

INTERNATIONAL JOURNAL OF INTERVENTIONAL CARDIOANGIOLOGY

Quarterly Journal of the Russian Scientific Society
of Interventional Cardioangioloogy

№ 11, 2006 г.

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

Address of the Editions:

101000, Moscow,
Sverchkov per., 5

Phone: (495) 624 96 36

Fax: (495) 624 67 33

Head of Editorial Office:

E.D. Bogatyrenko

Scientific editor of translations:

D.G. Gromov, S.P. Semitko,
O.G. Sukhorukov

Translation:

SWAN, NPO-Astek

Original layout prepared by:

A. Aksuk, V. Shelepukhin

**Computer type-setting and
makeup:**

I. Shishkarev

Corrector:

N. Sheludiakova

Special gratitude to

George Gigineishvili,

doctor and artist, for the offered
opportunity to put the photocopy of
his painting

"Interventional Cardioangioloogy" on
the cover of the magazine

Editorial Board

Editor-in-Chief D.G. Iosseliani

S.A. Abugov (Moscow)

A.M. Babunashvili (Moscow)

G.E. Belozеров (Moscow)

V.V. Chestukhin (Moscow)

V.V. Demin (Orenbourg)

D.P. Dundua (Moscow) – Managing Editor

A.A. Filatov (Moscow)

V.A. Ivanov (Krasnogorsk)

Z.A. Kavteladze (Moscow) – Deputy Editor-in-Chief

L.S. Kokov (Moscow)

A.V. Protopopov (Krasnoyarsk)

A.N. Samko (Moscow)

V.K. Sukhov (St. Petersburg) – Deputy Editor-in-Chief

B. E. Shakhov (Nijny Novgorod)

B.M. Shukurov (Volgograd) – Deputy Editor-in-Chief

Editorial Council

Andreas Adam (London)

I.S. Arabadjan (Moscow)

A.V. Arablinsky (Moscow)

V.A. Baranov (Yakutsk)

S.A. Biriukov (Riazan)

V.Yu. Bondar (Khabarovsk)

V.B. Boshkov (Moscow)

A.S. Bronstein (Moscow)

V.S. Buzaev (Ufa)

Antonio Colombo (Milan)

Carlo Di Mario (London)

Robert Dondelinger (Liege)

A.N. Fedorchenko (Krasnodar)

Francis Fontan (Bordeaux)

V.I. Ganiukov (Novosibirsk)

A.P. Golikov (Moscow)

O.G. Karakulov (Perm)

Matyas Keltai (Budapest)

A.F. Khamidulin (Kazan)

Spencer B. King III (Atlanta)

S.V. Kozlov (Ekaterinburg)

D.A. Korotkov (Siktivkar)

A.L. Krilov (Tomsk)

V.S. Kuzmenko (Kaliningrad)

S.G. Kuzmin (Belgorod)

V.V. Kucherov (Moscow)

N.V. Lapshina (Samara)

V.P. Mazaev (Moscow)

A.N. Maltsev (Ulianovsk)

Bernhard Meier (Bern)

E.V. Morozova (Penza)

A.P. Perevalov (Ijevsk)

V.G. Plekhanov (Ivanovo)

A.V. Pokrovsky (Moscow)

V.I. Prokubovsky (Moscow)

Witold Ruzyllo (Warsaw)

Yu.M. Saakian (Moscow)

Shigeru Saito (Kamakura)

S.P. Semitko (Moscow)

Patrick W. Serruys (Rotterdam)

V.I. Shumakov (Moscow)

Horst Sievert (Frankfurt)

Rudiger Simon (Kiel)

G.I. Sitnikov (Omsk)

V.A. Sulimov (Moscow)

A.G. Tirishkin (Barnaul)

A.F. Tsyb (Moscow)

A.Yu. Valkov (Arkhangelsk)

A.E. Vasiliev (Vladimir)

Jean-Charles Vernet (Bordeaux)

Alec Vahanian (Paris)

Yu.D. Volinsky (Moscow)

L. Samuel Wann (Milwaukee)

Petr Widimsky (Prague)

I.P. Zirianov (Tiumen)

ISSN 1727-818X



9 771727 818001

Instructions for authors

The International Journal of Interventional Cardioangiography (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 Cardioangiography.

All manuscripts should be addressed to:

Prof. David G. Iosseliani,
Editor-in-Chief,
International Journal
of Interventional Cardioangiography,
Sverchkov per., 5,
Moscow, 101000, Russia.
Fax: (7-495) 624 67 33
e-mail: davigdi@mail.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 Cardioangiography,
Sverchkov per., 5,
Moscow, 101000, Russia.
Fax: (7-495) 624 67 33
e-mail: davigdi@mail.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.

The manuscript should be typed double-spaced throughout, on one side only, on 22 x 28 cm (8.5 x 11") white paper with 3-cm margin on all sides (8-cm at bottom of title page). Please use a standard 10 cpi font or a laser printer font no smaller than 12 points.

Title page

Include the title, 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

Identify 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 consecutively in the order in which they are mentioned in the text.

Do not cite personal communications, manuscripts in preparation or other unpublished data in the references; these may be cited *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 clean photocopies in two separate envelopes. Two sets of glossy prints 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. All graphs and line drawings must be professionally prepared or done on a computer and reproduced as high quality laser prints. 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 title 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 duplicated 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.

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.

Board of the Russian Society of Interventional Cardioangiology

<i>President</i>	Kapranov S.A. (Moscow)
<i>Ivanov V.A. (Moscow-Krasnogorsk)</i>	Kozlov S.V. (Ekaterinburg)
	Koledinsky A.G. (Moscow)
<i>Vice-Presidents</i>	Korotkov D.A. (Syktyvkar)
<i>Iosseliani D.G. (Moscow)</i>	Krylov A.L. (Tomsk)
<i>Kokov L.S. (Moscow)</i>	Kuzmenko V.S. (Kaliningrad)
<i>Protopopov A.N. (Krasnoyarsk)</i>	Kukharchuk V.V. (Moscow)
<i>Kavteladze Z.A. (Moscow)</i>	Kuchеров V.V. (Moscow)
<i>Samko A.N. (Moscow)</i>	Mazaev V.P. (Moscow)
<i>Semitko S.P. (Moscow)</i>	Maltzev A.N. (Ulianovsk)
<i>Fedorchenko A.N. (Krasnodar)</i>	Morozova E.A. (Penza)
	Nemytin Yu.V. (Krasnogorsk)
<i>Board</i>	Oganov R.G. (Moscow)
<i>Abugov S.A. (Moscow)</i>	Osiev A.G. (Novosibirsk)
<i>Babunashvili A.M. (Moscow)</i>	Perevalov A.P. (Ijevsk)
<i>Belozеров G.E. (Moscow)</i>	Pokrovsky A.V. (Moscow)
<i>Bilan M.I. (Magnitogorsk)</i>	Prokubovsky V.I. (Moscow)
<i>Biriukov S.A. (Riazan)</i>	Sukhov V.K. (St. Petersburg)
<i>Bondar V.Yu. (Khabarovsk)</i>	Filatov A.A. (Moscow)
<i>Boshkov V.B. (Moscow)</i>	Khamidullin A.F. (Kazan)
<i>Buzaev V.S. (Ufa)</i>	Chestukhin V.V. (Moscow)
<i>Vasiliev A.E. (Vladimir)</i>	Shakhov B.E. (Nizny Novgorod)
<i>Volynsky Yu.D. (Moscow)</i>	Shukurov B.M. (Volgograd)
<i>Ganiukov V.I. (Novosibirsk)</i>	Shebriakov V.V. (Moscow region)
<i>Demin V.V. (Orenburg)</i>	
<i>Dolgushin B.I. (Moscow)</i>	<i>Secretaries</i>
<i>Dundua D.P. (Moscow)</i>	Arablinsky A.V. (Moscow)
<i>Zakharov S.V. (Moscow)</i>	Terekhin S.A. (Krasnogorsk)
<i>Zyrianov I.P. (Tiumen)</i>	

**Russia, 101000, Moscow, Sverchkov per., 5.
Moscow City Center of Interventional Cardioangiology
(for the Secretary of the Society)**

Phone.: (7-495) 624-96-36, 624-47-18.

Fax: (7-495) 624-67-33.

e-mail: info@noik.ru

website: www.noik.ru

HONORARY MEMBERS

of Russian Society of Interventional Cardioangiologology

COLOMBO Antonio

DORROS Gerald

FAJADET Jean

HOLMES David R., Jr.

IOSSELIANI David

KING Spencer B., III

MEIER Bernhard

PROKUBOVSKY Vladimir

RIENMULLER Rainer

SERRUYS Patrick W.

SHAKNOVICH Alexander

SIGWART Ulrich

SIMON Rudiger

SUKHOV Valentin

VAHANIAN Alec

VOLINSKY Youry

Milan, Italy

Phoenix, Arizona, USA

Toulouse, France

Rochester, Minnesota, USA

Moscow, Russian Federation

Atlanta, Georgia, USA

Bern, Switzerland

Moscow, Russian Federation

Graz, Austria

Rotterdam, Netherlands

New York, New York, USA

Geneva, Switzerland

Kiel, Germany

St.Petersburg, Russian Federation

Paris, France

Moscow, Russian Federation

Contents

INTERVENTIONAL CARDIOLOGY

The Possibility to Limit Reperfusion Injury of Cardiomyocytes Using Intracoronary Cytoprotectors During Endovascular Reperfusion of the Infarct-Related Artery D.G. Iosseliani, A.G. Koledinsky, N.V. Kuchkina	10
Endovascular Correction of Congenital Pathological Communications between Heart Chambers with Amplatzer Occluders Jozef Masura	17
Percutaneous Closure of Intracardiac Shunts and Left Atrial Appendage Anupam Bhambhani, Bernhard Meier	27
Clinical Outcome of Patients Undergoing Sirolimus-Eluting Stenting for Bifurcation Lesions Using the "Crush Technique" Issam Moussa	35
Transcatheter Alcohol Reduction of the First Septal Branch in the Treatment of Hypertrophic Obstructive Cardiomyopathy A.G. Ossiev, M.A. Vereschaguin, I.V. Maletina, A.M. Karaskov	40
Endovascular Surgery for Congenital Cardiovascular Pathology B.M. Shukurov, G.V. Kozlov, A.P. Dushkina, V.A. Nemchuk	43

INTERVENTIONAL ANGIOLOGY

Endovascular Approach to Arterial Injury G.Ye. Belozerov, N.R. Chernaya, A.B. Klimov, S.M. Bocharov, S.M. Prozorov, G.A. Isayev	48
Intravenous Stent-Filter to Prevent Pulmonary Embolism S.A. Kapranov, A.G. Zlatovratsky, V.F. Kuznetsova, A.N. Balan, A.A. Khachaturov	51

INTERVENTIONAL RADIOLOGY

Diagnostic and Therapeutic Radiology in Oncology B.I. Dolgushin	56
--------------------------------------------------------------------------	----

MISCELLANEOUS

LOZAP (Angiotensin-1-Receptor Antagonist) vs PRESTARIUM (ACE inhibitor) for the Treatment of Hypertension Prior to Endovascular Procedures I.Ye. Chernysheva, O.V. Zakharova, N.V. Kuchkina, M.V. Diagileva, D.G. Iosseliani	64
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----

The Possibility to Limit Reperfusion Injury of Cardiomyocytes Using Intracoronary Cytoprotectors During Endovascular Reperfusion of the Infarct-Related Artery

D.G. Iosseliani¹, A.G. Koledinsky, N.V. Kuchkina

Moscow City Center of Interventional Cardioangiography, Moscow, Russia

Earliest possible reperfusion of the infarct-related artery (IRA) is one of the most effective means to limit the injury area, minimize the consequences of acute myocardial infarction (AMI), thus improving the immediate and the long-term prognosis (6,8).

However, reperfusion of IRA in itself can cause reperfusion injury of myocardium. As a result, persistent contraction of myocardial cells, leading to their necrosis, can develop (2,3,22,25). Therefore, IRA reperfusion while producing favorable effect on the clinical course and prognosis of the disease, can initiate undesirable biochemical reactions inherent to myocardial reperfusion. Commonly used medical therapy of MI is mostly aimed at the decrease of myocardial oxygen demand or the increase of oxygen supply through vasodilation, having no substantial protective action on reperfused myocardium (23). Consequently, reperfusion procedures in MI become reasonable when the standard medical therapy is used in combination with agents effectively protecting the myocardium from reperfusion injury. For example, there are several agents called «metabolic», which protect hibernating or stunned myocardium (15,18,19,22).

The article analyses the results of studies of the effectiveness of two «metabolic» agents (Neoton and Mexicor) as regards to protection of ischemic myocardium from reperfusion injury in MI.

Neoton is an exogenous high-energy phosphocreatine - macroerg (ATP donor) widely used in myocardium as a reserve for rapid ATP production. Creatine kinase rapidly and effectively transforms phosphocreatine into ATP (Fig. 1). This transforma-

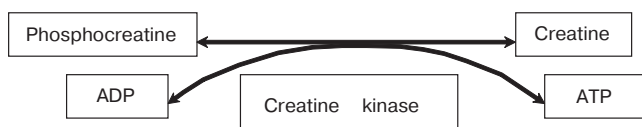


Figure 1. Scheme of biochemical action of exogenous phosphocreatine

tion hinders the function of sarcolemma in ischemic cardiomyocytes and stimulates the energy metabolism, thus decreasing the area of necrosis and ischemia. These properties have been confirmed in experimental models (26,27,28), where phospho-

creatine protected the myocardium from ischemic and reperfusion injury. However, clinical studies with intravenous administration of this agent in MI have failed to reveal significant preservation of the so-called «stunned» myocardium and the resulting limitation of injury area. The absence of clinical efficacy was explained by high bioavailability of this agent in various organs and tissues, which prevents the normal dose of drug from entering ischemic myocardium due to its absorption in other organs and tissues. Compromised access of the drug to the ischemic myocardium resulting from total coronary occlusion in the area also could contribute to ineffectiveness of its intravenous administration. Consequently, to obtain the required effect it would be necessary to find more effective access into ischemic myocardium using high doses of the drug. This has given rise to the idea of intracoronary administration of the drug during endovascular coronary recanalization.

The second agent – Mexicor (2-ethyl,6-methyl,3-hydroxypyridinsuccinate) – is analogous to Mexidol and has higher content of succinic acid (succinate), which is covalently bound to a potent antioxidant - emoxypin. The succinic acid enters the cardiomyocytes due to higher penetrating potential of emoxypin molecule. Mexicor is subsequently degraded in cytosol forming two products, each having positive effect: the first one – emoxypin – contributes to the decrease of free-radical processes, while the second one – succinic acid, participating the cycle of tricarboxylic acids, allows for FAD-dependent synthesis of ATP (acidosis is known to block the first half of the cycle, so that ATP can not be formed from NADN^+

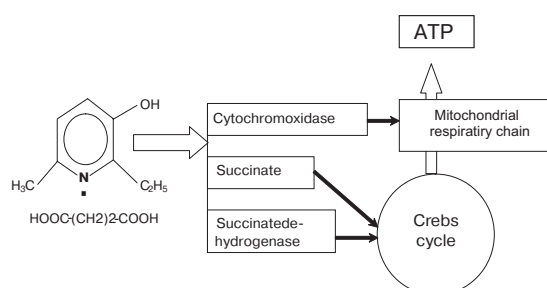


Figure 2. Scheme of Mexicor biochemical action

system, that is, the first half of the Krebs cycle is being blocked), producing higher amount of ATP for the cardiomyocyte as compared to glycolysis (Fig. 2). Pharmacodynamics of Mexicor lies in the stabilization of vascular wall structures, decreased platelet aggregation, improved blood rheology. The agent

¹ Moscow City Center of Interventional Cardioangiography
Russia, 101000, Moscow, Sverchkov per., 5
Phone: 007 495 624 96 36
Fax: : 007 495 624 67 33
e-mail: davidgi@mail.ru
Manuscript received on April 12, 2006
Accepted for publication on May 16, 2006

additionally reduces microcirculatory disorders at the early stages of atherogenesis. Most importantly, the drug improves blood supply and activates the metabolism of ischemic myocardium, thus decreasing the necrotic area and reducing the consequences of reperfusion syndrome in MI.

The publications reviewed suggest that there have been no clinical studies dedicated to intracoronary administration of Neoton and Mexicor after coronary recanalization.

This randomized study was aimed to the assessment of the potential of intracoronary Neoton and/or Mexicor in preservation of ischemic myocardium vitality in MI, as well as in prevention of myocardial reperfusion injury after IRA recanalization. Also we found it interesting to study clinical course and left ventricular function in our patients during their hospital stay.

Materials and Methods

The randomized study enrolled 103 consecutive patients with MI admitted to the Center of Interventional Cardioangiography between October 2004 and May 2005 within the first 5 hours after the onset of MI. Patients were randomly assigned to the three groups:

Group I included 21 patients with single intracoronary administration of phosphocreatine after recanalization and PTCA of IRA.

Group II included 38 patients who underwent intracoronary administration of Mexicor followed by medical therapy (see the regimen below) after recanalization and PTCA of IRA.

Group III included 44 patients who underwent recanalization and PTCA of IRA without intracoronary administration of any medications. These patients were used as control.

Primary inclusion criteria for MI patients were: ST elevation above 0.1 mV in two adjacent ECG leads; total occlusion of IRA (TIMI 0); successful reperfusion with PTCA and/or stenting (TIMI 2-3, \leq 30% residual stenosis). Patients with cardiogenic shock were not included in the study.

12-lead ECG was recorded and analyzed at baseline and at day 10 post-procedure.

Informed consent for participation in the study was obtained from all patients.

After the endovascular procedures all patients received standard disaggregant and antianginal therapy, which included acetylsalicylic acid 100 mg daily, Clopidogrel 75 mg daily throughout the entire hospital stay. All patients with systolic arterial pressure above 100 mm Hg received IV infusion of Nitroglycerine (0.25-0.5 μ g/kg/min) on the first day. The time period between the onset of pain and the reperfusion of IRA after recanalization and PTCA, i.e. the "door-to-balloon interval" was included into the analysis.

