	35.8	47.3	36.17	37.0
SV (ml)	74.0	76.6	77.6	86.5	89.0
MOC/kg	61.1	61.3	59.1	61.3	60.0
W/kg max	5.6*	5.4	–		
W max			428.0*	420.1	419.0

*P<0.05 according to the chi-square test (comparison between the groups by the sports type).

determined by a complex network of interactions between the genetic factors and extreme external impacts. Unfortunately, the molecular genetics methods are still insufficiently used in the high level sports. The association between ACE and PPARα genotype combinations and physical performance with further comparison of these findings to the results of general studies (using echocardiography and ergospirometry) allowed for the assessment of contribution of the above genetic markers to the development of physiological hypertrophy of the athlete's heart. The results of genotype distribution assessment revealed most effective combinations for I/D and G/C polymorphisms of ACE and PPARA genes among highly skilled athletes: DD - GC – for all-rounder skaters and ID-GG – for boat racers. Considering the association between the ACE and PPARα gene polymorphisms and the type of cardiovascular activity, the combination of DD-GC genotypes has predominant role in sports with mixed anaerobic-aerobic type of energy supply (e.g., in all-rounder skating). In contrast, the combination ID-GG was possibly more favorable in sports with predominant aerobic energy supply (e.g., in boat racing).

Further studies of genetic polymorphisms, morphological and functional cardiovascular changes in sports with various types of energy supply will reveal the relevant genetic markers of physiological and pathological remodeling of the "athlete's heart", determine the risk groups of cardiovascular and, particularly, coronary changes in athletes.

References:

1. Volkov N.I. Bioenergy metabolism in active muscular tissue and the ways to increase the performance of athletes. Thesis, Biology Doctor. Moscow, 1990, 100 pages.
2. Gavrilova E.A. Stress cardiomyopathy in athletes (myocardial dystrophy caused by physical stress). PhD Thesis. St.-Petersburg, 2001, 125 - 200.
3. Grayevskaya N.D., Goncharova G.A., Kalugina G.E. Another consideration of the problem of "athlete's heart". Teoria I praktika fizicheskoy kultury, 1997, 4, 2 - 5.
4. Degtyareva E., Linde E.V., Ide Khasan et al. Approaches to prediction of stress cardiomyopathy in young athletes of the reserve team and justification of protection methods. International medical journal (IMJ), 2002, 6, 521-526.
5. Linde E.V. Types of adaptation of cardiorespiratory system of young athletes practicing cyclic sports with maximum tredmill tests. Abstracts, 7th International research congress «Modern Olympic sports and sports for everyone». Moscow, May 2003, 89-90.
6. Linde E.V., Vinogradova O.L., Akhmetov I.I., Astratenkova I.V., Prostova A.B. «Athlete's heart» and genetic polymorphism. Fizkultura v profilaktike, lechenii I reabilitacii, 2006, 4, 19, 18-25.
7. Kechker M.I. Guidelines on clinical electrocardiography. Moscow, Medprom, 2000. 395 pages.
8. Meyerson F.Z. Adaptation, deadaptation and heart failure. Moscow, 1978, 320-339.
9. Ahmetov I., Astratenkova I., Komkova A., Rogozkin V. PPAR-α intron 7 polymorphism and response to power training 10th Ann. Congress ECSS - Belgrade, Serbia, Abstract Book, 2005, 213-214.
10. Ahmetov I.I., Linde E.V., Mozhayskaya I.A. et al. Effects of gene variants on cardiovascular system of athletes. 11th Ann. Congress ECSS, July 5-8, 2006, Lausanne, Switzerland, Book of Abstracts, 2006, 416.
11. Alvarez R, Terrados N, Ortolano R. et al. Genetic variation in the renin- angiotensin system and athletic performance. Eur. J. Appl. Physiol., 2000, 82, 117–20.
12. Braissant O., Foufelle F., Scotto C., et al. Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. Endocrinology, 1996,137, 354–366.
13. Costa O., Fraitas J., Puig J. Current perspectives in screening for cardiac diseases which most frequently cause sudden death during the practice of a sports activity. Rev. Port. Cardiol., 1998, 17(3), 273-83.
14. Danser A.H.J., Schalekamp M.A.D.H., Bax V.A, et al. Angiotensin converting enzyme in the human heart: Effect of the deletion/insertion polymorphism. Circulation, 1995, 92, 1387-1388.
15. Devereux RB, Lutas EM, Casale PN. et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. J. Am. Coll. Cardiol., 1984, 4, 1222–30.
16. Flavell D.M., Jamshidi Y., Hawe E., et al. Peroxisome proliferator-activated receptor α gene variants influence progression of coronary atherosclerosis and risk of coronary artery disease. Circulation, 2002, 105, 1440 –1445.
17. Futterman L.G., Myerburg R. Sudden death in athletes: an update. Sports Med., 1998, 26(5), 335.
18. Heine H. Grundheit – Krankcheit. Stress. Biol. Med., 1997, 26(5), 503-511
19. Heine H. Grundlagen der Regulationsmedizin. Arztezeitschrift fur Naturheilverfaren, 2000, 41, 82-93
20. Iokl E. Exersise and cardiac dearth . Sport cardiology. Eds. Zulicht., Venesando A., Bologna, Auto Gaddi., 1980, 233.

