INTERNATIONAL JOURNAL OF INTERVENTIONAL CARDIOANGIOLOGY

Monthly Journal of the Russian Scientific Society of Interventional Cardioangiologists

№ 1 - 2003

"International Journal of Interventional Cardioangiology" - peer-reviewed journal.
Created in 2002.

Address of the Editions:
101000, Moscow,Sverchkov per., 5
Phone: (095) 924 96 36
Fax: (095) 924 67 33

Head of Editorial Office:
E.D. Bogatyrenko

Scientific editors of translations:
D.P.Dundua, S.P.Semitko

Translation: Fast Forward Agency, SWAN

Original layout prepared by:
A. Aksuk, V. Shelepukhin

Computer type-setting and makeup:
E. Kim, A. Aksuk

Correctors:
N. Sheludjakova

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

INSTRUCTIONS FOR AUTHORS

The International Journal of Interven-tional Cardioangiology (IJIC) publishes peer-reviewed articles on all aspects of cardiovascular disease, as well as the abstracts of communications, presented at the scientific congresses, sessions and conferences, held by the Russian Scientific Society of Interventional Cardioangiology.

All manuscripts should be addressed to:

Prof. David G. Iosseliani,
Editor-in-Chief, International Journal
of Interventional Cardioangiology,
Sverchkov per., 5,
Moscow, 101000, Russia.
Fax: (7-095) 924 67 33
e-mail: davigdi@caravan.ru

Manuscripts are considered for review only under the conditions that they are not under consideration elsewhere and that the data presented have not appeared on the Internet or have not been previously published. On acceptance, written transfer of copyright to the IJIC, signed by all authors, will be required. The IJIC will maintain copyright records.

No part of materials published in IJIC may be reproduced without written permission of the publisher.

Address permission requests to:

Prof. David G. Iosseliani,
Editor-in-Chief, International Journal
of Interventional Cardioangiology,
Sverchkov per., 5,
Moscow, 101000, Russia.
Fax: (7-095) 924 67 33
e-mail: davigdi@caravan.ru

The Editors require authors to disclose any financial associations that might pose a conflict of interest in connection with the submitted article. If no conflict of interest exists, please state this in the cover letter.

Along with a cover letter, submit two complete copies of the manuscript, two sets of figures and tables, and two copies of the cover letter. If supplementary materials such as "in press" references are included, provide two copies. Please, enclose text file on any electronic carrier.

The manuscript should be typed double-spaced throughout, on one side only, on 22 x 28 cm (8.5 x II") white paper with 3-cm margin on all sides (8-cm at bottom of tide page). Please use a laser printer font no smaller than 12 points.

Title page

Include the tittle, authors' names (including full first name and middle initial, degrees and, where applicable, SICA), and a brief title of no more than 45 characters. List the departments and institutions with which the authors are affiliated, and indicate the specific affiliations if the work is generated from more than one institution (use the footnote symbols). Also provide information on grants, contracts and other forms of financial support, and list the cities and states of all foundations, funds and institutions involved in the work. Under the heading, "Address for correspondence," give the full name and complete postal address of the author to whom communications, printer" s proofs and reprint requests should be sent. Also provide telephone and fax numbers and E-mail address.

Structured abstract

Provide a structured abstract of no more than 250 words, presenting essential data in five paragraphs introduced by separate headings in the following order: Objectives, Background, Methods, Results, Conclusions. Use complete sentences. All data in the abstract must also appear in the manuscript text or tables.

Condensed abstract
(for table of contents)

Provide a condensed abstract of no more than 100 words, stressing clinical implications, for the expanded table of contents.

Include no data that do not also appear in the manuscript text or tables.

Text

To save space in the Journal, up to 10 abbreviations of common terms may be used throughout the manuscript. On a separate page following the condensed abstract, list the selected abbreviations and their definitions. Editors will determine which lesser known terms should not be abbreviated. Use headings and subheadings in the Methods, Results and, particularly, Discussion sections. Every reference, figure and table should be cited in the text in numerical order according to order of mention.

Statistics

All publishable manuscripts will be reviewed for appropriate accuracy of statistical methods and statistical interpretation of results. Provide in the Methods a subsection detailing the statistical methods, including specific methods used to summarize the data, method for hypothesis testing (if any) and the level of significance r hypothesis testing. When using more sophisticated statistical methods (beyond t tests, chi-square, simple linear regression), specify statistical package used.

References

Identity references in the text by Arabic numerals in parentheses on the line. The reference list should be typed double-spaced (separate from the text; references must be numbered consececutively in the order in which they are mentioned in the text.

Do not cite personal communications, manuscripts in prepation or other unpublished data in the references; these may be cited mi in parentheses.

Use Index Medicus (National Library of Medicine) abbreviations for journal titles. Use the following style and punctuation for references:

Periodical

List all authors if six or fewer, otherwise list the first three and add the et al.; do not use periods after the authors' initials. Provide inclusive page numbers.

Chapter in book

Provide inclusive page numbers, authors, chapter titles, book title, editor, publisher and year.

Book (personal author or authors)

Provide a specific (not inclusive) page number.

Figure legends

Figure legends should be typed double-spaced on pages separate from the text; figure numbers must correspond with the order in which they are mentioned in the text.

All abbreviations used in the figure should be identified either after their first mention in the legend or in alphabetical order at the end of each legend. All symbols used (arrows, circles, etc.) must be explained

If previously published figures are used, written permission from original publisher and author is required. Cite the source of the figure in the legend.

Figures

Submit two sets of laser prints or high-quality photocopies in two separate

envelopes. Two sets of prints on non-textured paper should be provided for all half-tone or color illustrations. Note: The artwork of published articles will not be returned to authors.

Figures, particularly graphs, should be designed to take as little space as possible. Lettering should be of sufficient size to be legible after reduction for publication. The optimal size after reduction is 8 points. Symbols should be of a similar size. The maximal width of one-column figures is 5.5 cm; of two-column figures, 11cm; of whole-page figures (three columns) - 17 cv/

All graphs and line drawings must be professionally prepared or done on a computer and reproduced as high quality laser prints with at least 600 dpi resolution. Decimals, lines and other details must be strong enough for reproduction. Use only black and white, not gray, in charts and graphs.

The first author's last name, the figure number, and the top location

should be indicated on the back of each figure, preferably on an adhesive label. Figure title and caption material must appear in the legend, not on the figure.

Tables

Tables should be typed double-spaced on separate sheets, with the table number and tide centered above the table and explanatory notes below the table. Use Arabic numbers. Table numbers must correspond with the order cited in the text.

Abbreviations should be listed in a footnote under the table in alphabetical order. Tables should be self-explanatory, and the data presented in them should not be dupli-

cated in the text or figures. If previously published tables are used, written permission from the original publisher and author is required. Cite the source of the table in the footnote.

In case you use special fonts (Greek, mathematical symbols), please, send those fonts together with the manuscript.

Submission of illustrations in electronic form

The illustrations should be submitted, if possible, in the form of prints and on any electronic carrier assuring safe read-out of the information. The illustrations must be submitted separately from the text, in definitive size with at least 250 dpi resolution, or in bitmap format with at least 600 dpi resolution. It is highly desirable to enclose the originals - hand-made drawings, laser prints with at least 600 dpi resolution, photographs.

Other paper categories

Special materials will be considered by the Editors. In order to avoid any conflict of interests the authors should follow the recommendations:

State-of-the-Art Papers. The Editors will consider both invited and uninvited review articles. Such manuscripts must adhere to preferred length guidelines. Authors should detail in their cover letters how their submission differs from existing reviews on the subject.

Editorials and Viewpoints. Succinct opinion pieces will also be considered. These papers should have a brief unstructured abstract.

Editorial Comments. The editors invite all Editorial Comments published in the Journal.

Letters to the Editor. A limited number of letters will be published. They should not exceed 500 words and should focus on a specific article appearing in IJIC. Type letters double-spaced and include the cited article as a reference. Provide a title page that includes authors' names and institutional affiliations and a complete address for correspondence. E-mail (davigdi@caravan.ru) or Mail two copies. Replies will generally be solicited by the Editors.

CONTENTS:

FROM THE EDITOR

On behalf of all those who suggested the idea of publishing this Journal and those who realized it in practice, I congratulate all interventional cardiologists and other specialists of all adjoining spheres of medicine with the first issue of this Journal dedicated to one of the most rapidly and effectively developing trends of modern medicine and health care service.

The process of putting our project into life was really a thorny path. Along with the devotees of this idea there were the opponents and skeptics who thought that at present time there was no need for such publication in Russia and it could not justify itself. However, as the saying goes, no pains, no gains. At their own responsibility a group of specialists acting on the basis of the decision of the Managing Board of the Russian Society of Interventional Cardioangiologists and with the support of this Society registered and published the first issue of the International Journal of Interventional Cardioangiology.

We hope that our magazine will contribute to more effective and objective coverage of the latest achievements in the field of cardioangiololgy, endovascular medicine, cardi- and vascularsurgery. We consider as our main goal to build a symbolic bridge between Russian and foreign specialists, to consolidate relationship between eastern and western physicians, between Europe and Asia. We hope that doctors will succeed in resolving the problems which politicians sometimes fail to manage. The Journal must facilitate the unity of different specialists of adjoining spheres working on solving the same problems. Unfortunately today they are very isolated and in some cases we even see definite antagonism, especially between interventional cardiologists and cardiac surgeons, as well as between interventional cardiologists and conservative cardiologists. There is a certain "fight " for the patient. However it should be remembered that in the nearest ten years there would be enough work for all, including interventional cardioangiologists, cardiovascular surgeons and conservative cardiologists, because the mortality and morbidity rate, caused by cardiovascular diseases, grows steadily in most countries.

And as far as the interventional cardioangiology is concerned, it will develop against all the odds and go straight on forward without making a step back like the famous Rutherford's crocodile.

So, let us wish our Journal good luck and successful life.

Good luck to all of you!

AN OVERVIEW OF DRUG-ELUTING STENT

Chi Hang Lee MBBS, MRCP; Patrick W Serruys MD PhD

Thoraxcenter, Erasmus Medical Center,
Rotterdam, The Netherlands

Abstract

Despite the success of coronary stent implantation in the last decade, instent restenosis due to neointimal hyperplasia remains a problem to overcome. Neointimal hyperplasia is a vascular response to stent injury; mainly consists of smooth muscle cells proliferation and extracellular matrix deposition. Recently, local drug delivery has been advocated as a potential strategy to prevent instent restenosis. Unprecedented results have been obtained in early clinical studies on sirolimus-eluting stent. The FIM trial, which was the first clinical study on sirolimus-eluting stent in de novo lesions, has shown an astonishing 0% restenosis rate. The RAVEL trial was the first prospective, double-blind, multi-center trial that randomized 238 patients with de novo lesions into sirolimus-eluting versus bare Bx velocity stent. Six-month binary restenosis rate in the sirolimus-group was again 0% compared to 26.6% in the control group. Angiographic late loss and major cardiac event were also significantly lower in the sirolimus-group. The SIRIUS trial was the largest study on sirolimus-eluting stent so far. It was conducted in 53 US centers that randomized 1101 patients with de novo lesion into sirolimus-eluting and bare stents. Final results have been recently reported, which showed a significant reduction in binary restenosis, late loss and repeat revascularization rates. Apart from de novo lesions, early experience of sirolimus-eluting stent implantation for instent restenosis in non-randomized study was also promising, achieving a single-digit repeat restenosis rate. As compare with standard coronary stent, a sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis and associated adverse clinical events.

[1] Professor Patrick W. Serruys MD, Ph.D.
Head, Department of Interventional Cardiology
Thoraxcenter, Bd-408
Erasmus Medical Center Rotterdam
Dr. Molewaterplein 40
3015 GD Rotterdam
Rotterdam-The Netherlands
Fax: 31-10-4369154
E-mail: Serruys@card.azr.nl

Introduction

Compared to plain balloon angioplasty, coronary stent implantation has been proved to reduce restenosis by eliminating elastic recoil and negative vessel remodeling.[1,2] Coronary stent implantation is the most commonly performed mechanical revascularization strategy nowadays. Currently, about 1.7 million stent implantation procedures are performed annually worldwide. However, stent implantation is associated with instent restenosis (ISR) due to vascular injury and subsequent exaggerated neointimal hyperplasia within 6 months. The incidence of ISR varies between 10-40%, depending on *patient specific factors,[4] lesion specific factors,[5,6] and procedure specific factors.*[7,8] ISR is notorious for being difficult to treat, with 30% to 80% of the patients develop recurrent restenosis regardless of the treatment strategies.[11] Intracoronary brachytherapy is the only proven effective therapy for treating ISR.[12] However, restenosis rate is only moderately reduced and widespread use of intracoronary brachytherapy is limited by considerable logistic requirements and potential side effects such as edge effect,[13] geographic miss,[14] delayed healing[15] and late thrombosis.[16]

Over the last two decades, efforts for preventing restenosis by systemic pharmacological therapy have not been successful.[17-19] Many different drugs have been investigated in clinical trials with disappointing results. Compared to systemic administration, local drug delivery offers obvious advantages. The active drug is applied to the vessel at the precise site of vessel injury. Local drug delivery is able to achieve higher tissue concentration of the drug, while systemic drug level remains minimal because of the small total dose administered, thereby eliminating the risk of systemic toxicity. The idea of combining the principle of mechanical scaffolding with that of local pharmacological action emerged early in the stent era. The goal is the controlled release of an efficient drug from an inert coating. Initially, the polymer matrices containing the drug proved not biocompatible.[20] Recently, the engineering of micrometer thick coatings releasing adequate doses of drugs proved feasible. Attention is now focused on using coronary stents as a local delivery vehicle of the anti-restenotic therapy. Many anti-proliferative agents are currently being investigated to assess their efficiency and safety in the prevention of ISR. Among these agents studied in different stent models, sirolimus and paclitaxel are the two for which clinical efficiency has been shown in randomized trials.[21]

Mechanism of restenosis

Unraveling the underlying pathophysiological process of restenosis enables more specific interventions. The underlying mechanisms of restenosis are comprised of a combination of effects: vessel recoil, thrombosis, neointimal hyperplasia and negative vascular remodeling.

1) Vessel recoil. Elastic recoil is a consequence of the natural elastic property of blood vessels in response to stretch and has been recognized to occur instantly after PTCA.

2) Thrombosis. Endothelial denudation, intimal disruption and medial layer damage occur in response to intervention procedures. This vascular injury leads to platelet aggregation and thrombus formation, which have been suggested as the foremost process leading to restenosis after coronary intervention. The aggregated platelets represent a source of attractants and mitogens for smooth muscle cells (SMCs). Besides, platelet derived growth factor (PDGF) secreted by endothelial cells and macrophages has been considered as the major promoter of SMCs migration. The hypothesis that thrombus represents the core of the restenosis process has been supported by studies using angioscopy providing clinical evidence of early thrombus formation after PTCA. Besides, inflammation has also been implicated with restenosis, since leukocytes have been found early and abundantly at the site of vascular injury.

3) Neointimal hyperplasia. The SMCs play a pivotal role in the process of restenosis, due to its ability to migrate, proliferate and synthesize extra-cellular matrix (ECM) upon stimulation. At the injured vessel, SMCs enter a proliferative phase and migrate into the intima through the disrupted internal elastic membrane. Metalloproteinases play an important role in this process. Thereafter, they continue to proliferate and synthesize ECM that ultimately constitutes the bulk of the restenotic lesion.

Neointimal hyperplasia has been shown to be predominantly a low-cellular tissue. Constituents of ECM, such as hyaluronan, fibronectin, osteopontin and vitronectin also facilitate SMCs migration. In addition, reorganization of the ECM, replacing molecules by collagen, may result in retraction of the vessel wall. Recent experiments have suggested that, apart from SMCs, adventitial myofibroblasts also proliferate and migrate into the neointima and play an important role in supplying the intimal layer with proliferative cellular elements for lesion formation. Furthermore, the adventitia has also been implicated in vascular remodeling, since myofibroblasts are capable of collagen synthesis and tissue contraction as seen in wound healing.

4) Negative vascular remodeling. The rationale for the use of the stent as a scaffolding device became more apparent after experimental and clinical studies identified early elastic vascular recoil and negative vascular remodeling were important contributors of the restenosis process.[22] With the advent in intravascular ultrasound (IVUS) technology, it is now realized that less than half of late lumen loss following PTCA is due to intimal hyperplasia and vascular remodeling contributes significantly to the restenosis phenomenon. The relative contribution of vascular remodeling and neointimal hyperplasia to the occurrence of restenosis may vary considerably from one patient to another and even from one site to another in a same vessel. The ultimate clinical consequence of the above-described puzzling processes is late lumen re-narrowing. All these steps give access for a diversity of pharmacological interventions.

Systemic pharmacological therapy

Before the recognition of vascular remodeling phenomenon, neointimal hyperplasia was presumed to be the sole mechanism of restenosis after PTCA. Based on this assumption, several clinical studies in attempts to prevent restenosis using various pharmacological agents have been conducted (Table 1). They were in common that these agents were given systemically, either orally or parentally. Although most of these therapies were based on sound scientific principle with or without prior animal data, with few exceptions, results have been largely disappointing.[23] In the majority of studies the rationale for testing that particular pharmacological agent or principle seemed justified. A proposed explanation for the repeated failure of these clinical drug studies has been that agents administered systemically cannot reach sufficient levels in injured arteries to significantly interfere with the restenotic process. In other words, drugs given in a dose that is tolerated systemically cannot likely block effectively the redundant pathways of the vascular response to injury.

Local drug delivery

With the repeated failure of systemic pharmacotherapeutic agents to reduce restenosis, site-specific local therapy targeting only the diseased segment of the vascular bed appears appealing. Local administration of a number of different agents has been shown to reduce neointimal formation in animal models of restenosis.

So far, only a few agents have been proceed to clinical trials, including heparin, steroid, antisense oligodeoxynucleotides (ODN) and cytochalasin B. In general, results were disappointing. Moreover, problem aroused from the damage inflicted by devices used in drug delivery and the pathological consequences of this, namely SMC initiated intimal hyperplasia[24,25] and stent dislocation.[26] Additional obstacles to be overcome were the efficiency of drug delivery and the low retention rates. Potential solutions to these problems included the development of strategies to target drugs through the use of antibodies directed at antigens newly released at the site of damage.[27] Furthermore, as it becomes increasingly recognized that stents are crucial in achieving better clinical response to intervention by their inherent physical properties, it also becomes obvious that stents have tremendous potential as a delivering device.

Drug-eluting stents

A drug-eluting stent consists typically of:

a) the metallic stent backbone,
b) a polymer layer on which the drug is bound, absorbed or blended,
c) sometimes a superficial polymer layer serves as diffusion barrier to prevent early drug dose dumping and
d) the drug.

The delivery layer must fulfill biocompatibility, pharmacokinetic and mechanical requirements. This means that apart from being non-toxic, the delivery layer must follow the geometric change of configuration during stent expansion and resist mechanical injury caused by the balloon inflation. Furthermore, the release of the drug into the recipient vessel must take place in a manner that is consistent with the drug's mode of action. Drug release must be predictable and in controllable concentration and time spent.[28,29]

Complying with prevailing theories about the restenosis process, drugs are released in days to weeks. Special precautions include dose control to minimize toxicity. Delivery to the underlying vascular tissue generally is in favor of lipophylic drugs, which bind to vascular structures. The ultimate selection of the candidate drug is typically based on favorable effects in the following model systems:

a) cell culture,
b) systemic administration in rodent models of vascular damage,
c) final eluting stent design in the porcine coronary model.

In cell culture drugs have to elicit more antiproliferative effects on vascular SMCs than to endothelial cells.[30] If positive, the next approach is systemic administration in a rodent model after vascular injury, usually endothelial or deeper vascular damage. Finally, biocompatibility and efficacy are studied in larger animals, preferably swine, to determine extent of neointimal inhibition in the stent, to demonstrate lack of pro-inflammatory features and lack of delay in general vascular wound-healing and reendothelialization. Once these phases are completed successfully, initial clinical testing seems warranted.

(A) Anti-thrombotic drugs

The antithrombotic efficacy of heparin has been be demonstrated in vitro and in animal models. However, an antirestenotic efficacy of a heparin-coating seems absent. Studies of platelet glycoprotein IIb/IIIa antibody eluting from stents showed improvement in patency rates up to 28 days in a rabbit model, but no difference in mean neointimal thickness was observed.

Hirudin and the prostacyclin analogue iloprost both have anti-thrombotic and antiproliferative effects. This combination of drugs was compared to non-coated controls in a sheep model with a significant 24% reduction of restenosis. A German trial with 20 patients enrolled showed no clinical adverse events.

(B) Anti-neoplastic drugs

Paclitaxel is a microtubule-stabilizing agent with anti-proliferative activity by interfering with the mitotic spindle in the M-phase, thereby preventing progression to anaphase and subsequent proliferation. Furthermore, it can inhibit SMC migration. Paclitaxel coated stents showed anti-restenotic efficacy in ani-

Table 1. Summary of systemic pharmacological therapy to reduce restenosis

Author/Study	Year	N	Device	Drug	Regimen	Results
Heparin & LMWH						
ERA	1994	458	B	Enoxaparin	40mg QD for 1 month after procedure	Restenosis 52% vs 51% (placebo) (p=NS) Enoxapain more minor bleeding
REDUCE	1996	652	B	Reviparin	7000u iv before, 10500u iv over 24 hrs & then 3500u sc BD for 28 days after procedure	Restenosis 33% vs 34.4% (placebo) (p=NS) Late loss 0.25 vs 0.29mm (placebo) (p=NS) MACE 31.7% vs 30% (placebo) (p=NS)
FACT	1997	354	B	Nadroparin	0.6 ml of 10250IU/ml sc QD 3 days before and continued for 3 mths after procedure	Restenosis 52% vs 49% (placebo) (p=NS) MLD 1.4 vs 1.9mm (placebo) (p=NS) MACE 30.3% vs 29.6% (placebo) (p=NS)
Gimple et al	1999	565	B	Ardeparin	50U/kg (low dose, LD) or 100U/kg (High dose, HD) sc BD for 3 mths after procedure	Restenosis 33%(HD) vs 30%(LD) vs 34%(placebo) (p=NS)
Grassman et al	2001	120	B	Certoparin	Self-administrated for 3 months after procedure	Restenosis 31% vs 49% (placebo) (p=NS) Late loss 0.14 vs 0.19mm (placebo) (p=NS) MLD 1.4 vs 1.5mm (placebo) (p=NS)
Garachemani et al	2002	191	B & S	Heparin & Coumadin	12-24 hrs heparin infusion & coumadin for 6 months after procedure	Restenosis 33% vs 30% (placebo) (p=NS) Diameter stenosis 39% vs 40% (placebo) (p=NS)
Steroids						
Stone et al	1989	102	B	Methylprednisolone& prednisone	125mg im the night before & morning of procedure, then prednisone 60mg po QD for 1 wk after procedure	Restenosis 36% vs 40% (placebo) (p=NS)
M-HEART	1990	915	B	Methylprednisolone	1.0g iv 2-24 hrs before procedure	Restenosis 40% vs 39% (placebo) (p=NS)
Lee et al	1999	140	S	Methylprednisolone	1.0g iv 6-12 hrs before procedure	Restenosis 18% vs 19% (placebo) (p=NS)
Statin						
Sahni R	1991	157	B	Lovastatin	20mg-40mg QD, depend on cholesterol level	Restenosis 12% vs 44.4% (placebo) (p<0.001) Restenosis 39% vs 42% (placebo) (p=NS)
LRTS	1994	404	B	Lovastatin	40mg BD started 7-10 days before procedure	Diameter stenosis 44% vs 46% (placebo) (p=NS) MLD 1.4 vs 1.5mm (placebo) (p=NS) Restenosis 29% vs 39% (placebo) (p=NS)
SHIPS	1996	207	B	Pravastatin	10mg BD started within 10mg before & for 3 mths after procedure	Restenosis (high grade lesion) 9% vs 45% (placebo) (p<0.05) Restenosis 39% vs 44% (placebo) (p=NS)
PREDICT	1997	695	B	Pravastatin	40mg QD for 6 mths after procedure	MLD 1.5 vs 1.5mm (placebo) (p=NS) Restenosis 28% vs 31% (placebo) (p=NS)
FLARE	1999	1054	B	Fluvastatin	40mg BD 2-4 wks before and for 6 mths after procedure	Late loss 0.23 vs 0.23mm (placebo) (p=NS) Death or MI 1.4 vs 4.0 (placebo) (p=0.025) Restenosis 22% vs 28% (no lovastatin) (p=NS)
CLAPT	1999	226	B	Lovastatin	33mg (mean dose) started 10 days before procedure	
Antioxidants						Restenosis 20% vs 40% (placebo) (p<0.05)
Watanabe et al	1996	118	B	Probucol	0.5mg QD started >7 days before & for 3 mths after procedure	Restenosis 50% vs 44% (placebo) (p=NS)
APPLE	1996	200	B	Probucol (P) & lovastatin (L)	P 500mg BD & L 20mg BD started between 48 hrs before & 24 hrs after procedure	Restenosis 23% vs 58% (placebo) (p=0.001)
PART	1997	101	B	Probucol	1000mg started 4 wks before & for 24 wks after procedure	MLD 1.5 ve 1.1mm (placebo) (p=0.02) Late loss 0.4 vs 0.6mm (placebo) (p=NS) Restenosis 21% (P) vs 29% (P+M) vs 40% (M)
MVP	1997	317	B	Probucol (P) & multivitamin (M)	Placebo, P(500mg), M or P(500mg)+M, all BD started 4 wks before & for 6 mths after procedure	vs 39% (placebo) (p=0.009 for P vs no P) Repeat angioplasty 11% vs 16% vs 24% vs 27% (p=0.009 for P vs no P) Restenosis 24% vs 23% (placebo) (p=NS)
EUROCARE	2000	406	DCA	Carvedilol	25mg BD started 24 hrs before & for 5 mths after procedure	TLR 15% vs 16% (placebo) (p=NS) MLD 2 vs 2mm (placebo) (p=NS) Event-free survival 80% vs 79% (placebo) (p=NS)
Calcium antagonists						Late loss 0.3 vs 0.3mm (placebo) (p=NS)
CAPARES	2000	635	B	Amlodipine	10mg QD started 2 wks before & for 4 mths after procedure	Re-PTCA 3.1% vs 7.3% (placebo) (p<0.05)
ACE inhibitors						TVR 8.9% vs 8.6% (placebo) (p=NS)
MERCATOR	1992	735	B	Cilazapril	2.5mg in evening after procedure & 5mg BD for 6 mths	Restenosis 46% vs 41% (placebo) (p=NS)
Desmet et al	1994	509	B	Fosinopril	10mg at 18hrs & 20mg at 4 hrs before procedure & 40mg QD for 6 mths	Diameter stenosis 36% (1mg) vs 35% (5) vs
MARCATOR	1995	1436	B	Cilazapril	1 or 2.5mg at the evening after procedure & 1,5 or 10mg BD for 6 mths	35% (10) vs 35% (placebo) (p=NS)Restenosis 40% (1mg) vs 36% (5) vs 34% (10) vs 33% (placebo) (p=NS) Restenosis 37% vs 24% (placebo) (p =NS)
PARIS	2001	345	S	Quinapril	40mg QD started within 48 hrs after procedure & for 6 mths in patients with ACE DD genotype	Late loss 1.11 vs 0.76mm (p<0.05)

Author/Study	Year	N	Device	Drug	Regimen	Results
Ellis et al	2002	1589	B & S	Any ACEI	No fixed regimen (observational study)	S: Revascularization: 6% vs 12% (placebo) (p<0.001) B: Revascularization: 14% vs 14% (placebo) (p=NS)
Trapidil						
STARC	1994	254	B	Trapidil (T) or Aspirin (A)	T 100mg TDS or A 100mg TDS 3 days before & for 6 mths after procedure	Restenosis 24% vs 40% (T vs A) (p<0.01)
Galassi et al	1999	118	S	Trapidil (T) or Aspirin (A)	T 400mg QD or A 325mg QD for 1 mth	Restenosis 30% vs 29% (T vs A) (p=NS) Adverse events 2% vs 2% (T vs A) (p=NS)
TRAPIST	2001	303	S	Trapidil	200mg 1 hr before and QD for 6 mths	Restenosis 31% vs 24% (placebo) (p=NS) MLD 1.6 vs 1.7mm (placebo) (p=NS) MACE 22% vs 20% (placebo) (p=NS)
Tranilast						
Kosuga et al	1997	192	DCA	Tranilast	Oral tranilast for 3 months (dose??-AHJ 97 134 712-8)	Diameter stenosis 30% vs 43% (placebo) (p=0.0001) Restenosis 11% vs 26% (placebo) (p<0.05)
TREAT	1999	255	B	Tranilast	600mg/day, 300mg/day or placebo for 3 mths afte procedure	Restenosis 18% (600mg) vs 39% (300) vs 39% (placebo) (p=0.005 for 600 vs placebo)
TREAT-2	2002	297	B	Tranilast	600mg/day for 3 mths after procedure	Restenosis 26% vs 42% (placebo) (p<0.05)
PRESTO	2002	11484	B & S	Tranilast	300 or 450mg BD started 4 hrs after procedure for 1 or 3 mths	Restenosis 32-35% vs 33% (placebo) (p=NS) MLD 1.7-1.8 vs 1.8mm (placebo) (p=NS)
Homocysteine lowering agents						
Schnyder et al	2001	205	B	Folate (F), vitamin B12 (VB) & pyridoxine (P)	F 1mg, VB400mcg & P 10mg for 6 mths after procedure	Restenosis 20% vs 38% (placebo) (p=0.01) MLD 1.7 vs 1.5mm (placebo) (p<0.05) TLV 11% vs 22% (placebo) (p<0.05)

mal models, which was dose-dependent.[31,32] At high doses, however, fibrin deposition was enhanced and vascular wound healing impaired.[33] Clinical studies are ongoing in Asia, Europe and United States.

The ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) trial was a dose-finding study comparing the use of an uncoated Supra G™ stent to the same stent coated with either a high-dose density of paclitaxel at 3.1 mcg/mm^2 or a low-dose density at 1.3 mcg/mm^2. Unlike the eluting-stents used in other trials, paclitaxel was directly bonded to the metal surface without a polymer layer. At 6-month follow-up, high-dose paclitaxel reduced angiographic late loss to 0.29mm compared to 1.04mm in the control group. The binary angiographic restenosis rate was reduced from 27% to 4%. A follow-up IVUS substudy showed a dose-dependent reduction in in-stent tissue from 31±22mm^3 in non-coated, to 18±15mm^3 in the low-dose and 12±14mm^3 in the high-dose stent. The stent was found to be safe at 12- month clinical follow-up.[34] The same non-polymer formulated paclitaxel-coated stent was also studied in a group of 21 patients with in-stent restenosis. In 2 patients stent thrombosis occurred after 14 days and 4 months. At 6 months, repeat restenosis was observed in 3 patients (14%).

The ELUTES trial, designed as a triple-blinded efficacy and safety trial, randomized 200 patients with single type A/B1 de novo lesions less than 15mm long to either a bare V-Flex stent, or a paclitaxel-coated stent in one of 4 dose-densities: 0.2 μg/mm^2, 0.7 μg/mm^2, 1.4 μg/mm^2, or 2.7 μg/mm^2. All patients received aspirin plus clopidogrel (300 mg/75 mg daily) for 3 months. In American College of Cardiology 2002 Congress, 6 months result was reported which showed a dose-dependent effect; diameter stenosis in patients receiving the highest dose-density paclitaxel-coated stent was 14%, compared to 34% in the control group (p<0.01). Late loss was 0.10mm in the high-dose group, compared to 0.73mm in the control group (p=0.0005). Binary restenosis was 3% in the high-dose group, compared to 21% in the control group, although these numbers did not quite reach statistical significance (p=0.055). Major adverse cardiac events (MACE) did not differ significantly between the groups at either 1 or 6 months. At 1 month, event-free survival was 97% in the control arm and 92% in the high-dose group. At 6 months, MACE was 89% in both the high-dose and control groups, with no late stent thrombosis in any of the trial arms.[35]

The ongoing In-Stent ELUTES study is a European study comparing the long-term safety and effectiveness of the V-Flex Plus paclitaxel (Cook Inc., Bloomington IN) drug-eluting coronary stent with conventional treatment (ie, balloon angioplasty, stenting) for instent restenosis.[36]

In the small, but randomized TAXUS I trial the polymer-based paclitaxel-eluting NIR-stent (n=31) reduced angiographic late loss at 6 months to 0.35mm vs 0.71mm (p=0.007) in non-coated controls (n=30). This resulted in a reduction of 6 months angiographic restenosis rate from 10% to 0% (p=0.11). Six-month MACE rates were 6.7% in the bare stents and 0% in the drug-eluting stent group (p=0.24), primarily due to a difference in need for revascularization (p=0.24). In animal studies a similar paclitaxel dose did not interfere with vascular healing and endothelialization. The larger 532 patient randomized TAXUS II study is ongoing. The TAXUS III study enrolled 28 patients with instent restenosis (ISR) meeting the criteria of lesion length <30mm and vessel diameter 3.0-2.5mm. At 6 months follow-up, there was 1 late total occlusion and 3 additional patients showed angiographic restenosis. The mean late loss was 0.54mm with neointimal hyperplasia volume of 20.3mm^3. The MACE event rate was 29% (n=8).[37] The TAXUS IV is an ongoing multicenter trial in US involving 1326 patients. The objective is to assess the safety and efficacy of slow-releasing formulation paclitaxel-eluting stent in de novo lesions. Preliminary results reported in Transcatheter Cardiovascular Therapeutic 2002 sympo-

sium suggested good safety with 30-day MACE similar to bare stent.

A different slow release microtubule inhibitor (QP2) was studied with a seamless ensheathed non-biodegradable polymer loaded stent containing 4mg of drug. At 3 to 8 month follow-up a lower restenosis rate was seen in the drug-releasing stent group (n=31). The subsequent SCORES trial, however, showed an increased rate of adverse events mainly due to stent thrombosis (12%) occurring later than 30 days, and 4% cardiac related deaths. After enrollment of 266 of intended 400 patients this trial was stopped.

The DELIVER trial is one of the first US drug-eluting stent randomized clinical trials to include multi-vessel disease patients. Non-polymeric delivery of paclitaxel is used with the ACHIEVE drug-eluting coronary stent system. The ACHIEVE stent was randomized to the stainless steel MULTI-LINK PENTA stent (Guidant corporation) in a population of 1043 individuals presenting with multi-vessel disease with focal de novo lesions in native coronary arteries. Preliminary results showed excellent 30-day safety results in this complex patient population.[38].

In 15 patients with instent restenosis, 7-hexanoyltaxol-eluting polymer stent (QuaDS-QP2; Quanam Medical Corp) was implanted as first human experience. One patient suffered from post-procedural non-Q wave myocardial infarction. At 6 months, 3 patients had target lesion revascularization (20%). Two patients had restenosis (13%). Minimal intimal hyperplasia was observed in all the segments covered by drug-eluting stent (late loss=0.47±1.01 mm with loss index=0.17±0.39). However, the anti-proliferative effect was not maintained at the 12-month follow-up, resulting in delayed occurrence of angiographic restenosis (61.5%).[39]

Actinomycin-D is effective against proliferating cells in all phases of the cell cycle. Animal studies showed a dose-dependent inhibition of in-stent restenosis. A randomized clinical trial (ACTION) studying stents releasing two doses versus a bare metal stent was put on hold prematurely because of lack of efficacy after interim analysis. Follow-up was continued to determine safety. The restenosis rates were reported by the principle investigator PW Serruys at the 2002 Congress of the European Society of Cardiology to be 11% for the controls and 25% for the Actinomycin-coated stents, respectively. The main feature of stent failure appeared to be restenosis at the stent edges, which appeared in 17 out of 39 of the first enrolled patients and was the main reason for discontinuation of the trial.

(C) Immunosuppressants

Sirolimus (Rapamycin), a potent immunosuppressive agent that inhibits cellular proliferation by blocking cell cycle progression in G1-phase showed significant reduction of arterial proliferative response after systemic administration in the porcine coronary model.[40] Interestingly, in a small series of atherectomy specimen obtained from patients with in-stent restenosis, different gene expression was compared with normal arterial tissue and revealed overexpression of FKBP12, the binding protein of tacrolimus and sirolimus.[41] Stent based sirolimus delivery showed up to 45% dose-dependent reduction in neointimal area in animal models.[42]

The first clinical application of the sirolimus-eluting stent (FIM Trial: First In Man) was performed in Sao Paulo and Rotterdam. Forty-five patients were recruited to receive sirolimus-eluting Bx Velocity stent for single de novo coronary lesions of length <18mm and vessel diameter 3.0-3.5mm. All patients were treated with an 18mm long sirolimus-eluting stent. Follow-up to 24 months revealed 0% in-stent restenosis and minimal neointimal hyperplasia. There was no subacute or late stent thrombosis. Only 1 patient required another PTCA at 14th month due to new progression at a site outside the previously stented segment.[43,44]

The Randomized Study with the Sirolimus Eluting Velocity Balloon Expandable Stent (RAVEL) trial included 238 patients at 19 medical centers.[45] At 6 months, the degree of neointimal proliferation, manifested as the mean (±SD) late luminal loss, was significantly lower in the sirolimus-stent group (-0.01 ± 0.33 mm) than in the bare-stent group (0.80 ± 0.53 mm, P<0.001). None of the patients in the sirolimus-stent group, as compared to 26.6% of those in the bare-stent group, had a diameter stenosis of >50% at follow-up (P<0.001). There was no incidence of stent thrombosis. Up to 1-year follow-up, the overall rate of MACE was 5.8% in the sirolimus-stent group and 28.8% in the bare-stent group (P<0.001). The difference was entirely due to a higher rate of revascularization of the target vessel in the bare-stent group.[49]

A subgroup analysis of RAVEL study showed that sirolimus-eluting stents effectively inhibit neointima growth and late luminal loss irrespective of the vessel size.[45] Side-branch analysis showed that the coating thickness of eluting stent did not adversely affect the side-branches, which originated in the lesion and covered by sirolimus-eluting stents.[46] The IVUS evaluation of the RAVEL trial was performed in a subset of 95 patients at 6-month follow-up.[47] Stent volumes, total vessel volumes, and plaque behind stent volumes were comparable between two groups. However, the difference in neo-intimal hyperplasia (2 ± 5 versus 37 ± 28mm^3) and % volume obstruction (1 ± 3 versus 29 ± 20) at 6 months between the two groups was highly significant (<0.001), showing the nearly complete abolition of neointimal proliferation. Analysis of the proximal and distal edges showed no significant difference between the two groups in the external elastic membrane, lumen and plaque volume. Patients implanted with sirolimus-elutings stents showed 21% incidence of incomplete stent apposition (ISA) compared to 4% in the bare-stents (p<0.05) at 6 months. However, IVUS was not performed immediately post-procedure and thus it was impossible to determine whether the ISA observed was the result of late acquired malapposition or persistence of acute incomplete deployment. Despite the higher incidence of ISA in the sirolimus group, this was not associated with any adverse clinical events at 1 year.

The SIRIUS trial is large-scale study conducted in 53 centers in the U.S. that randomized 1101 patients with de novo native coronary arterial lesions (2.5 to 3.5mm in diameter, 15 to 30mm in lesion length) into treatment with sirolimus-eluting or bare metal Bx Velocity™ balloon expandable stents. The primary endpoint is target vessel failure (death, MI, TLR) at 9 months. In addition, secondary endpoints were core laboratory analysis of angiographic and IVUS data to determine treatment effect on neointimal hyperplasia and instent restenosis. The final results of this study have recently been presented in the TCT meeting 2002. TLR at 9-month follow-up was 4.1% in the sirolimus-eluting stent group versus 16.6% in the bare-stent group (p<0.001). Likewise, ISR (3.2% versus 35.4%) and late loss (0.17mm versus 1.00mm) in the sirolimus-eluting stent were substantially lower than placebo group (p<0.001 for both). However, in-lesion restenosis rate was 7.2% and mostly was seen at the proximal edge (5.7%), presumably due to failure to cover the entire injured segment by eluting stent.

The potential of using sirolimus-eluting stent to treat recurrent ISR was also evaluated in Sao Paulo and Rotterdam. A total of

41 patients were enrolled to receive sirolimus-eluting Bx Velocity stent for treatment of ISR.

Rotterdam Experience for treatment of complex ISR. Sixteen patients with recurrent ISR in a native coronary artery (average lesion length 18.4mm) and objective evidence of ischemia were recruited. They received one or more 18mm slow release sirolimus-eluting Bx VELOCITY stents. Stent implantation (n=26) was successful in all 16 patients. QCA and 3D IVUS follow-up was performed at 4 months, and clinical follow-up at 9 months (Figure 10). Among the study patients, 4 had recurrent ISR following brachytherapy, and 3 had totally occluded vessels before the procedure. At 4-month follow-up, 1 patient died and 3 patients had recurrent restenosis. Instent late lumen loss was 0.21mm and the mean % volume obstruction of the stent was 1.2 by IVUS. At 9-month clinical follow-up, 3 patients had experienced 4 MACE.[48]

Sao-Paulo Registry in patients with ISR. Twenty-five patients with recurrent instent restenosis were treated with slow release sirolimus-eluting stent in Sao-Paulo and submitted to QCA and IVUS follow-up at 4 months. Angiographic late loss (-0.05mm in lesion, 0.07mm in stent) and IVUS % volume obstruction (0.8) were similar to the result of de novo lesions. There was no evidence of either instent or edge restenosis. Intimal hyperplasia by 3D IVUS was 0.9mm^3 and the % volume obstruction was 0.8 at 4-month follow-up. Nine-month clinical follow-up was uneventful in all patients.[49]

Everolimus is a new potent agent binding to cytosolic immunophyllin FKBP12 and inhibiting growth factor-driven cell proliferation, including T cells and vascular SMCs, with promising results in animal studies demonstrating a 50% reduction of neointimal proliferation compared with the bare metal stent. The FUTURE trial is a prospective, randomized and single blinded study to evaluate both the safety and the efficacy of the new Challenge stent, which is coated by a bioerodable polymer carrying the anti-proliferative agent everolimus. Preliminary 30 days clinical follow-up suggests safety.[50]

Dexamethasone was used on the Biodivysio PC-coated stent in the STRIDE trial, which is a pilot, prospective, nonrandomized trial including 71 patients conducted at 8 centers across Belgium. At 6 months, there were no cardiac death, no MI or CABG and a total of 2 (3.3%) TLR. MLD was 2.02mm compared to 1.02mm pre-procedure, while %DS was 32% compared to 65% pre-procedure. Late loss was minimal at 0.45mm, yielding a loss index of 0.32 and a restenosis rate of 13.3%. Although impressive, when compared to the 6-month 0% restenosis rates seen in RAVEL, and TAXUS I, or the 3% binary restenosis seen in ELUTES, STRIDE's 13.3% may be perceived as less satisfactory.

Mycophenolic acid coated to the Duraflex stent also showed positive efficacy results in a porcine model. The IMPACT registry is the first clinical study conducted with this stent and is expected to enroll up to 150 patients in South America and New Zealand

(D) Inhibitors of extracellular matrix and miscellaneous

Drugs in these categories have thus far been studied in pre-clinical experiments with variable results. An earlier study with p-cDNA encoding for VEGF reduced neointima in rabbits, but a recent study with the protein was negative. Batimastat is a synthetic metalloproteinase inhibitor that inhibits injury-induced activation of vascular SMCs[51] and negative vascular remodeling[52] in animal models, but proved only of limited efficacy in reducing neointimal thickness by 14% in a stent model in atherosclerotic swine. Because of lack of efficacy in interim analysis, a first clinical trial with stents loaded with batimastat (BRILLIANT) was prematurely stopped in February 2002. Estrogen can inhibit intimal proliferation and accelerate endothelial regeneration after angioplasty. In a trial studying 17-beta-estradiol-eluting stent in porcine model, there was a 40% reduction in intimal area in the high-dose stents compared with control stents (2.54±1.0 versus 4.13±1.1mm^2, for high dose versus control respectively; $P < 0.05$). There was complete endothelial regeneration at 30 days and similar inflammatory response to stenting on histopathology in all the stent groups. This was the first study to show that 17 beta-estradiol-eluting stents are associated with reduced neointimal formation without affecting endothelial regeneration in the pig model of instent restenosis.

Coated stents for the prevention of restenosis are currently attracting great interest among scientists, industry and the medical community. This is due to the promising clinical results reported from studies with the sirolimus- and paclitaxel-releasing stents. Enthusiasm has been further nourished by positive results from laboratory studies with other stents and drugs. Potential problems, such as delayed but not definite neointimal suppression and incomplete vascular healing were, however, observed in high-dose experimental studies. It now becomes clear that not all drug-eluting stents are equally effective. Several projects have been stopped prematurely, like SCORE, ACTION and BRILLIANT because of lack of efficacy or even excess adverse events. Anecdotal reports of late thrombotic occlusion were initially ascribed to specific stent configurations or individual drugs, but may now be regarded as an important safety issue for all drug eluting stents until more and longer follow-up results become available. A substantial 20% number of late stent strut malapposition has been presented for the sirolimus-coated stent compared to 4% in the control stents in the RAVEL-trial.[53] Thus far, this observation was not paralelled with an increase in clinical events. Careful observation of clinical results will show whether this phenomenon bears any clinical relevance.

