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When you are 60, and your professional and family life goes on perfectly; when you have reached the summits of your vocation – medicine; when your scientific achievements are commonly appreciated; when you are surrounded by true, time-proved friends; when you are full of interest for everything – theater, music, art…
Well, you can enjoy your life!

It's a good advice, but not for our Chief Editor.

Being a chief of a big staff, heading the cardiological service of a huge city, he still has the energy to create a new professional association, to organize symposia, to presents lectures, and with all this he performs daily operations, he consults the patients, he is regularly on duty in his clinic.

Because he is younger than many of us, forty-year-olds.

Happy birthday, Dr. Iosseliani!

We wish you a lot of happiness and health!

Editorial Board of "International Journal of Interventional Cardioangiology".

Carotid Artery Stenting with Neuroprotection: the first percutaneous revascularization technique shown to be clinically superior to surgery in a randomized trial

Carlo Di Mario M.D., Bernhard Reimers M.D., Francesco Liistro M.D.,

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Key words: Carotid stenosis, stenting, protection devices.

Two major randomized trial concerning the surgical treatment of Carotid Artery Stenosis (CAS) demonstrated the superiority of Carotid Endarterectomy (CEA) respect to medical treatment in reducing the overall risk of stroke in symptomatic or asymptomatic patients (1-4). The first phase of the North American Endarterectomy trial (NASCET) (1) demonstrated the superiority of endarterectomy over medical treatment for symptomatic carotid stenosis >70% and the second phase of the NASCET trial showed the benefit of CEA in patients with symptomatic moderate stenosis (50-70%) (4). The Asymptomatic Carotid study (ACAS) showed a reduction in stroke rate after CEA also in asymptomatic patients with carotid stenoses >60% (2).

Although CEA is nowadays considered the gold-standard therapy for the treatment of carotid occlusive disease, the approach is not free of complications. In the NASCET study population, 5.8% of patients suffered from perioperative death and stroke. Nevertheless, when CEA is performed in routine clinical practice without patient selection according to study criteria and neurological audit is performed by independent neurologists, the incidence of major events is reported with a higher rate (5). Since the first percutaneous transluminal carotid angioplasty (PTA) has been performed by Kerber in 1980 (6) the rapid improvement in interventional technology and materials has contributed to the increasing popularity of this technique intentionally developed as an alternative to surgical treatment (7-10). However, there has been concern regarding the safety of such interventions because of the risk of cerebral embolization during the procedure (11, 12). This may be explained by the presence of thrombotic material contained in carotid plaque frequently observed during surgical exploration (13). Preliminary studies evaluating the safety and efficacy of carotid angioplasty showed higher incidence of stroke-death complication compared to CEA (8, 14-16). One randomized trial, comparing carotid angioplasty with CEA for symptomatic severe ICA disease, was aborted after enrolling only 17 patients because of the unacceptably high stroke/death rate following angioplasty (71%) compared to CEA (0%) (17). It is however important to point that those patients were treated by interventionists with limited CBAS experience and were treated with inadequate antiplatelet therapy by today's standards. However, increasing operator experience led to better results as reported in the recently published Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) which randomized 504 patients with symptomatic carotid stenosis to either balloon angioplasty (bail-out stenting was performed in 26%) or CEA. The results at 30-day and 3-year follow-up were similar with both strategies (incidence of any stroke or any neurological deficit lasting more than 7 days or death was 10% at 30 days) (18). Nevertheless, these results belong to the pre-stent era and cannot be applied to current treatment which considers stent implantation the main strategy to optimize percutaneous treatment of carotid artery stenosis.

Carotid artery stenting (CAS) has its main goal in stenosis resolution but also in the containment of atherosclerotic plaque by stent barrier, avoiding once re-endotelized, the further thrombotic process potentially associated with distal embolization and flow impairment. In 1998 one of the largest early series of carotid artery stenting (CAS) (from 24 worldwide centers, with 2048 patients) reported technical success rate of 98.6% with a combined periprocedural stroke and death rate of 5.77% (this rate varied from 0-10% from the various centers) (19). Two years later updated survey was performed on 4757 patients (Carotid Artery Stent Placement - CASP registry) and the combined periprocedural stroke and death rate of 5.07% was reported (20). Long-term follow-up of CAS was reported by Roubin et al who evaluated the incidence of major adverse neurological event for 3 years after the index procedure with a freedom from any ipsilateral stroke of 92% (21).

Ex vivo human carotid artery stenting models showed that embolic particles consist of atherosclerotic debris, organized thrombus and calcified material (13).

The embolic potential of atherosclerotic plaque can be clinically assessed by ultrasound evaluation. Echolucent plaques are more frequently associated with emboli generation respect to echogenic plaques (13). Furthermore, stenosis severity (≥90%), total length of the stenosis or the presence of multiple stenosis also significantly correlate with the total number of particles produced by procedure and, consequently, with clinical outcome (22).

Reimers et al utilized 3 different types of distal protection devices in 88 consecutive lesions (84 patients) in the internal carotid arteries that had >70% diameter stenosis. Importantly, in 53% of filters, there was macroscopic evidence of debris (23). Collected material consisted of lipid-rich macrophages, fibrin material, and cholesterol clefts (24). Even higher inci-

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dence of atheromatous debris (83%) was described in the study of Tubler et al (25). Authors went a step forward attempting a correlation of the size of captured particles with the incidence of periprocedural neurological complications in 54 patients that underwent 58 CAS procedures using distal balloon protection. Relevant particles were defined as those with an area ≥10 000 μ^2. Although there was a pronounced overlap in the distribution between patients with and without neurological complications, authors concluded that the maximum area of aspirated particles seems to be an indicator of increased risk for peri-procedural neurological complications.

However, it is also important to state that neurologic events after revascularization procedures are relatively rare and transcranial Doppler monitoring and diffusion-weighted MR imaging have shown that many emboli are asymptomatic. Nevertheless, patients with higher number of particles generated by procedure should have higher peri-interventional stroke rate than patients among whom fewer particles are produced.

Prompted by the observation of high incidence of distal embolization during CAS, a variety of protection systems were designed to capture and remove atheromatous debris released during percutaneous interventions in carotid arteries. These systems can be divided in 2 major groups: balloon-occlusive devices and filter-devices. Balloon occlusive devices can be further divided into proximal and distal devices accordingly to the segment of carotid artery they occlude.

With both types of occlusion devices, a major limitation concerns the potential to induce acute ischemia of the homolateral cerebral hemisphere once the balloon is inflated, situation that occurs in case of lack of a sufficient collateral circulation provided by the contra-lateral system.

The PercuSurge GuardWire system (Medtronic Inc, Santa Rosa, CA) is based on the concept of temporary occlusion of the flow distal to the lesion during percutaneous intervention and debris retrieval by an aspiration system. Al-Mubarak et al (26) determined the effect of this device on the frequency of Doppler-detected microembolic signals during CAS in patients with (37 patients) and without (39 patients) distal protection. In patients without protection microembolic signals were observed during stent deployment, predilatation and postdilatation. On the contrary, in patients in whom the protection device was used, the frequency of microembolic signals was substantially reduced during these 3 phases. However, microembolic signals in protection group were still present and detected predominantly during carotid-sheath placement, guidewire manipulation, and distal-balloon deflation.

Recently, Henry et al reported the results of CAS performed with PercuSurge GuardWire system in 184 lesions[27]. Prophylactic occlusion during balloon dilation and stenting was well tolerated in 176 (95.7%) patients and technical success was 99.5%. Microscopic analysis of the aspirated blood showed different types of particles numbering between 7 and 145 per procedure with a mean diameter of 250 μm (56-2652 μm). The 30-day stroke and death rate was 2.7% and the author concluded that protection devices may play an important role in future carotid interventions and expand the applicability of the procedure. Similar results are reported also by Schluter et al in a consecutive series of 96 patients (102 lesions) (28). The device was successfully delivered in 93 patients (97%) and temporary occlusion was tolerated in all but 2 (2.1%). In 3 patients the leakage of the GuardWire's valve sealing ultimately ended in a non-protected procedure for a total feasibility rate of 92%. Major adverse neurologic events occurred in 3.1% of patients.

Randomized trials comparing surgery versus CAS with and without cerebral protection are still ongoing and only limited results are now available. The Carotid Angioplasty Free of Emboli (CAFE) is a 75-patient multicenter registry (Argentina, Germany and USA) evaluating the first generation GuideWire protection system during carotid artery stenting. Whitlow et al presented results from 40 patients enrolled and reported no strokes or deaths up to 30-day follow-up (29).

However, The CAFE-USA trial, designed to assess feasibility, safety and efficacy of the GuardWire Plus system in symptomatic (carotid stenosis >60%) and asymptomatic (carotid stenosis >70%) patients undergoing carotid Wallstent implantation, reported an incidence of death and stroke of 4.3% in the first 70 patients included in the registry (30).

Contrary to the PercuSurge system, the clinical experience with the other balloon occlusive devices is limited. The Parodi Anti-Embolization System (PAES) (ArteriA, Inc, San Francisco, CA) is a triple lumen-guiding catheter with an occlusion balloon attached to the outside of the catheter at the distal end. The Y-adapter allows insertion of several devices, including the Parodi external balloon to occlude the external carotid artery, and permits the connection to a sheath inserted in the femoral vein creating an artero-venous fistula with flow reversal. The main advantages of this system are: 1) ability to achieve cerebral protection before crossing the lesion, 2) the fact that particles of all sizes can be captured, 3) possibility for simultaneous use of other distal protection devices, 4) relative simplicity of use. Disadvantages are: 1) interruption of antegrade flow both in the external and the internal carotid arteries, 2) large size of the device (11F sheath/10F protection system).

The safety and efficacy of the Parodi Anti Embolism System (PAES) was evaluated in a small registry of 30 patients. In 3 of them the device had to be deflated because of acute cerebral ischemia, enhancing that the major limitation of this device is the sometimes inadequate collateral circula-

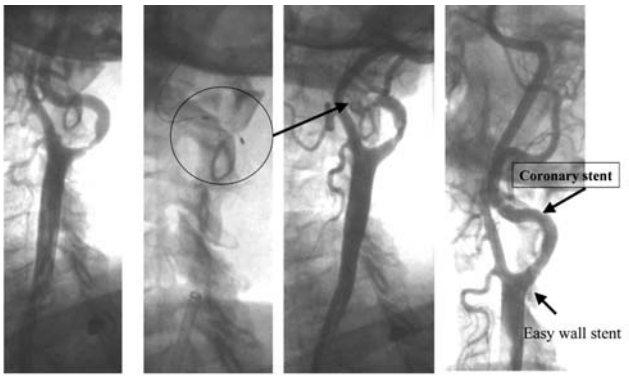

Figure 1. Selective left carotid angiography (fig 1 panel a) showing a severe lesion in the proximal segment of the ICA. Distal to the stenosis, the vessel appears severely tortuous with a double curve. The AngioGuard filter (panel b) failed to cross the lesion and caused an occlusive dissection (panel c) resolved with the implantation of 2 coronary stents (panel d).

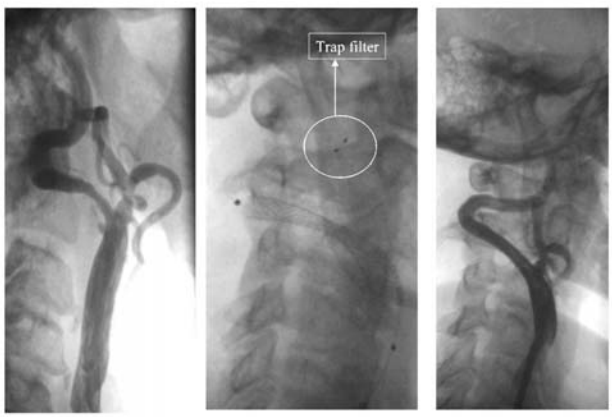

Figure 2. Moderate stenosis in the Right Internal Carotid Artery in a symptomatic male. Vessel appeared tortuous (panel a). A Trap filter device could be delivered through the severe angulation and carotid stenting performed (panel b) with optimal angiographic result (panel c).

tion ensured by the contralateral carotid system once the flow reversal is started (31).

In contrast to the balloon-based protection system, filters can prevent embolic events without interrupting blood flow distally. Another important advantage of filters is the ability to perform angiograms during procedure and therefore verify stent position prior to its deployment. The main weaknesses of filters are the presence of relatively large pore-size with the possibility of missing smaller particles, a relatively large crossing profile resulting in difficulties to cross tight or tortuous lesions and potential to cause spasm and dissection in the distal ICA (see figures). One of the major limitation in the use of filter-based protection devices is severe carotid vessel tortuosity. In these settings, filter devices which are delivered over a guide wire already positioned such as Trap filter (Microvena, White Bear Lake, Minnesota) or EmboShield System (MedNova Ltd. Galway, Ireland) might have higher push-ability and better chance for a successful delivery/retrieval maneuver compare to those which are delivered simultaneously with the guide wire (AngioGuard Cordis a Johnson & Johnson, Warren, NJ) (EPI Boston Scientific, Santa Clara, CA).

Clinical evaluation of CAS performed under filter protection is still based on results obtained from small registries while large randomized trials comparing CAS with and without filter protection vs CEA are still ongoing (32). A recent multicenter registry reported the results of CAS with distal protection in 308 patients with 320 lesions in the ICA that had >70% diameter stenosis. Three different devices were used: filters

Table 1. Features of different protection devices

Device	Pore Size (μm)	Crossing profile	Capture sheath profile	Diameters available (mm)
Angioguard XP	100	0.042-52"	0.066"	4-8
Mednova II	120	0.058-68"	0.096"	4-6
Mednova III	140	0.046-51"	0.084"	4-6
BSc FilterWire	80	0.049"	0.049"	3.5-5.5
Medtronic AVE	100	0.039"	0.039"	3.5-5.5
Guidant Accunet	120	NA	NA	4-8
Microvena Trap	200	0.037"	0.066"-78"	2.5-7
PercuSurge	No pores	0.028-36"	0.042"-70"	3-6

Table 2. Major clinical experience of CAS with distal protection

Device	Patient/Lesion (%)	Symptomatic (%)	Feasibility (%)	30-day MAE (%)	Reference
PercuSurge	167/184	50	95.7	2.7	27
PercuSurge	70	56	100	4.3	30
PercuSurge	96/102	46	92	3.1	28
Parodi	30	50	90	0	31
Multiple devices	308/320	59	95	2.5	33
Mednova	162/164	48	95	2	34
Mednova	50	42	98	4	35
AngioGuard	156	31	98	5.8	36
AngioGuard	408	42	98	6.9	36

(80.6%), occlusive distal balloon (17.2%), and clamping of the common and external carotid arteries (2.2%). The procedural success rate was 95%. 30-day major adverse neurological events rate was 2.5% (33).

A single-center experience reported the results of CAS in 162 patients (164 lesions) using the Mednova NeuroShield filter device (34). Angiographic success was obtained in 99% of the lesions and the filter could be positioned in 95% of them. 30-day event rate was 2% (2 minor strokes and 2 deaths). The same type of filter devices was also evaluated in a series of 50 consecutive patients (42 symptomatic) with ICA stenosis >70% (35). Procedural success was 100% for stenting and 98% for filter placement/retrieval. Nevertheless, the death and major disability from stroke rate was 4% (2 patients).

A multi-center randomized trial compared carotid stenting with distal protection to endarterectomy in high surgical risk patients (SAPPHIRE) selected according to the presence of selected clinical and/or anatomical variables. Clinical outcome was the incidence of Major Adverse Events (MAE) defined as death-stroke-myocardial infarction at 30 days and 30-day MAE plus death and ipsilateral stroke at 12 months. Non randomized patients entered a registry either for CAS (surgical refusal) than for CEA (interventional refusal). Carotid stenting was performed with the Cordis Nitinol Carotid Artery Stent and the protection device used was the Angioguard XP. Inclusion criteria were: common carotid artery or ICA stenosis ≥50% in symptomatic or ≥80% in asymptomatic patients, vessel diameter 4-9 mm and target lesion amenable to both CAS and CEA. Preliminary results were recently presented by Yadav (36) who reported about 307 randomized, 156 to CAS and 151 to CEA. 409 patients were refused by surgeons and entered a CAS registry and 7 patients were refused by interventionists and underwent CEA. Among stent patients, procedure success defined as residual diameter stenosis <30%, was achieved in 91% of lesions and AngioGuard delivery/retrieval success was 98%. The incidence of 30-day MAE in randomized patients was 5.8% in CAS arm and 12.6% in the CEA arm (p = 0.047) and a significant difference in favor of CAS was observed either in symptomatic or asymptomatyc patients. The results of the stent-registry patients were similar to those of patients randomized to CAS. Nevertheless, it is difficult to understand the high rate of patients refused by surgeons (407) which does not seem to correspond to routine surgical clinical practice.

The results of CAS with the Acculink for Revascularization of Carotids in High Risk Patients (ARCHER) study will also

evaluate the safety and efficacy of Acculink carotid stent system in patients at high risk or unsuitable for CEA 398 patients will be enrolled and clinical endpoints are composite of death, stroke and myocardial infarction at 30 days and at 1 year.

Conclusions.

Although the results of large randomized trial comparing CAS with distal protection versus CEA are still not completely available, CAS seems to be a safe and efficacy alternative to surgical CEA in the treatment of carotid occlusive disease. In addition, in patients at high surgical risk CAS with distal protection showed to be associated with a significantly (3) lower rate of MAE at 30 days.

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Percutaneous closure of patent foramen ovale

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Pathogenesis of paradoxical embolism

During embryogenesis the left-sided septum primum and the right-sided septum secundum each leave a gap by forming from the outside to the center. The gaps are slightly displaced with the septum primum gap more cranial and the septum secundum gap more caudal. While the septa fuse (Fig. 1A), a valve is formed that permits right-to-left but not left-to-right flow. The blood arriving from the placenta through the inferior vena cava keeps this valve open, bypassing the lungs. At birth, the lungs unfold and the pressure in the right atrium drops below that of the left atrium. In about three out of four people the valve closes and a solid interatrial septum will form (Fig. 1B). In the remainder of the population, the foramen remains patent, i.e., openable (Fig. 1C). It will open to a right-to-left shunt, when the left atrial pressure overrides the right atrial pressure, which occurs after a prolonged Valsalva maneuver when the venous blood is rushing back into the right atrium before reaching the left atrium. It may also open to the mere velocity of blood pounding against it in particular if the blood is guided against the septum by an Eustachian valve as in the platypnea orthodeoxia syndrome (1). Such a right-to-a-left shunt provides opportunities for clots originating in the venous system to cross into the arterial system, bypassing the lung filter. The crossing of large clots is a rare event. Yet it has allowed to document the mechanism of paradoxical embolism by echocardiography demonstrating clots caught in the act of crossing (2). Miniature clots, measuring a few mm, start to emanate from the venous system already in young adults and their incidence increases with age. They seem not to exist in children. Hence, paradoxical embolism before adulthood is virtually unheard of. Small clots can hardly be detected in the venous system, nor during their migration or passage through the PFO. However, if they wind up in a small end-artery in the brain, the eye, or the coronary tree, they may be clinically manifest or even devastating.

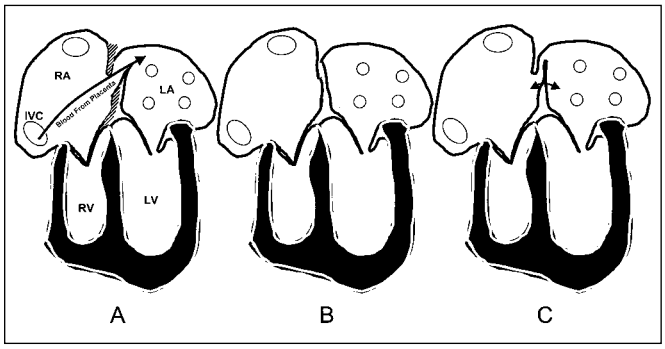

Fig. 1A. Foramen ovale. In the prenatal heart, the septum primum on the left side of the heart and the septum secundum (shaded area) on the right side grow from the periphery to the center without closing the gap completely. Later they fuse longitudinally. The initial gaps (septum primum more cranial and septum secundum more caudal) form a channel in line with the blood from the placenta arriving through the inferior vena cava (IVC, arrow). This bloodstream keeps the foramen ovale open. The foramen ovale forms a valve that is ready to close as soon as the pressure in the left atrium (LA) supersedes that of the right atrium (RA). LV = left ventricle; RV = right ventricle

Fig. 1B. At birth the left-sided part of the valve is pushed against the right-sided which mainly consists of the wedge-shaped septum secundum and the valve is functionally closed and usually fuses within weeks.

Fig. 1C. In about 25% of the population the fusion fails to occur and the foramen ovale remains patent, opening or closing according to the pressure and flow situation on both sides.

The potential causal relationship of patent foramen ovale with stroke was already suspected in 1877, when a pathologist connected the presence of a PFO with a stroke killing a young woman (3).

Diagnosis of patent foramen ovale

The gold standard today is transesophageal echocardiography (Fig. 2). The sensitivity of transthoracic echocardiography for this diagnosis is not as good as that of transesophageal echocardiography. The specificity is even poorer as it can rarely be ascertained transthoracically that the bubbles pass through the PFO. Bubbles appearing in the left atrium several heart beats after they appeared in the right atrium may result from a pulmonary shunt rather than a PFO. Bubbles passing through the lung filter are usually smaller. Therefore, the bubble mix is disparate in the left and the right atrium if the bubbles have not passed through a PFO.

The assessment of the number of high intensity transient signals (HITS) by transcranial Doppler recordings is sensitive too, but lacks specificity (4). Magnetic resonance or computed tomography hold great potential to match the yield of transesophageal echocardiography without the need for swallowing a tube. At present, they are less readily available and more expensive. Skin oximetry after a Valsalva maneuver (rapid and transient drop in saturation) has also been suggested but is of questionable value.

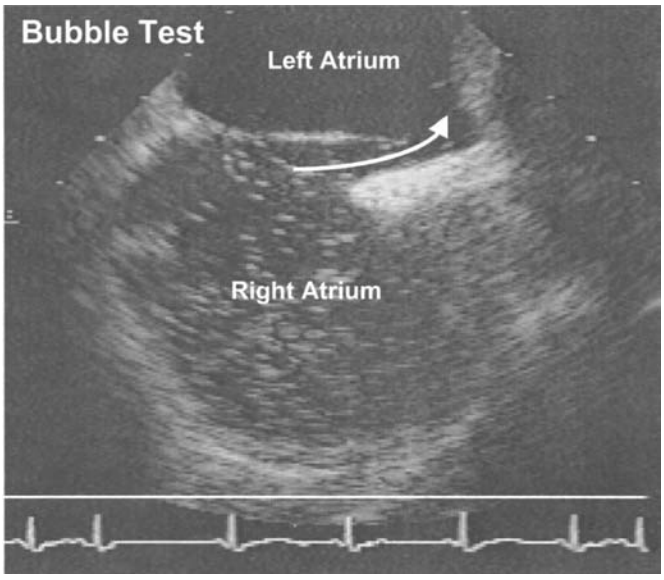

Fig. 2. Transesophageal echocardiography at the end of a prolonged Valsalva maneuver in a patient with a patent foramen ovale. An aerated colloid solution was injected into an arm vein containing bubbles that show up as small white dots on the echocardiogram. Some of them clearly cross into the left atrium (arrow) proving the patent foramen ovale.

Table 1. The Role of a Patent Foramen Ovale in Stroke Patients (8-14)

		Odds Ratio (95% CI)		
		PFO	ASA	PFO+ASA
All ages	Stroke versus non-stroke controls	2 (1-2)	2 (2-3)	5 (3-10)
	Cryptogenic stroke versus known stroke cause	3 (3-4)	3 (2-3)	21 (4-104)
	Cryptogenic stroke versus non-stroke controls	3 (2-3)	4 (3-6)	24 (3-185)
Age < 55 years	Stroke versus non-stroke controls	3 (2-4)	6 (3-15)	16 (3-86)
	Cryptogenic stroke versus known stroke cause	6 (4-10)	7 (2-31)	17 (2-133)
	Cryptogenic stroke versus non-stroke controls	5 (3-8)	19 (3-150)	24 (3-185)
Age • 55 years	Stroke versus non-stroke controls	1 (1-2)	3 (12-6)	5 (1-21)
	Cryptogenic stroke versus known stroke cause	2.0 (1-3)		
	Cryptogenic stroke versus non-stroke controls	1 (1-3)		

Clinical association between patent foramen ovale and stroke

An estimated 350,000 ischemic strokes occur yearly in Russia; 25% of these strokes are presumed cryptogenic (5-7). The prevalence in patients with cryptogenic stroke is about 50% (8-14). This extrapolates to almost 50,000 strokes per year attributable to a PFO. Should it prove necessary to close these PFOs, this will become an important part of interventional cardiology even before other indications such as peripheral paradoxical embolism, migraine, diving, or perhaps selective mortality with a PFO per se are considered.

The risk for paradoxical stroke increases with age. Yet other reasons of ischemic stroke increase to a larger degree, thereby relegating paradoxical stroke to the not so important issues at old age. Table 1 reflects this (8-14).

Risk factors in addition to the PFO

Atrial septum aneurysm

An atrial septum aneurysm consists of a flimsy and redundant central part of the septum primum that moves with cardiac motion in and out of both atria (Fig. 3). The myth of an atrial septum aneurysm per se being a risk factor for embolism has been laid to rest after recent studies showing no risk with an atrial septum aneurysm without a PFO (15-16).

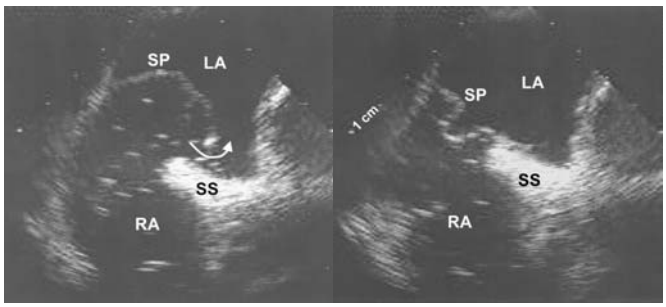

Fig. 3. Atrial septal aneurysm. The mobile central part of the septum primum (SP) in a leftward (left panel) and neutral (right panel) position. The septum secundum (SS) is a solid and immobile wedge. The patent foramen ovale is indicated between the two + signs. Some bubbles are seen in the right atrium (RA) about crossing to the left atrium (LA, arrow).

Other risk factors

A number of other factors enhancing the risk of a PFO are less well explored. There is the Eustachian valve, a ledge or membrane leading the blood from the inferior vena cava directly onto the foramen ovale (Fig. 4). A peculiar syndrome called platypnea orthodeoxia is probably associated with an Eustachian valve. In this syndrome, elderly people experience severe systemic hypoxia due to a massive right-to-left shunt while erect. Although the right atrial pressure remains below the left atrial pressure, the shunt is caused by the mere flow of the blood from the inferior vena cava directed (e.g., by a Eustachian valve) straight on to the mobile septum primum in the presence of a PFO, opening it like a draft of wind (1).

A further situation engendering a right-to-left shunt is pulmonary artery hypertension in the setting of chronic pulmonary disease or recurrent pulmonary embolism. Finally, coagulation disorders, such as pro-thrombotic genetic polymorphism (factor V Leiden mutation, anticardiolipin antibodies, protein C or S deficiencies, pro-thrombin G20210A mutation, etc) or thrombocytosis are of importance and particularly dangerous in the face of a PFO.