21. Jamshidi Y., Montgomery H.E., Hense H-W., et al. Peroxisome proliferator-activated receptor α gene regulates left ventricular growth in response to exercise and hypertension. Circulation, 2002, 105, 950-955.
22. Karjalainen J, Kujala UM, Stolt A. Angiotensinogen gene M235T polymorphism predicts left ventricular hypertrophy in endurance athletes. J. Am. Coll. Cardiol., 1999, 34 (Suppl. 2), 494–9.
23. Kagaya Y., Kanno Y., Takeyama D., et al. Effects of long-term pressure overload on regional myocardial glucose and free fatty acid uptake in rats. A quantitative autoradiographic study. Circulation, 1990, 81,1353-1361.
24. Longhurst J. et al. Echocardiographic left ventricular masses in distance runners and weight lifters. J. Appl. Physiol., 1980, 48(1), 154-162
25. Mccann G.P., Muir D.F., Hillis Athletic left ventricular hypertrophy: long-term studies are required. Eur., Heart J., 2000, 21, 351-353.
26. Montgomery H., Clarkson P., Dollery C.M., et al. Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. Circulation, 1997, 96, 741-747.
27. Nadaut S., Soubrier F., Seances C.R. Molecular biology and genetics of ON synthases. Soc. Biol. Fil., 1995, 189, 6, 1025-1038.
28. Nagashima J, Musha H, Takada H. et al. Influence of angiotensin-converting enzyme gene polymorphism on development of athlete's heart. Clin. Cardiol., 2000, 23, 621–4.
29. Northcote R., Ballantine D. Sudden death and sport. Lancet, 1984, 1, 113
30. Noakes T.,Rose A.,Benjamin J. Sudden death of a champion athlete. Autopsy findings. S. Afr. Med. J., 1984, 66(12), 458-9
31. Noakes T.D. Implication of exercise testing for prediction of athletic performance: a contemporary perspective. Med. Sci. Sport Exerc., 1988, 20, 319-330.
32. Osborne G, Wolfe LA, Buggraf GW. et al. Relationships between cardiac dimensions, anthropometric characteristics and maximal aerobic power (VO2-max) in young men. Int. J. Sports Med., 1992, 13, 219.
33. Pelliccia A., Maron B. et al. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. Circulation, 2005, 105, 944-949.
34. Pellicia A., Maron B. Athletes heart electrocardiogram mimicking hypertrophic cardiomyopathy. Curr. Cardiol. Rep., 2001, 3 (2), 147-51
35. Pfeffer M.A., Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation, 1990, 81, 116-172
36. Raschka C., Parzeller M., Kind M Organ pathology causing sudden death in athletes. Interna studi of autopsies (Germany, Austria, Switzerland). Med. Klin., 1999, 94(9), 473-7
37. Rankinen T, Wolfarth B, Simoneau JA. et al. No association between the angiotensin-converting enzyme ID polymorphism and elite endurance athlete status. J. Appl. Physiol., 2000, 88, 1571–5.
38. Rost R. The athlete's heart. Cardiol. Clin., 1997, (Suppl. 3), 493–512.
39. Rigat B., Hubert C., Alhenc-Gelas F., et al. An insertion/deletion polymorphism in the angiotensin-1-converting enzyme gene accounting for half the variance of serum enzyme levels. J. Clin. Invest., 1990, 86, 1343-1346.
40. Rigat B., Hubert C., Corvol P., Soubrier F. PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). Nucleic Acids Res., 1992, 20, 433.
41. Spataro A., Pellicia A. et al. Extreme cardiac hypertrophy in athletes. Morphological and functional echographic study. G. Ital. Cardiol., 1988, 18(3), 171-80.
42. Serra-Grima R., Estorch M. at al Marked ventricular repolarization abnormalities in highly trained athletes electrocardiograms: clinical and prognostic implication. J. Am. Coll. Cardiol., 2000, 36(4), 1310-6
43. Sharp NC., Koutedakis Y Sport and the overtraining syndrome: Immunological aspect. Br. Med. Bull., 1992, 48(3), 518-33.
44. Tabib A., Miras A., Taniere P., Loire R. Undetected cardiac lesions cause unexpected sudden cardiac death during occasional sport activity. A report of cases. Eur. Heart J., 1999, 20(12), 900-3
45. Urhausen A., Kindermann W. Sudden cardiac death in sports. Ther. Umsch., 1998, 55(4), 229-34.
46. Wei S., Chow L.T., Shum I.O. et al. Left and right ventricular collagen type I/III ratios and remodeling postmyocardial infarction. J. Card. Fail., 1999, 5,117-26.