Table 1 shows basic clinical and laboratory values of patients in the study groups.

Table 1. Clinical variables, history and laboratory values in the study groups at baseline

Groups: Value:	Group 1	Group 2	Group 3	P
Age (years).	52.3 \pm 8.5	55.7 \pm 9.2	59.4 \pm 11.6	NS
Men	(90.9%)	(76.5%)	(83.3%)	P=0.04
Arterial hypertension	(54.5%)	(64.2%)	(58.3%)	P=0.05
Smoking	(63.6%)	(69.7%)	(66.7%)	NS
CAD history (months)	4.8 \pm 1.9	5.4 \pm 2.3	7.2 \pm 3.1	NS
Hypercholesterolemia (%)	54.5 \pm 29.1	67.3 \pm 24.1	58.3 \pm 18.6	NS
Diabetes mellitus	--	(2.6%)	(4.8%)	NS
History of MI	(14.6%)	(18.6%)	(15.8%)	NS
Acute left ventricular failure	(37.3%)	(24.2%)	(30.1%)	P=0.04

As stated in the Table 1, the majority of patients were smokers, had arterial hypertension and lipid metabolism disorders.

Most patients were admitted within 4 to 5 hours after the onset of pain. All patients had ECG changes characteristic of acute ischemic phase of MI. Rhythm disorders including isolated or paired ventricular extrasystoles were detected in 4 (18.2%) patients in Group I, 3 (7.8%) patients in Group II and 3 (6.8%) patients in Group III on admission. Impaired intraventricular conduction (left anterior hemiblock or left posterior hemiblock) was found in three patients (14.3%) from group I vs three patients (7.9%) from group II. Acute left ventricular heart failure was manifested by rales in the lower portions of lungs, dyspnea and tachycardia.

Selective coronary angiography (CA) and endovascular interventions (EI)

CA and EI were performed in all patients according to the established procedure by four specialists (each having an experience of over 300 interventions yearly). To ensure adequate assessment of angiometrical values at the site of occlusion the vessel was predilated with 1.5-2.0 mm balloon. The lesion was analyzed using digital computed angiography, subsequently the appropriate length and diameter of the balloon were selected. PTCA was successful in all patients: there were no signs of threatening dissection, distal embolization, or impaired antegrade perfusion. The amount of contrast medium per group was similar between the groups and within the normal range.

IV heparin was started with 70 U/kg bolus injection followed by slow infusion to provide activated coagulation time (ACT) of 250 to 300 seconds. Cytoprotectors were started during the first dilation of IRA and continued for the first 10 minutes at 1.0 ml/sec.

Total dose of intracoronary phosphocreatine (Neoton, ALFA WASSERMANN) in Group I was 2.0 g. In Group II patients received a total of 200 mg

Mexicor. Neoton was administered as an intracoronary bolus, whereas Mexicor was administered as IV infusion in a dose of 600 mg daily, 5-day cycle, followed by daily i.m. injections for additional 9 days in a dose of 600 mg. Subsequently the patients were administered oral Mexicor in a dose of 300 mg daily. No patient had any signs of adverse events.

To assess the coronary artery territory, as well as global and regional contraction of the left ventricle, all patients underwent repeated selective coronary angiography with left ventriculography at day 10. After the treatment left ventricular function was analyzed using digital quantitative image processing (Hicor, Siemens).

Assessment of myocardial injury

The extent of myocardial injury was assessed using serial quantitative analysis of cardiac enzymes – troponin I and myoglobin. Blood sampling (5 ml from cubital vein) to detect injury of cardiomyocytes in accordance with the established guidelines was performed during recanalization, 12 and 24 h thereafter (20). After the 15-min incubation the blood was centrifuged at 4000 rotation/min during 10 min. Serum was frozen at 20°C. Quantification of serum troponin I and myoglobin was performed using enzyme-linked immunosorbent assay with monoclonal antibodies to myoglobin and cardiac isoform of troponin I (Myoglobin ELISA, Troponin I ELISA, DRG Instruments GmbH, Germany) on a microplate photometer (E-Liza Mat-3000, DRG International Inc., USA) at 450 nm. Sensitivity of the diagnostic sets used to detect myoglobin and troponin I was 5.0 ng/ml and 1.0 ng/ml, respectively. Myocardial necrosis was diagnosed with troponin I above 1.5 ng/ml and myoglobin above 90 ng/ml.

All patients were treated in the ICU during the first 1-2 days followed by reallocation to the Department of Cardiology. There the patients were additionally examined, including 24-hours ECG monitoring, echocardiography and bicycle ergometry (at day 8). At day 10 all patients underwent repeated selective coronary angiography and left ventriculography with the assessment of global and regional left ventricular contraction. Mean hospital stay was 12.3 ± 1.9 days. One month after the disease onset the information on patients was acquired by phone.

Statistical analysis

All values are presented as mean \pm SD (standard deviation), groups were compared using paired t-test. Differences between proportional values were assessed using chi-square test. Analysis of myocardial reperfusion injury and segmental contraction function was performed using Wilcoxon's paired test. The analyzed clinical values were: age, total time of ischemia, left ventricular failure, intracoronary administration of phosphocreatine and Mexicor, lumen diameter at the site of PTCA, changes of troponin I level, changes of myoglobin level, changes of LVEF, LV end-diastolic

volume and end-systolic volume. Logistic regression analysis was used to assess serious complications 1 month after the disease onset. Statistically significant difference was defined as $p < 0.05$.

Results

Basic clinical and angiographic values, as well as the results of endovascular procedures, are shown in Table 2 and Fig. 3.

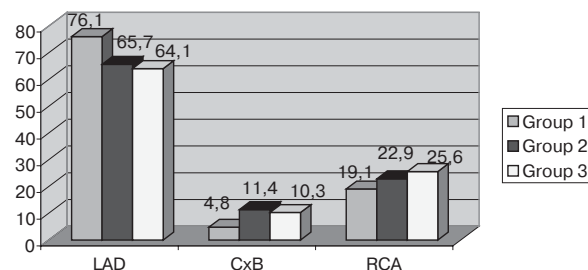
Table 2. Clinical signs, angiographic parameters and the results of endovascular procedures at baseline

	Group 1	Group 2	Group 3	p
The number of arteries involved	1.3 \pm 0.3	1.2 \pm 0.4	1.2 \pm 0.4	NS
Vessel diameter (mm)	3.5 \pm 0.3	3.4 \pm 0.3	3.3 \pm 0.4	NS
Occlusion length (mm)	23 \pm 6	21 \pm 7	24 \pm 6	NS
The presence of intra- or intersystemic pathways (%)	15.1	12.2	17.3	NS
IRA stenting (%)	0	21	8	P=0.02
Residual stenosis degree (%)	25	17	28	NS
Total time of ischemia (min)	318 \pm 35	288 \pm 24	294 \pm 24	NS
«Door-to-balloon» interval (%)	37 \pm 11	45 \pm 14	48 \pm 12	NS
Mortality rate (%)	0	0	0	NS

As shown in Table 2, most indices were similar between the groups, however, LAD occlusion was more common in Group 1 as compared to Groups 2 and 3. In 85% of cases there were no intra- or intersystemic collateral perfusion of IRA distal to occlusion. As stated above, IRA occlusion was managed with recanalization and PTCA. As shown on Fig. 3, LAD was the IRA in the majority of cases for all study groups.

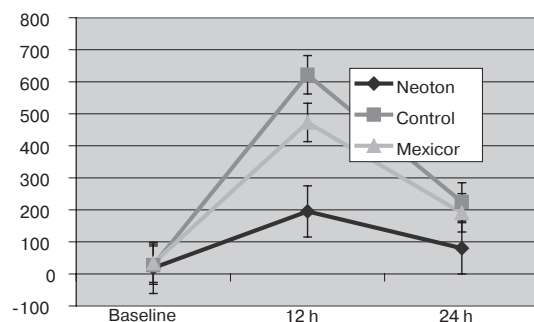
Serial study of serum cardiac enzymes revealed,

Figure 3. The frequency of endovascular interventions in various coronary arteries (%)



that the values were substantially higher than normal in all patients and peaked at 12 hours after the onset of heart attack. However, the level of serum enzymes was significantly different between the study groups ($p < 0.05$), (Fig. 4).

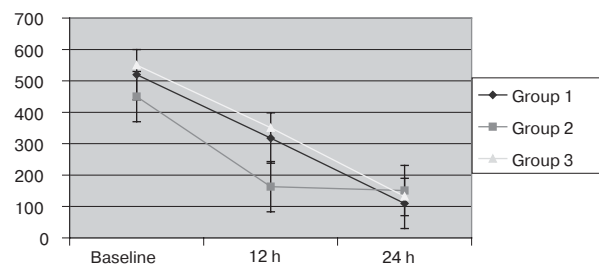
One can see that 12 hours after heart attack onset the level of troponin I in Group 3 was 690 ± 27.4 ng/ml, which was significantly higher compared to the other two groups (195.7 ± 31.9 ng/ml and 430.6 ± 25.3 ng/ml,

Figure 4. Changes of absolute troponin I level in the study groups (ng/ml)

respectively). At the same time, baseline value of this index was similar in all groups. This suggests the death of a larger mass of myocardium in group 3, as compared with two other groups.

Fig. 5 shows the profile of myoglobin – the earliest serum biochemical marker in MI.

As with troponin, the level of myoglobin was similar between the study groups at baseline

Figure 5. Changes of absolute serum myoglobin level in the study groups

(prior to endovascular interventions and intracoronary administration of cardiocytoprotectors in the first 2 groups), ($p>0.05$), i.e., there was no statistically significant difference, whereas at 12 hours after the disease onset and intracoronary administration of cytoprotectors myoglobin was significantly lower in Group II compared to Group III (163.1 ± 39.1 ng/ml and 351.2 ± 41.3 ng/ml, respectively).

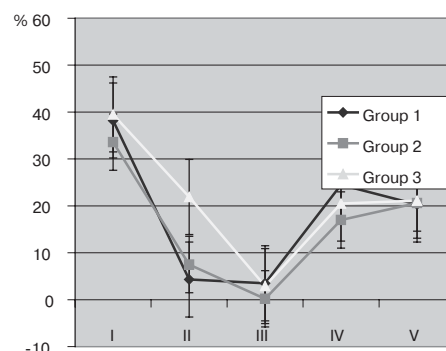
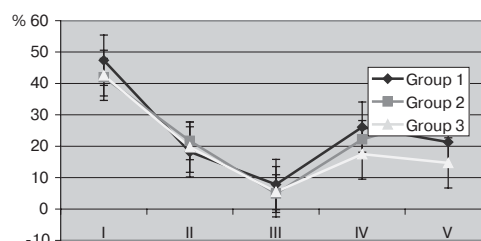
The results of left ventriculography performed at baseline and at day 10 in the patients studied are shown in Table 3, Fig. 6-10.

The study showed that in the majority of cases, the area of acute myocardial infarction as detected on ECG was characterized by LV akinesis, whereas intact LV segments were almost entirely hyperkinetic, which can be attributed to compensatory response of heart to the dysfunction of certain LV segments. Hyperkinesis, as revealed on serial echocardiography, decreased over time and the contractility returned to normal values within 1-2 weeks.

The study revealed significant increase in global LVEF at day 10 in the first 2 groups ($p<0.05$), in contrast, this parameter was decreased in Group III. The rate of postinfarction aneurysm formation was non-significantly lower in Groups I and II over Group III. This rate was 37.3%, 40.5% and 44.1%, respectively

Table 3. Global and segmental LV contraction in the study groups

		Baseline	Day 10	p
LVEF (%)	Group 1	39.4±7.3	50.8±5.4	<0.05
	Group 2	41.8±6.1	52.7±5.6	<0.05
	Group 3	52.1±5.8	48.9±7.2	NS
LV EDV (ml)	Group 1	176.2±11.4	180.4±15.2	NS
	Group 2	204.2±10.8	189.7±13.3	<0.05
	Group 3	172.6±9.2	190.5±12.5	<0.001
LV ESV (ml)	Group 1	106.7±7.3	88.8±8.1	<0.05
	Group 2	102.4±9.8	79.3±10.3	<0.05
	Group 3	94.6±9.6	97.3±11.4	NS
Segmental LV contraction (%)				
Segment I	Group 1	38.2±7.3	47.4±6.1	<0.05
	Group 2	33.6±5.1	42.0±5.9	<0.05
	Group 3	39.5±5.9	42.6±6.3	NS
Segment II	Group 1	4.3±6.7	18.2±7.5	<0.001
	Group 2	7.5±6.6	21.7±5.3	<0.001
	Group 3	21.9±7.3	19.7±5.5	NS
Segment III	Group 1	-1.5±7.4	6.8±5.9	<0.05
	Group 2	0.2±6.3	4.9±6.2	NS
	Group 3	2.9±6.3	5.5±7.6	NS
Segment IV	Group 1	24.5±5.6	26.1±8.9	NS
	Group 2	17.0±5.7	22.2±5.9	<0.05
	Group 3	20.5±4.8	17.5±6.2	NS
Segment V	Group 1	23.8±6.2	21.3±8.2	NS
	Group 2	20.6±6.0	30.1±6.4	<0.05
	Group 3	25.1±5.7	14.7±6.5	<0.05

Figure 6. Baseline segmental LV contraction in the study groups (%)**Figure 7.** Regional left ventricular ejection fraction in the study groups at day 10 (%)

for the study groups. Importantly, despite the higher baseline LV end-diastolic volume in Group II (Mexicor) as compared to Groups I and III ($p<0.05$), suggesting more severe impairment of the intracardiac hemodynamics, at day 10 LV function improvement in this very group was distinctly more pronounced than in two other groups.

cularization in MI, however, the effect was mainly produced by vasodilation in microcirculatory bed. The use of agents with cardiocytoprotective effect mediated by various mechanisms, including rapid replenishment of energy deficit in ischemic cardiomyocyte, is more effective and pathogenetically substantiated.

This became the basis for the study performed to assess the potential of two agents – Neoton and Mexicor, which can be regarded as cardiocytoprotectors due to their pharmacodynamics in intracoronary administration immediately after coronary artery reperfusion and the ability to prevent reperfusion myocardial injury and preserve the vitality of ischemic perinfarction myocardium in MI. Experiments have shown, that these agents effectively protected myocardium from reperfusion and ischemic injury, however, clinical studies failed to provide similar results, which was most likely due to high bioavailability of the agents in various organs and tissues, leading to the so-called steal-syndrome of the target organ, as the greater part of the dose was accumulated in other organs and tissues; merely 1/400 of the dose entered the infarction area at first passage. Secondly, this dose not necessarily was accumulated in the target area, as the passage to it was virtually closed by occlusion of the infarct-related artery. This brought us to the idea of intracoronary administration, thus avoiding the absorption of drugs by other organs and tissues and facilitating their transport to the target area, as the drugs were administered into the artery carrying blood to infarction site immediately after reperfusion. This route of administration is novel for such drugs and hasn't been used before, allowing the authors to patent the invention.

However, in contrast to experimental studies, it's very difficult to assess the size of affected and vital myocardial areas in clinical settings. Thus, we decided to use comparative dynamic analysis of cardiac enzymes (myoglobin, troponin I) as the efficacy criterion in patients, who were treated with cardiocytoprotectors or didn't receive them (9 -12). The second clinical efficacy criterion was the left ventricular function, as the extent of myocardial injury in the left ventricle is known to correlate inversely to its functional potential, namely the ejection fraction, end-diastolic and end-systolic volumes. The above parameters seem even more particularly convincing and informative in view of the fact that their baseline values were similar in the study groups and became different in the course of treatment. Baseline values of serum enzymes, as well as the left ventricular ejection fraction, were similar and had no statistically significant differences between the study groups. Before discussing the results it is reasonable to note, that intracoronary administration of Neoton in a total dose of 2 g, as well as Mexicor in a dose of 200 mg to AMI patients immediately after reperfusion of IRA, had no complications as regards to cardiovascular system in particular and the patients' health in

general. Consequently, the intracoronary administration of Neoton and Mexicor in AMI patients after reperfusion of the infarct-related artery is safe and has no serious complication during hospital stay. In addition, despite the similarity of clinical and laboratory values, including cardiac enzymes (troponin I, myoglobin) and global left ventricular ejection fraction, between the study groups at baseline, we found statistically significant difference between the AMI groups treated and not treated with intracoronary agents at 12 h after the disease onset – the time, when the peak serum concentration of cardiac enzymes is achieved in MI (13). The 12 h level of troponin I and myoglobin was 195 ng/ml and 430 ng/ml in groups I and II, respectively, which is significantly lower compared to Group III (690 ng/ml). At 24 h these values decreased and there were no difference between the study groups. Importantly, the total values of serum cardiac enzymes concentration were significantly lower in Groups I and II as compared to Group III (control). According to the results there is a high probability that patients receiving intracoronary Neoton and Mexicor immediately after reperfusion of IRA (approximately 4.0 to 4.5 hours after the disease onset) had significantly smaller extent of myocardial injury as compared to patients, who didn't receive intracoronary cardiocytoprotectors. An indirect evidence of this assumption is the fact that the left ventricular ejection fraction increased in Groups I and II at day 10 and only insignificantly changed in Group III. Repeated measurement of LVEF was performed at day 10, as stated above. This is the time, when, according to various authors, the compensatory hyperkinesis observed in AMI patients at the early stages disappears. As mentioned above, we found significant increase of LVEF in groups receiving intracoronary administration of metabolic cytoprotectors, as well as the positive changes of end-systolic volume. According to some authors, the end-systolic volume is one of the major predictors of the long-term outcome (29). Considering the significant decrease of the end-systolic volume in Groups I and II, we can conclude, that intracoronary cytoprotectors have favorable impact on the prognosis and prevention of consequent LV remodeling.

Therefore, the study brought us to a conclusion, that intracoronary administration of metabolic agents (Neoton and Mexicor) in acute myocardial infarction immediately after reperfusion of the artery is safe and has no significant clinical complications. At the same time, compared to AMI patients, who didn't receive such treatment, patients on intracoronary Neoton or Mexicor had significantly lower serum level of cardiac enzymes, which is the indirect evidence of smaller necrotic area in the infarction site. This is additionally indicated by the fact, that AMI patients receiving intracoronary Neoton or Mexicor had significantly higher LVEF, than patients without such treatment. Particularly important is the fact, that there were no statistically significant difference

in the level of enzymes and left ventricular function between the study groups at baseline.