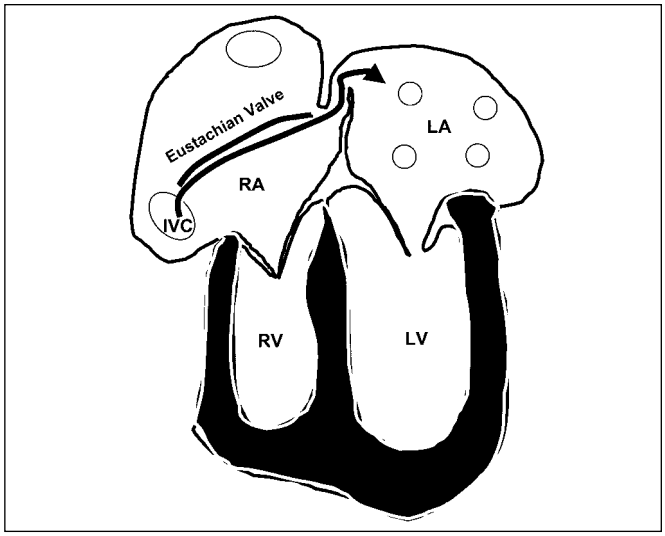

Fig. 4. Eustachian valve. A ledge or membrane that was useful during intra-uterine life to lead the blood from the inferior vena cava onto the open foramen ovale to facilitate the passage from the right atrium (RA) to the left atrium (LA) persists and remains directed to the PFO (or gets redirected to the PFO at a later age) This may also guide thrombi from the inferior parts of the body through a PFO.

LV = left ventricle, RV = right ventricle

While the etiologic role of the PFO can be deduced from its higher prevalence in ischemic stroke patients than patients dying without stroke in autopsy studies (17-27), the size of the PFO seems to understandably also play a role. It can be measured directly on a pertinent transesophageal echocardiographic still frame or deduced from the number of bubbles found in a still frame in the left atrium at the peak of bubble crossing after a prolonged Valsalva maneuver. The average PFO gap was measured to be 2.1 ± 1.7 mm in patients with clinical symptoms and 0.6 ± 0.8 mm in those without and the numbers of bubbles counted were 14 ± 11 versus 2 ± 1, respectively (28).

PFO and other disorders

Diving. Among other clinical entities and situations that have been identified as potential indications for PFO closure, underwater diving is the most commonly known. The compression illness leads to more brain defects in individuals with a PFO than in those without (29, 30). This has prompted diving schools to recommend to their students to have their fora-

men ovale checked and to either have it closed or to refrain from diving if it is patent.

Migraine. As a coincidental finding, migraine seems to be more prevalent among people with a PFO than among those without. The odds ratio for migraine was calculated to be about 5 in people under the age of 45 years (31). Closing the PFO appears to improve and sometimes even eliminate migraine, particularly the type with aura (32). We also found that brain lesions detected by magnetic resonance about double from 0,5 to 0,8, respectively, in migraine patients with a PFO compared with those without. Even looking at headache in general, the closure of PFO reduces significantly the incidence in our experience.

Other. It has been recognized that the presence of a PFO may be hazardous during surgical interventions that are prone for embolization of fat (orthopedic surgery) or air (neurosurgery, cardiovascular surgery) into the venous system (33).

Recurrence after cryptogenic embolism with and without PFO closure

Conservative treatment. The PFO Cryptogenic Stroke Study (PICSS) (34) a substudy of the Warfarin Aspirin Recurrence Stroke Study (WARSS) (35) yielded in the 42 patients with a cryptogenic stroke and a PFO randomized to warfarin treatment a recurrence (stroke or death) rate of 10% at two years compared with 18% in those randomized to acetylsalicylic acid. Although the difference was not significant, this suggests that warfarin might be the better treatment. Earlier studies had shown recurrence rates of stroke between 0 and 4.2% and of stroke or TIA of 3.4 to 16% (36-40) (Table 2). These studies did not differentiate between risk factors associated to the PFO. A French study on 581 patients with cryptogenic stroke who were treated with 300 mg of acetylsalicylic acid documented a risk of recurrent stroke or transient ischemic attacks (TIA) of 0% over 4 years for patients with an atrial septum aneurysm but no PFO, about 7% for those with a completely normal septum, about 12% for those with a PFO alone, and 35% for those with a PFO associated to an atrial septum aneurysm (40).

Table 2. Recurrence With Medical Therapy After Cryptogenic Stroke

Reference	Patients	Follow-Up (Months)	First Year CVA Recurrence	First Year CVA or TIA Recurrence
Comess (36)	33	12		16%/year
Hanna (37)	13	41	0%	
Mas (38)	132	22	1.2%	3.4%
Bogousslavsky	140	36	1.9%	3.8%
De Castro (40)	86	36	4.2%	5.5%

CVA = cerebo-vascular accident; TIA = transient ischemic attack

Percutaneous closure of the PFO

In 1976 a report on atrial septum defect closure with a transcatheter device appeared with a 2-year-follow-up (41). In the 80s, the Rashkind Clamshell Occluder was developed for the same purpose (42). It was later modified into the CardioSEAL and then the StarFlex device (Fig. 5). As for a couple of other

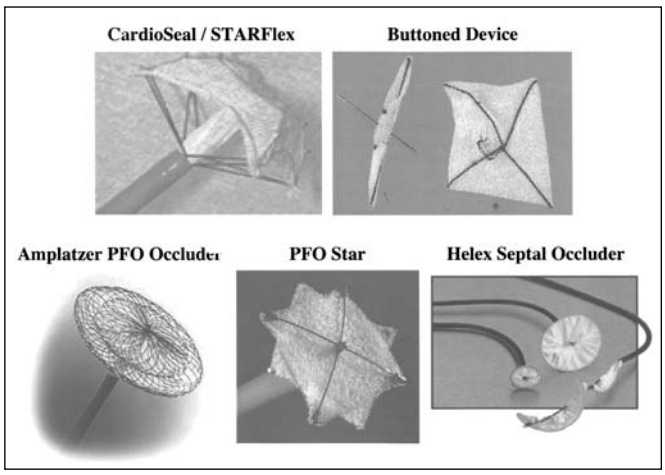

Fig. 5. Currently available percutaneous PFO occluders from top left to bottom right according to their appearance on the market: CardioSEAL/Star Flex (mostly used in the United States), Sideris Buttoned Device (virtually restricted to third world countries), Amplatzer PFO Occluder (overall best and most used device), PFO Star (used particularly in Germany) and the Helex Septal Occluder (the latest arrival and most expensive device).

devices developed for atrial septum defect, their easiest application turned out to be the patent foramen ovale. This was true for the Sideris Buttoned Device (43), the ASDOS device (44), the Monodisk (45) and the Angel-Wings device (46), (Fig. 5). It was also true for the Amplatzer Atrial Septal Defect (ASD) Closure Device (47).

The 90s saw the appearance of devices dedicated exclusively to PFO closure. The first was the Amplatzer PFO occluder (Fig. 5) of which we performed the world's first implantation in the presence of the inventor Kurt Amplatz on September 10, 1997, in Switzerland (48). Later followed the PFO star (49) and the Helex Septal Occluder (50) (Fig. 5). The latter is also marketed for ASD closure.

Several reports on series with different devices show complete closure rates of 90% and more and a low incidence of recurrent events that compares favorably with the reports of conservative treatment (51, 52).

Our experience with 375 patients aged between 18 and 80 years with a male percentage of 56% showed a complete closure rate at follow-up transesophageal echocardiography at 6 months of about 85%. However, there were clear differences between the result of various devices (Fig. 6). The Amplatzer device yielded the best results (complete closure rate about 90%, large residual shunt about 1%).

Complications have become extremely rare with modern techniques and are rarest with the Amplatzer device. Air

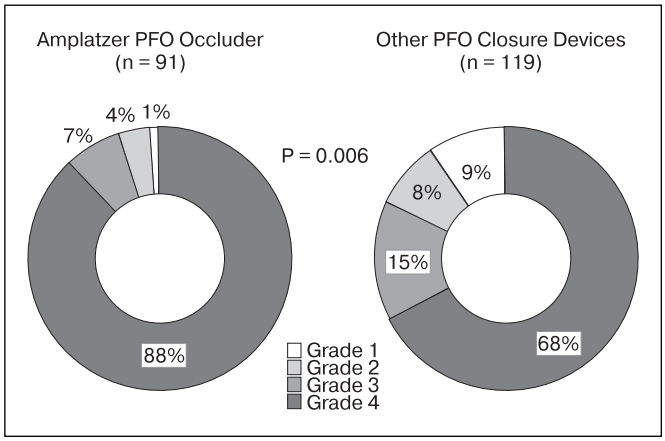

Fig. 6. Six months esophageal echocardiography follow-up results after PFO closure with an Amplatzer PFO Occluder (left) or a variety of other devices (right). The Amplatzer PFO Occluder results are superior.

embolism, atrial perforation, device migration, and puncture site problems have been reported. Long-term treatment varies among centers from coumadin/warfarin or clopidogrel combined with acetylsalicylic acid to no treatment at all. Thrombosis on the device is rarely seen and again seems to favor the Amplatzer device. It occurred in less than 1% in our series. In rare instances erosion of the atrial wall either into the pericardium or the aorta have been reported with all devices, again less with the Amplatzer device than with its competitors.

Surgical closure of PFO

Table 3 depicts results of surgical closure reported in the literature (53-56). The recurrence rates vary considerably. A 4% combined incidence of CVAs and TIAs, as reported from the Mayo Clinic in 1999, appears most reliable, although this study encompassed only 91 patients, with a follw-up of 4 years (56). Surgical closure is well established, safe (mostly young and otherwise healthy patients), and successful; however, it is not free from residual shunts or recurrent events.

Table 3. Surgical Results of Closure of Patent Foramen Ovale

Reference	Patients	Follow-Up (Months)	First Year CVA Recurrence	First Year CVA or TIA Recurrence
Zhu (53)	6	48	8.2%	
Devuyst (54)	30	24	0%	0%
Homma (55)	28	19	3.6%	19.5%
Dearani (56)	91	48	0	4.1%

CVA = cerebo-vascular accident; TIA = transient ischemic attack

Surgical closure has to date been largely replaced by percutaneous closure. Complete closure cannot be guaranteed surgically either, and complications related to surgery and general anaesthesia, such as wound infection, arrhythmia, and thrombosis from immobility have to be taken into account. Hence, surgery appears no longer an option for PFO closure. In our series, none of the patients in whom a device implantation was attempted for PFO needed a surgical closure later on.

Technique of percutaneous PFO closure

Implantation procedures vary among centers. Table 4 depicts the technique used at our center where echocardiography guidance is not used and PFO is not measured with a balloon prior to device implantation. The diagnosis is almost invariably established on the basis of a transesophageal echocardiography. Whether or not an atrial septum aneurysm is present, the 25 mm Amplatzer device is used. Only if this device cannot be safely anchored at the septum it is removed rather than set free and replaced by the 35 mm Amplatzer device. As the catheter gliding along the inferior part of the septum (septum primum) pushes this part away from the septum secundum, it is usually easy to canalize the PFO. Opening the left-sided part of the umbrella and pulling it back will close the valve like foramen ovale. There is significant resistance to pullin[9] the left-sided device through this closed foramen and therefore it is easy to correctly place the right-sided device, although the septum is not visible during fluoroscopy. We use a hand injection (Fig. 7) through the introducer sheath

Table 4. Technique of Percutaneous PFO Closure

- ≤ 1 night at hospital
- Local anesthesia
- Access: right femoral vein
- No balloon gauging
- No echocardiographic guidance
- Multipurpose catheter to cannulate PFO
- 0.035 inch (exchange) wire
- 6 - 14 French transseptal sheath
- Right atrial dye injections (by hand, LAO cranial)
- Antibiotics (1 - 3 doses)
- Acetylsalicylic acid 100 mg for 6 months and clopidogrel 75 mg for 1 month
- Recommendation for endocarditis prophylaxis for 6 months
- Final transesophageal echocardiography control at 6 months

(8-French for the 25 mm Amplatzer and 9 French for the 35 mm Amplatzer) to ascertain the correct position before setting the device free. Others use echocardiography (either transesophageal oder intracardiac) for the same purpose.

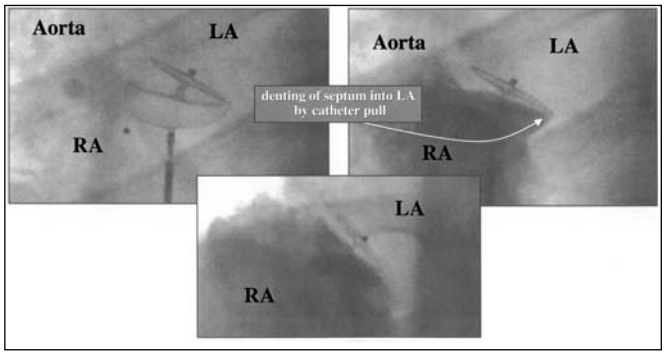

Fig. 7. Implantation of a 25 mm Amplatzer device to close a PFO. Top left: The typical position in an LAO cranial projection shows the two discs separated by the wedge-like septum secundum at 11:00 o'clock and practically touching at the lower part where the septum primum is very thin.

Top right: A hand injection of dye shows the correct position at the border of the right atrium with the lower part of the right-sided disc indenting the septum primum because of the catheter still pulling down the device.

Bottom: Final opacification of the right atrium after release of the device, confirming the perfect position.

LA = left atrium, RA = right atrium,

The implantation is easy to learn and might take as little as 10 minutes with the patient being able to get up after a couple of hours and leave the hospital without any restrictions.

The puncture is venous only and the device will not dislocate if properly inserted.

Clinical results of PFO closure

Our long term results are depicted in Fig. 8 and put in comparison with a series of patients with conventional treatment. While they are almost identical over the first two years, the following years seem to favor device closure. These results so

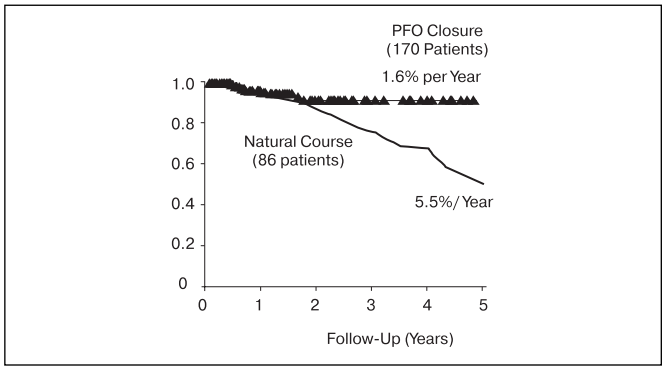

Fig. 8. Combined endpoints of death, stroke, or transient ischemic accidents during follow-up in our initial series in 170 patients using a variety of devices and a report on the natural course of patients with cryptogenic embolism (40).

far show two important points. First of all there seems to be an initial period where no improvement is apparent. This may indicate that a longer or more powerful antiplatelet or anticoagulant treatment is necessary for a prolonged period of time. Second, while the results look promising, a randomized trial is warranted to confirm them.

Outlook

A PFO unequivocally may have clinical importance. Children appear exempt from paradoxical embolism although they have a PFO. This is explained by the extremely low potential for thrombosis in their venous system. The older a person gets, however, the more likely a paradoxical embolism in the face of a PFO. Notwithstanding, left-sided embolic sources increase with age in an even more pronounced manner. Hence, the role of PFO as the culprit in ischemic embolic events peaks in middle age and current recommendations for indications account for this (Table 5). They may be subject to change.

Table 5. Current Indications of Percutaneous PFO Closure

- History of unequivocal and unexplained systemic embolism(s)
- Non-paradoxical source of embolism excluded by
  - ultrasound of
    - cerebral arteries
    - heart (transesophageal echocardiogram)
    - aorta
  - 24 hour electrocardiogram
  - screening for hypercoagulability
- PFO documented by echocardiography (spontaneous or provoked (period after Valsalva maneuver) shunt or bubble transit)
  - transthoracically, if clearly visible
  - transesophageally, if not clear transthoracically (period after Valsalva maneuver)

Randomized trials being underway, results are still lacking. Analyses of prospective series and matched comparisons do provide some evidence that PFO closure is indeed beneficial. It is already considered treatment of choice for patients with recurrent paradoxical embolic event and an atrial septum aneurysm associated with the PFO. Its use is also uncontested in the rare event of platypnea orthodeoxia. Percutaneous PFO closure, however, remains controversial in patients with a first embolic index event and a small PFO with no additional risk factors, in divers, and in patients with migraine.

Considering the fact that PFO closure can be accomplished with a negligible morbidity and mortality within 15 minutes, necessitating a local puncture at the groin only and the fact the patient can go back to a completely normal life including physical exercise a few hours after the procedure, one can envision a wide spread application of this treatment. The ultimate use being prophylactic closure of all PFOs in teenagers assuming a selective mortality of this anatomical variation.

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Stenting of the infarct-related artery within the first hours after acute myocardial infarction: immediate and mid-term results

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Introduction:

It has been established, that restoration of blood flow in infarct-related artery (IRA) performed within the first hours after an acute myocardial infarction (AMI) contributes to the limitation of size of the involved myocardium, uneventful course of the disease, prevention of pathological remodeling of left ventricle, and the decrease of mortality (1, 2, 3).

Among the methods of revascularization available today (thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA)), the latter is the most effective for the restoration of adequate antegrade flow in IRA (1, 2, 3, 6). However, despite the high efficacy of primary PTCA, the high rate of recurrent occlusion (5-10%) and restenosis (40%) is worthy of notice. This results in angina recurrence, the possibility of repeated infarction and the need for repeated revascularization (7, 8).

The implementation of coronary stenting into the clinical practice has given new opportunities for a more complete and long-lasting restoration of flow in IRA (4, 5, 6). Meanwhile, many questions concerning IRA stenting for AMI are yet to be answered. The most important of them include: 1) completeness of vessel lumen reconstruction, 2) the likelihood of acute or subacute stent thrombosis, 3) prospects of the results obtained, 4) the rate of restenosis and recurrent occlusion, 5) clinical prognosis of the disease (1, 2, 9).

The purpose of our study was to investigate immediate and mid-term results of IRA stenting in patients with AMI.

Material and methods

Since 1988 Moscow Center of Interventional Cardioangiology has acquired of over 800 endovascular procedures of myocardial revascularization performed within the first hours after AMI. Since 1997 we started to use IRA stenting procedure and we have performed it in 101 patients with AMI. These patients form group 1 of the study. Four hundred and thirteen (413) patients with AMI, who have underwent primary PTCA of IRA since 1997, served as control. They formed group 2. There were no significant differences in clinical pattern, past medical history or angiographic data between the two patient groups. (Tables 1 and 2.)

Table 1. Baseline clinical characteristics

CHARACTERISTICS	GROUP 1 (n = 101)	GROUP 2 (n = 413)	P
Age	54.8 ± 5.0	50.0 ± 2.5	P > 0.05
Male	77 (76.2%)	359 (86.9%)	P > 0.05
Arterial hypertension	68 (67.3%)	261 (63.2%)	P > 0.05
Smoking	47 (46.5%)	196 (47.5%)	P > 0.05
Diabetes mellitus	7 (6.9%)	41 (9.9%)	P > 0.05
Dislipidemia	73 (72.3%)	294 (71.2%)	P > 0.05
History of myocardial infarction	22 (21.8%)	61 (14.8%)	P > 0.05
Left ventricle ejection	55.2 ± 26.2	54.6 ± 23.3	P < 0.05
Time from the onset of heart attack:			
< 6 hours	53 (54.7%)	406 (98.3%)	P < 0.05
6 - 24 hours	44 (45.3%)	7 (1.7%)	P < 0.05

Table 2. Results of coronary angiography and description of angioplasty procedures in the groups studied

CHARACTERISTICS	GROUP 1 (n = 101)	GROUP 2 (n = 413)	P
Number of arteries involved			
-one	55 (54.4%)	240 (58.1%)	P > 0.05
-two	31 (30.7%)	130 (31.5%)	P > 0.05
-three or more	15 (14.8%)	43 (10.4%)	P > 0.05
Infarct-related artery:			
Left anterior descending artery (LAD)	49 (48.5%)	217 (52.5%)	P > 0.05
Circumflex branch	12 (11.9%)	31 (7.5%)	P > 0.05
Right coronary artery	36 (35.6%)	155 (37.5%)	P > 0.05
Marginal branch	2 (2.0%)	7 (1.7%)	P > 0.05
Diagonal branch	2 (2.0%)	3 (0.7%)	P > 0.05
Lesion type (AHA/ACC):			
A/B1 class	9 (8.9%)	109 (26.4%)	P < 0.05
B2 class	20 (19.8%)	52 (12.6%)	P > 0.05
C class	4 (3.9%)	4 (0.9%)	P < 0.05
Acute occlusion of IRA	68 (67.3%)	248 (60%)	P > 0.05
Lesion length, mm (as revealed after IRA recanalization)	14 ± 5.0	13 ± 4.0	-
Ultimate size of the balloon, mm	3.2 ± 0.8	3.0 ± 0.5	-
Maximum pressure, atmospheres	12 ± 2.2	9.0 ± 1.3	-

Those data show that the majority of patients in both groups were males (76-87%). Among the risk factors arterial hypertension (67.3% vs. 63.2%) and dislipidemia (72.3% vs. 71.2%) were most commonly observed in both groups (P > 0.05).

Procedures of stenting or PTCA were most commonly performed in the LAD - 48.5% and 52.5% of cases, the second most common location was the right coronary artery (RCA) - 35.6% and 37.5% of cases - and circumflex branch (CB) - 11.9% and 7.5% of cases, respectively. We found no significant differences in the prevalence and the extent of coronary lesions between the groups. The analysis of ACC/AHA lesion morphology revealed more severe type of lesions at baseline in the group of stenting: A/B1 class - 8.9% vs. 26.4% and C class - 3.9% vs. 0.9% in groups 1 and 2, respectively (P < 0.05). The number of occlusions was not significantly different between the groups (67.3% vs. 60%), P > 0.05. There was no difference in both minimal vessel lumen diameter at baseline

Table 3. Some details of IRA stenting procedure

CHARACTERISTICS	GROUP 1 (n = 101)
Stent type:	
- Cross-Flex (Cordis, Jonson & Jonson)	20 (18.0%)
- Angiostent (AngioDynamics NJ)	24 (21.6%)
- BxVelocity (Cordis, Jonson & Jonson)	20 (18.0%)
- Biodivysio (Biocompatible)	14 (12.6%)
- Multi-Link (Guidant, Santa Clara, CA)	10 (9.0%)
- Other	19 (17.1%)
Stent diameter:	
- 2.0-2.9 mm	15 (13.5%)
- 3.0-3.5 mm	78 (70.3%)
- 4.0 mm or more	18 (16.2%)
Stent length:	
- 8-11 mm	9 (8.2%)
-13-15 mm	56 (50.4%)
- 17-28 mm	46 (41.4%)
Total number of stents in IRA:	111

(MVLD) and diameter in stenosis site before the procedure between the groups (Table 4).

PTCA procedure was performed according to the procedure adopted in the Center (3).

We tried to restore the vessel lumen as completely as possible. Indications for stenting included: 1. Suboptimal outcome of primary PTCA (residual stenosis ≥ 50% with type A and B dissection) - 49 (85.5%) cases. 2. Complicated PTCA (acute occlusion or ACC/AHA type C-F dissection of intima) - 21 (20.8%) cases. Direct (without predilatation) and primary stenting were performed in 8 (8.2%) and 23 (22.8%) cases, respectively. Direct stenting was conducted in case of IRA stenosis (not occlusion). For precise selection of stent diameter we conducted computerized calculation of the stenosis degree, length of lesion and the diameter of adjacent intact vessel area using stenosis degree calculation program, provided by Siemens company on Hicor computer.

A total of 118 stents were implanted to 101 patients, among them 111 were placed in infarct-related arteries. Most frequently we used coil stents - CrossFlex (Cordis, Jonson & Jonson) - 18,0% and Angiostent (AngioDynamics NJ) - 21.6% of cases; modular stents - BxVelocity (Cordis, Jonson & Jonson) and Biodivysio (Biocompatible) were used in 18.0% and 12.6% of cases, respectively; among tubular stents Multi-Link (Guidant, Santa Clara, CA) were used in 9.0% of cases (Table 3).

Table 4. Immediate and midterm outcome of stenting and PTCA of IRA (quantitative angiographic criteria)

	GROUP 1	GROUP 2	P
Reference diameter, (mm):			
Before the procedure	3.06 ± 0.56	3.05 ± 0.46	P > 0.05
After the procedure	3.01 ± 0.46	3.02 ± 0.56	P > 0.05
Midterm period	2.99 ± 0.43	2.98 ± 0.53	P > 0.05
Stenosis distance. (%)			
Before the procedure	95 ± 10	94 ± 17	P > 0.05
After the procedure	11 ± 16	33 ± 14	P < 0.05
Midterm period	35 ± 23	46 ± 23	P < 0.05
MVLD. (mm)			
Before the procedure	0.23 ± 0.25	0.24 ± 0.24	P > 0.05
After the procedure	2.73 ± 0.4	2.12 ± 0.45	P < 0.05
Midterm period	2.03 ± 0.4	1.68 ± 0.76	P < 0.05

In 92 (91%) cases a single stent was implanted into IRA, in eight patients 2 IRA stents were used for each patient, in one patient 3 stents were implanted. In the overwhelming majority of cases we used stents ≈ 15 mm in length (mean 15 ± 7 mm) and ≈ 3 mm in diameter (mean 3.2 ± 0.8 mm). Stenting was performed using a pressure of 12 ± 2.2 atm. If successful angiographic image was obtained, stenting was completed; otherwise the balloon was inflated repeatedly until an optimal result was achieved. In most cases repeated inflation was done with the same balloon. Stent completely covered the affected area of the artery in all patients, vessel contour in the site of stenting was regular, smooth, without stenosis. Implantation result was assessed visually, in addition, vessel diameter was calculated before and after the procedure. Intravascular ultrasound study was not performed.

In case of multivessel lesions, simultaneously with IRA stenting other endovascular procedures were performed in other arteries of 16 patients (15.8%) from group 1 and 19 patients (4.6%) from group 2. Therefore, complete revascularization was conducted in 68 patients (67.3%) from group 1 and 259 patients (62.7%) from group 2.

Intravenous bolus of heparin was administered in a dose of 10000 IU prior to angioplasty. Nitroglycerin, dextrane, heparin were given I.V. in a drip controlled by activated coagulation time (ACT). ACT value was maintained at 330-350 seconds. Immediately before stenting the patients were administered ticlopidine 500 mg and aspirin 325 mg; IIb/IIIa platelet receptor inhibitors were not used. After the procedure the patients were observed in intensive care unit, where the infusion solutions were continued. Introducers were removed 8-12 hours after procedure. After the removal of introducers the patients were transferred to the Department of acute myocardial infarction.

Results

Hospital period. Immediate angiographic success of the procedure (residual stenosis <30%, no type C-F dissection with restoration of antegrade TIMI 2-3 flow) was high in both groups, however it was significantly higher after IRA stenting - 100% vs. 90.8%. Antegrade TIMI 2 flow after the procedure was observed in 4 (3.9%) patients from group 1 and 38 (9.2%) patients from group 2 ($P < 0.05$). The degree of residual stenosis after the procedure in the groups studied was 11 ± 16% and 33 ± 14%, respectively, ($P < 0.05$). Minimal vessel lumen diameter (MVLD) was higher in group 1 compared to group 2 - 2.73 ± 0.4 mm vs. 2.12 ± 0.45 mm, ($P < 0.05$). In group 1 residual stenosis was mostly under 20%, intimal edges in the site of stenting were regular, smooth, without stenosis.