Records of the Sessions of Moscow Scientific Society of Cardioangiology

Record №1
of the Session of Moscow Scientific Society of Cardioangiology.
November 2, 2005.

In his opening remarks by the President of the Society, Head Cardiologist of the Moscow Department of Healthcare Professor D.G. Iosseliani determined the objectives and the goals of the new Society and presented the members of the Society Board to the audience:

Chairmen: D.G. Iosseliani, G.P. Arutiunov, T. Szili-Torok
Subject of the Session: «Current Principles of Diagnostics and Treatment of Certain Heart Rhythm Disturbances »
The following presentations have been read over:
1. I.G. Fomina. «What's New in the Diagnostics and Drug Therapy of Atrial Fibrillation».
2. A. Sh. Revishvili. «Atrial Fibrillation: Electrophysiological Mechanisms, Indications and Results of Interventional Treatment
3. Tamasz Szili-Torok (Hungary). «Implantable Cardioverter Defibrillator (ICD) for the Treatment of Patients who are at Risk for Sudden Cardiac Death»
4. Questions and discussion

Attendance: 241 persons.

Secretary of the MSSC N.A. Lonskaya.

Record №2
of the Session of Moscow Scientific Society of Cardioangiology.
March 17, 2006.

Chairmen: D.G. Iosseliani, M.Ya.Ruda, J. Ludwig
Subject of the Session: «Current Principles of Diagnostics and Treatment of Acute Myocardial Infarction ».
The following presentations have been read over:
1. D.G. Iosseliani. «Possible Ways to Improve Treatment Tactics in Acute Myocaridal Infarction».
2. M.Ya. Ruda. «Drug Therapy of Acute Myocardial Infarction».
3. J. Ludwig (Germany). «Primary Percutaneous Coronary Intervention (PCI) for ST-Segment Elevation Myocardial Infarction (STEMI). Results of a German University Hospital».
4. Questions and discussion

Attendance: 257 persons.

Secretary of the MSSC N.A. Lonskaya.

Record №3
of the Session of Moscow Scientific Society of Cardioangiology.
June 09, 2006.