The facts indicated above confirm the assumption, that Neoton and Mexicor have favorable impact on preservation of ischemic, but vital myocardium, and prevention of myocardial reperfusion injury. However, small sample size precludes from the far-reaching conclusions and necessitates additional experience.

References:

1. Strukov A.N., Serov V.V. Human Pathological Anatomy. Moscow, Meditsina, 1993, p. 98.
2. Spirilakis N. Physiologu and Pathophysiology of the Heart. Moscow, Meditsina, 1988, v.2, p.348-349.
3. Bilenko M.V. Ischemic and Reperfusion Injuries of the Organs. Moscow, Meditsina, 1989.
4. Syrkin A.L. Myocardial Infarction. Moscow, Meditsina, 1991, p. 38-40.
5. Korpachova O.V., Viskov R.V. et al. Pathogenesis and Clinics of the Extreme States. Omsk, 1998. Proceedings of Scientific and Practical Conference.
6. Iosseliani D.G., Filatov A.A., Rogan S.V. et al. Restoration of Blood Flow in the Infarct-Related Artery: Effective or Just Spectacular? International Journal of Interventional Cardioangiologiy, 2003, 1, 33.
7. Van't Hof A., Liem A., Syapranata H. et al.. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction. Circulation, 1998, 97, 2302-2306.
8. Bilenko M.V. Theoretical and Experimental Basement for Antioxydant Therapy Use in the Prevention of Acute Ischemic Damage of the Organs. Moscow, Nauka, 1982, p. 195-213
9. Ravkilde J., Horder M., Gerhardt W. et al. The predictive value of cardiac troponin T in serum of patients suspected of acute myocardial infarction. Scand. J. Clin. Invest., 1993, 53, 677-85
10. Plebani M., Zaninotto M. Diagnostic strategies in myocardial infarction using mioglobin measurement. Eur.J.Cardiol., 1998, 19 (Suppl. N1), 12-15.
11. Chapelle J.P. Cardiac troponin J and troponin T: recent players in the field of myocardial markers" Clin. Chem. Lab. Med., 1999, 37(1), 11-20
12. Filippenko M.B., Staroverov I.I. et al. Determination of Cardiac Troponin T and Creatine Kinase Mass in the Diagnostics of Acute Myocardial Infarction. Kardiologia, 2001, 3, 17-20.
13. Katus H.A., Remppis A., Scheffold T. et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am. J. Cardiol., 1991, 67(16), 1360-1367.
14. Golikov A.P., Riabinin V.A., Pavlov V.A. et al. Therapeutic possibilities of Phosphocreatine Use in Complicated Myocardial Infarction. Kardiologia, 1987, 5, 50-53.
15. Golikov A.P., Riabinin V.A., Golikov P.P. et al. Effectiveness of Emoxypine and Neoton in Unstable Angina. Ther. Arkhiv, 1996, 1, 33.
16. Stewart J.T., French J.K. et al. Early noninvasive identification of failed reperfusion after thrombolysis in acute MI. J. Am. Coll. Cardiol., 1998, 31, 1, 1499-505.
17. Golikov A.P., Polumiskov V.Yu., Rudnev D.V. et al. What's New in the Prevention and Diagnostics of Reperfusion Injury in Myocardial Infarction. Abstr. of the 12th Congress of Therapeutists of the Ukrainian SSR (Ivano-Frankovsk, September 24-26, 1987). Kiev, 1987, 72-73
18. Rudnev D.V., Pichugin V.V., Konorev E.A. et al. Diagnostics and Prevention of Myocardial Reperfusion Injury in the Conditions of Experimental Myocardial Infarction. Kardiologia, 1988, 28, 12, 94-97;
19. The EMIR-FR GROUP. Effect of 48 intravenous trimetazidine on short-and long-term outcomes of patients with acute myocardial infarction, with and without thrombolytic therapy. Eur. Heart. J., 2000, 21, 1537-1546;
20. Iosseliani D.G., Koledinsky A.G., Kuchkina N.V. Does Intracoronary Injection of Phosphocreatine Prevent Myocardial Reperfusion Injury Following Angioplasty of Infarct-Related Artery in Acute Stage of Myocardial Infarction?, 2004, 6, 11.
21. Galankina I.E. Hemorrhagic Myocardial Infarction (Patho- and Morphogenesis). Doctoral Thesis. Moskva, 2004.
22. Shakhnovich R.M. Optimization of Energetic Metabolism in Patients with Ischemic Heart Disease. Russky Meditsinsky Journal, 2001, 15, 14-19.
23. Lopaschuk G., Belke D., Gamble J. et al. An imbalance between glycolysis and glucose oxidation. J. Pharm. Exp. Therap., 1993, 264, 135-144.
24. Ambrosio G., Tritto P. Reperfusion injury: experimental evidence and clinical implications. Am. Heart J., 1999, 138, 869-875.
25. Kloner R.A., Ganote C.E., Jennings R.B. The no-reflow phenomenon after temporary coronary occlusion in the dog. J. Clin. Invest., 1974, 54, 1496-1508.
26. Kuznetsov A.V., Khuchua Z.A., Saks V.A. Mitochondrial Phosphocreatinine Synthesis in Physiological Conditions. Eksperimentalnaya Kardiologia, 1989.
27. Kuprianov V.V., Lakomkin V.L., Shteinshneider A.Ya. et al. Role of Phosphocreatinine and ATP in Energy Procurement of Heart Contractions: Investigation using 31r-NMR Method. Eksperimentalnaya Kardiologia,, 1989.
28. Kryzhanovsky S.A., Kandelaki I.N. et al. Exogenous Phosphocreatine Influence on the Size of Experimental Myocardial infarction. Eksperimentalnaya Kardiologia, 1989.
29. White H.D., Norris R.M., Brown M.A., et al. Left ventricular end-systolic volume as major determinant of survival after recovery from myocardial infarction. Circulation, 1987, 76, 44-51.

Endovascular Correction of Congenital Pathological Communications between Heart Chambers with Amplatzer Occluders

Jozef Masura¹, MD, PhD

Children's Cardiac Center, University Children's Hospital, Bratislava, Slovakia.

Key words: atrial septal defect, patent ductus arteriosus, perimembranous ventricular septal defects; Amplatzer eccentric occluder; interventional cardiology,

Part 1

Percutaneous closure of perimembranous ventricular septal defects with the eccentric Amplatzer device: multicentric follow up study

Introduction

Ventricular septal defect (VSD) accounts for approximately 20% of all forms of congenital heart disease. PMVSD is the most common congenital cardiac malformation. About 75% of all VSDs are located in the mid portion of the upper region of the ventricular septum and are related to the aortic valve. Such VSDs are termed perimembranous trabecular defects or infracristal, subaortic, or type II Kirklin (1). Treatment has been classically indicated in the presence of significant left-to-right shunt resulting in left ventricular overload. Surgery has been performed safely at very low rates of mortality, although complications such as residual leaks, atrioventricular block (2) occurred. Occasional percutaneous attempts to close PMVSD with Raskhind and button device have been reported, however with high incidence of residual shunt and complications. The main reason was that those devices were designed for atrial septal defect (ASD) or patent ductus arteriosus (PDA) occlusion. (3,4,5).

A new device, the Amplatzer membranous VSD occluder with eccentric shape has been designed by AGA Medical Corporation (Golden Valley, Minnesota) specifically for this particular anatomical region to avoid previous problems and minimize potential risk for surrounding structures (6). Recent publications have reported the feasibility, safety and efficacy with the use of the Amplatzer membranous VSD occluder. The device description and device implantation technique have been previously well described (7-10).

In this paper, we report multicentric experience with Amplatzer eccentric PMVSD occluder focusing

on closure rate and ECG changes after implantation. Only centers with provable follow-up data were included in the study.

Results

One hundred eighty six patients (102 males, 84 females) with average weight of 43.5 (12.5 -77 kg) underwent an attempt at catheter closure of a perimembranous ventricular septal defect (PMVSD). Their age ranged from 3 to 51, an average age being 15.9 years (Table 1). The patients were divided into 3 groups according to the morphology of PMVSD.

Tabl. 1 Groups of patients

Age	15,9 (3-51) years
Weight	43,5 (12,5-77) kg
Size	5,1 (2,8 – 12,8) mm
Defect size	75, (4-16) mm
Fluoroscopy time	46,5 (15-140) min
Number of patients	186 (102 males, 64 females)

106 pts presented with single PMVSD; 63 pts with single PMVSD with aneurysmatic formation and 17 pts with multiple VSD with aneurysmatic formation. ACG size was measured between 2.5 and 12 with an average of 5.1 mm. In the last group of patients we did not measure the size of PMVSD and a device was selected according to the size of entry to aneurysm. The device was successfully implanted in all patients. The immediate closure rate was 90% in the first group and increased to 100% at 1 month and remained at that level during all follow up. The immediate closure rate in second group was 98% and remained the same during all follow up. The immediate closure rate in third group was 89% and during one-year follow-up remained the same. There was no clinical evidence of hemolysis and no incidence of device embolization or bacterial endocarditis after implantation.

ECG changes

Before the procedure, all patients showed normal ECG or LV enlargement. After the procedure (at least 3 months later) ECG in 9 pts showed left anterior hemi-

¹ Jozef Masura MD, SCAl,
University Children's Hospital, Cardiology center SR,
Limbova 1, 833 51
Bratislava 37, Slovakia
Tel: +4212 54792318
FAX: +4212 54792317
E-mail: masura@dkch.sk
Manuscript received on May 10, 2006
Accepted for publication on June 27, 2006

block (LAH), in 8 pts - complete right bundle branch block (CRBBB), in 7 pts - incomplete right bundle branch block (IRBBB). A complete heart block (CHB) developed in 2 pts after the procedure (1,07%). First patient developed LAH immediately after closure and CHB within 24 hours. The heart rate was 28/min. After treatment with steroids and atropine, CHB changed to sinus rhythm with LHA within two months. One year later, the ECG revealed the same findings. The second patient developed CHB immediately after procedure and was on temporary pacing for one week. After one month the patient recovered to sinus rhythm and ECG showed LAH.

Discussion

According to AGA registry over 1000 PMVSD's were closed with Amplatzer eccentric device. Technically speaking, the procedure is well established with high success rate, complications are small and are comparative to surgery (6-11). As described previously, angiography and TEE revealed a wide variation of VSD morphology, size and location (11,12). During the procedure following the placement of long sheath to the left ventricle, we found very helpful another LV angiogram. Not only for the proper device selection but for exact anatomy of PMVSD as well (Figure 1).

Morphological variation plays an important role during the device selection. Our policy in first group of PMVSD with single hole without aneurysm is to try to use as small device as possible. We used either the same size of device or 2 mm larger than the PMVSD. In the second group we used a device about 4 mm larger. In the most difficult third group with aneurysmatic formation and multiple holes we used as big device as possible to cover the whole entry space of aneurysm. After implantation many devices showed "mushrooming" effect of the body and right disc. Although non-from third group developed CHB the incidence of residual shunt was the highest. During the follow up period of 3 months to 2 years, the first group showed the best results and the second group very good results. The results in the last group are also encouraging although the new design of device might be helpful.

Conduction abnormalities and arrhythmias are well described after atrial septal defect closure using the Amplatzer septal occluder and ventricular septal occluder (10-13). In our paper we report two patients (1,07%) with CHB after device placement. After medical treatment and temporary pacing both resolved within one week and two months respectively. Another conduction abnormality appeared very soon after implantation and did not change during intermediate follow up. The conduction abnormalities are comparable with the surgery (2). However, long term follow up studies will be necessary to determine late arrhythmia disturbances and prospective study with patients after surgery and transcatheter treatment of VSD will be necessary.

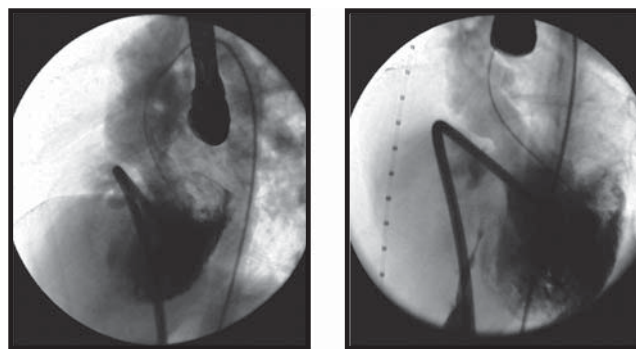


Figure 1. Left ventricular angiogram after long sheath placement.

Conclusion

Intermediate results of transcatheter closure PMVSD seem to be promising with high closure rate and lower morbidity comparable with surgery. After long term follow-ups a complementary procedure to the surgery might be carried out.

References:

1. Rudolph A.M. Ventricular septal defect. In: Rudolph AM, editor. Congenital diseases of the heart: clinical-physiological considerations, 2nd ed. Armonk, NY, Futura, 2001, p 197-244.
2. Backer C.L., Winters R.C., Zales V.R. et al. The restrictive ventricular septal defect: how small is too small to close? Ann. Thorac. Surg., 1993, 56, 1014.
3. Rigby M.L., Redington A.N. Primary transcatheter umbrella closure of perimembranous ventricular septal defects. Br. Heart J., 1994, 72, 368-371.
4. Vogel M., Rigby M.L., Shore D. Perforation of the right aortic valve cusp: complication of ventricular septal defect closure with a modified Rashkind umbrella. Pediatr. Cardiol., 1996, 17, 416-418.
5. Sideris E.B., Walsh K.P., Haddad J.L. et al. Occlusion of congenital ventricular septal defects by the buttoned device. Heart, 1997, 77, 276-279.
6. Gu X., Han Y.M., Titus J.L. et al. Transcatheter closure of membranous ventricular septal defects with a new Nitinol prosthesis in a natural swine model. Catheter. Cardiovasc. Interv., 2000, 50, 502-509.
7. Hijazi Z.M., Hakim F., Haweleh A.A. et al. Catheter closure of perimembranous ventricular septal defects using the new Amplatzer membranous VSD occluder: Initial clinical experience. Catheter. Cardiovasc. Interv., 2002, 56, 508-515.
8. Bass J.L., Karla G.S., Arora R. et al. Initial human experience with the Amplatzer perimembranous ventricular septal occluder device. Catheter. Cardiovascular. Interv., 2003, 58(2), 238-45.
9. Hijazy Z.M. Catheter closure of atrial septal and ventricular septal defects using the Amplatzer devices. Heart, Lung and Circulation, 2003, 12 (supplement), S63-72.
10. Thanopoulos B.D., Tsaousis G.S., Karanasios E et al. Transcatheter closure of perimembranous ventricular septal defects with the Amplatzer asymmetric ventricular septal defect occluder: preliminary experience in children. Heart, 2003, 89(8), 918-22.
11. Pedra C.A., Pedra S.R., Esteves C.A. et al. Percutaneous closure of perimembranous ventricular septal defects with the

Amplatzer device: technical and morphologic considerations. Catheter. Cardiovasc. Interv., 2004, 61(3), 403-10.

12. Arora R., Trehan V., Kumar A. et al. Transcatheter closure of congenital ventricular septal defects experience with various devices. J. Interv. Cardiol., 2003, 16(1), 83-91.

13. Hill S.L., Berul C.I., Patel H.T. ET AL. Early ECG abnormalities associated with transcatheter closure of atrial septal defects using the Amplatzer septal occluder. J. Interv. Card. Electrophysiol., 2000, 4(3), 469

Part 2

Amplatzer septal occluders and long-term outcome of transcatheter secundum-type atrial septal defect

Introduction

Transcatheter closure of secundum-type atrial septal defect (ASD II) is an increasingly widespread alternative to surgical closure (1). More than 30 years ago the first devices for transcatheter closure of secundum atrial defects required large introduction systems and were implanted in only a very limited number of older children and adults. Since then, the number of recently developed devices has increased considerably with various improvements, such as smaller – sized introduction systems and retrievable elements. It has become evident, however, that these patch types of occlusion devices can not be used in a significant proportion (up to 50%) of pediatric patients who have large defects with diameters greater than 20 mm, a small deficient atrial septal rim near the aorta, or defects with multiple interatrial communications. Furthermore, follow-up studies of more frequently used devices, such as the Bard Clamshell device (USCI, Billerica, MA) or the Buttoned device (Custom Medical Devices, Amarillo, TX) show a high incidence of residual shunts, late fracture of one or more arms, and unbuttoning or whole-device embolization. In animals, Sharafuddin et al. demonstrated the efficacy and safety of a new and different approach to closure by stenting the interatrial communication with a Nitinol prosthesis. This device, the Amplatzer Septal Occluder (ASO), appeared to overcome most of the disadvantages of previous devices, and the first clinical trials of its use started in September 1995 in Bratislava, Slovak Republic. The Amplatzer septal occluder (ASO) is currently one of the most frequently used devices for transcatheter closure of ASD II (2). Immediate-, short- and intermediate-term results of percutaneous closure of ASD II using ASO are promising (2,3,4,5,6). However, long-term data after ASO implantation are lacking. Therefore, the purpose of the present study was also to evaluate a long-term outcome of transcatheter closure of ASD II using ASO in a single institution.

The procedure

The procedure was done under general anaesthesia and transesophageal echocardiographic guidance. Before catheterization, a biplane transesophageal echocardiogram (TEE) was performed to evaluate the location and size of the defect and its distance from the superior and inferior vena cava, right pulmonary veins, aortic root, AV valves, and coronary sinus. Vascular access was obtained percutaneously from the right femoral vein, and heparin (100 IE/kg) and antibiotics (flucloxacillin 100 mg/kg) were administered intravenously. A complete hemodynamic evaluation was done, and contrast injec-

tions into the left innominate vein and the right upper lobe pulmonary vein were performed. To determine the stretched diameter of the defect and to select a device of corresponding size, a Meditech sizing balloon catheter (Boston Scientific Corporation, Watertown, MA) was passed to the left atrium, inflated with diluted contrast medium, and pulled back against the septum until the balloon passed into the right atrium with only slight resistance. After recording the inflation volume, the balloon was deflated, removed, reinflated, and passed through a sizing plate. Latter AGA sizing balloon with markers was used.