Currently, both sirolimus-eluting stents (Cordis, Johnson & Johnson) as well as paclitaxel-eluting stents (Cook, Inc.) have received CE mark in Europe in 2002. The promise of the drug-releasing stents is that they may position percutaneous coronary intervention as first line therapy in management of patients with coronary artery disease. This promise has off course to be substantiated by evidence obtained in clinical trials that are currently studying the drug-eluting stent in anatomical subsets like left main disease, bifurcation lesions, chronic total occlusions and long lesions.

Conclusion

These early clinical results of sirolimus-eluting stents are very promising, as they convincingly demonstrate the abolition of neointimal proliferation in almost all patients after coronary stent implantation, a phenomenon that has never been reported in the past. In the light of these results, we are witnessing the onset of a new era in interventional cardiology and revolution of catheter-based coronary intervention. Some concerns such as drug toxicity, incomplete vessel healing, excessive inflammation or hemorrhage, and delayed stent endothelialization need to be addressed in ongoing clinical trials for any type of drug-eluting stents. The data for sirolimus-eluting stent so far do not support these concerns. However, these early studies, by design, excluded patients presented with AMI and/or complex lesions such as chronic total occlusion or left main lesion. Efficacy of sirolimus-eluting stent in these patients/lesion subsets certainly deserves further investigations. Some ongoing studies

are addressed to answer these clinical problems. In our center, the RESEARCH (Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital) study has been recently completed. Since 16th April 2002, sirolimus-eluting stent (Cypher™; Johnson & Johnson - Cordis unit) implantation had been instituted as the default strategy for all PCI performed at our institution (Thoraxcenter, Rotterdam, The Netherlands). During the first 6 months after the introduction of the new treatment protocol, patients in whom sirolimus-eluting stent was actually implanted were enrolled in the RESEARCH registry. All clinical situations and lesion morphologies were considered eligible. Exclusion criteria included only participation in another trial within 30 days or unavailability of an adequate sirolimus-eluting stent at the time of the procedure (at this period, sirolimus-eluting stent were available at diameters from 2.25 mm to 3.0 mm and lengths of 8, 18, and 33 mm). Such broad inclusion/exclusion criteria were outlined in order to represent a typical patient population regularly treated in a catheterization laboratory.

After those promising findings, sirolimus-eluting stent begins to challenge the classical indications for CABG surgery. Previous studies which compared CABG surgery with balloon angioplasty (CABRI)[54] and coronary stenting (ARTS-1)55 in patients with multivessel coronary artery disease revealed 32 % and 14% difference respectively, in favor of surgery for event-free survival, mostly due to poor results of diabetic patients treated by PCI. However, the RAVEL trial showed 96.5 % event-free survival and essentially no late intimal hyperplasia in either diabetic or non-diabetic patients. Accordingly, the main problem of increased restenosis in diabetic patients may have an imminent solution. The questions regarding this problem will be answered with the results of ARTS-2 (Arterial Revascularization Therapies Study part II of the sirolimus-eluting Bx VELOCITY™ balloon expandable stent in the treatment of patients with de novo coronary artery lesions).

References

1. Serruys P.W., P. dJ, Kiemeneij F., Macaya C., et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489-95.

2..de Jaegere P., Serruys P.W., van Es GA, et al. Recoil following Wiktor stent implantation for restenotic lesions of coronary arteries. Cathet Cardiovasc Diagn 1994;32:147-56.

3. Hoffmann R., Mintz G.S., Mehran R., et al. Tissue proliferation within and surrounding Palmaz-Schatz stents is dependent on the aggressiveness of stent implantation technique. Am J Cardiol 1999;83:1170-4.

4. Abizaid A., Costa M.A., Centemero M., et al. Clinical and Economic Impact of Diabetes Mellitus on Percutaneous and Surgical Treatment of Multivessel Coronary Disease Patients: Insights From the Arterial Revascularization Therapy Study (ARTS) Trial. Circulation 2001;104:533-538.

5. Mintz G.S., Popma J.J., Pichard A.D., et al. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. J Am Coll Cardiol 1996;27:1678-87.

6. Prati F., Di Mario C., Moussa I., et al. In-stent neointimal proliferation correlates with the amount of residual plaque burden outside the stent: an intravascular ultrasound study. Circulation 1999;99:1011-4.

7. Kornowski R., Hong M.K., Tio F.O., et al. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. J Am Coll Cardiol 1998;31:224-30.

8. De Feyter P.J., Kay P., Disco C., et al. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. Circulation 1999;100:1777-83.

9. Radke P.W., Hanrath P., vom Dahl J. [Treatment of stent restenosis using rotational atherectomy: mechanisms and results]. Z Kardiol 2001;90:161-9.

10. Bauters C., Banos J.L., Van Belle E., et al. Six-month angiographic outcome after successful repeat percutaneous intervention for in-stent restenosis. Circulation 1998;97:318-21.

11. Lowe H.C., Oesterle S.N., Khachigian L.M. Coronary in-stent restenosis: current status and future strategies. J Am Coll Cardiol 2002;39:183-93.

12. Teirstein P.S., Massullo V., Jani S., et al. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2000;101:360-5.

13. Albiero R., Nishida T., Adamian M., et al. Edge restenosis after implantation of high activity (32)P radioactive beta-emitting stents. Circulation 2000;101:2454-7.

14. Sabate M., Costa M.A., Kozuma K., et al. Geographic miss: A cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. Circulation 2000;101:2467-71.

15. Kay I.P., Sabate M., Van Langenhove G., et al. Outcome from balloon induced coronary artery dissection after intracoronary beta radiation. Heart 2000;83:332-7.

16. Costa M.A., Sabat M., van der Giessen W.J., et al. Late coronary occlusion after intracoronary brachytherapy. Circulation 1999;100:789-92.

17. Lefkovits J., Topol E.J. Pharmacological approaches for the prevention of restenosis after percutaneous coronary intervention. Prog Cardiovasc Dis 1997;40:141-58.

18. Rosanio S., Tocchi M., Patterson C., et al. Prevention of restenosis after percutaneous coronary interventions: the medical approach. Thromb Haemost 1999;82:164-70.

19. De Feyter P.J., Vos J., Rensing B.J. Anti-restenosis Trials. Curr Interv Cardiol Rep 2000;2:326-31.

20. Van der Giessen W.J., Lincoff A.M., Schwartz R.S., et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996;94:1690-7.

21. Morice M.C., Serruys P.W., Sousa J.E., et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.

22. Lafont A., Guzman L.A., Whitlow P.L., et al. Restenosis after experimental angioplasty. Intimal, medial, and adventitial changes associated with constrictive remodeling. Circ Res 1995;76:996-1002.

23. De Feyter P.J., Vos J., Rensing B.J. Anti-restenosis Trials. Curr Interv Cardiol Rep 2000;2:326-331.

24. Kimura T., Miyauchi K., Yamagami S., et al. Local delivery infusion pressure is a key determinant of vascular damage and intimal thickening. Jpn Circ J 1998;62:299-304.

25. Kim W.H., Hong M.K., Kornowski R., et al. Saline infusion via local drug delivery catheters is associated with increased neointimal hyperplasia in a porcine coronary in-stent restenosis model. Coron Artery Dis 1999;10:629-32.

26. Baumbach A., Oberhoff M., Herdeg C., et al. Local delivery of a low molecular weight heparin following stent implantation in the pig coronary artery. Basic Res Cardiol 2000;95:173-8.

27. Gershlick A.H. Treating atherosclerosis: local drug delivery from laboratory studies to clinical trials. Atherosclerosis 2002;160:259-71.

28. Whelan D.M., van Beusekom H.M., van der Giessen W.J. Mechanisms of drug loading and release kinetics. Semin Interv Cardiol 1998;3:127-31.

29. Hwang C.W., Wu D., Edelman E.R. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001;104:600-5.
30. Mohacsi P.J., Tuller D., Hulliger B., et al. Different inhibitory effects of immunosuppressive drugs on human and rat aortic smooth muscle and endothelial cell proliferation stimulated by platelet-derived growth factor or endothelial cell growth factor. J Heart Lung Transplant 1997;16:484-92.
31. Drachman D.E., Edelman E.R., Seifert P., et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. J Am Coll Cardiol 2000;36:2325-32.
32. Heldman A.W., Cheng L., Jenkins G.M., et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation 2001;103:2289-95.
33. Farb A., Heller P.F., Shroff S., et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. Circulation 2001;104:473-9.
34. Park S., Shim W.H., Ho D., et al. Long-term follow-up in the ASPECT clinical study. Am J Cardiol 2002; 90(suppl 6A:1H).
35. Gershlick De Scheerder I., Chevalier B., et al. Long-term follow-up in the ELUTES clinical study. Am J Cardiol 2002; 60A: 1H)
36. De Scheerder I., for the In-stent European Evaluation of paclitaxel eluting stent trial (ELUTES) Investigators. The in-stent ELUTS Study: A prospective, randomized, cointrolled, multicenter study to evaluate the V-Flex Plus PTX drug-eluting coronary stent to treat in-stent restenosis. Am J Cardiol 2002;90(suppl 6A):71H.
37. Tanabe K., Serruys P.W., Grube E. TAXUS III Trial: In-stent Restenosis Treated with Stent Based Delivery of Paclitaxel Incorporated in a Slow Release Polymer Formulation. Circulation (in press).
38. Knopf W., O'Neill W., Midei M., et al. The deliver clinical trial: 30 days safety data from a Multicenter, Randomized clinical evaluation of the ACHIEVE drug-eluting coronary stent. Am J Cardiol 2002;90(suppl 6A): 70H.
39. Liistro F., Stankovic G., Di Mario C., et al. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. Circulation 2002;105:1883-6.
40. Gallo R., Padurean A., Jayaraman T., et al Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. Circulation 1999;99:2164-70.
41. Poon M., Badimon J.J., Fuster V. Overcoming restenosis with sirolimus: from alphabet soup to clinical reality. Lancet 2002;359:619-22.
42. Suzuki T., Kopia G., Hayashi S., et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188-93.
43. Sousa J.E., Costa M.A., Abizaid A., et al. Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries: A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study. Circulation 2001;103:192-195.
44. Sousa J.E., Costa M.A., Abizaid A.C., et al. Sustained Suppression of Neointimal Proliferation by Sirolimus-Eluting Stents: One-Year Angiographic and Intravascular Ultrasound Follow-Up. Circulation 2001;104:2007-11.
45. Regar E., Serruys P.W., Bode C., et al Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106:1949-56.
46. Tanabe K., Serruys P.W., Degertekin M., et al. Fate of side branches after coronary arterial sirolimus-eluting stent implantation. Am J Cardiol 2002;90:937-41.
47. Serruys P.W., Degertekin M., Tanabe K., et al. Intravascular Ultrasound Findings in the Multicenter, Randomized, Double Blind RAVEL Trial. Circulation 2002;106:798-803.
48. Degertekin M. Regar E., Tanabe K., et al. Sirolimus - Eluting Stent for treatment of patients with in Restenosis: The first European clinical experience. Eur Heart J. 2002.
49. Serruys P.W., Abizaid A., Foley D., et al. Sirolimus-eluting stents abolish neointimal hyperplasia in patients with in-stent restenosis: Late angiographic and intravascular ultrasoun results. J Am Coll Cardiol 2002; Suppl 39:8A.
50. Grube E., Gerckens U., Buellesfeld L., et al. First Human Experience using a new everolimus stent coating: Early findings of the FUTURE trial. Am J Cardiol 2002; 90(suppl 6A): 71H.
51. Lovdahl C., Thyberg J., Hultgardh-Nilsson A. The synthetic metalloproteinase inhibitor batimastat suppresses injury-induced phosphorylation of MAP kinase ERK1/ERK2 and phenotypic modification of arterial smooth muscle cells in vitro. J Vasc Res 2000;37:345-54.
52. De Smet B.J., de Kleijn D., Hanemaaijer R., et al. Metalloproteinase inhibition reduces constrictive arterial remodeling after balloon angioplasty: a study in the atherosclerotic Yucatan micropig. Circulation 2000;101:2962-7.
53. Degertekin M. Regar E., Tanabe K., et al. Incidence of incomplete stent apposition at Six month Follow-up in the multicenter RAVEL trial. J Am Coll Cardiol 2002; Suppl 39:38A.
54. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. Lancet 1995;346:1179-84.
55. Serruys P.W., Unger F., Sousa J.E., et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-24.

THE DRUG-ELUTING STENT ERA; INSIGHTS FROM THE USE OF INTRAVASCULAR ULTRASOUND

Vassilis Spanos, MD, Alaide Chieffo, MD, Antonio Colombo, MD[1]

EMO Centro Cuore Columbus and San Raffaele Hospital, Milan, Italy

Keywords: drug-eluting stents, intravascular ultrasound

Abbreviations' List.

ISR: in-stent restenosis
NIH: neointimal hyperplasia
FR, SR, MR: fast, slow, moderate release
MLD: minimal lumen diameter
IVUS: intravascular ultrasound
3D-IVUS: three-dimensional intravascular ultrasound
IA: incomplete stent apposition
TLR: target lesion revascularization
MACE: major adverse cardiac events
HD, LD: high, low dose

Introduction

Drug-eluting stents represent the third revolution in the field of Interventional Cardiology following balloon angioplasty and the implantation of bare metal stents.

Each component of this revolution contributed to the various steps that lead to the re-establishment of a normal luminal flow. Balloon angioplasty attained initial opening of the vessel with relatively good flow, whereas the coronary stent prevented recoil and elastic remodeling of the artery, decreasing restenosis (1-3). Furthermore, optimal stent implantation and appropriate antiplatelet therapy almost eliminated the risk of stent thrombosis due to early platelet activation (4). All these prompted a widespread acceptance of stenting as the default technique for coronary revascularization.

Despite the above in-stent restenosis (ISR), secondary to neointimal hyperplasia (NIH) development (1), occurred in up to 30% after treatment of complex lesions (5) or even higher in diabetic patients. The widespread use of stents resulted in growing numbers of ISR that proved to be a condition with high recurrence rates (up to 80% in the worst case) when any of the available treatment modalities are used (6).

The knowledge of the bio-molecular aspects of the cell cycle regulation has made possible the development of drugs that control cell proliferation and the development of an antiproliferative approach to restenosis (7). The concept of local drug delivery via dedicated stents binds the biological and mechanical means provided and offers the advantage of high drug concentrations at the treatment site, while minimizing systemic toxic effects. We are going to summarize the results of stents that release rapamycin or paclitaxel.

Rapamycin (Sirolimus)

Rapamycin acts by binding the cytosolic receptor FKBP12. It blocks an enzyme denominated TOR (target of rapamycin), upregulates p27 levels and inhibits the phosphorylation of the retinoblastoma protein (pRb) with blockage of the cell cycle progression at the G1-S transition (8).

Rapamycin has been demonstrated to inhibit smooth muscle cell proliferation and migration in vitro and to reduce neointimal formation in animal models of vascular injury (9-12).

The initial experience

The effectiveness of this compound in human studies has been first evaluated in the pioneer work of Prof. Sousa in Sao Paulo, Brazil. In the *FIM* (First In Men) study, two types of drug release stents were evaluated: one fast release (FR) and one slow release (SR) (13-15). The FR formulation releases 100% of the drug in the first 15 days, while the SR liberates only 20% of the drug in the first 15 days. The FIM study, initially performed in Sao Paulo and then extended to Rotterdam, enrolled 45 patients; the first 15 treated with the FR and 30 with the SR sirolimus-eluting stent. The minimal lumen diameter (MLD) inside the FR stent decreased from 2.74 mm following the procedure to 2.32mm at 1-year follow-up and stayed at 2.34mm at 2-years; for the SR stent the MLD was 2.67 mm post-procedure, became 2.47mm at 1 year and 2.63mm at 2 years (13-15). One patient had a myocardial infarction due to plaque rupture proximal to the stent and another underwent coronary artery bypass grafting for ostial circumflex disease progression (without plaque growth inside the stent). There were no other adverse events.

Intravascular ultrasound examination was performed post-procedure, at 4 months and at 1 year for the patients in Sao Paulo (15 FR and 15 SR) and post-procedure and at 6 months for the patients in Rotterdam (15 SR). Three-dimensional intravascular ultrasound analysis (3D-IVUS) was used to quantify the vessel, stent and lumen volumes. The NIH volume was 0.4±0.8mm^3 at 4 months and 3.2±8.5mm^3 at 12 months for the FR group resulting in 0.3±0.6% and 2.3±5.5% lumen volume obstruction respectively; in the SR group the NIH volume was 0.3±0.9mm^3, resulting in lumen volume obstruction of 0.3±0.8% at 4 months and 2.5±3.4mm^3 NIH volume with 2.2±3.4% lumen volume obstruction at 12 months. The NIH volume for the patients from Rotterdam was 5.7±17.7 mm^3 at 6 months with 2±4.98% obstruction volume (14).

The same two centers have reported results from a registry with the *rapamycin-eluting stent for ISR*. Twenty-five patients were enrolled in Brazil and 16 in the Netherlands (16). Four month and 12-month follow-up data from the patients in Brazil have recently been reported (17). In-stent late lumen loss was 0.07±0.2mm at 4 months and 0.36±0.46mm at 12 months. If we extend the analysis to in-segment measurements (considering the 5mm proximal and distal to the stent), the late lumen loss was -0.05±0.3 mm at 4 months and 0.16±0.42 mm at 12 months. No patient had in-stent or stent margin restenosis at 4 months and only one patient developed in-stent restenosis at 1-year follow-up. Intravascular ultrasound analysis was not feasible in the restenosis case. The NIH volume intrastent measured by 3D-IVUS was 0.92±1.9mm^3 at 4 months and 2.55±4.9mm^3 at 12 months, with percent volume obstruction of 0.81±1.7% and 1.76±3.4%, respectively. There were no deaths, stent thromboses, or repeat revascularizations at 12 months follow-up.

For the patients in Netherlands the mean intrastent late lumen loss was 0.21mm at 4 months and 0.43mm at 12 months. The NIH volume intrastent was 1.16±1.58mm^3 at 12 months, resulting in percentage volume obstruction of 0.79±1.04%

[1] Address for correspondence: Antonio Colombo, MD
Centro Cuore Columbus,
Via M. Buonarroti 48,
20145 Milan, Italy
Tel: + 39 02 4812920
Fax: + 39 02 48193433
e-mail: : info@emocolumbus.it

(http://www.tctmd.com/display/expert/pdf/53054/Abizaid-Sirolimus-ISR.pdf). Some concern has been raised due to the events that occurred in the patients treated in Rotterdam: two deaths, one non-Q wave myocardial infarction (late thrombosis), one total occlusion and two cases of restenosis intrastent at 12 months. The patients treated in the Netherlands had more complex clinical characteristics: more patients had diffuse and proliferative in-stent restenosis (only 19% had focal restenosis vs. 40% in Brazil) and more stents were implanted (1.9stent /lesion vs. 1.4 stent /lesion). Prior intracoronary brachytherapy involving the index lesion was performed in 19% of the cases in Rotterdam but was not performed for any of the patients in Brazil. It is interesting that among the patients with complications, one had three previous interventions for ISR including brachytherapy and another patient had five rapamycin-eluting stents implanted in the right coronary artery with a total stent length of 90mm.

The clinical trials

The exceptionally low values of angiographic late lumen loss with practical abolition of NIH in the IVUS examination have been confirmed in a large multicenter study, the RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial performed in 15 centers in Europe and 4 in Latin America (18). The astonishing findings of this randomized study which included 118 patients randomized to bare stent vs. 120 patients randomized to rapamycin-eluting stents (CYPHERTM, Cordis) are now of public domain with unique 0% angiographic restenosis and in-stent late loss of -0.01±0.33mm for the group treated with drug-eluting stents at 6 months (compared to restenosis rate 26.6% and late loss 0.80±0.53mm in the control group, p<0.001 for both comparisons). The late luminal loss at the proximal and distal stent edge was also significantly lower in the rapamycin-eluting stent group than in the control group (0.05±0.39mm proximal and -0.09±0.30mm distal to the Cypher stent vs. 0.29±0.48mm and 0.12±0.44mm respectively for controls, p<0.001 for both comparisons).

Intravascular ultrasound examination was performed 6 months post-procedure followed by 3D-IVUS analysis. The differences in NIH volume (2±5mm^3 in drug-eluting vs. 37±28mm^3 in bare stents, p<0.001) and percent volume obstruction (1±3% vs. 29±20% respectively, p<0.001) underline the practical disappearance of the proliferative process inside the rapamycin-eluting stent (19). An alarmingly high incidence of incomplete stent apposition in the drug-eluting stent group (21%, 10 out of 48 patients studied) has been reported in the IVUS sub-analysis of the trial. Incomplete stent apposition (IA) was defined as presence of at least one strut clearly separated from the vessel wall, with evidence of blood speckles behind it (Figure 1). The respective incidence of IA in the control group was 4% (2 out of 47 patients, p=0.001).

The lack of baseline IVUS does not allow us to draw conclusions whether this type of IA was due to sub-optimal stent implantation (Figure 2A) or it was late acquired IA with or without positive vessel wall remodeling (Figure 3A-B). Despite these morphological concerns no adverse events related to the stented lesions occurred at 12 months' clinical follow-up with TLR rate of 0% vs. 22.9% in the control group (p=0.001). Cumulative event free survival at 1 year was 94.1% in the rapamycin eluting stent group vs. 70.9% in the control group (p<0.001) (18).

There are also other trials performed with the same stent (CYPHERTM, Cordis), such as the multicenter, randomized "sirolimus-coated BX Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions" (SIRIUS US) trial (20), a randomized trial for bifurcated lesions (21) and the European arm of SIRIUS (E-SIRIUS) (22) study, extending the evaluation on vessels with a reference size of 2.5-3.0mm and a lesion length of 15-32mm.

The results of the *SIRIUS US* trial have been presented at the Transcatheter Cardiovascular Therapeutics meeting in September 2002 by the principal investigator Dr J. Moses (*http://www.tctmd.com/display/expert/pdf/44544/Moses-SIRIUSrevised.pdf*). Patients randomized to receive either rapamycin-eluting (n=545) or bare metal stent (n=556) had higher risk lesions for restenosis compared

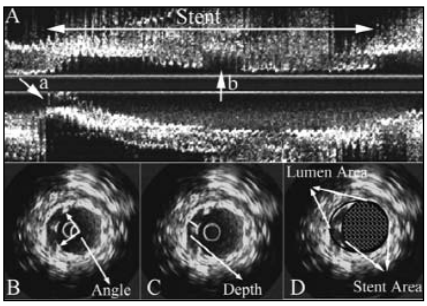


Figure 1. Incomplete stent apposition (IA) as reported in the Ravel trial. The points of IA are located on the IVUS longitudinal view (arrows a and b); the different ways used to quantify IA are also evident in this figure (angle, depth and IA area) (19)

to the Ravel trial. Twenty-five percent of the patients treated with drug-eluting stents were diabetics (16% in the Ravel trial) and the mean lesion length was 14.4mm (9.6±3.3mm in the Ravel trial, Table 1).

At 8 months, in-stent MLD was larger in the rapamycin group (2.50mm vs.1.68mm in the control group, p<0.001), while the in-stent late lumen loss (0.17mm vs. 1.0mm, p<0.001) and restenosis rate (3.2% vs. 35.4%, p<0.001) were lower. Late lumen loss was also lower in the rapamycin group at the segments proximal (0.17mm vs. 0.33mm, p<0.001) and distal to the stent (0.04mm vs. 0.24mm, p<0.001) with restenosis rate not significantly lower proximal (5.8% vs. 8.1%, p=0.3) and significantly lower distal (2.0% vs. 7.2%, p=0.002). When the analysis was extended to in-segment measurements (including the 5mm proximal and distal to the stent) the MLD was still significantly larger in the rapamycin group (2.15mm vs. 1.60mm for the control group, p<0.001) with a maintained advantage in late lumen loss and restenosis rate (0.24mm vs.0.81mm, p<0.001 and 8.9% vs. 36.3%, p<0.001 respectively). There were 2 cases (0.4%) of stent thrombosis in the rapamycin group (one sub-acute and one late) and 4 (0.8%) in the control group (one sub-acute and three late stent thromboses). At 9 months target lesion revascularization (TLR) rate was lower in the rapamycin group (4.1% vs. 16.6% in the control group, p<0.001), resulting in lower major adverse cardiac events (death, myocardial infarction and

Table 1. Drug-eluting stent trials - Characteristics at baseline

	Stent used	Patient number *	Diabetes mellitus (%)	Reference vessel diameter (мм)	Lesion length (мм)
Ravel	CYPHER™	120 vs. 118	16	2,6	9,6
Sirius US	CYPHER™	545 vs. 556	25	2,8	14,4
Taxus II MR	TAXUS NIRx	135 vs. 134	17	2,7	10,2
Taxus II SR	TAXUS NIRx	131 vs. 136	11	2,8	10,5
Bifurcations	CYPHER™	86	22	2.6/2.1**	11.1/5.4**

* - number of patients with drug-eluting stent vs. number of patients in the control group;

** - mean values for main branch/side branch of the bifurcated lesion

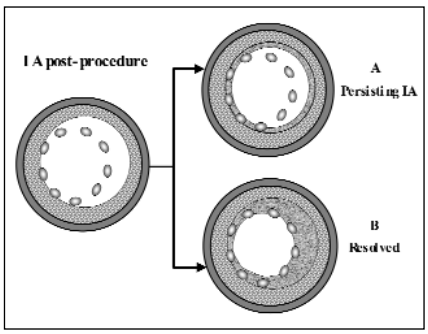


Figure 2. Incomplete stent apposition (IA) post-procedure, due to sub-optimal stent implantation. This may (A) or may not be evident at follow-up (B)

TLR) rate (7.1% vs. 18.9% in the control group, p<0.001). Target vessel failure, the primary end-point of the trial (including death, myocardial infarction and target vessel revascularization) was also less common in the rapamycin group (8.6% vs. 21.0% in the control group, p<0.001).

The IVUS and 3-D IVUS sub-analysis (99 lesions with drug-eluting stent vs. 76 control) was presented at the Transcatheter Cardiovascular Therapeutics meeting in September 2002 by Dr M. Leon (*http://www.tctmd.com/display/expert/pdf/44484/Leon-SIRIUS.pdf*). There was minimal NIH inside the rapamycin-eluting stent (4.1mm^3 vs. 56.8 mm^3 in the control group, p<0.001) with resultant small percentage of volume obstruction (2.6% vs. 34.2% in the control group, p<0.001).

One hundred-forty one sequential IVUS examinations (81 rapamycin group vs. 60 controls) were interrogated for IA. There was similar incidence of IA post-procedure (Figure 2) in rapamycin-eluting stents (13 cases, 16.3%) and bare metal stents (9 cases, 14.7%) that persisted at 8 months follow-up in 6 rapamycin-eluting and 6 bare metal stents (7.5% vs. 9.8%, p=non significant). There were 7 cases (8.7%) of late IA (Figure 3) in the rapamycin group compared to none in the control group (p<0.05). In 3 of these cases (3.7%) positive vessel wall remodeling was also present (external elastic membrane area enlargement > 20% compared to baseline measurements). None of the cases of IA was associated to any clinical event up to 9 months' clinical follow-up.

This was the first rapamycin-eluting stent clinical trial with sequential IVUS interrogation and therefore adequate to provide insights concerning IA. There was not any case of late acquired IA in the control group reported so far, although the background incidence of late acquired IA from the bare metal stent era is reported to be around 4.4% (23). Shah et al. have studied retrospectively 206 patients with de-novo lesions who had tubular-slotted bare-metal stent implantation and IVUS post-procedure and at 6±3 months of follow-up. There were 9 patients (4.4%) with late acquired IA, all accompanied by positive vessel wall remodeling. Eight out of the 9 cases occurred at the stent edges.

The rapamycin-eluting stent has also been used to treat coronary bifurcated lesions in the course of a clinical trial (21). Eighty-five patients with 86 bifurcated lesions have been randomized to either a double stenting strategy or stenting of the main branch (MB) with balloon angioplasty for the side branch (SB). Intravascular ultrasound examination was performed post-procedure and at 6 months angiographic follow-up. There was a high rate of crossover to double stenting, due to operator's intention to optimize the final angiographic outcome in the SB. As a result, both branches were stented

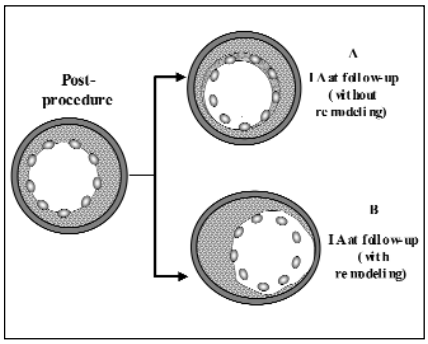


Figure 3. Late acquired incomplete apposition (IA). In case B this is accompanied by enlargement of the vessel at this site (positive vessel wall remodeling)

in 63 cases. The preliminary results of the trial have been presented at the American Heart Association Scientific Sessions in November 2002 (*http://www.tctmd.com/display/expert/pdf/53167/ Colombo-SIRIUSBifurcation.pdf*). One patient died suddenly 4.5 months post-procedure. This was a case with diffuse disease of the left anterior descending coronary artery and the second diagonal branch with history of bare metal stent implantation for unprotected distal left main disease and normal left ventricular function. There were 3 cases of stent thrombosis (3.5%) that occurred one day, three days and thirty-two days post-procedure. In-segment restenosis occurred in 14 cases (21.9%); in the great majority of these cases (12 out of 14) the restenosis site was at the ostium of the SB (Figure 4). There was one case of restenosis at the segment proximal to the stent in the MB and one distally to the stent in the SB; in six of these cases (7.1%) a new intervention (target lesion revascularization) was undertaken.

In the IVUS examination there was abolition of NIH development intrastent; the NIH volume was 1.53±2.63mm^3 for the MB and 1.81±2.66mm^3 for the SB, resulting in percentage of intrastent volume obstruction of 1.17±1.84% and 2.46±2.83% respectively. An IVUS catheter was advanced in the SB in 3 of the cases with restenosis at the ostium. The IVUS analysis in these cases is indicative of incomplete coverage of the ostium by stent struts, with evidence of NIH development focally at the ostium, both inside and outside the stent (Figure 4). There were 2 cases of IA at 6 months' follow-up in the MB (4.9%); one of these cases was accompanied by positive vessel wall remodeling (24).

Closing remarks

The above data indicate that sirolimus-eluting stent has managed to counteract NIH development intrastent, leading in drastically reduced restenosis rates. The safety results are also very encouraging, since the adverse clinical event rates (especially the thrombosis rate) were low and IA was not related to any events.

The more skeptics claim that a longer-term follow-up may reveal results that are less permanent than anticipated. And that the presence of a significant higher fibrin deposition close to struts of rapamycin-eluting stent may elicit a late inflammatory reaction as occurred in an animal model (11). This is not the case judging from the extended clinical follow-up so far, especially the sustained safety and efficacy reported at two years follow-up in the FIM study (15).

Paclitaxel (Taxol)

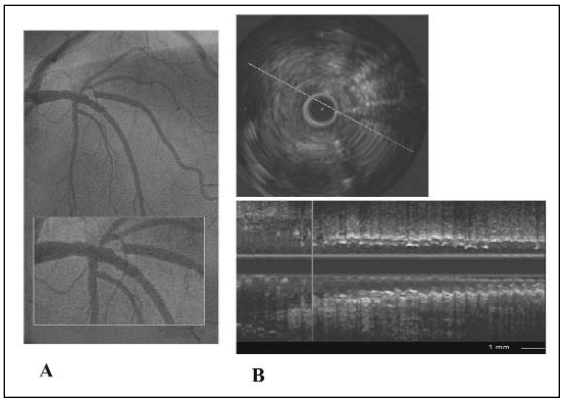


Figure 4. Side branch restenosis from the bifurcated lesions trial. (A): angiographic image (B): IVUS longitudinal view and 2D image corresponding at the part of the ostium not covered by stent struts

Paclitaxel (Taxol) is a microtubule-stabilizing agent with potent antiproliferative activity. The binding of paclitaxel to tubulin results in blockade of cell division in the G0/G1 and G2/M phases of the cell cycle (25,26). Paclitaxel has been demonstrated to inhibit smooth muscle cell proliferation and migration in a dose-dependent manner in vitro and to prevent neointimal formation after balloon angioplasty (27,28) and after stenting (29,30) in animal models.

The initial experience

Initial clinical experience has been attained with the QuaDS-QP2 stent (Quanam Medical Corp). A taxane analogue (7-hexanoylpaclitaxel, QP2) was embedded on polymer sleeves mounted on the stent in a dosage of 800 μg/2.4mm and released slowly in a total period of 180 days. Results from implantation in 15 native coronary lesions with sequential IVUS evaluation have been reported (31); measurements were performed at 4 cross-sections within the stent and 2 cross-sections in each reference segment. At 8.3 months the calculated intrastent NIH area was 1.2±1.3mm^2, with resultant percent area stenosis of 13.6±14.9%. A significant increase in plaque area at the segments proximal (from 8.7±2.2 mm^2 to 10.7±3.0 mm^2, p<0.05) and distal (from 7.5±3.7 mm^2 to 9.4±4.2 mm^2, p<0.05) to the stent was observed, without change in the vessel area; no patients showed in-stent or edge restenosis.

The first randomized trial to evaluate the use of the QuaDS-QP2 stent vs. bare stent in the prevention of restenosis has been the SCORE (Study to COmpare REstenosis rate between QueST and QuaDS-QP2) (32). The study planned to randomize 400 patients but it was interrupted following enrollment of the first 266 patients (128 drug-eluting vs. 138 bare stent) due to the high incidence of major adverse cardiac events (MACE) in the drug-eluting stent group. The MACE incidence in this group at 30 days was 10.2%; 7.1% of the patients experienced a peri-procedural myocardial infarction, while sub-acute stent thrombosis was reported in 5.5%. The high incidence of events was partly a consequence of the coverage of side branches due to the polymer sleeve and partly explained by the high subacute thrombosis rate. Nevertheless, at six-month angiographic follow up the QuaDS-QP2 achieved 60% relative reduction in mean late lumen loss (1.2 mm vs. 3.0 mm for the bare stent group). Sequential IVUS analysis was performed for 122 lesions treated (66 QuaDS vs.56 QueST stents) (32). At 6-months follow-up, the intrastent NIH volume (calculated per mm of stented segment) was 68% lower in the drug-eluting stent group (0.79±0.51mm^3/mm vs. 2.48±1.49mm^3/mm for the bare stent group, p<0.0001). There was no evidence of late stent IA in either group.

The important finding of these early reports was the ability of this system to inhibit NIH development. The need of a more effective biocompatible drug-eluting system was obvious, due to the high incidence of events. This improvement came with lower drug doses, better polymer technology and a different drug release formulation.

Experience with the TAXUS paclitaxel-eluting stent

The TAXUS paclitaxel-eluting stent (Boston Scientific Corp.) utilizes 1μg/mm^2 of paclitaxel aiming to reduce restenosis, while preserving stent endothelialization. The polymer on which the drug has been impregnated is biocompatible to avoid an inflammatory response. There are two formulations with diverse release kinetics: a moderate release (MR) formulation, where most of the drug is released within the first 2 days after stent implantation and a slow release (SR) formulation, where there is continuous drug release throughout the first 15-20 days. The Boston Scientific Program "TAXUS" is evaluating this stent in different clinical situations.

The *TAXUS I* was a double blind clinical trial evaluating the safety and performance of the TAXUS NIRx stent (SR formulation, n=31) vs. bare NIR stent (n=36) in de novo or restenotic coronary lesions with length 12mm (33). The MACE rate at 12 months was 3% in the paclitaxel-eluting stent group vs. 10% in the control group (p=0.6). Six-month angiographic follow-up revealed significant reduction of late lumen loss (0.36±0.48 mm for TAXUS vs. 0.71±0.47mm for control, p=0.008) and loss index (0.22±0.29 vs. 0.45±0.29 respectively, p=0.004) in the TAXUS group. The restenosis rate was 0% in the TAXUS vs. 10% in the control group (p=0.11); there was no evidence of edge restenosis in either group. Sequential IVUS analysis and 3D-IVUS measurements were also performed. Six months after the procedure, the mean minimal lumen area was larger in the TAXUS group (5.6±1.2mm^2 vs. 4.8±1.3mm^2 in the control group, p=0.027) and the normalized NIH volume was lower (14.8±10.8mm^3 versus 21.6±10.7mm^3 in the control group, p=0.028).

The *TAXUS II* was a randomized, triple blind clinical trial evaluating the safety and efficacy of the TAXUS NIRx stent (in both the SR and MR formulation) compared with bare NIR stent. De novo coronary artery lesions 12 mm length, located in vessels with reference diameter between 3.0mm and 3.5mm were included (Table 1). The primary endpoint of the trial in both cohorts was percent intrastent volume obstruction as determined by IVUS. A total of 536 patients were randomized into 2 consecutive and independent cohorts: 267 in the TAXUS-SR arm (131 TAXUS vs. 136 controls) and 269 in the TAXUS-MR arm (135 TAXUS vs. 134 controls).

The trial results were presented at the Transcatheter Cardiovascular Therapeutics meeting in September 2002 (*http://www.tctmd.com/display/expert/pdf/44619/Colombo-TAXUS%20SR.pdf and http://www.tctmd.com/display/expert/pdf/44651/Colombo-TAXUS%20MR.pdf*). Late lumen loss was lower in both TAXUS-SR (0.3+0.4 mm) and TAXUS-MR (0.3+0.4mm) compared to control group (0.8+0.5mm, p<0.0001), resulting in lower restenosis rates at 6 months in both TAXUS-SR (2.3%) and TAXUS-MR (4.7%) compared to control (19%, p<0.0001). Moreover, late lumen loss was also significantly lower at the proximal edge in TAXUS-SR (0.2±0.4mm) and TAXUS-MR (0.2±0.4mm) compared to the control group (0.4±0.4mm, p<0.0003) as well as at the distal edge (0.1±0.3mm in TAXUS-SR, 0.1±0.3mm in TAXUS-MR vs. 0.3±0.4mm in controls, p<0.0001).

The percent intrastent volume obstruction, which was the primary end-point of the trial, was lower in the TAXUS groups compared to control (TAXUS-SR arm 7.8±9.9%, TAXUS-MR arm 7.8±9.7%, combined control 21.9±17.5%, p<0.0001). Finally the incidence of MACE at 6 months was lower in both TAXUS-SR and TAXUS-MR arms compared to control (8.5% and 7.8% respectively vs. 19.8%, p<0.003), mainly due to lower target vessel revascularization rates in both TAXUS groups (7.7% in TAXUS-SR and 3.1% in TAXUS-MR arm vs. 16% for controls).

TAXUS III is a single arm registry addressing the efficacy of the TAXUS NIRx stent for in-stent restenosis (34). Thirty patients in two centers were included. At 210 days there was a 17.2% MACE rate mainly due to late target vessel revascularization; there were no major events as myocardial infarction and death. This relatively positive result leaves the doors open to paclitaxel-

Table 2. Drug-eluting stent trials - Follow-up results

	Stent used	3 D-IVUS Volume obstruction (%)	Late Loss* (mm)	Restenosis rate* (%)	MACE** (n, %)
Ravel	CYPHER™	1,0	-0,05	0/-	5,9
Sirius US	CYPHER™	2,6	0,17/0,24	3,2/8,9	8,6
Taxus II MR	TAXUS NIRx	7,8	0,30/-	4,7/8,6	7,8
Taxus II SR	TAXUS NIRx	7,8	0,31/-	2,3/5,5	8,5
Bifurcations	CYPHER™	1,2/2,8***	0,24/0,53***	21,9 (3,1/20,3) §	17,6

* - reported as in-stent /in-segment values;

** - MACE including in-segment repeat revascularization in Sirius and Taxus trials, all MACE reported at 6 months (except Sirius study: 9 months and Ravel: 12 months);

*** - mean values for main branch/side branch of the bifurcated lesion;

§ - 21.9% is bifurcated lesion restenosis; separate restenosis for main and side branch in the parenthesis

\- (main branch first)

eluting stents as treatment option for in-stent restenosis.

In the light of the above results, a series of U.S. pivotal studies are planned (TAXUS IV-VII), designed to comprehensively evaluate the safety and efficacy of both the SR and MR formulations of the TAXUS NIRx stent in a broad range of patient and lesion subgroups.

Paclitaxel-eluting stent without polymer

Following the achievements of stents that use a polymer as a base for drug release in preventing ISR, there are studies addressing the effect of different drugs carried by the metal stent. The rationale is to minimize any potential effect related to the presence of the polymer. A number of studies have been performed, confirming the efficacy of this approach, but without any clear advantage over the polymer-based drug-eluting stents.

Encouraging preliminary data come from two randomized trials, the *ASPECT* (ASian paclitaxel-Eluting stent Clinical Trial) trial and the ELUTES (European evaLUation of a Taxol-Eluting Stent) study. The ASPECT is a randomized, triple-blind trial that evaluated the safety and efficacy of Supra G paclitaxel-eluting stent (Cook Inc, Bloomington, IN) at the dosage of 3.1μg/mm^2 (high dose, HD), the same stent with a paclitaxel dosage of 1.3μg/mm^2 (low dose, LD) and bare metal stent in the prevention of restenosis (35). Six months' results have been presented at the American Heart Association Scientific Sessions in November 2002 (*http://www.tctmd.com/display/expert/pdf/52714/ASPECT-AHA.pdf*). Mean late lumen loss was significantly lower for both HD (0.29mm) and LD (0.57mm) groups compared to control (1.04mm, p<0.0001 and p<0.003 respectively). The binary restenosis rate was also significantly reduced in HD (4%) and LD (12%) compared to controls (27%, p<0.0001).

Sequential IVUS analysis was performed for 81 lesions (28 treated with HD paclitaxel-coated stent, 28 with LD stent and 25 controls). The results have been recently published (36). There was a stepwise reduction in intrastent NIH volume with increasing paclitaxel doses (31±22mm^3 in control, 18±15mm^3 in low dose and 13±14mm^3 in high dose, p<0.001). Post hoc analysis showed less IH accumulation when low- and high-dose patients were compared with control (p =0.009 and p <0.001, respectively), but not when low-dose patients were compared with high-dose patients (p =0.2). Focal late IA was seen in one HD patient. With increasing doses, there was no significant change in the reference segments.

Similar results were reported from the *ELUTES* study, in which the V-Flex Plus paclitaxel eluting stent (no polymer) was evaluated (37). This was a dose-finding study; patients were randomized into five treatment arms: control stent (no paclitaxel), low-dose density (0.2μg/mm^2), medium-low dose density (0.7μg/mm^2), medium-high dose density (1.4μg/mm^2), high dose density (2.7μg/mm^2). At six-month angiographic follow up the binary restenosis was 3% in the high-dose paclitaxel eluting stent group vs. 21% in the control group (p=0.055). Event free survival at 6 months' follow-up was high for all groups, ranging from 89% to 97% (*http://www.tctmd.com/display/expert/pdf/52801/ELUTES.pdf*).

Based on Cook's paclitaxel coating applications, the "Prospective, Non-randomized, Multicenter Evaluation of the AchieveTM Paclitaxel Eluting Coronary Stent System in the Treatment of Lesions with a High Risk of Revascularization" (DELIVER II) study has enrolled 1500 patients. This study will evaluate the AchieveTM (3μg/mm^2) paclitaxel-coated coronary stent system (Guidant Corp.) in the treatment of lesions with high risk of revascularization (including multivessel disease, chronic total occlusions, bifurcated lesions, long lesions, small vessels, ISR).

Closing remarks

The experience with the different paclitaxel-eluting stent systems highlights the importance of the vehicle we use to administer an effective drug. The achievement of the TAXUS stent to counteract NIH development, resulting in drastically reduced restenosis rates indicates that TAXUS-SR is the minimum effective dose for treatment of de-novo lesions; future studies should focus on optimum formulation for more complex and high-risk lesions.

Although the data from the paclitaxel-coated stent (no polymer) are encouraging, we should probably recognize that the controlled release of the polymer-based system appears more interesting and potentially effective.

Conclusions

Drug-eluting stents represent one of the most promising fields in Interventional Cardiology. However, several unanswered questions have to be solved before being sure of their real potential. Hopefully, after the completion of planned and ongoing trials many of these issues will be answered.

Furthermore, these new technologies have to prove their efficacy in real-world lesions such as long lesions, small vessels, chronic occlusion, bifurcation lesions, multivessel and left main disease and in acute myocardial infarction.

The landscape of interventional cardiology is changing and as Dr P. Teirstein says we are "living the dream of no restenosis" (38).