Mid-term results assessment using quantitative angiographic criteria revealed direct correlation between the rate of restenosis in the target segment and the degree of residual stenosis immediately after the angioplasty procedure in both groups. Evaluation of the fate of side branches in case of bifurcational IRA lesion revealed, that IRA bifurcational lesions were seen in 29 of cases in group 1, i.e. 28.7% of patients were at risk of side branch involvement. However, only in 4 (13.8%) patients IRA occlusion resulted from stenting. In all four cases tubular stents were used. Bifurcational lesions were mostly observed in the left anterior descending branch of

LCA (LAD). In group 2 the bifurcational lesions were found in 56 patients, i.e. the risk of side branch involvement was 13.6%. However, side branch occlusion was seen in 27 (6.5%) patients. One can consider, that coronary angioplasty doesn't always result in occlusion of side branches, which origin from the site of intervention, regardless of the fact whether PTCA or stenting was performed. At the same time, IRA stenting is less commonly associated with occlusion, than PTCA. This is particularly true for coil stents. It has to be noted, that in the majority of cases side branch occlusion following IRA angioplasty, performed with PTCA or stenting, was not associated with negative ECG or clinical signs, indicating the enlargement of affected area. This can be explained by the fact, that these branches were initially located distally to IRA occlusion and their flood flow was restored only after IRA recanalization.

Table 5. In-hospital clinical and angiographic outcomes

VARIABLE	Group 1 (n = 101)	Group 2 (n = 413)	P
- ABSENCE OF ANGINA	94 (93.1%)	360 (87%)	P < 0.05
- AMI RECURRENCE	1 (0.9%)	9 (2.2%)	NS
- MORTALITY RATE			
- total	3 (2.9%)	21 (5.1%)	NS
- cardiac	3 (2.9%)	16 (4.0%)	NS
STENT THROMBOSIS/ RECURRENT IRA OCCLUSION	7 (6.9%)*	33 (8.0%)*	NS
URGENT REPEATED PTCA	3 (2.9%)	15 (3.6%)	NS
CINICAL SUCCESS**	89.1%	82.8%	P < 0.05

* Including patients with lethal outcome

** Freedom from death, recurrent AMI, angina necessitating repeated PTCA/CABG

Basic parameters, characterizing the clinical course of the disease before the discharge in patients with AMI following IRA angioplasty, are presented in Table 5.

Among severe complications seen in the hospital, acute stent thrombosis occurred in group 1, in 5 cases (4.9%) within the first 4-12 hours and in 2 cases (1.9%) - within 2 days after the beginning of disease. In three of those cases (2.9%) patients died. In three cases of acute and subacute stent occlusion we used Cross-Flex (Cordis, Jonson & Jonson) stent 4-3,5-3 mm in diameter and 20-18-15 mm in length, in two more cases BxVelocity (Cordis, Jonson & Jonson) stent 3,0 mm in diameter and 18-20 mm in length was deployed. One case of acute and subacute occlusion was observed after stenting with both Angiostent (AngioDynamics NJ) 3.5 x 15 mm stent and Multi-Link (Guidant, Santa Clara, CA) 3.5 x 23 mm stent.

In group 2 vessel thrombosis (recurrent occlusion) was seen in 33 cases (8.0%), among these 16 (4.0%) resulted in death, 9 (2.2%) led to recurrence of acute myocardial infarction. In 3 patients (3.1%) from group 1 and 15 patients (3.6%) from group 2 we performed mechanical recanalization of occlusion and successful repeated PTCA with restoration of vessel lumen and blood flow. In these patients further course of disease was uncomplicated. In the remaining patients the attempt of mechanical revascularization and angioplasty was unsuccessful.

Therefore, clinical success after stenting (89,1%) was higher than after primary PTCA of IRA (82.8%), P < 0.05. In group 1 the number of patients without angina was significantly higher, as compared to group 2 (93.11% vs. 87%). During hospital period some parameters were slightly more favorable in group 1 than in group 2, these were: cardiac mortality rate (2.9% vs. 4.0%), recurrence of myocardial infarction (0.9% vs. 2,2%), IRA thrombosis (6.9% vs. 8.0%); however this difference wasn't significant (P > 0.05).

Mid-term period. (Table 6). Information on the midterm follow up was obtained after 8.9 ± 2.7 months from 91 (92.8%) patients in group 1 and from 376 patients (91%) in group 2. Out of these, repeated coronary angiography was performed to 71 patients (78%) in group 1 and 351 patients (93.3%) in group 2. There were no significant differences in baseline clinical and historical data between the groups studied.

Control coronary angiography detected significant differences between the groups studied: in group 1 IRA restenosis and recurrent occlusion were significantly less common as compared to group 2: (22.5% vs. 32.7%) and (4.2% vs. 9.1%), respectively (P < 0.05). The need for repeated endovascular procedures (19.7% vs. 27.6% of cases) and coronary artery bypass grafting (7.0% vs. 14.2%) were also significantly lower in group 1 compared to group 2, P < 0,05.

The analysis of factors potentially influencing the development of in-stent stenosis in mid-term period showed, that the use of coil stents in AMI patients was significantly more frequently associated with in-stent stenosis, than the use of modular or tubular stents - 52.6% vs. 31.6% and 15.8% of cases, respectively (P < 0.005). In addition, in-stent stenosis was more common with the stents less than 3 mm in diameter (26.3% vs. 11.5% of cases) and more than 15 mm in length (31.6% vs. 15.4% of cases), respectively (P < 0.005). Severe complications during the mid-term period (angina recurrence, repeated MI, death) were mostly observed in patients with restenosis or recurrent occlusion of IRA (Table 6).

The following parameters were significantly lower in IRA stenting group: cardiac mortality (0.9% vs. 4.5%), repeated AMI of IRA territory (1.9% vs. 6.9%), angina recurrence demanding repeated endovascular procedures/coronary artery bypass grafting (26.7% vs. 41.8%) (P < 0.05). Patient survival rate was 95.6% vs. 93.3% of cases in PTCA group (P < 0.05). The analysis showed, that the survival rate after endovascular procedure is directly related to the severity of coronary atherosclerosis and the state of left ventricle myocardium.

Table 6. LONG-TERM CLINICAL AND ANGIOGRAPHICAL RESULTS

VARIABLES	GROUP 1 (n = 91)	GROUP 2 (n = 376)	P
- ABSENCE OF ANGINA	71(81.6%)	229 (60.9%)	P < 0.05
- REPEATED MI (non-fatal)	2 (1.9%)	26 (6.9%)	P < 0.05
- MORTALITY RATE • Total • Cardiac	 4 (3.9%) 1 (0.9%)	 25 (6.6%) 17 (4.5%)	 NS P < 0.05
Primary effect of IRA restoration maintained	52 (73.2%)	204 (58.1%)	P < 0.05
RECURRENT OCCLUSION	3 (4.2%)	32 (9.1%)	P < 0.05
RESTENOSIS	16 (22.5%)	115 (32.7%)	P < 0.05
REPEATED PTCA	14 (19.7%)	97 (27.6%)	P < 0.05
NEED FOR CORONARY ARTERY BYPASS GRAFTING	5 (7.0%)	50 (14.2%)	P < 0.05

The assessment of left ventricle ejection fraction in the mid-term period showed, that this value increased generally as compared to baseline characteristics from 55.3 ±

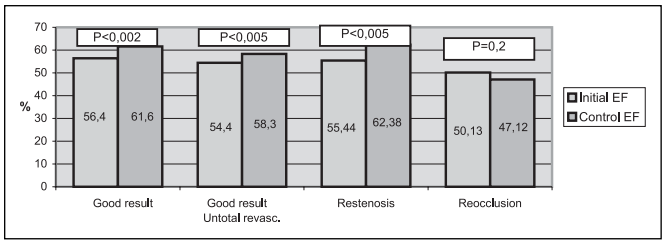


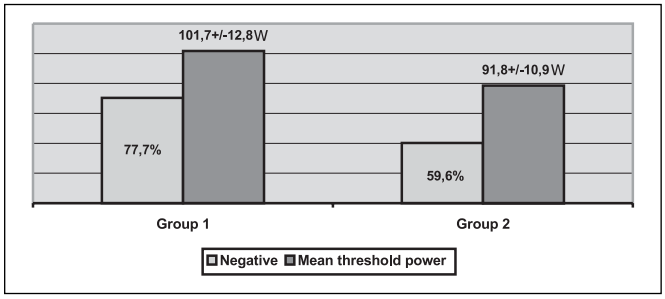
Fig. 1. Long-term dynamics of left ventricle ejection fraction

11.4% to 60.2 ± 12.7% P < 0.005. The study also revealed, that left ventricle ejection fraction significantly increased in patients with preserved antegrade flow in IRA, this applies even to cases, when in-stent stenosis was diagnosed. The most significant growth of left ventricle ejection fraction was observed in patients with complete myocardial revascularization (from 56.4 ± 11.2% to 61.6 ± 11.8%), P < 0.005.

Meanwhile, in patients with IRA recurrent occlusion there were no significant positive changes. The most convincing growth of left ventricle ejection fraction was seen in patients with Q-wave infarction, with initial ejection fraction <40%. The faster revascularization procedure was initiated after AMI, the more pronounced effect it was.

In order to determine the reserve capabilities of coronary flow and its dependence from myocardial revascularization, we performed physical stress test (Fig. 2).

Physical exercise test results showed more favorable results in patients after stenting. These patients had higher mid-term exercise tolerance 101.7 ± 12.8 W compared to



91.8 ± 10.9 W, and higher rate of negative test results: 77.7% vs. 59.6% (P < 0.005). The results obtained can be doubtlessly related to mid-term IRA state and its effect on myocardium function in the mid-term period.

Therefore, the assessment of mid-term results revealed substantial differences in the rate of severe cardiac events (death, repeated AMI, need for coronary artery bypass grafting and repeated PTCA), which was more favorable in IRA stenting group - 68.1% vs. 56,9% in PTCA group, respectively (P < 0.01).

We found it interesting to investigate the mid-term outcomes in the groups studied depending on the completeness of myocardium revascularization. For this purpose, we divided the patients into subgroups of complete and incomplete revascularization in both groups (Table 7).

As shown in the table, such important characteristics as the absence of angina, mortality rate and repeated AMI, differ significantly between the groups studied.

Table 7. Mid-term results in patients with complete/incomplete myocardium revascularization

VARIABLES	GROUP 1 n = 91		GROUP 2 n = 376		P
	Complete n = 66	Incomplete n = 25	Complete n = 259	Incomplete n = 117	
Absence of angina	59	18 (72%)	172	55 (47.0%)	P < 0.05
Cardiac mortality	1 (1.5%)	0%	5 (1.9%)	12 (10.2%)	P < 0.05
Repeated MI in IRA	1 (1.5%)	1 (4.0%)	10 (3.8%)	16 (13.6%)	P < 0.05
Repeated MI in the territory of another coronary artery (used for endovascular procedure)	1 (1.5%)	0%	6 (2.3%)	14 (11.9%)	P < 0.05

Discussion

Numerous studies have proved the high efficacy of PTCA in terms of restoration of antegrade flow in IRA, significant improvement of peri-infarction area perfusion, limitation of necrosis area and improvement of prognosis in patients with AMI (1, 2, 11). However, the main negative aspects of IRA PTCA have been restenosis and recurrent occlusion, occurring immediately after the procedure (7-15% and 5-10% of cases) and in the mid-term period (25-40% and 9-15% of cases), and potentially leading to severe complications (angina recurrence, repeated AMI, need for repeated revascularization, death) (7, 8, 9). The results appear dramatic when PTCA procedure is associated with serious complications (acute thrombosis, threatening or real intimal dissection of type C-F causing vessel occlusion). In such patients early recurrent occlusion, repeated AMI are common, mortality rate and the need for emergency coronary artery bypass grafting increase (7). These patients are apparently candidates for stenting. Nevertheless the use of stenting for acute coronary syndrome, when acute coronary thrombosis is common and, hence, the likelihood of acute stent thrombosis increases, has been studied incompletely. The extensive use of new desaggregants in clinical practice (especially plavix and ticlid) has opened the prospects of successful stenting both in patients with chronic CHD forms as well as with acute myocardial infarction (10).

In this study stenting was done in cases of suboptimal result, as well as after unsatisfactory outcome of primary IRA PTCA (85.5% and 20.8%, respectively). In cases, when non-occlusive thrombosis or subtotal stenosis of IRA occurred, we used direct stenting (without predilatation) and primary stenting in 8.2% and 22.8% of cases, respectively.

Despite the less favorable baseline anatomic conditions in group 1 patients, as assessed by coronary angiography, their immediate angiographic success rate (<30% residual stenosis and restoration of TIMI 2-3 antegrade flow) was higher, reaching 100% vs. 90.8% in group 2 (P < 0.005). In addition, residual stenosis degree (12 ± 16% vs. 33 ± 14%) was substantially lower in the stented group (P < 0.05). In other words, changes of vessel geometry following stenting are more significant, than in group 2. MVLD is increased (2.03 ± 0.4 mm vs. 1.68 ± 0.76 mm) and residual stenosis degree - decreased, thus contributing to the restoration of antegrade flow.

Clinical success rate (89.1%) was also higher compared to primary IRA PTCA (82.8%), P < 0.05. During hospital stay these patients didn't differ by cardiac mortality rate (2.9% vs. 4.0%), repeated myocardial infarction (0.9% vs. 2.2%), IRA thrombosis (6.9% vs. 8.0%) (P > 0,05). At the same time, in group 1 there

were more patients without angina (93.1% vs. 87%) and lower need for repeated endovascular interventions, P < 0.05. Meanwhile, a serious problem was acute/subacute stent thrombosis, seen in 7 (6.9%) cases. Therefore, one can consider, that stenting in AMI patients is associated with a slightly more frequent thrombotic occlusion of coronary arteries as compared to patients with chronic CHD.

The reasons for this complication are yet to be cleared completely. However, it is worthy of notice, that activated coagulation time during and immediately after the procedure in all these patients was lower, than the required level, which could serve as the cause of thrombosis. This group of patients is reported to have the highest per cent of stent thrombosis during hospital stay (13, 14) (8-18%), which is significantly higher, than in patients after primary (routine) stenting (0-3%). Several authors report, that the main causes of stent thrombosis are: (1) coagulation disorders after AMI; (2) marginal dissection of intima, which occurs due to unfolding and intrusion of stent into the vessel wall; (3) Low contractility of myocardium on admission (Killip class III-IV); (4) Compensated antegrade flow (TIMI grade <3); (5) Less smooth surface and poor geometry of stenting segment with subsequent blood viscosity disorders in case of bailout stenting (12, 14).

The assessment of mid-term results revealed significant differences in cardiac mortality rate and the percentage of repeated AMI in IRA territory (0.9% and1.9%), whereas after PTCA the mortality rate was 4.5%, and the frequency of repeated myocardial infarction was 6.9% (P < 0.05). In both groups there were patients without angina - 81.6% and 60.9%, respectively. Control coronary angiography showed a total rate of restenosis and recurrent occlusion to be lower in patients after stenting (26.7% vs. 41.8%), which determined the low need for repeated endovascular procedures (19.7% vs. 27.6%, P < 0.05). It is doubtless, that the major causes of cardiac events in the long-term period were restenosis and recurrent occlusion in both stenting and PTCA groups. The maintenance of good outcome after endovascular procedure performed in IRA also has an effect on reserve capabilities of myocardium and contractility of the left ventricle, and, therefore, on the survival rate. The study has clearly shown, that complete revascularization of myocardium is associated with lower rate of mortality, repeated AMI and angina recurrence. Hence, complete revascularization should be performed in emergency cases.

Therefore, this study has shown, that stenting performed in patients with AMI improves clinical course of the disease both during hospital stay and in the long-term period, compared to similar patients, who underwent PTCA. In AMI patients, stenting reduces the rate of restenosis and recurrent occlusion in the mid-term period, thus improving the prognosis.

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Clinical, laboratory, angiographic and genetic factors of restenosis following coronary stenting

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Purpose: to analyze the role of clinical, laboratory, angiographic and genetic factors in the development of restenosis after coronary stenting

Materials and results: we analyzed clinical, laboratory and angiographic factors in 86 male patients with post-coronary stenting CAD. Restenosis developed in 30 patients after surgery. There were no significant differences in conventional risk factors of CAD between patients with and without restenosis. Analysis of the results of coronary angiography showed restenosis to be more common in patients with lesions in proximal third of the left anterior descending (LAD) (64% vs. 46%; $p < 0.05$), long lesions (15.8 ± 2.8 mm vs. 8.9 ± 3.4 mm; $p < 0.05$) and/or eccentric lesions (53% vs. 25%; $p < 0.01$). There were no significant differences in polymorphisms of the genes assessed, however a trend was revealed towards greater prevalence of DD genotype in patients with restenosis ($p = 0.06$). In 17 patients without restenosis CAD symptoms recurred at follow-up, coronary angiography showed hemodynamically significant stenoses of other locations. The 35% prevalence of DD genotype in this group was comparable to that of patients with restenosis and was significantly higher, than in patients without restenosis or stenosis of other location - 16% ($p < 0.05$).

Conclusion: "Conventional" risk factors for atherosclerosis and CAD don't have any substantial effect on restenosis development. The role of restenosis morphology (involvement of proximal one third of LAD, long lesion and/or eccentric lesion) seems more important. The role of DD genotype of ACE gene in restenosis is less obvious.

Keywords: ID polymorphism of angiotensin-converting enzyme gene, methylenetetrahydrofolatereductrase gene polymorphism, apo-E lipoprotein gene polymorphism, restenosis, risk factors, stenting.

Technical improvement in coronary angioplasty and stenting for CAD and the decrease of the rate of complications have considerably expanded the indications for this method use. This, in its turn, has determined the formation of a large group of patients with recurrent stenosis in the operated artery (restenosis). Restenosis develops within 6 months postoperatively after approximately one third of successful interventions (1, 2, 3, 4).

To date the major role in pathogenesis of restenosisis attributed to the proliferative processes induced by mechanic injury rather than to atherosclerosis (5, 6). From this point of view the publications suggesting the absence of any significant influence of the main CAD risk factors, such as arterial hypertension, hyperlipidemia, smoking and obesity, on restenosis frequency are becoming explainable (7).

Reports of the role of genetic polymorphisms, which are supposed to influence the likelihood of restenosis, are more contradictory. The choice of culprit genes in this work is based on both information taken from the literature and on possible effects of expression products of these genes on pathogenic mechanisms of restenosis, particularly on endothelial and smooth muscle cell hyperplasia and proliferation accompanied with production of collagen and elastin (8, 9, 10, 11, 12, 13, 14).

The purpose of the study was to analyze the role of clinical, laboratory, angiographic and genetic factors in the development of restenosis following coronary stenting.

Materials and methods

The study enrolled 86 male patients aged from 34 to 69, who underwent coronary angioplasty with stenting. All patients were examined according to the standard guidelines prior to intervention and at follow-up visits 6-8 months thereafter. Overall assessment included the analysis of clinical data and conventional risk factors of CAD, such as dislipidemia, arterial hypertension, excessive body weight, smoking, glucose intolerance and diabetes mellitus, hypodynamia; in addition, echocardiography, exercise tests and coronary angiography were performed. Coronary angiography was repeated in case of CAD symptoms recurrence. The period of follow-up was 2.5 to 4 years.

The analysis of coronary angiograms included lesion location, length, reference diameter of the vessel, degree of coronary artery stenosis, presence of multivessel coronary atherosclerosis. Restenosis after successful intervention was determined as recurrent narrowing of the dilated coronary artery segment that diminished the arterial lumen by 50% or more.

Genotype of all patients was analyzed using DNA polymerase chain reaction for three polymorphisms - ID polymorphism of angiotensin-converting enzyme (ACE), C677T mutation polymorphism of methylenetetrahydrofolatereductase (MTHFR) and apo-E lipoprotein gene polymorphism (apo E).

Statistical analysis was performed with Student t-test and Fisher exact test for significance of proportion difference.

Results

Control examination revealed restenosis in 30 patients, with 27 patients having angina, and 3 patients - silent myocardial ischemia. No clinical or instrumental signs of myocardial ischemia were observed in the remaining 50 patients.

There were no significant differences in conventional risk factors of atherosclerosis and CAD between the groups (Table 1).

Analysis of coronary angioplasty results showed restenosis to be more common in patients with preexisting lesion in proximal left anterior descending artery, with high degree or nearly occlusive stenosis, and prolonged and/or eccentric lesions (Table 2).

Table 1. Risk factors in the groups studied

	Patients with restenosis	Patients without
Hyperlipidemia	73%	61%
Arterial hypertension	43%	50%
Smoking	53%	54%
Body mass index >27 kg/m^2	33%	41%
Diabetes mellitus and glucose intolerance	13%	9%

We found no significant differences in assessed gene polymorphisms, however, considerable trend towards a greater prevalence of DD genotype in patients with restenosis was detected (p = 0.06) (Table 3).

Table 2. Comparison of angiography results between the groups

		Patients with restenosis (n = 30)	Patients without restenosis (n = 56)
Left anterior descending artery	Proximal segment	64%*	46%
	Other location	13%	20%
Circumflex Artery	Proximal third	22%	18%
	Other location	5%	2%
Right coronary artery	Proximal third	37%	29%
	Other location	-	5%
Lesion length		15.8 ± 2.8*	8.9 ± 3.4
Multiple lesions		61%	64%
Relative diameter		2.99 ± 0.42	3.32 ± 0.39
Occlusion		27%	13%
Eccentric location		53%**	25%

* - significant difference, p < 0.05,

** - p < 0.01,

In 17 patients symptoms of CAD recurred after 3 years. Coronary angiography failed to reveal restenosis of the operated area, while hemodynamically significant stenoses of other location were found.

Table 3. Genetic polymorphisms in the groups studied

	Patients with restenosis (n = 30)	Patients without restenosis (n = 56)
DD genotype patients	37%	21%
ID genotype patients	43%	55%
II genotype patinas	20%	21%
TT and CT genotype patients	33%	27%
CC genotype patients	67%	73%
22, 23, 34 genotype patients	33%	39%
33 genotype patients	67%	61%

The 36% DD genotype prevalence in this group is similar to that in restenosis patients, being significantly higher, than in patients without restenosis or stenoses of other location, where the prevalence of this genotype was 16% (p < 0.05).

Discussion

The obtained results suggest that conventional risk factors of atherosclerosis and CAD, such as dislipidemia, arterial hypertension, smoking, increased body mass index, don't play a considerable role in restenosis development, which agrees completely with published data. However, in contrast to our results , diabetes mellitus is found to have considerable effect by the majority of authors. This discrepancy is perhaps due to the small number of patients with diabetes mellitus in the study group (4 patients) and their inclusion in the group together with glucose intolerance patients.

The role of stenosis morphology, including its location in the proximal segment of left anterior descending artery, lesion length and/or eccentricity, occlusion or subocclusion, seems to be more important.

The role of DD genotype of ACE gene in restenosis development is less apparent. The proliferative action of renin-angiotensin system components is most likely to play a certain role both in restenosis development following coronary interventions and in progression of coronary atherosclerosis.

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Balloon angioplasty in the treatment of coronary artery disease in the transplanted heart

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The problem: The absence of painful symptoms in allogfaft ischemic myocardial injury makes coronary angiography one of the principal techniques for the diagnosis of coronary artery disease in the transplanted heart.

Results: We present the results of 124 examinations of 46 patients in the different periods after heart transplantation. The stenosing coronary artery lesion was recognized in 41% of cases. Stenoses in proximal segments of major branches were recognized in 44% of patients with signs of transplant coronary artery disease. In cases when the degree of stenosis exceeded 50% of arterial size, PTCA was performed. 9 patients underwent coronary angioplasty in the period from 9 days to 8 years after orthotopic cardiac transplantation. Since the calcification in the transplanted heart vessels was uncommon, in most cases (90%) the stenoses were amenable to balloon angioplasty and didn't demand the use of stents. Incidence of restenoses in the cardiac allogfafts is higher than in the native arteries of patients with CAD, which can be explained by the particularities of pathogenetic mechanisms in developing vascular lesions of the transplanted heart and by individual variability of immunologic activity in recipients. In the other cases (7 patients) the character of coronary artery lesion didn't permit to perform the balloon angioplasty. In one case the heart retransplantation was performed, in another case it was the aortocoronary bypass surgery. However, in view of diffuse character and generally distal localization of coronary artery lesion, the aortocoronary bypass surgery is ineffective and connected with higher risk for patient. Heart retransplantation is characterized by suboptimal transplant survival rate as compared with the initial cardiac transplantation. Under these conditions, the coronary angioplasty appears an alternative technique of treatment in patients with lesions of large subepicardial arteries in the transplanted heart.

Key words: cardiac transplantation, coronary angioplasty, transplant coronary artery disease.

The development of pathology in cardiac allograft's coronary arteries is one of the principal causes of donor heart injury and of the mortality in the long-term periods after cardiac transplantation (3, 34).

The development of allograft coronary angiopathy by virtue of absent afferent innervation is going on without anginal symptoms characteristic for ischemia and can clinically manifest itself as a developing acute miocardial infarction, heart failure or sudden death. In this connection the early recognition of coronary artery lesions takes on the most actuality.

Coronary angiography is the most appropriate method of diagnosis for the recognition of the symptoms of transplant's coronary angiopathy (13, 14, 23).

Most authors agree, that the most important factors influencing the development of transplant coronary artery disease are the immunological incompatibility by HLA-antigens between donor and recipient and acute crises of cellular and humoral rejection (1, 5, 9, 18, 25, 26, 27). But not only immunological mechanisms contribute to the progression of transplant coronary artery disease. Non- immunological factors include characteristics of donor and recipient as well as the different variants of immunosupressive therapy. The age of recipient, post-transplantation arterial hypertension, dislipidemia, previous ischemic disease of the native heart, cytomegaloviral and herpetic infections, diabetes mellitus are the factors determining the probability of coronary lesions in the transplanted heart. Previous diseases of recipient, duration of ischemia and reperfusion lesions of transplant also play a significant role.

Pathomorfology of transplant vascular lesion has been described in details by M.E. Billingam in 1987 (6). According to his data, the transplant coronary artery lesions can be divided into two large groups: 1) chronic rejection, 2) atherosclerosis.

The chronic rejection appears as a concentric intimal proliferation evenly distributed along the whole length of epicardial vessels, including small branches. This thickening consists of intimal cells, monocytes and macrophages and also of a small amount of lymphocytes. The medial vascular layer and internal elastic membrane are usually intact, although sometimes the medial fibrosis can be seen . Since the intimal thickening is uniform, the small-sized epicardial arteries suffer more than the large ones. This fact differentiates the chronic rejection from atherosclerotic lesions, which are discrete, affect the larger proximal coronary vessels, are eccentric and in these cases the internal elastic membrane and a muscular system of the media are often affected. The most characteristic sign of transplant coronary disease on autopsy or in explants is the presence of cord-like, orange-colored coronary vessels at the surface of the heart. As a rule they can be more readily palpated than visualized (7, 8). Microscopic examination indicates that neither elastic nor medial membranes are involved in the stenosis of vascular lumen. Small-sized injuries are sometimes found on the membrane, but its form is intact and the media is thickened only in some vessels. And only internal layer (the intima), affected by concentric proliferation, obstructs completely or partially the vessel's lumen. It is the proliferation of intima that causes reduction of the vessel's diameter. This event is observed not only in the large epicardial vessels, but often also in small intramyocardial vessels (2, 32).