A 7-F long sheath was introduced (an 8-12 F sheath was used for devices greater than 17 mm) over an exchange guidewire and passed into the left midatrium. The device was screwed onto the tip of the delivery cable, immersed in saline solution, and pulled into a short loader, which was inserted into the long sheath. By pushing the delivery cable, the device was delivered into the sheath. The left atrial disc and the waist of the device were deployed into the left atrium under fluoroscopic and TEE guidance. The partially deployed device was pulled against the septum which resulted in self-centering of the device within the defect. By fixing the delivery cable with one hand and withdrawing the sheath with the other hand, the right atrial disc was deployed. Before unscrewing the device, a careful TEE investigation was carried out to document the proper position of the device and to demonstrate the sites of the AV valves, the superior vena cava, the coronary sinus, and blood flow in the right upper pulmonary vein. In addition, the secure and stable position of the device was checked by gentle pushing and pulling of the delivery cable (Minnesota Wiggle). The device was deployed by unscrewing it from the cable. Then a right ventricular angiogram, a fluoroscopic study of the device, and a final TEE examination were performed to evaluate the position of the device and to identify any residual shunting. After the procedure the patients were transferred to an intensive care unit and received intravenous heparin (400IE/kg/day) for 24 h, followed by oral aspirin (2-3 mg/kg/day) for 6 months.

Before discharge, the patients underwent a clinical evaluation with an ECG, TTE, and a bipane chest X-ray. Further follow-up examinations at 1,3,12, and 24 months after implantation included an ECG and TTE. A biplane chest X-ray was repeated at 12 months and yearly than after.

Methods

Patient population

From September 1995 to January 2006, 420 patients having isolated ASD II underwent transcatheter closure using ASO. Patients from September 1005 to January 2000 were followed up until May 2004. All patients were included in our previous study analysing morphological characteristics of isolated

ASD II (7). At the time of implantation, the mean patient age was 11.9 ± 11.6 years and weight 36.0 ± 20.9 kg. The study was part of a clinical trial approved by an authorised ethics committee. An informed written consent has been obtained from all patients or their parents.

The Amplatzer Septal Occluder (AGA Medical Corporation, Golden Valley, MN, USA) is constructed as a round, self-expanding, self-centering, and repositionable double disc device. (fig. 2 a, b).

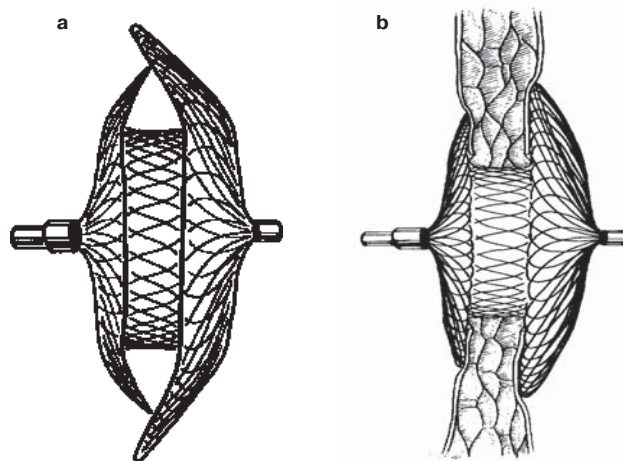


Figure 2.

Mechanisms of leakage-proof closure with the Amplatzer.

a) The two retention discs are angled inward with the right atrial retention disc slightly smaller than the left, resulting in tight cross-clamping against the septal margin around the defect

b) Closure is accomplished by a combination of two mechanisms: 1) impaction of the defect by direct stenting with the central waist of the device, and 2) Dacron-augmented secondary thrombosis

The disc consists of a tightly woven mesh of 72 Nitinol wires (wire diameter 0.004-0.005 inch). The two discs are connected by a short, cylindrical waist. In order to stent the defect, the diameter of the waist has to correspond to the so-called stretched diameter of the defect, determined by a sizing balloon catheter. Devices with waist diameters from 4 to 40 mm are available. For device sizes between 4 and 10 mm waist diameter, the left atrial disc is 12 mm larger than the connecting waist and the right atrial disc is slightly smaller (8mm). For device sizes between 11 and 40 mm, the left atrial disc is 14 mm larger than the waist and the right atrial disc is 10 mm larger. To induce stasis and thrombosis, polyester patches are sewn to the retention discs and into the waist. The device is connected to a delivery cable by a microcrew affixed to the right atrial disc and withdrawn into a loader for introduction into a long 7-12 F curved long catheterization sheath.

Selection of patients suitable for transcatheter closure

The selection of patients suitable for a transcatheter closure using ASO was based on the measurement of the maximal defect diameter and morphological characteristics of the defect. In fact, ASD II characteristics of all patients included in the present study were reported in details previously (7). Briefly,

transesophageal echocardiography (TEE) was performed in all patients deemed after transthoracic echocardiography (TTE) to be suitable candidates for percutaneous closure and in patients with TTE of inadequate quality. Both TTE and TEE were performed using Hewlett-Packard Sonos 1000 and 5500 echocardiographic machines (Andover, MA). TEE examination was performed with a 5.0/7.5 MHz biplane pediatric transesophageal probe. Percutaneous closure has been attempted in patients having a maximal TEE diameter of the defect < 30 mm as well as one of the following morphological defect variations: a centrally placed defect, a defect with a deficient superior anterior rim, a perforated aneurysm of the interatrial septum or multiple defects of the interatrial septum. Thus, patients with TEE defect diameter > 30 mm and totally or partially deficient (< 5 mm) inferior posterior rim, inferior anterior rim, superior posterior rim, posterior rim or rim toward the opening of the coronary sinus were referred for surgical closure and were not included in the present study.

Follow-up protocol

Immediately after the ASO release, a precise TEE examination was performed. The shape of the occluder was evaluated. At the same time, thrombus formation on the device was sought. A detailed color Doppler interrogation of the interatrial septum was performed to detect and quantify any residual shunts. A color Doppler signal width < 2 mm was considered as a small residual shunt, 2 - 4 mm as a moderate shunt and > 4 mm as a significant residual shunt. Relationships between the occluder and both atrioventricular valves were evaluated. In particular, an encroachment of the ASO upon either of the atrioventricular valves was sought. Drainage of both caval veins, right pulmonary veins and the coronary sinus were evaluated for obstruction.

At 24-hour follow-up, ECG, chest radiograph and TTE were performed. Both chest radiograph and TTE allowed evaluation of the ASO shape. Thrombi on both discs of the ASO were searched for using TTE. Residual shunts were sought and quantified using the same color Doppler criteria as during TEE examination. A relationship of both atrioventricular valves toward the occluder was assessed. Drainage of both caval veins, right pulmonary veins and coronary sinus were evaluated for obstruction.

Thereafter, follow-up ECG and TTE were performed at 1 month, 3 months, 12 months and then annually after the implantation. The same TTE examination protocol was used throughout a follow-up period as performed 24 hours after the procedure. In addition, complications related to the ASO implantation were noted at each follow-up visit. Aspirin, 5 mg / kg daily, was prescribed for 6 months after the procedure in all patients. Infective endocarditis prophylaxis was recommended during the same time period.

Statistics

The data are expressed as mean \pm SD or as median and ranges as appropriate.

Results

There were no deaths, cardiac perforations, device embolization s or malpositions, thrombus formations or thromboembolisms, significant arrhythmias, infective endocarditis or other morbidity associated with ASD II closure during the entire follow-up period ranging from 52 to 104 months (median 74).

The mean maximal defect diameter measured by TEE was 12.9 ± 4.4 mm. The mean stretched defect diameter was 15.9 ± 4.8 . The defect with a deficient superior anterior rim was revealed in 80 patients (53.0%), centrally placed defect in 45 patients (29.8%), perforated aneurysm of the interatrial septum in 15 patients (9.9%) and multiple defects of the interatrial septum in 11 patients (7.3%) (7). Altogether, 152 occluders have been implanted. Two occluders were implanted in a single patient having two widely - separated defects. The mean size of the implanted ASO was 16.1 ± 5.3 .

Immediate complete closure assessed by TEE was achieved in 120 of 151 patients (79.4%). Residual shunts were moderate in 6 patients (3.9%) and small in 25 patients (16.5%). Twenty-four hours after the procedure TTE revealed a complete closure in 138 patients (91.3%) and residual shunts in 13 patients (8.6 %) with 4 patients having moderate (2.6%) and 9 patients small residual shunts (5.9%). At 1-month follow-up complete closure was confirmed in 144 patients (95.3%). Moderate residual shunts were detected in 3 patients (1.9%) and small shunts in 4 patients (2.6%). Three months after the procedure the defect was completely closed in 149 patients (98.6%). A moderate residual shunt was present in 2 patients (1.3%). A follow-up at 1-year revealed complete closure in 150 patients (99.3%). A residual shunt in a single patient (0.6%) was small. At 3-years follow-up evaluation all defects were completely closed and remained closed thereafter.

The mitral valve and tricuspid valve were not encroached on by the occluder in any patient in the study. Both caval veins, right pulmonary veins and the coronary sinus drained freely in all patients during the follow-up period.

Deformation of implanted occluder or occluder integrity problems were not detected during follow-up in any patient.

Discussion

The present study demonstrates an excellent outcome of percutaneous ASD II closure using ASO during a follow-up period ranging up to 8.6 years. The transcatheter closure by ASO proved safe – no deaths or significant complications were observed in this study. All defects were completely closed at 3-years follow-up evaluation demonstrating effectiveness of ASO implantation.

Safety of ASD II closure using ASO

Complications of percutaneous ASD II closure using ASO reported in the literature were rare and were early in the vast majority of patients (6,9). Exceptionally, reported complications were late (9,10,11,13). No deaths or significant complications were experienced in the present study. Therefore, this study confirms safety of percutaneous ASD II closure using ASO both early and during follow-up ranging up to 8.6 years.

The cardiac perforation is a rare, life-threatening complication of transcatheter closure of ASD II and was not experienced in the present study. A cardiac perforation due to the guidewire occurred in 1 of 258 patients reported by Chessa et al. and needed surgical drainage of the effusion (9). However, a procedure-related cardiac perforation is an avoidable complication of ASO implantation. In contrast, a cardiac perforation occurring 6 months after ASO implantation causing hemodynamic collapse remained unexplained and is therefore more worrisome (10). An aorta-to-right atrial fistula is an additional rare complication caused by erosion into the aorta by the right atrial disc of ASO (11). It was detected 3 months after ASO implantation in a defect with a deficient superior anterior rim. A 26 mm device was implanted in a defect with a stretch defect diameter of 26 mm. Selecting a device 2 – 4 mm larger than the stretch defect diameter might probably prevent the development of fistula in this defect morphology.

Device embolization s and malpositions are well known complications of percutaneous ASD II closure and were not encountered in our group of patients. The reported incidence of ASO embolization was 0.55% (21 embolization s in 3 824 device placements) (12). Of the 21 embolization s, 15 of the devices were retrieved percutaneously and 6 devices were retrieved at surgery. Most embolization s occurred due to undersized implanted devices or inappropriate selection of defects suitable for ASO implantation. Some embolization s were also caused by operator-related technical issues. Therefore, a device embolization is an avoidable complication of percutaneous ASD II closure using ASO. Device malposition occurred in 2 of 258 patients reported by Chessa et al. and is similarly to device embolization an avoidable complication of ASO implantation (9). In addition to early embolization, delayed ASO embolization, occurring 1 week post-implantation, was also reported (13). The defect was oval in shape and therefore undersized ASO was implanted causing late device embolization.

The incidence of thrombus formation on ASD II closure devices, particularly on ASO, is low (14,15). Thrombi develop on devices both early and late during follow-up. Precise TEE evaluation is crucial for detection of small, clinically silent thrombi. In majority of patients thrombi resolve with medical therapy without clinical consequences. Exceptionally, a sur-

gical explantation of the device due to progressive increase in the size of the thrombus is necessary. Neither thrombus formation nor systemic thromboembolism were detected in our group of patients either immediately after implantation or during follow-up. However, TEE was performed only immediately after the device implantation in the present study and therefore small, clinically silent thrombi may not be detected in our group of patients during follow-up.

Arrhythmias were the second most frequent complications reported by Chessa et al.(9). The most frequent arrhythmia in their experience was atrial fibrillation encountered in 7 of 258 patients during implantation procedure. However, the vast majority of patients in their study experiencing atrial fibrillation were adults. Only children were included in our study and therefore atrial fibrillation was not detected in our group of patients. Hill and co-workers reported an acute increase in supraventricular ectopy, mainly supraventricular premature beats following ASO implantation.(16) Similarly, we noted premature supraventricular beats in 3 patients following ASO implantation resolving completely at 1 month follow-up. In addition, premature ventricular beats were detected in a single patient in this study that were not present at 1 month follow-up examination. Chessa and co-workers experienced a complete heart block in 1 of 258 patients after an implantation of an oversized device (9). A complete heart block resolved after device removal and the defect was later successfully closed by a smaller device. Three of 41 patients (7%) included in a study reported by Hill et al. experienced changes of an atrio-ventricular conduction necessitating a pacemaker implantation in 1 patient (16). A complete atrio-ventricular dissociation occurred in a 6-year old patient having a 24 mm stretch defect diameter with a thin and redundant postero-inferior rim. A 24 mm ASO was implanted in close proximity to both atrio-ventricular valves interfering with an atrio-ventricular conduction. Atrio-ventricular conduction abnormalities were not detected in our study either early or late after the device implantation. We believe that both selection of defects suitable for percutaneous closure and an implantation of an appropriate-sized ASO may prevent occurrence of significant atrio-ventricular conduction abnormalities.

Infective endocarditis on ASO was not experienced in our study. We have recommended antibiotic prophylaxis for six months after the device implantation. However, an infective endocarditis on an ASO was reported in a single patient almost 2 months after implantation underscoring the need for antibiotic prophylaxis until a complete endothelialization of the device. Endothelialization is usually completed within 1 to 3 months after implantation (8,17).

The function of both atrioventricular valves and drainage of both caval veins, right pulmonary veins and coronary sinus were undisturbed immediately

following ASO implantation and during follow-up. A precise evaluation of ASD II size and morphology is crucial to prevent encroachment of these structures by implanted ASO (7). In addition to careful patient selection, a careful evaluation after device positioning is necessary to prevent a compromise of structures surrounding the device.

So far, device integrity problems were not reported after ASO implantation and were also not observed in this study. In addition, deformations of implanted occluders were not reported so far and were also not detected in our patients (18).

Effectiveness of ASD II closure using ASO

The present study confirmed effectiveness of percutaneous ASD II closure using ASO. Our group of 151 patients was selected from a group of 190 consecutive children having isolated ASD II (7). Thus, 79.4% of patients with isolated ASD II underwent successful implantation of ASO. Similarly, Fischer et al. reported successful ASO implantation in 200 of 236 consecutive patients (84.7%) (6). An immediate complete closure was demonstrated by TEE in 120 of 151 patients in the present study (79.4%). Residual shunts were moderate in 6 patients and small in the remaining 25 patients. The following day, TTE proved a complete closure in 138 of 151 patients (91.3%). The closure rate increased steadily thereafter and at 3-years follow-up TTE proved a complete closure in all patients. Other authors also reported excellent immediate-, short- and intermediate-term closure rates (2,3,4,5). For comparison, at a median follow-up of 2.3 years, Fischer et al. reported a complete closure in 94% of patients with a trivial residual shunt in the remaining patients (6).

Conclusions

The present study proved that percutaneous closure of ASD II using ASO is safe and effective during a follow-up period ranging up to 8.6 years. A precise selection of suitable patients based on ASD II size and morphology, a selection of ASO of appropriate size, attention to technical details during implantation and consideration for infective endocarditis prophylaxis and low-dose aspirin during a 6-months period following ASO implantation are crucial to prevent complications and to achieve a high closure rate.

References:

1. Holzer R., Hijazi Z.M. Interventional approach to congenital heart disease. *Curr. Opin. Cardiol.*, 2004, 19(2), 84-90.
2. Masura J., Gavora P., Formanek A., Hijazi Z.M. Transcatheter closure of secundum atrial septal defects using the new self-centering Amplatzer septal occluder: initial human experience. *Catheter. Cardiovasc. Diagn.*, 1997, 42, 388-393.
3. Thanopoulos B.D., Laskari C.V., Tsaousis G.S. et al. Closure of atrial septal defects with the Amplatzer occlusion device: preliminary results. *J. Am. Coll. Cardiol.*, 1998, 31, 1110-1116.
4. Chan K.C., Godman M.J., Walsh K. et al. Transcatheter closure of atrial septal defects and interatrial communications with a new self expanding nitinol double disc device (Amplatzer septal occluder): multicentre UK experience. *Heart*, 1999, 82, 300-306.
5. Berger F., Ewert P., Björnstadt P.G. et al. Transcatheter closure as standard treatment for most interatrial defects: experience in 200 patients treated with Amplatzer Septal Occluder. *Cardiol. Young*, 1999, 9, 468-473.
6. Fischer G., Stieh J., Uebing A. et al. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single center study in 236 consecutive patients. *Heart*, 2003, 89, 199-204.
7. Podnar T., Martanovič P., Gavora P., Masura J. Morphological variations of secundum-type atrial septal defects: feasibility for percutaneous closure using Amplatzer septal occluders. *Catheter. Cardiovasc. Intervent.*, 2001, 53, 386-391.
8. Sharafuddin M.J.A., Xiaoping G., Titus J.L. et al. Transvenous closure of secundum atrial septal defects. Preliminary results with a new self-expanding nitinol prosthesis in a swine model. *Circulation*, 1997, 95, 2162-2168.
9. Chessa M., Carminati M., Butera G. et al. Early and late complications associated with transcatheter occlusion of secundum atrial septal defect. *J. Am. Coll. Cardiol.*, 2002, 39, 1061-1065.
10. Preventza O., Sampath-Kumar S., Wasnick J., Gold J.P. Late cardiac perforation following transcatheter atrial septal defect closure. *Ann. Thorac. Surg.*, 2004, 77(4), 1435-1437.
11. Chun D.S., Turrentine M.W., Moustapha A., Hoyer M.H. Development of aorta-to-right atrial fistula following closure of secundum atrial septal defect using Amplatzer septal occluder. *Catheter. Cardiovasc. Intervent.*, 2003, 58:246-251.
12. Levi D.S., Moore J.W. Embolization and retrieval of the Amplatzer septal occluder. *Catheter. Cardiovasc. Interv.*, 2004, 61(4), 543-547.
13. Verma P.K., Thingnam S.K., Sharma A. et al. Delayed embolization of Amplatzer septal occluder device: an unknown entity. A case report. *Angiology*, 2003, 54(1), 115-118.
14. Krumdorf U., Ostermayer S., Billinger K. et al. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale devices in 1000 consecutive patients. *J. Am. Coll. Cardiol.*, 2004, 43, 302-309.
15. Anzai H., Child J., Natterson B. et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. *Amer. J. Cardiol.*, 2004, 93(4), 426-431.
16. Hill S.L., Berul C.I., Patel H.T. et al. Early ECG abnormalities associated with transcatheter closure of atrial septal defects using the Amplatzer septal occluder. *J. Interv. Card. Electrophysiol.*, 2000, 4(3), 469-474.
17. Bullock A.M., Menahem S., Wilkinson J.L. Infective endocarditis on an occluder closing an atrial septal defect. *Cardiol. Young*, 1999, 9, 65-67.
18. Cao Q.L., Du Z.D., Joseph A. et al. Immediate and six-month results of the profile of the Amplatzer septal occluder as assessed by transesophageal echocardiography. *Am. J. Cardiol.*, 2001, 88, 754-759.