References:

1. Hoffmann R., Mintz G.S., Dussaillant G.R., et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996;94:1247-54.

2. Fischman D.L., Leon M.B., Baim D.S., et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496-501.

3. Serruys P.W., de Jaegere P., Kiemeneij F., et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489-95.

4. Colombo A., Hall P., Nakamura S., et al. Intracoronary stenting without anticoagulation

accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676-88.
5. Kastrati A., Schomig A., Elezi S., et al. Prognostic value of the modified american college of Cardiology/American heart association stenosis morphology classification for long-term angiographic and clinical outcome after coronary stent placement. Circulation 1999;100:1285-90.
6. Spanos V., Stankovic G., Tobis J., Colombo A. The challenge of in-stent restenosis: insights from intravascular ultrasound. Eur Heart J 2003;24:138-150.
7. Braun-Dullaeus R.C., Mann M.J., Dzau V.J. Cell cycle progression: new therapeutic target for vascular proliferative disease. Circulation 1998;98:82-9.
8. Marx S.O., Marks A.R. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001;104:852-5.
9. Poon M., Marx S.O., Gallo R., Badimon J.J., Taubman M.B., Marks A.R. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest 1996;98:2277-83.
10. Gallo R., Padurean A., Jayaraman T., et al. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. Circulation 1999;99:2164-70.
11. Suzuki T., Kopia G., Hayashi S., et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188-93.
12. Sun J., Marx S.O., Chen H.J., Poon M., Marks A.R., Rabbani L.E. Role for p27(Kip1) in Vascular Smooth Muscle Cell Migration. Circulation 2001;103:2967-72.
13. Sousa J.E., Costa M.A., Abizaid A., et al. Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries : A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study. Circulation 2001;103:192-195.
14. Sousa J.E., Costa M.A., Abizaid A.C., et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001;104:2007-11.
15. Sousa J., Abizaid A., Abizaid A., al. e. Late (two-year) follow-up from the First-in-Man (FIM) Experience after the implantation of sirolimus-eluting stents. J Am Coll Cardiol 2002;39:21A.
16. Serruys P.W., Abizaid A., Foley D., Abizaid A. Sirolimus-Eluting Stents Abolish Neointimal Hyperplasia in Patients With In-stent Restenosis:Late Angiographic and Intravascular Ultrasound Results. JACC 2002;39:37A.
17. Sousa J.E., Costa M.A., Abizaid A., et al. Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2003; 107:24-7.
18. Morice M.C., Serruys P.W., Sousa J.E., et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.
19. Serruys P.W., Degertekin M., Tanabe K., et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002; 106:798-803.
20. Moses J.W., O'Schaughnessy C., Caputo R., et al. The U.S. multicenter, randomized, double-blind study of the sirolimus-eluting stent in coronary lesions: safety outcomes at 9 months. Eur Heart J 2002;23:264.
21. Colombo A., Leon M.B., Morice M.C., et al. The Bifurcation Study: An evaluation of the CypherTM sirolimus-eluting stent in the treatment of bifurcation lesions. Circulation 2002;106:2390.
22. Schofer J., Breithardt G., Kuntz R.E., Popma J.J. A European multi-centre, randomised, double-blind study of the sirolimus-eluting stent in patients with de novo coronary artery lesions. Eur Heart J 2002;23:265.
23. Shah V.M., Mintz G.S., Apple S., Weissman N.J. Background incidence of late malapposition after bare-metal stent implantation. Circulation 2002;106:1753-5.
24. Spanos V., Toutouzas K., Chieffo A., et al. Six-month angiographic follow-up after implantation of the sirolimus drug-eluting stent at coronary bifurcations; a three-dimensional intravascular ultrasound study. Circulation 2002;106:1945.
25. Donaldson K.L., Goolsby G.L., Kiener P.A., Wahl A.F. Activation of p34cdc2 coincident with taxol-induced apoptosis. Cell Growth Differ 1994;5:1041-50.
26. Wahl A.F., Donaldson K.L., Fairchild C., et al. Loss of normal p53 function confers sensitization to Taxol by increasing G2/M arrest and apoptosis. Nat Med 1996;2:72-9.
27. Axel D.I., Kunert W., Goggelmann C., et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997;96:636-45.
28. Herdeg C., Oberhoff M., Baumbach A., et al. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo. J Am Coll Cardiol 2000;35:1969-76.
29. Heldman A.W., Cheng L., Jenkins G.M., et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation 2001;103:2289-95.
30. Farb A., Heller P.F., Shroff S., et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. Circulation 2001; 104:473-9.
31. Honda Y., Grube E., de La Fuente L.M., Yock P.G., Stertzer S.H., Fitzgerald P.J. Novel drug-delivery stent: intravascular ultrasound observations from the first human experience with the QP2-eluting polymer stent system. Circulation 2001;104:380-3.
32. Kataoka T., Grube E., Honda Y., et al. 7-hexanoyltaxol-eluting stent for prevention of neointimal growth: an intravascular ultrasound analysis from the Study to COmpare REstenosis rate between QueST and QuaDS-QP2 (SCORE). Circulation 2002;106:1788-93.
33. Grube E., Silber S., Hauptmann K.E., et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38-42.
34. Grube E., Serruys P.W. Safety and performance of a paclitaxel-eluting stent for treatment of in-stent restenosis. preliminary results of TAXUS III trial. J Am Coll Cardiol 2002;39:58A.
35. Park S., Shim W., Ho D., et al. The clinical effectiveness of paclitaxel coated coronary stents for the reduction of restenosis in the ASPECT trial. Circulation 2001;104:464.
36. Hong M.-K., Mintz G.S., Lee C.W., et al. Paclitaxel Coating Reduces In-Stent Intimal Hyperplasia in Human Coronary Arteries. A Serial Volumetric Intravascular Ultrasound Analysis From the ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT). Circulation 2003:01.CIR.0000054163.42072.D4.
37. Gershlick A., Descheerder I., Chevalier B., et al. Local drug delivery to inhibit coronary artery restenosis.Data from ELUTES(evaluation of paclitaxel eluting stent)clinical trial. Circulation 2001;104:416.
38. Teirstein P.S. Living the dream of no restenosis. Circulation 2001;104:1996-8.

STENT IMPLANTATION FOR THE LESIONS IN THE UNPROTECTED LEFT MAIN TRUNK DISEASE

Shigeru Saito, Kazuharu Sunami [1]

General Hospital ShonanKamakura, KamakuraCity, Japan

Introduction

Angioplasty for unprotected left main trunk (LMT) disease is generally considered contraindicated, since it might be associated with high-risk events during not only the in-hospital but also the follow-up periods. If the left main coronary lesion will have critical narrowing due to restenosis in the following period, it might be related to sudden cardiac death. According to the guideline proposed by ACC/AHA task force committee [1], the recommended treatment for LMT disease is coronary artery bypass graft surgery (CABG) but not percutaneous coronary intervention (PCI).

However, the introduction of coronary stent and the refinement of its implantation technique have continuously improved the short- and long-term safety and efficacy of PCI, and expanded the indication of PCI.

Tips in stenting for unprotected LMT disease

Patient selection

Still even now, the 1st choice of treatment for unprotected LMT disease is CABG. However, if the lesion is located at the ostium or body of LMT, and if the patient has good left ventricular function, stenting for LMT can also be accepted as the 1st treatment strategy. If the lesion is located at the bifurcation of LMT, or if the patient has poor left ventricular function, CABG should be chosen first.

Hemodynamic support during stenting

If the patient's left ventricular function is good, no hemodynamic support is necessary. If the patients have hemodynamic instability especially in cases of unstable angina or acute myocardial infarction (AMI), the hemodynamic support by using intra-aortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS) should be started as fast as possible.

Guiding catheter selection

A standard left Judkins' curve (JL) is enough. If debulking is not necessary, a 6 French guiding catheter is used. If the lesion is located at the ostium of LMT, a JL-3.5 guiding catheter is preferable in order to get an adequate positioning of the stent.

Guidewire selection

When the lesion is located at the ostium or body of LMT, a single regular guidewire is inserted deeply into the left anterior descending artery (LAD). It is necessary to put this guidewire as deeply as possible, so that the guiding catheter can be pushed away from the ostium of LMT while pushing this guidewire against the coronary artery. Hydrophilic-coating guidewires (Whisper from Guidant, USA or Choice-PT from Boston-Scientific, USA) are not recommended, since these guidewires easily move during the manipulation and will arterial perforation at the tip of the guidewires during the deep insertion into LAD.

For the bifurcation lesion in LMT, 2 regular guidewires should be inserted into both LAD and the left circumflex artery (LCX).

Predilatation and inflation pressure

Direct stenting without predilatation is not recommended for unprotected LMT disease, because myocardial perfusion can be obstructed while achieving correct stent positioning. This obstruction of blood flow may lead to the hemodynamic instability. A 2.0 or 2.5 mm balloon in diameter is enough to achieve a lumen diameter enough to preserve the blood flow while determining the stent position. A 3.0 or 3.5 mm balloon is not recommended because of the risks in making intimal dissection after the predilatation. A relatively high inflation pressure (>10 atmospheres) is used during the predilatation. The pressure at the postdilatation should be very high (>18 atmospheres) to secure the complete stent expansion and apposition to the vessel wall.

Types of stents

Coil stent is not used any more. Link or slotted tube stents are used for LMT disease. If the lesion is located at the ostium or body, closed-cell stents are recommended. These include BX-Velocity (Cordis, USA), NIR (Medinol, Israel), Express (Boston-Scientific, USA) or others. If we used the open-cell stents in the ostial lesion, the most proximal stent strut would be separated and protruded into the Aorta. If the lesion is located at the bifurcation site, open-cell stents are recommended to secure the side-branch access. These stents include the Multi-Link family (Guidant, USA), S670/S770 (Medtronic, USA), or others.

Bifurcation stenting

Y-stenting technique is not used any more due to its terrible short- and long-term results. The usual way in stenting for the bifurcation lesion is a stenting only from LMT to LAD. Its detailed procedure includes: 1) simultaneous kissing balloon dilatation from both LMT to LAD and LCX, 2) stenting from LMT to LAD while leaving a guidewire in the LCX, 3) re-crossing a guidewire through a stent strut from the inside of the stent into the LCX, 4) simultaneous kissing balloon dilatation from the inside of the stent to both LAD and LCX.

A kissing stenting technique is another option. After the simultaneous kissing balloon dilatations from LMT to both LAD and LCX, 2 stents are placed simultaneously from LMT to both LAD and LCX [Figure 1]. This technique is useful especially in emergent situation, since it can achieve the restoration of blood flow to the myocardium quickly.

Intravascular ultrasound (IVUS) examination

In order to confirm both full stent expansion and good apposition to the vessel wall, IVUS

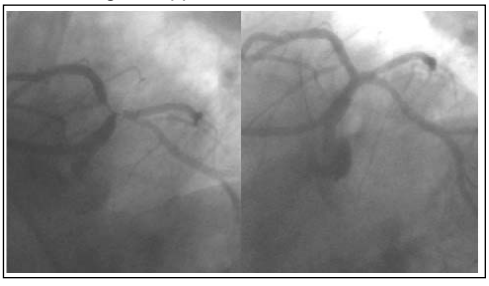


Figure 1. A case of kissing-stent implantation for the lesion at the bifurcation of the left main trunk

[1] Shigeru Saito, MD, FACC, FSCAI, FJCC, Kazuharu Sunami, MD
Division of Cardiology & Catheterization Laboratories, Heart Center of ShonanKamakura General Hospital
1202-1 Yamazaki, Kamakura City, Japan 247-8533
Phone: +81-467-46-1717, Facsimile: +81-467-46-1907
E-mail: saito@shonankamakura.or.jp

examination is mandatory especially after stent deployment.

Debulking strategy

Debulking strategy is useful for the bifurcation lesions in LMT disease. However, if the lesion is located at the ostium or body of LMT, debulking is generally not necessary. If LMT disease shows the superficial calcification in the bifurcation, Rotablator will be necessary to achieve the full stent expansion [Figure 2]. If the lesion has no fluoroscopic evidence of calcification, DCA is preferred [Figure 3].

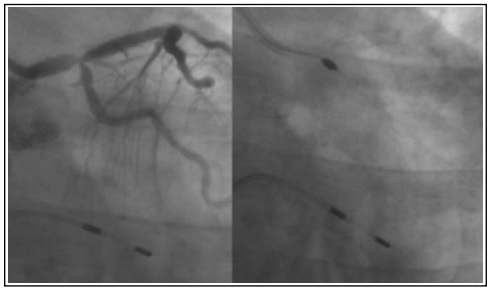


Figure 2A. A case of stent implantation after Rotablator for the lesion at the bifurcation of the left main trunk (This case was treated during the live transmission from Shonan Kamakura General Hospital to TCT'99 at Washington DC, USA)

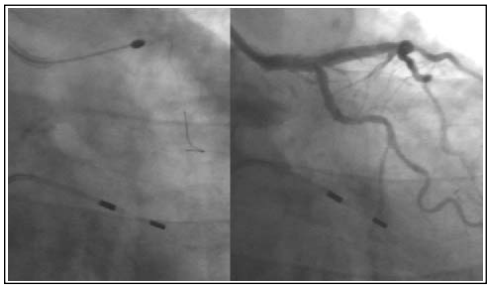


Figure 2B. A case of stent implantation after Rotablator for the lesion at the bifurcation of the left main trunk (This case was treated during the live transmission from Shonan Kamakura General Hospital to TCT'99 at Washington DC, USA)

The results in ShonanKamakura General Hospital

In ShonanKamakura General Hospital, the main therapeutic strategy for LMT disease is still CABG. However, PCI for LMT disease has been performed in selected cases.

Patient population and method:

Total of 38 consecutive patients, for whom PCI was performed in LMT disease under the elective or urgent conditions between January 2000 and December 2001 in ShonanKamakura General Hospital, were included in this analysis. During the study period, we had more than 2,000 cases of PCI in total. All of the study patients had the first therapy on their LMT disease.

(1) Inclusion criteria:

For the elective cases, only patients with the lesions, which was adequate for PCI, who and whose family denied CABG, and/or for whom CABG was considered to be associated with high mortality due to the associated cerebrovascular or other medical disorders, were considered eligible for PCI. For the urgent cases, only the patients, for whom PCI for LMT disease were considered inevitable for the restoration of their hemodynamic conditions, and from whose family the written informed consent was obtained, were included.

(2) Procedures:

All of the procedures were performed under systemic heparinization (6,000 units for the elective cases and 10,000 units for the urgent cases). After stenting, all patients were maintained with 200 mg of ticlid and 182 mg of aspirin a day without coumadin or heparin. Transradial, transbrachial, and transfemoral approaches were used in 20 (50%), 3 (8%) and 15 (39%) patients, respectively.

In the 13 patients with the lesions at the ostial or body of LMT, NIR, Bx-Velocity and Multi-Link Duet stents were used in 10, 2, and 1 lesions respectively. All of the stent implantations were performed with predilatation followed by the postdilatation at 16 to 24 (20.7 +/- 2.7) atmospheres.

In the 25 patients with the lesion at the bifurcation of LMT, debulking procedures prior to stenting were performed by using DCA or Rotablation in 2 or 4 patients, respectively. Kissing stent implantation for both LAD and LCX was used in 8 patients.

(3) Hemodynamic support:

IABP was used only in 12 patients with AMI. PCPS was used only 1 patient with cardiogenic shock in AMI.

(4) Definitions and angiographic analyses:

All of the quantitative angiographic analyses were performed by using on-line QCA method equipped with Philips' H-5000 angiography system. Angiographic success was defined as the achievement of TIMI 3 flow and residual % diameter stenosis <30%. Procedure success was defined as angiographic success without any major in-hospital adverse events including death, myocardial infarction (MI) or target lesion revascularization (TLR). All of the patients were asked to receive the follow-up coronary angiograms at (1), 3, 6 and 12 months post procedure. Restenosis was defined as 50% stenosis at the follow-up angiograms. All of the patients received the clinical inquiries by using telephones or letters during the follow-up periods.

(5) Statistical analyses:

Data were expressed as mean value +/- SD. Comparison of continuous and categorical variables between equivalent groups were calculated by ANOVA and Chi-square test, respectively. P value >= 0.05 was considered statistically not significant.

Table 1. Baseline Clinical Characteristics

	N=38	%
Age (years)	71,5±10,5	
Male	31	81,6
Hypertension	17	44,7
Diabetes Mellitus	11	28,9
Hypercholesterolemia	17	44,7
Smoker	13	34,2
Obesity (BMI>25)	10	26,3
Dialysis dependence	2	5,3
Previous MI	9	23,7
Previous PCI	14	36,8
Clinical conditions:		
AMI	14	36,8
Unstable angina	9	23,7
Stable angina	15	39,5

BMI: Body Mass Index, MI: Myocardial Infarction,
PCI: Percutaneous Coronary Intervention,
AMI: Acute Myocardial infarction

Results:

(1) Patient demographics:

Patient demographics are shown in Table 1.

(2) Angiographical characteristics and clinical outcomes:

The angiographic success was observed in 100% and 96% in patients with the ostial/body and bifurcation lesions, respectively. In-hospital death was observed only in 5 patients with AMI (4 patients) or unstable angina (1 patient). In-hospital TLR or MI was not observed in any patients. Thus, the overall procedure success rate of PCI was 87% (71% and 96% in urgent and elective cases, respectively) [Table 2][Table 3].

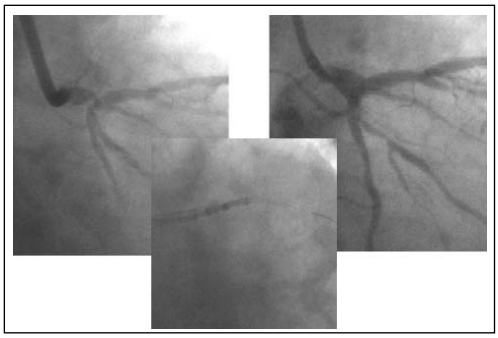


Figure 3. A case of stent implantation following directional coronary atherectomy for the lesion at the bifurcation

Table 2. Baseline Angiographic Characteristics and Procedural Results

Lesion site	Ostium/Body		Bifurcation		Overall
N	13		25		38
Lesion length (mm)	4,7±1,7		7,4±3,4		
Pressure (atmospheres)	20,7±2,7		13,6±4,4		
	Pre PCI	Post PCI	Pre PCI	Post PCI	
RVD (mm)	3,5±0,8	3,7±0,7	3,2±0,7	3,4±0,6	
MLD(mm)	1,3±0,4	3,5±0,7	1,1±0,5	3,2±0,6	
%DS (%)	62±6	7±8	64±16	8±8	
Angiographical success (%)	100		96		97
Procedural success (%)	92		84		87

RVD: Reference Vessel Diameter, MLD: Minimum Lumen Diameter, DS: Diameter Stenosis

Table 3. In-Hospital Major Clinical Events

	All	AMI	UAP	SAP	Os/Body	Bifurcation
N	38	14	9	15	13	25
Death	5	4	1	0	1	4
Cardiac death	4	4	0	0	1	3
Non-cardiac death	1	0	1	0	0	1
MI	0	0	0	0	0	0
TLR	0	0	0	0	0	0

UAP: Unstable angina, SAP: Stable angina, Os/Body: Ostium or body lesion,
MI: Myocardial Infarction, TLR: Target Lesion Revascularization

(3) Long-term clinical outcomes [Table 4]:

Six-months' follow-up coronary angiograms were taken in 28 (85%) of 33 patients who were discharged alive from the hospital. In these patients, the angiographic restenosis rate was 32% (9% in patients with the ostial/body and 47% in patients with the bifurcate lesions, respectively). During the clinical follow-up period of 14.6 +/- 5.7 months, one patient had death, and 10 patients had TLR (9 by PCI and 1 by CABG). Nine of these 10 patients with TLR had the original lesion at the bifurcation. The survival rate in patients with elective stenting was 92% during the follow-up period of 14.2 +/- 6.3 months.

(4) Predictors for mortality in patients with AMI [Table 5]:

Four patients (29%) died in the hospital among 14 patients with AMI. The predictors for mortality in these patients were ventricular tachycardia and fibrillation (p<0.01), and initial TIMI 0 or I flow (P<0.02).

Discussion

If the lesions are located at the ostium or body of the unprotected LMT, now stenting with balloon predilatation followed by high-pressure postdilatation can achieve acceptable short- and long-term clinical results as good as CABG. This can be reasonablly understood, because those lesions have relatively short lesion lengths and relatively big reference vessel diameters, both of which have been known as the strong predictors for the good long-term outcome after stenting. Even in these lesions, IVUS examination is essential especially after stent implantation to confirm the full stent expansion and good appsotion to the vessel wall, both of which are considered important to avoid stent thrombosis.

The situation is totally different, if the lesions are located at the bifurcation of LMT. In these lesions, stenting can achieve good clinical outcomes only in the short-term period but not in the lon-term period. Debulking strategies using DCA or Rotablator might be necessary in these lesions in order to improve the long-term outcomes.

History and current prospectives of stent implantation for the unprotected left main trunk diesease

Angioplasty for the lesion in LMT had been considered a contraindication for many years. Crowley reported the results of balloon angioplasty (POBA) in 15 patients with unstable angina caused by LMT disease [2]. Major complication was encountered in 1 patient, and one-year survival was achieved in 13 patients (87%). Although 4 patients had restenosis in LMT, all of them were successfully treated by repeat angioplasty. From Japan, one case of the LMT disease treated by directional coronary atherectomy (DCA) was reported [3]. The patient was an 85-year-old female patient with unstable angina in cardiogenic shock due to an unprotected LMT disease, and successfully treated by using DCA and POBA.

Garcia, et al [4] reported the 1st case of stent implantation in unprotected LMT. They had one patient with stenting in LMT among total of 35 patients treated by stent implantation for acute myocardial infarction. However, before Park reported his series of stent implantation in 42 patients with stable angina caused by unprotected LMT disease [5], stenting for LMT had been considered contraindicated.

Although stenting in LMT disease had un acceptable short- or medium-term results in single-center experiences, multicenter registry (ULTIMA registry) results could not show the follow-up results as good as single-center experience [6]. This discrepancy of clinical results evoked the significance of

Table 4. Medium-Term Clinical Events

	ALL	AMI	UAP+SAP	Os/Body	Bifurcation
N	33	10	23	12	21
Follow-up (%)	85	80	87	92	81
Restenosis rate (%)	32	25	35	9	47
Cumulative Events					
Follow-up periods (months)	14,6±5,7	15,4±8,4	14,2±6,3	13,4±4,4	15,1±6,3
Death	1	0	1	1	0
MI	0	0	0	0	0
TLR	10	2	8	1	9
Re-PCI	9	2	7	1	8
CABG	1	0	1	0	1

AMI: Acute Myocardial infarction,
UAP: Unstable Angina, SAP: Stable Angina,
Os/Body: Ostium or body lesion, MI: Myocardial Infarction,
TLR: Target Lesion Revascularization,
PCI: Percutaneous Coronary Intervention,
CABG: Coronary Artery Bypass Grafting

Table 5. Univariate Analysis on the Predictors of Death in Acute myocardial Infarction

	Death	Survival	p
N	4	10	
Age (years)	72,0±9,9	76,4±9,7	NS
Male (%)	100	70	NS
VT/VF (%)	100	10	P<0,01
TIMI 0 or 1(%)	100	30	P<0,02
Shock (%)	100	50	NS
IABP (%)	100	80	NS
Bifurcation lesion (%)	75	70	NS
Diabetes Mellitus (%)	25	10	NS
Hypertension (%)	25	50	NS
Prior MI (%)	25	30	NS

VT/VF: Ventricular Tachycardia and/or Fibrillation,
TIMI: Thrombolysis in Myocardial Infarction,
IABP: Intraaortic Balloon Pumping,
MI: Myocardial Infarction

debulking strategy prior to stenting and intravascular ultrasound guidance [7]. If stenting is performed adequately with ultrasound guidance and/or debulking, the long-term outcomes of patients after stenting of unprotected LMT disease is favorable, provided they are good candidates for CABG [8][9], or have normal left ventricular function [10].

Although the short- or medium term outcomes after stenting for LMT lesions are acceptable, the long-term outcomes are still not good due to the relatively high angiographic restenosis and repeat revascularization, with a relatively high incidence of cardiac death. Reference vessel size and left ventricular function are the most important predictors of favorable follow-up in these patients [11]. Finally, stenting for LMT disease can be safely performed through the transradial approach [12].

From these considerations, we can conclude at this moment that: 1) stenting for the lesions at the ostium or body of the unprotected left main trunk can be the 1st-choice treatment as well as coronary artery bypass surgery, provided the reference vessel diameter is relatively big and the left ventricular function is relatively good, 2) if the lesions are located at the bifurcation of the unprotected LMT, the 1st-choice treatment is still CABG, 3) if we have to treat the lesions at the bifurcation of the unprotected LMT in the elective situations, debulking procedures by using directional coronary atherectomy or Rotablator are mandatory before stenting, 4) if we have to treat the lesions at the bifurcation of the unprotected LMT in an emergency situation, kissing stent implantation from LMT to both LAD and LCX is a good treatment strategy, and 5) intravascular ultrasound examination is mandatory to secure the full stent expansion and good apposition to the vessel wall especially after stent implantation.

References:

1. Eagle KA, Guyton RA, Davidoff R, Ewy GA, Fonger J, Gardner TJ, Gott JP, Herrmann HC, Marlow RA, Nugent W, O'Connor GT, Orszulak TA, Rieselbach RE, Winters WL, Yusuf S, Gibbons RJ, Alpert JS, Garson A Jr, Gregoratos G, Russell RO, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). Circulation 1999; 100: 1464-80.

2. Crowley ST, Morrison DA. Percutaneous transluminal coronary angioplasty of the left main coronary artery in patients with rest angina. Cathet Cardiovasc Diagn 1994; 33: 103-7.

3. Toeda T, Miida T, Oda H, Higuma N. A case of unprotected left main coronary stenosis rescued by directional coronary atherectomy as a last resort. Jpn Circ J 1995; 59: 231-5.

4. Garcia-Cantu E, Spaulding C, Corcos T, Hamda KB, Roussel L, Favereau X, Guerin Y, ChaletY, Souffrant G, Guerin F. Stent implantation in acute myocardial infarction. Am J Cardiol 1996; 77: 451-4.

5. Park SJ, Park SW, Hong MK, Cheong SS, Lee CW, Kim JJ, Hong MK, Mintz GS, Leon MB. Stenting of unprotected left main coronary artery stenoses: immediate and late outcomes. J Am Coll Cardiol 1998; 31: 37-42.

6. Tan WA, Tamai H, Park SJ, Plokker HW, Nobuyoshi M, Suzuki T, Colombo A, Macaya C, Holmes DR Jr, Cohen DJ, Whitlow PL, Ellis SG; ULTIMA Investigators. Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. Circulation 2001; 104: 1609-14.

7. Park SJ, Hong MK, Lee CW, Kim JJ, Song JK, Kang DH, Park SW, Mintz GS. Elective stenting of unprotected left main coronary artery stenosis: effect of debulking before stenting and intravascular ultrasound guidance. J Am Coll Cardiol 2001; 38: 1054-60.

8. Silvestri M, Barragan P, Sainsous J, Bayet G, Simeoni JB, Roquebert PO, Macaluso G, Bouvier JL, Comet B. Unprotected left main coronary artery stenting: immediate and medium-term outcomes of 140 elective procedures. J Am Coll Cardiol 2000; 35: 1543-50.

9. Black A, Cortina R, Bossi I, Choussat R, Fajadet J, Marco J. Unprotected left main coronary artery stenting: correlates of midterm survival and impact of patient selection. J Am Coll Cardiol 2001; 37: 832-8.

10. Park SJ, Park SW, Hong MK, Lee CW, Lee JH, Kim JJ, Jang YS, Shin EK, Yoshida Y, Tamura T, Kimura T, Nobuyoshi M. Long-term (three-year) outcomes after stenting of unprotected left main coronary artery stenosis in patients with normal left ventricular function. Am J Cardiol 2003; 91: 12-6.

11. Takagi T, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, Sivieri G, Paloschi R, Di Mario C, Colombo A. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. Circulation 2002; 106: 698-702.

12. Sunami K, Saito S, Tanaka S. Successful Transradial Coronary Angioplasty and Stenting Using a Self-Expandable RADIUS Stent to the Anomalous Left main Coronary Artery. J Invasive Cardiol 2003; 15: 46-8.

RESTORATION OF BLOOD FLOW IN THE INFARCT-RELATED CORONARY ARTERY IN ACUTE MYOCARDIAL INFARCTION: EFFECTIVE OR JUST SPECTACULAR?

D.G. Iosseliani, A.A. Filatov, S.V. Rogan, A.V. Arablinsky, S.P. Semitko, A.V. Koledinsky

Moscow city Center of Interventional Cardioangiology Hospital No 15, Moscow[1].

Today, the important role of acute coronary artery occlusion in pathogenesis and clinical course of acute Q-wave large-focal myocardial infarction is unquestionable. After the pioneer works by Rentrop et al. in 1979 and by Meyer et al. in 1982, the possibility of restoration of the coronary blood flow by the thrombolysis or PTCA became evident. Since that time, many thousands of procedures of restoration of a disturbed blood flow in coronary arteries were performed in patients with AMI within the first hours of the disease. Today, on the basis of the experience accumulated, we can say with certainty that the infarct-related artery (IRA) recanalization procedure performed within the first several hours after the beginning of the disease allows to reestablish TIMI II-III blood flow in the vessel in more than 90% of cases. This fact is incontestable, and it is not a subject of discussions anymore. It is evident that, among endovascular recanalization techniques, the most valuable one is PTCA of the IRA following mechanical recanalization of the vessel with or without stenting of this artery. The advantage of PTCA as compared to intracoronary thrombolysis (IT) is that there is virtually always a residual stenosis caused by an atherosclerotic plaque after IT. However, the fact of blood flow restoration in the IRA doesn't mean that cardiologists now possess an effective technique for the treatment of acute myocardial infarction which is more effective than the commonly used conservative drug treatment. In order to confirm the effectiveness of this method of treatment, we have to answer a number of important questions, the most important one being as follows:

Does IRA recanalization and, consequently, myocardial reperfusion have any advantages as compared to common drug treatment, as regards the following:

a. The longevity of the effect of IRA blood flow restoration ;
b. Immediate and long-term survival rate;
c. Life quality improvement;
d. Prevention of AMI recurrence;
e. Limitation of necrotic area and, thus, protection of the heart's functional capacity.

Review of publications on the issue allows to conclude that, in spite of numerous studies, no single question asked has a definite and final answer. That is why research in this direction goes on. Since 1984, we have been studying various aspects of IRA recanalization influence at different stages of the clinical course of the disease. At the beginning, we used IT only, in 1988, we began to use PTCA of IRA, and since 1997, we have been using a combination of PTCA of IRA and stenting (in some patients).

Methods

From 1984 to December, 2002, we accumulated the experience with 1283 endovascular procedures for AMI, 874 of which are PTCA procedures (group N1), 308 are intracoronary thrombolysis (IT) procedures (group N2), and 101 are combined procedures of PTCA and stenting. Taking into consideration the fact that patients who underwent PTCA of IRA are much more numerous than patients after IT and stenting of IRA, and that, as we have already mentioned before, PTCA has certain advantages from the viewpoint of full restoration of the blood flow in IRA as compared to IT, in this article we mostly analyze results of PTCA, while a group of patients after IT served as control. For the same purpose, we also used 99 patients who underwent selective coronary angiography at the acute stage of AMI, but for some reasons IRA recanalization was not performed in them, or it failed (group N3). In one of the next issues, we will publish an article on the results of stenting in patients with AMI recurrence within the first hours of the disease, so in this article we will not discuss results of stenting in patients with AMI.

The study is not randomized, but, as Table 1 shows, patients from the groups compared were reliably similar from the point of view of many clinical angiographic indices characterizing the patient's condition, i.e. they were quite comparable.

In the overwhelming majority of cases (91.8%), the procedure of recanalization was performed within the first 6 hours after the beginning of anginal pain. The indication for selective coronary angiography and IRA

Table 1. Initial clinical, laboratory and history data of patients of the studied groups

Indices	1 group (n=874)	2 group (n=308)	3 group (n=99)	P
Age, years	52.3+3.2	52,0+1.2	51.2+1.6	>0.05
Duration of the ischemic disease, years	2.2+0.9	3.0+0.5	2.6+0.9	>0.05
History of AMI	15%	15.9%	12%	>0.05
Smoking	65%	58.6%	61%	>0.05
Arterial hypertension	55%	55.5%	60%	>0.05
Family history of CAD	21.7%	25%	20%	>0.05
Diabetes mellitus	5%	3.8%	6%	>0.05
Hypercholesterolemia	47.8%	55.1%	52%	>0.05
Localization of acute myocardial infarction:				
Anterior	62.8%	66%	60%	>0.05
Posterior	24.7%	23.1%	28%	>0.05
Lateral	4.7%	3.5%	2%	>0.05
The number of affected arteries (on the average)	1.2+0.08	1.3+0.06	1.2+0.07	>0.05
Left ventricular ejection fraction (%)	54.6+3.3	54.4+4.1	51.7+3.8	>0.05

[1] The Scientific Practical Center of Interventional Cardioangiology of the Health Committee of Moscow, Moscow, 101000, Sverchkov per.,5, e-mail: davidgi@caravan.ru

recanalization was the clinical presentation of an acute myocardial infarction (anginal pain lasting over 30 minutes and non-responding to nitroglycerin, elevation or depression of the ST segment of more than 1 mm with inversion of the T wave on the ECG, leucocytosis, angiographic picture of an acute total or subtotal IRA occlusion). Urgent coronary angiography and revascularization procedure after the first 6 hours of anginal pain was carried out only in cases of sustained anginal attacks against the background of a developed acute myocardial infarction. Selective coronary angiography was performed using the regular technique. The only particularity consisted in catheterization of a main vein for infusion of nitroglycerin at the rate of 0.04-0.8 mg/min, and for a quick introduction of a catheter to the right ventricle (when necessary) for temporary cardiac pacing. Angiographic picture of acute occlusion of coronary arteries with neither antegrade, nor retrograde opacification of their distal parts was considered as an acute IRA occlusion. For differential diagnostics of an occlusive spasm and a thrombotic occlusion of a vessel, 200 μg of nitroglycerin were introduced intracoronary. If occlusion persisted, we proceeded to the vessel recanalization. For this purpose, we used either intracoronary thrombolysis, or mechanical recanalization of the occluded vessel followed by PTCA (in some cases it was combined with the coronary artery stenting).

The IT procedure was begun with bolus dosing of 25,000 U of a thrombolytic agent (in most cases, Streptase [Behring, Germany], was used) into the coronary artery, followed by a dosed drop-by-drop introduction of the same agent intracoronary at the rate of 225-250,000 U for an hour. After the infusion was completed, a control angiography was performed, and, depending on its results, the final result of the procedure was evaluated. In case of IRA recanalization corresponding to the appearance of vascular opacification all along the vessel, the procedure was considered successful. As a rule, in case of IRA recanalization by means of intracoronary thrombolysis, a residual stenosis of the vessel exceeding 50% of the lumen was registered. IT, as well as PTCA and/or stenting of IRA was accompanied with a bolus dosing of 10,000 U of heparin, an intravenous drop-by-drop infusion of Dextran at the rate of 100 ml/hour, and nitroglycerin at the rate of 3 mg/hour. PTCA and/or stenting of IRA was performed according to the common standard. The only particularity was the mechanical recanalization of the occluded vessel with a guide Shinoby 0.014 in., Cordis, J&J. Later, all stages of the above procedure were identical to those performed for patients with chronic forms of coronary artery disease. Before the control coronary angiography, 0.2 mg of nitroglycerin was introduced intracoronary. The procedure of PTCA was considered successful if there was a lumen all along the previously occluded vessel. Stenosis in the previously occluded area was supposed not to exceed 50% of the vessel diameter. On completion of the procedure, intravenous infusion of heparin at the rate of 1000 U/hour was continued for 6 to 8 hours, then the infusion was stopped, and 1.5 to 2 hours later, the introducer was removed (provided blood coagulation indices are suitable). Within 6 to 8 hours after the procedure, patients had an intravenous drop-by-drop infusion of nitroglycerin at the rate of 4 mg/hour. The left ventricular ejection fraction before PTCA and in the long-term follow-up (at least six months after the reperfusion procedure) was studied in almost all patients. At the same time, the left ventricular segmental contractility was studied using the Lipton technique in 184 patients. Five segments were determined: 1. anterior basal, 2. anterior lateral, 3. apical, 4. posterior diaphragmatic, 5. posterior basal. Segmental contractility corresponded to the percentage of shortening of axes connecting the center of each segment with the geometrical center of the left ventricle (segmental contractility of length) and the percentage of reduction of the area of the sector adjacent to the corresponding segment (segmental contractility of area).

In order to determine the state of vascularization of the peri-infarction area in 42 patients who had PTCA of IRA within the first hours of AMI, stress scintigraphy of myocardium with TL^{201} was performed 12 to 14 days after the procedure. For radionuclide studies , we used a mobile camera DINAMO (Piker, USA), with a built-in computer DEC (USA). For scintigraphy, we used TL^{201} chloride, 65 to 74 MBc of which were introduced to the cubital vein at the peak of stress test. We started myocardial scintigraphy 5 to 6 minutes after the agent introduction in three projections: anteroposterior projection, left oblique 45° projection, and left lateral 90° projection, with the patient in right decubitus position. Scintigrams were processed using the Wacers technique, 1985, implemented in the standard TL^{201} program by Piker. It involves a comparison of two myocardial images, the initial and delayed (6 hours later) ones, in each view. As a result of processing we obtained the image of the left ventricle divided into 5 segments in each view and constructed the graphs of the radiopharmacological agent distribution in the myocardium. Myocardial perfusion was quantitatively evaluated by such criteria as the average number of myocardial segments with a perfusion defect, the average number of myocardial segments with a persistent perfusion defect, the average number of myocardial segments with ischemia, the maximum depth of the myocardium perfusion defect. Segments with transient defects of accumulation of the radiopharmacological agent or its reduced wash-out were considered as the areas of myocardial ischemia.

The follow-up examination of the patients was performed at least 6 months after the discharge. During the follow-up examination performed, on the average, 7.1+1.6 months later for all patients (provided they had no contraindications), the following procedures were performed: 1. ECG at rest and a stress test; 2. Selective coronary angiography and left ventriculography. In cases of IRA restenosis or reocclusion, PTCA or stenting of the corresponding vessel was performed.

Statistical analysic was performed using student's t-test.

Results and discussion

Results of the study at the hospital stage and at the follow-up are shown in Tables 2 and 3. The study confirms the opinion that a timely and adequately performed IRA PTCA in the overwhelming majority of cases allows to completely restore the blood flow in this vessel. In 90.7% of cases, we were able to recanalize the vessel and to restore TIMI II-III blood flow in IRA. With IT, this figure was only 72.8%. As for the longevity of the achieved IRA recanalization, we performed

Table 2. Immediate (in-hospital) results of treatment of patients with AMI

	1 Group	2 Group	3 Group
Frequency of recanalization of IRA (%)	90.7	72.8	–
MORTALITY (%):			
total	5.1	9.8	11.5
cardiac	2.7	6.4	11.5
Recurring AMI (%)	2.02	5.6	3.3
Lack of anginal attacks (%)	92.1	89.4	81.4

Table 3. Long-term results of PTCA in studied groups of patients (24,3±4<2 months)

Mortality (%):			
Total	4.4	7.9	12.9
Cardiac	3.1	5.8	9.8
Recurrent AMI (%)	9.3	13.6	12.9
Free from anginal attacks (%)	77.1	52.4	48.4
Effect of PTCA preserved:			
Fully	68.2	59.2	-
Restenosis of IRA	18.1	15	-
Reocclusion	13.7	25.8	-
Negative stress test(%)	75.5	43.5	48.6
LVEF	59.2+4.2	54.5+5.6	51.3+3.6

selective coronary angiography and left ventriculography in 390 patients in average 24.3+4.2 months after the procedure. Other patients either refused a follow-up examination because they felt well, or were not found, as they reside in other cities and countries former USSR republics). The patients in whom the follow-up was too short for the study of late results, were not included in this investigation. The examination showed that in 68.2% of patients the effect of PTCA in the IRA was entirely preserved, while in 18.1%, a restenosis was registered (narrowing of the vessel lumen by more than 50%), and the remaining 13.7% had a reocclusion of the vessel. It is worth mentioning that in the group of patients who underwent successful IT procedure, in an approximately the same period of time, the angiographic picture of IRA remained basically unchanged in 59.2% of cases, in 15% of cases the stenosing process significantly progressed, and on the remaining 25.8% of cases, patients had a reocclusion of IRA. However, it should be emphasized that in almost all patients who underwent a successful thrombolysis, there was a substantial stenosis of the vessel, sometimes exceeding 50% of the lumen. Such condition of the vessel hardly allows to consider the blood flow through it absolutely normal.

Thus, our study allows us to come to the conclusion that the effect of PTCA of IRA is preserved in about two thirds of patients after about two years.

As for the rate of mortality in patients after PTCA of IRA, it is worth mentioning that, after this procedure, 94.9% patients with AMI were discharged from the hospital, so that the total in-hospital mortality amounted to 5.1%, and the cardiac mortality, to 2.7%. Cardiac mortality was caused by: cardiogenic shock or acute left ventricular failure - in 9 cases, rupture of the left ventricle wall - in 2, recurrent AMI - in 4 cases. Among non-cardiac causes of death let's mention cerebral stroke (2 patients), gastric hemorrhage (2 patients).

At the same time, after intracoronary thrombolysis the total mortality amounted to 9.8%, while cardiac mortality - to 6.4%. In patients who underwent no recanalization or in whom the recanalization failed, the total mortality was 11.5%. In this group of patients, all deaths were cardiac. Late survival after PTCA of IRA was 95.6% (in-hospital mortality not included). Hence, the total mortality was 4.4%, and the cardiac one, 3.1%; in the other two groups, these figures were 7.9 % (5.8%) and 12.9 % (9.8%), respectively. Thus, we can conclude that the survival after PTCA of IRA is reliably higher than after IT; it's also higher than in patients who did not undergo IRA recanalization.

In-hospital recurrent acute myocardial infarction after successful PTCA of IRA was registered in 2.02% of cases, while in the remaining two groups it was 5.6% and 3.3%, respectively, P<0.05. During the follow-up, 9.3% of patients from the first group had a recurrent AMI, and in 4.6% of them the myocardial infarction occurred in the IRA pool; in the other two groups, 13.6% (8.5%) and 12.9% (10.8%) of patients, respectively (P<0.01), had AMI. Thus, from the point of view of prevention of AMI recurrence, PTCA seems preferable as compared to the other two methods of treatment.

Before the discharge, 92.1%, 89.4%, and 81.4% of patients, respectively, were free from anginal pains. About two years later, these figures were 77.1.5%, 52.4%, and 48.4% respectively. Stress test in long-term follow-up was negative in 75.5% of patients after PTCA. The stress threshold in this group was 103.6+8.8 Wt in average. In the groups of patients who underwent IT and conservative therapy, the stress test was negative in 43.5% and 48.6% of cases, respectively, and the stress threshold was 79.5Wt and 74.6+4.4 Wt, respectively.

Thus, our study allows us to conclude that from the point of view of quality of life, the patients after PTCA of IRA have better chances as compared to patients after IT, as well as to patients who were treated with drugs and didn't undergo IRA recanalization.

The issue of influence of myocardial reperfusion on the preservation of the viability of peri-infarction necrotic area and, consequently, on the improvement of left ventricle performance, is still the least examined one and represents a point of controversions. In order to study these issues, 42 patients with AMI had a stress myocardial scintigraphy with TL^{201} 12 to 14 days after PTCA of IRA,. For the purposes of control, we selected 16 patients with AMI who underwent no myocardial recanalization or in whom the recanalization failed. Both groups were reliably similar by most of initial clinical, laboratory, and history data. As a result of the study (Table 3), we found out that patients with PTCA of IRA had signs of ischemia in the peri-infarction area only in 4.8% of cases, while in the other group this index was 62.5%. By all indices characterizing the myocardial perfusion condition, the group of patients after PTCA of IRA was in a better situation than the control group, even though, as Table 4 shows, the groups were reliably similar, when compared by initial clinical and laboratory data. The number of myocardial segments with perfusion defects in the two groups examined was 0.4+0.09 and 4.39+0.8, respectively (P<0.001). The maximum depth of the perfusion defect was, in average, 4.4+0.9 and 10.0+1.2 (P< 0.05).

Thus, our study showed that the blood supply to the peri-infarction area of myocardium in patients after successful PTCA of IRA is much less disturbed than in patients who did not undergo this procedure.

It is worth to emphasize that the majority of patients (95%) who had PTCA of IRA within the first hours of the disease were free of signs of peri-infarction ischemia. This can suggest the restoration of normal blood supply to the peri-infarction area of myocardium after a successful recanalization and PTCA of IRA. Another confirmation of this is the

Table 4. Data of TL^{201} scintigraphy of the left ventricle in patients with acute myocardial infarction on days 12-14 after a successful PTCA of IRA

	1 Group (PTCA)	2 Group (without PTCA)	P<
The number of LV segments with myocardial perfusion defects (mean)	2.08+0.4	4.95+0.6	0.05
The number of LV segments with a stable perfusion defect (mean)	1.74+0.5	3.4+0.7	0.05
The maximum depth of myocardial perfusion defects (%)	4.5+0.9	10.0+1.2	0.01
The number of LV segments with transient myocardial perfusion defects (mean)	0.4+0.07	4.59+0.8	0.001

Table 5. Follow-up of PTCA of IRA depending on the IRA state (24.3+4.2 months)

	Effect of PTCA preserved	Reocclusion after PTCA	P<
Free from anginal attacks, %	93.8	54.5	0.01
Recurrent AMI, %	5	19.3	0.01
LVEF, %	61.6	52.6	0.05

uncomplicated course of the disease in such patients and their higher tolerance to physical stress as compared to the control group. At the same time, we can not completely exclude the fact that after reperfusion of the peri-infarction area, the damaged area gets larger due to hemorrhagic necrosis, in other words, so-called reperfusion syndrome occurs. However, this assumption is disproved by the lesser amount of segments with a persistent defect of drug accumulation in patients after successful PTCA of IRA, and by reliably higher indices of left ventricular ejection fraction (LVEF) dynamics in this group, provided that these two groups were reliably similar when compared by original indices.