Atheroma, usually present in spontaneous atherosclerosis is rarely found in patients with transplant coronary artery disease (6). Platelet aggregation is practically absent. This is explained by long-term use of desaggregants and anticoagulants, prescribed to all patients after cardiac transplantation (31).

In contrast to asymmetric plaques characteristic of atherosclerosis, when the large coronary arteries are predominantly affected, lesions of transplant vessels are characterized to a greater extent by symmetric occlusions along the whole length of small coronary arteries resulting in the formation of triangular-shaped microinfarctions (19).

Angiographic alterations recognized during the examination of allograft coronary bed have a number of specific signs that differentiate them from coronary lesions inherent in atherosclerosis with ischemic heart disease. The classification of angiographic signs of coronary disease in the transplanted heart suggested by Gao S.Z. et al.in 1988 (15) included 4 principal types of lesion:

Type A - local and (or) tubular extensive stenosis as well as multiple stenoses in proximal, medial and distal segments of branches;

Type B1 - diffuse concentric stenosis with normal proximal diameter of vessel and drastic onset of distal concentric stenosis up to total occlusion;

Type B2 - gradual progressive cone-shaped narrowing from normal proximal segment to severe stenosis at the distal part of the vessel;

Type C - irregularly shaped vessels with diffuse lesion, stump and complete obstruction of arterial distal segments, with occluded branches and absence of collaterals.

The above-mentioned variants of anatomic alterations as a manifestation of transplant coronary disease with different degree of expressiveness are present in arteries of the first, second and third order.

Percutaneous transluminal coronary angioplasty (PTCA) for obliterating atherosclerotic alterations in the vascular wall of cardiac allogfaft came into use since 1985 (4). By now the leading transplantology centers possess information regarding the results of 20-30 PTCA in the long-term follow-up (20, 29, 33).

Results: This study includes 41 men and 6 women (aged 16-54). A total of 124 coronary angiographic examinations was carried out within the period lasting from 9 days to $11^{1}/_{2}$ years after cardiac transplantation. All the patients received triple immunosuppressive therapy, including cyclosporine A, azatioprine and methyl-prednizone. Stenotic lesions of coronary arteries were recognized in 19 patients, i.e. in 41,3% cases, that is consistent with published data (6, 11).

Alterations in the form of isolated or multiple local stenoses located in proximal, medial and distal segments of large coronary arteries of the first and second order were attributed to the first type of coronary artery lesions.

The second type represents diffuse lesion of coronary arteries of the first, second and third order with gradual or drastic onset of stenosis and obliteration of distal bed and small terminal arteries.

Stenotic lesions of the first type were observed in 47,5% of cases, those of the second type - in 52,5%. With this the incidence of the first type lesions in the arteries of the first order is 69,4%; in the arteries of the second order - 30,6%. We didn't reveal coronary lesions of distal segment corresponding to the first type of angiographic alterations. Lesions of the second type in arteries of the first order were seen in 12%; in arteries of the second order - in 32% and in arteries of the third order - in 56% of cases. Occlusion of coronary arteries was observed in 19,7% of cases. With this 50% of these lesions are localized in proximal segments, 18,8% - in medial and 31,2% - in distal ones. The obtained results show that angiographic alterations of the first type are characteristic of the stenotic lesion in proximal and distal segments of the coronary arteries of the first and second order. The lesions of the second type are more often localized in distal segments as well as in arteries of the third order.

Twenty-one PTCA procedures were performed in 14 patients with transplant's coronary artery lesions of type A. The age of patients varied between 25 and 65 years. The period between heart transplantation and PTCA was from 9 days to 7 years.

To perform PTCA we follow the indications based on the angiographic signs of coronary artery lesion according to the following criteria:

1. Localization of dominating stenosis in proximal or medial segment in coronary arteries of the first or the second order.
2. Vascular lumen stenosis over 50%.

Given the angiographic criteria, additional indication for the performance of PTCA was myocardial ischemia recognized and documented by ECG and radionuclide study. Angioplasty of one coronary artery was performed in 8 cases: left anterior descending artery (LAD) - 6 cases and right coronary artery (RCA) - 2 cases. Angioplasty of two coronary arteries was performed in 6 cases : LAD and circumflex branch (CxB) of LCA system (1 case); LAD and RCA (3 cases); CxB and diagonal branch (DB) of LCA system (1 case). A total of 17 stenoses were treated with the use of balloon angioplasty: 11 stenoses of LAD (57%); 5 stenoses of RCA (21%); 2 stenoses of CxB (14%); 1 stenosis of DB (8%). The majority of those stenoses (14) were readily amenable to dilatation without signs of dissection complicating angioplasty. It can be related to the fact, that contrary to typical signs of atherosclerosis in CAD, the vessels of the transplanted heart rarely calcify. Some extent of cacification can be observed only in patients, surviving over 10 years (28). To determine the degree of residual stenosis the control coronary angiography was performed within 15-18 hours after PTCA in all cases before the removal of introducers. Initial positive effect from PTCA in patients suffering from vascular lesions of transplanted heart, on evidence of some authors, is obtained in over 90% of cases, that agrees with the results of PTCA in patients with coronary atherosclerosis and CAD (10, 21, 22).

The long-term results were evaluated within 6-24 months after PTCA. Restenoses demanding repeated intervention were recognized in 7 cases. In two other cases moderate restenoses (stenosis <50%) were revealed; they didn't progress during a year of follow-up. Two patients died at home 3 and 4 months after PTCA; autopsy was not performed. In 3 patients a stable angiographic effect of PTCA was noted, the degree of the stenosis of dilated arterial segments didn't exceed 25% during 2 years of follow-up. Stenting was necessary in 4 cases.

A case of 26-years old recipient of the heart from the 45-years old donor without previous coronary angiography is worth special mention. Persistent post-transplantation heart failure required the use of biventricular bypass. In order to understand the causes of incurable heart failure, on day 9 heart catheterization and coronary angiography were per-

Coronary angiogram of the Patient K., 26 years:

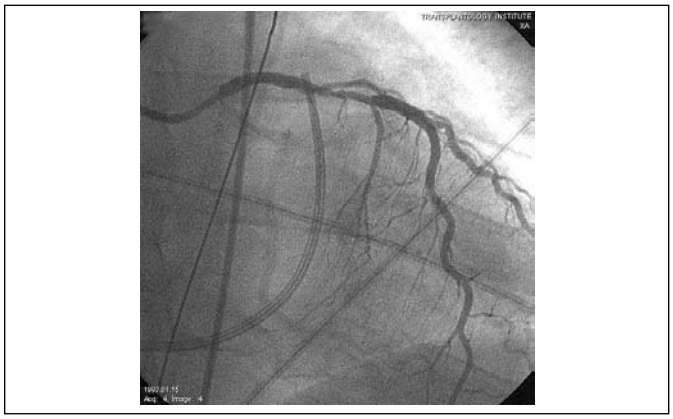

Fig. 1. LAD stenosis before PTCA

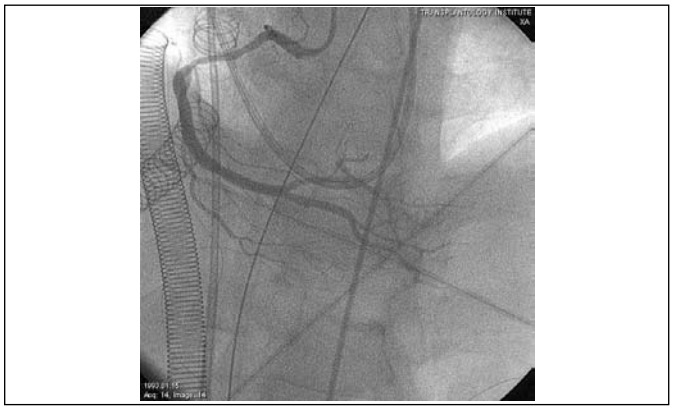

Fig. 2. RCA stenosis before PTCA

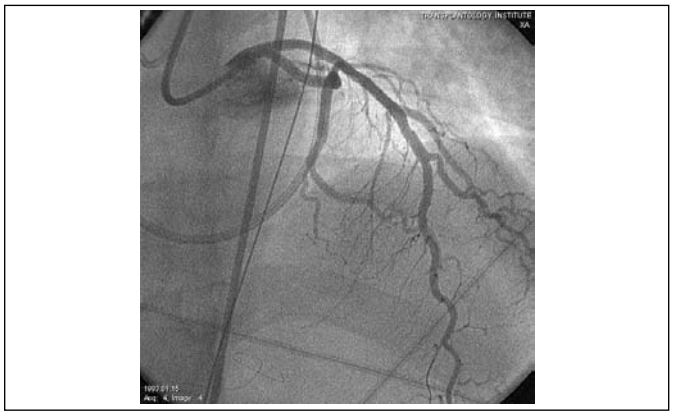

Fig. 3. Result of PTCA in the LAD

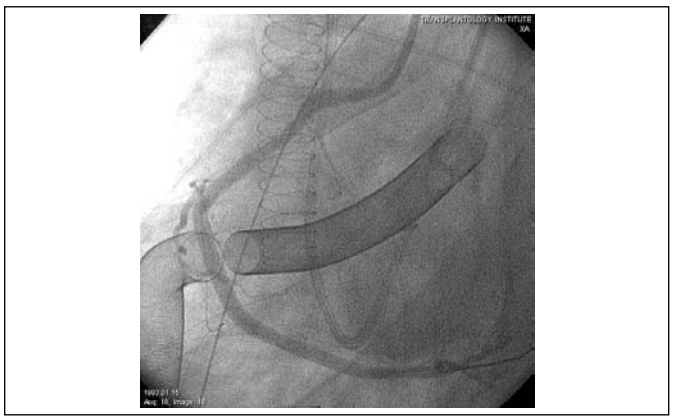

Fig. 4. Result of PTCA in the RCA

formed. They revealed stenotic lesions of the transplant's coronary arteries (Fig.1 and 2). PTCA with stenting of LAD and RCA (Fig.3 and 4) gave good hemodynamic effect and allowed to avoid the left ventricular bypass.

According to the results achieved in some medical centers, the incidence of restenoses development in cardiac allografts runs to 55-61% already within 6 months after PTCA, which is significantly higher than similar indices in patients with CAD (11, 30). The reasons for higher level of restenoses can lay with the particularities of pathogenetic mechanisms leading to vasculopathy of the transplanted heart and with individual variability of immunologic activity (11, 24). Some authors suggest wider use of coronary stenting as a possible mean for the decrease of restenosis rate (10, 20, 21, 22, 29).

In one case renal excretory function was seriously damaged after PTCA, leading to the development of renal insufficiency; probably, it was caused by side-effect of the contrast medium (Omnipaque 350). After some courses of hemofiltration and 6 courses of hemodialysis normal renal function was resumed. We didn't see any PTCA-related cardiac complications.

In 7 cases the character of coronary artery lesion didn't permit to perform the balloon angioplasty. One patient underwent heart re-transplantation, another patient died during aortocoronary bypass surgery. Adequate revascularization by aortocoronary bypass in view of diffuse character of process and principally distal localization of coronary artery lesion is ineffective and connected with higher risk for patient life (12). Heart re-transplantation is characterized by suboptimal survival rate of the transplant as compared with the initial cardiac transplantation (16).Under these conditions PTCA appears to be an alternative technique of palliative treatment for patients with lesion of large subepicardial arteries in the transplanted heart (17).

In conclusion it should be noted that coronary angiography plays a decisive role in the diagnosis of transplant coronary artery disease. Transplant revascularization with the use of PTCA and, maybe, with wider use of coronary stenting, is the most effective and safe technique of treatment.

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Management of coronary atherosclerosis: the influence of massive use of stenting on immediate and long-term outcomes of coronary angioplasty

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AIM: We report a prospective analysis of immediate and long-term effects of two coronary angioplasty methods - balloon dilatation and stenting - in different periods of work of two endovascular laboratories. For the last 10 years the number of stents implanted has grown 30-fold, and stenting is used today in 95% to 97% of coronary angioplasty procedures.

RESULTS: The strategy of massive use of stents has improved the immediate outcomes of angioplasty as suggested by substantial decrease of the rate of AMI, emergency coronary artery bypass grafting and acute coronary occlusions (from 2.7% after balloon angioplasty to 0.6% after stenting; p = 0.001). Stenting improved the long-term prognosis by decreasing the frequency of cardiovascular events. The 5-year survival rate after stenting was 98.8%, after balloon angioplasty - 92.7% (p = 0.004). However, the rate of angiographically revealed restenosis (27.1% vs. 30.4%) and the need for repeated myocardial revascularization after stenting decrease less significantly as compared to balloon angioplasty (30.1% vs. 34.5%, p = 0.0025).

Keywords: Coronary angioplasty, coronary stenting, in-stent restenosis, restenosis risk factors, long-term outcome of coronary angioplasty.

During the last decade coronary stenting (CS) has become the most widely accepted method of Percutaneous coronary interventions (PCI) and has substantially replaced balloon angioplasty (1, 2, 3, 4, 5). Percutaneous transluminal coronary angioplasty (PTCA) in pre-stent era has been associated with an increased rate (5-10%) of acute coronary occlusion, high rate of in-hospital complications and restenosis of 30 to 60% during the follow up (6, 7, 8, 9, 10, 11). Advances in stenting technology during the last 10 years allowed us to achieve better immediate and long-term results compared with balloon angioplasty (BA) alone (12, 13, 14). However, despite the encouraging results and the enthusiasm of investigators, many questions concerning clinical use of CS remained unanswered. The most important of them can be formulated as follows:

1. What types of coronary atherosclerosis are proved to be treated more successfully by stenting rather than by other methods of coronary angioplasty?

2. What is the clinical and cost effectiveness of CS in terms of both immediate and long-term results?

3. What is to be the optimal proportion of CS in invasive treatments of coronary atherosclerosis?

4. What is the best treatment option for in-stent restenosis?

In addition, stenting itself does not exclude recurrent stenosis within the stent (in-stent restenosis) (15, 16, 17, 18), thus making the treatment of patients with recurrent angina more complicated, difficult and expensive, for yet there have been no optimal methods and technologies of management of in-stent restenosis (19, 20, 21, 22).

We performed our first CS procedure on December 18, 1992, and since 1994 the stenting has been extensively used in our clinical practice. A total of 1890 CS procedures were performed.

The purpose of this collaboration of two endovascular laboratories consisted in a retrospective analysis of immediate and long-term efficacy of the two methods of coronary intervention – balloon angioplasty and stenting – during various periods of our activity.

Materials and metods:

We have analyzed the results of treatment of 299 patients enrolled in this study who were divided into two groups: group 1 consisted of 148 patients with balloon angioplasty alone treated during the period of 1992-1994 and group 2 of 151 patients, who underwent CS during the period of 1995-1997. Only the patients who underwent control angiography in the long-term period after the first intervention were included into the study. Patients, who didn't have control angiography performed or who didn't undergo this procedure in our clinic, were

Table 1. CLINICAL AND ANGIOGRAPHIC DATA

		Group 1 Balloon angioplasty (n = 148)	Group 2 Coronary stenting (n = 151)
Age, years	30-40	7 (4.7%)	8 (5.3%)
	40-50	45 (30.4%)	33 (21.9%)
	50-60	62 (41.9%)	57 (37.7%)
	60 or more	34 (23.0%)	53 (35.1%)
Sex	M	142 (95.9%)	137 (90.7%)
	W	6 (4.1%)	14 (9.3%)
CCS angina functional class	II	42 (28.4%)	12 (7.9%)
	III	95 (64.2%)	107 (70.9%)
	IV	11 (7.4%)	32 (21.2%)
ACC/AHA lesion grade	A	62 (40.5%)	22 (14.3%)
	B	68 (44.4%)	80 (51.9%)
	C	23 (15.1%)	52 (33.8%)
	Occlusion	21 (14.2%)	37 (24.5%)
Coronary artery	LAD	100 (56.8%)	103 (53.9%)
	CA	41 (23.3%)	28 (14.7%)
	RCA	34 (19.3%)	55 (28.8%)
	Left main	1 (0.6%)	5 (2.6%)
	TOTAL	176	191
Left ventricular ejection function (EF)	<0.5	15 (10.1%)	25 (16.6%)
	>0.5	133 (89.9%)	126 (83.4%)
Single vessel disease		82 (55.4%)	82 (54.3%)
Multivessel disease		66 (44.6%)	69 (45.7%)
Diabetes		17 (11.5%)	14 (9.3%)

EF - ejection fraction; CCS - Canadian Cardiac Society;
ACC/AHA - American College Cardiology/American Heart Association.

excluded from the analysis. Clinical and angiographic profile of patients, included into the above-mentioned groups, is presented in Table 1.

The mean age of patients in balloon angioplasty group was 52.8 ± 0.2 years, while in stenting group it was 55.3 ± 0.3 years. Note the increase in the number of women, patients with CCS functional class IV angina and with coronary artery (CA) occlusions in the group of CS. As a total the interventions were performed in 176 arteries (1.2 per patient) in balloon angioplasty group vs. 191 arteries in the stenting group (1.3 vessel per patient).

The verification of homogeneity of the compared groups revealed statistical differences by the following criteria: age, sex, lesion distribution, and type of lesion according to ACC/AHA classification. However, both groups were similar as for the distribution of the majority of parameters, suggesting the homogeneity of patient population. There were no substantial differences between the groups in clinically relevant characteristics (diabetes, number of CA involved and left ventricular function).

A total of 217 stents were implanted to patients in group 2 (1.44 per patient), among them 129 (59.4%) were the stents with the length less than 20 mm, implanted to 90 patients (59.6%), while 88 stents longer than 20 mm (40.6%) were implanted to 61 patients (40.4%).

The following criteria were used to assess immediate results: 1. Successful angiographic result (A-C dissection, residual stenosis less than 20%, TIMI III flow); 2. "Major" cardiac complications (AMI, non Q-wave MI, emergency myocardial revascularization - coronary artery bypass grafting or PTCA, cardiac death, acute coronary occlusion following angioplasty); 3. Peripheral arterial complications (cerebrovascular ischemia, thrombosis or bleeding from the access-artery).

The analysis of angiographic signs in both groups gives the idea on the comparative severity of atherosclerotic lesions of the coronary bed and their distribution in those groups. The results of this analysis are listed in Table 2.

Table 2. ANGIOGRAPHIC PROFILES OF CORONARY ATHEROSCLEROTIC LESIONS IN TWO GROUPS OF PATIENTS

	Balloon angioplasty	Coronary stenting	p value
Bifurcation	29 (19.6%)	23 (15.5%)	0.002
Long lesions (>20 mm)	42 (28.4%)	39 (25.8%)	0.0025
Angulated (<60°) lesions	9 (6.1%)	5 (3.3%)	0.05
Ostial lesions	18 (12.2%)	11 (7.3%)	0.05

Follow-up results were assessed at 25.6 ± 1.3 months (6-132 months in average) after the procedure. In balloon angioplasty group the mean period of long-term outcome assessment was - 38.6 ± 1.04 months (2-132 months), in coronary stenting group - 12.9 ± 0.9 months (2-63 months). Control angiography was performed to all 299 patients. The following endpoints were used to assess long-term outcomes:

1. MACE (MI, stroke, cardiac death);

2. Restenosis on angiography;

3. Repeated myocardial revascularization (coronary artery bypass grafting or PTCA);

Statistical analysis:

Data grouping, mean values, diagrams, correlation methods (parametric and non-parametric) were used, as well as testing of hypothesis of equality of mean values and dispersions (to assess the homogeneity of groups compared). Student t-test was used to assess significant differences. To determine the statistical significance of qualitative criteria z и χ^2 values were calculated. Long-term outcomes were evaluated using Kaplan-Meier method.

Results:

1. Immediate results of PCI:

Table 3 summarizes the results of long-term outcome analysis in the two patient groups.

Table 3. IMMEDIATE OUTCOMES OF BALLOON ANGIOPLASTY COMPARED TO STENTING IN TWO GROUPS OF PATIENTS

	AMI	mortality	ACO	Emergency CABG	SO
Balloon angioplasty	1.35%	0	2.7%	2.1%	94.6%
Stenting	0.7%	0	0.6%	0	98.1%
p value	0.05	-	0.001	0.001	NS

AMI - acute myocardial infarction; CABG - coronary artery bypass grafting, SO - successful outcome as revealed by angiography; ACO - acute coronary occlusion; ns - non-significant.

Stenting significantly decreases the rate of AMI and the risk of acute coronary occlusion following PCI (0.7% and 0.6%, respectively), compared to balloon angioplasty (1.35% and 2.7%, respectively, p = 0.001). Interestingly, no emergency coronary artery bypass grafting was needed in stenting group (emergency CABG was performed in 3 cases for acute coronary occlusion in balloon angioplasty group). There were no significant differences between two groups by other criteria of successful angiographic result.

Type and location of coronary atherosclerotic lesions also played a certain role in defining the outcome of an invasive intervention. The influence of lesion type and its location on immediate results in both groups is shown in Table 4.

Table 4. ASSOCIATION BETWEEN THE IMMEDIATE OUTCOMES AND THE LENGTH AND LOCATION OF CORONARY ATHEROSCLEROTIC LESIONS

	Balloon angioplasty				Coronary stenting			
	AMI	mortality	ACO	SO	AMI	mortali-	ACO	SO
Bifurcation	1	0	0	28	1	0	0	22
Long lesions (>20 mm)	1 (2.4%)	0	1 (2.4%)	40 (95.2%)	2 (5.1%)	0	0	39 (94.9%)
Angulated (<60°) lesions	0	0	1 (11.1%)	8 (88.9%)	1 (20%)	0	1 (20%)	3 (60%)
Ostial	1	0	1	12*	0	0	0	11*

SO - successful outcome as revealed by angiography; ACO - acute coronary occlusion;
* - p < 0.0025.

The table shows similar immediate outcomes in both groups regardless of the length and location of lesion. Therefore, the use of both technologies yields approximately the same immediate results in patients with different lesions.

Table 5. VALUES OF PARAMETRIC AND NON-PARAMETRIC CRITERIA IN TWO GROUPS OF PATIENTS

Parametric criteria: correlation coefficients

Item		Immediate outcome				Long-term outcome			
		AMI	mortality	ACO	SO	MI	Mortality	RMR	Recurrence
Bifurcation	Stenting	-0.06	-	-0.03	0.06	-0.03	0.11	0.02	0.06
	Balloon	-0.06	-	-0.08	0.12	-0.13	-0.02	0.04	0.00
Angulated lesion	Stenting	0.24	-	0.13	-0.24	-0.02	-0.02	0.09	0.07
	Balloon	-0.03	-	0.44	-0.06	-0.06	0.13	-0.16	-0.13
Long lesion	Stenting	0.13	-	-0.05	-0.13	0.14	0.20	0.17	0.19
	Balloon	0.06	-	-0.01	0.02	0.09	0.14	0.05	0.05
Ostial lesion	Stenting	-0.04	-	-0.02	0.04	-0.02	-0.03	0.05	0.03
	balloon	0.14	-	0.07	-0.19	0.25	0.04	0.23	0.30
Diabetes*		0.04	-	0.10	-0.05	0.24	0.03	0.21	0.19
LV function < 0.5*		-0.05	-	0.10	-0.03	-0.02	0.33	0.01	-0.02
Stent length > 20 mm*		-0.08	-	0.07	0.08	-0.10	-0.14	-0.37	-0.39

Non-parametric criteria: Pearson's correlation coefficient

Item		Immediate outcome				Long-term outcome			
		AMI	Mortality	ACO	SO	MI	Mortality	RMR	Recurrence
Bifurcation	Stenting	-0.06	-	-0.03	0.06	-0.03	0.11	0.01	0.05
	Balloon	-0.06	-	-0.08	0.11	-0.11	-0.02	0.03	0.00
Angulated lesion	Stenting	0.22	-	0.49	-0.22	-0.01	-0.02	0.03	0.03
	Balloon	-0.03	-	0.12	-0.05	-0.05	0.10	-0.08	-0.06
Long lesion	Stenting	0.13	-	-0.05	-0.13	0.14	0.20	0.16	0.17
	Balloon	0.06	-	-0.01	0.02	0.09	0.14	0.04	0.04
Ostial lesion	Stenting	-0.04	-	-0.02	0.04	-0.02	-0.03	0.03	0.02
	Balloon	0.14	-	0.06	-0.18	0.25	0.04	0.17	0.21

Note: Grey cells contain correlation coefficients of any significance. The higher is the value, the stronger is the correlation between characteristics;
* - stenting group only.

The only exclusion is ostial lesion in which stenting provides significantly more favorable angiographic outcomes.

Comparison between parametric and non-parametric criteria in both groups showed the following (see Table 5):

1. Calculation of non-parametric and parametric criteria suggested that the immediate results of both techniques of PCI (balloon and stent) were comparable regardless of the location and length of lesion.

2. In the balloon angioplasty group we noticed significant correlation between acute coronary occlusion rates and the presence of angulated lesion. Stenting yields better immediate outcomes in this type of lesion. Immediate outcomes of PCI of bifurcation stenosis (one of the most complicated lesions for intervention) were similar in both groups. In other words, in the terms of immediate results stenting has no advantages over balloon angioplasty alone for bifurcation lesions.

3. The following correlations between immediate or long-term results and the location and length of lesion were found:

a) in the balloon angioplasty group ostial lesions were strongly associated with AMI during in-hospital and recurrent angina in the long-term period;

b) in the stenting group the strong correlation has been established between lesion length and angina recurrence and long-term mortality. The risk of AMI after PCI for angulated stenoses is increased in this group as well. Therefore, ostial lesions are less favorable for balloon angioplasty, while prolonged and angulated stenoses are poorly eligible for stenting.

2. Long-term outcomes of PCI:

Taking into account the above listed criteria, we assessed the long-term outcomes of PCI and obtained the following results (Table 6):

As shown in Table 6, stenting significantly improved long-term outcomes of coronary angioplasty compared to balloon dilatation. Benefits of stenting are particularly expressed in substantial (10-fold) decrease of the rate of cardiovascular events (mortality, MI). However, despite the optimistic estimation, angiographic restenosis rate (27.1%) and the rate of repeated myocardial revascularization (30.4%) were only slightly decreased in comparison with balloon angioplasty (30.1% and 34,5%, respectively). Stenting improves the long-term prognosis, however, the need for repeated myocardial revascularization remains high (although lower than that of balloon angioplasty).

Table 6. LONG-TERM OUTCOMES IN BALLOON ANGIOPLASTY AND STENTING GROUPS

	Balloon angioplasty	Stenting	p value
CVE	14.1%	1.3%	<0.05
Restenosis revealed by angiography	30.1%	27.1%	0.0025
RMR	34.5%	30.4%	0.001

CVE - cardiovascular events (MI, stroke, cardiac death);
RMR - repeated myocardial revascularization.

This trend is further confirmed by Kaplan-Meier analysis. In particular, the 5-year survival rate after balloon angioplasty was 92.7%, compared to 98.8% after stenting (p = 0.004) (Fig. 1).