Part 3

Transcatheter patent ductus arteriosus closure using Amplatzer duct occluders and long-term outcome

Introduction

Percutaneous closure is an established method of treatment for the majority of patients with patent ductus arteriosus (PDA) (1,2). Currently, coils are the most widely used occluders for closure of small-sized PDA (3). For closure of moderate- and large-sized PDA Amplatzer duct occluders are most often used (4). Immediate-, short- and intermediate-term results of transcatheter PDA closure using ADO are excellent (4-8). However, long-term results of ADO implantation were not reported so far. Therefore, the aim of this study was to evaluate long-term results of percutaneous PDA closure using ADO in a single institution.

Methods

Patient population

From September 1996 to April 2002, 64 patients having isolated PDA with minimal diameter ≥ 2 mm underwent percutaneous closure using ADO and were followed up until April 2005. Some patients were included in our previous reports (3, 4, 10). At the time of the procedure, the median patient age was 3.4 years (range 0.5 to 29.2 years) and weight 15 kg (range 4.9 to 58 kg). The study was part of a clinical trial approved by an authorized ethics committee. An informed written consent was obtained from all patients or their parents.

The Amplatzer duct occluder and delivery system (AGA Medical, Golden Valley, MN) have been described in detail previously (10, 11). In 9 patients, a modified device - an angled Amplatzer duct occluder was implanted (10, 12).

The selection of patients suitable for transcatheter closure using ADO was based solely on the measurement of the minimal PDA diameter on aortogram. Amplatzer duct occluders were selected for closure of PDA with a minimal diameter ≥ 2 mm (3, 4, 10). Coils were selected for closure of PDA with a minimal diameter < 2 mm.

A physical examination, a standard 12-lead electrocardiogram (ECG), chest radiograph and trans-thoracic echocardiography (TTE) were performed in all patients.

The protocol for ADO implantation has been reported in detail previously (4, 10). Ten minutes after ADO release, descending aortogram was performed to assess the degree of a residual shunt. A left-to-right shunt without a jet was classified as a smoke-like shunt, with a jet < 2 mm in diameter as a small shunt and with a jet diameter > 2 mm in diameter as a large shunt. Pullback pressure measurements were performed to exclude obstruction of the descending aorta and left pulmonary artery.

At 24-hour follow-up, chest radiograph and TTE

were performed. Both chest radiograph and TTE allowed assessment of ADO position and shape. Thrombus formation on the device was excluded by TTE. A color Doppler interrogation was performed to detect and quantify any residual shunts. A minimal color Doppler signal width < 1 mm was considered as a minimal residual shunt, 1 - 2 mm as a small residual shunt and > 2 mm as a large residual shunt. A color Doppler, pulsed Doppler and continuous-wave Doppler interrogation were performed to assess blood flow pattern and velocity in the descending aorta and left pulmonary artery.

Follow-up TTE was performed at 1 month, 3 months, 12 months and yearly thereafter. Throughout the follow-up period the same TTE protocol was used. At each follow-up visit, complications related to ADO implantation were noted. Infective endocarditis prophylaxis and aspirin (5 mg/kg/daily) were recommended for 6 months in all patients.

Statistics

The data are expressed as mean \pm SD or as median and ranges as appropriate.

Results

From September 1996 to April 2002, transcatheter PDA closure using ADO was attempted in 64 consecutive patients having minimal PDA diameter ≥ 2 mm. Implantation of the device was successful in all patients.

The mean PDA diameter was $3.5 \text{ mm} \pm 1.6 \text{ mm}$. Morphology of PDA was assessed and was of type A in 53 patients, type B in 1 patient, type C in 1 patient and type E in 9 patients (Krichenko).

Follow-up period ranged from 36 to 104 months (median 57). There were no deaths or significant complications (arterial or venous complications, device embolization or malpositions, hemolysis, thrombus formation or thromboembolism, infective endocarditis or other morbidity) during the follow-up period.

Aortogram performed at the end of the procedure revealed residual shunts in 26 patients (40%) and were smoke-like in all of them. After 24 hours, TTE revealed minimal residual shunt in 1 patient. At 1-month follow-up visit, PDA were completely closed in all patients and remained closed throughout the follow-up period.

After device release, no pressure gradient was detected by pullback from the ascending to the descending aorta or from the left pulmonary artery to the main pulmonary artery in any patient. After 24 hours, Doppler interrogation revealed increased blood flow velocities in the descending aorta in 3 patients: 2 m/s in 2 patients and 2.5 m/s in the third patient. Blood flow velocities in the left pulmonary artery measured by continuous-wave Doppler were increased up to 2.7 m/s in 2 patients. Deformation of implanted device or device integrity problems were not detected in any patient in this study.

Discussion

This study demonstrates excellent results of transcatheter PDA closure using ADO in a single institution during a follow-up period ranging up to 8.5 years.

Complications of transcatheter PDA closure using ADO are rare and so far, only early complications were reported (6-8, 14, 15). No deaths or significant complications were encountered in the present study thus confirming safety of transcatheter PDA closure using ADO both early and during long-term follow-up period.

Death is an exceptional complication of transcatheter PDA closure using ADO reported in a single patient after device embolization to the descending aorta (6). Either percutaneous or surgical retrieval of the device is necessary immediately after embolization to the descending aorta to prevent ischemic damage of abdominal organs.

Device embolizations or malpositions are rare after ADO implantation (6-8). Device embolizations were reported to occur immediately or within 24 hours of the procedure. So far, late embolizations were not reported. Devices embolised to the pulmonary artery or to the descending aorta and were retrieved either percutaneously or surgically. In the present study, device embolizations and malpositions were not encountered. Both selection of ADO of appropriate size and precise device positioning are crucial to prevent device embolizations or malpositions.

Residual high velocity jets are rare following ADO implantation and therefore, mechanical hemolysis is rarely experienced early after the procedure (Godart). Late hemolysis was not reported so far. In our group of patients, hemolysis was not detected either early or during follow-up.

Thrombus formation and thromboembolism were not reported after ADO implantation. We recommended aspirin (5mg/kg/daily) for 6 months in all patients and thrombus formation or thromboembolisms were not detected in our group of patients.

Infective endocarditis on an implanted ADO was not reported so far and was not experienced in the present study. We recommended infective endocarditis prophylaxis for 6 months in all patients.

Aortic obstruction is a well-known complication of transcatheter PDA closure using ADO (7,8,15). In the vast majority of patients, obstructions were clinically insignificant, detected only by Doppler echocardiography (7,8). Furthermore, blood flow velocities decreased during follow-up examinations (8). Exceptionally, significant obstructions were caused by protrusion of the ADO into the descending aorta and device removal was necessary in these patients (15). Pullback pressure measurements failed to detect pressure gradient in any of patients in this study. However, Doppler echocardiography performed 24 hours after the procedure revealed blood flow velocities up to 2.5 m/s in the descending aorta in 3 of our patients. Relatively low body weight (9, 12

and 17 kg) and PDA type (type A in a patient weighing 12 kg, type E in the remaining 2 patients) both contributed to the mild protrusion of the aortic disc of the device into the descending aorta (8). In order to prevent protrusion of the aortic disc into the descending aorta, a modified device (an angled ADO) was implanted in 9 patients in the present study (10). Using an angled ADO, we successfully closed type A PDA with a minimal diameter of 2.1mm in an infant weighing 4.9kg without causing aortic obstruction.

Obstruction of the left pulmonary artery is possible after percutaneous PDA closure using ADO (6,8). In the present study, pullback pressure measurement excluded pressure gradient after ADO implantation. However, Doppler echocardiography revealed increased blood flow velocities up to 2.7 m/s in 2 patients weighing 10 and 14kg at the time of procedure (8).

So far, device integrity problems and deformations were not reported after ADO implantation and were also not detected in the present study throughout the follow-up period.

This study confirmed effectiveness of transcatheter PDA closure using ADO. In the present study, implantation of ADO was attempted in 64 consecutive patients and was successful in all of them. Similar results were reported by other authors (5-8). Smoke-like shunts are frequently detected on aortogram after ADO implantation and were seen in 40% of our patients. However, minimal residual shunt persisted after 24 hours in a single patient and at 1 month follow-up, all PDA were completely closed and remained closed thereafter. High complete closure rates particularly at follow-up evaluations were reported also by others (5-8). For comparison, at 1-year follow-up complete closure in 359 of 360 patients (99.7%) was reported by Pass et al. (8).

Reopening after successful PDA coil occlusion was reported during follow-up (16). In contrast, reopening after successful ADO implantation was not reported so far and was not detected in this study.

PDA closure in infants using ADO. Reported data support the manufacturer's recommendation, that ADO implantation should not be attempted in patients weighing ≤ 5 kg (7). However, technical difficulties during implantation are frequently encountered also in infants and young children weighing ≥ 5 kg (17). In addition, complications are more frequent in infants and young children particularly with large PDA (17). Aortic obstruction due to protrusion of the aortic disc of the device is possible in this group of patients sometimes necessitating device removal (7,15). An angled ADO was therefore designed to prevent protrusion of the aortic disc into the aorta and was successfully implanted in 9 patients included in the present study (10). Altogether, we successfully implanted an angled ADO in 12 patients. However, further clinical trials are necessary to confirm safety and effectiveness of the device. Obstruction of the left pulmonary artery is also detected more frequently

in infants and young children having large PDA after ADO implantation. Fortunately, both aortic and left pulmonary artery obstruction decrease during follow-up (8, and this study).

Conclusions

This study proved that transcatheter PDA closure using ADO is safe and effective during a follow-up period ranging up to 8.5 years. A precise assessment of PDA size and morphology, a selection of ADO of appropriate size, attention to technical details during implantation, and consideration for infective endocarditis prophylaxis and low-dose aspirin 6 months after ADO implantation are crucial to prevent complications and to achieve a high closure rate.

References:

1. Moore J.W., Levi D.S., Moore S.D. et al. Interventional treatment of patent ductus arteriosus. *Catheter. Cardiovasc. Interv.*, 2005,64,91-101.
2. Moore J.W., George L., Kirkpatrick S.E., et al. Percutaneous closure of the small patent ductus arteriosus using occluding spring coils. *J. Am. Coll. Cardiol.*, 1994, 23, 759-765.
3. Podnar T., Masura J. Percutaneous closure of patent ductus arteriosus using special screwing detachable coils. *Catheter. Cardiovasc. Diagn.*, 1997,41,386-391.
4. Masura J., Walsh K.P., Thanopoulos B. et al. Catheter closure of moderate- to large-sized patent ductus arteriosus using the new Amplatzer Duct Occluder: immediate and short-term results. *J. Am. Coll. Cardiol.*, 1998,31(4),878-882.
5. Thanopoulos B.D., Hakim F.A., Hiari A. et al. Further experience with transcatheter closure of the patent ductus arteriosus using the Amplatzer duct occluder. *J. Am. Coll. Cardiol.*, 2000,35(4),1016-1021.
6. Faella H.J., Hijazi Z.M. Closure of the patent ductus arteriosus with the Amplatzer PDA device: immediate results of the international clinical trial. *Catheter. Cardiovasc. Interv.*, 2000,51:50-54.
7. Bilkis A.A., Alwi M., Hasri S. et al. The Amplatzer duct occluder: experience in 209 patients. *J. Am. Coll. Cardiol.*, 2001,37(1),258-261.
8. Pass R.H., Hijazi Z.M., Hsu D.T. et al. Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial. Initial and one-year results. *J. Am. Coll. Cardiol.*, 2004,44,513-9.
9. Podnar T., Gavora P., Masura J. Percutaneous closure of patent ductus arteriosus: complementary use of detachable Cook patent ductus arteriosus coils and Amplatzer duct occluders. *Eur. J. Pediatr.*, 2000,159,293-296.
10. Masura J., Gavora P., Podnar T. Transcatheter occlusion of patent ductus arteriosus using a new angled Amplatzer duct occluder: initial clinical experience. *Catheter. Cardiovasc. Interv.*, 2003,58,261-267.
11. Sharafuddin M.J.A., Gu X., Titus J.L. et al. Experimental evaluation of a new self-expanding patent ductus arteriosus occluder in a canine model. *J. Vasc. Interv. Radiol.*, 1996,7(6),877-887.
12. Kong H., Gu X., Bass J.L. et al. Experimental evaluation of a modified Amplatzer duct occluder. *Catheter. Cardiovasc. Interv.*, 2001,53,571-576.
13. Krichenko A., Benson L.N., Burrows P. et al. Angiographic classification of the isolated, persistently patent ductus arteriosus and implications for percutaneous catheter occlusion. *Amer. J. Cardiol.*, 1989,63,877-880.
14. Godart F., Rodes J., Rey C. Severe haemolysis after transcatheter closure of a patent arterial duct with the new Amplatzer duct occluder. *Cardiol. Young*, 2000,10(3),265-7.
15. Duke C., Chan K.C. Aortic obstruction caused by device occlusion of patent arterial duct. *Heart*, 1999,82,109-111.
16. Daniels C.J., Cassidy S.C., Teske D.W. et al. Reopening after successful coil occlusion for patent ductus arteriosus. *J. Am. Coll. Cardiol.*, 1998,31,444-450.
17. Al-Ata J., Arfi A.M., Hussain F. et al. The efficacy and safety of the Amplatzer ductal occluder in young children and infants. *Cardiol. Young*, 2005,15(3),279-285.

Percutaneous Closure of Intracardiac Shunts and Left Atrial Appendage

Anupam Bhambhani, MD; Bernhard Meier¹, MD

Swiss Cardiovascular Center Bern, University Hospital, Bern, Switzerland

Intracardiac defects such as atrial septal defect (ASD), patent foramen ovale (PFO), and ventricular septal defect (VSD) are common forms of congenital or acquired unphysiological intracardiac apertures which can be successfully closed percutaneously. Intracardiac shunts form a major proportion of congenital heart defects. The dawn of the era of percutaneous closure of intracardiac shunts began with the pioneering work of King et al (1). It has observed development of new devices from the Rashkind Clamshell occluder to recently evaluated novel "implant-less" closure systems.

Transcatheter closure scores over surgical methods as it is less invasive resulting in shorter recovery times, avoids deleterious neurocognitive effects of cardio-pulmonary bypass, is devoid of pro-arrhythmic effects of atrial or ventricular scars (albeit rarely arrhythmogenic in itself) and enjoys cosmetic superiority.

Percutaneous closure of ostium secundum ASD

Fetal atrial septation is a complex multi-stage process. Initially, a septum primum forms along the roof of the common atrium in the developing heart and grows towards the atrioventricular cushions. Before the septum primum fuses with the AV cushions, apoptosis creates a hole in septum primum, the ostium secundum, which maintains the right-to-left atrial blood flow during fetal development. The septum secundum then forms to the right of the septum primum, leaving a one-way communication between right and left atria, the foramen ovale. At birth, a higher pressure develops in the left compared with the right atrium, forcing the flap valve against the septum secundum, thus eliminating the interatrial shunt. Autosomal dominant mutations in the gene encoding the cardiac homeodomain transcription factor NKX2-5 have been correlated with secundum ASD in rare families in which the defect is known to be inherited (2).

Interventional ASD closure is now widely practised and has practically replaced surgical closure for small to medium sized ASD secundum (Fig. 1).

Transcatheter closure of the majority of secundum ASDs is feasible (3), while it is not yet fea-

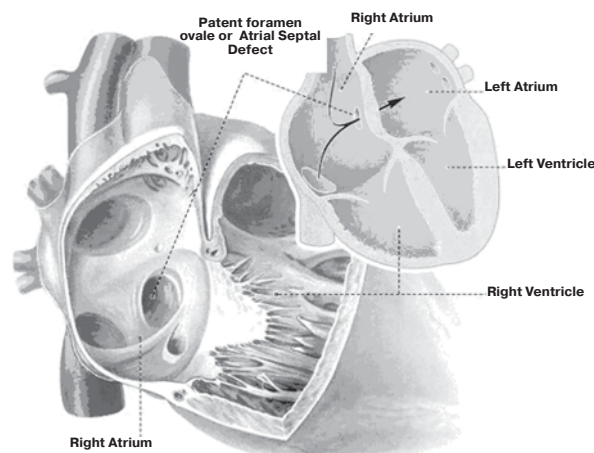


Figure 1: Anatomical site for secundum ASD or patent foramen ovale.

sible for ostium primum and sinus venosus ASDs. Many different types of devices are in use. Some are patch type occlusion devices represented by the CardioSEAL, or its modification, the STARFlex occluder (NMT Medical, Boston, Massachusetts, USA). The Amplatzer septal occluder (ASO) (AGA Medical Corporation, Golden Valley, Minnesota, USA) is a unique self centering disc type device. It was believed that a minimum of 5mm of tissue surrounding the margins of ASD is required to allow adequate anchoring of the device without compressing the adjacent structures. But in experienced hands, devices can be successfully deployed with lesser rims in a limited sector of the circumference. This is specially true for the anterior-superior region near the aortic root. Tissue margin here is frequently absent but successful device deployment is still possible using the aortic root for support.