One knows, that after AMI left ventricular function is significantly disturbed, and later, regardless of the used methods of treatment, this feature improves to a certain degree. In our study, we observed this pattern, too. For example, initial values of the LVEF in groups of patients examined were 54,6±3,3%, 54.4±4.1%, and 51.7±3.8%, respectively. The difference between these figures was statistically insignificant. With this, it is worth mentioning that the analysis of LV segmental contractility showed that reduction of contractility of infarct-related segments was more pronounced in cases of lesion location on the anterior wall, than on the posterior wall of the left ventricle (11.3+4.3% vs. 18.9+5.8%). At the same time, compensatory hyperkinesia of unaffected segments of the left ventricle was more pronounced in patients with AMI of the posterior, than of the anterior wall of the left ventricle. A long-term follow-up showed that left ventricular ejection fraction in the studied groups was 59.2+4,2%, 54.5±5.6%, and 51.3+3,6%, respectively. The difference is evident between the first and the other two groups. It should be emphasized that the LVEF reliably increased in the group of patients with preserved antegrade blood flow in IRA, even though there was a trend to restenosing of this vessel (60.9±9.8% vs. 48.2±126%, P<0,01). At the same time, no reliable increase of the LVEF was observed in patients with IRA reocclusion. The LVEF increase in the group of patients with preserved blood flow in IRA occurred primarily due to the improvement of contractility of affected segments of the left ventricle accompanied with the elimination of compensatory hyperkinesia of unaffected segments observed at the acute stage of AMI. Long-term follow-up study of LV function also allowed to make sure that, with the blood flow in IRA preserved, the volume of the left ventricle decreases. This dynamics is especially pronounced in the group of patients with a fully preserved blood flow (with no restenosis) in IRA In this group end-diastolic pressure was decreased from 143,2±27,1 to 134.7±24.04 ml, while end-systolic pressure - from 65.8±28.1 to 54.8±24.01 ml . In the group with IRA re-occlusion, the volume of the left ventricle not only didn't decrease, but also reliably increased. In this group the mentioned indices were 148.2±31.5 vs 159.1±33.5 and 73.2±23.8 vs 87.7±29.2 ml. Our study also showed that, the earlier IRA was recanalized, the higher is the probability of the rise of LV ejection fraction. For example, if the blood flow in IRA was restored within the first 2 hours after the unset of anginal pain, LVEF improved reliably in 75% of patients; in cases when this interval was two to six hours, the improvement was seen in 47% of patients, and when the interval between the onset of anginal pain and the restoration of the blood flow in IRA varied from 6 to 12 hours, the improvement was evident in only 14%.

Thus, we can conclude that, after a myocardial infarction, the disturbed performance of the left ventricle reliably improves in cases of preservation of the blood flow in IRA, and the fuller is the blood flow in this vessel, the more pronounced is this improvement. It should also be mentioned that the quicker the blood flow in IRA is restored after an attack of anginal pain, the higher is the probability of improvement of left ventricle function. For example, in the group of patients in whom the procedure was carried out within the first three hours, the LVEF rose to 68.5+7,6%, while in the other group it was only 55.9%.

Finally, we found it interesting to study in-hospital and long-term prognosis after PTCA depending on the condition of IRA. We divided our patients in two groups, the first one was constituted by patients with a completely preserved effect of the procedure, and the second group included patients with IRA re-stenosis and re-occlusion (Table 5). We discovered a reliable difference between these groups, both at the in-hospital stage and in a long-term follow-up. At the in-hospital stage, there was no single case of postinfarction angina pectoris or recurring AMI in patients with the susteined effect of PTCA, while in the other group, 50% of patients had postinfarction angina, and 25% had AMI recurrence. The mortality in the first group was 1.3%, while in the other group it amounted to 40.5%.

In a long-term follow-up, in the group with the preserved effect of PTCA, 93.8% of patients were free from anginal attacks, while in the other group, this figure amounted to 45.5%; 4.3% and 18.1% of patients, respectively, had a recurrent myocardial infarction. The LVEF was 61.6% in the first group, and 53.6% in the other group.

Thus, we can conclude that PTCA of IRA allows to achieve myocardial revascularization in the vast majority of patients with AMI, and is associated with a reduction of mortality and other severe complications as compared to drug treatment only and intracoronary thrombolysis. Myocardial reperfusion performed within the first three hours after the onset of the disease allows to preserve better indices of LV function, as compared to drug therapy.

References:

1. Meyer J. et al.: PTCA immediately after intracoronary streptolysis of transmural myocardial infarction. Circulation, 1982, 66, 342-348

2. Rentrop K.P., Blanhe H., Karsch K.R. et al. Initial experience with transluminal recanalization of the recently occluded infarct-related coronary artery in acute myocardial infarction: Comparison with conventionally treated patients. Clin. Cardiol., 1979, 2,92

3. Arablinsky A.V., Iosseliani D.G.: Perfusion of peri-infarction area of the myocardium and functional state of the left ventricle in patients with acute myocardial infarction after PTCA. Kardiologia, 1998, №11, pp.9-13

THE USE OF DIRECTIONAL CORONARY ATHERECTOMY IN CORONARY ANGIOPLASTY

A.N. Samko, S.I. Provatorov

The Russian Cardiologic Scientific Production Complex of the Ministry of Health of the Russian Federation, Moscow ; A.L. Myasnikov Scientific Research Institute of Clinical Cardiology

Introduction.

Introduction of PTCA in everyday clinical practice allowed to fundamentally change the tactics of treatment of patients with coronary artery disease, thus saving many patients from the necessity to undergo the coronary artery bypass operation [2,3]. At the same time, PTCA itself normally does not allow to restore a vessel lumen, particularly in cases with eccentric stenosis, when elastic rebound of the wall of a vessel reduces to zero the entire effect of the procedure. Besides, consequences of PTCA are not always predictable. In some cases, the trauma of the arterial wall leads to the development of uncontrolled dissection, which can result in vessel occlusion. At present, most of these problems can be eliminated with stenting, but just fifteen years ago, when basic principles of coronary stenting were yet at the development stage, and stents themselves were far from perfect, the technique for the removal of atheromatous debris, or directional atherectomy, offered by John Simpson was perceived as a potential break-through in interventional cardiology. Atherectomy consists in mechanical endovascular removal of atherosclerotic debris. This technique is based on the concept stating that mechanical atherosclerotic plaque removal traumatizes the vessel wall less than PTCA and allows to achieve better hemodynamic effect. Unlike surgical endarterectomy, endovascular atherectomy involves partial removal of atherosclerotic plaque material, and the healthy part of arterial wall is less traumatized. The first procedure with the use of Atherocath catheter was performed by Simpson in October 1986 [21], and initiated the clinical study of coronary atherectomy and numerous discussions regarding advantages and disadvantages of the procedure that go on till now.

According to the principles of their action, all devices for mechanical removal of atherosclerotic plaque material can be divided into two groups: tissue debris collectors and sprays [10]. The first group includes devices that both cut atherosclerotic plaque material and remove it from the arterial lumen. This group includes catheters for directional atherectomy that combine a rotating blade for atherosclerotic plaque cutting and a container for its removal. The second group consists of devices that perform fine dispersion of plaque content, the material thus formed remains in the lumen of the vessel, passes freely through the coronary channel, and is further caught by cells of the reticuloendothelial system. This is the principle of action of rotablator, a quickly rotating milling cutter with a very fine dent.

Structure and the principle of action of a catheter for atherectomy

Fundamentally, all catheters for directional atherectomy have a similar structure (Fig. 1-3). The operating portion of a catheter for directional atherectomy is a cylinder with a longitudinal hole, a working window. Inside the hole, a disk knife made in the form of a

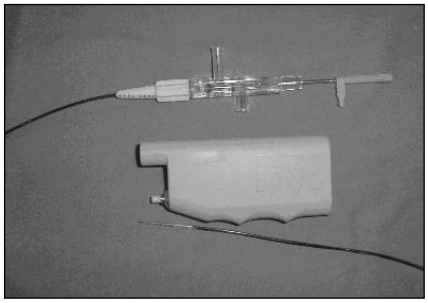


Figure 1. Overall view of the device

piston with a sharp cutting edge moves longitudinally, rotating at the speed of 2000 rpm. On the side of the cylinder opposite to the hole there is a balloon; when it is inflated, the operating portion of catheter is pressed against the plaque, its material enters into the window and gets cut, as the cutting tool passes. The motor rotating the knife and the power source are located on the handle of the device, as well as the lever that allows to control longitudinal movement of the blade. Rotation is transmitted to the blade with the help of a metal wire passing along the whole length of the catheter in one of its longitudinal channels. Two other channels are intended for placement of a coronary wire and for inflation of the balloon. After the intubation of the orifice of the coronary artery with the guiding catheter, the coronary wire is passed through stenosis. The operating portion of the catheter with the window closed is placed in the stenotic part of the vessel with the window oriented towards the most prominent part of the plaque. The knife is placed in the proximal position, which results in the opening of the working window of the device. The fixing balloon is inflated, stabilizing the catheter position relative to the plaque. Then, the motor of the device is started, and, as the knife pass-

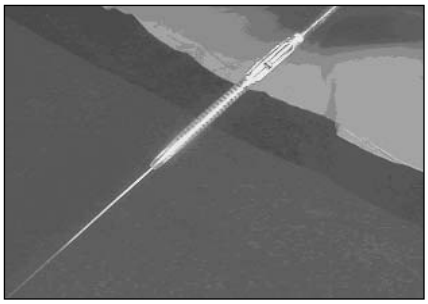


Figure 2. Operating part of the Flexi-cut catheter

es, the cut portion of the plaque is pushed into the container placed in the distant end of the device. In its distant position, the knife closes both the hole on the operating surface of the catheter and the container for cut material. After the balloon is deflated, the catheter turns by a certain angle around its longitudinal axis in order to grasp a new portion of the plaque. Normally, the knife can pass several (4 to 10) times before the container gets filled with atheromatous debris. Then the catheter should be taken out. In order to empty the container of the extracted catheter, it should be washed with a spurt of saline from a syringe directed into the hole through which the wire passes with the window open. After the container is emptied and the performance is checked up, one can go on using the device in the procedure of angioplasty. The manufacturer doesn't recommend to re-sterilize and re-use the device for other procedures.

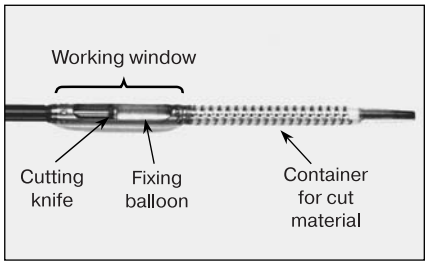


Figure 3. Structure of the operating part of the Flexi-cut catheter.

The directional atherectomy allows to excise plaques localized in proximal and medium parts of coronary arteries. Due to their small diameter, distant parts of the coronary channel are hardly reachable for directional atherectomy. The equipment of the operating room and the preparation of the patients for directional atherectomy is similar to the equipment and preparation for PTCA. Patients planned for directional coronary atherectomy should be prepared for the operation of bypass surgery in case of emergency.

Indications for directional coronary atherectomy:

- Isolated stenoses of proximal and middle parts of coronary arteries. The proper diameter of the stenotic portion of the artery is no less than 2.5 mm.
- Stenoses of aortocoronary shunts
- Restenoses of proximal and middle parts of coronary arteries after PTCA
- Bifurcational lesions of coronary arteries
- Stenoses of coronary ostia

Contraindications to directional coronary atherectomy:

- Stenosis of the left main artery. The decision should be taken on the case-to-case basis whether the procedure should be used for treating the stenosis of a "protected" (by coronary shunt or apparent collaterals) left main trunk.
- Severely calcified lesions
- Apparent tortuosity of the stenotic or more proximal part of the coronary artery
- Calcified aorto-ostial lesions.
- Total occlusion of the coronary artery, when it is impossible to pass a coronary wire through it.

Complications

Complications that can accompany directional atherectomy are similar to those of PTCA. Among the main complications, one can mention the occlusion of a lateral branch (1-8%), arterial wall perforation (1%), spasm (2%), acute occlusion of the coronary artery (1-8%), and distant coronary artery embolization (0-13%) [22].

Data about the incidence of these complications are discrepant, but in most studies dealing with the issue, a higher incidence of distant coronary embolization was observed.

Mechanism

The mechanism of the arterial lumen increase after directional atherectomy is still subject to discussion. The atherectomy principle itself involves removal of atheromatous debris as the main mechanism of this increase. However, the comparatively large diameter of catheter for atherectomy allows to suggest that the device can just stretch the wall of the stenotic part of the vessel [27]. The contribution of the vessel wall stretching to the lumen increase during directional atherectomy was confirmed by the studies using intravascular ultrasound [17] and evaluating the volume of the tissue removed [20]. At the same time, a lot of modern works using intravascular ultrasound for the control showed that the main mechanism of action of directional atherectomy consists in the removal of tissue from the vascular wall [13, 23, 26,24]. Obviously, both factors contribute to the resulting increase of the artery lumen, and their correlation depends on the size of original stenosis and aggressiveness of the procedure. If a catheter for atherectomy passes through the occlusion or subtotal stenosis, it plays the role of a probe, which also contributes to increasing the arterial lumen after the procedure. If atherectomy is used for treatment of large arteries' stenosis, and large volumes of tissue are removed, the main role in the resulting lumen increase will be played by the volume of the tissue removed.

Clinical aspects of directional coronary atherectomy.

Among the most widely known multicenter clinical studies of directional coronary atherectomy, in three (CCAT, CAVEAT-I, BOAT) the results of atherectomy was compared to PTCA, and in one (CAVEAT II) - with coronary bypass surgery as the methods for the treatment of coronary stenoses. All those studies showed that atherectomy can provide a better extension of the coronary lumen than PTCA. As for the fate of patients, the results of studies are contradictory. In the CCAT study (6), 18 months after the procedure no difference was observed between the clinical state of patients after atherectomy or PTCA. The BOAT study (4) showed the best immediate results after directional atherectomy (residual stenosis of 15% as compared to 28%) and the best follow-up (the incidence of restenoses 31.4% as compared to 39.8%). In the CAVEAT-I study (8), also, the best immediate results of directional atherectomy were noted, but 6 months later the incidence of myocardial infarction and cardiac mortality in the group of patients who underwent coronary atherectomy was definitely higher. Thus, we have no compelling evidence of a significant advantage of directional atherectomy as compared to PTCA, and it is obvious that, when choosing between these two techniques, other things being equal, PTCA should be considered as the method of choice being cheaper and technically less complicated. Directional atherectomy should be reserved to the cases when PTCA does not allow to achieve the optimal result. Hence, atherectomy can be used for the treatment of superficial dissections developing after PTCA, though in this case the use of coronary stenting is considered be much more effective [12].

It is worth mentioning that from the technical viewpoint atherectomy is a more time consuming and more expensive procedure than PTCA. The cost of a catheter for atherectomy is higher than that of a coronary stent; diameter and rigidity of the device which are larger than those of a balloon catheter require more efforts when passing the stenosis, and the necessity of a precise orientation of the working window against the plaque increases the procedure duration as compared to PTCA. As a result of the above, at present directional atherectomy is rarely used as the isolated technique for coronary stenoses treatment, and is mostly combined with PTCA or stenting.

Today, coronary stenting is one of the most rapidly developing directions of interventional cardiology, and in the last 10 years this technique has significantly ousted directional atherectomy [1]. Stenting allows to substantially decrease the probability of intimal dissection, to achieve a larger arterial lumen than PTCA, and to decrease significantly the incidence of restenoses; with this its cost is comparable to that of atherectomy. The use of directional atherectomy in combination with coronary stenting is considered as one of possible fields of application of this method, particularly in complex lesions, when stenting itself can fail to provide optimal results. The SOLD research aimed at the study of the combination of atherectomy with stenting revealed the incidence of restenoses of 11%, which is two times less than the incidence of restenoses after a conventional stenting of coronary arteries. It is worth mentioning that the incidence of non-transmural infarctions after the use of atherectomy with stenting was higher than after of isolated stenting; for this reason such treatment tactics should be used for lesions with a high risk of restenosis (extensive stenoses with a proper diameter from 2.75 to 3.5 mm, bifurcational stenoses, aorto-ostial lesions, chronic coronary occlusions) [14,15].

Surprising results were obtained in the Japanese START study, in which the Palmaz-Schatz stents were implanted in 62 diseased segments, while in other 60 segments directional atherectomy under the control of ultra-

sound was performed. Immediate results of atherectomy and stenting were similar, but 6 months after the procedure, the ultrasound control revealed much more pronounced proliferation of neointima and much higher incidence of restenoses in stented portions (32.8% as compared to 15.8%) [25].

In case of a bifurcational lesion in the part subject to stenting, the use of atherectomy on the lateral branch provides better results than pre-stenting PTCA of the main branch. One of the studies included 67 patients who had a large diagonal branch originating from the stenotic portion of the left anterior descending artery (LAD) subject to stenting. The use of atherectomy (rotational or directional) in a stenotic diagonal branch significantly decreased the need for re-intervention as compared to PTCA of the diagonal artery [9].

Similar data were obtained regarding ostial lesions of major coronary arteries. In a study comparing two tactics of ostial lesions treatment, PTCA followed by stenting and atherectomy combined with stenting, it was shown that in this combination atherectomy increases the rate of the procedural success and decreases the probability of restenosing by two times [16].

One of the fields of use of directional atherectomy can be the treatment of restenoses after previous PTCA. Directional atherectomy is known to be an effective and safe procedure for treatment of restenoses [18]. The advantages of the combination of balloon angioplasty with atherectomy for treatment of in-stent stenoses as compared to isolated PTCA has been shown. The above tactics significantly decreased the probability of recurrent restenosis [18]. In most cases, atherectomy inside a stent is not associated with technical problems, though one case of balloon rupture after atherectomy has been reported [11].

Prospects of the technique.

The possibilities of atherectomy can be increased with further technical improvement of atherectomic catheters themselves, and firstly, the decrease of their external diameter and rigidity, which should improve their maneuverability, as well as assure a more reliable entrapping of the debris removed, thus decreasing the risk of distant bed embolization. Besides, the development of techniques of pharmacological support of the procedure, in particular, the use of IIb/IIIa inhibitors, can also decrease the probability of complications.

Improvement of tools for directional atherectomy resulted in the possibility to use the procedure in arteries of intermediate size (2.5-2.9 mm). A pilot study IVAT comprising 50 patients, proved a good efficiency of atherectomy in vessels of such diameter [5].

With the accumulation of the experience with the use of this procedure, some physicians begin to use atherectomy for treatment of the left main trunk. It is worth mentioning that in manuals supplied together with the tools for directional atherectomy manufacturers usually do not recommend to use them in cases of stenoses of the unprotected left main trunk. Nevertheless, the number of publications reporting successful use of atherectomy for the treatment of trunk lesions has been constantly increasing. South Korean authors compared the results of left main coronary artery stenting with the results of directional atherectomy combined with stenting. Both approaches allowed to achieve a technical success, no significant complications were seen during the intervention; however, the incidence of restenoses in the group of patients who underwent atherectomy combined with stenting proved substantially lower than in the group of patients who underwent only the stenting of the left main coronary artery. [19]

Our experience of application of the procedure.

In our practice of invasive cardiology, directional atherectomy, particularly on coronary arteries, is performed so rarely that each case of its practical application can be considered unique. We accumulated the experience of use of directional atherectomy in 12 patients. Some procedures were performed in the Medical Center of the Boston University, USA, in the Laboratory of D. Faxon in 1991; other procedures were performed in the Laboratory of Endovascular Treatment Techniques of the Russian Cardiologic Scientific Production Complex of the Ministry of Health of the Russian Federation. In 8 cases, the intervention was performed for the stenoses of the proximal part of LAD, 4 patients had a lesion of the right coronary artery. In 10 cases, the intervention was successful; in 1 case it was impossible to pass the catheter through a 90% stenosis of the right coronary artery, so we had to perform PTCA with subsequent stenting of the diseased artery. We saw no complications during the procedure and during the hospital stay after the procedure in patients after directional coronary atherectomy. In our practice we used Flexi-cut (Guident, USA), a device for atherectomy with an operating part 6 F in diameter, which allows to use a conducting catheter 8 F in diameter. There are three modifications of the device with different diameters of the operating part allowing to perform the procedure on vessels 2.5 to 2.9 mm, 3.0 to 3.4 mm, and 3.5 to 4 mm in diameter.

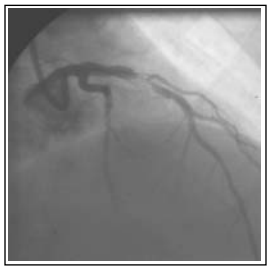


Figure 4. Stenosis of LAD in patient V. before PTCA

The first directional coronary atherectomy in Russia was performed in the Russian Cardiologic Scientific Production Complex of the Ministry of Health of the Russian Federation in 2001. Patient V., aged 55, was hospitali-zed with progressive unstable angina and the appearance of the attacks of rest angina. The patient had been suffering exertional angina for a year, six months before the admission he had an inferior MI after which attacks of angina pectoris became more frequent. Coronary arteriography showed an eccentric stenosis of the LAD, located at the level of origin of the 1st diagonal artery (Fig. 3). The proper diameter of the stenotic part of the artery was 3.6 mm. As the ostium of a large branch was situated within the stenotic part and the lesion was eccentric, we decided to use directional atherectomy. A Flexi-cut catheter was placed in the stenosis, then five passages of the cutting knife were performed (Fig. 4). After atherectomy, the stenosis severity decreased significantly, but a residual narrowing still remained (Fig. 6). It led us to implant a stent, and this resulted in a complete elimination of the residual stenosis (Fig. 7). Six months after the procedure, the patient underwent a control coronary angiography. No significant restenosis of LAD was seen (Fig. 8).

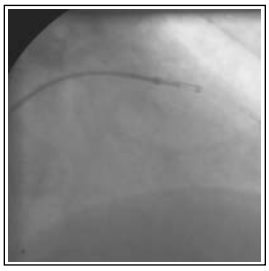


Figure 5. Flexi-cut is placed in the stenotis, the cutting knife passes along the window of the operating part

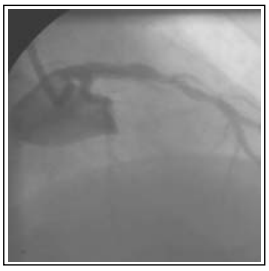


Figure 6. After the completion of directional atherectomy, the artery lumen significantly increased, but residual stenosis still remains

Conclusion.

Like any other method, atherectomy is

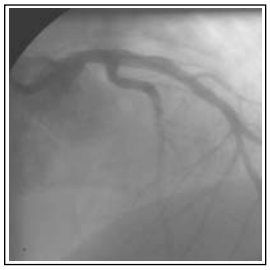


Figure 7. Stent Ephesos (NEMED, Turkey) is installed in the stenotis. The diagonal artery is wide patent

just one of the tools in the constantly growing range of invasive techniques. Consequently, it has certain advantages and disadvantages and its own indications for application. It is always the responsibility of an interventional cardiologist to take a decision about the choice of an intravascular intervention technique on the basis of his/her experience and preferences, but the technical availability of directional atherectomy and an experience of its performance undoubtedly extends the possibilities of a staff.

References

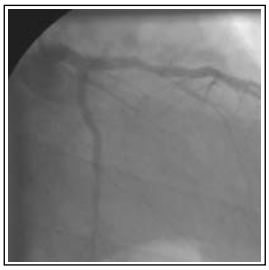


Figure 8. 6 months after directional atherectomy with stenting, no significant re-stenosis of LAD is seen

1. Samko A.N., Pavlov N.A. Coronary stenting. Moscow, 2001. p. 28.

2. Samko A.N., Savchenko A.P. Some modern directions of coronary angioplasty. Kardiologia, 1993, N 9, p. 62-27.

3. Chazov E.I. Place and role of high technologies in cardiological practice. Terapavtichesky Arkhiv, 1999, N 6, p.11-16.

4. Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, Feldman RL, Shani J, Senerchia C, Zhang Y, Lansky AJ, Popma JJ, Kuntz RE. Final results of the Balloon vs Optimal Atherectomy Trial (BOAT) Circulation 1998 Feb 3;97(4):322-31

5. Cannon L, Senior D, Feit F, Attubato MJ, Rosenberg J, O'Donnell MJ, Hirst J, Gibson M. Directional coronary atherectomy in intermediate sized vessels: final results of the intermediate vessel atherectomy trial (IVAT). Catheter Cardiovasc Interv 2000 Apr;49(4):396-400

6. Cohen EA, Sykora K, Kimball BP, Bonan R, Ricci DR, Webb JG, Laramee L, Barbeau G, Traboulsi M, Corbett BN, Schwartz L, Adelman AG. Clinical outcomes of patients more than one year following randomization in the Canadian Coronary Atherectomy Trial (CCAT). Can J Cardiol 1997 Sep;13(9):825-30

7. Dauerman HL, Baim DS, Cutlip DE, Sparano AM, Gibson CM, Kuntz RE, Carrozza JP, Garber GR, Cohen DJ. Mechanical debulking versus balloon angioplasty for the treatment of diffuse in-stent restenosis. Am J Cardiol 1998

8. Elliott JM, Berdan LG, Holmes DR, Isner JM, King SB, Keeler GP, Kearney M, Califf RM, Topol EJ. One-year follow-up in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT I) Circulation 1995 Apr 15;91(8):2158-66

9. Gambhir DS, Singh S, Sinha SC, Nair GM, Arora R. Treatment of true bifurcation stenosis by elective stent implantation in parent vessel and non-stent dilatation of side branch: immediate and follow-up results. Indian Heart J 2000 May-Jun;52(3):289-96

10. Gerald Dorros et al : Percutaneous Atherectomy for Occlusive Peripheral and Coronary Artery Disease. In: Techniques and Applications in Interventional Cardiology. Ed. Daniel L. Kulick, Shabudin H. Rahimtoola. Mosby Year Book, 1991,p.194-195

11. Gonschior P, Christian V, Berthold H, Franz-Josef N. Rupture of an angioplasty balloon after treatment of a recurrent in-stent restenosis-lesion of the left anterior descending coronary artery with directional coronary atherectomy. J Invasive Cardiol 2000 Feb;12(2):105-8Aug 1;82(3):277-84

12. Hofling B. Directional coronary atherectomy in coronary dissection? (Article in German). Z Kardiol 1996;85 Suppl 1:59-66

13. Matar FA, Mintz GS, Farb A, Douek P, Pichard AD, Kent KM, Satler LF, Popma JJ, Keller MB, Pinnow E, et al. The contribution of tissue removal to lumen improvement after directional coronary atherectomy. Am J Cardiol 1994 Oct 1;74(7):647-50

14. Moussa I, Di Mario C, Colombo A. Plaque removal prior to stent implantation in native coronary arteries: why? When? And how?: Semin Interv Cardiol 1998Jun;3(2):57-63

15. Moussa I, Moses J, Colombo A. Atherectomy plus stenting: what do we gain? Semin Interv Cardiol 2000 Dec;5(4):217-25

16. Muramatsu T, Tsukahara R, Ho M, Ito S, Inoue T, Akimoto T, Hirano K. Efficacy of directional coronary atherectomy before stent implantation for coronary ostial lesions. J Invasive Cardiol 2000 Sep;12(9):440-5

17. Nakamura S, Mahon DJ, Leung CY, Maheswaran B, Gutfinger DE, Yang J, Zelman R, Tobis JM. Intracoronary ultrasound imaging before and after directional coronary atherectomy: in vitro and clinical observations. Am Heart J 1995 May;129(5):841-51

18. O'Brien ER, Glover C, Labinaz M. Acute outcome with the flexicut directional coronary atherectomy catheter for the treatment of coronary in-stent restenosis. : J Invasive Cardiol 2001 Sep;13(9):618-22

19. Park S, Lee C, Kim Y, Lee J, Hong M, Kim J, Park S. Technical feasibility, safety, and clinical outcome of stenting of unprotected left main coronary artery bifurcation narrowing. Am J Cardiol 2002 Aug 15;90(4):374

20. Pels K, Heintzen MP, Motz W, Strauer BE. Mechanism of action of directional coronary atherectomy. Z Kardiol 1994 Nov;83(11):851-8

21. Simpson J.B., Robertson GC, Selmon MR: Percutaneous coronary atherectomy. Circulation 1988;78(suppl II):II-82

22. Stephan Windecker, Bernhard Meier. Intervention in coronary artery disease Heart 2000;83:481

23. Suzumura H, Hosokawa H, Suzuki T, Fukutomi T, Ito S, Itoh M. Comparison of dilatation mechanism and long-term vessel remodeling between directional coronary atherectomy and balloon angioplasty assessed by volumetric intravascular ultrasound.: J Invasive Cardiol 2002 Jun;14(6):315-20

24. Tenaglia AN, Buller CE, Kisslo KB, Stack RS, Davidson CJ. Mechanisms of balloon angioplasty and directional coronary atherectomy as assessed by intracoronary ultrasound. J Am Coll Cardiol 1992 Sep;20(3):685-91

25. Tsuchikane E, Sumitsuji S, Awata N, Nakamura T, Kobayashi T, Izumi M, Otsuji S, Tateyama H, Sakurai M, Kobayashi T. Final results of the STent versus directional coronary Atherectomy Randomized Trial (START) J Am Coll Cardiol 1999 Oct;34(4):1050-7

26. Umans VA, Baptista J, di Mario C, von Birgelen C, Quaedvlieg P, de Feyter PJ, Serruys PW Angiographic, ultrasonic, and angioscopic assessment of the coronary artery wall and lumen area configuration after directional atherectomy: the mechanism revisited. Am Heart J 1995 Aug;130(2):217-27

27. Umans VA, Haine E, Renkin J, de Feyter PJ, Wijns W, Serruys PW. The mechanism of directional coronary atherectomy. Eur Heart J 1993 Apr;14(4):505-10

CORONARY ANGIOPLASTY IN THE TREATMENT OF CORONARY ARTERY DISEASE WITH LOW LEFT VENTRICULAR EJECTION FRACTION: IS IT JUSTIFIED TO REVASCULARIZE THE NONVIABLE MYOCARDIUM?

S. A. Abugov, Y. M. Saakyan, R. S. Polyakov, M. V. Puretsky, O. V. Sankov, S. A. Davydov, I. V. Zhbanov

Russian Scientific Center of Surgery, RAMS

Abstract: The existence of viable myocardium in postinfarction area is one of the direct indications for coronary revascularization. At the same time there is no definite answer to the question: should the myocardial revascularization be performed in the absence of the clinical data of the myocardial viability.

Methods and results: 68 patients with coronary artery disease and left ventricular ejection fraction (LVEF)<35% were included in this study. According to the clinical data of patients the absence of viable myocardium in postinfarction area was detected. Depending on the strategy of the planned revascularization all patients have been divided into two groups: those who have to undergo complete revascularization (n=39, Group 1), and those who have to undergo only the revascularization of ischemic myocardium (n=29, Group 2). The successful revascularization has been achieved in Group 1 and Group 2 in 94,9% and 96,6% of cases (p>0,05) respectively, and immediate clinical success has been observed in 91,9% and 96,4% (p>0,05) respectively. The analysis of the long-term (24 months) clinical success and mortality rate didn't reveal any significant statistic differences between the groups.

Long-term clinical course and mortality of patients did not differ between the groups. During the 24 month of follow-up the clinical improvement was still evident in 65,5% of Group 1 patients, and in 62,5% of Group 2 patients (p>0.05). Mortality rate was 31,1% in Group1 and 31,2% in Group 2 (p>0.05).

Conclusion: coronary angioplasty is an effective method of treatment of CAD with LVEF<35%. The successful revascularization of nonviable myocardium in the patients included in the study has no effect on the clinical status and immediate as well as late mortality rate.

Keywords: coronary angioplasty, coronary stenting, low left ventricular ejection fraction, complete and incomplete revascularization.

Introduction

Coronary artery disease (CAD) is the main cause of mortality in the developed countries. It has been proved that chronical impairment of cardiac function due to ischemia is one of the leading causes of mortality from CAD. According to the Framingham Heart Study, about 80% of men and 65% of women die within 6 years after the onset of symptoms of congestive heart failure (CHF) [1]. At the same time it is worth to notice that the mortality rate of patients with ischemic CHF is 1,4-3,8 times higher than the mortality of patients with CHF of other etiology [2]. Ejection fraction (EF) is one of the main predictors of mortality in such cases. The CASS study [3] has demonstrated that four-year survival among the patients with CAD and EF of 35-49% was 71%, whereas for patients with EF<35% the rate of survival did not exceed 50%, despite the adequate drug therapy.

Meanwhile it has been revealed [4-6] that the adequate myocardial revascularization in patients with CAD and low LVEF contributes both to increase the LVEF and to improve the immediate and long-term prognosis. The presence of viable myocardium in infarcted area is one of the direct indications for revascularization.

However there is no agreement concerning the importance of revascularization of the nonviable myocardium. The aim of our study was to establish the immediate and long-term clinical results of coronary angioplasty for patients with the absence of viable myocardium in postinfarction area and inducible ischemia of LV myocardium in non-infarcted areas.

Materials and methods

The study included 68 patients with CAD and EF<35% chosen on the base of retro- and prospective analysis. All patients were male, their mean age was 58±6. All patients underwent complete clinical and instrumental examination. According to the data of dobutamine stress-echocardiography and/or myocardial thallium scintigraphy in none of the patients there was an evidence of the viable myocardium in infarcted area, although ischemia of other segments of the LV was detected. Coronary angiography revealed at least two-vessel disease in all patients: significant stenosis (>50%) or occlusion of the proximal LAD in combination with the significant stenosis (>60%) of circumflex artery (CxA) or right coronary artery (RCA).

Depending on the strategy of revascularization all patients were divided into two groups: those who have to undergo complete revascularization (n=39, group 1) and those who were scheduled only for the revascularization of ischemic myocardium (n=29, group 2). The complete revascularization means the elimination of all significant lesions in coronary arteries with the diameter more than 2,75 mm. The Group 2 consisted of 29 patients, which had to undergo only the revascularization of ischemic myocardium (functional revascularization). *The functional revascularization* means the elimination of all significant lesions in coronary arteries with the diameter more than 2,75 mm, supplying the viable myocardium.

Table 1. Clinical characteristics of the patients

	Group 1, n=39	Group 2, n=29
Age	59+5	61+4
Male	39 (100%)	29 (100%)
Angina pectoris*		
class III	21 (53,8%)	16 (55,2%)
class IV	18 (46,2%)	13 (44,8%)
Risk factors:		
Diabetes	4 (10,3%)	4 (13,8%)
Arterial hypertension	18 (46,2%)	16 (55,2%)
Smoking	24(61,5%)	19 (65,5%)
Myocardial infarction (MI)	39 (100%)	29 (100%)
Stage of CHF**		
I	11 (28,2%)	8 (27,7%)
IIa	28 (71,8%)	21 (72,3%)
LVEF, %	31+3	32+2

In all cases p>0,05

* According to the Canadian Cardiovascular Society functional classification

** According to the classification of N. D. Strazhesko, V. H. Vasilenko

Table 2. Angiographic characteristics of the patients

	Group-1 n=39	Group-2 n=29
LAD: occlusion	31 (79,5%)	22 (75,9%)
stenosis	8 (20,5%)	7 (24,1%)
Stenosis of the CxA	15 (38,4%)	11 (37,9%)
Stenosis of the RCA	24 (61,6%)	18 (62,1%)
Type of the lesion* of the RCA or CxA: A	4 (10,3%)	2 (6,9%)
B1	11 (28,2%)	9 (31,0%)
B2	19 (48,7%)	14 (48,3%)
C	5 (12,8%)	4 (13,8%)
Percent stenosis, %	82+15	81+14
Length of lesion (mm)	13.8+9	14.1+7

In all cases p>0,05

* According to the American College of Cardiology (ACC)/American Heart Association (AHA) classification

Both groups were comparable by the main clinical (table 1) and angiographic (table 2) characteristics.

The patients with left main coronary artery lesion (>50%), acute stroke 6 months before the inclusion and/or acute myocardial infarction (AMI), cardiac decompensation of the stages IIb-III according to the classification of N. D. Strazhesko, V. H. Vasilenko, coronary artery bypass surgery and/or coronary angioplasty were excluded from the study.

All patients received standard antiplatelet therapy before angioplasty. The patients received Ticlid (Ticlopidin) - 250 mg, 2 x day - started five days before the intervention, or Plavix (Clopidogrel) - 75 mg daily - started 3 days before it. The patients kept on taking those drugs for one month after the intervention. Aspirin (100 mg daily) was prescribed for a life-term. Immediately before the intervention a 10 000 IU bolus of unfractionated heparin was injected intravenously. Infusion of heparin (1200 IU per hour under ACT control) was continued during the first day after the procedure. Following types of stents were used: GFX, S670, BeStent, BeStent2 (Medtronic AVE, USA) and Crossflex, Crown, BxVelocity (Johnson & Johnson). The length of the stents was determined by the necessity to cover the stenotic segment completely and make the stent edges to lean on the unaffected wall of the coronary artery.

The success of the intervention at coronary stenting (CS) means angiographic success as judged by the absence of significant hospital clinical complications (death, myocardial infarction, emergency coronary artery bypass grafting - CABG, acute stroke). We define the angiographic success after coronary stenting as the absence of residual stenosis, dissections at stent edges and TIMI III flow restoration blood flow at least in one major epicardial coronary artery supplying the viable myocardium.

We define *immediate clinical success of stenting* as the absence of objective and subjective signs of myocardial ischemia and the improvement in functional class of angina by at least 2 classes.

The sustained clinical success of coronary angioplasty implies that the immediate clinical success can be observed for the next 24 months.

Results

Immediate success of coronary stenting was achieved in 65 out of 68 (95,8%) patients with CAD and LVEF<35%. At the same time the intervention was successful in 37 of 39 cases (94,9%) in the Group 1, whereas in Group 2 the success was achieved in 28 out of 29 cases (96,6%) (p=0.8). Total operative mortality was 2,9% (2 cases), AMI was observed in 1 case (1,8%) and mortality + AMI rate was 4,2% (3 cases). The only death in the Group 2 was caused by arrhythmia (ventricular tachycardia followed by ventricular fibrillation and asystoly) following the RCA predilatation. The left main coronary artery dissection and acute occlusion in the ostium of the CxA with rhythm disturbances were the reasons of death of one patient in Group 1. This injury appeared as the result of the guidewire ejection from the left main trunk after the attempted balloon catheter placement in occluded LAD segment. The second patient of Group 1 died from subacute stent thrombosis two days after successfully completed stenting of the circumflex artery (table 3).

In patients with successful intervention in Group 1 complete revascularization was achieved in 29 (78,4%) cases. The reasons of the incomplete revascularization in all 8 cases (21,6%) were the difficulties of recanalization of LAD. In 5 cases we failed to cross the occlusion by guidewire. In 2 cases we were not able to bring the balloon catheter to the occlusion (despite the successful guidewire recanalization), and once result was sub-optimal after the implantation of the stent in LAD (residual stenosis>20%).

No statistically significant differences were seen between the groups in terms of successful intervention and the quantity of the hospital complications.

The immediate clinical success was observed in 61 (93,8%) out of 65 patients with successful intervention. At the same time all 65 patients had no angina. However 4 patients (6,2%) complained of dyspnea at minimal physical activity. All differences between the groups were not statistically significant (table 4).

Hence, in the course of the analysis of the left ventricular ejection fraction after the intervention and in order to assess long-term clinical results we conducted the following changes in the groups. 5 patients from the Group-1 with the successful intervention but incomplete anatomic revascularization were transferred to the Group 2. Consequently the number of patients in the Group 1 came down to 29 and in the Group 2 went up to 32. Both groups were similar as before according to the main clinical and angiographic criteria. The only difference was in the amount of the revascularized myocardium.

Table 4. The immediate clinical results

	Group 1 n=37	Group 2 n=28	p
Immediate clinical success	34 (91,9%)	27 (96,4%)	p=0,8
Angina pectoris	0 (0%)	0 (0%)	-
Dyspnea at minimal physical activity	3 (8,1%)	1 (3,6%)	p=0,8

In general, left ventricular ejection fraction of the patients with CAD before and after revascularization increased in each group. In the Group 1 the pre-revascularization EF was 31±4% and it rose to 33±4% (p=0.04). In Group 2 the EF increased from 32±2% to 34±4% (p=0.01) after the intervention.

However the improvement in EF after revascularization did not differ significantly between the groups (table 5).

The long-term results of coronary stenting in Group 1 patients with EF<35% are shown on the diagram 1. In the course of the observation the progressive decrease of the clinical success rate was seen. At the same time the rise of the mortality rate was observed.

By the 24th month of the follow-up the clinical success rate was 65,5% (19 patients) and the mortality rate was 31,1% (9 patients).

Table 3. The immediate results of the intervention

	group 1 n=39	group 2 n=29	p
Success of the intervention	37 (94,9%)	28 (96,6%)	p=0.8
Death	1 (2,7%)	1 (3,4%)	p=0.6
AMI	1 (2,7%)	0	p=0.9
AMI + Death	2 (5,1%)	1 (3,4%)	p=0.8
Complete revascularization at the successful intervention	29 (78,4%)	not planned	

Table 5. The left ventricular ejection fraction before and after revascularization

	Group 1 n=29	Group 2 n=32	p
LVEF before revascularization	31±3	32±2	p=0,1
LVEF after revascularization	33±4	34±4	p=0,3

The situation was very similar in patients with functional revascularization (Group 2) (diagram 2).

By the 24th month of the follow-up the clinical success in the Group 2 was sustained for 21 patients (62,5%) and 10 patients died (mortality rate was 31,2%).

Comparing the clinical success and mortality rates between the groups with complete revascularization and functional revascularization no significant differences in the long-term follow-up was observed (diagrams 3 and 4).

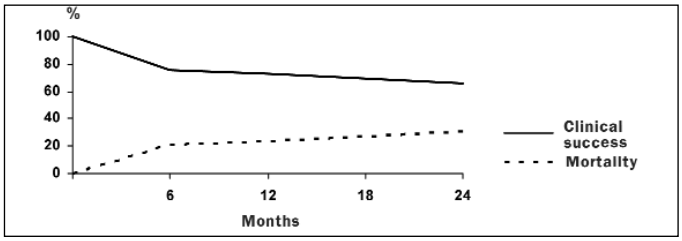


Diagram 1. The long-term clinical success and mortality in the group

The analysis of the long-term results showed that the decrease of the achieved clinical improvement of the patients was more commonly observed in the first 6 months after the intervention. In the group with complete revascularization the deterioration of clinical status was seen in 7 cases (24,1%) and in the group with functional revascularization the deterioration was observed in 9 cases (28,1). The deterioration of clinical results in both groups was accompanied by the rise of mortality rate.

Discussion

The exponential growth of coronary angioplasty procedures during the last decade is due not only with the less invasiveness of the procedure. First of all it is the result of significant progress in development of endovascular techniques and better accompanying and following medical therapy. Gradually coronary angioplasty as the special technique of myocardial revascularization has been introduced to those spheres where the advantages of coronary artery bypass grafting has been indisputable. First of all it concerns the patients with multi-vessel lesions with low left ventricular ejection fraction and comorbidities like diabetes. Certainly both types of revascularization can not be considered as competitive or alternative because they are just the elements of the complex treatment of CAD.

The present research proves the high efficiency of the coronary angioplasty in treatment of patients with CAD and multi-vascular coronary lesions and LVEF<35%.

In general, the immediate clinical success was achieved in 93,8% of all cases and had no effect on the strategy of revascularization. All patients, who had undergone the angioplasty both in the group with complete revascularization and in the group with functional revascularization, became free of angina. Only in 4 cases (6,2%) the dyspnea during light physical activity persisted. The high clinical efficiency of coronary revascularization may be referred to the fact that the patients included in the present study can be considered as the patients with a single-vessel lesion regarding the remains of the viable myocardium. That is why the incomplete but functionally adequate revascularization was quite enough for the disappearance of angina.

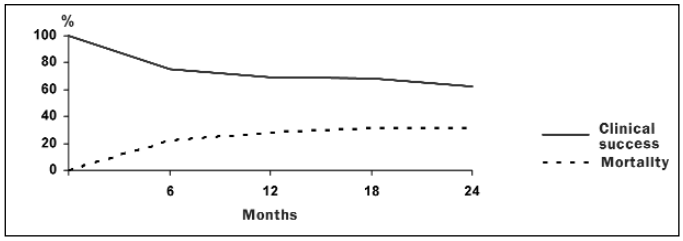


Diagram 2. The long-term clinical success and mortality in the group with functional revascularization (Group-2)

The question arises based on the successful immediate clinical results of our research: is there a neccessity to perform the revascularization of nonviable myocardium? There is no definite answer on this question. On the one hand, according to the data collected in the course of noninvasive examination of the patients included in our study there were no indications of viable myocardium in the large-focal postinfarction areas. Hence it was impossible to expect the full or partial restoration of the myocardial function in these segments of the LV. However on the other hand, both the dobutamine stress-echocardiography and Thallium scintigraphy have definite sensitivity and specificity in detection of viable myocardium [7-9]. Even the combination of those techniques can not be taken as the absolute criterion for the exclusion of the viable myocardium existence. That is why the only indisputable argument is the fact that the final decision on the expediency of the artery restoration can be made only retrospectively after revascularization. At the same time one of the main indications of the revascularization efficiency is the improvement of LVEF. The fact that the "open" artery may serve potentially as the collateral donor at occlusions in other coronary basins helping to avoid the development of fatal myocardial infarction (MI) proves to be the additional argument in favor of full anatomic revascularization.