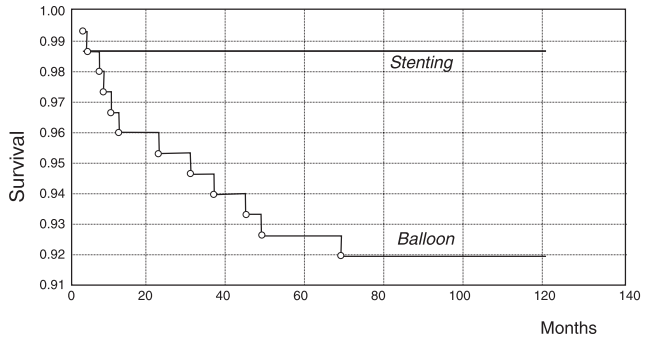
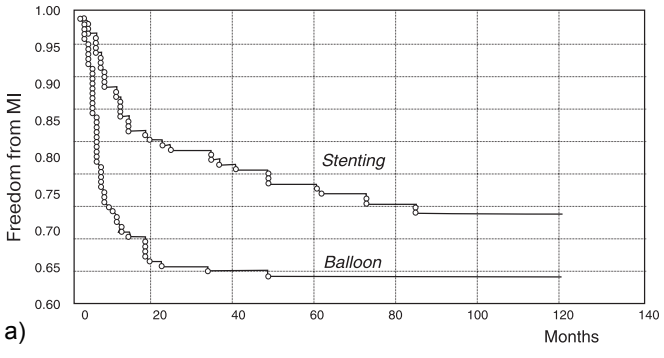
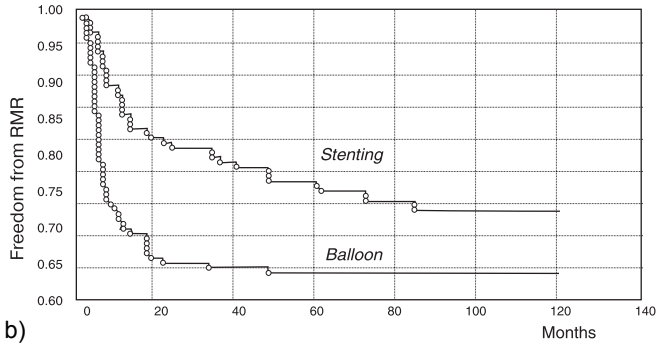


Fig. 1. Comparison of long-term survival rate of angioplasty vs. stenting





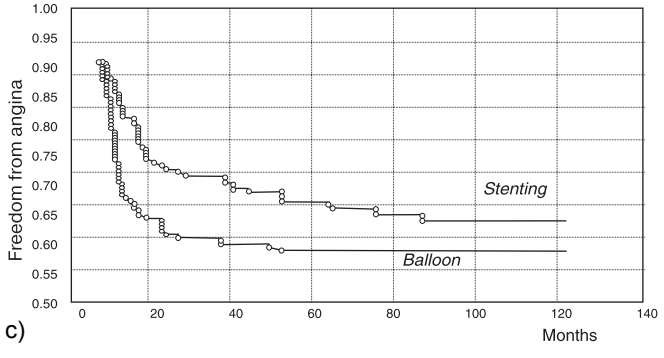


Fig. 2. Comparison in the long-term outcomes between the two patient groups:
a) MI in the long-term period;
b) rate of repeated myocardium revascularization;
c) angina recurrence.

The long-term benefit of stenting is the decrease of cardiovascular events and angina recurrences (Fig. 2).

As one can see from Fig. 2, angina recurrence and repeated revascularizations peak during the first 20 months. In balloon angioplasty group the majority of repeated myocardial revascularization procedures (up to 97%) were performed within this period of time (restenosis at the site of balloon angioplasty), whereas in stenting group (despite the decrease of total number of repeated revascularizations) almost $^{1}/_{3}$ of the repeated interventions were performed within 20-80 months, which was mainly the result of atherosclerosis progression and the development of new lesions. Therefore, repeated revascularization in the balloon angioplasty group is required earlier and more frequently, as compared to the group of stenting.

Discussion:

Theoretical advantages of positive remodeling of arterial lumen after stenting, as compared to balloon angioplasty, were demonstrated by quantitative coronary angiography (23, 24, 25) and intracoronary ultrasound studies (5, 26, 27, 28). The opinion about the improvement of vessel lumen geometry following stenting is further confirmed by our results (29).

The increase in arterial cross-sectional area following stenting provides the rise of coronary volumetric blood flow, thus increasing the coronary flow reserve. The improvement of vessel geometry after stenting contributes to less turbulent flow, which, in turn, diminishes the risk of acute and subacute coronary artery thrombosis after stenting.

The above listed hemodynamic advantages of stenting against balloon angioplasty explain the more beneficial immediate outcomes of coronary angioplasty after stenting, as compared to balloon angioplasty (See table 3).

These benefits of coronary stenting had faded out slightly with time. Despite our expectations, stenting didn't substantially decrease the restenosis rate – compared to balloon angioplasty (27.1% vs. 30.1%). The rate of repeated myocardial revascularization had decreased, but remained high (30.4%). On the other hand, stenting improved long-term prognosis, particularly by increasing patients' survival and diminishing the likelihood of cardiovascular events.

Several important trends are to be mentioned as well: First, the proportion of coronary stenting in the management of coronary atherosclerosis has increased since 1993 (Fig. 3). For the last 5 years it made 95.1% in average and nearly replaced lone balloon angioplasty. It appears, that massive use of stents today is the optimal method for invasive treatment of CHD and other methods may be disregarded in view of their lower efficacy. What benefits did this strategy give us?

The purpose of our study was to determine how reasonable is this massive use of stents. We understood, that the study was

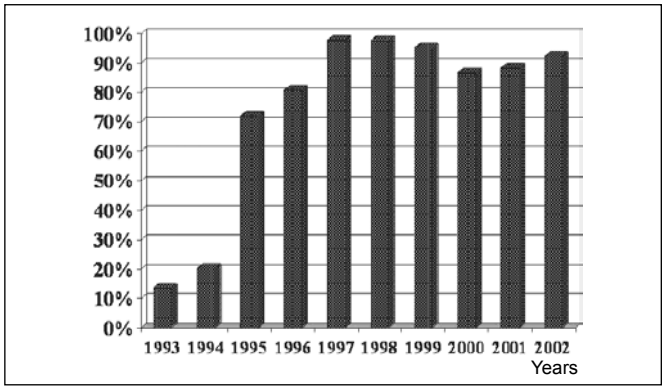


Fig. 3. Proportion of stenting method of all PTCA procedures in our clinical practice from 1993 throughout 2002.

not a randomized one; nevertheless we selected patients, who were treated with balloon angioplasty alone in the "era before stents" and with stenting, starting from 1992, when we used an intracoronary stent for the first time. The only condition was repeated angiography performed in the long-term period after intervention. Judging on the obtained results, we are able to state with certainty that stenting improves both immediate and long-term outcomes of treatment; this particularly applies to the immediate outcomes. It would be enough to say, that since 1997 throughout 2002 no case in our clinical experience necessitated emergency coronary artery bypass surgery, the rate of stent thrombosis during hospital stay was 0.8%, mortality rate (cardiac deaths) - 0.19%, and rate of AMI - 0.48%.

Secondly, the analysis of long-term results suggests, that the frequency of in-stent restenosis and the need for myocardial revascularization after stenting did not decrease substantially (by 3-5%), between the two patient groups. Stent is a foreign body and inflammatory and proliferative reactions to its implantation into arterial lumen may lead to restenosis, which responds poorly to repeated interventions. Correlation analysis of the association between qualitative criteria revealed two independent risk factors, which increase the rate of in-stent restenosis and the need for repeated myocardial revascularization during the follow-up: 1. the length of the implanted stent over 20 mm (the length of the lesion); and 2. multiple stenting (implantation of two or more stents). In addition to these factors, characterizing the angioplasty procedure, there is a strong correlation between the long-term outcome of coronary angioplasty (stenting) and the two functional features: 1. baseline systolic function of the left ventricle (LV) and 2. presence of diabetes (refer to table 5). Particularly, there is significant association between long-term mortality and left ventricle function (especially in balloon angioplasty group). While diabetes didn't influence significantly the immediate results, we saw a direct association between the presence of diabetes and the rate of MI, angina recurrence and repeated myocardium revascularization in both patient groups.

Analyzing the association between the location and the type of coronary atherosclerotic lesions, one should note that the long-term outcomes are influenced mainly by the three factors: 1. Ostial location of the lesion; 2. Length of the lesion; and 3. The number of coronary arteries involved.

Interventions on ostial lesions strongly correlate with myocardial infarction and angina recurrence in the long-term period in both groups. There is a direct association between the length of stenosis, the number of coronary arteries involved and the mortality rate in the long-term period.

It is obvious, that in order to improve the long-term outcomes of stenting, one should exclude or diminish the number of risk factors listed above, which negatively influence the long-term results. However, the analysis of our results suggests, that in patients with short (less than 20 mm) stenoses and single-artery lesions, with no diabetes and preserved left ventricle function, the long-term results after balloon angioplasty and stenting don't differ significantly (see table 7). We believe, that in such settings the future proportion of coronary stenting will stay low and the more cheap method of balloon angioplasty should be preferred.

On the other hand, considering the trends of the last years, the procedure of coronary angioplasty (with stenting) is performed more and more often in patients with multivessel and long lesions. Taking into consideration more beneficial long-term outcomes, we think, that this population of patients must undergo stenting procedure. We can hope now that the improvement of long-term results in patients with risk factors of restenosis is possible. These prospects are mostly based on the use of drug-eluting stents (sirolimus-coated stent "Cypher", produced by Cordis). Another way to decrease angina recurrence following stenting is associated with medical therapy, particularly with statins (30, 31). Combination of coronary stenting with statin administration may decrease the long-term risk of cardiovascular events and angina recurrence.

Table 7. COMPARISON BETWEEN INTERVENTION OUTCOMES OF THE TWO SUBGROUPS OF PATIENTS

	IMMEDIATE OUTCOME				LONG-TERM OUTCOME			
	AMI	Mortality rate	CAO	SO	MI	Mortality rate	Angina recur-	RMR
BALLOON (n = 74)	1 1.4%	–	22.8%	72 97.3%	1 1.4%	–	14 19.2%	13 17.8%
STENT (n = 51)	–	–	–	51 100%	11.9%	–	9 17.6%	8 15.7%
p value	<0.025	_	0.001	0.04	ns	_	<0.05	<0.05

AMI-Acute myocardial infarction; MI - Myocardial infarction; CAO - Coronary artery occlusion; SO -Successful outcome as revealed by angiography; RMR-repeated myocardium revascularization.

Conclusions:

1. The strategy of massive use of stents (in 95-97% cases of coronary angioplasty procedures) has improved the immediate results of angioplasty by decreasing "major" in-hospital complications (AMI, need for emergency coronary artery bypass grafting). Stenting significantly diminishes the rate of acute occlusions of coronary artery after angioplasty.

2. Despite the improvement of long-term prognosis after stenting (higher survival and lower risk of cardiovascular events), angina recurrence and the frequency of repeated myocardial revascularization (27.1% and 30.4%, respectively) decrease not so substantially, as compared to balloon angioplasty (30.1% and 34.5%, p = 0.0025). In other words, massive use of stents increases safety of coronary angioplasty, but doesn't significantly diminish the rate of angina recurrence and repeated myocardial revascularization procedures.

3. Diabetes and low baseline left ventricular function are significant risk factors, increasing the rate of angina recurrence and cardiovascular events in the follow-up after stenting.

4. There are no differences in immediate and long-term outcomes between balloon angioplasty and stenting in patients with single-vessel lesions and segment stenoses less than 20 mm in length, with no diabetes and with satisfactory left ventricular function. Hence, in such patients coronary stenting should not be obligatory.

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Lesion-specific approach to PTCA in multivessel coronary atherosclerosis

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The purpose of this study was to assess the outcomes of PTCA with or without stenting in patients with multivessel coronary atherosclerosis. PTCA was performed in 125 patients with multivessel coronary disease with an initial success rate (per lesion) of 96% and complication and/or technical failure rate of 4%. In-hospital mortality rate was 0.8%. The rate of restenosis at follow-up coronary angiography was 14.9%.

Keywords: PTCA, multivessel coronary disease, restenosis.

Over the last decades coronary heart disease occupied the first place in morbidity and mortality in most developed countries. Over a half of the world population dies from cardiovascular diseases. Most patients admitted to departments of cardiac surgery have multivessel coronary disease. Wide application of PTCA in cardiac surgery provides significant changes in the course of chronic coronary artery disease (CAD) such as elimination or reduction of the rate of ischemic episodes. Already at the dawn of the use of PTCA, it was observed that this method results in elimination of anginal signs and symptoms, improvement in exercise tolerance and reduction in mortality. Introduction of coronary stenting in interventional cardiology improved immediate outcomes of PTCA and decreased the restenosis rate. Nevertheless, the necessity of stenting of any coronary lesion after PTCA remains controversial. The objective of this study was to evaluate the efficacy of PTCA with or without stenting in multivessel coronary atherosclerosis.

Material and methods

In 1997-2001 in Nizhny Novgorod Clinic of Cardiac Surgery PTCA was performed in 125 patients with multivessel coronary disease. Their age ranged from 31 to 75 years (mean, 55 ± 7.5 years). The study enrolled 107 men (85.6%) and 18 women (14.4%). Duration of clinical signs of CAD varied from one month to 17 years (Table 1).

Table 1. Clinical characteristics of patients enrolled in the study

Characteristic	n	%
Number of patients	125	100
Total number of stenoses	321	
Men	107	85.6
Women	18	14.4
Age, years (M ± s)	55 ± 7.5	
Previous myocardial infarction	32	29.9
Arterial hypertension	58	54.2
Diabetes mellitus	6	5.6
Previous coronary artery bypass grafting	7	5.6

All patients underwent ECG, echocardiography, stress echocardiography, treadmill test, ambulatory ECG monitoring, and selective coronary angiography.

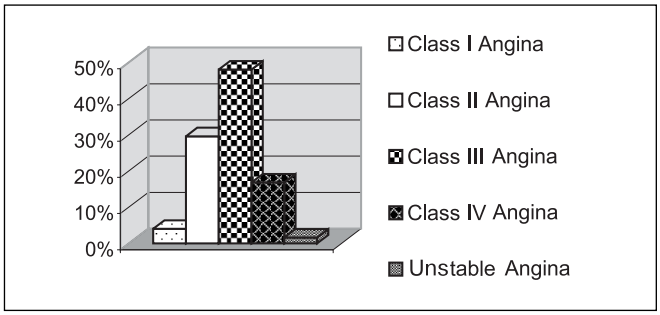

Fig. 1. Clinical characteristics of patients before PTCA.

According to the examination results, 5 (4%) patients had class I, 37 (29.6%) patients had class II, 60 (48%) patients had class III, and 21 (16.8%) patients had class IV angina. Two (1.6%) patients had unstable angina (Fig.1).

According to the results of coronary angiography, 70 (56%) patients had two-vessel coronary artery disease, 11 (8.8%) patients had three-vessel coronary artery disease, and 44 (35.2%) patients had multiple lesions within the same coronary artery and its branches (Fig. 2).

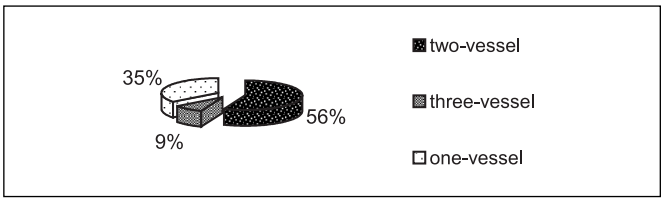

Fig. 2. Characteristics of coronary artery lesions.

All patients underwent PTCA with or without stenting or stenting without pre-dilation for treatment of hemodynamically significant stenoses. The necessity of stenting of a specific lesion was determined in accordance with the guidelines developed in our hospital. Indications for obligatory stenting were:

- coronary lesions of ACC/AHA class B or C;
- high grade stenosis (>75% diameter);
- chronic occlusion;
- proximal stenoses in LAD (left anterior descending artery), CxA (circumflex artery), and RCA (right coronary artery);
- coronary venous bypass graft stenoses.

In other cases the procedure of coronary revascularization was initiated with PTCA. Residual stenosis >30% and/or signs of intimal dissection were considered as indications for stenting.

Results

96% of lesions were successfully treated (Fig. 3). An optimal result of intervention was defined as a residual post-stenting stenosis <10% and a residual post-PTCA stenosis <30% without any complications (cardiac death, myocardial infarction, signs of significant intimal dissection of a coronary artery).

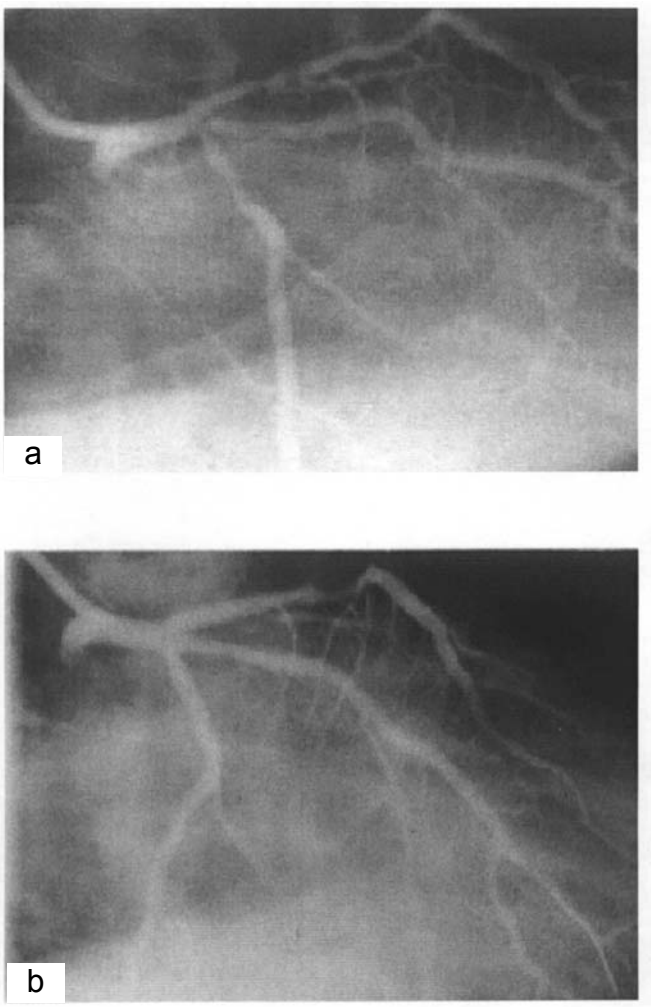

Fig. 3. Coronary angiograms of a patient with two-vessels coronary lesion: stenoses of the 3rd degree in the region of proximal LAD segment and CxA (a). At first we performed LAD stenting, then - CxA stenting (b).

During coronary angioplasty 157 stents were implanted. Other lesions were treated by PTCA.

During PTCA one patient developed an acute heart failure which subsequently led to death. In the early postoperative period one patient developed Q-wave myocardial infarction in the pool of the revascularized coronary artery due to acute thrombosis; it was treated by a successful intracoronary thrombolysis. Two patients developed non Q-wave myocardial infarction due to possible occlusion of stenotic side branch originating from the stented artery segment. In-hospital mortality rate was 0.8% (1 patient).

94 (75%) patients were followed for 6 to 36 months after PTCA. During the follow-up the following long-term outcomes were evaluated: development of myocardial infarction in the area of the revascularized coronary artery; recurrence of angina pectoris; progression of angina pectoris; restenosis of the reflecting exercise tolerance level.

In the long-term follow-up, 77.7% patients had no clinical signs of CAD; this was confirmed with ECG and stress test results (Fig. 4). 22.3% patients had signs of CAD recurrence. All these patients underwent coronary angiography. Restenosis rate defined by follow-up coronary angiography was 14.9% (14 patients). Recurrence of angina pectoris in 5 patients was associated with progression of atherosclerosis in previously intact segments of coronary arteries. Two patients had no significant coronary artery stenoses. Repeat PTCA was performed in 8 patients with coronary restenosis; 6 patients (6.3%) with restenosis underwent coronary artery bypass surgery.

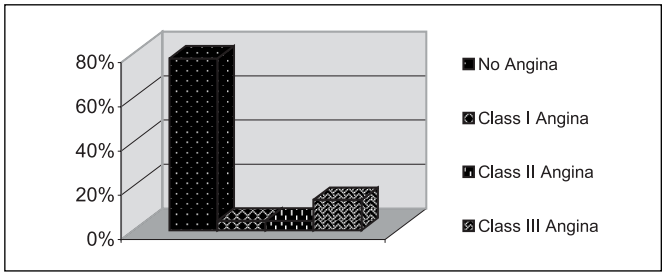

Fig. 4. Clinical characteristics of patients after PTCA

During the follow-up three patients died and one patient developed Q-wave myocardial infarction in the territory of the revascularized coronary artery.

Discussion

There is no common viewpoint among authors concerning the advantages of PTCA over coronary artery bypass grafting (CABG) or vice versa in patients with multivessel coronary atherosclerosis. In late 80's a number of large randomized trials were initiated (BARI, RITA, GABI, EAST, CABRY, ERACI) to compare these two main approaches in myocardial revascularization. Those trials differed by their design and conduction, but all of them had one common goal - to compare the efficacy of PTCA and coronary bypass surgery in multivessel coronary disease. Early outcomes of PTCA and coronary bypass surgery were similar; however, long-term outcomes of PTCA were worse than those of coronary surgery (5, 6, 13, 21, 25, 26). On the one hand, the conventional PTCA provided a short-term hospitalization and quick return to daily activities. On the other hand, PTCA was less effective in relief of angina as compared to CABG and was associated with threefold rate of repeat interventions during the first year. Coronary bypass surgery, which is more traumatic and followed by 2-3 month of recovery, is usually associated with more stable clinical course and low repeat revascularization rates (3, 4, 7, 10, 11, 14, 16, 18, 20). Therefore, some authors give preference to an individual approach. For example, PTCA may be more appropriate in young patients in attempt to delay CABG. PTCA may be considered in old patients and in patients with concomitant diseases which increase the risks associated with CABG.

Graft occlusion in a certain percentage of patients after coronary surgery, restenosis and inadequate revascularization in PTCA group, and progression of atherosclerosis in both groups may change the ratio of some endpoints with prolongation of follow-up. Moreover, one must remember that patients were enrolled in large trials in the middle of 80's. Therefore, the results of these trials were not affected by introduction of new technology in the clinical practice. At the same time the last advances in interventional cardiology, in particular, stenting, significantly increased the effectiveness of PTCA and decreased the rate of coronary restenosis (1, 2, 8, 9, 15, 19, 27).

Application of new medications in interventional cardiology also improved both short-term and long-term outcomes of coronary angioplasty. The EPIC study (10) reported that administration of IIb/IIIa platelet receptors inhibitors improves the immediate results of PTCA, and this effect may persist in long-term fol-

low-up. The lipid-lowering therapy improves the clinical course of CAD; however, it remains unclear whether the effect is the same in CABG and PTCA patients.

These important achievements in modern cardiology limit the extrapolation of results of previous trials to the current clinical practice. We emphasize that no one patient enrolled in above-mentioned trials had undergone stenting, which may decrease the rate of early restenosis by approximately 50%.

The ARTS was the first study in which stenting-based revascularization strategy was compared with CABG for the treatment of multivessel CAD. The results of 1-year follow-up showed similar rates of mortality for stenting and surgery groups. This study also represents an approximately 50% reduction in repeat revascularization rate with respect to earlier trials when PTCA without stenting was compared to CABG (28).

The multicenter APPROACH study (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) was initiated in 1995. The main aim of this study was to examine cumulative survival to 5 years in patients with multivessel CAD randomized into groups managed with medical therapy, PTCA, or CABG. This study showed similar survival rates in those treated with PCI and CABG. Long-term survival was improved by surgery only in patients with 3-vessel CAD and impaired LV function and in those who had 2-vessel CAD with a severe proximal LAD stenosis (12).

ACIP study (1997) compared three groups of patients who had one or more episodes of asymptomatic ischemia on 48-hour ECG or exercise stress testing and angiographic evidence of coronary artery disease. Two groups were treated with drug combinations and the third one - with revascularization (CABG or PTCA). The authors concluded that a strategy of initial complete revascularization with CABG or PTCA appeared to improve the prognosis in high-risk patients with silent ischemia, as compared with medical therapy. There were no significant differences between PTCA and CABG long-term outcomes (15, 17).

Thus, CABG и PTCA are considered now as two competing revascularization strategies. At the same time it should be kept in mind that the technique of coronary angioplasty undergoes significant changes (21). Continued improvement of PTCA techniques and stent design including application of drug-coated stents leads to a further reduction in number of repeat interventions.

At the same time we found no references to Russian or foreign publications on lesion-specific approach to coronary angioplasty in multivessel coronary atherosclerosis. In the randomized trials mentioned above, either stenting according to common indications or elective balloon angioplasty were applied. We consider it necessary to distinguish the lesions which are appropriate for stenting unconditionally, i.e., regardless the pre-dilation results (if it was applied). Indications for obligatory stenting are ACC/AHA class B or C of coronary lesions; high-grade stenosis (>75% diameter); chronic occlusion; proximal stenoses in LAD, CA, and RCA; coronary venous bypass graft stenosis.

In other cases we performed PTCA, and its results determined the subsequent actions. We emphasize that lesion-specific approach in coronary angioplasty provided not only the adequate treatment of all hemodynamically significant stenoses but also complete revascularization in patients with abnormal coronary anatomy. The absence of clinical manifestations of CAD in 80% patients during 6 to 36 months follow-up proves high effectiveness of this approach.

Our study had no objective to evaluate the cost-benefit of lesion-specific approach in coronary angioplasty; we investigated mainly the immediate and long-term outcomes. However, it is obvious that the clinical decision to refuse from stenting of a hemodynamically significant stenosis and treatment of such a lesion with elective PTCA decreases the total cost of the intervention.

Conclusion

Advantages of PTCA in multivessel coronary disease are obvious: it is less invasive; there are no negative factors associated with major surgery; the recovery period is shorter, and patients can carry out normal daily activities. Adequate revascularization improves the clinical condition of patients. Individual approach in the choice of coronary angioplasty reduces the cost of intervention.

Thus, the proposed complex coronary angioplasty method of treatment of multivessel coronary disease may be considered as one of the most effective treatment strategies in multivessel coronary atherosclerosis.

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Carotid angioplasty: the first experience

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The problem: Those days carotid stenting is becoming increasingly important. As a result, numerous problems occur related both to patient selection and the details of such procedures.

Methods and results: Twelve carotid stenting procedures were performed in 11 patients in the Central Military Hospital №3. The mean age of patients was 65 ± 9 years. Cerebral protection with endovascular protection filter device was used in all patients during stenting. We used nitinol self-expanding stents. Distal microembolism was assessed by transcranial Doppler intraoperatively. The rate of neurological complications was 9,1% (1 patient). These included transient ischemic attacks due to prolonged spasm of the internal carotid artery (ICA). No deaths were observed.

Conclusion: carotid stenting is a minimally invasive and effective method of arterial stenosis management.

Keywords: carotid stenting, cerebral protection filter, transcranial Doppler study during stenting.

For the recent years the pattern of cerebrovascular disease has shifted towards the ischemic forms. The high prevalence of extracranial stenoses has been reported by many authors (5, 6). In Russia this disease accounted for 25.4% of all cardiovascular pathology in 2001 (2).

Ischemic stroke is the leading cause of prolonged disability, resulting in enormous economic losses. Stroke is disabling in 40 to 60% of patients, persistent residual deficit is observed in 30% of patients, and only 10% restore their working capacity (3, 11, 12). In economically developed countries the proportion of stroke-related mortality in the overall mortality ranges from 12 to 20%, with only heart-related and tumor-related mortality being more frequent (4, 7). Therefore, prevention and treatment of cerebrovascular accidents have great social and economic impact, as the growth rate of ischemic stroke mortality is highest in patients aged from 30 to 50.

In view of this fact, minimally invasive endovascular procedures are crucial in such patients. However, this problem, to our great regret, is poorly addressed in Russia. Yet the progress of modern interventional radiology has substantially increased the role of endovascular methods in cerebrovascular surgery.