The diameter of the waist of the ASO has to correspond to the so called "stretched" diameter of the ASD determined by a measuring balloon catheter. ASOs large enough to close defects of up to 40 mm in diameter are available. Other devices can only close smaller defects (4). Polyester fibres are sewn into the ASO device promoting tissue coverage and complete defect occlusion. Waist diameters ranging from 4 to 40mm are available. For devices between 4 and 10 mm, the left atrial disc is 12 mm and the right atrial disc is 8 mm larger than the waist. For bigger devices the left atrial disc is either 14 mm (waist diameter 11 to 30 mm) or 16 mm (waist diameter 32–40 mm) larger than the waist. The right atrial disc is 10 mm larger than the waist for devices of 11–40 mm (3). A device with a waist diameter similar to, or according to our recommendation, 20 to 50% bigger than the stretched ASD diameter is chosen. The wire

¹Bernhard Meier, MD
Professor and Chairman of Cardiology
Swiss Cardiovascular Center Bern
University Hospital
CH-3010 Bern
Switzerland
Tel.: + +41 (0)31 632 3077
Fax: + +41 (0)31 382 1069
Email: bernhard.meier@insel.ch
Manuscript received on June 02, 2006
Accepted for publication on June 27, 2006

mesh of the Amplatzer occluder is non-ferromagnetic, making magnetic resonance imaging for cardiac or non-cardiac indications possible.

Since the technique of ASD closure is almost identical to that of PFO closure, they are described together.

Rare occurrence of vena azygos continuation may make the procedure difficult. In such a case, alternative approaches, such as the hepatic or jugular routes can be tried.

Absolute contraindications include left atrial hypoplasia such that the left atrium cannot accommodate the left atrial device disc, intra-cardiac thrombi, sepsis or associated cardiac conditions requiring surgery.

The complication rate varies according to the type of device deployed. The most commonly observed complications are device embolization, myocardial perforation, arrhythmias, air embolism and thrombus formation (5). Rarely, mitral regurgitation or right lower pulmonary vein obstruction is observed. Late complications are rare but potentially serious and include erosion of the device into the aorta, delayed pericardial effusion or device infection.

Percutaneous closure of PFO

In about 25% of people, the foramen ovale remains patent after birth, opening to a right to left shunt when right atrial pressure overrides left atrial pressure. This typically occurs immediately after a prolonged Valsalva maneuver while venous blood momentarily retained in the abdomen is rushing back into the right atrium before reaching left atrium. It also opens to the high velocity blood pounding against it in presence of an Eustachian valve or as seen in the platypnea orthodeoxia syndrome.

Presence of a PFO with or without an atrial septal aneurysm (flaccid, undulating cranial portion of the septum primum) significantly increases the risk of (recurrent) strokes, a fact used as rationale for device closure (table 1) (6-8).

Table 1 The role of patent foramen ovale in stroke patients (6-8).

		Odds Ratio (95% CI)		
		PFO	ASA	PFO+ASA
All ages	Stroke versus non-stroke controls	2 (1-2)	2 (2-3)	5 (3-10)
	Cryptogenic stroke versus known cause stroke	3 (3-4)	3 (2-3)	21 (4-104)
	Cryptogenic stroke versus non-stroke controls	3 (2-3)	4 (3-6)	24 (3-185)

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

The possibility that a young woman had an embolus pass through a PFO to cause a fatal stroke was first suggested by Cohnheim in 1877 (9). The right to left shunt provides opportunity for thrombi from systemic veins to cross into the arterial system bypassing the lung filter. In fact, large clots have been repeatedly documented crossing the PFO. The so called "economy class stroke syndrome" is a similar manifestation described in young patients in whom ischemic stroke occurred in relation to a long air travel and who had a PFO (10). Different studies (table 2) have shown PFO closure to be more effective (11, 12) or at least as effective as medical treatment in preventing stroke recurrence with significant advantage in subgroups (13).

Table 2 Incidence of recurrent stroke with medical therapy versus transcatheter PFO closure (11-13).

Study	Percent incidence of recurrent stroke	
	Medical therapy	PFO closure
Khairy et al11.	3.8-12 / y	0-4.9/y (p<0.0001)
Schuchlenz et al12.	Acetylsalicylic acid: 13/y Warfarin: 5.6/y	0.6/y (p<0.001)
Windecker et al13.	22.2/4y	7.8/4 y (p=0.08)

y = year (s).

In a systematic review of the relative benefits of percutaneous PFO closure compared with medical treatment, Khairy et al. (11) have reported a protective effect of percutaneous PFO closure compared with medical treatment on stroke or TIA recurrence

(annual incidence 0 to 4.9% vs. 3.8 to 12%; relative risk 0.4, 95% CI 0.2–0.6, $p < 0.0001$). At 1 year follow up, 1 of every 23 patients undergoing percutaneous PFO closure was protected from recurrent stroke or TIA compared with medical treatment. However, all studies do not support this statement (14).

An estimated 350,000 ischemic strokes occur yearly in Russia; 25% of strokes are presumed cryptogenic (15-17). The prevalence of PFO in patients with cryptogenic stroke is about 50% (6-8). This extrapolates to almost 50,000 strokes per year attributable to a PFO. Should it prove necessary to close these PFOs, this will become an important part of interventional cardiology even respecting the restrictive indications that other causes for stroke (atherosclerosis of ascending aorta or cerebral vessels, atrial fibrillation, intracardiac thrombus) have to be absent. These restrictions are controversial, as the PFO remains a threat even in the presence of other causes for stroke.

Moreover, PFO seems to be playing a significant role in divers with decompression sickness (DCS). DCS because of a PFO was first reported in a scuba diver and clinically can be as severe as mental confusion, coma or focal neurological deficits. A strong relationship has been demonstrated between DCS severity and PFO size (18).

Another albeit controversial correlate for PFO is migraine headache. The odds ratio for migraine in people with or without PFO is 5 under the age of 45 years. The recently reported MIST I trial (presented by Dr Andrew Dowson, King's College Hospital, London, UK, in American College of Cardiology (March 13, 2006) meeting) did show improvement in headache after PFO closure but missed the primary end point of 50% cure. Similar trials (MIST II, PREMIUM, and PRIMA) have been planned for further confirmation of this issue. Results from ongoing trials are required to draw final conclusions.

A rare but clinically important indication for PFO closure is the platypnea orthodeoxia syndrome (19), i.e. hypoxia in elderly occurring in upright position due to right to left shunt caused by inferior vena caval blood directed straight through PFO by an Eustachian valve redirected onto the PFO by age related remodelling of chest and heart structures.

In addition, a PFO can be hazardous in surgical procedures prone for fat embolism (20) as well as in refractory hypoxemia due to right-to-left shunt in patients with right ventricular infarction. It has also been correlated with clinical manifestations of obstructive sleep apnea syndrome (21).

The gold standard for diagnosing PFO is transesophageal echocardiography (TEE) with contrast. Bubbles appearing in the left atrium several beats after appearing in the right atrium result from a pulmonary shunt rather than a PFO. In case of normal pulmonary bubble transit, bubble mixture between the two atria is disparate, since only relatively smaller bubbles pass through the lung filter. Other available diagnostic modalities are assessment of the number

of high intensity transient signals (HITS) by transcranial Doppler (22), computed tomography or magnetic resonance imaging scans or skin oximetry after a Valsalva maneuver showing rapid and transient drop in saturation. The size of PFO plays an important role in its etiologic relationship to stroke and can be deduced as measured echocardiographic dropout in TEE or from maximum number of bubbles seen in the left atrium following a Valsalva maneuver. The average size in patients with and without symptoms has been measured to be 2.1 ± 1.7 mm and 0.6 ± 0.8 mm and the corresponding number of bubbles were 14 ± 11 versus 2 ± 1 respectively (23). Transcranial Doppler signal patterns observed after microbubble contrast injection (at rest or post Valsalva maneuver) can also determine the magnitude of right to left shunt by counting maximum number of signals in the middle cerebral artery in any single frame. These are classified as small right to left shunt (< 10 signals) or large right to left shunt (> 10 signals). The latter group can reveal a "shower pattern" (> 25 signals) or a "curtain pattern" (uncountable intermingled signals) (24).

Various devices (fig. 2) have been developed for closing PFOs. These are the Rashkind Clamshell occluder, its modification CardioSEAL, the StarFlex and the PFO Star devices, the Amplatzer family and finally the recently introduced "implant-less" PFXTM closure system and biodegradable BioSTAR device. Other devices like the Sideris Buttoned Device (25), the ASDOS device (26) and the Angel-Wings device (27) are obsolete.

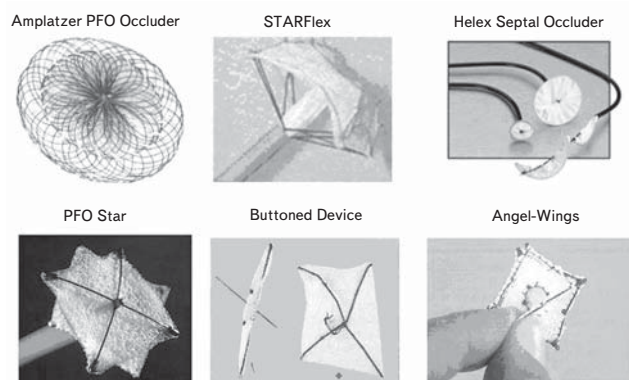


Figure 2: Devices for percutaneous transcatheter PFO closure from top left to bottom right: Amplatzer PFO Occluder (overall best and most frequently used), CardioSeal/ StarFlex, Helex Septal Occluder, PFO Star, Sideris Buttoned Device, Angel Wings.

A relatively new device is the Premere PFO closure device, consisting of a right atrial disk like anchor, a left atrial anchor and a tether in between the two (fig.3). The advantages are the adjustable distance between the anchors aiding device adaptation to each patient's unique anatomy with minimal septal distortion as well as its low surface area in the left atrium. The CLOSE-UP trial is under way to confirm its efficacy (multicenter trial including our center).

Recently, a novel PFO closure system has been introduced that does not leave foreign material in the atria, the PFXTM closure system. It employs mono-

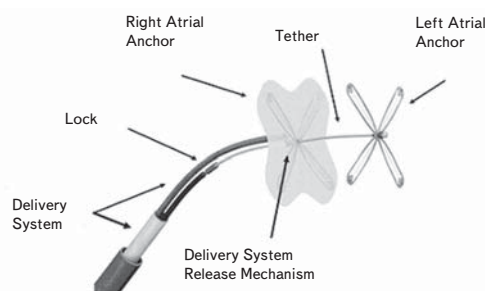


Figure 3. Premere PFO closure device

polar radiofrequency energy to weld the tissues of the septum primum and secundum together. The system consists of a special catheter, the main parts of which are a distal housing with a metallic “mesh electrode”, a vacuum housing, and a retractable outer sleeve. For proper docking of the device, the electrode should be in contact with the tissues of the septum primum and the septum secundum. A single center first in man trial (PARADIGM I) has shown initial feasibility and safety in patients with a mean PFO diameter of 9.1 ± 2.9 mm. In 6 of 8 patients, instant complete PFO closure was documented. A larger trial (PARADIGM II) has already started in three centers including ours.

Another recently introduced device for closing interatrial shunts is BioSTAR (NMT Medical, Boston, MA). This is a bio-absorbable implant comprised of collagen matrix which can be incorporated into the atrial septum with gradual resorption of the device. Early results of BEST trial (BioSTAR Evaluation Study) presented at EuroPCR May 2006 (Mullen M. MD; Royal Brompton Hospital, London, UK) suggest promising safety and efficacy of this device.

Absolute contraindications to PFO closure include presence of intracardiac thrombi or uncontrolled sepsis.

Technique of percutaneous PFO/ASD closure by Amplatzer device

The technique varies among centers. In our center, echocardiographic guidance is not used and balloon measurement is done in ASDs but not in PFOs. Diagnosis is invariably pre-established based on a TEE. In most PFOs, a 25mm Amplatzer PFO device is used. Only if this device does not anchor securely, it is replaced by a 35mm device. The defect is crossed with a 0.035" wire directly in many cases but sometimes a multipurpose catheter is required to steer the wire through the PFO. A trans-septal sheath (8 French for 25mm device and 9 French for a 35mm device) is advanced over the wire up to left atrium or one of the pulmonary veins. Opening the left side of the umbrella and pulling it back closes the valve like structure. The right disc is deployed by releasing it by sheath withdrawal while maintaining stretch onto the device. We use a hand injection through the introducer sheath to ascertain the position (left projection showing the device in perfect profile) before setting the device free. It is useful to look for the so-called “pacman sign” before releasing the device which refers to the shape acquired by the correctly

deployed device on fluoroscopy (28). Seen in profile, the cranial halves of the left and right atrial discs should appear like open jaws biting into the thick septum secundum, resembling the arcade figure pacman about to gobble up a dot (fig.4). In some centers TEE or transthoracic echocardiography is used for this purpose.

We prescribe acetylsalicylic acid 100mg daily for 5 months and clopidogrel 75mg daily for 1 month to all our patients along with infective endocarditis prophylaxis for a duration of 6 months, at which time a concluding TEE follow-up is the rule. The procedure can be performed on an outpatient basis and usually takes less than 30 minutes, with a fluoroscopy time of below 5 minutes. The patient can resume unrestricted physical activity as soon as a few hours after the intervention.

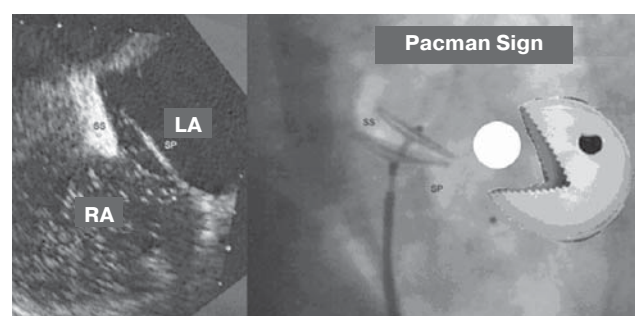


Figure 4: Left: transesophageal echocardiogram depicting the thick septum secundum (SS) and the paper-thin septum primum (SP) with bubbles passing through the PFO between them from the right atrium (RA) to the left atrium (LA). Right: pacman sign documenting correct placement of an Amplatzer PFO occluder. The cranial side of the device “bites” into the tongue-like septum secundum reminding of the arcade figure pacman biting into a dot (28).

The long-term follow-up after PFO closure from our center has indicated that when the combined end point of stroke, TIA or death is compared in patients undergoing device closure and those on conservative therapy, results are almost identical for initial 2 years but in following years they favor device closure (Fig. 5). This may be interpreted as that initial lack of improvement may indicate the need for a longer (and more powerful) antiplatelet therapy (13).

Although randomized controlled trials are underway, analysis of prospective series do provide some evidence in PFO closure. It is already uncontested in patients with recurrent paradoxical embolism with PFO. Considering the negligible procedure related risk one can envision an ultimate indication being prophylactic closure of all detected PFOs or at least those associated with an atrial septal aneurysm (about 5% of the population).

Percutaneous closure of VSD

VSD closure still lacks long-term follow-up data. It requires more experience and a broader armamentarium of devices since VSD position, form, and anatomical relations are complex and variable. Of all the VSDs 80% are perimembranous whereas muscular VSDs account for 5-20% cases (29). Transcatheter

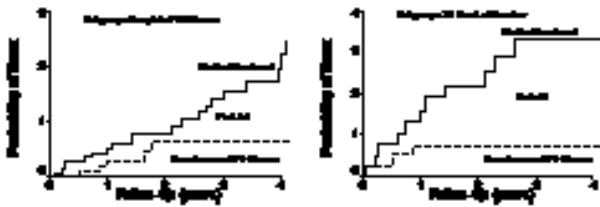


Figure 5: Combined end point of stroke or transient ischemic attacks in patients with PFO undergoing device closure (dashed line) and those on medical therapy (continuous line); probability of combined end point of stroke or transient ischemic attack in the subgroups of patients with >1 cerebrovascular event at baseline (right panel) stratified for medical treatment (continuous line) and percutaneous patent foramen ovale (PFO) closure (dashed line) (13)

closure of muscular VSDs was first reported in 1988 by Lock et al. (30). Percutaneous closure of defects in apical or muscular septum is now an established treatment alternative to surgery, which, due to their anatomical position pose problems in surgical closure. Similar is the case with multiple VSDs or postoperative residual VSDs which are clinically significant but difficult to treat surgically. Transcatheter closure is an alternative strategy for management of both these categories of defects (31). Apart from these, device closure of postinfarction VSDs is gaining popularity although perturbed by the high risk typical in these severely ill patients.

Transcatheter closure of perimembranous VSDs presents unique anatomy related problems. Chordae tendinae, tricuspid valve, and the high pressure in the left ventricle represent tricky obstacles for the device deployment, further complicated by the frequently encountered ventricular septal aneurysm or a multiperforated septum. These VSDs lie immediately beneath the aortic valve and therefore devices are likely to interfere with its normal functioning.

The Rashkind Occluder was the first device to be implanted for VSD closure, followed by the Bard Clamshell device, Gianturco coils (Cook inc., Bloomington, Illinois), the Sideris Buttoned device (32), the Amplatzer occluder (33-38) and Nit Occlude Coils (PFM, Cologne, Germany). Of all the VSD occluding systems, mainly the Amplatzer family (membranous and muscular VSD occluder, eccentric and concentric VSD occluders), the PFM coils, and the STARflex device supplied stable results so far.