Such convincing arguments induced us to carry out the analysis of the long-term survival rate and clinical efficiency of coronary angioplasty for the patients included in the study with different strategies of revascularization.

Analysis of the EF after coronary angioplasty in the group with complete revascularization revealed significant increase of the LVEF (from 31±3% to 33±4%, p=0.04). However the same changes were observed in the group with incomplete revascularization. The present results may be explained in the following way. First of all the accuracy of the size measurement

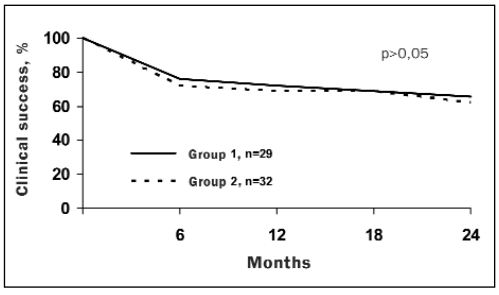


Diagram 3. The long-term clinical success in the groups with complete (1) and functional (2) revascularization

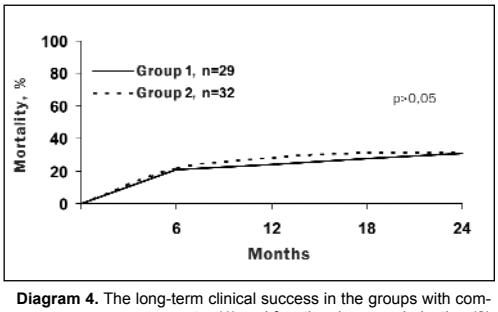


Diagram 4. The long-term clinical success in the groups with compete (1) and functional revascularization (2)

of the LV, the calculation of its volume and the ejection fraction have the certain limitations. The degree of inaccuracy in measuring diastolic and systolic size of the LV may vary from 5 to 10%. According to J. Gottdiener et al. [10] calculations the changes of the EF over the range of ±5% may not be taken into account because they are the results of unavoidable measuring inaccuracy of echocardiography. On the other hand, the increase of the LVEF may really occur. First of all it is connected with the restoration of the myocardial contractility and/or the development of the hyperkinesia of those segments of the LV with preexisting ischemia.

Concerning the long-term survival rate and clinical efficiency no statistically significant differences between the groups were detected. The largest percentage rate of deterioration of clinical state along with the increase of mortality rate was detected in both groups during the first 6 months. Most likely the reason for this is restenosis of coronary arteries that is observed in 17-32% of all cases after coronary stenting during the first 6 months. Further deterioration of clinical state of the patients with CAD and EF<35% in both groups in the following period of observation referred to the increase of severity of cardiac decompensation and progression of coronary atherosclerosis. According to the present results, complete revascularization of the patients with the proven absence of the viable myocardium in the area of cardiosclerosis has no effect on the long-term survival rate. Most likely the structural and functional changes of the LV in the process of postinfarction remodeling continue even after the elimination of the ischemic factor.

Conclusion

Our study allows to draw the following conclusions:

1. Coronary angioplasty is an effective technique in the treatment of patients with CAD and the LVEF<35%.
2. The revascularization management had no effect on the immediate clinical success of coronary angioplasty in patients with CAD and EF<35%.
3. The successful revascularization of the nonviable myocardium in patients with CAD and EF<35% has no effect on immediate and long-term clinical course and mortality.

References

1. Kannel WB, Kannel C, Paffenbarger RS, Cupples LA :Heart rate and cardiovascular mortality: the Framingham Study. // Am Heart J 1987 Jun 113: 6 1489-94
2. Adams KF Jr, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, Jensen LR, Tomasko L, Koch G. Relation between gender, etiology and survival in patients with symptomatic heart failure. // J Am Coll Cardiol 1996 Dec;28(7):1781-8
3. Mock, M.B., Ringvist, I., Fisher, L.D., et al.: Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. // Circulation 662. 1982.
4. Pierard L.A. Comparison of approaches in the assessment of myocardial viability and follow-up of PTCA/CAGB. The role of echocardiography // Am.Heart J. 1997 vol.18 p.764
5. Shivalkar B., Maes A., Borgers M. et.al Only hibernating myocardium invariably shows early recovery after coronary revascularization // Circulation 1996 vol.94 p. 308-315
6.Van der Berg E.K., Popma I.I., Dehmer G.I. et al. Reversible segmental left ventricular disfunction after coronary angioplasty // Circulation 1990 vol.81 p.1210-1216
7. Afridi I, Kleiman N.S., Raizner A.E., Zoghbi W.A. Dobutamine echocardiography in myocardial hibernation. Optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty // Circulation, 1995, vol.91,p.663-670
8. Rocco T.P., Dilsizian V., McKusick K.A. et.al Comparison of tallium redistribution with rest reinjection imaging for detection of viable myocardiym // Am.J.Cardiol. 1990 vol 66 p. 158-163
9. Guidelines for Clinical Use of Cardiac Radionuclide Imaging // JACC 1995:521-47 Vol. 25, No. 2 February
10. Gottdiener JS, Livengood SV, Meyer PS, Chase GA. Should echocardiography be performed to assess effects of antihypertensive therapy? Test-retest reliability of echocardiography for measurement of left ventricular mass and function.// J Am Coll Cardiol. 1995;25:424-30.
11. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease: Stent Restenosis Study Investigators. // N Engl J Med 1994;331:496 -501.
12. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease: Benestent Study Group. // N Engl J Med 1994;331:489 -95.

TIPS AND TRICKS IN ANGIOPLASTY FOR CHRONIC TOTAL OCCLUSION

Shigeru Saito[1]

General Hospital ShonanKamakura, KamakuraCity, Japan

Abstract

The success rate of percutaneous coronary intervention (PCI) has been continuously improved. However, PCI for chronic total occlusion (CTO) is still technically challenging. We have to understand the pathology of CTO lesions in order to improve the success rate of PCI in these lesions. In this article, several tips and tricks for these lesions are shown.

Keywords: Tapered-tip guidewire, Hydrophilic-coating guidewire, Double guidewire technique, Anchor-balloon technique, Deep engagement, Over-the-wire support system.

Significance and indication of PCI for CTO lesions

Successful recanalization of chronic total occlusion (CTO) of coronary arteries by percutaneous coronary intervention (PCI) can not only reduce the need for subsequent coronary artery bypass surgery but also increase the long-term survival of patients [1][2][3]. These long-term beneficial results are based on several effects produced by the opening of CTO lesions:

1) successful opening of CTO lesions reduces distal ischemia,
2) this reduction in distal ischemia improves regional wall motion,
3) the improvement in regional wall motion leads to the electrical stability and the decrease of ventricular arrhythmias,
4) the improvement in regional wall motion also improves global geometry of the left ventricle,
   and
5) the opened artery can work as the collateral source artery for the opposite arteries.

Based on these possible effects of successful recanalization, we can define the indication of angioplasty in CTO lesions. These include:

1) clinical evidences for partially or completely reversible ischemia in the distal myocardium,
2) CTO lesions without evidences of distal ischemia in patients with multivessel disease, where the other lesions had been successfully treated by PCI,
3) CTO lesions with complete distal necrosis in patients with several coronary risk factors, where the risks of acute coronary syndrome in the opposite arteries are considered not very low in future.

Pathology of CTO lesions

Plaques in CTO lesions are composed of dense fibrous tissue, loose fibrous tissue, cellular fibrous tissue, calcium, pultaceous debris, foam cells, and lymphocytes infiltration without foam cells [4]. Histological examination and their 3 dimensional reconstruction study in 10 patients with chronic total occlusion > 1 year revealed 4 types of occlusion classified according to the presence of a tapering or abrupt types of occlusion, and to the presence or absence of a loose fibrous tissue mass penetrating continuously from the proximal to the distal site of the occlusion [5][Figure 1]. In each type, there are small vascular channels coursing from the proximal lumen, which cannot be visualized by the premortem coronary angiograms. The diameter of these small vascular channels ranges from 160 to 230 micrometers. Generally, it is difficult to detect a coronary artery < 300 micrometers in diameter with coronary cineangiography [6]. This limitation of cineangiography might be improved by the introduction of the modern high-resolution digitalized angiography. However, even the digitalized angiography cannot detect these small channels, since antegrade flow through these channels may disappear as a result of decreased pressure gradient by the presence of collateral distal flow.

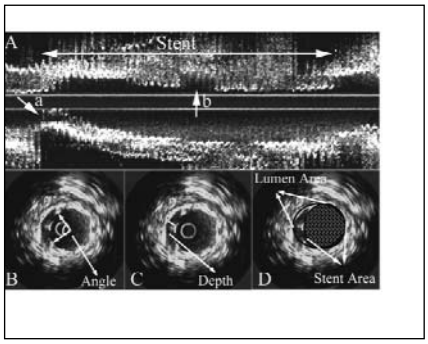


Figure 1. Pathology of CTO Lesions

When we should quit the procedure?

Although successful recanalization of CTO lesions is beneficial for the patients, we have to decide how long to continue or when to quit the procedure. If we spend longer time for the attempt of PCI in CTO lesions, the success rate might be increased. However, the plot of the success rate versus the elapsed time follows the horizontal parabolic line. On the other hand, if we spend longer time, adverse effects to the patients by increased radiation exposure or contrast dye will increase directly parallel to the elapsed time. According to our retrospective analyses [7], the following guidelines when we should quit the PCI procedure for CTO lesions are reasonable, since we could get the overall success rate of >80%; 1) time from the arterial access to the successful penetration of a guidewires through the occlusion <= 30 minutes, 2) total procedure time <= 90 minutes, and 3) total dye volume <= 300 ml.

Definitions of CTO lesions

Generally, CTO lesions are defined as the lesions with TIMI 0 antegrade flow and the duration of occlusion >= 3 months. However in several literatures, the lesions with TIMI 1 antegrade flow or the duration of occlusion < 3 months buy >= 1 month are also included. The duration of occlusion is defined as the interval from the last diagnostic coronary angiograms with total occlusion in patients with the previous angiograms, or from the first onset of clinical symptoms suggesting the ischemic heart disease in patients without the previous angiograms to the timing of the coronary intervention. PCI success is generally defined as the successful recanalization of the CTO lesions with resultant TIMI 3 flow without any adverse events.

Predictors for success in PCI for CTO lesions

Several predictors for failure in PCI for CTO lesions have been identified. Those include:

1) the lesions not in the left anterior descending artery, especially in the right coronary artery,
2) the duration of occlusion > 3 months,
3) CTO lesions in triple vessel disease,
4) the presence of bridge collaterals,

[1] Shigeru Saito, MD, FACC, FSCAI, FJCC
Division of Cardiology & Catheterization Laboratories,
Heart Center of ShonanKamakura General Hospital
1202-1 Yamazaki, Kamakura City, Japan 247-8533
Phone: +81-467-46-1717,
Facsimile: +81-467-46-1907
E-mail: saito@shonankamakura.or.jp

5) the abrupt type of occlusion,
or
6) the longer lengths of the occlusion [2] [8] [9].

Tips in PCI for CTO lesions

Tips in angiography before and during PCI

It is very important to take coronary angiograms in detail, so that we can know the types of occlusion (abrupt or tapered), the presence of bridge collateral, the presence of branches that can indicate the passage of the main route, or the collateral arteries. High-resolution digitalized angiography is essential, but bi-plane angiography is not essential. If the ipsi-lateral coronary angiography cannot show the artery distal to the occlusion through the collateral filling, contra-lateral simultaneous angiography is necessary. In this situation, uni-lateral femoral puncture is preferred to bi-lateral puncture.

Tips in the selection of arterial access sites

Transfemoral coronary intervention (TFI) is preferred to transradial coronary intervention (TRI) in PCI for CTO lesions, since the former approach can provide the stronger back-up support by the guiding catheters of 7 or 8 French in diameter, compared to 6 French guiding catheters used usually in TRI. In case of bi-lateral coronary angiographies, TFI is easier to do it. However, TRI can also result in reasonable success rate in PCI for CTO lesions, if case selection is adequate [7].

Tips in guiding catheter selection

Especially in PCI for CTO lesions, it is essential to choose those guiding catheters, which can provide the strongest back-up support.

For the lesions in the right coronary artery (RCA), standard Judkins' right curve is the 1st choice. For the inferiorly oriented RCA, the multi-purpose type works well. Left Amplatz's or Hockey-Stick type is chosen in order to increase the back-up support. However, these guiding catheters can easily make a severe intimal dissection from the ostium of RCA, and must be used very cautiously. If RCA shows a Shepherd-Crook type, the internal mammary guiding catheter works well.

For the lesions in the left anterior descending artery (LAD), the standard left Judkins' curve (JL) is essential. If we use the short-tip JL curve, the deep-engagement of the guiding catheters can be done more easily. Left Voda curve (from Boston-Scientific, USA), EB (eXtra Back-up from Cordis, USA), EBU (Extra Back-Up from Medtronic, USA), or GL (Geometric Left from Guidant, USA) curves are also used to increase the back-up support.

For the lesions in the left circumflex artery (LCX), the groups of the Voda or left Amplatz's curve are preferable.

Tips in guidewire selection

There are essentially 3 types of PCI guidewires; namely regular, tapered-tip and hydrophilic-coating guidewires.

1. *Regular guidewires:*

For regular guidewires, there are several types of different stiffness; from floppy or intermediate to standard guidewires. In Japan, we have very stiff guidewires in this group, Miracle-6, 9 and 12 (Asahi Intech, Japan). These numbers mean how many grams are necessary to bend the tip of each guidewire. Intermediate guidewire has almost 3 grams stiffness in this manner.

2. *Hydrophilic-coating guidewires [Figure 2]:*

For hydrophilic-coating guidewires, there are 3 types of guidewires in the market: Choice-PT floppy, intermediate or standard (Boston-Scientific, USA), Whisper-LS

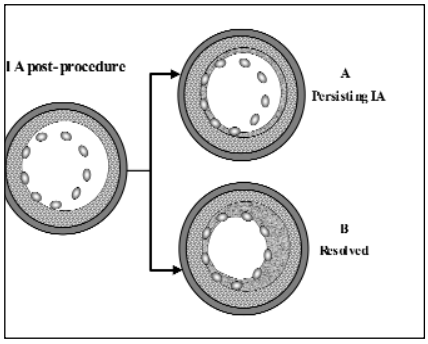


Figure 2. Hydrophilic-Coating Guidewire in PCI for CTO Lesions

or MS (Guidant, USA) and Crosswire-EX (TERUMO, Japan). These guidewires have the lowest friction resistance against the vessel wall or lesions. If the stiffness of CTO lesion is not so high, these guidewires work well. However, if the stiffness of the lesion is high, the tip of these slippery guidewires can easily create the false lumen under the intima.

3. *Tapered-tip guidewires [Figure 3]:*

For tapered-tip guidewires, there are 2 types of guidewires in the market: Cross-it (Guidant, USA) and Conquest (Asahi-Intech, Japan). Cross-it has the tip tapered to 0.010 inches in diameter and several types of stiffness (from Cross-it 100 similar to intermediate type, 200 or 300 to the stiffest one, Cross-it 400). Conquest has more tapered (0.090 inches) and stiffer tip than Cross-it 400.

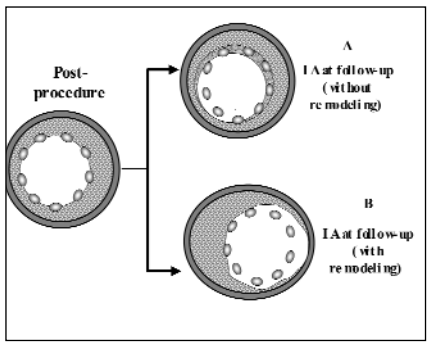


Figure 3. Tapered-tip guidewire in PCI for CTO Lesions

The most common cause of procedure failure in CTO lesions is inability to cross the lesion with a guidewire [8][Figure 4]. For the penetration by guidewires, the small vascular channels must be the easiest ways to pass through. It can be expected that PCI guidewires with tapered-tip end advances through these small channels more easily than conventional guidewires, since its tip diameter (254 micrometers for Cross-it) is closer to the diameter of these channels. Also, it is expected that hydrophilic guidewires can advance more easily through these small channels by its lower friction with the tissue than the conventional guidewires [10]. Since the dense fibrous tissue is hard for the penetration by guidewires, the 2nd easiest way for the guidewire passage will be through the loose fibrous tissues. The careful manipulation of the intermediate-strength guidewires, whose tip is bent by 45 to 90 degrees at the distal 2 to 5 mm, can lead the guidewires through the loose fibrous tissues. However, the intermediate-strength guidewires cannot penetrate the border between the loose and dense fibrous tissues. At this point, we can advance the OTW support system and exchange the guidewire to the stiffer one with tapered-tip end (Cross-it 300 or 400, or Conquest). This stiff and tapered-tip guidewire has bigger possibility to penetrate through the dense connective tissues into the distal true lumen than conventional guidewires, and could improve the success rate of PCI in CTO lesions from 64% before

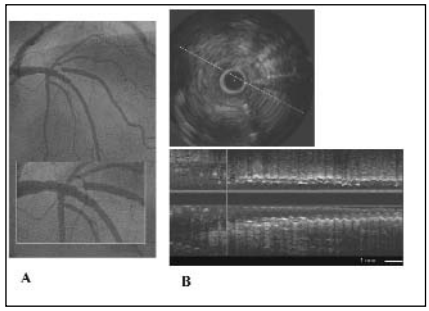


Figure 4. Reasons for Failure in PCI for CTO Lesion in ShonanKamakura General Hospital between April 1997 and December 1999

1999 to 89% in the year of 2001 in Shonankamakura General Hospital [7].

Over-the-wire support system

Over-the-wire (OTW) support system is helpful in PCI for CTO lesions, since it can improve the torque control of the guidewires as a result of the reduced friction between the guidewire shaft and vessel wall, it can support the tip of the guidewire, and it can enable the guidewire exchange, when it is advanced near the CTO lesions. For the OTW support system, we can use a 1.5 mm or 2.0 mm OTW balloon, or infusion catheters like Excelsior (Boston-Scientific, USA) or Transit (Cordis, USA).

Double guidewire technique

Double guidewire technique is helpful, when the 1st guidewire goes into the side branch [Figure 5] or the false lumen [Figure 6]. The 1st guidewire can occlude not only the entry into the false lumen, but also modify the arterial geometry and also become a landmark for the navigation of the 2nd guidewire. Thus the 2nd guidewire can more easily find the true lumen than the 1st guidewire. In this situation, the tapered-tip guidewires are considered more adequate for the 2nd guidewire than the conventional guidewires, because they could create the channel different from the channel created by the 1st guidewire owing to their stiff and tapered tips.

How to increase the penetration power through CTO lesions

1. In order to increase the penetration power of a guidewire:

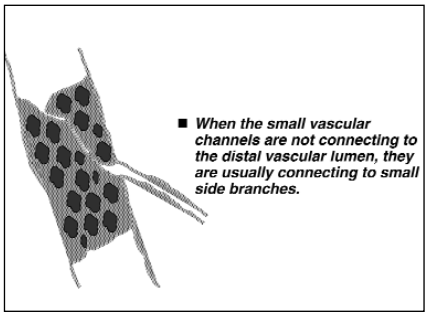


Figure 5. Double Guidewire Technique in CTO Lesions

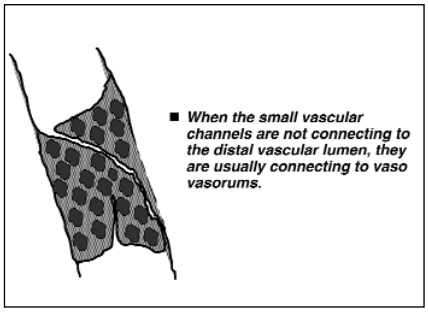


Figure 6. Double Guidewire Technique in CTO Lesions

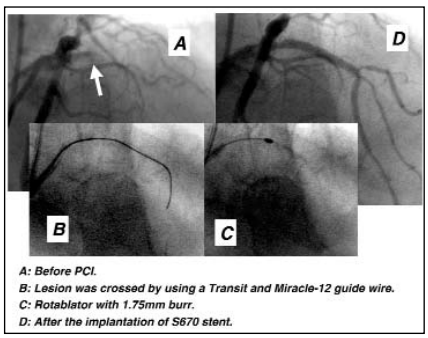


Figure 7. Case O.A., PCI for Calcified CTO Lesion in LAD

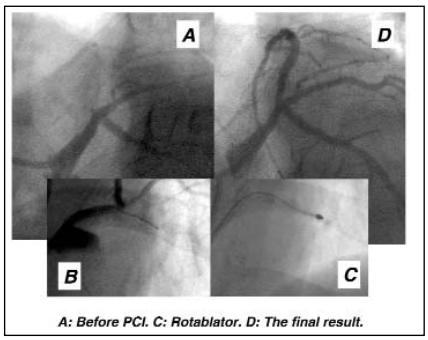


Figure 8. Case S.Y., PCI for Calcified CTO Lesion in LAD

a) To advance the OTW support system near the lesion;
b) To inflate the OTW support balloon at the proximal normal part by low (4 - 6 atmospheres) pressure and lock the support system to the coronary artery.

2. In order to increase the penetration power of a balloon catheter:

a) To insert the tip of a guiding catheter deeply into the coronary artery over the balloon catheter (Deep engagement technique);
b) To insert another guidewire and balloon catheter into the small branch proximal to the lesion, and inflation the balloon in the small branch in order to lock the guiding catheter against the coronary artery (Anchor-balloon technique).

Debulking strategy for CTO lesions [Figure 7][Figure 8]

It is reasonable to do debulking for CTO lesions, since these lesions contain more plaque material than not-occluded lesions. For the debulking strategies, we have 2 methods such as directional coronary atherectomy (DCA) and Rotablator. The actual problem in using these devices is that we have to exchange the guidewires to device-specific guidewires (Flex-wire for DCA and Rotawire for Rotablator). For this purpose, we can utilize the OTW support system. Also, there is a risk of making arterial rupture or perforation after the debulking strategies. The true efficacy of the debulking strategies in CTO lesions has not yet been confirmed.

Stenting for CTO lesions

Stenting can provide a better angiographic result, a better long-term clinical outcome and a lower incidence of re-occlusion in the follow-up period compared to balloon angioplasty after the successful recanalization of CTO lesions [11][12][13]. Even after stenting for CTO lesions, the angiographic restenosis rate is not as good as stenting for non-occlusive lesions. However, stenting can obviously decrease the re-occlusion rate [Figure 9][Figure 10].

Tricks in PCI for CTO lesions

When we use a very stiff or hydrophilic-coating guidewire in PCI for CTO lesions, perforation of the coronary artery and subsequent extravasation may happen. Fortunately, these complications generally do not lead to cardiac tamponade. If the extravasation continues, the 1st thing to do is to occlude the site just at or proximal to the extravasating site by low-pressure inflation of a balloon catheter. The 2nd thing to do is to neutralize heparin by giving protamine sulfate.

The artery, which had previously a bypass graft at the distal part to the CTO lesion, frequently shows an unnatural bent at the site of the bypass anastomosis. This bent is confusing [Figure 11].

Conclusion

Still even now, PCI for CTO lesions is technically challenging. However, if we follow the

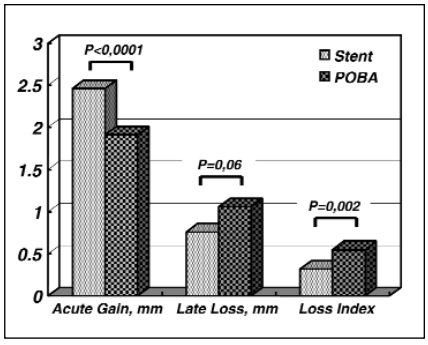


Figure 9. Importance of Stent Implantation after Successful PCI for CTO

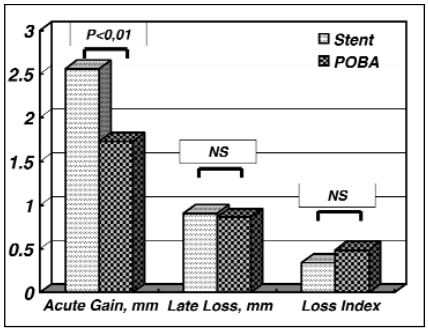


Figure 10. Importance of Stent Implantation after Successful PCI for CTO – SPACTO Trial

proposed guidelines and use several tips, we can achieve a reasonably high success rate in angioplasties for these lesions.

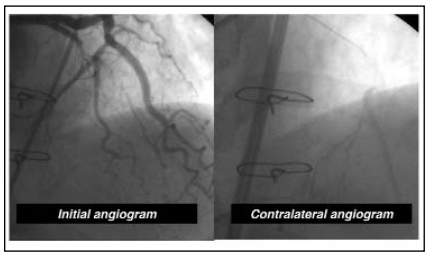


Figure 11. PCI for CTO Lesion in LAD, which had a previous LIMA graft (occluded)

References

1. Warren RJ, Black AJ, Valentine PA, Manolas EG, Hunt D. Coronary angioplasty for chronic total occlusion reduces the need for subsequent coronary bypass surgery. Am Heart J 1990; 120: 270-4.

2. Ivanhoe RJ, Weintraub WS, Douglas JS Jr, Lembo NJ, Furman M, Gershony G, Cohen CL, King SB 3rd. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Primary success, restenosis, and long-term clinical follow-up. Circulation 1992; 85: 106-15.

3. Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, Johnson WL, Rutherford BD. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. J Am Coll Cardiol 2001; 38: 409-14.

4. Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of atherosclerotic plaques in the four major epicardial coronary arteries in acute myocardial infarction and in sudden coronary death. Circulation 1989; 80: 1747-56.

5. Katsuragawa M, Fujiwara H, Miyamae M, Sasayama S. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion and short and long occluded segments. J Am Coll Cardiol 1993; 21: 604-11.

6. Stadius ML, Alderman EL. Coronary artery revascularization. Critical need for, and consequences of, objective angiographic assessment of lesion severity. Circulation 1990; 82: 2231-4.

7. Shigeru Saito, MD, FACC, FSCAI, Shinji Tanaka, MD, Yoshitaka Hiroe, MD, Yusuke Miyashita, MD, Saeko Takahashi, MD, Shutaro Satake, MD, Kazushi Tanaka, MD. Angioplasty for Chronic Total Occlusion by Using Tapered-Tip Guidewires. Catheter Cardiovasc Interv 2003: in press.

8. Puma JA, Sketch MH Jr, Tcheng JE, Harrington RA, Phillips HR, Stack RS, Califf RM. Percutaneous revascularization of chronic coronary occlusions: an overview. Am Coll Cardiol 1995; 26: 1-11.

10. Corcos T, Favereau X, Guerin Y, Toussaint M, Ouzan J, Zheng H, Pentousis D. Recanalization of chronic coronary occlusions using a new hydrophilic guidewire. Cathet Cardiovasc Diagn 1998; 44: 83-90.

9. Noguchi T, Miyazaki MD S, Morii I, Daikoku S, Goto Y, Nonogi H. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. Catheter Cardiovasc Interv 2000; 49: 258-64.

11. Hoher M, Wohrle J, Grebe OC, Kochs M, Osterhues HH, Hombach V, Buchwald AB. A randomized trial of elective stenting after balloon recanalization of chronic total occlusions. J Am Coll Cardiol 1999; 34: 722-9.

12. Lotan C, Rozenman Y, Hendler A, Turgeman Y, Ayzenberg O, Beyar R, Krakover R, Rosenfeld T, Gotsman MS. Stents in total occlusion for restenosis prevention. The multicentre randomized STOP study. The Israeli Working Group for Interventional Cardiology. Eur Heart J 2000; 21: 1960-6.

13. Rubartelli P, Niccoli L, Verna E, Giachero C, Zimarino M, Fontanelli A, Vassanelli C, Campolo L, Martuscelli E, Tommasini G. Stent implantation versus balloon angioplasty in chronic coronary occlusions: results from the GISSOC trial. Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche. J Am Coll Cardiol 1998; 32: 90-6.

USE OF BALLOON MITRAL VALVULOPLASTY IN HIGH-RISK PATIENTS

Kochkina T.A., Kokov L.S., Protopopov A.V., Timoshenko K.V.

Regional Clinical Hospital of Krasnoyarsk,
Vishnevsky Institute of Surgery, RAMS, Moscow

Abstract: We discuss the experience with balloon valvuloplasty of the mitral valve in 14 patients who were not suitable for transcatheter surgery. Immediate and remote results of the intervention are presented.

Keywords: catheter balloon valvuloplasty, mitral stenosis.

Introduction

Common development of transcatheter techniques of intravascular and intracardiac surgery in various pathologic states resulted in a prompt increase of the number of interventions performed in this field of modern medicine. The mastering of methodical approaches, professional skills, and improvement of surgical tools result in the broadening of indications for transcatheter interventions, increasing the spectrum of clinical conditions of patients with various diseases. In particular, a randomized study showed that, provided favorable anatomical conditions, the results of catheter balloon valvuloplasty (CBV) are comparable the results of surgical correction of mitral stenosis (1), and a study of national registeres revealed that most CBV in developed countries are performed in patients with severely diseased mitral valve (2).

Recently, the Russian clinical experience with CBV was limited, while the activity of cardiac surgeons with open commissurotomies and mitral valve replacement kept growing. That is why we present our own experience with CBV in patients who are not suitable for a transcatheter intervention, in order to illustrate the possibilities of the technique.

Materials and techniques

CBV following the Silin-Sukhov technique (5) was performed in 14 patients with mitral valve stenosis. The age of patients varied from 36 to 57 years. All the patients were in III-IV class according to NYHA. Two patients previously had a closed commissurotomy. Four patients (28.5%) had a permanent or a paroxysmal form of atrial fibrillation. Three patients (21.4%) had an aortic valve disease with predominant insufficiency, and six patients (42.8%) additionally had a moderate mitral valve insufficiency.

The average area of a mitral valve was 1.21 + 0.23 cm^2. In four patients (28.5%), it was less than 1 cm^2, and in the remaining, the area of the mitral valve initially did not exceed 1.5 cm^2. Hemodynamic significance of mitral stenosis was confirmed by values of systolic blood pressure in the pulmonary artery, where it was increased up to 53+12.2 mm Hg in average.

Qualitative assessment of morphological alterations of the mitral valve according to the results of EchoCG confirmed the presence of marked lesions of cusps and subvalvular structures in all patients. Pre-operational state of the patients was assessed using the system of ranged distribution of the signs of mitral valve lesions and the indices of central hemodynamics suggested by L.S. Kokov in 1992 (Table 1).

The use of a complex ranged assessment (CRA) on the basis of several signs (including echomorphometric and hemodynamic) allows not only to fully evaluate a patient's condition before the operation, but also to correctly predict the effectiveness of CBV.

The maximal CRA score is 32. All our patients had this index over 28, four patients had the maximal score 31.

CPV consists of several stages: right heart catheterization, transseptal punction (TSP) and left heart catheterization, passing of a dilatation balloon into the mitral orifice,

Table 1. Ranged distribution of the signs of mitral valve lesion and the indices of central hemodynamics

Sign	Score	Characteristic of the sign
Mobility of cusps of the valve	1	- high valve mobility with the limitation on the cusps' edges; the EF velocity ≥ 40 mm/sec;
	2	- limited mobility, the EF velocity 40-30 mm/sec;
	3	- rigid valve, the EF velocity 30-20 mm/sec;
	4	- the minimum movement of cusps, the EF velocity < 20 mm/sec;
Cusps' thickness	1	- nearly normal thickness of the cusps - 2-3 mm;
	2	- thickening of the cusps's edges up to 4-6 mm;
	3	- thickening of the entire cusp up to 6-8 mm;
	4	- cusp's thickness > 8 mm;
Calcification	0	- none;
	1	- isolated foci with increased echo density
	2	- small areas of increased echo density up to 2 cm in one of the cusps;
	3	- areas of increased echo density merge into large foci, but are limited in the cusp tissue;
	4	- merged areas of increased echo density fill the outlines of cusps and pass over the limits of the fibrous ring;
Lesion of subvalvular structures	1	- thickening of the chords in the attachment sites up to 6 mm, chord bundles are differentiated, the amplitude of the chords' motion i 15 mm;
	2	- thickening of the chords up to 8 mm involves 2/3 of the length, the inter-chordal distance J 10 mm;
	3	- thickening of the chords up to 10 mm, the distance between bundles 5-10 mm;
	4	- chords' thickness i10 mm, they are shortened, non-differentiated and pull cusps into the LV cavity, amplitude of motion 3 to 5 mm;
Initial area of the mitral valve	1	- ≥2.0 cm^2;
	2	- 1.5 - 1.99 cm^2;
	3	- 1.0 - 1.49 cm^2;
	4	- ≤ 1.0 cm^2;
Size of the left atrium	1	- ≤ 30.0 mm;
	2	- ≤ 40.0 mm;
	3	- ≤ 50.0 mm;
	4	- > 50.0 mm;
The maximum gradient of pressure on the mitral valve	1	- ≤ 15 mm Hg;
	2	- ≤ 20 mm Hg;
	3	- ≤ 25 mm Hg;
	4	- > 25 mm Hg;
Systolic pressure in the pulmonary artery	1	- ≤ 30 mm Hg;
	2	- ≤ 50 mm Hg;
	3	- ≤ 80 mm Hg;
	4	- > 80 mm Hg.

[1] Protopopov A.V.,
Department of Radiosurgical Diagnostics and Treatment Techniques,
Regional Clinical Hospital,
660049, Krasnoyarsk, P. Zheleznyaka street, 3 A
e-mail: invcard@online.ru

and valvuloplasty itself. Right heart catheterization during the operation has control and diagnostic functions and does not differ from usual diagnostic manipulations. The role of TSP significantly increases, because during the operation this procedure transformd into a surgical approach. It should be mentioned that TSP technique in various forms and at different stages of the disease has its own particularities. Marked mitral stenosis is accompanied by the development of atriomegalia. The interatrial septum bulges towards the right atrium, and it becomes difficult to find the fossa ovalis with the catheter's tip. For this reason we performed the intervention under the control of transesophageal echocardiography. The intraoperative control with a transesophageal sensor significantly increases the precision of TSP procedure, thus increasing safety and effectiveness of the entire operation.

After TSP of the left atrium and registration of pressure curves, a transseptal guide was used to place a rigid wire with a soft, specially shaped tip into the cavity of the left atrium. The guide was removed. Dilatation of the punctured hole in the septum was performed for an unimpeded and nontraumatic conduction of the dilatation balloon catheter to the mitral valve and back. For this purpose, a balloon catheter 8 mm in diameter was used.

After dilatation of the punctured hole in the septum, we started the advancement of the rigid wire conductor previously placed into the left atrium, into the left ventricle through the mitral valve This manipulation was performed with the use of a guiding catheter passed from the left atrium to the apex of the left ventricle with a careful advancing of the tip of the wire followed by the removal of the guiding catheter. Then, a Silin-Sukhov dilatation catheter was passed over the wire. After the balloon was placed in the mitral valve position, it was inflated. Upon the completion of the balloon valvuloplasty, the catheter was taken off the wire and removed from the vessel.

All operations were finished by removal of catheters and introducers, manual hemostasis, and application of a compressing bandage for 24 hours. Postoperative drug regimen included fractionated low-molecular heparin, and antibiotics.

Results

Direct results of CBV of the mitral valve were evaluated on the basis of EchoCG data and invasive measurement of pressure in the right heart. The operation resulted in the increase of the mitral orifice area by more than two times. On the average, this value increased to 2.9+0.53 cm^2. Gradient of the mitral valve decreased by 2.3+0.51 times in average. Pressure in the right heart also decreased, and the most evident decrease was seen in patients with initially high pulmonary hypertension. The dynamics of pulmonary artery pressure were observed for several days after CBV; in 6 (42.8%) patients it was completely normalized.

Sinus rhythm resumed spontaneously in two patients, in other two cases sinus rhythm was restored with the help of cardiac version.

No complications related to CBV were observed.

All patients were discharged in a satisfactory state in NYHA functional class no higher than I.

Long-term results of CBV of the mitral valve stenosis were followed up to 5 years. The follow-up control included general clinical analyses, ECG, EchoCG. During the observation period, no lethal outcomes. All 14 patients received standard antirheumatic prophylaxis. Development of restenosis of the mitral valve in 2 years with a narrowing of the mitral orifice up to 50% as compared to the postoperative value was registered in two patients (14.2%). As a result of restenosis, one patient had a recurring atrial fibrillation, and his cardiac failure worsened, so he had repeated catheter valvuloplasty. In other patients, no signs of the worsening were observed, 10 patients resumed active labor activity.

Discussion

Catheter balloon valvuloplasty (CBV) for correction of mitral stenosis was first suggested in Japan by Professor K. Inoue's group in 1984. Starting from 1987, clinics of Kirov Military Medical Academy and Vishnevsky Institute of Surgery, RAMS, were the first to begin to implement these operations in our country. Despite 15-years use of CBV in Russia, the technique never became wide-spread in clinics of cardiac surgery in this country. According to statistical data, during the last five years, CBV of mitral stenosis was performed only in 6 Russian hospitals, and the total number of interventions does not exceed 40-45 per year (3). In spite of the existence of numerous scientific works by Russian authors (4, 5), reflecting the experience with the use of the original technique suggested by V.A. Silin and V.K. Sukhov, CBV never occipoed the due place in the treatment of mitral stenosis in Russia.

The presented experience with the use of mitral CBV in patients who are not suitable for a transcatheter intracardiac intervention allows to hope for wider use of this direction of interventional cardiology in Russian clinics of cardiac surgery. Carrying out of catheter operations with satisfactory immediate and long-term results proves high effectiveness of this technique, even for patients with marked morphological signs of rheumatic stenotic process. The use of intraoperative transesophageal EchoCG control allows to perform sophisticated intracardiac manipulations with disturbed anatomy safely and with maximal effectiveness.

References

1. Turi Z.G., Reyes V.P., Raju B.S., et al. Percutaneous balloon versus surgical closed commissurotomy for mitral stenosis: a prospective, randomized trial. Circulation 1991; 83: 1179-1185.

2. Herrmann H.C., Feldman T., Isner J.M., Bashore T., Holmes D.R. Jr., Rothbaum D.A., Bailey S.R., Dorros G. Comparison of results of percutaneous balloon valvuloplasty in patients with mild and moderate mitral stenosis to those with severe mitral stenosis. The North American Inoue Balloon Investigators. Am. J. Cardiol. 1993; 71(15): 1300-3.

3. Bokeria L.A., Gudkova R.G. Cardiovascular Surgery - 2001. Diseases and Congenital Anomalies of the Blood Circulation System. M.: Publishing House of Bakoulev SCCVS, RAMS, 2002, p.26.

4. Kokov L.S. Percutaneous Catheter Balloon Valvuloplasty for Patients with Mitral Stenosis. Thesis of the Doctor of Medicine, Moscow, 1992.

5. Sukhova I.V. Immediate and Long-term Results of Mitral Stenosis Treatment Using the Catheter Balloon Valvuloplasty Technique. Thesis of the Candidate of Medicine, St.Petersburg, 2000.

ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS AND ANEURYSMS OF ILIAC ARTERIES

Z.A. Kavteladze, A.P. Korshok , D.S. Kartashov, S.A. Drozdov, D.P. Dundua, A.M. Babunashvili, K.V. Bylov, O.V. Gordina[1]

The Center of endosurgery and lithotripsy in Moscow

Abstract

Endovascular repair of abdominal aortic aneurysms and aneurysms of iliac arteries were performed in 76 patients. Endoprosthesis placement was conducted in 63 patients with abdominal aortic aneurysms and in 13 patients with isolated aneurysms of iliac arteries. The original stent-graft device and stent delivery system were applied by the authors. The results of two different stages of the study are presented. At the first stage (1995-1998) ZA stent with polyethylene coating have been used. At the second stage (1999-2001) the ZA stent with Dacron coating was applied. At the same time the original technique of the surgical intervention characterized by the separate percutaneous delivery of the stent and graft with their assembling inside the vessel lumen was used. Five international patents for all the devices and operation techniques have been received. At the first stage good results were achieved in 31of 47 patients (65,9%) and at the second stage endovascular repair was successful in all 29 cases. Good results were achieved in all 13 cases with isolated aneurysms of iliac arteries. In the course of 75 months of the follow-up 17 (22,36%) patients died. The six-year survival rate comes to 77,64%.

Key-words: abdominal aortic aneurysm, iliac artery aneurysm, endovascular repair, stent-grafts, vascular endoproprosthesis

Introduction

Abdominal aortic aneurysm (AAA) is a life-threatening disease. During the 5 years after the disease has been diagnosed 50% of patients experience the rupture of aneurysmatic sac leading to fatal hemorrhage. According to various authors the prevalence of AAA comes from 2 up to 5% of men at the age after 60. In the USA about 15 000 people die from different complications of AAA annually. Aortic aneurysm occupies the 10th place among the main causes of death in men over the age of 55 years (1).

Despite the significant progress in surgical treatment of AAA, the operative mortality is still quite high (5-30% at elective surgical interventions, 20-68% at emergency interventions) (2). The period of rehabilitation is quite long which is mainly related to the significant intraoperative trauma. The risk of surgical intervention increases due to the considerable frequency of concomitant diseases.

Development of endovascular technique and general technological progress led to elaboration of a new technique of surgical treatment of abdominal aortic aneurysms. This technique is less traumatic than surgery. Endovascular treatment consists in separation of the aneurysmatic sac from blood flow with the use of a special device consisting of a metallic stent and a woven vascular graft.

During endovascular repair of AAA the stent and tissue prosthesis are introduced inside the aneurysmatic sac without laparotomy via arteriotomy or percutaneous transfemoral approach. The aneurysmatic sac is isolated from bloodstream preventing the possibility of the rupture of thin arterial walls. The minimal invasion, reduced risk of the surgical intervention, dropping rate of postoperative complications and their severity lead to the increase of number of patients (including those who were not accepted for standard reconstructive surgical operations), which may undergo the aneurysm repair.

Endovascular repair of thoracic and abdominal aortic aneurysms with the use of Z-stents coated with Dacron was performed for the first time in experimental study in dogs in 1987 by D. Lawrence and his coworkers (USA).

The first endovascular repair of abdominal aortic aneurysm in the clinical practice was performed in 1991 by X. Parody and his colleagues in Argentina (3).

During the past 10 years about 10 devices for endovascular repair of aortic aneurysms were developed, almost 20 000 patients were operated on. However as a matter of fact this operation remains innovative and prospective.

The treatment of abdominal aortic aneurysm and aneurysms of iliac arteries remains a serious problem. On the other hand, imperfection of the devices for endovascular repair of vascular aneurysms and of delivery systems, applied today in the world, give the reasons to continue the efforts to find out less invasive and less traumatic methods of treatment.

Since the end of the 80-ies we (Z.A.Kavteladze, A.P.Korshok) have been conducting scientific and research works on development of new Nitinol self-expandable stent. Nowadays 3 modifications are developed, the last of which is recognized on the world medical market under "ZA stent" brand name (William COOK EUROPE A/S, Denmark). Certain constructive features of this stent allowed us to start our research devoted to the problem of endovascular treatment of aortic aneurysm. Using the metal stent as the internal frame we coated it with polyethylene (the first stage of clinical studies, 1995-1998) or thin Dacron (the second stage of clinical studies, 1998-2001). At the same time first we used the stent and polyethylene fixed along the perimeter of proximal end of the metal stent as the single device. At the second stage of our study we introduced the new scheme of the intervention when the weaved vascular graft of Dacron and metal stent were delivered inside the aorta separately with the subsequent assembling into a single device inside the vessel. In both cases the diameter of the delivery system did not exceed 16 F that let us to perform the operations percutaneously. Such operative technique was used to conduct the intervention without use of general anesthesia, incisions and significant hemorrhage with the minimum trauma.

We suggested an original stent, a device for endovascular repair of aneurisms (see fig. No. 1 and 2) and its delivery system, as well as a technique of the intervention, which were granted international patents (6, 7, 8, 9, 10).

[1] Prof. Z.A.Kavteladze,
Department of cardiovascular surgery
Center of endosurgery and lithotripsy,
111123, Moscow , shosse Entuziastov, 62
zaza@celt.ruz

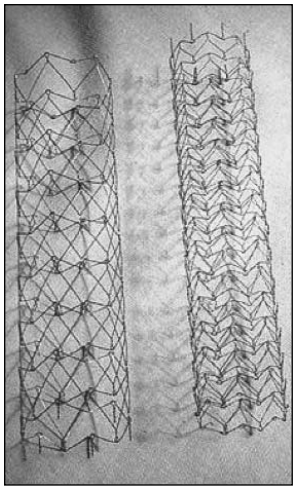


Figure 1.

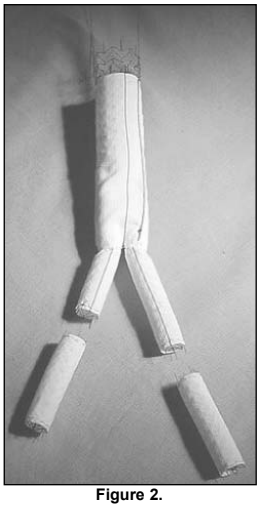


Figure 2.

Taking into account the advanced age of most patients and the considerable amount of concomitant diseases and significant surgical risk, the possibility of radical treatment of such patients by means of less traumatic and less invasive technique may save their lives.