Purpose

The purpose of the study was to assess the benefits of PTA for carotid stenosis as compared to conventional surgery.

Objectives

To demonstrate the efficacy of cerebral microembolism protection.

Materials and methods

The first internal carotid artery stenting procedure was performed in our hospital in February 2002. To date we have the experience of angioplasty conducted in 11 patients for 12 proximal ICA stenoses. All patients were males. The mean age of patients was 65 ± 9 years. Three patients (27.3%) presented with a history of ischemic stroke, transient ischemic attacks (TIA) were found in 5 (45.4%) patients and 3 (27.3%) patients had asymptomatic stenoses (27.3%). In one patient carotid stenting was performed in stenosed contralateral ICA a week after the first procedure.

The assessment of stenosis degree was based on Doppler study (DS), angiography (NASCET criteria) and intravascular ultrasound study (IVUS). The mean stenosis degree was 81.6 ± 9.3%. Endovascular interventions were carried out in an operating room equipped with ADVANTX DLX angiography unit (General Electric). We used combined anaesthesia and

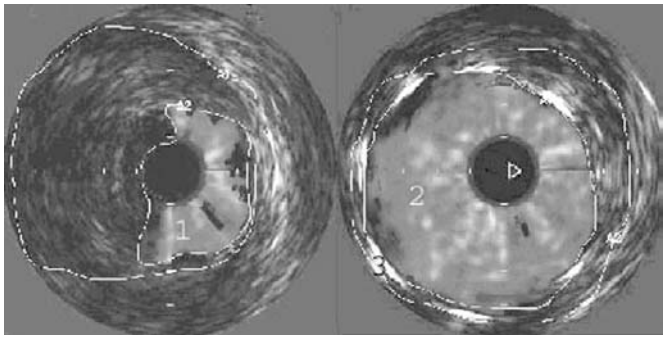

Fig. 1. IVUS scan: Left - ICA stenosis before stenting (1); right - restored arterial lumen (2), stent frame (3).

Seldinger's approach through femoral artery. All patients received Aspirin (325 mg daily) and Ticlid (250 mg BID) 2 days prior to surgery.

Considering the threat of cerebral embolism with plaque debris and clots, AngioGuard cerebral protection filter device (Cordis) was placed distal to stenosis in all patients. Diameter of the filters used ranged from 5.0 to 8.0 mm. Afterwards IVUS (EndoSonic) was performed to determine the nature of lesion and arterial lumen diameter (Fig. 1). The results were used for precise selection of stent diameter. "SMART" or "PRECISE"

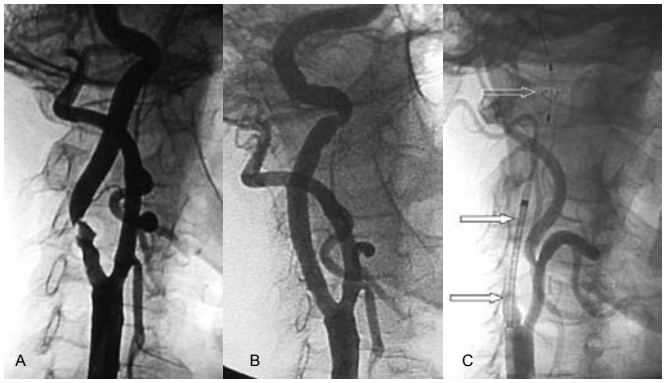

Fig. 2. Angiography of a subtotal proximal ICA stenosis before (a) and after (b) stent implantation. One of the stages (c) shows filter location (clear arrowhead) and the stent fixed on stent delivery system (filled arrowheads).

self-expanding stents (Cordis) were then implanted without predilation (this was required in one patient). Additional balloon dilation (PowerFlex P3, OPTA PRO balloon catheter) was performed in case of incomplete stent expanding (Fig. 2). Atropine 1 mg I.V. was administered to avoid bradycardia during balloon inflation. Transcranial Doppler was used for intraoperative detection of microembolism from the stenosis area; the flow was assessed in ipsilateral middle cerebral artery (MCA). Protective filter was retrieved after the procedure. The patient received heparin 10000 to 150000 IU intraoperatively. Dextran 400 ml and trental 10 mg were administered I.V. within 24 hours postoperatively. Aspirin 325 mg daily and Ticlid 250 mg BID were continued for one month after surgery.

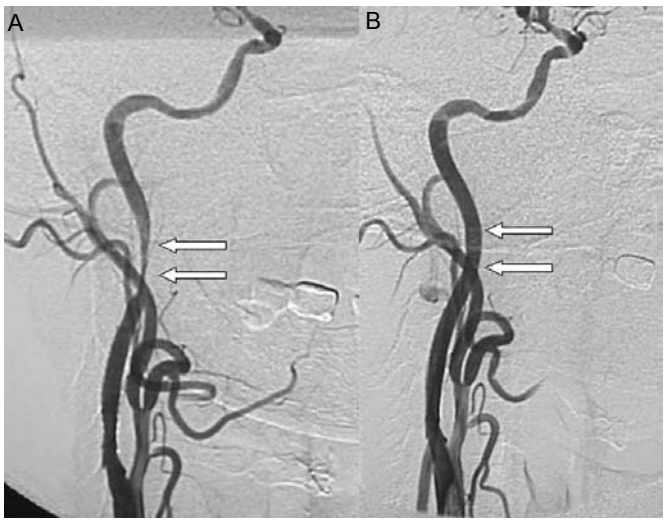

Fig. 3. Angiography (a) of a severe ICA spasm (arrowheads) distally to the stent deployed. The spasm was relieved after medical therapy and filter removal (b).

Results and discussion

Technical success of PTA in ICA was 100%. Prolonged spasm of distal ICA branches causing a TIA was observed in one case (9.1%) as a response to repeated displacement of protective filter within the arterial lumen during the procedure (Fig. 3). Partial reduction of the spasm was achieved by nitrate administration, thus allowing for completion of intervention. Control angiography performed after stenting and filter removal revealed no ICA damage in the area of filter location. No further neurological events were noted in this patient. In addition, arterial wall rupture causing dye extravasation occurred in one case (9,1%) due to stent expansion (Fig. 4), which required partial manual occlusion of the common carotid artery. Submandibular region appeared unchanged on examination. Angiography performed 20 minutes later found no dye extravasation. The patient was placed in the Intensive Care Unit of Neurological Department. Control angiography performed 2 days after surgery revealed no evidence of false aneurysm formation and confirmed proper stent position.

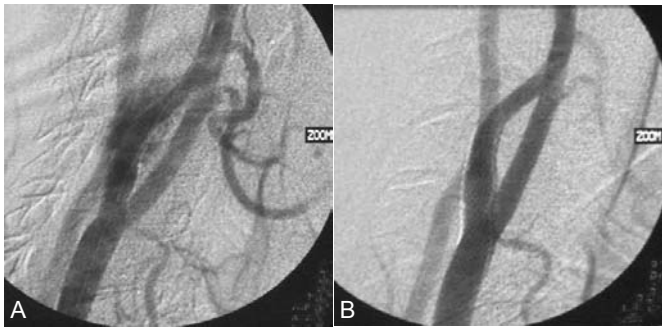

Fig. 4. Dye extravasation from proximal ICA (a). After 20 min partial digital occlusion stopped the bleeding completely (b).

Table 1. Patients and results of stenting.

Number of patients	11
Number of stenoses	12
Mean age	65 years
Males	11 (100%)
History of stroke or TIA	8 (72,7%)
Coronary heart disease	6 (54,5%)
Multifocal atherosclerosis	4 (36,4%)
Arterial hypertension	7 (63,6%)
Immediate effect of stenting	11 (100%)
Macroscopic particles in the filter	8 (72,7%)
Complications: TIA Arterial rupture	 1 (9,1%) 1 (9,1%)

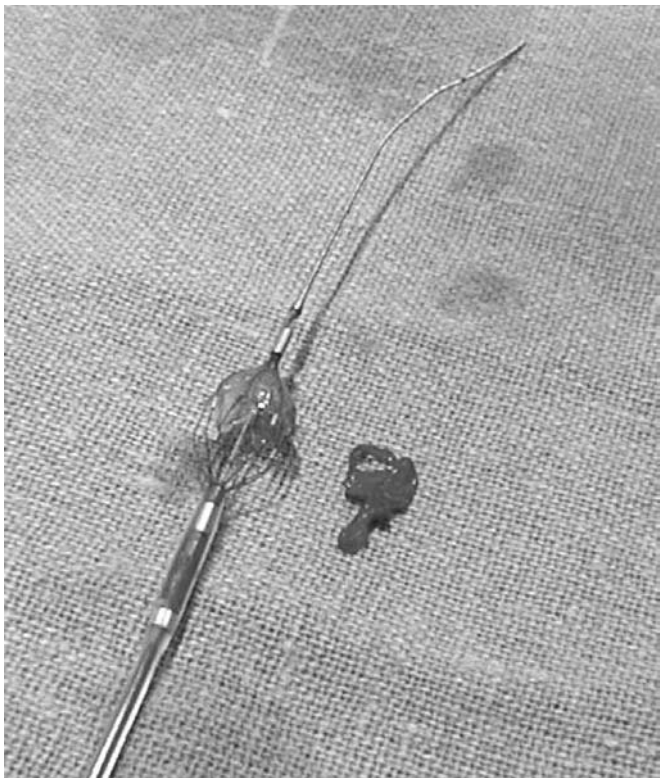

Fig. 5. Removed cerebral filter, containing microscopic particles and clots.

There were no deaths or complications related to vascular approach. The results of interventions are summarized in the table below.

Inspection of filters removed revealed microscopic particles containing clots in 72.7% of cases (Fig. 5). Though histological examination wasn't performed, the microscopic particles are reported to contain debris, fragments of macrophages and cholesterol deposits, which are characteristic for atherosclerotic plaques (1, 18, 21).

Despite the presence of filter, microembolism of distal MCA branches was detected by transcranial Doppler in 4 cases. It had no neurological manifestations and was considered a result of stent implantation (Fig. 6). This finding con-

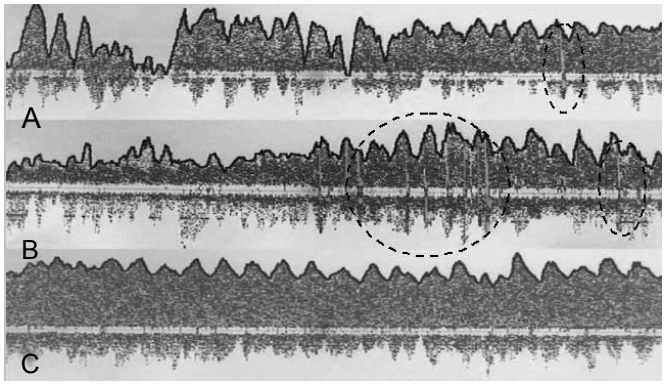

Fig. 6. Intraoperative transcranial Doppler study of MCA. Episodes of microembolism (outlined) into MCA territory caused by passing the cerebral filter through stenosis area (a), stent placement and expanding (b). Good MCA blood flow after implantation (c).

firms the opinion of many authors (14, 15, 17, 19, 22, 23), that cerebral protection during carotid surgery is reasonable. The presence of plaque fragments and clots in the majority of filters suggests that these devices are capable of retaining migrating particles, associated with risk of cerebrovascular embolism.

Considering our first experience and data reported by other investigators (8, 9, 10, 13, 16, 20) one can conclude, that the frequency of complications during carotid stenting doesn't exceed that of conventional surgery. The rate of mild and severe complications was 1.6 and 2.9%, respectively. The percentage of complications is as well associated with the skills of medical staff performing endovascular interventions. The complications described above occurred in our first patients. With the accumulation of experience we were able to avoid such complications.

The question of indications to PTA of ICA stenoses is yet to be cleared. However, there is a large number of patients at high risk of surgery (elderly patients, patients with serious comorbidities, severe renal failure), in which stenting is a doubtless alternative to conventional surgery.

Conclusions

Endovascular surgery is a minimally invasive and effective method of ICA stenosis management, being an adequate alternative to open surgery. This method avoids complications, such as nerve damage, infections and haematomas, which are observed after endarterectomy. Stenting should be used in patients with severe comorbidities as a method of choice. In addition, one has to keep in mind, that PTA has to be performed under cerebral protection. Protection filter reduces the rate of cerebral embolism with plaque debris during stent deployment. All procedures are to be performed by experienced specialists.

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Endoluminal Treatment of Large Vein Obstruction

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Introduction

Stenosis or occlusion of large veins is not a rare event : it can be responsible for dramatic symptoms and occasionally even be lethal. Percutaneous transluminal angioplasty (PTA), while successfully applied in the treatment of arterial stenoses, is only occasionally successful in veins due to the elastic recoil of the venous wall, mural fibrosis, intimal hyperplasia, persistent perivascular compression by tumour, and endoluminal tumour growth. Repeated dilatations with high-pressure balloons, laser-assisted PTA, or simultaneous inflation of several balloons placed side by side in the caval veins have not been consistently successful (1-3). The rationale for using expandable metal stents is the immediate and permanent achievement of venous patency, obviating more invasive surgery.

Clinical Indications

Potential indications for percutaneous stenting are stenoses of the superior vena cava (SVC), innominate veins (4-10), inferior vena cava (IVC) and iliofemoral veins (5-14), mainly caused by primary or secondary malignant tumours. Stenoses of benign origin include stenoses caused by central venous catheters, stenosed haemodialysis shunts (15-19), postoperative or graft anastomotic stenoses in the caval or portal system (20, 21), Budd-Chiari syndrome (23-28), iliac vein compression or May-Turner syndrome (29), and post-thrombotic occlusion (30, 31).

Superior Vena Caval Obstruction

Clinical Symptoms. The SVC syndrome can develop progressively or acutely. Clinical symptoms include headache, which is exacerbated during changes of position, disturbances of consciousness, oedema, tension or pain in the face and neck, blurred vision, retro-orbital pressure, and orthopnoea. Oedema and collateral circulation develops to a variable degree over the chest wall and periscapular region.

Malignant Obstruction. Most strictures of the caval system and venous tributaries are of malignant origin. The tumours most commonly responsible for compression of the SVC and large mediastinal veins are bronchogenic carcinoma or small-cell lung cancer with mediastinal lymph node enlargement caused by metastases from intra- or extrathoracic malignancies, malignant lymphoma or Hodgkin's disease, and tracheal malignancies. Radiotherapy is effective in about 90% of cases, but the recurrence rate is 20%. Patients with involvement of the confluence of the innominate veins should be treated early, as reconstruction of the caval bifurcation with stents becomes more hazardous when a Y-shaped stricture has occurred (Fig. 1).

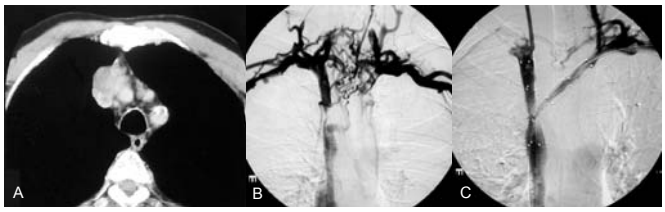

Fig. 1. 65-year-old male presenting with severe SVC obstruction.

a. Thoracic CT showed large mediastinal metastatic lymphadenopathies, caused by bronchogenic carcinoma, compressing the SVC.

b. Superior vena cavography confirmed complete obstruction of both innominate veins, fresh endoluminal clot in the left innominate vein and extensive venous collaterals.

c. Phlebographic result after stent placement in both innominate veins and the SVC. Disappearance of collateral flow. Rapid clinical regression of SVC obstruction syndrome.

In patients given nephrotoxic chemotherapy, and in patients in whom extensive tumour lysis with hyperuricaemia, hypercalcaemia, and emesis-related dehydration is expected, high-volume hydration is required. In these patients, vena caval stenosis should be treated before chemotherapy is initiated to facilitate venous return (9).

Inferior Vena Caval Obstruction

Obstruction of the IVC causes venous claudication, and oedema of the lower limbs, pelvis, perineum, scrotum and the abdominal wall. Renal dysfunction may develop. When the hepatic veins are obstructed, hepatocellular function is altered, and hepatomegaly and ascites may ensue. IVC or iliac vein stenoses do not usually lead to severe clinical symptoms necessitating stent placement. Obstruction of malignant origin may be attributable to compression of the IVC by hepatic tumour or retroperitoneal metastatic lymph node enlargement caused by pelvic malignancies, such as prostatic, cervical, ovarian, bladder and other carcinomas (12).

Contraindications

In malignant disease, contraindications to venous stenting include extensive thrombosis, anatomical considerations predisposing to severe technical difficulties, and advanced disease in preterminal patients. Uncovered-stent placement may be ineffective in the rare case of transmural venous tumour invasion, and placement of Dacron or other polymer-coated stents is indicated.

Technique

Before percutaneous stent insertion, biplanar superior or inferior cavograms are routinely obtained. When puncture of the axillary or femoral vein is problematic due to oedema, CO_2 phlebography may be obtained by peripheral injection of 60 ml CO_2, which gives a roadmap for more proximal vein puncture.

When venous thrombosis masks the lesion, local chemical thrombolysis should precede stent placement (1, 5, 9, 11). When bilateral iliac or innominate vein thrombosis is present, simultaneous bilateral infusion is used. We use urokinase as a plasminogen activator, at a mean infusion rate of 100 000 IU/h. Check phlebography is carried out 12-24 h after the start of plasminogen activator infusion. When a stenosis is unmasked, percutaneous stenting is performed immediately to ensure flow. Low-dose anticoagulant therapy is given concurrently with the local thrombolysis, by infusion of heparin (300 U/h) continuously through the haemostatic

valve sheath. Mechanical thrombectomy is not recommended in large central veins, as the risk of pulmonary embolism from a clot located in a large sidebranch, is high (i.e. migration of a residual clot from the jugular vein after successful thrombectomy in the innominate vein).

Stenoses located in the SVC or right innominate vein are best stented via a right femoral approach. Stenoses of the left innominate vein are treated either via a femoral or a left axillary approach. Venous stents should be placed sequentially, first in a distal position then more proximally, in relation to the puncture site.

The right femoral vein provides the most direct route for stenting the IVC. As the left iliac vein has a more tortuous course, advancing long and rigid metal stents through an introducer in the left iliac vein may be occasionally difficult. Iliac stents are usually inserted via an ipsilateral femoral approach. Use of the iliac crossover technique is not recommended. The hepatic veins are stented before the IVC.

In apprehensive patients, premedication before the procedure may be helpful. As endovascular stent placement is not painful, only local anaesthesia at the puncture site is required. PTA is occasionally painful when the adventitia is stretched during full dilatation. Local infiltration with anaesthetics can be helpful in some patients during dilatation of stenoses of peripheral haemodialysis fistulae.

All types of metal stents available, either balloon-expandable or self-expanding, can be placed in the venous system, provided the stent diameter is choosen large enough (1.5 times the normal vein diameter). However, treatment of stenoses in large veins requires the use of stents of sufficiently large calibre. Gianturco or Z-type stents, Wallstents endoprostheses, and Palmaz stents are among the most commonly used.

Results

Malignant Stenoses

In patients with SVC or IVC obstruction of malignant origin, cure of the primary condition is rare. Furthermore, as the life expectancy of patients with irresectable mediastinal or abdominal tumour is limited, the main aim of treatment should be immediate relief from disabling symptoms. The long-term effects of stent placement are not a major concern. Following successful stent deployment, almost immediate complete or partial relief from symptoms is obtained in 68%-I00% of cases at follow-up of up to 16 months, without any need for further intervention (6-8, 11-13). Patients experience relief of tension in the face and neck almost immediately after stent expansion in the SVC. In our initial experience, 85% of patients remained symptom-free after stenting until death (9). The best results are obtained in the SVC, IVC, innominate and iliac veins. Results tend to be less favourable when circumferential tumour encasement is shown by CT.

No significant difference has been demonstrated in the clinical results following placement of different types of stents. The left innominate vein is particularly prone to tumour encasement because of its long transverse course through the mediastinum. Also, the junction of the left innominate vein and SVC can present an obstacle to stenting. Although it may not be necessary to stent both innominate veins to achieve a good clinical result, bilateral stenting helps to re-establish optimal flow and limit the number of reinterventions. Relief of IVC obstruction achieves similar results to SVC stenting, but complete resolution of symptoms may take several weeks or even months (9, 12, 14).

Treatment of stent occlusion includes local thrombolysis, thrombectomy, balloon dilatation and placement of additional stents. The possible causes of occlusion are intraluminal tumour growth, progressive tumour growth at the free ends of the stent, vessel contraction or inadequate stent diameter leading to central migration.

In a personal study of 37 consecutive patients, the following results were obtained. Full or partial regression of symptoms was observed after stenting in 95% of patients with SVC obstruction and 100% of cases in IVC stenosis. Reintervention by PTA or additional stenting was required during follow-up in 50% of the patients, probably due to large variations in anticoagulant treatment regimens. Primary assisted patency was only 55% in the SVC system and 73% in the IVC system at death of patients (32).

Benign Stenoses

In the literature, only approximately 3% of all clinically significant SVC stenoses are said to be related to benign causes. Actually, the main causes of benign stenoses are catheter-related injury, haemodialysis shunt-related obstruction, mediastinal fibrosis secondary to trauma, surgery, post-anastomotic stenoses, infection, radiotherapy, Budd-Chiari syndrome (BCS) and other rare causes of external compression, such as retroperitoneal fibrosis (Ormond disease) or polycystic liver (Fig. 2). Benign stenoses of fibrotic origin should always be probed with a balloon to prove distensibility of the venous wall before stent placement. Benign stenoses are usually more resistant than are malignant strictures.

Membranous obstruction or long segmental stenosis of the hepatic veins or the retrohepatic IVC in BCS and pseudo-Budd-Chiari syndrome can be corrected by metal stents. Only

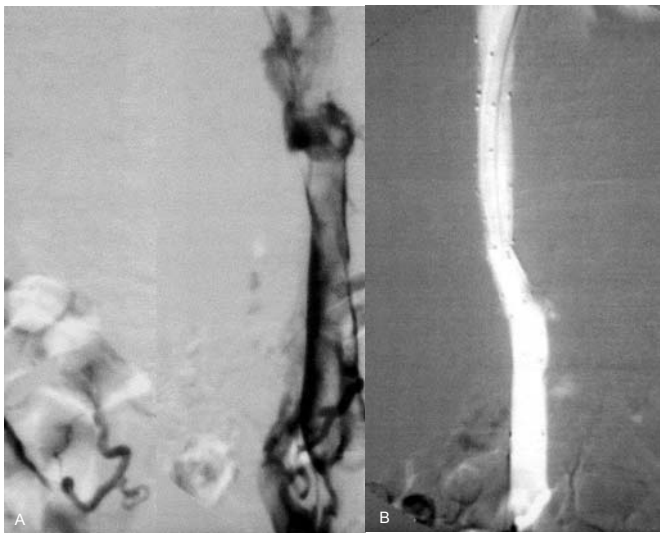

Fig. 2. 73-year-old male with known hepatic polycystic disease presented with swelling of both lower limbs and ascitis. CT (not shown) evidenced compression and thrombosis of the IVC by polycystic hepatomegaly.

a. Inferior cavography showed extensive fresh thrombus in the infrahepatic IVC. Local thrombolytic infusion of Urokinase was given for 24 hours.

b. Restoration of flow in the IVC after thrombolysis and stent placement, preventing further compression by liver cysts. Simultaneous percutaneous aspiration of the most prominent hepatic cysts and intracystic alcohol injection was performed. The patient is symptom-free since 5 years.

a few series of patients with BCS treated with metal stents have been reported in the literature (23, 26).

Either the IVC or hepatic veins or both are stented. Intrahepatic venous connections allow decompression of venous outflow following restoration of flow in the dominant, usually the right, hepatic vein only. of the 33 cases reported by Wang et al., 24 were treated by stents alone (22). There were excellent clinical results in all but one, 6-23 months following treatment. Transjugular intrahepatic portosystemic stent shunt (TIPS) is another technique for treating BCS in selected patients with advanced disease, when no hepatic vein lumen is identifiable beyond the ostium.

Stenoses occurring in the peripheral or central venous outflow of haemodialysis fistulae, hike most benign venous stenoses, respond poorly to PTA alone. Stents are reserved for patients in whom PTA has failed because of recoil, or in whom stenosis has recurred. However, results are not particularly encouraging: a 40% 1-year patency has been reported in central stenoses, and a 2-year patency of 25% was found in both central and peripheral stenoses (15,17).

In our experience with benign venous stenoses, immediate successful stent placement was achieved in 21/26 patients (88%). Initial stent placement was unsuccessful in 4 cases of subclavian vein stenosis, resulting in reobstruction. Actually, we are reluctant to place stents in the subclavian vein. Primary stent patency was 72% after an average follow-up of 16 months (range 1-46 months). Reintervention consisting of PTA and placement of additional stents was required in 6 cases. These interventions were performed at an average of 8 months after primary stent placement. There was 1 case of obstruction after 18 months despite reintervention; thus secondary patency was 80% (9, 10). Similar results of 78% and 83% stent patency in the SVC and IVC were found in a more recent personal survey (32).

Complications

Complications related to venous stenting are relatively few. Misplacement or stent migration are the most feared potential complications. Stents should be long enough to cover the stenosis entirely. Stents with an insufficient diameter are prone to migration, even hours after placement. Heparinization during the procedure avoids acute SVC thrombosis. Stent thrombosis caused by external compression also has been observed (15). Stent infection, bacteraemia, septicaemia and shock are potential complications, which should be minimized by use of strict aseptic technique.

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Case report of a successful emergency endovascular procedure performed in an AMI patient with acute occlusion of the left main coronary artery

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Acute occlusion of coronary artery is known to underlie the Q-wave myocardial infarction of the left ventricular region supplied with blood from this artery in the majority of cases. Among other factors, the mass of necrotic myocardium, depends largely on the part of the left ventricle supplied by the occluded artery. The larger is the artery's territory, the larger muscle volume is involved. In this respect the myocardium is mostly threatened by acute occlusion of the left main coronary artery proximal to its branches. In such cases the necrosis may at once spread to the territory of two major vessels - left anterior descending (LAD) and circumflex branch (CxB) of the left coronary artery, i.e. the major part of left ventricular myocardium can be lost. It is thought, that occlusion of the left main coronary artery is most commonly a fatal condition. Reports suggest that 99.5% of patients with such condition die within the first day after myocardial infarction. Chronic occlusion of left main coronary artery is observed in 0.01-0.7% of cases (4). For instance, since 1999 throughout 2003 diagnostic coronary angiography was performed in Moscow City Center of Interventional Cardioangiology (Moscow CIC) in 5000 patients. Only 4 of them were found to have chronic occlusion of left main coronary artery, which accounts for 0.08% from the overall number of patients. Acute occlusion of left main coronary artery was a little more common in AMI patients. During the same period in Moscow CIC over 1000 diagnostic coronary angiography procedures were performed within a few hours after AMI. In 600 cases the cause of myocardial infarction was acute occlusion of infarct-related coronary artery. Acute occlusion of left main coronary artery was observed in 3 cases (0.2%). All these patients were admitted to hospital with severe arterial hypotension and acute left ventricular failure or cardiogenic shock, which is a very strong predictor of hospital mortality (5). It has been demonstrated, that, when possible, early and adequate restoration of antegrade flow in infarct-related coronary artery (IRA) provides a more favorable clinical course of AMI due to the preservation of viable myocardium and the minimization of the period of electrophysiological instability (3). This particularly applies to patients with proximal occlusions of coronary arteries or occlusion of left main coronary artery. Among the methods of urgent revascularization the preference is currently given to transluminal coronary angioplasty, as the most safe and effective procedure (1, 2).