Technique of percutaneous VSD closure

A single muscular VSD can be closed without TEE, however for multiple defects, TEE guidance is recommended. The Amplatzer Muscular VSD occluder is designed specifically for the muscular septum. Percutaneous VSD closure is possible from either femoral or internal jugular vein approaches. It requires both arterial and venous accesses. In VSDs located in mid, posterior, or apical septum, the right internal jugular vein is accessed (35). After a routine right heart catheterization, a left ventricular angiogram in LAO cranial view is performed to assess the size of the VSD. The appropriate device size is chosen to be 1-2 mm larger than the VSD size as assessed by TEE or angiography at end diastole. Defects are usually crossed

retrogradely first from left ventricle with a catheter (Judkins right) and a wire. The wire is then snared and exteriorized through the venous side forming a continuous arterio-venous wire loop allowing passage of a Mullin's type sheath, advanced from the vein to the RV and positioned into the LV. A pigtail catheter positioned in the LV is helpful in guiding device position. The LV disk is deployed in the middle of the LV. Then the entire assembly (cable/sheath) is pulled into the VSD with further retraction of the sheath to expand the waist inside the septum. Once position is confirmed, to expand the RV disk, further retraction of the sheath is performed. Prior to release, LV angiographic and TEE confirmations for device placement, and detection of residual shunting and any valvular obstruction or regurgitation induced by the device are performed.

With the Amplatzer perimembranous VSD occluder, defects with <5mm margin from the aortic valve can also be closed. VSDs associated with aortic valve prolapse or AR are excluded. Perimembranous VSDs are closed by a procedure similar to muscular VSD closure but require continuous TEE guidance to exclude entangling of important structures like mitral valve apparatus by the LV disk. The perimembranous Amplatzer device is an asymmetrical device with a platinum marker which should be directed caudally to keep the device properly oriented. The smaller right sided disc avoids interference with tricuspid valve. The left disc is asymmetrical with a 1mm superior rim to dodge the aortic valve and a 5mm inferior rim to clasp the muscular septum. Presence of an aneurysm is useful in closing perimembranous VSD because the device can be parked in the aneurysmal sac away from aortic valve.

Perventricular VSD closure is a procedure performed in the operating room when the patient has to undergo other surgical repairs or pulmonary artery de-banding, etc. The advantage is that closure can be achieved prior to initiating cardio-pulmonary bypass especially in infants too small to undergo device closure. After the chest and pericardium is opened, an epicardial echocardiography is performed. The right ventricle free wall is punctured with an 18 G needle, through which a 0.035" guide wire is passed through VSD into left ventricle. The device can be deployed by same procedure as for percutaneous closure.

Device closure is not feasible for supracristal or inlet VSDs.

Common complications include hemodynamic instability, bradyarrhythmias, tricuspid or aortic valve regurgitation, device embolization, and rarely cardiac perforation. Device arm fracture was seen more frequently with larger devices such as the Clamshell device. Reported success rates are as high as 92 % with Amplatzer occluder (38).

Post MI VSD closure

Postmyocardial infarction (MI) ventricular septal rupture carries a poor prognosis despite best of medical and surgical management. With surgical

closure, the early mortality has been reported to be as high as 19-46% (40). Immediate intervention is recommended in these patients regardless of clinical status. Poor prognostic factors include cardiogenic shock as well as inferior myocardial infarcts, which are more frequently associated with morphologically complex VSDs (40-42). Sudden increase in size of the defect with hemodynamic collapse is common.

The experience with post MI VSD intervention is inadequate (43-46). The largest series has been reported by Lock et al.(45) using the Rashkind double umbrella. The Amplatzer post MI VSD closure device (AGA Medical) has revealed better results. The reported 30 day mortality after procedure is 28% (40) which is comparable with mortality after surgical closure (19-46%). To reduce the risk of device embolization or significant residual shunting, a device 50% larger than the measured diameter of the VSD is suggested to allow for enlargement of the VSD size due to lysis and ongoing necrosis of the tissues surrounding the VSD (40).

This is potentially a good option for those whose medical condition precludes surgery. Even if complete closure is not feasible, a reduction in shunt can normalize the hemodynamics. This allows survival through the early unfavorable period. However, this concept needs confirmation by long-term trial results.

Percutaneous obliteration of left atrial appendage (LAA)

The left atrial appendage (LAA) is a trabeculated remnant of the embryonic left atrium. This is an important source of emboli related to atrial fibrillation. Due to these observations and possibility of successful percutaneous obliteration of the mouth of this structure, it is worthwhile to consider it along with percutaneous closure of intra-cardiac shunts.

Anatomically, LAA has a wind-sock like configuration consisting of multiple lobes and a narrow junction with left atrium (Fig.6). The size of LAA varies considerably with an orifice measuring 5 to 27mm in diameter and length measuring 15 to 51mm.

Atrial fibrillation (AF) is responsible for 15% of all ischemic strokes (47). Atrial fibrillation, whether intermittent or sustained, increases the risk for cardioembolic events leading to an overall annual stroke rate of 4.5% per year (48-50). Oral anticoagulants constitute the mainstay of therapy reducing stroke risk by 65% compared to placebo and by 45% compared to Aspirin.

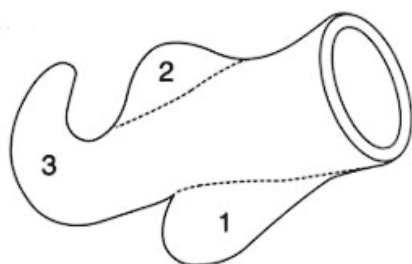


Figure 6: Diagrammatic representation of multi-lobed anatomy of left atrial appendage.

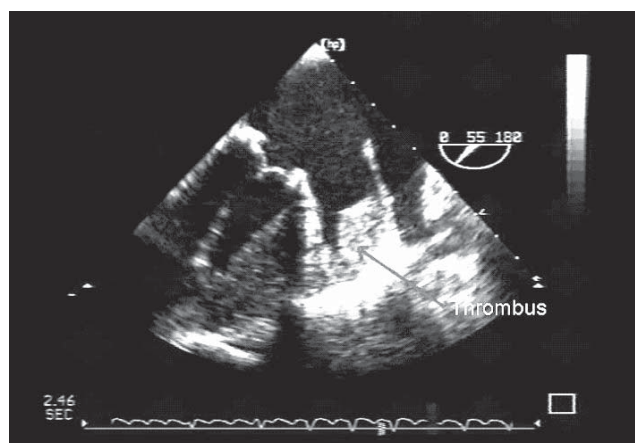


Figure 7: A large left atrial appendage thrombus as seen in trans-esophageal echocardiogram

However, there is a marked underutilization of oral anticoagulation therapy due to a narrow therapeutic window, unpredictable pharmacokinetics, contraindications and fear of bleeding complications (51, 52).

In patients with AF, the Doppler flow velocities observed in LAA are lower than normal as is the LAA ejection fraction. These changes result in blood stasis predisposing to thrombus formation. Strokes related to LAA thrombus are larger, presumably because of larger thrombus nested within LAA cavity (Fig.7). More than 90% of all thrombi in patients with non-rheumatic AF forming in the left atrium originate in the left atrial appendage (53). Therefore, occluding the LAA would seem to be a logical approach to preventing thrombus formation and subsequent cardioembolic events in these patients to obviate the need for anticoagulation. First attempts at LAA exclusion were reported by cardiac surgeons either during open heart surgery (54, 55) or with a thoracoscopic intervention (56).

These observations stirred the therapeutic interest to percutaneously obliterate LAA. This has been tried with Amplatzer group of devices (57) as well as with certain dedicated devices like Percutaneous Left Atrial Appendage Occluder (58) (PLAATO system, ev3 Inc., Plymouth, Minnesota). The PLAATO device (fig.8) consists of a nitinol cage with 3 rows of anchors along the struts to stabilize the device in LAA. It is covered by a polyvinyl tetrafluoroethylene (PTFE) membrane.

The implantation procedure utilizes a transfemoral venous approach followed by a septal puncture to access left atrium. In our center, we perform the procedure without echocardiographic guidance. A LAA angiogram is performed through delivery sheath placed

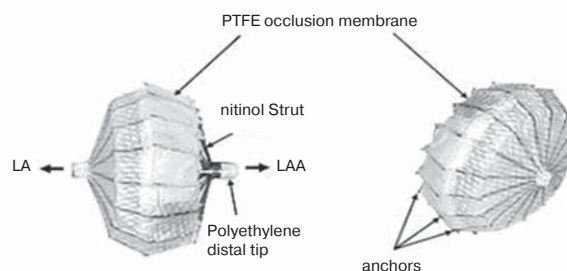


Figure 8: Percutaneous Left Atrial Appendage Occluder (PLAATO) system (PTFE = poly tetra fluoro ethylene).

in LAA to determine size of the implant. In case of the Amplatzer device, an implant size with central part about 5 mm larger than the neck of the appendage is selected. The implant is deployed by withdrawing the sheath in case of the Amplatzer device while in PLAATO, it is achieved by actively opening the device. The implant position security is confirmed by wiggling maneuver. Finally, position is confirmed by a left atrial angiogram. Device embolization can be prevented by careful observation of release technique, by oversizing it by 20-40% as well as by hook-anchors in case of PLAATO.

The efficacy of procedure in preventing stroke is still not established and awaits confirmation from trial results. The annual stroke risk of 2.2% has been observed in 58 patients who underwent PLAATO implantation. When the expected stroke rate for these patients was calculated according to CHADS score (52) (an acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and stroke or transient ischemic attack), it was 6.3%. This can be assumed to show a 65% risk reduction with the procedure. But confirmation in a larger trial is required.

Conclusion

Device closure of intracardiac shunts and LAA is a rapidly progressing treatment modality. While closure of secundum ASDs is the procedure of choice. Device closure of PFOs still faces some controversies regarding its effectiveness compared with medical management with some ongoing trials addressing these issues.

While long-term follow-up ASD and PFO studies have been published, VSD closure still lacks such data. Furthermore, VSD closure requires more experience and a broader armamentarium of devices as VSD position and form are quite variable. Transcatheter closure of muscular VSDs is an attractive alternative to surgical closure especially for apical defects or those anterior to the moderator band. Investigations are underway to prove efficacy of closure of post-infarction VSDs however this remains a high risk procedure. Although early experience compares favorably well with surgical closure. Phase 1 investigations have proved successful for device closure of perimembranous VSDs. LAA closure may remain restricted to patients not tolerating oral anticoagulation.

References:

1. King T.D. Secundum atrial septal defect: nonoperative closure during cardiac catheterization. *JAMA*, 1976,235,2506-2509.
2. Biben C., Weber R., Kesteven S. et al. Cardiac septal and valvular dysmorphogenesis in mice heterozygous for mutations in the homeobox gene *Nkx2-5*. *Circ. Res.* 2000,87,888-895.
3. Fischer G., Stieh J., Uebing A. et al. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart*, 2003,89,199-204.
4. Hausdorf G., Kaulitz R., Paul T. et al. Transcatheter closure of atrial septal defect with a new flexible, self-centering device (the STARFlex Occluder). *Am. J. Cardiol.*, 1999,84,1113-1116.
5. Krumsdorf U., Ostermayer S., Billinger K. et al. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. *J. Am. Coll. Cardiol.*, 2004, 43,302-309.
6. Hausmann D., Mugge A., Becht I., Daniel W.G. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am. J. Cardiol.*, 1992,70,668-672.
7. Webster M.W., Chancellor A.M., Smith H.J. et al. Patent foramen ovale in young stroke patients. *Lancet*, 1988,2,11-12.
8. Lechat P., Mass J.L., Lascault G. Prevalence of patent foramen ovale in patients with stroke. *N. Engl. J. Med.*, 1988,318,1148-1152.
9. Cohnheim J. Thrombose und Embolie: Vorlesung über allgemein Pathologie. Hirschwald, Berlin (Publishers), Berlin, Germany, 1877, 134.
10. Isayev Y., Chan R.K.T., Pulicino P.M. "Economy Class" stroke syndrome?: *Neurology*, 2002,58,960-961
11. Khairy P., O'Donnell C.P., Landberg M.J. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann. Intern. Med.*, 2003,139,753-760.
12. Schuchlenz H.W., Weihs W., Berghold A. et al. Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int. J. Cardiol.*, 2005,101,77-82.
13. Windecker S., Wahl A., Nedeltchev K. et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J. Am. Coll. Cardiol.*, 2004,44,750-758.
14. Homma S., Sacco R.L., Di Tullio M.R. et al. Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke study. *Circulation*, 2002,105,2625-2631.
15. Hart R.G., Miller V.T. Cerebral infarction in young adults: a practical approach. *Stroke*, 1983,14,110-114.
16. Sacco R.L., Ellenberg J.H., Mohr J.P. et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann. Neurol.*, 1989,25,382-390.
17. Steiner M.M., Di Tullio M.R., Rundek T. et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke*, 1998,29,944-948.
18. Torti S.R., Billinger M., Schwerzmann M. et al. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur. Heart J.*, 2004,25,1014-1020.
19. Cheng T.O. Platypnea-orthodeoxia syndrome: etiology, differential diagnosis, and management. *Catheter. Cardiovasc. Interv.*, 1999, 47,64-66.
20. Sukernik M.R., Mets B., Bennett Guerrero E. Patent foramen ovale and its significance in the perioperative period. *Anesth. Analg.*, 2001,93,1137-1146.
21. Agnoletti G., Iserin L., Lafont A. et al. Obstructive sleep apnoea and patent foramen ovale: successful treatment of symptoms by percutaneous foramen ovale closure. *J. Interv. Cardiol.*, 2005,18,393-395.
22. Droste D.W., Ringelstein E.B. Detection of high intensity transient signals (HITS): how and why? *Eur. J. Ultrasound.*, 1998,7,23-29.
23. Homma S et. al.: Characteristics of patent foramen ovale

associated with cryptogenic stroke. A biplane transesophageal echocardiographic study. *Stroke*, 1994,25,582-586.

24. Serena J., Segura T., Perez-Ayuso M.J. et al. The Need to Quantify Right-to-Left Shunt in Acute Ischemic Stroke: A Case-Control Study. *Stroke*, 1998, 29, 1322-1328.

25. Sideris E.B., Sideris S.E., Fowlkes J.P. et al. Transvenous atrial septal defect occlusion in piglets with a "buttoned" double-disk device. *Circulation*, 1990,81,312-318.

26. Babic U.U., Grujicic S., Djuricic Z., Vucinin M. Transcatheter closure of atrial septal defects. *Lancet*, 1990,336,566-567.

27. Das G.S., Voss G., Jarvis G. et al. Experimental atrial septal defect closure with a new, transcatheter, self-centering device. *Circulation*, 1993, 88,1754-1764.

28. Meier B. Pacman sign during device closure of the patent foramen ovale. *Catheter. Cardiovasc. Interv.*, 2003,60,221-223.

29. Graham T.P. Ventricular septal defect. In *Heart Disease in Infants, Children, and Adolescents*. Edited by Adams FH, Baltimore, MD: Lippincott, Williams and Wilkins, 1989,;724-746.

30. Lock J.E., Block P.C., McKay R.G. et al. Transcatheter closure of ventricular septal defects. *Circulation*, 1988,78,361-368.

31. Knauth A.L., Lock J.E., Peryy S.B. et al. Transcatheter device closure of congenital and postoperative residual ventricular septal defects. *Circulation*, 2004,110,501-507.

32. Sideris E.B., Walsh K.P., Haddad J.L. et al. Occlusion of congenital ventricular septal defects by the buttoned device. *Heart*, 1997,77,276-279.

33. Chessa M., Carminati M., Cao Q.L. et al. Transcatheter closure of congenital and acquired muscular ventricular septal defects using the Amplatzer device. *J. Invasive Cardiol.*, 2002,14, 322-327.

34. Amin Z., Gu X., Berry J.M. et al. New device for closure of muscular ventricular septal defects in a canine model. *Circulation*, 1999,100,320-328.

35. Hijazi Z.M., Hakim F., Al-Fadley F. et al. Transcatheter closure of single muscular ventricular septal defects using the Amplatzer muscular VSD occluder: initial results and technical considerations. *Catheter. Cardiovasc. Interv.*, 2000, 49,167-172.

36. Thanopoulos B.D., Tsaoasis G.S., Konstadopoulou G.N., Zarayelyan A.G. Transcatheter closure of muscular ventricular septal defects with the Amplatzer ventricular septal defect occluder: initial application in children. *J.Am.Coll. Cardiol.*, 1999,33,1395-1399.

37. Hijazi Z.M. Device closure of ventricular septal defects. *Catheter. Cardiovasc. Interv.*, 2003,60,107-114.

38. Bass J.L., Kalra G.S., Arora R. et al. Initial human experience with the Amplatzer perimembranous ventricular septal occluder device. *Catheter. Cardiovasc. Interv.*, 2003, 58,238-245.

39. Amin Z., Gu X., Berry J.M. et al. Periventricular closure of ventricular septal defects without cardiopulmonary bypass. *Ann. Thorac. Surg.*, 1999, 68,149-154.

40. Holzer R., Balzer D., Amin Z. et al. Transcatheter closure of postinfarction ventricular septal defects using the new Amplatzer muscular VSD occluder: Results of a U.S. Registry. *Catheter. Cardiovasc. Interv.*, 2004, 61,196-201.

41. Crenshaw B.S., Granger C.B., Birnbaum Y. et al. Risk factors, angiographic patterns, and outcomes in patients with ventricular septal defect complicating acute myocardial infarction: GUSTO-I trial investigators. *Circulation*, 2000,101,27-32.

42. Moore C.A., Nygaard T.W., Kaiser D.L. et al. Postinfarction ventricular septal rupture: the importance of location of infarction and right ventricular function in determining survival. *Circulation*, 1986,74:45-55.

43. Mulasari A.S., Umesan C.V., Krishnan U. et al. Transcatheter closure of post-myocardial infarction ventricular septal defect with Amplatzer septal occluder. *Catheter. Cardiovasc. Interv.*, 2001,54, 484-487.

44. Pienvichit P., Piemonte T.C. Percutaneous closure of postmyocardial infarction ventricular septal defect with the CardioSEAL septal occluder implant. *Catheter. Cardiovasc. Interv.*, 2001,54,490-494.