On June 22, 1996 the linear endovascular repair of abdominal aneurysm was performed for the first time in the world from percutaneous approach without arteriotomy and general anesthesia. The patient was discharged three days after the operation (4).

On February 18, 1999 the first bifurcational endovascular repair of abdominal aneurysm was conducted from percutaneous approach (5)

Nowadays we have gained the experience of endovascular repair of abdominal aneurysms and iliac arteries in 76 patients. The AIM of the present study is the analysis of the devices used for endovascular repair of aortic aneurysms and systems of their delivery, regimens of interventions and achieved results of clinical studies.

Methods

Clinical studiy included 76 patients, among them 63 patients had abdominal aortic aneurysms with or without involvement of iliac arteries, and 13 patients had isolated aneurysms of iliac arteries.

At the first stage (1995-1998) applying the polyethylene coating we performed the following interventions: linear endoprosthesis placement in 32 cases; unilateral endovascular repair with cross-over femoro-femoral bypass and embolization of contralateral iliac artery in 4 cases; stenting of thrombosed aneurysms in 4 cases; endovascular repair of iliac arteries in 7 cases.

At the second stage (1998-2001) using the Dacron graft we performed the following interventions: linear stent-graft placemenent in 11 cases; unilateral endovascular repair with cross-over femoro-femoral bypass and embolization of contralateral iliac artery in 4 cases; bifurcational endovascular repair of AAA in 8 patients; stenting of iliac artery aneurysm in 6 cases.

70 patients were male and 6 were female. The mean age was 74,4 (from 50 to 87 years).

Risk factors: diabetes mellitus in 9 cases, smoking in 51 cases, essential hypertension of different stages in 42 cases, hyperlipidemia in 58 cases, cardiovascular diseases, other than aneurysm, in 45 cases, carotid lesions in 9 cases, chronic renal diseases in 41 cases, chronic pulmonary diseases in 31 cases. So the most common risk factors were smoking, hypercholesterolemia, essential hypertension and cardiac diseases.

Preoperative study:

Computed tomography was applied in 47 cases. All patients underwent angiography and ultrasonic duplex scanning. Nuclear-magnetic resonance was used in 5 cases. Only 6 patients underwent intravascular ultrasound study.

The basic diagnostic studies were the ultrasonic duplex scanning and angiography.

Ultrasonic duplex scanning was the main screening technique because it is a non-invasive and highly informative method of diagnostics. At the same time due to the application of modern ultrasonic devices it is possible to perform the precise topical diagnostics, define the size of the aneurysms and attached unaffected vessels, find out the presence of a clot inside the sac, reveal the relation of the aneurysm to renal, visceral and iliac arteries.

The next step in the diagnostic algorithm was computed tomography and nuclear-magnetic resonance imaging, which gives the detailed topical characteristics of the vascular lesion. Unfortunately some reasons made it impossible for us to apply these techniques in our study as often as we'd like.

Angiographic study

The results of angiographic study proved greatly important especially in the assessment of the internal lumen and the progress of aneurysm (using the special instruments such as measuring guide, catheters, rulers). Nowadays it is possible to conduct the densimetric studies for the determination of precise size of the lesion due to the modern angiographic equipment.

Before the technique of endovascular repair of abdominal aneurysm was introduced into practice the following criteria were of fundamental importance: the assessment of the size of aneurysm, presence of clots, information on the relation of the aneurysmatic sac to surrounding tissues, to the renal arteries and inferior vena cava. Recently new notions have been introduced, such as the internal lumen or the progress of aneurysm, internal bents, presence of the proximal and distal necks, availability of clots in the proximal neck, precise modeling of the process of endoprosthesis placing etc. There is the need in conducting the angiographic study to get the complete information of the mentioned characteristics.

As the percutaneous approach is widely used in the present study, the assessment of the femoral arteries deserves the special attention at angiographic study. The following parameters were assessed: the diameter, characteristics of atherosclerotic changes, possibilities of early bifurcation of femoral arteries. This made it possible to avoid the entry of the needle at the bifurcation of femoral arteries, perform puncture of one of the arterial walls, avoid the manipulation of the needle at the site of significant atherosclerotic changes, which, in its turn, facilitates the success of compressive hemostasis and promotes the prevention of false aneurysms formation at the arterial puncture site.

In 54 cases (71,05%) the aneurysm was diagnosed accidentally during the ultrasonic study examination.

In 41 cases (40,78%) the stenosis of renal arteries of different stages was detected, among which in 90% of all cases (37 patients) the stenosis of the left renal artery was observed.

Lesions of iliac arteries were observed in 11 (14,47%) cases, of femoral arteries in 9 (11,84%) cases.

Chronic venous insufficiency was observed in 3 (3,94%) cases, and chronic renal insufficiency was observed in 2 (2,63%) cases.

Patients' histories included strokes in 2 (2,63%) cases, stenosis of carotid arteries in 9 (11,84%) cases, infarctions in 17 (22,36%) cases, angina pectoris of different stages in 45 (59,21%) cases.

It is worth to notice that 54 (71,05%) patients were refused to reconstructive sur-

gery because of severe concomitant diseases.

Altogether 76 (100%) patients were operated on, among them 47 (61,8%) patients had the isolated abdominal aneurysm, 2 (2,63%) had the abdominal aneurysm with one of the iliac arteries involvement and 14 (18,42%) had the abdominal aneurysm with both iliac arteries involvement. Isolated aneurysms of iliac arteries were detected in 13 (17,1%) cases. In 4 (5,2%) cases separate abdominal aneurysms and aneurysms of iliac arteries have occurred.

Isolated aneurysms of iliac arteries were observed in 13 (100%) cases. One patient (7,69%) had bilateral isolated aneurysm of iliac arteries. In 5 (38,46%) cases an aneurysm of the right common iliac artery was detected. Two (15,38%) patients had aneurysm of the right common iliac artery with the propagation to the ostium of the right internal iliac artery.

In 2 (15,38%) cases the aneurysm of the left common iliac artery spread to the ostium of the left internal iliac artery. Aneurysm of the left common and external iliac arteries was observed in 3 (23,07%) cases. One patient (7,69%) had aneurysm of the left external iliac artery.

Accesses: right-side arteriotomic access was used in 8 (10,52%) cases, which are the clinical cases of the interventions combined with crossover bypasses.

The majority of patients - 68 of 76 (89,47%) were operated by percutaneous access: 62 patients (81,57%) through the right femoral artery, 6 (7,89%) patients - through the left femoral artery

Anesthesia: general anesthesia was not applied, local anesthesia was used in 33 (43,42%) cases, and the combination of epidural and local anesthesia was used in 43 (56,57%) cases.

Additional manipulations: peripheral angioplasty was performed in 24 (31,57%) cases, closure of the puncture site because of the false aneurysm formation was executed in 3 (3,94%) cases, the crossover femoro-femoral bypass was conducted in 8 (10,52%) cases, 5 patients (6,57%) had angioplasty of renal arteries, 8 patients (10,52%) underwent embolization of iliac artery, one patient (1,3%) had embolization of abdominal aneurysm and extra-anatomical bypass was performed in 1 case (1,3%).

The mean blood loss was 100 ml (from 50 to 1200 ml). The mean duration of the intervention was 55 minutes (from 25 to 180 minutes).

The clinical indication for endovascular repair of abdominal aneurysm with or without the transfer to iliac arteries was:

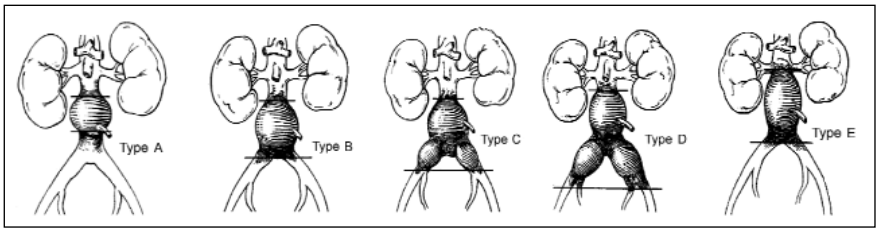
Abdominal aneurysm with the diameter more than 45 mm.

The clinical indication for conducting of endovascular repair of isolated aneurysm of iliac artery was:

Aneurysm of iliac artery with the diameter more than 18 mm.

As long as all manipulations are performed inside the vessel such angioarchitectural characteristics as internal lumen or internal progress of aneurysm and attached segments of aorta become of fundamental importance at determination of indications and contraindications for the endovascular interventions. In the clinical study the great attention was paid to the pre-interventional examination. Such techniques as ultrasonic duplex scanning, angiography, spiral computed tomography, magnetic resonance imaging, intravascular ultrasound study were applied. According to these complex data the detailed characteristics of the internal lumen of aneurysm were obtained, that was quite helpful at making the individual endoprosthesis for each patient. Unfortunately only ultrasonic and angiographic study was conducted in all cases. Other techniques were used when available.

Angioarchitectonic indications were: the presence of proximal neck of aneurysm in infrarenal segment of aorta with the length not less than 15 mm, with the distal cuff proximal to aortic bifurcation or with one or both iliac artery involvement before their bifurcation. These were types "A", "B", "C", "D" according to the scheme below.

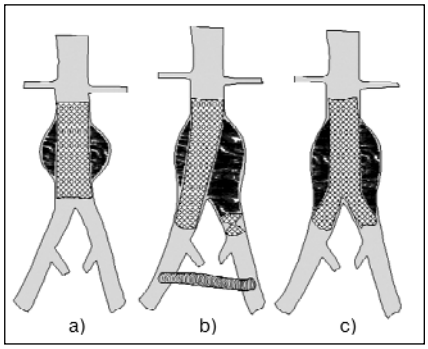


Contraindications were: absence of the proximal neck and the transfer of aneurysm to the bifurcations of iliac arteries - type "E".

Other contraindications for endovascular repair of abdominal aneurysm were as follows: bilateral occlusion of femoral or iliac arteries, significant iliac artery tortuosity and bends equal to almost 90 degrees, detection of clots in the proximal neck.

Altogether in the course of our study 3 types of surgical interventions were applied:

a) linear endoprosthesis placement



Types of the intervention

b) unilateral endovascular repair with crossover bypass and embolization of contralateral iliac artery

c) bifurcational endoprosthesis placement

In all patients with iliac artery aneurysms the linear endovascular repair was performed. In 7 cases it was combined with embolization of internal iliac arteries. The idea of embolization consists in elimination of retrograde blood flow to closed aneurismal sac.

Results

Study of the long-term results of endovascular repair of abdominal aneurysms and aneurysms of iliac arteries is one of the basic parts of the present research. The results of the study were followed for 1- 75 months. All patients underwent ultrasonic studies during their follow-up, in 46 cases angiographic study was conducted and computed tomograpy was performed in 33 cases. The mean duration of the follow-up was 12,6 months. The maximum time of observation came up to 75 months.

The assessment of the immediate results of the intervention regarding the degree of isolation of the aneurysmal sac was conducted according to the following criteria:

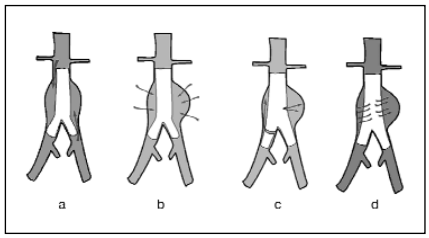
Good result - complete internal isolation of the aneurysm.

Satisfactory result - complete proximal isolation of aneurysm with insignificant distal leak.

Unsatisfactory result - the presence of proximal leak.

The assessment of the short- and long-term results regarding the degree of separation of the aneurysmatic sac was conducted according to the following the "types of leak":

a) proximal and distal leak
b) retrograde blood flow from lumbar and mesenteric arteries
c) crippling of the stent or coating



Types of leak

Table 1. The results of clinical studies

Result	Linear ER of AAA	Unilateral ER of AAA and AIA	ER of AIA	Stenting of AAA
Good (complete closure)	20 (62,5%)	4 (100%)	7 (100%)	-
Satisfactory (distal leak)	6 (18,75%)	-	-	4 (100%)
Unsatisfactory (proximal leak)	6 (18,75%)	-	-	-

d) porosity of the coating

Clinical cases

The clinical case: abdominal aneurysm with the transfer to iliac arteries.

Patient O., 70 years old, Case history No. 1462 of 22.06.1995. Diagnosis: aneurysm of infrarenal abdominal aorta, detected during outpatient ultrasonic examination. The size of aneurysm was 6,0 x 8,5 cm.

In the course of angiographic study the following parameters were detected: the proximal neck length 25 mm, diameter 22 mm and the distal cuff diameter 19 mm and length 18 mm.

The occurrence of favorable angioarchitectonics of aneurysm was the indication for linear endovascular repair of AAA

On 22.06.1995 linear endovascular repair of AAA was performed.

The length of the implanted stent was 120 mm, diameter 25 mm, the length of the polyethylene coating was 110 mm, diameter 25 mm. Expanded stent-polyethylene coating system made the aneurysmatic sac completely separated from bloodstream.

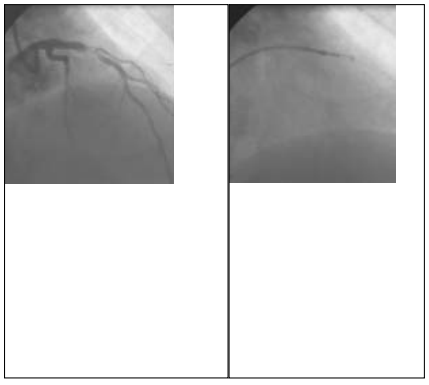


Figure 3. **Figure 4.**

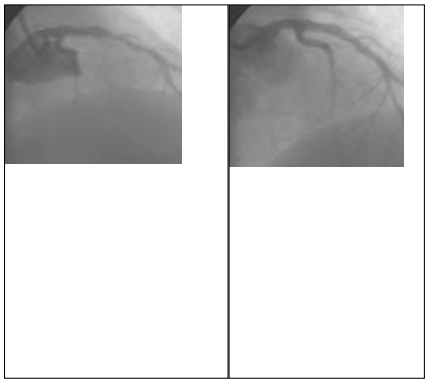


Figure 5. Follow up 12 months

Figure 6. Follow up 60 months

At control angiography the good visualization of the stent and abdominal aorta with its branches with the complete separation of the aneurysmatic sac without any indications for proximal and distal leak was observed. The patient was discharged 3 days after the intervention.

This clinical case is the first example of endovascular repair of abdominal aneurysm by means of percutaneous access.

Patient K., 65 years old, Case History No. 1339 of 04.04.1996

Diagnosis: abdominal aneurysm with both iliac artery involvement up to their bifurcation.

The results of the angiographic study: size of AAA was 6,5 x 8,0 cm. The length of the proximal neck is 20 mm, the diameter is 23 mm. The absence of the distal neck of aneurysm is detected as well as aneurysms of the both common iliac arteries and stenosis of the left renal artery equal to 35%.

Unilateral endovascular repair of abdominal aneurysm and left iliac artery with embolization of the right common iliac arteries and crossover bypass from the left to the right femoral artery was performed. (Figure 7, 8)

On figures No.3 and 4 angiograms before the intervention and immediately after the unilateral endovascular repair of abdominal aortic aneurysm with left iliac artery involvement and crossover bypass along with embolization of the right common iliac artery are represented. The length of the implanted stent was 150 mm with 25 mm diameter, and the length of the polyethylene coating was 145 mm with the diameter of 25 mm.

Intraoperational complications

The complications were observed in 2 cases:

In the first case during the passage of the system stent-polyethylene coating through iliac arteries the disruption of the stent coating was detected with the following dislocation of the coating into the superficial femoral artery. The coating was surgically removed through the arteriotomic access.

Access site thrombosis has occured in the second case. Thrombectomy was performed successfully.

All patients with the proximal leaks were advised the reconstructive vascular surgery. Because of the multiple concomitant diseases the open surgical intervention was performed only in 2 cases within 6 months after endovascular stenting. These 2 patients died immediately after the operation. The remaining 4 patients died of the abdominal aneurysm rupture within 72 months of the follow-up.

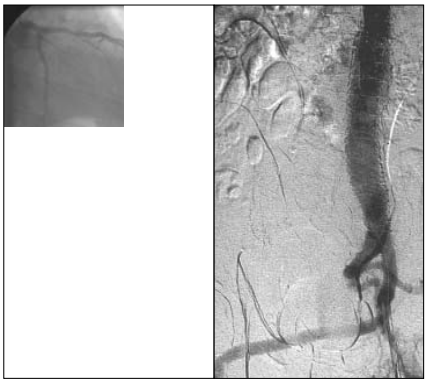


Figure 7. **Figure 8.**

Two out of 6 patients with the distal leaks died in the period from 1 to 72 months after the procedure; one death was caused by aneurysm rupture after linear endoprosthesis placement, another death was caused by cancer. Two patients had no particular complications and had the complete isolation of aneurysmal sac (12 months after endoprosthesis placement). The remaining 2 patients underwent reconstructive surgical interventions because of persistence distal leak (they were examined 12 and 26 months after endoprosthesis placement).

Among 20 patients with good immediate results after linear endovascular repair 16 patients were examined 1 to 75 months after the procedure. Four patients died of concomitant diseases.

In the group of patients with unilateral endovascular repair of AAA and AIA with crossover bypass and embolization of contralateral iliac artery 3 patients have been examined in the course of the follow-up. One patient died of myocardial infarction.

After the 1st stage of the study we noticed a high rate of satisfactory and non-satisfactory results in the group of linear endovascular repair of isolated abdominal aneurysms - 37% in total

The results were determined by:

1. The imperfection of the devices applied during the first stage of the study.
2. Possible exceeding of the indications for endovascular repair of abdominal aneurysms regarding the lack not only of the author's but also of worldwide clinical experience. This was the period of general international euphoria on the appearance of the new technique of the treatment of aortic aneurysms.

With this it is worth indicating that stents with the polyethylene coating were rather attractive due to their simplicity and small diameter (16 F) of the delivery system. However they allowed to perform the linear and unilateral endovascular repair of abdominal aneurysm and aneurysm of iliac arteries with the following crossover femoro-femoral bypass grafting. There was no possibility of bifurcational endovascular repair according to some technical problems.

Taking into account this defect, the absence of porosity of polyethylene for attachment of the coating to the vascular walls, and the possibility of perforation and rupture of the thin-walled tape, we had to look for another, more "usual" coating for the vascular surgery. That is why the ultra thin Dacron (Vascutec) was chosen.

At the second stage of clinical studies 29 patients were operated on. Complete internal separation of the aneurysmatic sac was achieved with the good result in all cases, among them 6 patients with isolated aneurysm of iliac arteries.

At the second stage of clinical studies we used the scheme of the intervention consisting of separate delivery of the vascular graft and metal stent into aorta with their subsequent assemblage into the single device. This original scheme of the intervention was used for the application of the delivering system with maximal diameter of 16 F that gave us, in its turn, the possibility to conduct the intervention by means of percutaneous approach.

By means of using the mentioned above technique of the intervention and introduced devices for endovascular repair of aneurysm we performed the bifurcational endovascular repair of abdominal aneurysm and aneurysm of iliac arteries percutaneously for the first time in the world clinical practice.

Patient K., 52 years old, Case history No. 748. Diagnosis: aneurysm of ifrarenal part of abdominal aorta with both iliac artery involvement or more precisely with the complete absence of the distal cuff. The size of aneurysm was 6,7 x 8,9 cm.

The bifurcational endovascular repair of AAA was performed.

The length of the main body of the bifurcational vascular graft was 110 mm, diameter 24 mm; the length of the cut branches was 5 mm. The length of the stent was 130 mm, diameter 25 mm. The diameter of iliac stent-graft was 12 mm, length 50 mm. The patient was discharged 3 days after the intervention.

Figures No. 9 and 10 show angiograms before the surgical intervention and immediately after the bifurcational endovascular repair of abdominal aneurysm and aneurysm of iliac arteries.

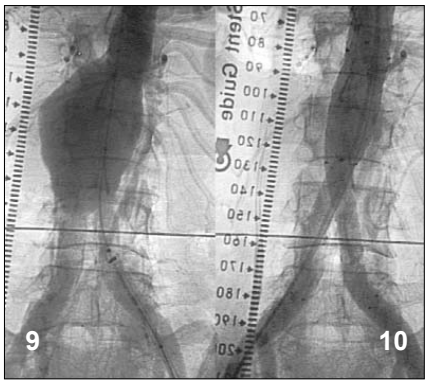


Figure 9, 10.

In the group of patients with linear endovascular repair of AAA 9 patients have been examined during the follow-up lasting from 1 to 30 months. No peculiarities were found.

In the group of patients with unilateral endovascular repair of AAA and AIA with crossover bypass grafting and embolization of contralateral iliac artery during the period of 1 - 30 months 3 patients have been examined. One patient died of myocardial infarction.

Seven patients have been examined in the group of patients with bifurcational endovascular repair of AAA and AIA 1 to 30 months after the procedure. One patient died of myocardial infarction.

Isolated aneurysms of iliac arteries.

In all 13 cases the positive result was achieved with the complete isolation of the aneurysmatic sac; seven of those patients underwent embolization of the internal iliac artery. One patient had bilateral aneurysms of both common iliac arteries with bilateral internal iliac artery involvement and he underwent the procedure for complete right-sided isolation of the aneurysmatic sac with the closure of the internal iliac artery and incomplete left-sided isolation in order to avoid the ischemia due to acute closure of the both internal iliac arteries. Later on (2-3 months) this patient was scheduled for the second left-sided operation to isolate the aneurysmatic sac. However the patient died in 2 months of concomitant diseases.

The characteristics of the surgical interventions depending on lesions localization.

Within 2 weeks after the procedure the thrombosis of the replaced segment developed in 1 patient case. After the repeated endovascular intervention the positive result was achieved.

During the follow-up from 2 to 72 months 11 patients underwent the examination. No occured events.

Table 2. The characteristics of the surgical inter ventions depending on lesions localization

Aneurysm localization	Type of the intervention	
	Linear ER	Linear ER and embolization of EIA
CIA	5	
CIA + IIA		4
CIA + EIA		3
EIA	1	

The clinical example

The isolated aneurysm of the right common iliac artery.

The patient B. T., 68 years old; diagnosis: the isolated aneurysm of the right common iliac artery. Diameter is 65 mm, length 43 mm. The patient had triple vessel CAD.

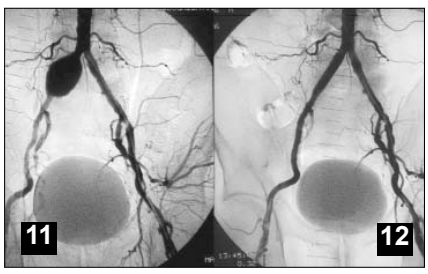


Figure 11, 12.

In the figures No. 11 and 12 angiograms before and after endovascular repair are represented.

In retrospective analysis of our results we used the program-scheme of the examination-observation of multicenter European study of endovascular repair of abdominal aneurysms "Eurostar" (88 centers in 29 countries, 2310 patients, the maximum follow up 60 months") (11).

Intraoperative events

Proximal leak - 6 cases.

Distal leak - 6 cases.

Retrograde perfusion from lumbar or mesenteric arteries - 2 cases.

Retrograde perfusion from internal iliac arteries - 0.

Intraoperational problems - complications

Related to:

- The system of the endoprosthesis - 1 case.
- Technical imperfection of the device - 3 cases.
- Impossibility to deliver the device into abdominal aorta - 5 cases.
- Migration of the endoprosthesis - 0.

Related to the process of the intervention:

- Transfer to the open operation - 0.
- Intraoperational mortality - 0.

Related to arterial complications:

- Thrombosis - in 1 case
- Embolism - 0.
- Damage of the ostia of renal arteries - 0.
- Other - 0.

Observation in intensive care unit - 8 patients.

The hospital stay varied from 2 to 23 days (4,3 days on average).

The main attention in drug therapy was paid to antibiotics. Heparin administration was restricted during the hospital stay and antiplatelet agents was advised for a month only in cases of endovascular repair of iliac arteries.

The short-term follow-up (up to 1 month).

Postoperative complications:

Related to systemic complications:

- Cardiac- in 1 case
- Cerebral - in 1 case
- Pulmonary - 0
- Renal - 0
- Hepatic - 0
- Septic - 0
- Other - 0

Related to the operation and applied devices:

- Stent migration - 0
- Thrombosis of the endoprosthesis - in 1 case
- Thrombosis of one branch - 0
- Repeated femoral intervention - 1 case
- Repeated abdominal intervention - 1 case
- Repeated extra-anatomical intervention - 0
- Laparotomy at complications - 0

Related to the access and complications in lower extremities:

- Haemorrhage, hematoma, false aneurysm - 3 cases
- Arterial thrombosis - in 1 case
- Peripheral embolism - 0
- Lymphorrhea - 2 cases
- Other - 3 cases

Comments: local complications such as haemorrhages, hematomas, arterial thromboses, embolism, etc., were observed in 6 (7,8%) cases.

Table 3. Final results of the terms of the follow-up: 1, 3 and 6 years

Events	Follow-up		
	1 year	3 years	6 years
Examined/ No events	39/29	15/11	1/1
Proximal leak	4	0	0
Leak through the tissue graft	1	0	0
Distal leak	4	0	0
Stenosis of the device: stent-graft	1	0	0
Flexure of the device: stent-graft	0	1	0
Migration of the device	1	1	0
Other	3	2	0

Table 4. Final results of the terms of the follow-up: 1, 3 and 6 years

Events	Follow-up		
	1 year	3 years	6 year
Migration of stent-graft	1	2	0
Stenosis of stent-graft	1	2	2
Thrombosis of stent-graft	0	0	0
Rupture of the stented aneurysm	2	2	1
Femoral interventions	0	0	0
Abdominal interventions	3	3	1
Extra-anatomical interventions	0	0	0
Mortality	6	9	2

Postoperative period and time of hospitalization

Taking into account that catheter systems we used were quite big in diameter (16 F) and, hence, created large puncture sites, we paid great attention to the thorough hemostasis (time of the manual hemostasis was less than 30 minutes; in 4 cases the manual hemostasis had to be continued up to 2 hours). After the tight bandaging with the application of compressive bandage we advised 48 hours of bed rest to avoid the false aneurysm formation. Hospitalization times were basically defined according to the condition of the access site and varied from 2 to 23 days (4,3 days on average). However we also include in this data the patients with false aneurysm formation at access sites (3 patients), and patients, who underwent arteriotomy. In the group of patients operated on only by means of percutaneous access the hospitalization period was 3,2 days.

Short- and long-term results

Short- and long-term results were evaluated in the follow-up that lasted 1 to 75 months. The assessment of the results was based on the data of the clinical examination, ultrasonic duplex scanning, spiral computed tomography, angiography and intravascular ultrasound study.

The main technique of assessment was ultrasonic duplex scanning, used for the assessment of the size of the aneurysm, patency of the endoprosthesis and its effectiveness, i. e. isolation of the aneurysmatic sac from blood flow, occurrence of the retrograde blood flow in the cavity of aneurysm, possible damage of a stent, rupture of the graft tissue, displacement of some parts of the device, etc. Non-invasive, highly informative technique of the duplex scanning makes it one of the basic methods in the practice of assessment of the results of the intervention.

Spiral computed tomography is also highly effective. It is quite reliable and is applied for defining of all mentioned results of endovascular repair of abdominal aortic aneurysms and aneurysms of iliac arteries. The defects of this technique are its high cost and X-ray exposure.

Intravascular ultrasound study is one of the most authentic techniques. However its application is limited by its high cost and invasiveness.

The following accidents were seen during the observation:

1. Migration of the metal stent (the first stage of the study) - in 3 cases. 2 patients underwent the reconstructive surgical intervention, 1 patient died of stented aneurysm rupture;

2. Stenosis of the device: stent-graft, was detected in 2 cases without any clinical complications;
3. Flexure of the stent-graft device was observed in 1 case without any complications;
4. Rupture of the coating (polyethylene) was detected in 3 cases. Two patients underwent the repeated endovascular intervention, and reconstructive surgical intervention was performed in 1 case;
5. Disruption of the coating from the stent took place in 1 case. The surgical removal was conducted by means of the femoral access;
6. False aneurysm at access site developed in 3 cases. Surgical closure of puncture site was performed.
7. Thrombosis of access site was detected in 1 case. Thrombectomy was performed;

During the 75 months period 17 patients (22,36%) died, among them 5 patients (6,5%) died of replaced aneurysm rupture. 10 patients died of other reasons. Two patients died after reconstructive vascular surgery carried out for unsatisfactory results of endoprosthesis replacement. Four patients died of aneurysm rupture after endovascular repair. They belong to the group of patients with unsatisfactory results with the occurrence of proximal leak in the area of the aneurysmatic neck of abdominal aorta, except one patient from the group of patients with satisfactory results and occurrence of distal leak. Six-year survival rate was 77,64%.

Figure 13.

We failed to deliver the device for endovascular repair in the aorta because of extreme angulations of iliac arteries in 5 cases (these patients were not included in the clinical study).

Figure 13. Angiogram 60 months after linear endoprosthesis replacement. This is the first patient of the clinical study. The stent has clear-cut edges, no deformation, damage of leak in the aneurysmatic sac is detected. The lateral branches remain in the stenting level (there is no coating at this place).

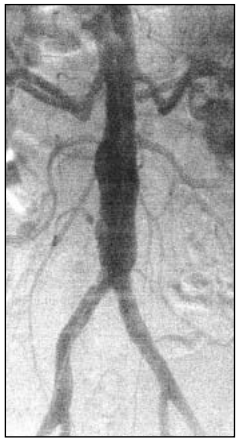


Figure 14

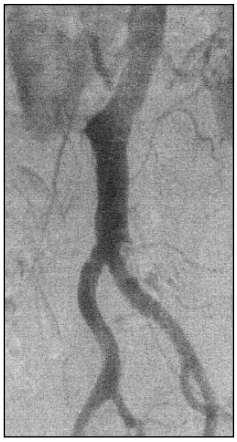


Figure 15

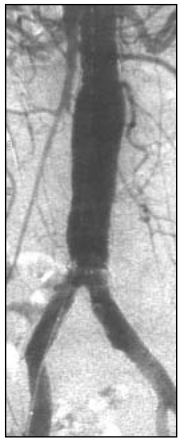
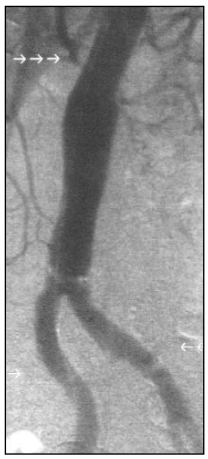


Figure 16



Figue 17

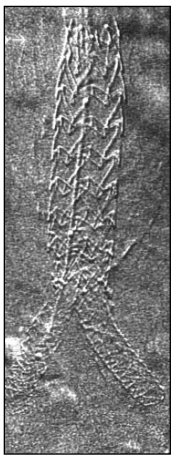


Figure 18

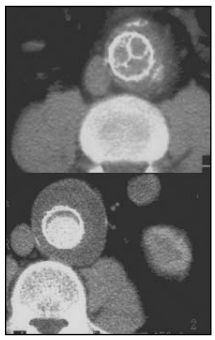


Figure 19

The most significant amount of observations was followed for 12 months after the procedure.

The Figures No. 14, 15, 16, 17, 18 and 19: angiograms before the intervention in frontal and lateral views. The thrombosed portion of the aneurysm has the clear-cut edges; angiogram immediately after bifurcational endoprosthesis replacement; angiogram in 12 months after the intervention; metal construction (term of the follow-up is 12 months - no damage or visual breakages are seen); computed tomographic scan of the same patient - the follow-up is 12 months, with clear-cut edges of the thrombosed aneurysmatic sac and metalic construction inside it.

During the clinical study, as it has been mentioned above, we changed the coating for endoprosthesis. In our study we also used metallic stents of three modifications. The last modification was recognized as the best one and it was used at the second stage of the study.

Indications for endovascular repair became more strict with the accumulation of experience. Almost every other intervention was exploratory, innovative with constant revision of the technique of the intervention and improvement of the instruments.

At the same time taking into account the lack of the international experience with percutaneous technique and the use of of the big-size introducers, we had to develop and solve not only merely technical problems connected with the devices and systems of their delivery, but also problems related to anesthesia, postoperative and hospital care.

Conclusions

Is there any need for endovascular repair of abdominal aortic aneurysms and aneurysms of iliac arteries? This question has been discussed at different scientific conferences, symposia and round-table meetings both abroad and in Russia. Not once at our domestic symposia we had to face all the rest vascular surgeons, trying to prove the possibility of endovascular treatment of aortic aneurysms. However all it happened two or three years ago. Nowadays in the medical scientific community there is no reason to ask such questions. The results of the introduction of this technique into clinical practice placed endovascular repair of abdominal aortic aneurysms and aneurysms

of iliac arteries in the complex of treatment of such "frightful" diseases.

Careful consideration of the process of our clinical studies made it possible to establish indications and contraindications for the intervention, to improve devices for endovascular repair and systems of their delivery. Finally it led to the dramatic improvement of the results of the intervention at the second stage of clinical studies.

In conclusion it is worth indicating that it is necessary to gain more clinical experience in the future for the improvement of the technique of endovascular repair of abdominal aneurysms and aneurysms of iliac arteries in the wide clinical practice. More strict indications and contraindications, improvement of the devices for endovascular repair and systems of their delivery, gaining more surgical experience serve to the significant improvement of the results of the intervention both in the immediate and short- and long-term follow-up.

References

1. Zarins C., Harris E. Operative repair for aortic aneurysms: The gold Standart.// J. Endovasc.Surg.-1997.-vol.4.-P. 232-241.

2. Dietrich E. Endoluminal repair of abdominal aortic aneurysms: State of the art.// J. Vascular Multimedia Magazine.- 1988-99.-vol.2.p.59.

3. Parodi J. Endovascular repair of abdominal aortic aneurysms and other arterial lesions.// J. Vasc. Surgery.-1995.-vol.21.-p.549-557.

4. Z. A. Kavteladze et al. Aortic stent-graft. First clinical results // Cardiovascular and Interventional Radiology.-1997.-vol.21.-P.566

5. Z. A. Kavteladze et al. Aortic stent-graft . Single center experience // Cardiovascular and Interventional Radiology.-2000.-vol.27.-P. 8;562

6. Z. A. Kavteladze et al. A prosthetic device for sustaining a blood-vessel or Hollow organ lumen.// PCT- Patent Number : WO 94/03127. Date: 17 febr. 1994

7. Z. A. Kavteladze et al. An aggregate for transluminal insertion of a tubular stent, and an endovascular graft device.// PCT - Patent Number: WO 97/03678. Date: 5 sept.1997

8. Z. A. Kavteladze et al. A medical article for implantation into the vascular system of a patient.// PCT -Patent. Number: WO 95/27448. Date: 19 oct.1995

9. Z. A. Kavteladze et al. A medical article for implantation into the vascular system of a patient.// United States Patent Number : 5,683,411. Date: nov.4, 1997

10. Z. A.Kavteladze et al. Prosthetic device for sustaining a blood-vessel or hollow Organ lumen.// United States Patent Number : 5,643,339. Date: jul.1 ,1997

11. Progress report: including the data of the overall patients cohort.// Eurostar data registry centre.- January 2000.

NEW DIRECTIONS IN ENDOVASCULAR PREVENTION OF PULMONARY EMBOLISM

S.A. Kapranov, B.Yu. Bobrov. A.G. Zlatovratskiy, V.V. Manueva, A.N. Balan

The Russian Federal Center of Roentgenosurgical Diagnostics and Treatment Techniques, Moscow

Abstract

On the basis of the analysis of results of 1456 radio-endovascular interventions performed in 1395 patients with acute thromboses of the inferior vena cava system, authors come to the conclusion that the effectiveness of pulmonary embolism prevention is sufficiently high and amounts to 97.9%.

At the same time, authors state that one of the most common techniques of PE prevention, implantation of permanent models of cava filters, has a number of significant drawbacks. In a long-term follow-up, they are mostly caused by total thromboses of the infrarenal portion of the inferior vena cava, destruction of the metallic structure of cava filters, and perforation of the walls of the inferior vena cava by the with rays of the cava filter.

In relation with this, authors have developed new original tools for endovascular PE prevention protected by patents of the Russian Federation, provided a detailed description of the technique and clinical results of the use of endovascular catheter thrombectomy, implantations of removable models of cava filters, intravenous stent filters for iliac veins.

According to authors, a wide clinical use of these new techniques can provide an alternative solution of the problem, it allows to eliminate drawbacks of traditional implantation of permanent cava filters, enhances the effectiveness of endovascular PE prevention and broadens the algorithm of its use.

Keywords: thromboembolism, pulmonary artery, vein, thrombosis, catheter, prevention, cava filter, thrombectomy, stent filter.

Introduction

Prevention of pulmonary embolism (PE) in patients with acute thromboses of the inferior vena cava and its confluents is still one of the most appealing issues of vascular surgery. A substantial incidence of phlebothrombosis of deep veins of lower extremities and the pelvis predetermines its medical and social importance [1]. This is related to severe consequences of these diseases, as well as to limited possibilities and unsatisfactory results of other methods of treatments [2].

At present, cava filters implantation is still as actual as ever, and it remains one of the leading techniques for the prevention of pulmonary embolism in patients with acute thromboses of the inferior caval system and its confluents. According to J.A. Reekers [3], in US alone, 90,000 cava filters are implanted annually.

Our long-term experience with the use of REPRE cava filters allowed us to evaluate objectively positive and negative aspects of this technique, to specify the requirements for cava filters design, to review the tactics of combined techniques intended to improve the effectiveness of treatment of acute thromboses in the inferior caval system and to prevent PE.

In the light of the above, the Surgical Clinic of the Russian State Medical University together with the Komed Ltd. (Russia), developed new original designs of cava filters and tools for endovascular thrombectomy from the inferior vena cava (IVC) and the iliac vein. The use of these devices enhanced possibilities of effective treatment of venous thromboses and PE prevention by means of endovascular surgery.

Material and techniques

From November 1995 to December 2002, 1395 patients had 1456 radio-endovascular interventions. These included 70 thrombectomies from the IVC and the iliac vein, 35 regional thrombolyses, 1062 implantations of the permanent cava filter Sand-glass or its modifications, 197 implantations of the removable cava filter Umbrella, 21 implantations of the universal filter Fir-tree, 7 operations for the placement of stent filters in the iliac vein or the IVC, 3 operations of bringing down of the giant floating thrombus with the help of a Dotter basket followed by cava filter implantation, and a combination of these interventions in 61 patients.

26 (1,86%) of patients had non-traditional interventions, including: 1) endovascular catheter thrombectomy of the floating thrombus formed above the cava filter, 3) cava filter implantation under the combined ultrasound and X-ray control without the use of a contrast medium, 4) temporary implantation of cava filters in the suprarenal portion of the IVC, 5) endovascular correction of an inadequately installed cava filter, 6) endovascular bringing-down or removal of migrating cava filters.

All endovascular interventions were carried out under standard anticoagulant and antiaggregant therapy.

Long-term follow-up was obtained in 416 (29.8%) patients 2 to 72 months (mean, 31.4 months) after the intervention aimed at PE prevention.

Only domestically manufactured products made serially by the Komed Ltd. (Russia), were used in all endovascular interventions. All tools are disposable, prepared for use, covered with heparin, equipped with a complete set of accessories, and packaged in sterile packaging.

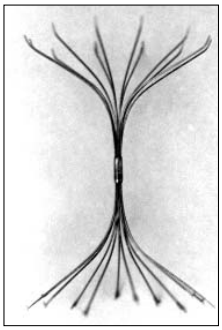


Figure 1A. Permanent cava filter Sand-glass, appearance

The permanent cava filter Sand-glass (patent of the Russian Federation No 2040278, priority dated July 25, 1992) (Fig. 1) consists of two cones whose tops are connected. The distal fixing cone consists of 12 metallic rays equipped with holders with delimiters at the ends. Due to spring qualities, the twelve rays of the proximal cone line up the filter with the axis of the IVC. The presence of two levels of fixation significantly increases functional possibilities of the anti-embolic device. In the Shuttle cava fil-

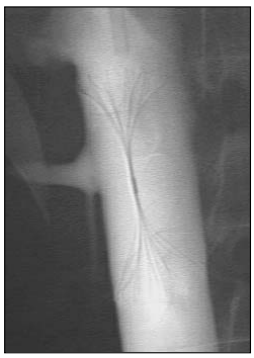


Figure 1B. Permanent cava filter Sand-glass, inferior cavography after the intervention: the filter completely blocks the inferior vena cava lumen and reliably protects it from PE

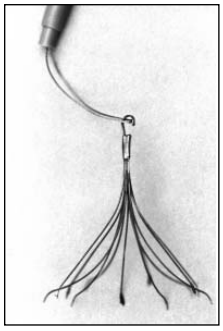


Figure 2A. Removable cava filter Umbrella, appearance

ter modification (a working model certificate of the RF No 6996, priority dated May 28, 1997), equivalent distal and proximal cones are formed by alternating centering and fixing rays. Cava filters are implanted percutaneously through the right internal jugular, subclavian, or femoral vein approach with the help of a guiding cannula and a pusher.

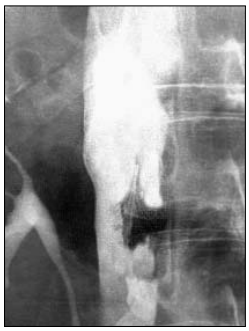


Figure 2B. Removable cava filter Umbrella,radiographic contrast study of the inferior vena cava - embolus caught by the cava filter

Removable cava filter Umbrella (patent of the RF No 2103015, priority dated February 12, 1996) (Fig. 2) is designed for temporary or permanent implantation in the inferior vena cava. It consists of two lined-up cones, their tops connected, constituted by 12 alternating metal rays of various lengths and bending radius. The top of the cone of a cava filter is equipped with a metal hook. Ends of longer rays are bent inside the cone, so that, when they are pulled out, their spring qualities allow to line up the filter in the lumen of the IVC. Shorter rays of the filter have a holder and a delimiter on the free end, which allows to ensure reliable fixation of the cava filter and to prevent perforation of the walls of the inferior vena cava. At the final stage of a cava filter implantation, both types of rays form two circles of equal diameter, lining it up and fixing it at two levels.

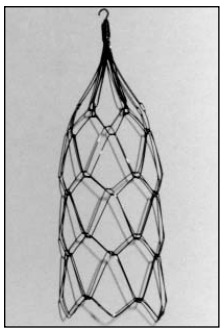


Figure 3A. Stent filter for iliac veins, appearance

Stent filter (patent of the RF No 2143246, priority dated June 03, 1999) (Fig. 3) is designed for temporary or permanent implantation in the common or external iliac vein. It can also be placed in the infrarenal portion of the IVC. The filter is made of nitinol, it is a wattled structure with diamond-shaped cells forming one or two cylinders whose ends are closed in the form of cones. The top of the proximal cone of the stent filter is directed outwards from the cylinder and equipped with a metal hook. In a two-level structure, the top of the distal code is directed inside the cylinder. The stent filter is fixed inside a vessel with the help of its cylindrical part due to the self-expansion quality of the metal with the memory of shape. Cones of the stent filter line themselves up, ensuring filtration of blood flow inside the vessel and preventing migration of thromboemboli.

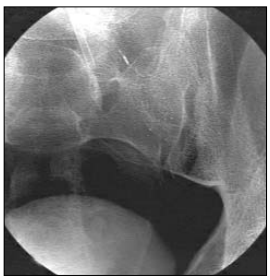


Figure 3B. Stent filter for iliac veins, radiograph showing the metal structure (nitinol) of the implanted stent filter

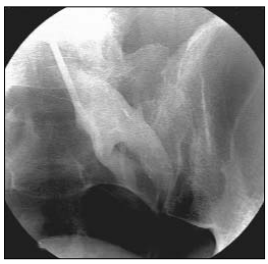


Figure 3C. Stent filter for iliac veins, control iliocavographs after the intervention: the filter is fixed in the lumen of the vein

The both models' implanting device for placement of removable filters consists of a guiding cannula with a probe and a pushing catheter whose ends are equipped with a moving metal two-leg clamp with a spring fixing handle. When the handle is pushed, the two-leg clamp goes out of the catheter and opens, releasing the hook of the cava filter. When the spring handle is released, the branch clamp is automatically pulled inside the pushing catheter.

For the endovascular removal of a previously implanted removable filter, we use a set of tools consisting of a guiding cannula with a probe and a fixing catheter equipped with a moving metal loop with a controlling handle. When the handle is pushed, the metal loop goes out of the catheter at the right angle and opens to the preset diameter, than it is thrown upon the hook of the filter. When the handle is pulled backwards, the metal loop gets drawn into the fixing catheter. The end of a fixing catheter is bent at the angle of 120? at the length of 1-1.5 cm.