Moscow CIC has the experience of three urgent transluminal angioplasty procedures performed on the left main coronary artery in patients with AMI. In two cases despite the successful restoration of antegrade blood flow with the use of PTCA we couldn't save the patients' life, and they died from progressive left ventricular failure. In another case successful transluminal angioplasty with stenting accompanied by intraaortic balloon counterpulsation (IABC), to our opinion, saved the patient's life, thus emphasizing the necessity and advisability of active treatment scheme in this group of patients.

In support of the premises we call your attention the following case report.

Patient C., 49 years old, male, case history № 895/2003, was admitted to the Acute Coronary Care Unit of the Moscow CIC (13-00, 06.03.2003) by emergency crew. The patient presented with prolonged heart attack and ECG signs of acute circular myocardial infarction of left ventricle.

Diagnosis on admission: CHD, acute Q-wave anterolateral myocardial infarction involving the apex, lateral and posterior walls of the left ventricle (06.03.2003). Cardiogenic shock.

Past medical history: the patient had suffered arterial hypertension for over 10 years with transient episodes of blood pressure rise to 190/120 mmHg. No continuos antihypertensive therapy was administered. Smoking (around 30 cigarettes a day). The patient denied alcohol abuse, no evidence of hereditary diseases was revealed. The patient didn't suffer diabetes mellitus. Comorbidities included gastric ulcer with the last aggravation 5 years ago. The patient has been troubled with chest pain resulting from moderate exercise stress (200-500 m walk.). He received no continuous antianginal therapy, occasionally took nitrates to relieve the pain. In the morning on 06.03.2003 (10-00 a.m.) severe chest pain that wasn't relieved by nitrate intake made him call emergency care service. When ambulance team arrived the general state of the patient was poor: arterial blood pressure 60/20 mmHg, skin paleness, diffuse rales in the lower lung segments. Narcotic analgesics were administered for pain syndrome: intravenous fentanyl 2.0 ml; intravenous morphine 1.0 ml, however, no substantial effect was observed, intravenous administration of cardiotonic agents was instituted (dopamine 8 μg/kg/min.). The patient was delivered to CIC in 12-55 p.m.

Severe general condition was seen on arrival. Pale skin covered with death-damp. Rough, diminished breath sounds. Moderate bilateral diffuse rales. Respiration rate - 22/min. Muffled heart sounds without murmur. Dopamin infusion was associated with heart rate acceleration to 88 b.p.m. Arterial blood pressure 90/60 mmHg. Liver edge reached the costal margin.

ECG showed regular sinus rhythm, normal axis position. HR = 90/min. Monophase ST segment elevation up to 9 mm was revealed in leads V1-V6, reciprocal ST segment depression up to 3 mm in leads II, III, aVF (Fig.1).

Echocardiography showed non-dilated heart chambers, mild reduction of left ventricle contractility, akinesia of the apex, lateral and posterior walls on the level of middle and apical thirds. Left ventricular ejection fraction 37%, end-diastolic volume 5.8 cm, end-systolic volume 4.3 cm, interventricular

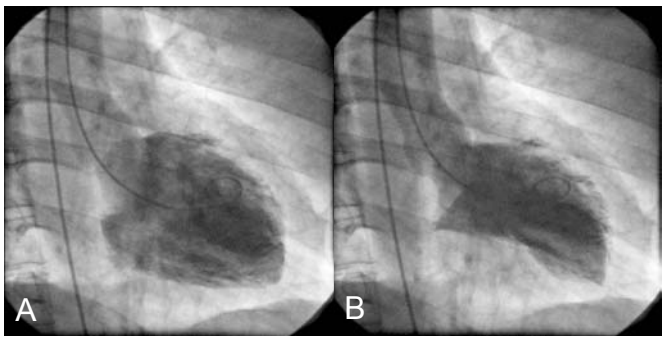

Fig. 1. Left ventriculography. Patient C.
A - left ventricle diastole; B - left ventricle systole, the figure shows anterolateral and apical akinesia of the left ventricle.

septum 11 mm, posterior wall of the left ventricle 12 mm. Left ventricular function was relatively well preserved, which, to our opinion, could be explained by the presence of good collateral circulation between the right coronary artery and the left coronary artery distally to the occlusion site (Fig. 2B). Heart valves appear normal. Doppler study revealed no flow abnormalities.

Dopamine was continued in coronary care unit in a dose of 10 μg/kg/min. Desaggregants and anticoagulants according to the scheme (Trombo-ass 100 mg, heparin 100 mg/kg bolus and drip. AST level was controlled).

Considering the prolonged pain, acute myocardial infarction, cardiogenic shock, emergency diagnostic coronary angiography was performed. Left ventricle opacification revealed extensive apical and anterior dyskinesia of the left ventricle, hyperkinesia of posterior and inferior segments (Fig. 1). Ejection fraction: 34%, end diastolic volume -145 ml, end systolic volume - 96 ml. No mitral regurgitation was observed.

Selective coronary angiography: Left main coronary artery occlusion. (Fig. 2A). RCA: diffuse changes with maximum stenosis reaching 70% (Fig. 2B) Retrograde opacification of the left anterior descending artery and the LCA circumflex branch is seen during selective RCA coronary angiography.

Immediately after diagnostic coronary angiography JL 8F guidewire catheter was introduced into LCA origin, mechani-

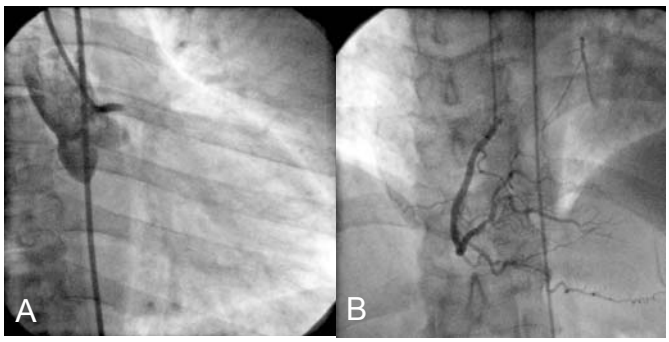

Fig. 2. Diagnostic angiograms of patient C., aged 49:
A - left main coronary artery occlusion; B - RCA coronary angiography, well-marked intersytrunk collateral pathways in LCA.

cal recanalization with transluminal angioplasty were subsequently performed in left main coronary artery (Fig. 3, 4A).

After PTCA of left main bifurcation and the origin of left anterior descending artery with 3 mm x 13 mm balloon, "Guidant" "Multilink Tetra" coronary stent (3.5 mm x 8 mm) was deployed under a pressure of 14 atmospheres, dilatation time 45 seconds (Fig. 4B). Distal end of the stent extended beyond the origin and proximal segment of the left anterior descending artery.

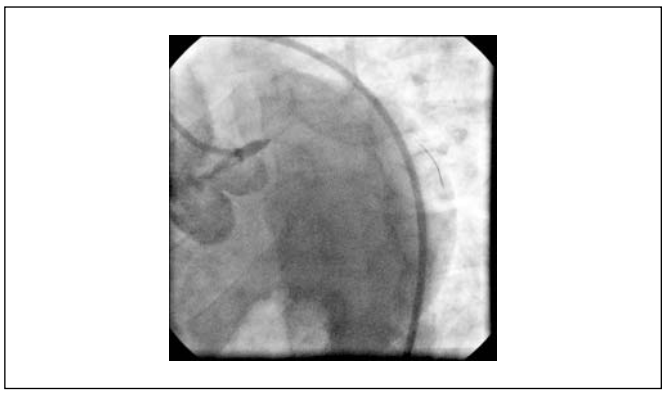

Fig. 3. Mechanic recanalization of left main artery

Control angiography shows successful stenting of left main coronary artery and the origin of left anterior descending artery,

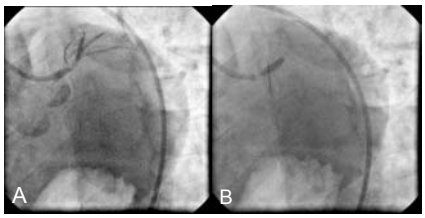

Fig. 4. PTCA and stenting of left main coronary artery:
A - predilatation with "Cordis" "U-PASS" 3.0 mm balloon, length 13 mm, dilatation time 60 seconds;
B - LCA trunk stenting with "Guidant" "Multilink Tetra" stent (3.5 mm x 8 mm), dilatation time 45 seconds.

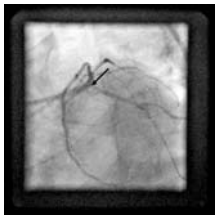

Fig. 5. Completion angiography following stent placement in left main coronary artery, arrowhead points to stenosis in the origin of circumflex branch.

(there is no residual stenosis or dissection, TIMI 3 antegrade flow is observed). However, we found stenosis in the origin of circumflex branch (Fig. 5). Coronary guidewire was advanced through the stent cell into the distal portion of circumflex branch with subsequent successful PTCA of its origin using "Cordis" "U-PASS" 3 mm x 13 mm balloon (Fig. 6, 7).

Despite the good outcome of endovascular procedure, complete restoration of blood flow in LCA territory, intravenous

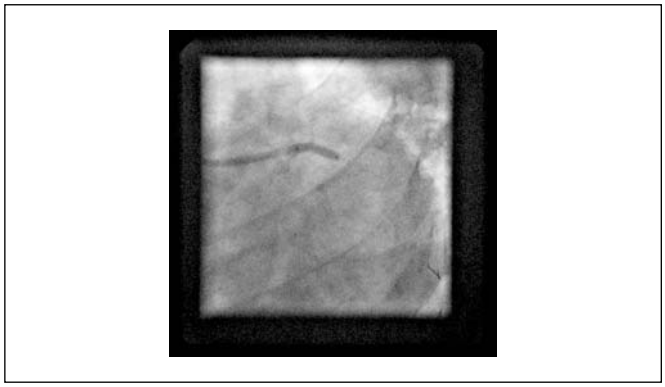

Fig. 6. Guidewire and balloon advanced through stent cell in left main coronary artery, PTCA of the origin of circumflex branch was performed.

administration of cardiotonics (dopamine 12 μg/kg/min), the patient had unstable hemodynamic parameters with a trend towards hypotension (80/30 mmHg). This was due to low cardiac output resulting from the large involvement of myocardium. Controlled by fluoroscopy, a balloon for intraaortic conterpulsation was introduced distally to the left subclavian artery. After several attempts of balloon inflation (1:1 - 1:4 regimens were used) we obtained maximum hemodynamic effect with 1:2 regimen. Intraaortic counterpulsation was performed using 1:2 balloon inflation regimen. Stable hemodynamics: BP - 100/60 mmHG, HR - 82 b.p.m. The patients was reallocated to intensive care unit. After the 18-hour therapy dopamine dose

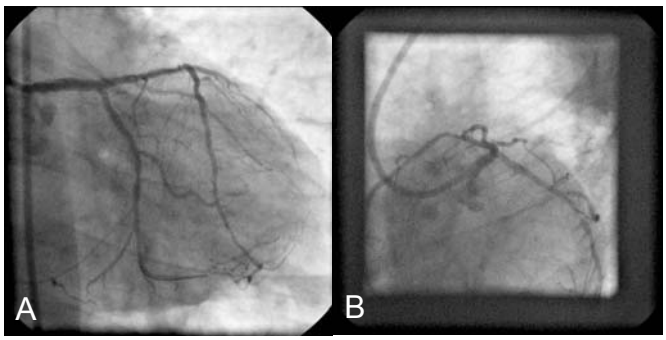

Fig. 7. A, B - Control angiography of LCA performed in two views before the end of procedure.

was decreased to 4 mg/kg/min, circulatory failure regressed. The patient also received desaggregant therapy (Ticlid, Trombo-ass), anticoagulants (heparin, controlled by AST level), cardiac glycosides (digoxin), diuretics (furosemide, aldactone).

In order to assess the outcome, control coronary angiography was performed 5 days after the procedure (Fig. 8). Successful result of angioplasty of left main coronary artery was confirmed, TIMI 3 antegrade flow was revealed, no angiographic signs of thrombosis or dissection were present.

On the 5-th day after the procedure the patient was transferred from intensive care unit to the department of cardiology. General condition was stable. By the 6-th day physical activity was extended to ward regimen. There were no further angina recurrence, as well as circulatory failure events. On examination: normal general condition, normal color and moisture of skin and visible mucosa. Normal breath sounds, mild harsh-

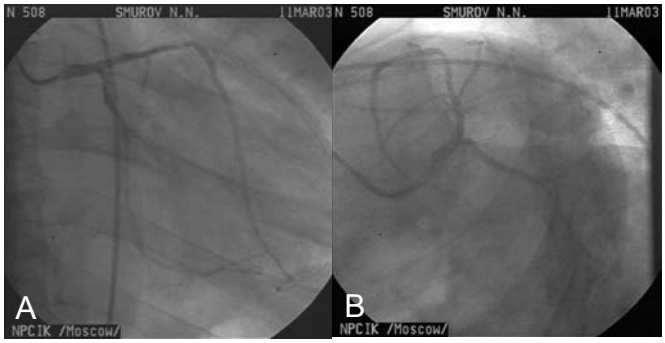

Fig. 8. A, B - Control coronary angiography of LCA performed in two views 5 days after the procedure.

ness, no rales are heard. Respiration rate - 18/min. BP - 120/70 mmHg. HR - 82/min. Heart sounds were muffled, regular. No murmur was heard. Liver edge reaches the costal margin. Neurological state was normal.

ECG showed well-marked positive changes, ST segment was normal, T-wave inversion seen in standard and chest leads. Echocardiography (as compared to previous evaluation) heart chambers were not enlarged, total and segmental contractility of the left ventricle improved: apical and posterior hypokinesia of the left ventricle. Ejection fraction 53%, end diastolic volume 5.8 cm, end systolic volume 4.0 cm, interventricular septum 11 mm, posterior wall of the left ventricle 12 mm. Heart valves were apparently normal. Ambulatory ECG monitoring detected sustained sinus rhythm with a mean rate of 72-94/min. ST segment was stable. Desaggregant (Trombo-ass, Ticlid), antianginal (cardiket) and duiretic (Triampur) therapy was continued. In addition, ACE inhibitor was administered (prenidopril). Fourteen days after admission to Moscow CIC (19.03.2003) the patient was discharged in stable condition and recommended repeated examination (including diagnostic coronary angiography) 6 months later.

Therefore, this case report demonstrates, that despite the unfavorable prognosis of urgent endovascular interventions performed in patients with acute occlusion of left main coronary artery (6, 7), aggressive tactics of therapy (the earliest possible restoration of antegrade flow in the occluded artery, supported by intraaortic counterpulsation) is effective and reasonable. It is probably the only chance to survive in this patient group. Successful outcome was doubtlessly supported by the fact, that the patient had collateral pathways between RCA and LCA. As a result, acute occlusion of left main coronary artery didn't cause total necrosis of the myocardium supplied with blood from the LCA vascular bed, because the circulation in this area was supported by collateral flow from RCA.

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Clinical case: Angioplasty of the occluded common iliac artery with an additional renal artery arising from its patent proximal segment

Z.A. Kavteladze, S.A. Drozdov, D.P. Dundua, A.M. Babunashvili, K.V. Bilov, D.A. Kartashov*

Additional renal arteries are found in 20%-30% of people (1). According to K.S. Satyapal et al., single additional artery is seen in 23,2% of cases, two additional renal arteries - in 4,5%, they supply the left kidney (32,0%) more often than the right one (23,3%). Bilaterally located additional renal arteries are encountered in 10,2% of cases. Men are affected more commonly than women (28,0% vs. 16,4%) (2). The variants of these arteries' origin are quite diverse: they can arise from the abdominal aorta or from the iliac arteries. We present a clinical case of additional renal artery, arising from the patent proximal segment of distally occluded common iliac artery.

A 53-year-old male patient presented with complaints on left calf pain while walking at 50-100 m. He had a history of intermittent claudication for about one year; conservative treatment had a temporary positive effect. At clinical examination: right lower extremity was of normal color, warm, with arterial pulses palpable at all levels; left lower extremity was also of normal color, cooler than the right one, calf muscles were soft, painless, there were no ulceration or skin changes, arterial pulses on the left lower extremity were absent at all levels. Limb ischemia corresponded to Fontain class 2B.

Ultrasonic scanning of leg arteries revealed a total occlusion of the left common iliac artery (CIA), patent external iliac artery (EIA) and collateral blood flow at distal levels.

Angiographic examination revealed an occlusion of the distal portion of the left CIA with an additional renal artery supplying the lower segment of the left kidney arising from the short stump of left CIA. External and internal iliac arteries and common femoral artery were patent, without changes (Fig. 1).

Considering the short duration of occlusion and the good distal runoff we decided to perform the recanalization and balloon angioplasty of the left CIA immediately after the examination. The presence of an additional renal artery made the situation very unusual.

Left common iliac artery was catheterized from the contralateral approach, the guidewire was inserted into the additional renal artery. After it we perfomed retrograde puncture of the left femoral artery and were able to recanalize the left CIA with the Road Runner guidewire ("W. Cook", USA). Then balloon catheters were passed over the guidewires into the recanalization area and in the additional renal artery. Balloon angioplasty of the left CIA was performed using a 40 mm long, 9 mm balloon ("Cordis", USA). The balloon (diameter 5 mm, length 20 mm, "Cordis", USA) placed into the additional renal artery was not inflated (Fig. 2). Left CIA was stented with ZA-stent ("Cook", USA), 10 mm in diameter and 8 cm in length, with only a guidewire placed in the additional renal artery. The proximal end of the stent was placed at the CIA ostium. After stenting of the CIA the guidewire from the additional renal artery was removed and then passed again into this artery through the stent strut, then a 10 mm balloon (length 40 mm, "Cordis", USA) was placed inside the stent and inflated. Control angiography showed patent left common iliac artery without signs of residual stenosis, additional renal artery also was patent, without stenosis of its ostium (Fig. 3). 6 month

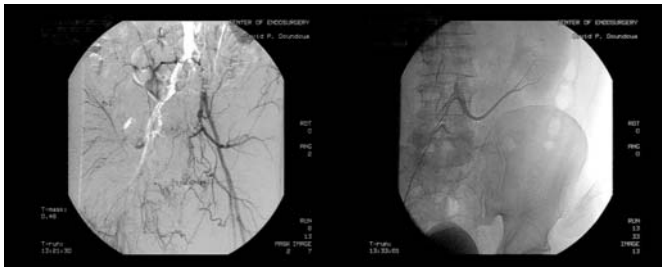
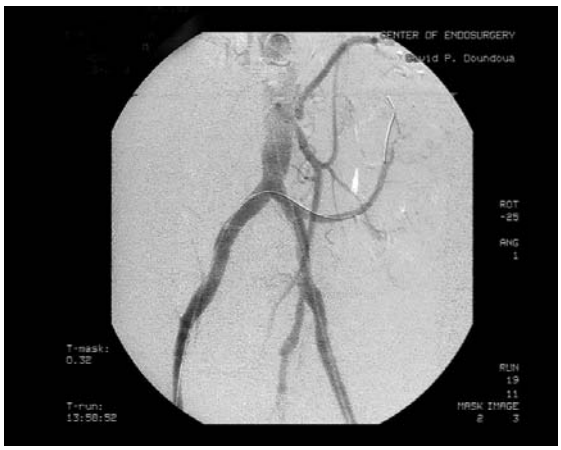


Fig. 1.



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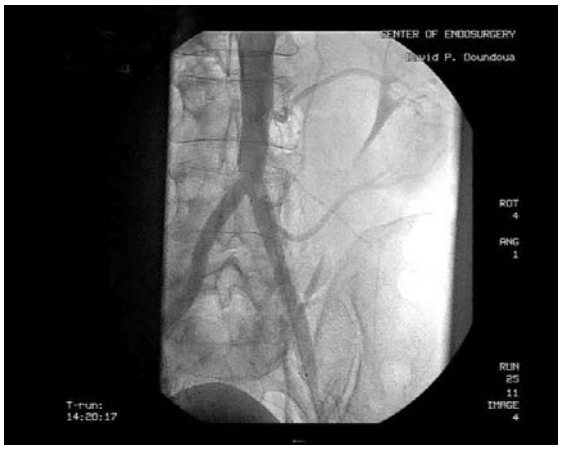

Fig. 3.

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later patent was free of symptoms with sustained antegrade flow to his left leg.

The patient received Plavix and Aspirin according to the standard scheme. We didn't see complications at the puncture sites, no data suggesting of kidney infarction were revealed in the immediate follow-up. The patient was discharged on the 2nd day after the procedure, the circulation in the lower extremity was fully restored, arterial pulses in the lower extremities were perceived at all the levels.

Percutaneous treatment of occluded iliac arteries is widely used in modern practice with good short-term and long-term results. The presence of an additional renal artery, arising from the lesion area, requires special manipulations for the preservation of patency of the above-mentioned artery, which has been demonstrated in this clinical case.

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Myocardial-specific troponins in diagnosis, risk stratification and prognosis of acute coronary syndrome.

1. Diagnostic value of conventional and novel markers of myocardial injury

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Cardiovascular diseases (CD) are the world's major cause of mortality. The proportion of CD-related mortality in the overall mortality (including neoplasms, infections, etc.) is over 50%, accounting for 24000 deaths per 1 million of population yearly, the age being over 30 (7). Though hypertension is the most common CD, acute myocardial infarction (AMI) remains the leading mortality cause. Every year over 300000 deaths in USA are due to AMI.

Yet, for the last decade this parameter in the Western Europe have decreased by 20-25% due to both precise and timely diagnosis and novel effective treatments of patients with acute coronary syndrome (ACS).

According to WHO guidelines (9) the diagnosis of AMI has been traditionally based on the three major postulates: 1) clinical pattern; 2) ECG; and 3) increase of serum enzyme activity (concentration of myocardial enzymes).

In accordance with this document, the diagnosis of AMI is considered certain if two of the above listed criteria are unquestionable and unambiguous, and it seems reasonable to improve the WHO recommendation for each criterion mentioned above.

Clinical pattern. According to WHO guidelines listed above, the clinical pattern is considered typical in the presence of acute, severe and prolonged (>20 min), nitroglycerin-resistant angina.

It is known, however, that there exists a larger number of patients with "classical" pain, but without further confirmed AMI.

On the other hand, 20-30% of patients present with silent onset of the disease ("silent AMI") or mild pain. These include patients with diabetes, hypertension, elderly patients, patients with chronic heart failure, peripheral occlusive disease, patients during or after surgery, stroke or coma. In this population AMI may start with signs of acute left ventricular insufficiency (cardiac asthma, pulmonary edema, cardiogenic shock). There are other types of manifestation: abdominal (nausea, vomiting, abdominal tenderness), arrhythmic, cerebrovascular.

Therefore, clinical pattern of AMI onset varies greatly and is obviously beyond the doubtless estimation in many instances.

ECG. The formation of pathological, persistent Q-wave, which is detected in at least two standard ECG leads, as well as the typical behavior of ST segment of T-wave, are reliable signs of AMI as determined by WHO guidelines.

ECG remains the first and the most important diagnostic method of AMI, but many authors report, that the above listed ECG profile is absent in over 50% of AMI patients, particularly within the first hours. It is now believed that ECG changes are not as specific for AMI as they once were thought to. The interpretation of ECG is difficult or, sometimes, impossible, if it was affected by previous infarctions (repeated AMI), some rhythm disorders (atrial fibrillation, WPW syndrome), intraventricular conduction disorders (especially left bundle branch block), the presence of pacemaker, certain valvular diseases.

Therefore ECG may be of no diagnostic value in many cases (>50%) of AMI.

Blood serum enzymes (myocardial markers). According to WHO classification (9), the typical curve of serum enzymes activity with initial growth and subsequent decline as assessed by a serial study is considered reliable. These changes must clearly correlate with a certain enzyme (MM) and the time passed between the onset of first symptoms and blood sampling.

Proceeding from the mechanisms of irreversible ischemic myocardial injury, death of cardiomyocytes is always associated with the release of numerous intracellular components, including protein molecules, into extracellular matrix. Therefore, myocardial necrosis of any degree and location is always associated with the increase of activity (concentration) of conventionally measured enzymes and structural proteins in the blood of AMI patients, which is confirmed by numerous experimental and clinical trials.

Conventional enzyme (isoenzyme) test-programs

For many years serum activity of a number of enzymes and isoenzymes has been used to diagnose AMI. These extensively known enzyme-isoenzyme parameters (Table 1) constitute the so-called enzyme diagnosis of myocardial infarction (1, 2, 6).

Radioassay provided the possibility to detect serum level of myoglobine (Mg) - an intracellular protein of myocardiocytes, which doesn't possess enzymatic activity. Mg has enlarged the range of important biochemical tests, which,

Table 1. Biochemical markers of myocardial injury

Major markers	
Conventional test-programs	Novel test-programs
LDH (lactate dehydrogenase) AST (aspartate aminotransferase) CK (creatine kinase) CK-MB (activity) Myoglobin (MG) LDH-1/LDH-2 ratio; hydroxybutyratedehydrogenase	Troponin I Troponin T CK-MB (mass) Myoglobin (MG) CK (creatine kinase)

since recently, have been called biochemical markers of AMI along with enzymes.

Therefore, by the end of the 1980-s a group of biochemical parameters was clearly outlined, which can be defined as traditional or classical diagnostic test-program (diagnostic menu) used for diagnosis and clinical assessment of AMI (Table 1).

For a period of 50 years from 1953, extensive and numerous surveys concerning analytical, metabolic and clinical aspects of the use of cardiac markers in AMI diagnosis, have been conducted. To summarize these studies, several basic postulates of AMI biochemical diagnosis can be formulated (1, 2, 6).

- All conventional markers have marked diagnostic value; i.e. their increased activity is found in the majority of patients (up to 90-98%) with documented AMI. It results from a number of factors: a) a higher level of specific activity (concentration) per 1 g of myocardium compared to other intracellular proteins and other macromolecules; b) their absolute or preferred location in the cytoplasm of cardiomyocytes; c) the absence of strong binding of these proteins with membrane or other intracellular components.

- They can be divided into early (Mg) and delayed markers of AMI (all enzyme-isoenzyme tests).

- Diagnostic value of the above mentioned tests varies with the frequency of tests in the time course of AMI. However, one has to note, that single measurement of myocardial markers within the first day of AMI or later (e.g., the next day after admission) is unacceptable and almost completely compromises the diagnostic value of these tests.

- Diagnostic value criteria for a marker include:

а) diagnostic significance range, i.e. the period of time, when elevated (pathological) level of the marker is detected;

б) "clinical relevance" of the marker's pathological value, i.e. the degree of its rise compared to normal range (as a rule, compared to the higher limit of this range).

Diagnostic specificity. The most "vulnerable" place in biochemical diagnosis of AMI in terms of "conventional" tests is their inadequate diagnostic specificity. It depends mostly on topical (in this case - myocardial) specificity of a protein marker.

If the blood marker is found in tissues and organs other than myocardium, their damage will increase its blood level, thus causing false positive results. All history of analytical and diagnostic development of novel myocardial markers can be described as the search for absolutely specific tests.