Chairmen: D.G. Iosseliani, A DeMaria, G.P. Arutiunov
Subject of the Session: «Diagnostic Options in Cardiology ».
The following presentations have been read over:
1. Anthony De Maria (USA). «Current Possibilities of the Assessment of the Coronary Arteries and the Left Ventricular State using Myocardial Contrast Echocardiography».
2. Information concerning current options of pharmacological therapy for cardiovascular diseases.
3. Questions and discussion

Attendance: 228 persons.

Secretary of the MSSC N.A. Lonskaya.

Record №4
of the Session of Moscow Scientific Society of Cardioangiology , dedicated to the 10th Anniversary of Moscow City Center of Interventional Cardioangiology
October 27, 2006.

Part 1. Chairmen: D.G. Iosseliani, V.V. Kukharchuk, Z.A. Kavteladze
The following presentations have been read over:
1. D.G. Iosseliani. «Results of 10-year Activities of the Center of Cardioangiology ».
2. S.A. Abugov. «Drug-Eluting Stents: the Present and the Future ».
3. V.V. Kukharchuk. «Correction of Lipid Metabolism Disturbances as an Important Factor of Secondary Prophylactics of Atherosclerosis ».
4. A.G. Koledinsky. «Does Intracoronary Administration of Metabolic Cytoprotectors Limit Reperfusion Cardiomyocytes Damage in Acute Myocardial Infarction?»
5. B.I. Dolgushin. «Diagnostic and Therapeutic Interventional Radiology in Oncology ».
6. Z.A. Kavteladze. «Endovascular Treatment of the Aneurysms of Abdominal and Thoracic Aorta ».

Part 2. Chairmen: G.P. Arutiunov, A.V. Arablinsky
The following presentations have been read over:
7. G.P. Arutiunov. «Inflammation in the Acute Period of Myocardial Infarction and in Acute Coronary Syndrome».

8. V.I. Makolkin. «Possibilities of Restenoses Prevention in Patients with Arterial Hypertension after PTCA ».
9. I.V. Isaeva. «Current Approaches to the Treatment of Combined Coronary and Carotid Lesions ».
10. V.A. Ivanov. «Endovascular Treatment of the Left Main Lesions ».
11. S.N. Tereshchenko. «Current Recommendations on Diagnostics and Treatment of Acute Heart Failure ».
12. Questions and discussion

Attendance:275 persons.

Secretary of the MSSC N.A. Lonskaya.

Record №5
of the Session of Moscow Scientific Society of Cardioangiology.
April 06, 2007.

Chairmen: D.G. Iosseliani, C. Nienaber, I.V. Isaeva
Subject of the Session: «Diagnostics, Clinical Picture, Methods of Treatment of the Dissecting Aneurysm of the Thoracic Aorta ».
The following presentations have been read over:
1. C. Nienaber (Germany). «Principles of Endovascular Treatment of the Thoracic Aorta Diseases: Diagnostics, Analysis of the Data, Technical Tricks»
2. I.V. Isaeva. «Clinical Picture and Diagnostics of the Dissecting Aneurysm of the Thoracic Aorta »..
3. Information concerning current options of pharmacological therapy for cardiovascular diseases.
4. Questions and discussion

Attendance:121 persons.

Secretary of the MSSC N.A. Lonskaya.

Record №6
of the Session of Moscow Scientific Society of Cardioangiology.
June 27, 2007.

Chairmen: D.G. Iosseliani, J. Masura, S.P. Semitko
Subject of the Session: «New Methods of Endovascular Treatment of Pathological Interatrial Communications in the Heart ».
The following presentations have been read over:
1. Josef Masura (Slovakia). «Endovascular Correction of Congenital Pathological Communications between the Heart Chambers using Amplatzer Occluders».
2. T.A. Melnikova (pharmaceutical company «PharmStandard»). «Information concerning current options of pharmacological therapy for cardiovascular diseases».
3. Questions and discussion

Attendance: 284 persons.

Secretary of the MSSC N.A. Lonskaya.