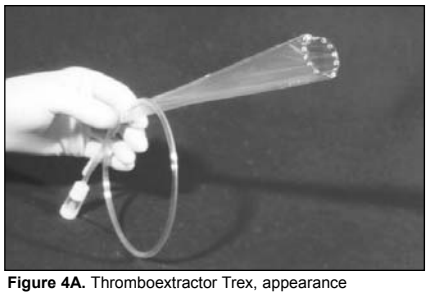


Figure 4A. Thromboextractor Trex, appearance

Thromboextractor Trex (patent of the RF No 2152757, priority dated September 21, 1999) (Fig. 4) is designed for removal of thrombotic mass from the inferior vena cava and the iliac vein. It is a cone-shaped polyethylene bag with one of its ends connected to a 10-Fr dual-lumen polyurethane carrying catheter. A nitinol string ending with a loop playing the role of a cutting tool is passed through the lesser lumen. The loop goes out of the channel at a distance of 1.5 cm from the end of the catheter and passes through the wide distal part of the synthetic bag of the "pouch" type. The loop is so configured that, when opened, it becomes perpendicular to the longitudinal axis of the carrying catheter and represents a synthetic bag in the form of a "hood" with one side left open. In the proximal part of the synthetic bag, there are 12 orifices, 2 mm in diameter each; they ensure an adequate blood flow through the hood at the moment of its complete opening in the lumen of the IVC. The main lumen of the carrying catheter serves for passage of the guide and for introduction of the contrast medium, and can also be used for introduction of auxiliary devices. In the part of the catheter situated within the hood, there is an additional orifice for introduction of the contrast medium, which allows to control the course of the intervention. The thromboextractor is introduced into the IVC through the venesection of the right internal jugular vein.

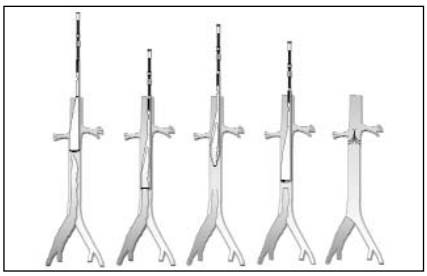


Figure 4B. Thromboextractor Trex, catheter thrombecto-

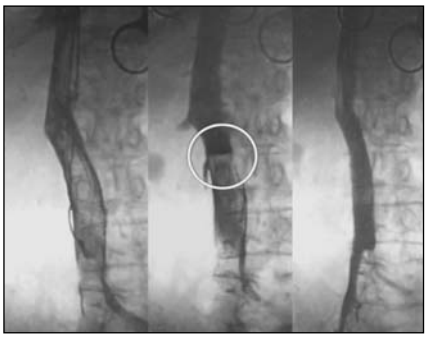


Figure 4C. Thromboextractor Trex, stages of endovascular removal of the giant floating thrombus of the inferior vena cava

A detailed description of the endovascular interventions technique with the use of these tools is provided in our earlier publications [4-6].

Results

The total effectiveness of PE prevention after endovascular interventions amounted to 97.9%. Only 29 patients (2.1%) had signs of recurrent pulmonary embolism at different periods; in 3 patients (0.2%), the embolism was massive.

After implantation of various models of cava filters, 44 patients (3.4%) had a full occlusion of the infrarenal part of the IVC. In early post-operative in-hospital period, it was documented in 13 patients (1%), and in the follow-up, in 31 patients (2.4%).

50 (3.6%) patients had various complications after endovascular interventions: hematomas formation after thrombolysis in 5 patients; rupture of the thromboextractor bag during thromboectomy followed by a massive PE in 1 patient; perforation of the inferior vena cava walls by the rays of the cava filter in 1 patient; cava filter migration in 5 patients; deflection of cava filters by 15 or more degrees from the longitudinal axis of the IVC in 15 patients; rupture of the metallic structure of the filter during follow-up in 6 patients; crossing of the filter's legs in 5 patients; apparent pain syndrome of the lumbosacral area in 12 patients.

The total level of in-hospital mortality was 1.9%. The reason of death of 24 (1.7%) patients was cardiopulmonary decompensation combined with the previous massive PE, and only 3 (0.2%) patients died because of the recurrent PE, in spite of the endovascular prophylaxis they underwent.

Discussion

It is common knowledge that today one of the main endovascular techniques for PE prevention is the implantation of intravenous cava filters.

Modern requirements to the design of cava filters [7] include :

1) a high embolus-catching performance creating no significant obstacles for the blood flow;
2) non-thrombogeneity, biological inertness, mechanical strength, corrosion resistance;
3) the minimal diameter of the delivering device and a small length of the cava filter, when it is open;
4) technical simplicity and safety of implantation in the optimal and strictly orientable position using percutaneous antegrade and retrograde access;
5) reliable fixation in the optimal position with the minimal risk of lesion of the IVC and surrounding structures;
6) the possibility of simple and safe removal from the inferior vena cava using percutaneous intravenous antegrade and retrograde access.

Our experience and results of implantation of a permanent model of a Sand-glass cava filter and its modification Shuttle prove that these tools correspond almost completely to the above requirements.

The effectiveness of PE prevention, when using them, was as high as 98.4%. Pulmonary embolism was seen only in 17 (1.6%) patients who underwent this intervention. These results correlate with the data of foreign authors who observed PE after the use of various models of cava filters in 2.4-2.9% of patients [8-9].

At the same time, these filters also have some drawbacks related, first of all, to the impossibility of their removal, so that they remain forever in the patient's body. In the long run, this can lead to the most frequent complications of intervention, such as total thrombosis of the infrarenal portion of the IVC in the subfilter area and destruction of the metallic structure of the cava filter.

The resulting situation is paradoxical. On the one hand, in an urgent situation, a cava filter saves the patient's life, reliably preventing pulmonary embolism, while on the other hand, in a long-term perspective, when the risk of PE has already been eliminated, the filter can damage the patient's health irreparably.

A way out of the situation was found due to the development of two new tools: a catheter thromboextractor Trex and removable cava filter structures Umbrella and Fir-tree, as well as a stent filter.

The use of endovascular catheter thromboectomy allowed to detect the possibility of removal of the floating top of the thrombus from the inferior vena cava and iliac veins, which is a kind of PE prophylaxis in itself.

With the help of this device, a partial thromboectomy of the floating thrombus reaching renal veins' orifices was performed in 24 patients, which allowed to clear some room for implantation of a cava filter.

The main group consisted of 46 patients who underwent a full thromboectomy; in 29 of them, we initially decided not to use a cava filter after the intervention. However, in the long-term follow-up, PE was detected in 2 patients. This made us terminate full endovascular catheter thrombectomy by the implantation of removable models of cava filters. In cases of repeated thrombus formation and persistent risk of PE, the cava filter was left in the IVC. When, on the background of anticoagulant and disaggregant therapy, the homeostatic system responded adequately, and the remaining part of the thrombus stood occlusive, the cava filter was removed using endovascular technique.

Till recently, indications for cava filters implantation were quite limited. In our clinic, they included:

1) embolo-threatening thrombi of the inferior caval system, both complicated and not complicated by PE;
2) massive pulmonary embolism; or
3) recurrent pulmonary embolism of non-identified source.

The potential possibility of cava filters removal provided for in their design allowed to significantly increase the indications for their use [10-11]. In our practice, they were temporarily implanted to 59 patients: 13 patients had them for the period of surgical thromboectomy from femoral and iliac veins; 18 - before regional thrombolysis; 18 - during the course of anticoagulant and antiaggregant therapy; 7 - after catheter thromboectomy; one patient had her filter implanted for the period of delivery at term (temporary implantation of a cava filter in the suprarenal portion of the IVC); and 2 patients with severe injuries of lower extremities and pelvis had cava filters placed before surgery for trauma and left in place during the immediate recovery period.

Within the period from 1 to 54 days, removable cava filters were removed from 29 (49.2%) out of 59 patients. In one case only, the attempt to remove an Umbrella cava filter failed because of the filter's significant deflection from the longitudinal axis, which resulted in a tight adjacency of its hook to the wall of the IVC and the impossibility of throwing a loop on it. We decided not to remove the cava filter for embolism in the cava filter (7 patients), its thrombosis (1 patient), flotation of the thrombus or an increase of its size (15 patients), perforation of the inferior vena cava wall by the rays of the filter (1 patient), and a late visit to the hospital or patients' refusal of the intervention (5 patients).

And, finally, if PE prevention is required in patients with acute unilateral venous thromboses, this purpose can be achieved with the use of a stent filter. This endovascular device combines almost all advantages of permanent and removable cava filter

models, while having none of their drawbacks.

After the intervention, provided the benign course of drug therapy, when the thrombus is not threatening anymore, and there is no risk of PE, the stent filter can be easily removed using endovascular technique. Its detachment from the walls of the vein and putting into the cannula is extremely simple because of the absence of fixing hooks.

In cases when a stent filter is a permanent device, even in case of thrombosis of subfilter area, this does not result in the blockage of the blood flow through the infrarenal portion of the IVC or in lesions of deep veins of the contralateral lower extremity. Besides, the closed design of a stent filter and the absence of fixing hooks almost excludes the possibility of perforation of the venous walls.

We implanted a stent filter to 7 patients and from one of them it was removed 11 days later. In other 6 patients, the stent filter was left permanently in relation with the growth of the upper border of the thrombosis, on the background of anticoagulant therapy and persisting risk of PE. It should be emphasized that a follow-up of these patients 12 to 36 months after the intervention (14.3 months on the average) revealed no signs of lesion of the iliac veins' walls, nor dislocation or destruction of the stent filter. Most probably, intravenous stent filters can be considered as one of the most promising models of endovascular device for PE prevention.

In conclusion, we would like to emphasize that endovascular prevention of pulmonary embolism is highly effective and barely traumatic, and the wide spectrum of modern tools used allows to achieve the best clinical result in almost any clinical situation.

References

1. Collins L. "Deep venous thrombosis", Nurse Pract. Forum, 1998, vol. 9, № 3, p. 163-169.

2. Plate G., Einarsson E., Ohlin P. et al. "Thrombectomy with temporary arteriovenous fistula: the treatment of choice in acute iliofemoral venous thrombosis", J. Vasc. Surg., 1984, № 1, p. 867-876.

3. Reekers J.A. "Mechanical thrombectomy and vena cava filters", Cardiovasc. Intervent. Radiol., 2000, v. 23 (suppl. 1), p. 54-55.

4. Prokubovsky V.I., Yablokov E.G., Stupin I.V., et al. "Antiembolic Cava Filter Sand-glass, Grudnaya i Serdechno-Sosudistaya Khirurgia, 1995, No 2, p. 21-35.

5. Savelyev V.S., Prokubovsky V.I., Kapranov S.A., et al. "Removable Cava Filter Umbrella - New Possibilities in Endovascular Prevention of Pulmonary Embolism", Angiologia i Sosudistaya Khirurgia, 2000, vol. 6, No 3, p. 17-24.

6. Savelyev V.S., Yablokov E.G., Prokubovsky V.I., Kapranov S.A., et al. "Endovascular Catheter Thrombectomy ftom the Inferior Vena Cava", Angiologia i Sosudistaya Khirurgia, 2000, vol. 6, No. 1, p. 61-71.

7. Prokubovsky V.I., Kapranov S.A. "Endovascular Interventions for Patients with Thrombosis and Embolism" in the book "Phlebology" (physicians' manual) under the editorship of Academician V.S. Savelyev, Moscow, Medicine, 2001, pages 351 to 389.

8. Irie T., Yamauchi T., Makita K., Kusano S. "Retrievable IVC filter: preliminary in vitro and in vivo evaluation". J. Vasc. Interv. Radiol., 1995, vol. 6, № 3, p. 449-454.

9. Levine M.N. "Thrombolytic therapy for venous thromboembolism. Complications and contraindications", Clin. Chest Med., 1995, vol. 16, № 2, p. 321-328.

10. Linsenmaier U., Rieger J., Schenk F. et al. "Indications, management, and complications of temporary inferior vena cava filters", Cardiovasc. Intervent. Radiol., 1998, vol. 21, № 6, p. 464-469.

11. Rogers F.B., Shackford S.R., Ricci M.A. et al. "Routine prophylactic vena cava filter insertion in severely injured trauma patients decreases the incidence of pulmonary embolism", J. Am. Coll. Surg., 1995, № 180, p. 641-647.

INTRAVASCULAR ULTRASOUND SCANNING DURING CORONARY INTERVENTIONS: OPTIMAL APPLICATION AND ASSESSMENT CRITERIA

V.V.Demin, V.V.Zelenin, A.N.Zheludkov, A.V.Demin, A.G.Degtyarev, V.N.Shigaranov[1]

Department of interventional radiology of Orenburg regional clinical hospital

Abstract

The goal of the study was to optimise the indications for the application of iintravascular ultrasound study (IVUS) of coronary arteries and to develop the convenient, available and feasible criteria of IVUS assessment of the results of interventions.

Methods and results

Seventy patients with CHD have been examined between 1996 and March, 2002. The mean age of the patients was 48,88±0,80.

One hundred and four IVUS, quantitative and qualitative analysis of 508 segments of coronary arteries have been made. During coronary angioplasty 15 examinations of 10 patients have been made, and 75 examinations of 48 patients have been made on different stages of coronary stenting. Before the intervention 9 studies have been conducted during coronary angioplasty and 29 during stenting. After recanalization and predilatation 10 studies have been conducted during stenting, 2 in the course of the intermediate control procedure at angioplasty and 11 during stenting. At the final stage of the intervention 4 and 25 studies have been conducted duirng angioplasty and stenting, respectively.

The comparison of the results of intravascular ultrasound and angiographic quantitative measurements showed that they were significantly different according to the most parameters. Practically all the absolute values of the measured indices were much higher according to the IVUS data. The difference in the measured indices was more explicit in stenotic parts than in normal coronary arteries. After the intervention the difference in the results of IVUS and angiography was the greatest and reached 33,7% on average after coronary angioplasty and 40,9% after stenting.

The quantitative criteria of optimal indices of IVUS at the end of the operation were suggested on the basis of the retrospective analysis. For coronary stenting such criteria are as follows: the complete apposition of the stent to the vascular wall along the full circumference, the symmetry index is more than 0,8 (the minimal acceptable value is 0,7), stenosis less than 30% in diameter (the minimal acceptable result is less than 40%), the lumen area is over 7 mm^2 (the minimal acceptable value is 6 mm^2), the stent diameter is not less than 80% of the nominal diameter. At coronary angioplasty the following criteria are applied: the symmetry index of the lumen over 0,7; stenosis over 40% in diameter; the lumen area over 6mm^2 (the minimal acceptable value is 5 mm^2).

Conclusions

The differentiated indications for the application of the IVUS on different stages of the operation have been developed based upon the priority of the clinical significance of the study. IVUS at the initial stage of the operation helped to verify precisely the true vessel dimensions and adequately choose the size of the stent or balloon. The main purpose of the intermediate studies was to specify the situation in cases of angiographic uncertainty. The controls IVUS at the final stage verifies the degree of the approaching to the optimal result and helps to predict the long-term result and make the conception of the further treatment. In case the optimal ultrasonic results have not been achieved there are some indications for control coronary angiography in 3-4 months after the operation.

[1] 460018, Orenburg, Aksakov st., 23
Regional clinical hospital
Tel.: (3532) 41-56-22, 41-70-12;
Fax: 41-45-89;
E-mail: angioren@mail.oris.ru

Keywords: IVUS, ICUS intravascular ultrasound study, coronary angioplasty, coronary stenting.

Introduction

Coronary angioraphy has been "the gold standard" in the studies of coronary arteries during the last 40 years. However it does not always meet such criterion. Certain limitations of coronary angiography are peculiar for any angiographic study and referred to the possibility of only silhouette two-dimensional evaluation of the vascular lumen, are aggravated by the complexity of the spatial arrangement of coronary arteries. The last condition leads to the overshortening or even overlapping of certain vessel segments on the coronary angiogram, which makes their assessment more difficult and sometimes even impossible.

During the last decades the demands for detailed and reliable image of coronary arteries have increased in relation with rapid development of endovascular techniques. The success of interventional radiology depends even more on the accuracy of vessel quantitative and qualitative assessment than on of traditional cardiac surgery. The development and introduction of Intravascular Ultrasound study (IVUS) became a response to the needs of interventional cardiology.

IVUS of coronary arteries became a widely recognised technique in the last few years that is used all over the world as well as in our country. The study of coronary arteries accounts for most cases of IVUS use. In its turn the main part of the scanning of heart arteries consists of ultrasound studies at interventions, and mainly at coronary stenting. A decisive step in the development of interventional treatment of CHD was taken in 1995 after the introduction of the IVUS guided stenting conception (A.Colombo, J.Tobis) that contributed to the rejection of indirect anticoagulants and decrease the risk of subacute stent thrombosis [9, 22]. Later, the routine use of big and high pressure balloons has been applied by the majority of interventional cardiologists and good results were achieved, even in cases when IVUS has not been used [18, 19]. The use of IVUS technique permits to apply the strategy of "spot" stenting with the partial covering of the lesion by the stent [10]. The application of IVUS in accordance with specially developed criteria (MUSIC) reduces the incidence of restenosis after stenting [11].

The application of IVUS in some clinics in Russia is becoming the usual procedure at coronary stenting. We have come a long way from the first studies of the single instances of intracoronary IVUS to the research projects describing the several tens of procedures [2-4, 6]. The problems of IVUS application are touched upon in the first monographs of Russian researchers devoted to coronary angioplasty and stenting [1, 5].

Nevertheless, there are still many problems concerning the application of IVUS of coronary arteries especially in clinical practice. The questions of use of IVUS scanning of coronary arteries on the diagnostic stage are not adequately explored. Indications for the application of IVUS at coronary angioplasty procedures, stenting and other interventional operations require a more precise definition and differentiation. The introduction of IVUS procedure into everyday clinical practice of interventional radiology has not been yet developed. That is the reason of the wide diversity of indications for its application and the frequency of its use in different clinics. The problems of more detailed specification of the clinical application of IVUS of coronary arteries has fundamental importance for the clinical practice.

Materials and methods

Seventy patients with CHD (69 men and 1 women) have been examined between 1996 and March 2002. Twelve patients had IVUS during the diagnostic coronary angiography, fifty-eight patients had IVUS at different stages of surgical treatment. One hundred and four IVUS have been carried out and quantitative and qualitative analysis of 508 segments of coronary arteries has been conducted. During coronary angioplasty 15 examinations of 10 patients have been made, and 75 examinations of 48 patients have been performed at different stages of coronary arteries stenting. The mean age of patients was 48,88±0,80.

The data were collected on two generations of IVUS scanning systems made by the company EndoSonics (now called Jomed) - Oracle and Oracle-InVision. The diagnostic catheters with a phased-array transducers Visions F/x and Visions Five-64 F/x were used along with the sensors combined with the balloon catheters - Oracle F/x Plus and Oracle MegaSonics F/x. The working frequency of all types of sensors was 20 MHg.

Results and discussion

IVUS during percutaneous interventions is associated with the best results of its application on different stages of operation [21]. However the use of IVUS is not always appropriate and often impossible. According to the conception of differentiated application of IVUS [4] we often made use of it on the initial stage of operation so that the accurate measurements of the vessel could be verified. The adequate selection of stent or balloon size allowing to choose their optimal size with the first instrument, makes it possible to reach the ultimate goal - the maximal lumen diameter [15] with minimal complications, as compared with multiple changes of instruments and repeated angioplasty. At the initial study the largest number of images was analysed because we have to assess the condition of adjacent segments of arteries, ostia of big side branches and the left main coronary artery. The purpose of intermediate studies consisted in more precise definition of the situation in cases of angiographically controversial results (e. g. finding of a dissection). Although they could become intermediate because of the necessity of the operation continuation as control IVUS did not provide the optimal indices. The control IVUS at the final stage verifies the degree of approaching to the optimal result. Regarding it the control IVUS is rather helpful for long-term prognosis and making the concept of the further treatment (especially at the prescription of the programming control coronary angiography).

In terms of IVUS data the affected segments of coronary arteries had significant differences in comparison with the unaffected segments. The differences between the results of ultra sonic and angiographic quantitative measurements were also considerable. Only the sizes of stenotic area and diameter in the group of patients, undergo coronary angiography were similar in comparison with other comparable characteristics. Practically all absolute values of measured indices became much higher according to the IVUS data. As it was indicated by other researchers [23] the difference in diameter and area measurements of the lumen, the whole vessel and atherosclerotic plaque was more evident in stenotic segments than in normal coronary arteries. The correlation of the data of IVUS and angiography in the stenotic segment is low according to all characteristics that coincide with the literary works. The exception is the diameter and area of the angiographic reference segment of the vessel in comparison with the proper indices ("media-media") of stenotic part at IVUS, which closely correlates.

Angiographic data after predilatation and especially after recanalization can not be taken into account for reliable assessment of vessel. Apart from the input data angiographic indices underestimate the degree of stenosis. The difference in area assessment of the lumen runs up to 46,6% and the same parameter of the plaque comes up to 61,1%. At the initial stage the input indices differ in 30,1%, but after predilatation and recanalization they come up to 34,6%.

The comparable indices seem to be rather conflicting at the stage of intermediate study. The sizes of the minimum luminal diameter prove to be quite similar, especially after coronary angioplasty. Practically all indices obtained with the help of IVUS and angiography easily correlate in the group of patients where stenting was not applied. At the same time the difference in assessment of the plaque area at coronary angioplasty comes up to 79,8% and at stenting up to 81,9%. Consequently the difference in stenosis assessment comes up to 32,8% and 41,9% correspondingly. This information indicates the tendency of angiography to "embellish" the results of the operation due to intramural leakage of contrast after coronary angioplasty and fusion of stent and vessel edges after endoprosthesis placement [17, 21].

At the final control procedure the tendency mentioned above stays the same and the differences are even more explicit, especially in the group with stenting. The difference in assessment of stenotic and plaque area comes up to 57,9% and 85,6% correspondingly. In general the average measuring after coronary angioplasty and after stenting differed in 33,7% and 40,9% correspondingly.

The analysis of the mechanism of the achieved lumen enlargement is very important for the development of the criteria for the evaluation of intervention results. Various authors provide different information with controversial results [6, 13, 16]. In our studies of coronary angioplasty and stenting the average absolute value of the plaque area reduction was larger than the value of increase of the whole vessel area, defining the degree of its expansion. At the same time the predominance of this or that technique at stenting was observed in the equal number of cases. However concerning the increase of the luminal area the contribution of the plaque reduction was not so significant.

The retrospective comparative angiographic assessment is considered to be

helpful in the process of defining the degree of initial stenosis with rather sufficient degree of reliability. However it gives the overestimating positive result of the stenosis size at intermediate and final control stages and that is why can be taken into account only as the guiding point at measuring of diameter and area sizes of the lumen and the vessel. As it was stated by J. Tobis and A. Colombo (2000) "interventional cardiologists familiar with IVUS presume the largest degree of atherosclerotic lesion even at the slightest irregularities on the angiogram. Nowadays when we study the angiogram we try to picture what possible pathology could have been indicated by IVUS and see the vast plaque, which has developed even before the slightest lesion may be observed by angiography" [21].

Everything what has been said above determines the main indications for IVUS application at coronary interventions. Even with the exclusion of all the possibilities of IVUS in quantitative assessment of the initial morphology of the vessel and its intra-operative modifications, the precise assessment of the vessel parameters and values obtained during the operation have enormous, even definitive significance for immediate and long-term outcomes of the intervention.

Most studies were conducted before the intervention or after predilatation and recanalization. We did not use guiding of ultrasound catheter through the zone of critical stenosis or occlusion to reduce the possibility of peripheral embolization and avoid the increase of ischemic time. To our mind the main indications for the initial ultrasonic study are as follows: impossibility to define the proper vessel diameter, well-reasoned doubts in accuracy of the angiographic measurements and "special cases of stenting" when the extra accuracy of measuring is required.

The typical example of the impossibility of conducting accurate angiographic measurements is the occlusion and sometimes-critical stenosis of the artery. Even after recanalization or predilatation the peripheral channel does not comply with the required parameters of dilatation. Consequently the measuring of the true vessel diameter may be only approximate. In case of a lesion in the periostial segment of the artery (more often it is referred to the left anterior descending artery) it is impossible to obtain the accurate image of the artery size regardless of any stenosis size, because only the distal reference segment is analysed. At last, it is very difficult to chose the right size of an instrument guided by angiographic indices because of the significant difference between the proximal and distal reference diameters that is often connected with the considerable extension of the lesion or origin of large side branch.

As it was mentioned above, angiography has the tendency to reduce absolute values of the measured vascular parameters. However the importance of these distinctions is not the same for the different artery diameters. For example, when angiographic and IVUS data differ by 20%, the vessel with 2 mm diameter according to angiographic data will be considered as having the diameter of 2,4 mm at ultrasound assessment, which can be easily corrected by high pressure due to the balloon compliance. At the same time the diameter of 3,5 mm correspond to the diameter of 4,2 mm at IVUS, and diameter of 4 mm comply with the diameter of 4,8 mm. Since the difference in assessment of minimum luminal diameters was about 30% at stenting, according to our information, the influence of this factor will be even more explicit. To correct such difference with the help of rising pressure is impossible and as the result the wrong size of an instrument will be chosen without conducting of IVUS. That is why we believe that the reference luminal diameter of more than 3,5 mm according to angiographic quantitative data can be the indication for the IVUS (Fig. 1). In the other case the more accurate definition of angiographic data is required at

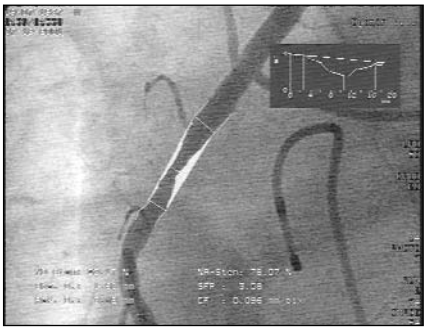


Figure 1A. The difference in angiographic and IVUS data at big vascular diameters, according to quantitative angiographic data the reference diameter of the right coronary artery is 3,48

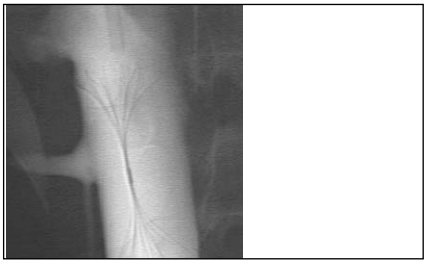


Figure 1B. The difference in angiographic and IVUS data at big vascular diameters, at IVUS the diameter "media-media" in stenotic part was 5,0 - 5,2 mm

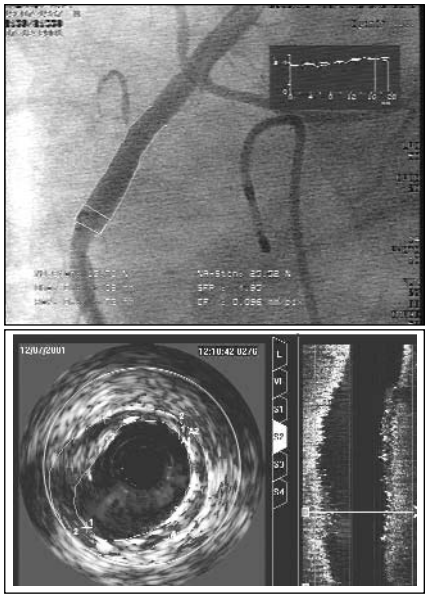


Figure 1 C, D. The difference in angiographic and IVUS data at big vascular diameters, the results of the JoStent implantation that was mounted on the balloon Taker Mega with the diameter 4,5 mm and the following predilatation by the balloon Taker Mega with the diameter 5,0 mm. Major plaque substance is distributed along the circumference and partly pressed (plaque area decreased by 2,5 mm^2). Remodelling of the artery has good visibility on the angiogramm and the third projection of IVUS. The stent lumen diameter is 3,9 - 5,3 mm

the "border-line" stenotic values. Since the angiographic and IVUS indices of the stenosis degree are quite similar at the initial stage of the study the qualitative evaluation of a lesion becomes more important. IVUS can help to detect the eccentric plaque that requires correction, and to visualise the signs of plaque instability, which are taken into account for making positive decision of the operation when other indications are the same. IVUS may be also useful for assessment of the significance of instent restenosis. At last, there is one more indication for conducting IVUS at the initial stage referred to the suspicion of the arterial segment involvement, which is proximal to involvement.

It is worth mentioning the situations concerning "special cases of stenting". Among which we consider the application of stents where the accurate choice of sizes is even more important than at usual stenting, and additional exposure after the installation is rather difficult. First of all it is the implantation of stent-grafts in scheduled situations at coronary-cardial fistulas and aneurysms of coronary arteries. The "sandwich type" structure of a stent-graft with the double metal layer guarantees its higher of rigidity regarding the additional exposure and less pliability to balloon compliance especially at the wrong size of the last. Application of stents with antiproliferative coating (Cypher was the first type among other stents, which introduced the new era in stent application)

assumes the limitations of additional exposures on the stent after implantation in accordance with the possible coating damage. The general exultation regarding the insufficient percentage of restenosis and stent "tolerance" to possible inadequate opening due to the cytostatics activity backgrounded for some time the specific problems connecting with the vast application of such stents. Some announcements were made about formation of aneurysms in the stenting zone that is referred to inadequate apposition of the stent. Co-operation of stents at their overlaying in bifurcational parts, at long lesions and at restenosis stenting in a stent almost has not been studied. Particularly regarding the moments mentioned above there is a considerable amount of research indicating the necessity of more thorough approach to the choice of sizes and stent-grafts, and coated stents based on IVUS data [8,12]. It is not by chance that on all stages of experimental and clinical tests of the stent Cypher IVUS served as the "gold standard".

The choice of an instrument at initial stages of coronary angioplasty and stenting was made according to IVUS data in 89,4% of all cases. It helped to keep the mean level of indices of the balloon inflation pressure at angioplasty about 11 atm along with the low bound of high pressure at the level of 14 atm. Interactions of the balloon/artery and stent/artery compiled 1,12:1 and 1,16:1 correspondingly. The low rate of intimal dissection after stenting (6,25%) was referred to sparing conditions of interventions.

All intermediate IVUS may be divided in 2 groups. "True intermediate" control is required when there are some angiographic suspicions of not quite satisfactory results of an operation, i. e. more precise definition of the dissection character or condition of the part that has some signs of dissection according to angiographic data. Detecting the presence of some insufficient residual deformations or residual narrowing of a stent at examining of doubtful parts on angiograms is always proved by IVUS as it was already mentioned before [10]. The intermediate control is necessary in case there are some other stenotic parts in the artery except the operated one, and the stenosis character and the plaque stability may change after the artery intervention. The necessity to provide an additional assessment of a proximal to stenosis segment of an artery occurs more often. At last the control IVUS is quite necessary to detect the possible complications and their development in the course of an operation, in case the additional visualisation is required and the condition of a patient is stable and gives some time for diagnostic manipulations. Among such cases we consider stents which have not been fully open or have not been open at all, stents implanted in a wrong way and cases when there is a necessity to make a more precise definition of the condition of uncovered parts (Fig. 2).

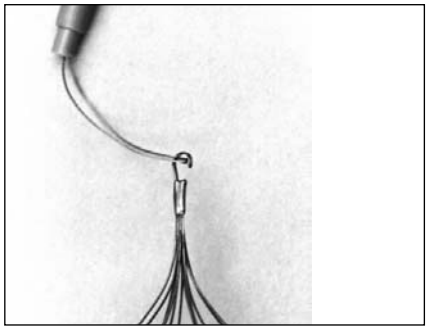


Figure 2A. Identification of the unexpanded state of the stent at IVUS, control angiography after stenting of the right coronary artery - good angiographic result

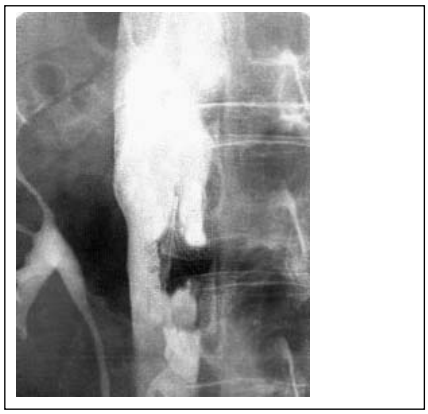
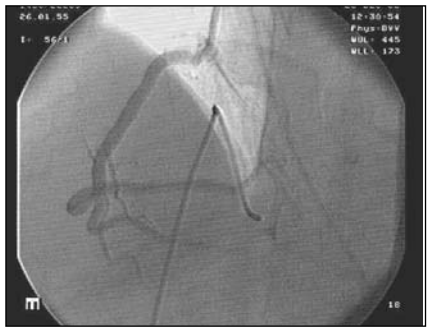


Figure 2B. Identification of the unexpanded state of the stent at IVUS, control angiography after stenting of the right coronary artery - good angiographic result

The choice of qualitative and quantitative criteria of assessment of angioplasty and stenting results is proved to be the most important aspect that may affect stenting management and long-term results of an operation. The criteria of dilatation adequacy or stenting at the intermediate or final control IVUS must be reliable for providing immediate and long-term positive results. They also must be used in cathlab, i.e. they must be simple in use and referred to the minimum number of measuring procedures. At last the chosen criteria must be feasible, because too overestimated requirements are more theoretically than practically applicable.

MUSIC research criteria [11] fit only with the first of those approaches. These requirements for the results of stent expanding turned to be classic and the most strict criteria of optimal stenting at the use of IVUS control. 1) The complete adjacency to the walls of a stent (apposition) along the full length must be achieved. 2) Minimum luminal area of a stent must be more or equal to 90% of an average reference area of a lumen or more or equal to 100% of a luminal area of the minimum reference area of a lumen. 3) The luminal area of a proximal entrance of the stent must be more or equal to 90% of a proximal reference area of a lumen. 4) The index of symmetry of the stent lumen must be 0,7 and more. 5) In case the minimum area of a stent lumen is more or equal to 9 mm^2 the minimum area of a stent lumen must be more or equal to 80% of an average reference area of a lumen or more or equal to 90% of a luminal area of the minimum reference area of a lumen. The methodology of this study include the considerable amount of measuring procedures and relative calculations and was meant for the deep scientific analysis. It does not entirely meet the requirement of fast assessment of the results and making a decision. Even in case the high pressure and large balloons are used only 50% of stenting lesions can be optimised within the limits of the research [21]. Nevertheless the results of stenting with IVUS were better than in patients without the control IVUS [11]. The study CLOUT makes less strict demands to the stenting results: the area of the cross-section of a stent must be more than 7,5 mm? or exceed 80% of an average area of the cross-section of the artery [14]. J. Tobis and A. Colombo considered 5 different approaches to IVUS in retrospective analy-



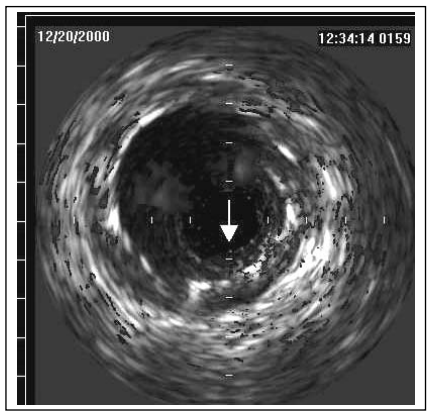


Figure 2 C, D. Identification of the unexpanded state of the stent at IVUS, angiographic and ultrasonic control after the additional angioplasty in a stent

sis for the defining of a successful result [21]. The degree of criteria achievement varies from 23% (the area of a lumen more than 9 mm^2) to 79% (the area of a cross-section of a vessel more than 80% of an average reference area or more than 90% of a distal reference area). The difference in criteria took place for the development of a restenosis only at realisation of the following conditions: the obtaining of a luminal area more than 9 mm^2 or exceeding of 70% of a nominal area of the biggest balloon cross-section. Concerning the criteria based on the comparison with the area of reference segments it was indicated that in case the vascular diameter is reduced the rate of restenosis does not differ regardless to the strict following of indicated requirements or their neglecting. J. Tobis and A. Colombo tried to stick to the following criteria in their research work of 1993-1996: the minimum area of the cross-section must be more than 60% of an average reference area at the complete adjacency of a stent to the vascular walls. The total achievement of optimal criteria comes up to 94% taking into account the additional dilatation. However the authors indicate in their following works that these criteria can be achieved only in 66% of cases.

In this connection the characteristics used in the studies of "spot" stenting are not based on the comparison of area sizes but diameters: the chosen balloon is by 0,5 mm smaller than the diameter of the vessel in the lesion or equal to the average reference diameter. The minimum acceptable criteria are even lower: the luminal area is more than 5,5 mm^2 or more than 50% of the vascular area in the lesion [10].

Though different researchers use different criteria in the assessment of results of balloon angioplasty their approaches do not differ greatly. A. Abizard and his co-author [7] in their research work considered the choice of the balloon according to the average vascular diameter in the area of stenosis. The result was considered to be optimal when the obtained area was more than 65% of an average luminal area of reference segments or more than 6 mm^2, and suboptimal results run up to 61%.T. Seo with his co-author [20] considered the dilatation to be insufficient when the luminal area was less than 5 mm^2 or stenosis was more than 60%. A. Colombo with his co-authors [10] aim at the obtaining of the luminal area more than 5,5 mm^2 at the angioplasty, or more than 50% of the vascular area in the lesion.

Regarding the mentioned above research works there is no unified point of view on criteria of optimal stenting or balloon angioplasty at present. It is important that with time the approaches of the same authors may change considerably. No randomized studies dealing with the comparison of different approaches have been conducted. We consider it symptomatic that some researches in their studies chose the reference segments of the vessel as the basis of comparison instead of the proper size of the lesion, including the diameter "media-media". The logic of the diameter but not area analysis is caused by the fact that the enlargement of the lumen is achieved rather by means of vessel dilatation than due to the plaque constriction in the majority of cases (and in most cases with calcified or solid plaques). The large amount of residual plaque material unavoidably leads to comparatively considerable scverity of stenosis according to area assessment even when the visual IVUS images show the successful result in every respect.

Referred to these reasons and taking into account the stated above requirements for the criteria of optimal interventional results we have carried out the retrospective analysis of the conducted operations. The luminal symmetry index at stenting was more than 0,7 in all cases and more than 0,8 in all segments with the visually optimal result and in 71% of the parts with the minimal lumen. The luminal area at the minimal lumen was more than 6 mm^2 in all cases, more than 7 mm^2 in 83% of all cases, more than 8 mm^2 in 67% of all cases, more than 9 mm^2 in 46% of all cases and more than 10 mm^2 in 33% of all cases. Interestingly, in most cases these figures comply with the results of the studies that met the requirements of the corresponding criteria. Almost in 100% of all cases the achieved luminal area was equal to 50% of the total vascular area. However the value of 60% referred to the 40% of stenosis was exceeded only in 4% of observations. In the part with optimal stent expanding this result ran up to 32%. In the course of analysis of the luminal diameter enlargement regarding the total diameter of the vessel in the part of the minimal lumen this value was equal to 50% in 100% of all observations, 60% in 96%, 70% in 78% and 80% in 13% of cases. Finally, the ratio between the minimal achieved luminal diameter and nominal diameter of the used stent was analysed. This ratio exceeded 0,7 in 100%, exceeded 0,8 in 75% (for the parts with the optimally expanded stent - in 100%) and exceeded 0,9 in 33% of all cases (at the optimal expansion - in 83%).

The symmetry index in the course of the balloon angioplasty was over 0,7 in 100%, over 0,8 in 60% and over 0,9 in 40% of all cases. In 100% of all cases the luminal area exceeded 5 mm^2, in 80% it exceeded 6 mm^2, in 60% was over 7 mm^2 and in 40% of all cases exceeded 8 mm^2. The ratio between lumen area and the total area of the vessel was over 45% in 60% of operated patients and over 50% only in 40% of operated patients. Finally, the rati of minimal lumen diameter to the total vascular diameter was over 60% in 100% of patients and exceeded 70% in 40% of all cases.

Regarding the received information we consider that it is really important for the practical use to take into account the following guiding points at the control IVUS. The mandatory condition that is supposed to be fulfilled is the complete apposition of the stent to the vascular wall along the full circumference. The stent congruence, the symmetry of its expansion are also the final guiding points. We succeeded in achievement of the average symmetry index of the stent lumen equal to 0,94±0,02 in the parts of the optimal expansion of the stent. In the parts with the minimal stent lumen this index was 0,86±0,02. In some cases (more often at calcified lesions) it is impossible to achieve the complete stent symmetry without any risk of complications. Moreover when the coiled stents are applied there is a possibility of considerable disorder of their configuration as far as the structure loss. At such serious lesions the elliptical form of the cross-section of the stent without marked deformations may be considered as the acceptable result. The target value of the symmetry index is 0,8 and the minimal value is 0,7. The next criterion is the achievement of value equal to more than 70% of the relation between the minimal diameter of the lumen and the vascular diameter that is referred to the stenosis less than 30% in diameter (the minimal acceptable result is the stenosis less than 40% in diameter). The achievement of the size of the luminal area more than 7 mm^2 (the minimal acceptable value is 6 mm^2) is the next guiding point. At last we consider it is important to achieve 80% of the stent diameter in comparison to its nominal value.

For the balloon angioplasty the criteria of the adequate results is the symmetry index of the lumen which is more than 0,7: the indication of the relation between the minimal diameter of the lumen and the diameter of the vessel is more than 60% that refers to

the stenosis less than 40% in diameter; the area of the lumen is more than 6 mm^2 (the minimal acceptable value is 5 mm^2).

When assessing intimal dissection following angioplasty or in the areas adjacent to the stent it is important to apply angiographic and ultrasonic assessment criteria. It is also connected with the fact that it is rather difficult to assess the progress or stability of dissection with the help of IVUS, because the second entering of a catheter in the lesion is required. Concerning ultrasonic criteria of the necessity of additional correction we suggest that the approach of A. Colombo is the most useful. It is indicated that the additional stenting is conducted in case the false lumen takes a half or more of the total lumen of the vessel.

In cases when according to the results of IVUS control the additional intervention was required, it was done using either the high pressure or the balloons of the larger diameter. In the latter case we tried to use the balloons of the length smaller than the implanted stent. It is absolutely necessary to emphasize that the effectiveness of the additional intervention after the intermediate ultrasonic control is proved by the fact that the main indices, i. e. diameter and area of the lumen, area of the plaque, stenosis in diameter and area, were certainly different at intermediate and final control.

The assessment criteria at the second control after additional dilatation are less strict than at the intermediate control. If there are no additional complications it is necessary to conduct the compulsory correction of the incomplete apposition of the stent in accordance with non-optimal size or without it. The study of the total stenting segment helps to define the part of the visually optimal opening of the stent. Its quantitative analysis is necessary at the second control study if the borderline values of stenting criteria are achieved in the part of the maximal stenosis. The absence of the "optimal" part indicates the incongruity of the chosen instrument parameters and requires the continuation of the intervention. In case the high pressures and large diameters of the balloon are used and there are optimally open stent parts and the angiographically acceptable results, more aggressive intervention is unsuitable and the operation may be finished. As it was stated before it is not always possible to reach the ideal criteria of IVUS, but attempts to achieve them improve early and late results of the intervention. We suppose that in case we fail to reach the optimal ultrasonic results there are indications for performing control coronary angiography 3-4 months later.

The application of the balloons combined with ultrasonic sensors appeared to be very useful. The use of such balloons helps to reduce the time required for the change of an instrument and carry out fast and precise control of the results of angioplasty and stenting. "MegaSonics" catheters are applied with the balloons of high pressure and contribute to the successful application of the technique "3 in 1" with simultaneously mounted stents. For this purpose we used the matrix stents of the following three types: Palmaz-Schatz, River-S, JoStent. Altogether the combined technology during the operation has been applied on 16 patients (27,6%), including 11 cases when ultrasonic sensors attached to the balloon for angioplasty have been used and 5 cases when the simultaneously mounted stent has been applied.

Nowadays economically accessible systems JoSonics have appeared on the market. They use the technique "3 in 1" and make the realization of any intervention more convenient due to lower profile.

Conclusions

The application of IVUS at the initial stage of the intervention helps to define the morphometric parameters of the vessel more precisely and choose the optimal size of the necessary instruments.

The control IVUS in the course of an intervention helps to assess the adequacy of the conducted intervention, specify some angiographic uncertainties and decide whether there is a necessity for continuing the intervention and if so, with what means, or the intervention may be finished.

The application of ultrasonic catheters combined with the balloons for angioplasty or intracoronary stents helps to reduce the time of the operation and optimise its results.

Suggested quantitative criteria for the adequacy of the conducted intervention establish precise practical guiding points and useful for clinical use including direct application in the cathlab.

References

1. Babunashvili A.M., Ivanov V.A., Biriukov S.A. Endoprostheses (stents) of the coronary arteries. - Moscow, ASB Publishers, 2001, 704 p.

2. Belenkov Yu.N., Savchenko A.P., Rudenko B.A., Cherkavskaya O.V. Results of repeated balloon angioplasty for implanted stent re-stenosis as judged by the data of coronary angiohraphy and intravascular ultrasound study. // Kardiologia, - 2001. - № 8. - pp. 26-30.

3. Bockeria L.A., Alekyan B.G., Buziashvili Yu.I. et al. Use of intravascular ultrasound in endovassular interventions on the coronary arteries. // 1st All-Russian Congress on Endovascular Surgery for Congenital and Acquired Heart Pathology: Proceedings / Serdechno-sosudistye zabolevania. - 2002. - v.3. - № 6. - pp. 28-29.

4. Demin V.V. IVUS in coronary pathology: from the first experience to differential application // 1sr Russian Congress of Interventional Cardioangiologists: Proceedings. - Moscow, 2002. - p. 101.

5. Interventional methods for the treatment of coronary disease / L.A. Bockeria, B.G.Alekyan, Yu.I.Buziashvili, eds. - Moscow., 2002. - 417 p.