Diagnostic specificity of "conventional" myocardial markers

AST (aspartate aminotransferase) and LDH (lactate dehydrogenase) are the highly sensitive AMI markers. Their level is substantially increased within the first days of acute MI, which is due to the high specific activity (concentration) of these enzymes in cytoplasm of myocardiocytes. In view of extensive prevalence of re-amination in various tissues besides myocardium, AST is found in many other target organs: liver, muscles, erythrocytes. It results in the increase of blood enzyme activity in patients with different diseases involving liver and skeletal muscles. Similarly, LDH, due to its prevalence in various organs and tissues (liver, skeletal muscles, erythrocytes, kidneys, etc.), also has low diagnostic specificity for AMI. As a result, both tests are currently not used for biochemical AMI diagnosis.

CK (creatine kinase) - muscle-specific enzyme (skeletal and heart muscles, smooth muscle cells). It worthy of notice, that myocardial specific activity of CK is slightly lower as compared to that in skeletal muscles. Considering the difference in the bulk of skeletal and heart muscles one can postulate the high frequency of elevated blood CK in patients with various skeletal muscle diseases.

Importantly, the diagnostic value of CK depends on the measurement method. Currently, the only eligible measurement method for enzyme's catalytic reactivity is the so-called optimized activated (with sulfhydryl donors included into the reaction mixture) kinetic method.

CK MB isoenzyme. Among the conventional markers, CK MB activity had been till recently regarded as a "golden standard" of biochemical diagnosis of AMI. Indeed, high levels of CK MB, unlike total CK and CK MM isoenzyme, are found in myocardium (15-38% from total CK) and, in negligible amounts (3-4%), in skeletal muscle cells. This enzyme wasn't identified in other organs and tissues (except brain). The rise of CK MB in AMI patients is a very specific and sensible sign of AMI. However, it was established by long-term studies, that heart specificity of CK MB isoenzyme is not absolute, which seems to be mostly due to its release from the damaged skeletal muscles.

CK isoenzymes were initially measured by electrophoresis, which separated the three fractions of CK: CK MM, CK MB and CK BB. Serum electrophoresis in healthy subjects revealed no BB fraction (brain isoenzyme), whereas MB fraction was detected only in trace amounts (0-2%). Therefore, the increase of its percentage was thought to be due to release of isoenzyme from damaged (necrotic) myocardium, indicating the ongoing AMI. This fraction was increased during 4-7 hours after onset of the disease and peaked at 16-26 hours, subsequently decreasing to baseline level at 48-72 hours. When used for CK MB detection, this method revealed some cases of false positive results. The attempt to use a certain percentage of CK MB from total CK (5-6%) as a criterion of AMI only slightly increased the diagnostic value.

In addition, the results of isoenzyme electrophoresis were affected by the presence of serum atypical isoenzymes and CK BB in both diseased and healthy subjects.

Therefore, difficulties, poor accuracy of a semi-quantitative electrophoresis study have made us to seek for novel methodological ways to identify serum CK MB. Particularly, we suggested a method of separation of CK isoenzymes using ion-exchange resin. However, it required sufficiently large volume of specimens, remained difficult and had poor reproducibility.

Since 1966-1967 a new method of CK MB assessment has been introduced into clinical practice - immune inhibition with non-precipitating antibodies (antiserum antibodies) and M-subunit of CK. This method, which is remarkable for its good analytical sensitivity and reproducibility, easiness, was used in the majority of biochemical analyzers, and, due to the features stated above, became extensively adopted in clinical and biochemical studies and replaced all the previously used methods of CK MB measurement.

Clinical testing revealed, that the diagnostic sensitivity of CK MB activity measurement in AMI patients approximated 100%, considering the strict time intervals and frequency of this study. However, simultaneous clinical experience with the use of this marker is also characterized by a number of disadvantages, which aggravate the situation with its insufficient diagnostic specificity, partially associated with the problems in analytical specificity (shifts in CK isoenzyme profile and the formation of complexes), which resulted in false-positive results.

Myoglobin. The main benefit of this low molecular weight protein (18000 Da) is its high sensitivity during all stages of AMI development. However, like CK, it has quite low diagnostic specificity, as it is found in relatively big amounts in myocardium, as well as in all skeletal muscles. Given that, this parameter is used today extensively in novel diagnostic test-programs (Table 1), later we shall discuss its clinical relevance in detail.

Therefore, the main advantage of the above listed "conventional tests" consists in their high sensitivity, sufficient for AMI. Their substantial drawback consists in their low and insufficient myocardial specificity, affecting their diagnostic value.

Troponins (I or T) - the basis of modern diagnosis of AMI and acute coronary syndrome (ACS)

For the last years the search for "ideal" biochemical markers of myocardial injury - highly sensitive and, at the same time, absolutely specific for myocardiocytes - has been extensively conducted. These criteria were met by intracellular proteins of myocardiocyte contraction system - Troponins I (TnI) and TroponinsT (TnT).

On the threshold of the new millenium there was an event, which can doubtlessly be considered as a revolution in modern cardiology, in its most important part, which concerns the diagnosis and assessment of acute forms of coronary heart disease - MI and unstable angina (UA).

A consensus document, dedicated to the revision of AMI diagnostic criteria, was published in 2000 by the prominent cardiological societies of Europe and USA - European Society of Cardiologists, American College of Cardiologists and American Heart Association (8). According to this document, the major diagnostic criterion of an acute, progressing or recent MI consists in a characteristic increase and subsequent gradual decline of one of serum Tns - high-specific biochemical markers of myocardial necrosis - accompanied by at least one of the following characteristics:

- Q-wave ECG;
- other ECG changes, suggesting myocardial ischemia (ST segment elevation or depression).

For the interpretation of the basic regulation in the document it was stated, that: **"The most commonly mentioned biological marker of myocardial injury, which is preferred in most cases, is heart troponin, which has almost absolute myocardial specificity, as well as high sensitivity… In cases when heart Tn is unavailable, its best alternative is CK-MB (measured as mass), which is less specific, than Tn.".**

Therefore, these documents summarize almost 50-year research and use of various myocardial markers (MM), from enzymes-isoenzymes to structural proteins of myocardiocytes. Its core comes to a postulate, that modern diagnosis of AMI is impossible without myocardial markers, such as Tn.

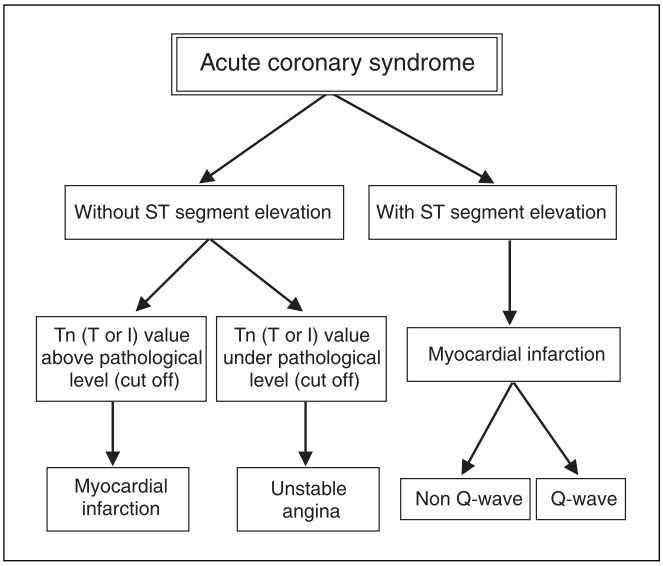

Fig.1. Diagnosis of acute coronary syndrome

Moreover, in guidelines for the treatment of acute coronary syndromes without ST elevation, published in 2000 (4, 5), increased blood level of Tn in ACS patients is considered the main criterion of MI. In addition, the documents emphasize the importance of Tn level measurement in the assessment of the risk of complications in these patients.

The diagnostic algorithm, presented in the above listed documents, is based on ECG data, but with obligatory Tn testing, without which the precise diagnosis between a non-ST elevation MI (NSTEMI) and UA is impossible. Fig. 1 shows quite simple and clinically tested diagnostic classification of ACS.

The documents, mentioned above, contain detailed account of a number of statements, concerning the use of Tn for MI detection:

1. Troponins (T or I) are the "gold standard" of myocardial necrosis detection, which has replaced the CK-MB measurement. Therefore, those healthcare centers, which had acquired sufficient experience of Tn use for MI diagnosis, don't practice CK-MB test, leaving myoglobin as the only early marker in the diagnostic "menu". Besides, we would like to note, that in some patients with non-ST elevation ACS, an isolated increase of Tn without the rise of CK-MB level is detected.

2. High sensitivity of Tn allows for the detection of microscopic necrosis zones (less than 1 g), defined as minimal myocardial injury. But the fact, that blood MM were found to be increased in patients, doesn't provide the possibility to assess the causes of protein release from the affected myocardial cells, as well as the mechanisms, underlying this event. Hence, the detection of serum Tn increase in the absence of clinical and/or ECG signs of ischemia, makes the ischemic nature of myocardial injury doubtful and implies the search for other causes of cardiac injury, such as myocarditis or drug intoxication.

3. In previous WHO letter (9) it was emphasized, that the phenomenon of initial rise and subsequent gradual decline of activity (concentration) of myocardial markers (MM) is crucial for MI diagnosis; those necessary serial assays increase

dramatically the efficacy of biochemical diagnosis. It is recommended to carry out Tn studies on the following schedule: on admission, 6-9 hours later and, most optimal, after 12 hours.

4. The rise of Tn level is more likely to reflect irreversible injury, rather than reversible one, however, this question is not clear yet.

5. Tn measurement is extensively used for the assessment of risk and prognosis of acute coronary syndrome in order to improve therapy and management of such patients, particularly in cases without ST segment elevation.

6. Tn blood level is always increased in patients after surgery and till now it has been a problem to distinguish between injuries, associated with MI and surgery (various intraoperative procedures).

7. Modern methods of MI diagnosis, including biochemical assays, scintigraphy, echocardiography and contrast ventriculography, allow for the detection of minimal ischemic injury of myocardium. Some clinicians, who use the entire spectrum of the existing novel methods, categorize the myocardial necrosis as a microscopic one (microinfarction), small (small focal) and moderate or substantial (vast, macrofocal, extended). This is commonly based on "peak" levels of Tn and CK-MB. Therefore, assuming that myocardial necrosis of any size caused by ischemia can be detected, each patient with initial diagnosis of unstable angina can be regarded as MI patient.

8. All ECG criteria, which suggest myocardial ischemia (ST segment elevation or depression, T-wave inversion), are, by themselves, not sufficient for definite diagnosis of MI. Moreover, not all patients with myocardial necrosis of ischemic origin present with ECG changes. Hence, normal ECG doesn't suggest the absence of MI. Final diagnosis in all such cases depends on the detection of increased blood levels of cardiac biomarkers.

9. The value of Tn concentration, exceeding 99 percentiles for reference group, is defined as increased. Reference values must be determined in each laboratory for the Tn test-system used, provided that an appropriate quality control is conducted. An analytical accuracy (coefficient of variation) on the pathological level is considered acceptable, if the values make 10% or less from this parameter.

Troponins - their structure and functions in myocardiocyte

Troponins (I, T and C) in a ratio of 1:1:1 are included into troponin complex, bound with tropomyosin, which, together with actin, forms thin filaments of myocytes - the crucial component of contraction system of cross-striated muscles. All the three troponins are engaged in calcium-dependent regulation of contraction-relaxation (Fig. 2).

Tn1 is an inhibitory subunit of this complex, which binds actin during relaxation and slows down the ATPase activity of actomyosin, thus preventing muscle contraction in the absence of calcium ions.

TnT is a regulatory subunit, which binds troponin complex to thin filaments, thus participating the calcium-dependent contraction.

TnC is a calcium-binding subunit and contains four calcium receptor sites.

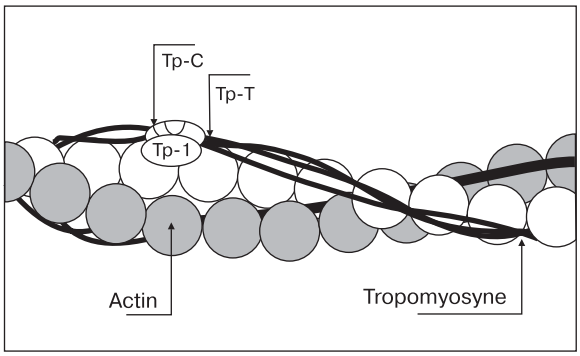

Fig. 2. Troponins are components of muscle (myocardial) cell contraction system.

Tn1 and TnT exist in three isoforms, each of unique structure for every type of cross-striated muscles (rapid, slow and cardiac), coded by various genes.

Cardiac isoform of Tn1 is substantially different from Tn1 isoforms found in skeletal muscles. About 44% of aminoacid chain sites of cardiac Tn1 are specific for this protein. In addition, Tn1 contains ancillary N-terminal polypeptide, composed of 31 aminoacid residua. Therefore, Tn1 is an absolutely specific myocardial protein. Tn1 molecular weight is around 24,000 Da.

Cardiac TnT is, by its molecular structure, also substantially different from the two types of TnT, present in skeletal muscles (rapid and slow muscles): there is 43% difference between the aminoacid sequence of myocardial TnT and slow muscle, and 56% difference between myocardial and skeletal forms. Thus, TnT is absolutely heart-specific protein. TnT molecular weight is 34,500 Da.

Cardiac TnI and TnT can be distinguished from similar skeletal muscle proteins with monoclonal antibodies, which are used in immune assays.

Cardiac TnC, in contrast to Tn1 and TnT, is, by its structure, completely identical to muscular TnC and, therefore, is not specific for heart.

To summarize the first part of current review, it is to be noted, that the clinical use of highly sensitive and specific diagnostic criteria of MI, such as troponins, may lead to the increase of the rate of this disease revealing in the population and, simultaneously, decrease the mortality rate, as it has been reported during the last years (2001 and 2000).

At the same time, the use of strict quantitative parameters, such as Tn and CK-MB levels, will decrease the subjectivism in ACS diagnosis, especially without ST elevation, this being particularly important for domestic cardiology, where ECG is traditionally preferred for the diagnosis of ACS and MI.

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Managing patients at risk of contrast-induced nephropathy

ECR Symposium

Sunday 9 March 2003 Austria Center, Room F1

Professor Jarl A Jakobsen

Dear Colleague

Welcome to the ECR 2003 Amersham Health symposium Managing patients at risk of contrast-induced nephropathy (CIN).

For those of us working with contrast media in everyday practice, this is an exciting time. Recent developments now mean that we have new options that present us with real choices about the contrast media we use for our patients. With this comes the chance to reduce their risk of CIN, improve cardiac safety and increase comfort upon injection.

We have therefore decided to focus debate at this symposium upon the clinical management of patients at risk of CIN. I am delighted to welcome three speakers with extensive clinical and research experience in this field for what I am sure will be an illuminating and lively event.

I hope that this educational forum will give delegates the opportunity to put CIN into perspective, as well as to discuss developments in the prevention of this serious and debilitating condition.

Professor Jarl A Jakobsen,
University of Oslo, Norway

10:30-10:35	**Welcome and introductions** Professor Jarl A Jakobsen, University of Oslo, Norway
10:35-11:00	**Scope of the problem** Professor Fulvio Stacul, University of Trieste, Italy
11:00-11:25	**How to prevent contrast media-induced nephropathy (CIN)** Dr Sameh Morcos, University of Sheffield, UK
11:25-11:50	**Role of contrast media (CM)** Professor Peter Aspelin, Huddinge University, Sweden
11:50-12:00	**Discussion**

The clinical burden of contrast-induced nephropathy (CIN)

Professor Fulvio Stacul

Fulvio Stacul qualified in diagnostic radiology at the University of Trieste in 1982. He was appointed Consultant Radiologist at the Institute of Radiology, University of Trieste, in 1990 and became Head of the Ultrasound Unit in 1998.

Dr Stacul has written more than 150 publications on diagnostic radiology, specialising in contrast media, uroradiology, vascular radiology, ultrasonography and interventional radiology. He has spoken at more than 140 national and international meetings.

Currently Secretary of the Journal of the Italian Society of Medical Radiology, Dr Stacul has been a member of a number of scientific societies including the European Society of Urogenital Radiology, the Contrast Media Safety Committee and the Scientific Editorial Board of European Radiology.

The use of iodinated contrast media (CM) in diagnostic and interventional procedures has increased greatly over the last 30 years, with an estimated 60 million doses applied worldwide each year. Increasing numbers of patients who may be at risk of CM-induced nephropathy (CIN) are being referred for procedures requiring the use of CM, and nephrotoxic reactions are among the most costly to treat (1).

CIN is typically defined as an impairment of renal function characterised by an increase in serum creatinine of more than 25% or 0.5 mg/dl (44 u,mol/l) over baseline, occurring within three days of the administration of CM, in the absence of an alternative aetiology. The reported prevalence of CIN varies, according to definition and patient group, from <5% where there are no risk factors up to an incidence of 20-30% in patients with risk factors (2, 3) However, in clinical practice its prevalence may be underestimated because serum creatinine is a comparatively insensitive measure of renal function in patients without kidney disease and, furthermore, patients do not always undergo renal function tests prior to and following procedures.

Renal failure induced by CM is usually non-oliguric and temporary, with serum creatinine returning to baseline within 7-10 days. In some patients, however, particularly those at high risk, CIN can take the form of severe acute renal failure (ARF) in which oliguria can develop within 24 hours of CM administration, serum creatinine may increase by over 5 mg/dl (440 nmol/l) and dialysis may be necessary.

Overall, CIN (following injection of ionic agents) was considered the third-leading cause of hospital-acquired ARF, accounting for 12% of all cases (2). It is questionable whether this is still the case following the widespread use of non-ionic agents (3).

The clinical burden of CIN can be minimised by identifying at-risk patients. The percentage of patients at particular risk has been estimated to be between 3.5 and 15.5% (4). Several independent patient-related and procedure-related risk factors contribute to the likelihood and extent of CIN.The most important risk factor is pre-existing renal impairment, increasing the risk of CIN more than 20-fold (5). The risk of CIN increases exponentially in relation to baseline serum creatinine above a baseline of 106 nmol/l (6). It is questionable whether diabetes mellitus is actually an independent risk factor (3-7). However, patients with both diabetes and pre-existing renal impairment are at highest risk. In one study, CIN occurred in 0.6% of patients with diabetes and normal renal function, in 5.7% of patients with renal insufficiency alone and in 19.7% of patients with diabetes and renal insufficiency (5). In another study, 50% of patients with diabetic nephropathy and creatinine clearance below 30 ml/min showed a rise of at least 25% in serum creatinine and 12% required dialysis (8). Other possible patient-related risk factors include dehydration, old age, congestive heart failure, history of CIN and concurrent administration of nepfirotoxfc drugs. CM-related risk factors include contrast dose, contrast osmolality, previous CM injection and route of administration of CM (intra-arterial administration carries higher risks). The extent to which some of these factors pose a risk in patients without existing renal damage is unclear.

In summary, CIN is a problem that is often under-recognised in clinical practice. It is costly, prolonging hospitalisation

and potentially necessitating dialysis.The burden of CIN could be reduced by identifying at-risk patients, making sure that these patients are well hydrated, minimising the contrast dose, and administering contrast agents with a more favourable renal profile.

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General approaches to lowering the risk of nephropathy

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Sameh Morcos was appointed Consultant Radiologist at the Northern General Hospital in Sheffield in 1983 and is an Honorary Clinical Reader at the University of Sheffield.

Dr Morcos is currently Secretary/Treasurer of the European Society of Urogenital Radiology and Secretary of its Contrast Media Safety Committee. He chairs the urogenital scientific subcommittee of the European Congress of Radiology (2002-3). He is also an Associate Editor of the British Journal of Radiology.

Dr Morcos' research interests include the mechanisms responsible for the side effects of contrast media. This has led to a new insight into the pathophysiology of contrast-induced nephrotoxicity.The author of many scientific papers, Dr Morcos has received the Flude Memorial Prize (1993) and the Barclay Prize of the British Institute of Radiology (1997).

Although evolution in the profiles of contrast media (CM) has reduced some of their adverse effects, nephrotoxicity in patients with impaired renal functioning remains a clinically significant problem. The first step in reducing the risk of CM-induced nephropathy (CIN) is to identify patients at risk. The practice of serum creatinine measurement before procedures and its interpretation is variable; consensus and standardisation of practice are desirable (1). Patients at risk can be identified using a screening questionnaire (2). If CM cannot be avoided, they should be used as infrequently as possible and at the minimum dose (3). The relationship between dose and risk of nephropathy is probably a threshold effect related to underlying renal function, rather than a linear one (4). Serum creatinine should be monitored and controlled in at-risk patients before and after the procedure, and concomitant administration of other nephrotoxic agents such as non-steroidal anti-inflammatory drugs and chemotherapy agents should be avoided.

Improved understanding of the pathogenesis of CIN has provided a variety of potential prophylactic approaches. One of the most well established and straightforward is hydration, demonstrated in animal studies to inhibit the functional and pathological abnormalities of CIN. The comparative efficacies of different hydration regimens have not been extensively investigated, but a recent study in 1620 patients undergoing coronary angioplasty has suggested that isotonic hydration with 0.9% saline is superior to the more typically employed half-isotonic hydration (5).

Although it reduces the concentration of CM in plasma, prophylactic haemodialysis does not lower the risk of CIN (6). Diuretics such as furosemide, postulated to lessen medullary ischaemia, have not proven effective in controlled studies and their routine use is not recommended (7). Activation of the DA-1 dopamine receptor increases renal blood flow, but results with dopamine have been conflicting, perhaps as a consequence of its non-specific stimulation of receptors other than DA-1; it may be renoprotective in patients without diabetes (7). More definitive evidence with the selective DA-1 agonist fenoldopam should result from an ongoing trial (8).

Adenosine, a renal vasoconstrictor, is thought to be involved in the pathogenesis of CIN, but outcomes with the adenosine antagonists theophylline and aminophylline have also been conflicting (7). Similarly, the utility of atrial natriuretic peptide (which increases renal blood flow) and antagonists of endothelin (a vasoconstrictor) remain to be established (7). Inadequate production of renal prostaglandins may be a factor in CIN, and infusion of 20 ng/kg/min prostaglandin E1 has been shown to significantly lessen CM-induced serum creatinine increases (9). However, the side effect profile of parenteral prostaglandin Er which includes hypotension and tachycardia, may limit its clinical utility.

On the assumption that reactive oxygen species are involved in CIN, prophylactic oral administration of the antioxidant *N*-acetylcysteine to patients with renal impairment has been investigated. In 83 patients undergoing CT, 2% of patients given acetylcysteine versus 21% of controls developed nephropathy (10). Acetylcysteine also reduced the incidence of nephropathy in 54 patients exposed to higher doses of CM through cardiac catheterisation (8% in comparison with 45% in the placebo group) (11). In three other trials, however,

acetylcysteine was not found to reduce CIN significantly (12–14), so its effectiveness remains unclear.

CIN is a common problem in patients with pre-existing renal impairment. The European Society of Urogenital Radiology (ESUR) has published guidelines for the avoidance of CIN (15). In terms of general measures, currently only hydration is a generally accepted method of reducing risk, and further trials are needed to prove the effectiveness of other potential prophylactic treatments. In addition, selection of the specific CM used for procedures, especially in at-risk patients, can provide a significant contribution to lowering the risk of nephropathy.

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Using isosmolar contrast media to lower the risk of nephropathy

Professor Peter Aspelin

Peter Aspelin trained at Malmo University Hospital in the 1970s and was Associate Professor there for 13 years. In July 1989, he became Professor of the Department of Diagnostic Radiology, Karolinkska Institutet, Huddinge University Hospital. Professor Aspelin later became Vice-Dean of the Medical School at the Karolinska Institutet and was Vice-President of the Karolinkska Institutet from 1995-2001.

Professor Aspelin has been researching into contrast media since 1972 and has written more than 140 scientific publications to date. He has a special interest in the development of non-ionic contrast media, their effects on medical imaging and of side effects in patients.

Contrast media (CM)-induced nephropathy occurs in up to 50% of high-risk patients, such as those with renal impairment and/or diabetes mellitus (1). Different classes of CM are associated with differing risks of CM-induced nephropathy (CIN). As renal damage associated with CM results largely from diuretic and hypertonic effects in the kidney - effects that are related to the agent's osmolarity - it is not surprising that high-osmolar CM (HOCM) are associated with the highest, low-osmolar CM (LOCM) an intermediate, and isosmolar CM (IOCM) the least risk of renal impairment (4).

Iodixanol is a non-ionic dimeric CM that is isosmolar to blood at all concentrations. The risk of nephrotoxicity associated with iodixanol administration has been examined in subjects with differing risk profiles for CIN, including subjects both with and without existing renal impairment and those with both renal impairment and diabetes mellitus. Analysis of early studies comparing iodixanol and LOCM in subjects with normal or very slightly impaired renal function did not demonstrate a consistent advantage for iodixanol (4, 5). However, the low rates of CIN seen in subjects with normal renal function were unlikely to discriminate between CM with respect to putative differences in their effects on the kidney. More striking findings have been observed in patients at greater risk of CIN, namely those with existing renal impairment with or without concomitant diabetes mellitus.

In the study by Chalmers and Jackson (3), 124 patients with existing renal impairment (inclusion criterion: serum creatinine [SCr] >150 nmol/l) undergoing renal and/or peripheral angiography, of whom 34 also had diabetes mellitus, received either iodixanol or the LOCM iohexol. In this study, 15% of patients given iodixanol-in comparison with 31% of those given iohexol-experienced a rise in serum creatinine of >10% in the week after the procedure ($p < 0.05$) (3). This study demonstrates that, in patients with existing renal impairment (mean baseline SCr -280 u.mol/l), the majority of whom were not diabetic, iodixanol has a more advantageous renal safety profile compared with iohexol.

The lower nephrotoxicity of IOCM in comparison with LOCM has now been demonstrated in patients at greatest risk of CIN: those with both impaired renal function and diabetes mellitus. The NEPHRIC study evaluated 129 patients with stable diabetes. Inclusion criteria were a SCr of 133-308 u.mol/l for men and 115-308 u.mol/l for women or a calculated creatinine clearance of s60 ml/min. (6) Subjects were randomised to receive either iodixanol 320 mg of iodine (I)/ml or iohexol 350 mg I/ml during coronary or aortofemoral angiography. Iodixanol was associated with a significantly lower mean peak increase in SCr during the first three days following the procedure than iohexol (11.2 ± 19.4 [imol/l versus 48.2 ± 87.0 nmol/l, $p = 0.001$).The mean change in SCr during days 0-7 was also significantly lower with iodixanol (6.3 u.mol/l) than iohexol (21.4 [xmol/l, $p = 0.003$), and significantly fewer patients given iodixanol, 3.1% versus 26.2%, experienced a rise in SCr >44.2 u,mol/l ($p = 0.002$). SCr rose by more than 88.4 u.mol/l in 15.4% of the patients given iohexol but in none of the patients in the iodixanol group ($p = 0.001$). Patients given iodixanol were 11 times less likely than those given iohexol to develop CIN, defined as a rise in SCr of >44.2 [imol/l. In patients given iohexol, but not in those given iodixanol, a higher baseline SCr was associated with a

higher peak increase in SCr between day 0 and day 3. There were 13 adverse events associated with iodixanol and 29 with iohexol; all seven serious CM-related events were in the iohexol group.

In summary, the results of the NEPHRIC study demonstrate that iodixanol significantly reduces the risk of CIN in patients 'at risk' as conferred by the presence of existing renal impairment with diabetes mellitus. The overall risk of developing nephropathy in this patient group was lower than that seen in any previous study with LOCM alone in at-risk patients, and lower than or comparable with rates in studies using potential prophylactic treatments such as fenoldopam or *N*-acetylcysteine in combination with LOCM (2-8%) (7-9). Use of iodixanol in at-risk patients therefore minimises the risk of CIN without the need for additional prophylactic means.

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