6. Cherkavskaya O.V. Intravascular ultrasound investigation of the coronary arteries for complex diagnosis and optimization of endovascular treatment of coronary disease: Thesis for the degree of Candidate of Medical Sciences. - Moscow, 2000. - 198 p.

7. Abizaid A., Pichard A.D., Mintz G.S. et al. Acute and long-term results of an IVUS-guided PTCA/provisional stent implantation strategy // Am. J. Cardiol. - 1999. - Vol. 84. - P. 1381-1384.

8. Barrow D. American Heart Association Scientific Sessions - Meeting report // Int. J. Cardiovasc. Intervent. - 2001. - Vol. 4. - N 4. - P. 197.

9. Colombo A., Hall P., Nakamura S. et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance // Circulation. - 1995. - Vol. 91. - P. 1676-1688.

10. Colombo A., Tobis J. Evolution in our approach to stenting // Techniques in coronary artery stenting / Edited by A.Colombo, J.Tobis. - Martin Dunitz, 2000. - P. 111-127.

11. De Jaegere P., Mudra H., Figulla H. et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasonnd Stenting in Coronaries Study (MUSIC Study) // Europ. Heart J. - 1998. - Vol. 19. - P. 1214-1223.

12. Gerckens U., Mueller R., Cattelaens N. et al. First clinical experience with a covered stent the JoStent coronary // Int. J. Cardiovasc. Intervent. - 1998. - N 1. - P. 68-74.

13. Gil R., Di Mario C., Prati F. et al. Mechanisms of percutaneous transluminal coronary balloon angioplasty assessed by ultrasound imaging: prediction of immediate results // Intravascular Ultrasound / Edited by R.Erbel, J.R.Roelandt, J.Ge, G.Gorge. - Martin Dunitz, 1998. - P. 163 - 171.

14. Hodgson J.M., Stone G.W., Linnemeier T.J. et al. Oversized balloons defined by intracoronary ultrasound results in dramatic improvements in angioplasty results: initial ultrasound analysis of the CLOUT pilot study // Eur. Heart J. - 1995. - Vol. 16. - P. 487.

15. Kasaoka S., Tobis J. Angiographic and ultrasound descriptors of in-stent restenosis // Techniques in coronary artery stenting / Edited by A.Colombo, J.Tobis. - Martin Dunitz, 2000. - P. 83-95.

16. Marsico F., De Servi S., Kubica J. et al. Influence of plaque composition on luminal gain after balloon angioplasty, directional atherectomy, and coronary stenting // Am. Heart J. - 1995. - Vol. 130. - N 5. - P. 971-975.

17. Moussa I., Moses J., De Gregorio J. et al. The discrepancy between quantitative coronary angiography and intravascular ultrasound in determining true vessel size: a homogeneous or a selective phenomenon? // J. Am. Coll. Cardiol. - 1999. - Vol. 33. - Suppl. A. - P. 76A.

18. Nakamura S., Hall P., Gaglione A. et al. High pressure assisted coronary stent implantation accomplished without intravascular ultrasound guidance and subsequent anticoagulation // J. Am. Coll. Cardiol. - 1997. - Vol. 29. - N 1. - P. 21-27.

19. Sancardas M.A., McEniery P.T., Aroney C.N., Bett J.H. Elective implantation of intracoronary stents without intravascular ultrasound guidance or subsequent warfarin // Cathet. Cardiovasc. Diagn. - 1996. - Vol. 37. - N 4. - P. 355-359.

20. Seo T., Yamao K., Hayashi T. et al. Intravascular ultrasound in determining the end point percutaneous transluminal coronary angioplasty // J. Cardiol. - 1996. - Vol. 28. - N 4. - P. 183-189.

21. Tobis J. Intravascular ultrasound imaging // Techniques in coronary artery stenting / Edited by A.Colombo, J.Tobis. - Martin Dunitz, 2000. - P. 1-57.

22. Tobis J.M., Colombo A. Do you need IVUS guidance for coronary stent deployment? // Cathet. Cardiovasc. Diagnos.- 1996. - Vol. 37. - P. 360-361.

23. Yamashita Y., Takazawa K., Fujita M. et al. Intravascular ultrasound assessment at the site of balloon angioplasty: comparison with quantitative coronary angiography // J. Cardiol. - 1994. - Vol. 24. - N 6. - P. 423-431.

ANGIOGRAPHIC ASSESSMENT OF COARCTATION OF AORTA IN VIEW OF BALLOON ANGIOPLASTY PERSPECTIVE

Sharabrin E. G., Shahov B. E., Rybinskiy A. D.

The State Medical Academy of Nizhni Novgorod

Summary

The results of the analysis of aortograms in 112 patients with coarctation of aorta allowed to reveal a certain range of angiographic symptoms, the combination of which helped is to make reliable and objective definition of four angiographic types of CA. The definition of the angiographic type of CA at the preoperative stage provides the possibility to make an objective choice of either surgical or endovascular technique.

Keywords: coarctation of aorta, balloon angioplasty, classification

The coarctation of aorta (CA) is one of the most common congenital heart diseases (CHD). According to different authors its rate comes to 6 -14,2% of all CHD [1, 2, 3].

Nowadays there are two known techniques of CA correction: surgical and endovascular (balloon angioplasty (BA) that can be supplemented in some cases with stenting of dilated section of aorta).

The presence of systolic gradient > 20 mm Hg between upper and lower extremities serves as the indication for surgical correction of aortic coarctation [2, 3]. The operation in children is indicated also in cases of heart failure non-responding to conservative treatment [4].

The indications for balloon angioplasty are not so evident. According to some authors such indications are sustained hypertension and/or progressive cardiac failure, systolic gradient between upper and lower extremities ≥ 20 mm Hg, documented collateral blood flow in lower extremities, angiographic narrowing in the isthmus region and the presence of associated defects of the heart and great vessels [5,6,7].

It is worth mentioning that the indications for the correction of the defect are determined without detailed appreciation of the angiographic aspects of the lesion, but mainly of the base on hemodynamic disturbances and combination of coarctation with other defects, making it impossible to carry out an objective and reasonable choice of the technique of correction (balloon angioplasty or operation).

Besides in some cases, despite the observance of the mentioned above indications for the manipulation and strict adherence to the dilatation technique (the use of the optimal sized balloon catheter, positioning of the balloon, etc.), it's either impossible to achieve the required result in the course of the procedure or the achieved result is of short duration [8, 9]. Such situation has not merely discounting effect on the BA but causes the significant material and moral damage both for the patients and for medical institutions. This problem is especially vital from the viewpoint of controlling the dosages of radiation for the patient and the medical staff.

The main purpose of our study consisted in the developing of angiographic classification of aortic coarctation that may serve for the objective and precise choice of the technique of correction: either surgical or endovascular.

Material and methods. Since 1988 till 2002 we have examined 442 patients with coarctation of aorta. The age of patients varied from 9 months to 29 years (mean, 9,4±4,6). The isolated CA was diagnosed in 236 cases, in association with PDA in 62 cases and in association with other congenital heart diseases in 144 patients.

Patients underwent the complete clinical examination, including ECG, chest X-ray study in three views, ultrasound examination of the heart, angiography of the aorta, performed in 112 cases (25,3%).

Endovascular manipulations were carried out on the X-ray-angiographic complex "Angioscope D33". The visualization of the aortic isthmus was achieved with the aortography from the distal part of aortic arch in antero-posterior and second oblique standard views.

Results and discussion. The analysis of aortograms in antero-posterior and second oblique standard views allowed us to distinguish four angiographic types of aortic coarctation (priority reference of the invention, State registration number: 2002, 129064/14, dated 31.10.02) [11]).

The first angiographic type was detected in 32 of 112 patients (40,2%), who underwent the intravascular intervention.

They had an identical picture of the defect on the aortograms in antero-posterior and second oblique standard views. Circular stenosis seen on the level of the aortic isthmus was caused by the symmetrical filling defects with parallel edges, located both on lateral (defined in antero-posterior view), as well as on the anterior and posterior aortic walls (defined in second oblique standard view). The edges of the filling defect were perpendicular to the aortic walls (fig.1a; 1b).

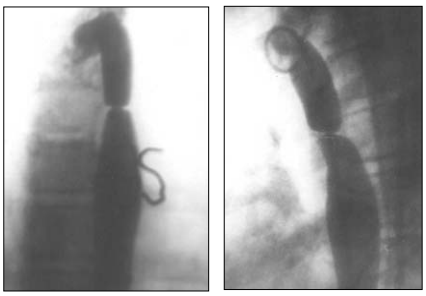


Figure 1. Photoaortogram of the patient A., 5 years old, female. Coarctation of aorta, I angiographic type

A. The antero-posterior view **B.** The second standard oblique view

The length of the stenosis was 1,4±0,6 mm in average (range, 1,0 - 2,0 mm). An orifice of mean diameter 4,3±1,6 mm (range, 1,5 - 6,1 mm) was located centrally. No stenotic or deviating regions were seen along the full length of the aorta.

The second angiographic type of aortic coarctation with its two subtypes (A and B) was detected in 27 patients (24,1%). In IIA type (17 patients) there was a circular concentric stenosis of aorta formed by the two symmetric filling defects with parallel edges on medial and lateral aortic walls (fig. 2a) seen in antero-posterior view. The edges of filling defects were located perpendicular to the aortic wall.

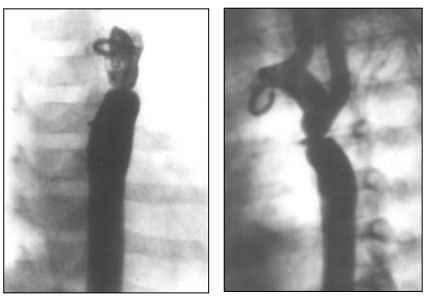


Figure 2. Photoaortogram of the patient A., 5 years old, female. Coarctation of aorta, IIA angiographic type

A. The antero-posterior view **B.** The second standard oblique view

The moderate anterior deviation of aortic isthmus was seen in the second oblique view. In accordance with it the deviation of the axis of the pre- and poststenotic aortic regions from the vertical (cranio-caudal) direction was defined. The filling defect with the smooth parallel edges located at right angles to the aortic wall was visualized on the posterior wall (fig. 2b). The angle between the longitudinal axes (following the blood flow) of the pre- and poststenotic regions of aorta (defined in the second oblique view) exceeded 45°.

In 6 patients with coarctation of aorta of the IIA angiographic type the opacification of non-obliterating aortic part of the PDA was seen. Seven patients had the juxtaductal form of coarctation.

The IIB angiographic type (10 patients) had the following angiographic features. The concentric stenosis formed by two symmetric filling defects in the form of cones with the peaks directed into the aortic lumen was defined in the antero-posterior view, (fig. 3a). According to the analysis of images, such

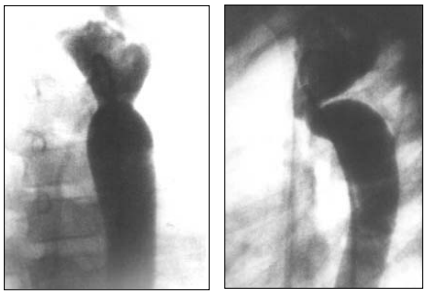


Figure 3. Photoaortogram of the patient K., 7 years old, female. Coarctation of aorta, IIB angiographic type

A. The antero-posterior view **B.** The second standard oblique view

picture was caused only by the superposition of the shades of the aortic isthmus secondary to the local anterior bend of this region.

The significant ventral deviation of the anterior wall of the isthmus in combination with the posterior bend of the aortic parts, immediately adjacent to coarctation, was detected in the second oblique view. With this the longitudinal axis of the poststenotic region was directed horizontally. The angle between the axes of the pre- and poststenotic parts was less than 45° (fig. 3b). The aortic lumen was located nearer to its anterior wall.

The third angiographic type of aortic coarctation was seen in 41 cases (36,6%). The local concentric stenosis, formed by symmetric filling defects with parallel edges, located symmetrically at right angles to the medial and lateral aortic walls was seen in antero-posterior view (fig. 4a).

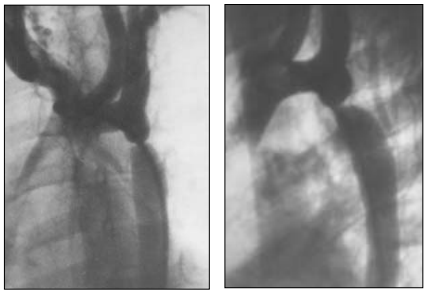


Figure 4. Photoaortogram of the patient R., 5 years old, female. Coarctation of aorta, III angiographic type

A. The antero-posterior view **B.** The second standard oblique view

The filling defect in the form of cone with the peak directed into the aortic lumen was visualized on the posterior wall of aorta in the second oblique view (fig. 4b). The anterior wall of the aortic isthmus remained smooth, no filling defects in this region were seen. The anterior deviation of the anterior was not observed. The directions of the longitudinal axes of the pre- and poststenotic regions of the aorta coincided: the direction of axes was cranio-caudal. The aortic lumen was located at the anterior aortic wall. Aorta was dilated manly in dorsal direction.

In the IV angiographic type the tubular stenosis of the isthmic part of the aorta, formed by two filling defects in the form of trapezium with the short base directed into the aortic lumen, was seen in antero-posterior and second oblique views (fig. 5a; 5b). This angiographic type of coarctation was observed in 12 patients (10,7%). The length of the stenotic part was 11,3±4,4 mm in average (range, 6 - 14 mm).

In total, 58 patients underwent balloon angioplasty of CA, 52 of those were examined in the course of 9 years after the intervention.

Variability is the characteristic feature of the contrast image of CA. However there is a definite range of angiographic signs. On the basis of their combination it is possible to make reliable and objective definition of four angiographic types of CA.

The determination of the angiographic type of aortic coarctation at pre-operative stage allows for the precise evaluation of the

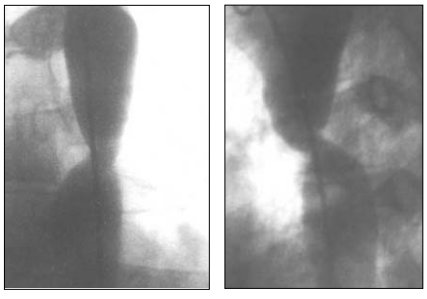


Figure 5. Photoaortogram of the patient R., 12 years old, female. Coarctation of aorta, IV angiographic type

A. The antero-posterior view **B.** The second standard oblique view

stenotic area and the objective choice of either surgical or endovascular technique of correction.

According to our personal experience we believe, that balloon angioplasty should be considered as the technique of choice in patients with the CA of I and II A angiographic types. It allows to achieve the long-term results, comparable with the results after the surgical correction of the defect, in all cases.

In II B, III and IV angiographic types balloon angioplasty is ineffective, so patients with those types of defect should be considered as candidates for surgical treatment.

References

1. Belokon N.A., Podzolkov V.P. Congenital Heart Diseases. Moscow, Meditzina publ., 1991. p. 159-167.

2. Berezov Yu.E., Melnik I.E., Pokrovsky A.V. Coarctation of the aorta. Kishinev, 1967.

3. Pokrovsky A.V. Clinical angiology. Moscow, Meditzina publ.; 1979. p.63-83.

4. Sharikin A.S. Aortic coarctation in infants. Moscow, 1994

5. Alekyan B.G., Perrosian Yu.S., Podzolkov V.P. Catheter therapy of congenital cardiac and vascular defects. Vestnik rentgenologii i radiolologii, 1995; 2: 16-26.

6. Alekyan B.G., Spiridonov A.A., Kharpunov V.F. Transluminal balloon angioplasty and stenting in the treatment of corctation and re-coarctation of the aorta. Grudnaya i serdechno-sosudistaya khirurgia, 1996; 3: 117-121.

7. Endovascular and minimally invasive cardiac and vascular surgery in children // L.A. Bockeria, B.G. Alekyan, V.P. Poszolkov, eds. Publishing house of the Bakoulev SCCVS, RAMS; 1999: 91-104.

8. Brandt B., Marvin W.J., Rose E.F., Mahoney L.T. Surgical treatment of coarctation of the aorta after balloon angioplasty. J. Thorac. Cardiovasc. Surg.1987;94: 715-719.

9. Sada S.E. et al. Balloon coarctation angioplasty: follow-up of 103 patients. J. Cardiol., 2000; 12(8): 402-406.

10. Shakhov B.E., Sharabrin R.G., Ribinsky A.D. A method for the diagnosis of isolated coarctation of the aorta and the choice of tactics for its treatment. State registration number 2002, 129064/14 of 31.10.02.

ENDOVASCULAR EMBOLIZATION OF PATENT DUCTUS ARTERIOSUS BY THE NEW TYPE OF THE DETACHABLE COILS

Shukurov B. M., Chigogidze N. A., Kozlov G. V., Pisetsky P. B., Egin E. I., Dushkina A. P.

Volgograd Centre of Cardiology, Bakoulev Scientific Centre for Cardiovascular Surgery, RAMS

Patent ductus arteriosus (PDA) is one of the most common heart defects. According to literature, its incidence comes to 5-10% of all congenital heart diseases (CHD) [1]. The main pathogenetic sign of this defect is the drastic increase of pulmonary blood flow, which leads to gradual sclerosis development in the system of pulmonary artery. Mean life span of patients with PDA at natural course is 39 years. Those patients who underwent surgical operation live longer and have better hemodynamic indices [2].

This article deals with the first attempts of clinical application of the new type of the detachable coils designed by the Bakoulev Scientific Centre of Cardiovascular Surgery (SCCVS) of RAMS [3], for endovascular treatment of PDA.

Materials and methods

The embolization of PDA with the new type of coils was carried out in Volgograd Centre of Cardiology and Bakoulev SCCVS, in 15 patients. The age of patients varied from 2 to 14, there were 12 male and 3 female patients.

On admission five patients had no complaints, 7 had increased fatigue, 3 had exertional dyspnea at minor physical activity, 2 complained of periodical palpitation and 6 patients had the history of frequent respiratory diseases.

In 10 patients the PDA was isolated, with this 3 patients had PDA recanalization after surgical ligation, and in 5 cases, along with PDA, there were pulmonary artery stenosis (1), patent foramen oval (1), restrictive VSD (1), aortic insufficiency of the I degree (1), umbilical hernia (1). Those associated defects had no marked clinical and hemodynamic significance.

Auscultation revealed systolic murmur in 2nd- 3rd intercostal space to the left of the sternum.

ECG showed the signs of left ventricular hypertrophy and left atrium in 8 cases, 5 patients had incomplete bundle branch block and in 2 cases no electrocardiographic changes were detected.

In all 15 cases the X-ray investigation revealed the increase of lung pattern, the bulging of pulmonary artery arch of variable degree was observed in 5 cases and 8 patients had hypertrophy of the left heart.

One of the main diagnostic tools used for the determination of surgical indications consisted in echocardiography for the measuring of the duct diameter, the determination character of the velocity of the blood flow into the pulmonary artery.

However such ultrasonic study could not always provide the full information for defining the indications for an operation. Especially, it was rather difficult to obtain exact data on diameter, anatomic form and length of the duct, while those data served as the governing factor for the determination of surgical technique. In such cases (6 patients) we applied nuclear magnetic resonance imaging (MRI) of the heart with Magnetom vision device (Siemens, Germany). It helped us to define precisely anatomic characteristics of the duct, that were confirmed later on by the data of invasive study.

All operations were performed in the cathlab BICOR TOP (Siemens) under intravenous and local anesthesia.

In all cases we have used Seldinger femoral artery puncture. After the placement of an introducer, in order to prevent arterial thromboses, all patients received heparin injection (75 -100 U/kg). After that the pulmonary artery was catheterized through PDA and blood samples were taken. Systolic pressure in the pulmonary artery varied from 15 to 60 mm Hg (mean, 42 ±16 mm Hg). The volume of the left-to right shunt was 30±13% in average.

Aortography was performed in frontal and lateral views, with this the pigtail catheter was placed in the region of the aortic isthmus, somewhat higher of PDA origin. It helped to define exact dimensions and anatomic configuration of the duct (fig. 1). We have used the special program of vascular diameter calculation on the base of "Ancor" angiographic system (Siemens, Germany). Our calculations were based the commonly accepted angiographic classification of ducts following their anatomic structure, suggested by A. Krichenko et al. [4]. In 14 patients the ducts were of the type A with well-pronounced aortic ampulla, 1 patient had the defect of the type B (short duct, narrowest in the aortic part). Duct diameters varied from 2 mm to 6 mm (see Table).

Figure 1. Patient B., two-years-old.
Thoracic aortography in lateral view before the coil implantation.
1 - PDA (type A)
2 - Contrasted blood shunting in the pulmonary artery

Duct diameter (mm)	Quantity
2	7
3	4
4	3
5	1

Quantity of embolized PDA

The coils for embolization were chosen according to duct dimensions. The diameter of coils varied from 5 to 12 mm - 0,38``.

We have used introducers of 5-6F and "cobra" catheter (5F). Coil delivery system consisted of the metallic metal-coated bar with a lock, to which the coil was attached. With this the bar could pass through the whole system and thereby straighten the coil turns.

The tip of the catheter was advanced to the narrowest part of the duct and the coil was pulled out in order to release 2/3 - 4/5 of its turn. Then the catheter and the internal bar of the coil were drawn back till the complete placing of the turn at the pulmonary opening of the duct. Then the catheter was withdrawn into the aorta and the turns were placed in the aortic part of the duct. After the

surgeon was sure of the accurate placement of the coil, it was disconnected from the delivery device. In case of non-satisfactory placement of the coil, we corrected the turns' position or pulled the coil back into the catheter, after that the procedure was repeated.

The availability of an internal bar, fixing device and delivering catheter gave additional advantages for safe and accurate coil implantation into the PDA.

The control aortography was carried out immediately or 10 - 15 minutes after the procedure, and the effectiveness of embolization was determined on the base of its

Figure 2. Patient B., two-years-old.
Thoracic aortography in lateral view 15 minutes after the embolization.
1 - The implanted coil in PDA.
No signs of contrast blood shunting in the PA

results (fig. 2). In cases of a residual shunt the additional coils were implanted following the same technique. All patients received large-spectrum antibiotics for prophylactic purposes for 2 days after the operation.

Results

The embolization proved successful in all 15 cases, a total of 16 coils was implanted. PDA was closed with one coil in 14 cases and in one case 2 coils were used. No complications or dislocation of coils were observed. The duration of X-ray exposure varied from 4 to 12 minutes (mean, 6,8 ± 2,1 min.).

The complete occlusion of PDA immediately after the coil implantation was observed in 9 cases, in 3 cases it was observed after 15-30 minutes, in 1 case - after 18 hours and 2 patients had the PDA occluded in 21 hours.

In 12 cases post-operative auscultation didn't reveal any systolic-diastolic murmur, in the remaining patients it disappeared 18 hours after the operation.

The control ultrasonic study carried out on the next day (18-34 hours after coils implantation) showed good stabilization of coils and no signs of the shunt.

All patients were discharged on the 3rd - 4th day after the operation.

The data of long-term follow-up (1- 2,5 years after the operation) were obtained in 10 patients. The control ultrasonic and X-ray investigations revealed stable fixation of coils in the sites of implantation without any signs of shunt.

Transcatheter closure of PDA with various degree of success depending on the type of the applied occluder has been used for the last 35 years [5-24]. Despite the fact that the idea of endovascular embolization of PDA was suggested a long time ago, this technique wasn't widely applied, and only few clinics in our country have the experience of such operations [10, 25-27].

The most experienced clinics in our country in the field of endovascular embolization of PDA are the Bakoulev SCCVS, RAMS, and the Clinic of surgical diseases of the Russian State Medical University (RSMU) [10, 18-20].

This situation could be explained by the absence of the reliable endovascular device suitable for the operation in the wide range of patients. On the one hand, the devices applied by now have undoubted advantages, but at the same time they have a range of deficiencies, limiting their application, especially for paediatric use. Among such devices one could name free Gianturco coil [15-18], botallo-occluders of Savelyev-Prokubovsky [9] and Rashkind devices [7,8]. According to the data of various authors, the effectiveness of Gianturco coils makes 96-98,3% [16,18], the Savelyev occluder can be used effectively in 93-94,5% of cases [10]. The literature offers the description of the application of the devices designed for septal defects closure, for the treatment of large PDA [11-14].

In order to be applied in clinical settings any device should possess such characteristics, as the simplicity and the safety of implantation, full control on the implantation process with the possibility to reposition the device in case of unsatisfactory placement, the secure elimination of the pathologic shunt, the smallest possible diameter of the delivery system, etc.

According to the literature, only few of the currently applied devices meet the mentioned above requirements [16, 17].

The detachable coils used in our series have some indisputable advantages, that make their usage preferable. The proposed constructive features of those coils provide the operator with the additional possibilities, i.e. full control on the turns' placement and the possibility to change the position of the coil, the possibility to use the delivery device

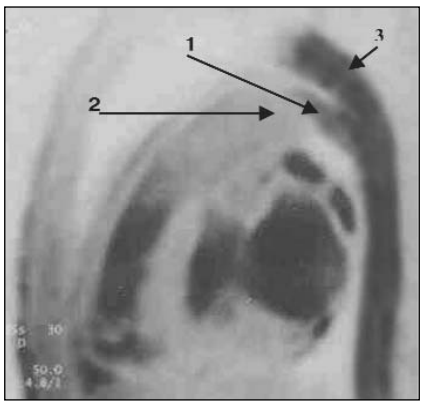


Figure 3. Patient K., five-years-old.
MRI of the heart and great vessels before the embolization (lateral view).
1 - PDA (type A).
2 - Distinct image of the junction with the pulmonary artery through PDA.
3 - Aorta

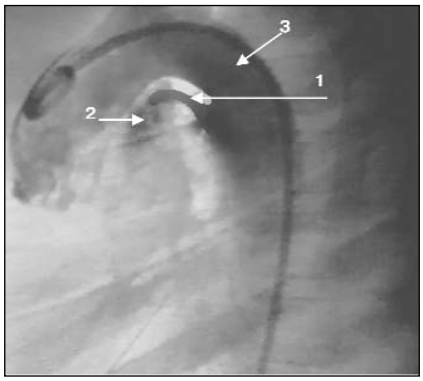


Figure 4. Patient K., five-years-old.
Thoracic aortography in lateral view before coil implantation.
1 - PDA (type A).
2 - Contrasted blood shunting in the pulmonary artery.
3 - Aorta

as the guide. The relatively small diameter of the device allows its use in children with the low body weight [24-26].

We consider the embolization of PDA by means of the detachable coils as an effective and safe technique in cases with the duct diameter not exceeding 6 mm and favorable anatomy of the duct.

The essential condition of the successful intervention consists in correct determination of the surgical indications, accurate determination of anatomic particularities of the duct and the possibility of its endovascular elimination. The commonly accepted "Gold standard" is the aortography. Unfortunately, it cannot be applied as the screening technique before the operation because of its invasiveness and expensiveness. That is why the ultrasonic study is commonly used for those purposes. Although it can be considered highly informative, the ultrasonic study is unable to provide answers to all the questions. In our practice we used the MRI in 6 cases for determining the indications for the operation, and in all those cases we got the complete information that was proved

Figure 5. Patient K., five-years-old.
Thoracic aortography in lateral view
after coil implantation in the pulmonary artery
(no signs of contrasted blood shunting through PDA)

by the data of intra-operative aortography (fig. 3-5). This approach resulted in the refusal to apply the endovascular intervention in two cases with unfavorable anatomy of the duct; both patients were operated on with traditional technique.

Thus, the first application of detachable coils for embolization of PDA provided us with the encouraging results. It is worth adding that we have such coils also for the elimination of coronary-cardiac fistulas (2), arteriovenous and carotid-cavernous communications (3) with positive clinical results. With this it is obvious that the existing experience with the coils application is not quite sufficient and it is absolutely necessary to accumulate and generalize it in order to define the place of new devices in the modern spectrum of endovascular techniques.

References

1. Bourakovsky B.I., Bockeria L.A. et al. Handbook on cardiovascular surgery. Moscow, 1995.
2. Belokon N.A., Poxzolkov V.P. Congenital heart defects. Moscow, 1991.
3. Chigogidze N.A., Ivanitzky A.V., Shukurov B.M. Proceedings of the 4th All-Russian Congress of Cardiovascular Surgeons. Moscow., 1998, p. 289
4. Krichenko A., Benson L., Burrows P. et al. Am J Cardiol 1989;63:887- 889
5. Porstmann W, Wierny L,Warnke H. Thoraxchirurgie 1967; 15:109-203.
6. Wierny L, Pluss R. CardiovascInterventRadiol 1986; 9:279-85
7. Rashkind WJ. Circulation 1983; 67:711-6
8. Piechaud JF, Delogu A, Kachaner J. Arch Pediatr 1995 Dec; 2(12): 1149-55
9. Kolody S.M., Saveliev V.S. Grudnaya Khirurgia,1988,№1, p. 42-47
10. Saveliev V.S., Prokubovsky V.I. Vestnik Rentgenologii I Radiologii, 1994, №5, p. 18-23.
11. Sideris EB, Sideris SE, Thonopoulous BD. Am J Cardiol 1990;66:1524-6
12. Sideris EB et al. J.Amer.Coll.Cardiol 1995; 2- P.302A
13. Bockeria L.A., Alekyan B.G. et al. Grudnaya I Serdechno-Sosudistaya Khirurgia, 1998, №11, p. 4-9.
14. Shipulin V.M., Merunko A.A., Sideris EB. Grudnaya I Serdechno-Sosudistaya Khirurgia, 1998,№11, p.9-12.
15. Alekyan B.G, Coulson G, Kardenas K. Abstract, Venice, Italy, 1996, p.48
16. Alekyan B.G, Kardenas K.E. et al. Grudnaya I Serdechno-Sosudistaya Khirurgia,1997,№1, p. 20-24.
17. Endovascular and Minimally Invasive Cardiac and Vascular Surgery. Ed. L.A. Bockeria, B.G. Alekyan, V.P. Podzolkov. Moscow,1999.
18. Kardenas K.E., Alekyan B.G,, Podzolkov V.P. et al. Proceedings of the 1st All-Russian Congress on Endovascular Surgery. Moscow, 2002, p. 18
19. Klestov K.B., Kokov L.S., Glagolev S.V. et al. Proceedings of the 1st Congress of the Russian Scientific Society of Interventional Cardioangiologists. Moscow, 2002, p. 27
20. Shevakin A.G., Sitnikov A.V. Proceedings of the 1st Congress of the Russian Scientific Society of Interventional Cardioangiologists. Moscow, 2002, p. 28
21. Baranov V.A., Bugaev G.D. et al. Proceedings of the 1st Congress of the Russian Scientific Society of Interventional Cardioangiologists. Moscow, 2002, p. 29
22. Borisova N.A., Ilyin A.SA., Liubomudrov V.G. Proceedings of the 1st All-Russian Congress on Endovascular Surgery of Congenital and Acquired Heart Diseases. . Moscow, 2002, p. 4
23. Dadabaev M.Kh., Maralov A.N. et al. Proceedings of the 1st All-Russian Congress on Endovascular Surgery of Congenital and Acquired Heart Diseases. . Moscow, 2002, p. 7
24. Shukurov B. M., Chigogidze N. A., Kozlov G. V. et al. Proceedings of the 5th All-Russian Congress of Cardiovascular Surgeons, Novosibirsk, 1999, p. 134
25. Shukurov B. M., Chigogidze N. A., Kozlov G. V. et al. Proceedings of the 6th All-Russian Congress of Cardiovascular Surgeons, Moscow, 2000
26. Shukurov B. M., Kozlov G. V. et al. Proceedings of the 1st Congress of the Russian Scientific Society of Interventional Cardioangiologists. Moscow, 2002, p. 33

THE NEW CONCEPT - TEMPORARY STENTS, AN EXPERIMENTAL STUDY

Kavteladze Z.A., Dundua D.P., Dondelinger R. F., Snaps F.**

Center of Endosurgery and Lithotripsy, Moscow

University Clinic, Liege, Belgium

Abstract: Stenting has allowed to obtain appreciable improvement of immediate and late results of percutaneous endovascular interventions. However in-stent restenosis developes in 10-50% of cases after stent implantation at different periods of time. Thus, any attempt aimed at lessening restenosis rate is of a great scientific and practical importance. The new concept of temporary stent usage serves as one of the prospective trends in endovascular surgery.

AIM of the study is to develop an arterial stent for temporary implantation and a system for its retrieval.

Material and methods: 42 temporary stents with the diameters of 6, 8, 10 mm and lengths of 30, 40, and 60 mm have been implanted to 13 experimental pigs into supra- and infrarenal segments of aorta and iliac arteries. 14 stents have been retrieved from 4 animals immediately after implantation (acute experiment). The remaining 9 experimental animals have been divided into 3 groups (3 animals in each group). Stents in those groups were retrieved on day 2, 3 and 7 day after implantation. The diameter for stent delivery and retrieval system was 8F.

Results: 40 stents have been implanted and retrieved without complications. In two cases the stents did not open up completely, in two cases a distal dislocation was observed immediately after implantation. 28 stents have been retrieved on the 2nd, 3rd and 7th day after the implantation. In all cases, arterial segments were patent stented by the moment they were retrieved. In one case an arterial spasm was observed, in another - an acute artery thrombosis immediately after stent retrieval. There were no cases of late migration or stent breakage, as well distant arterial embolism. At morphological study of arterial segments an indentation of inner elastic membrane of arterial wall by the stent struts with partial loss of smooth muscle elements was noticed, in some cases with local focuses of smooth muscle cells necrosis.

Conclusion: The possibility for safe implantation and retrieval of temporary vascular stents has been demonstrated in experimental study. It has been shown that vascular wall undergoes minimal alterations.

Key words: stents, temporary stents, restenosis prevention

[1] Prof. Z.A.Kavteladze,
Department of cardiovascular surgery
Center of endosurgery and lithotripsy,
111123, Moscow , shosse Entuziastov, 62
zaza@celt.ruz

Introduction

Endovascular methods allows us to achieve clinically relevant results in treatment of stenotic arterial lesions. Percutaneous balloon angioplasty and stenting of arteries is successful in 95% of the cases (1). Though, restenosis following intervention occurs after different periods of time in 10-50% of cases.

Balloon angioplasty is based on the action on two mechanisms:

1. Mechanical stretching of arterial wall. Therefore, after the balloon is deflated recoil of vessel lumen occurs, due to elastic properties of arterial wall and in some cases the effect of angioplasty is lost by time. The implantation of scaffolding metal stent inside the vessel prevents the recoil but unavoidably leads to reaction of foreign body implantation. Initial damage is followed by mural thrombosis, intimal proliferation, smooth muscle cell migration and endothelisation of stent (2) that makes the stents' surface smooth and athrombogenic. Sometimes such reaction is abundant and results in re-narrowing of vascular lumen - the process named restenosis. The problem of restenosis can be solved by means of targeted drug therapy, when a stent is bedspread with antiproliferative drugs. Although such approach has a considerable potential deficiency. The inhibition of the endothelisation processes might result in late thrombosis. It's not clear how innocuous the discharge of potentially toxic substances might be. Taking into consideration these factors, the idea of temporary stents implantation (for 5-7 days) is extremely attractive. Firstly, prolonged dilatation of arterial lumen could be more effective than balloon angioplasty, secondly, the stent retrieval might be the best way of restenosis prevention.

2. Another mechanism of lumen enlargement after balloon angioplasty based on the appearance of microfractures, ruptures in the inner layer of artery, which might sometimes lead to occlusive dissection of intima. This complication also requires the stent implantation. Stenting is indicated in cases of accidental damage of intact intima. In these cases temporary stent use seems to be a logical alternative.

The aim of the study was the development of arterial stent for temporary implantation and the system for its retrieval. With this, the following tasks were being accomplished: the development of the technique for stent implantation and safe retrieval; the study of angiographic and morphological characteristics of artery after stent implantation and retrieval; establishment of optimal periods for temporary stent retrieval.

Material and methods

A modification of self-expandable ZA-stent (William COOK Europa A/S, Denmark), with additional anchoring elements for stent retrieval was tested in experimental study (Fig.1). 8 and 10 mm diameter stents and 30, 40, and 60 mm long were used in the study. 8F delivery system was used for stent implantation and retrieval. For stent retrieval a three-hook collet chunk was used.

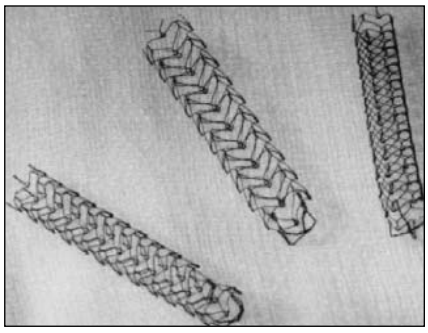


Figure1. Temporary ZA-stents with additional sells for the capturing at the distal ends

13 domestic pigs were involved into experiment. After intravenous analgesia and endotracheal intubation the animals were given a full mechanical ventilation. Femoral artery was punctured under fluoroscopy and angiography was performed. Eight and 10 mm stents and with the length of 40 and 60 mm were implanted into suprarenal and infrarenal segments of aorta. Stents with the diameter of 8 mm and the length of 30 and 40 mm were implanted into iliac arteries. Angiography was repeated. 4 animals

underwent acute experiments, the purpose of which was to practice the methods of stent implantation and retrieval. In this group, the stents were retrieved immediately after implantation. 9 experimental animals were divided into 3 groups. Stents in those groups were retrieved on the 2d,3d and 7th day after implantation. Angiographic study was done before and after implantation and before and immediately after stent retrieval.

After the stents were retrieved an autopsy was done, stented elements of arteries and aorta were defined and photographed. After this the segments were fixed in formalin solution and sent to microscopic investigation.

In all cases during stent implantation and retrieval the animals were getting an injection of 5000 ME un-fractionated heparin. After implantation, before the stents were retrieved, all animals were getting injections of low molecular weight heparin - Nadroparin Calcium 2 850 ME twice a day.

Results

38 stents were implanted without complications. In two cases the stents did not open completely, necessitating balloon dilatation inside the stent. In two other cases distal dislocation of stents occurred. In these cases reposition of stents was achieved after additional intravascular manipulations. Retrieval of 40 stents was performed without complications. At the 2nd, 3d and 7th day after implantation all arterial segments were patent. There was one case of arterial spasm after stent retrieval, and one case case of an acute thrombosis of an artery immediately after stent retrieval. There were no cases of late migration or stent break, as well as no distal embolism.

Gross inspection of arterial segments 24 hours after implantation showed clear marks, caused by the stent's struts compression, on the arterial and aortic endothelium, with parts of subendothelial hemorrhage and parietal thrombosis (Fig.2). On the day 3 the macroscopic picture was almost the same (Fig.3). At day 7, however, notwithstanding the fact, that the stent's marks were clearly visible, the endothelium surface looked least of all damaged (Fig.4).

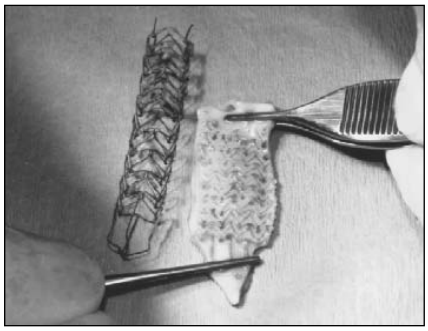


Figure 2. A segment of porcine abdominal aorta after the retrieval of a temporary stent. The stent (on the left) was retrieved on the 2nd day after the implantation

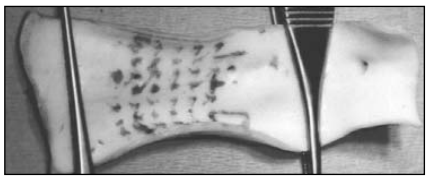


Figure 3. A segment of porcine abdominal aorta after the retrieval of a temporary stent. The stent was retrieved on the 3rd day after the implantation

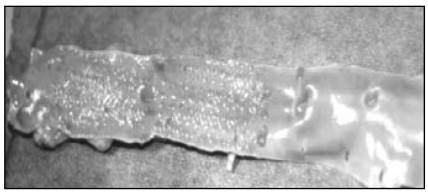


Figure 4. A segment of porcine abdominal aorta after the retrieval of a temporary stent. The stent was retrieved on the 7th day after the implantation

Morphological examination revealed two types of morphologic changes of vessel wall: In elastic arteries (aortic segments) stent wires compressed internal elastic lamina and media with local loss of smooth muscle cells in the media. Whereas in transitional type (iliac) arteries stent wires compressed internal elastic lamina and media with local necrosis of the media. Minimal amount of thrombotic material around the site of the area of the stent wires was present in this type of arteries in all segments (pic.5). Depending on the interval between the stent implantation and its retrieval, the examined areas differed in quantity of thrombotic material. Mural thrombosis was more characteristic of segments, where a stent was retrieved 24 hours after implantation. Following retrieval of the stent at day 7 mural thrombosis and subintimal hemorrhage was the least characteristic.

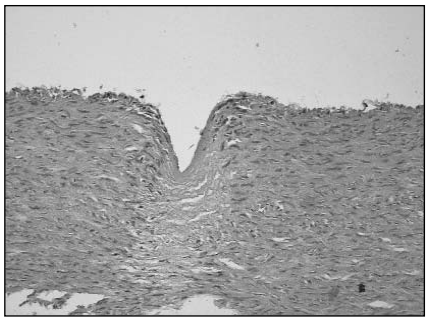


Figure 5. Micro-specimen of a segment of experimental animal's iliac artery. The mark left by the stent is seen on the 7th day, the destruction of the elements of smooth muscle layer is evident

Discussion

The idea of temporary device for management of dangerous complication of balloon angioplasty - occlusive dissection of intima - is not a new one.

Perfusion balloons appeared at the dawn of endovascular cardiology (3). They made it possible to perform long balloon dilatation as if "sticking" the intimal tears, keeping minimal level of blood flow distal to the lesion. In some cases this method makes it possible to eliminate dissection (4). The problem of dissection inside of artery became practically solvable with appearance of stents. Implantation of a stent became a routine, as it gives the opportunity to achieve better immediate and long-term results, compared to balloon angioplasty. At the same time restenosis inside a stent due to intimal hyperplasia induced by implant, is marked in 15-50% cases after stenting. Safe extraction of stent some time after its implantation theoretically may be without this drawback. Technically it may be performed in several ways. There are experimental studies of provisional nitinol stents with a "memory" effect (5;6). Instant warming of stent by physiological solution makes it possible to "fold" the stent to its minimal diameter and take it out through delivery device. Imperfection of such stents' design and risk of thermal damage of the vessel's wall made it impossible to introduce it in clinical practice. Another way is to use coils, that become smaller as they twist, and may be extracted through a catheter (7). It's well known, coil stents do not have enough radial rigidity, and as the result they are virtually not used in practice today.

We are not aware of any works dealing with the usage of a temporal stent, in which a well tested and clinically approved stent would be used. A number of positive characteristics of the ZA stent, among them its high radial rigidity, absence of shortening and flexibility give an opportunity to use it in different clinical situations. A fundamental possibility of safe retrieval of a temporary ZA-stent has been demonstrated in our work. It seems to be a technological achievement. We have also proved that the first effect of endoprosthesis replacement is preserved after stent retrieval as well. Temporal stent retrieval is optimal on day 7. If clinical research prove temporary stent effective in the future, it would be possible to use them as pharmacological matrix for the delivery of antiproliferative, cytostatic or anti-inflammatory agents to arterial endothelium.

In conclusion it is worth indicating that only immediate results of temporal stents

usage were estimated in our research. There is no doubt that the effect must be demonstrated in the long-term basic. The technique for the implantation and retrieval of temporal stent is tested on animals with intact arteries. Undoubtedly, experimental results cannot be fully extrapolated on patients with atherosclerosis.

Nevertheless, it should be noted that our experimental study demonstrated a possibility of safe implantation and retrieval of temporary vascular stents. It proved that after temporary stent retrieval the vascular wall undergoes minimal damage. The 7th day after implantation should be considered the most optimal term for temporal stent retrieval.

References

1.Rankin JM, Spinelli JJ, Carere R.G., et al. Improved clinical outcome after widespread use of coronary-artery stenting in Canada. N Engl J Med 1999; 341:1957-65

2. Edelman ER, Rogers C. Pathobiologic responses to stenting. Am J Cardiol 1998;81;4-6E.

3. Heuser RR, Mehta S, Strumpf RK. ACS RX flow support catheter as a temporary stent for dissection or occlusion during balloon angioplasty: initial experience. Cathet Cardiovasc Diagn 1992;27(1):66-74

4. Gibbs JS, Sigwart U, Buller NP. Temporary stent as a bail-out device during percutaneous transluminal coronary angioplasty: preliminary clinical experience. Br Heart J 1994;71(4):372-7

5. Eigler NL, Khorsandi MJ, Forrester JS, Fishbein MC, Litvack F. Implantation and recovery of temporary metallic stents in canine coronary arteries. J Am Coll Cardiol 1993;22(4):1207-13

6. Rechavia E, Fishbien MC, DeFrance T, Nakamura M, Parikh A, Litvack F, Eigler N.Temporary arterial stenting: comparison to permanent stenting and conventional balloon injury in a rabbit carotid artery model. Cathet Cardiovasc Diagn 1997; 41 (1):85-92

7. Stefanadis C, Kallikazaros L, Vlachopoulos C, Stratos C, Triposkiadis F, Toutouzas K, Toutouzas P. A new adjustable temporary stent catheter for management of acute dissection during balloon angioplasty. Cathet Cardiovasc Diagn 1996;37(1):89-98