45. Landzberg M.J., Lock J.E. Transcatheter management of ventricular septal rupture after myocardial infarction. *Semin. Thorac. Cardiovasc. Surg.*, 1998,10,128-132.

46. Birnbaum Y., Fishbein M.C., Blanche C., Siegel R.J. Ventricular septal rupture after acute myocardial infarction. *N. Engl. J. Med.*, 2002,347,1426-1432.

47. Sandercock P., Bamford J., Dennis M. Atrial fibrillation and stroke prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire Community Stroke Project). *Brit. Med. J.*, 1992,305,1460-1465.

48. Wolf P.A., Benjamin E.A., Belanger A.J. et al. Secular trends in the prevalence of atrial fibrillation the Framingham Study. *Am. Heart J.*, 1996,131,790-795.

49. Hart R.G., Pearce L.A., Rothbart R.M. et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. *Stroke Prevention in Atrial Fibrillation Investigators. J. Am. Coll. Cardiol.*, 2000,35,183-187.

50. Atrial Fibrillation Investigators, Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch. Intern. Med.*, 1994,154,1449-1457.

51. Brass L.M., Krumholz H.M., Scinto J.M., Radford M. Warfarin use among patients with atrial fibrillation. *Stroke*, 1997,28,2382-2389.

52. Gage B.F., van Walraven C., Pearce L. et al. Selecting patients with atrial fibrillation for anticoagulation—stroke risk stratification in patients taking aspirin. *Circulation*, 2004 110, :2287-2292.

53. Stoddard M.F., Dawkins P.R., Prince C.R., Ammash N.M. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event a transesophageal echocardiographic study. *J.Am.Coll. Cardiol.*, 1995,25,452-459.

54. Blackshear J.L., Odell J.A. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann. Thorac. Surg.*, 1996,61,755-759.

55. Johnson W.D., Ganjoo A.K., Stone C.D. et al. The left atrial appendage: our most lethal human attachment! surgical implications. *Eur. J. Cardiothorac. Surg.*, 2000, 17, 718-722.

56. Odell J.A., Blackshear J.L., Davies E. et al Thoracoscopic obliteration of the left atrial appendage: potential for stroke reduction? *Ann. Thorac. Surg.*, 1996, 61,565-569.

57. Meier B., Palacios I., Windecker S. et al. Transcatheter left atrial appendage occlusion with Amplatzer devices to obviate anticoagulation in patients with atrial fibrillation. *Catheter. Cardiovasc. Interv.*, 2003,60,417-422.

58. Ostermayer S.H., Reisman M., Kramer P.H. et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J. Am. Coll. Cardiol.*, 2005,46,9-14

Clinical Outcome of Patients Undergoing Sirolimus-Eluting Stenting for Bifurcation Lesions Using the “Crush Technique”

Issam Moussa¹

Columbia University Medical Center / NY Presbyterian Hospital, Cardiovascular Research Foundation
New York City, NY

Key Words: bifurcation, crush technique, sirolimus-eluting stent

While sirolimus-eluting stents (SES) have been shown to reduce angiographic and clinical recurrence in non bifurcated coronary lesions (1-3), its impact on coronary bifurcations remains unclear. The “Randomized Study to Evaluate Sirolimus-Eluting Stents Implanted at Coronary Bifurcation Lesions” (4), which compared planned elective T-stenting to main vessel (MV) stenting with provisional side branch (SB) stenting, demonstrated excellent mid-term patency of the MV but restenosis of the SB remained a problem with both approaches. It has been postulated that the lack of efficacy of SES in the SB is due to the incomplete wall coverage of the SB ostium with T-stenting. To overcome this limitation, Colombo et al (5) proposed the “crush” technique with the intent of achieving two goals: 1) secure the immediate patency of the MV and the SB; and 2) provide optimal lesion coverage of the SB ostium and hence reduce the rate of restenosis at this site. Despite the theoretical advantage of this approach, the long-term outcome of this technique remains unclear. In this report, we present the results of a prospective registry of consecutive patients treated with SES implantation for coronary bifurcation lesions using the “crush technique”.

Methods

Between April 2003 and May 2004, all consecutive patients with ischemic coronary disease and bifurcation lesions who were treated with SES implantation using the crush technique were included. In this period, the crush technique was used whenever a decision has been made by the operator to stent both the MV and the SB. Demographic and procedural data were collected through medical chart review and all films were analyzed off-line by individuals not participating in the procedure. Clinical follow-up was performed through patient visits, charts review and phone calls. This registry included patients with de novo bifurcation lesions, patients with bare metal in-stent restenosis, as well as patients with severely calcified or thrombus-containing lesions. Written

informed consent was obtained before all procedures.

The “Crush” Technique

The crush stent technique has been reported in detail elsewhere (5). In brief, both branches are wired and predilated. Rotational atherectomy, thrombectomy and cutting balloon were used selectively for lesion preparation when needed. After lesion preparation the first stent is advanced into the SB, but not deployed while a second stent is advanced into the MV to cover fully the bifurcation. The SB stent is then retracted into the MV so that its proximal edge is 3-4mm proximal to the carina of the bifurcation and then deployed. The SB stent delivery balloon and the wire are removed after a contrast injection ensures that no distal dissection is present and no additional SB stents are needed. The stent in the MV is then deployed. In our initial experience (14 patients) kissing balloon inflation was not performed, but later all patients undergoing crush stenting underwent kissing balloon inflation regardless of the angiographic appearance of the SB. All patients received aspirin 325mg and a 300mg loading dose of clopidogrel were administered before the procedure. The use of Glycoprotein IIb/IIIa inhibitors and bivalirudin was left to the discretion of the operator. All patients were prescribed to receive aspirin (81-325mg/day) indefinitely and clopidogrel (75mg/day) for 1 year.

Angiographic Analysis and Clinical Follow-up

Cineangiograms were independently analyzed by the Cardiovascular Research Foundation's Angiographic Core Laboratory. Quantitative coronary angiography (QCA) was performed using the CMS-GFT® algorithm (MEDIS, Leiden, the Netherlands). The accuracy of the method has been reported in detail (6). For the MV, the minimum lumen diameter (MLD) and the mean reference diameter (RD, obtained from averaging 5mm segments proximal and distal to the target lesion location) were used to calculate the diameter stenosis $[DS=(1-MLD/RD) \times 100]$ at baseline and after final intervention. For the SB, the MLD and the mean RD (obtained from the segment 5 mm distal to the target lesion location) were used to calculate the diameter stenosis at baseline and post-intervention. All quantitative measurements were performed: within the stented segment (“in-stent”) and “in-lesion,” spanning the stented segment plus the 5mm proximal and dis-

¹Issam Moussa, MD
Columbia University Medical Center & New York Presbyterian Hospital, NY, NY
161 Fort Washington Ave, 5th floor
New York, NY 10032
Phone: 212-342-3605 ;
Fax: 212-342-3660 ;
E mail: im2132@columbia.edu

tal peri-stent area. For patients with angiographic follow-up (not mandatory), binary restenosis was defined as >50% diameter stenosis, and was classified as focal (< 10mm in length) or diffuse (≥ 10mm in length).

Clinical follow-up was obtained around 6 months after treatment by telephone or direct patient interview.

Definitions and Endpoints

Procedure success was defined as successful treatment of the bifurcation lesion with final TIMI 3 flow and diameter stenosis <30% (visual estimation) in both branches plus absence of death, myocardial infarction (MI), and repeat percutaneous intervention of the treated lesion during the index hospitalization. Device success was defined as successful deployment of SES in both MV and SB with crush stenting plus final TIMI 3 flow plus <30% stenosis in both branches. The study's endpoint was the incidence of target lesion revascularization (TLR) – defined as any repeat percutaneous intervention to the target lesion (MV or SB) or any coronary bypass graft (CABG) to the treated vessel – at 6 months follow-up. Major adverse clinical events – MACE, was defined as death, MI, TLR or TVR (target vessel revascularization, defined by TLR or TVR by CABG) during the follow-up period plus in-hospital MACE.

Statistical Analysis

Patients were analyzed on an intent-to-treat basis. Data are presented as mean±1SD or frequencies. Clinical follow-up results are presented as percentages (frequency of events). Statistical analyses were performed using StatView 5.0 (SAS Institute, Cary, NC, USA). For comparisons of categorical data, the Fisher's exact test was performed; for comparisons of continuous variables, a 2-tailed, either paired or unpaired student's t-test was used. A p value <0.05 was considered significant.

Results

Baseline Clinical and Angiographic Characteristics

Baseline clinical and angiographic characteristics for the study population are shown in tables 1 and 2.

Twenty two patients (18%) had bare metal in-stent restenosis, 30% had moderate or severe calcification, and 14 patients (11.7%) presented with non-Q wave or Q-wave MI. Compared to the MV, SB lesions were shorter, with smaller reference diameter (Table 3).

Table 1. Baseline clinical characteristics

Mean age, years	n = 120
Male gender, %	64,3 ± 10,7
Hypertension, %	69,2
Гипертензия, %	84,7
Diabetes mellitus, %	36,0
Type I (insulin dependent), %	8,1
Hyperlipidemia, %	77,5
Smoking, %	38,7
CRI*, %	12,6
Previous MI, %	21,6
Previous CABG, %	8,1
History of CHF, %	7,2
History of CVA, %	3,6
Unstable angina, %	55,0

Values are expressed as mean ± 1SD (median) or frequencies (% of column total). *Defined as preprocedure serum creatinine level >1.5mg/ml. CABG=coronary artery bypass graft surgery; CAD=coronary artery disease; CHF=cardiac heart failure; CRI=chronic renal insufficiency; CVA=cerebral-vascular accident.

Table 2. Angiographic Morphology.

Main vessel/side branch, %	n = 120
LAD/Diagonal	
ПМЖВ/диагональная ветвь	69,2
LCX/OM	19,2
PDA/PLSA (i.e. RCA)	3,3
LAD/LCx or Ramus (i.e. LM)	8,3
Type of bifurcation D/F†, %	65,8/34,2
Calcium (moderate/severe), %	30,8
Multivessel disease, %	72,4
LVEF, %	49,0 ± 12,8
Baseline (Main vessel/side branch), %	
Thrombus	4,2/0,8
TIMI 0 or 1	9,2/4,2
TIMI 2	1,7/3,3
TIMI 3	89,2/92,5
Final (Main vessel/side branch), %	
Dissection	0,0/0,0
Thrombus	0,0/0,0
TIMI 0 или 1	0,0/0,0
TIMI 2	1,7/0,8
TIMI 3	98,3/99,2

Values are expressed as frequencies (% of column total). LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; LM=left main coronary artery; LVEF=left ventricular ejection fraction; OM=obtuse marginal branch; PDA=postero-descending artery; PLSA=postero-lateral side branch artery; LVEF=left ventricular ejection fraction; TIMI=Thrombolysis In Myocardial Infarction.

Table 3. Quantitative Angiography (n=120).

Baseline	Main Vessel	Side Branch	p value
Lesion length, mm	18,62 ± 6,93	12,35 ± 5,15	<0,0001
RD, mm	2,87 ± 0,31	2,36 ± 0,31	<0,0001
MLD, mm	0,88 ± 0,41	0,66 ± 0,33	<0,0001
% DS	69,4 ± 13,1	72,2 ± 13,0	0,04
Final	Main Vessel	Side Branch	p value
RD, mm	3,00 ± 0,31	2,47 ± 0,31	<0,0001
In-Stent MLD, mm	2,82 ± 0,34	2,20 ± 0,44	<0,0001
In-Stent %DS	5,9 ± 8,1	10,8 ± 15,1	0,0005
In-Lesion MLD, mm	2,47 ± 0,33	2,00 ± 0,39	<0,0001
In-Lesion % DS	17,5 ± 8,2	19,2 ± 11,6	0,18

Values are expressed as mean ± 1SD (median). DS=diameter stenosis; MLD=minimum lumen diameter; RD=reference (vessel) diameter.

Procedure

Procedure success was achieved in 97.5% – 3 patients had final TIMI 2 flow (2 MV and 1 SB), and device success was achieved in all but 3 patients who received bare-metal stents in the SB lesions due to inability to cross the lesion with a SES. Figure 1 shows an example of the procedure steps of a bifurcation lesion (LAD/diagonal) successfully treated with crush stenting. MV received more

stents per vessel (1.49 ± 0.72 vs. 1.19 ± 0.42 stents, $p < 0.0001$), which were larger (3.13 ± 0.29 mm versus 2.79 ± 0.32 mm, $p < 0.0001$) and longer (23.67 ± 5.83 mm vs. 20.55 mm, $p < 0.0001$) compared to SB stents. Also, post-dilatation balloon was larger in the MV (3.48 ± 0.36 mm vs. 2.99 ± 0.35 mm, $p < 0.0001$). Final kissing balloon inflations (KB) were performed in 87.5% of lesions. Table 4 shows the comparison between patients with vs. without KB. Glycoprotein IIB/IIIA inhibitors were used in 15% of cases; and bivalirudin was administered in 69% of patients.

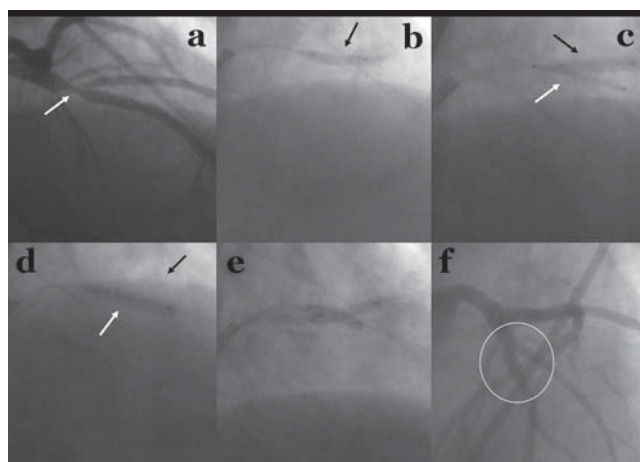


Figure 1. a. Bifurcation lesion (arrow) involving both the main vessel (MV) and the side branch (SB) origin. b. Predilation of the SB ostium (arrow). c. SB stent deployment (black arrow) with the MV stent (white arrow) in "position" covering fully the bifurcation. d. MV stent deployment (white arrow). Black arrow indicates SB stent struts. e. Post-dilation with kissing balloon inflation. f. Final angiographic view showing optimal angiographic result in both branches.

Table 4. QCA comparison between patients with final kissing balloon inflations (KB, n=106) versus patients without final KB (No-KB, n=14).

	Main Vessel			Side Branch		
	KB	No KB	p value	KB	No KB	p value
Baseline						
Lesion length, mm	18,9 ± 6,9	16,6 ± 7,0	0,25	12,3 ± 5,1	12,6 ± 5,2	0,86
RD, mm	2,9 ± 0,3	2,7 ± 0,2	0,008	2,4 ± 0,3	2,3 ± 0,4	0,51
MLD, mm	0,9 ± 0,4	0,7 ± 0,4	0,20	0,7 ± 0,3	0,6 ± 0,3	0,34
% DS	69,0 ± 13,0	72,5 ± 13,5	0,34	71,8 ± 13,1	75,2 ± 12,1	0,36
Final						
RD, mm	3,0 ± 0,3	2,8 ± 0,3	0,04	2,5 ± 0,3	2,4 ± 0,3	0,55
In-Stent MLD, mm	2,8 ± 0,3	2,7 ± 0,3	0,11	2,2 ± 0,4	2,2 ± 0,4	0,91
In-Stent %DS	6,0 ± 8,2	5,6 ± 8,0	0,88	11,1 ± 15,5	8,9 ± 11,9	0,62
In-Lesion MLD, mm	2,5 ± 0,3	2,4 ± 0,3	0,36	2,0 ± 0,4	2,1 ± 0,4	0,58
In-Lesion %DS	17,7 ± 8,2	15,7 ± 8,0	0,38	19,7 ± 11,7	15,7 ± 10,8	0,23

Values are expressed as mean ± 1SD (median). DS=diameter stenosis; MLD=minimum lumen diameter; RD=reference (vessel) diameter.

In-Hospital and 30-day outcome

In-hospital complications included thrombocytopenia in 3 patients and hematoma at the puncture site in 2 patients. One patient developed pseudoaneurysm at the puncture site. There were no cardiac related in-hospital complications. At 30-day follow-up, two patients (1.7%) had stent thrombosis. Other 30-day events are shown in table 5.

Table 5. 30-days and 6 months clinical follow-up (n=115).

OUTCOME, % (n)	30 Days	6 Months
MACE	1,7 (2)	13,0 (15)
Death	0 (0)	0,9 (1)
Myocardial infarction	1,7 (2)	1,7 (2)
TLR	1,7 (2)	11,3 (13)
- PCI	0,9 (1)	8,7 (10)
- CABG	0,9 (1)	2,6 (3)
TVR	1,7 (2)	12,2* (14)
Stent thrombosis	1,7 (2)	1,7 (2)

Values are expressed as percentages. *1 patient had patent stents but underwent CABG during follow-up due to disease progression in other vessels. CABG=coronary artery bypass graft; MACE=major adverse clinical events; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Mid-term Clinical Follow-Up

Clinical follow-up was available in 115 patients (96%) at a mean follow-up of 5.9 months. One patient died 45 days after the procedure at a nursing home due to a malignancy.

As shown in table 6, TLR at 6 months was needed in 13 patients (11.3%), all of whom had focal restenosis (1 patient had multifocal restenosis). Restenosis was limited to the SB ostium in 9 patients, at the SB ostium and the MV in 1 patient, and only in the MV in 3 patients. Ten patients underwent repeat PCI and 3 patients were referred to CABG.

Patients who underwent TLR, compared to those who did not, had a non significant trend towards higher frequency of diabetes (54% vs. 33%, $p=0.24$) and calcified lesions (46% vs. 28%, $p=0.30$). However, there were no differences in the frequency of using KB inflation between those who needed TLR versus those who did not (90% vs. 87%, $p=0.82$). Table 6 shows the QCA comparison between patients with versus without TLR.

Table 6. QCA comparing patients with TLR (n=13) versus patients without TLR (n=101).

Variable	Main Vessel			Side Branch		
	TLR	No-TLR	p value	TLR	No-TLR	p value
Baseline						
Lesion length, mm	19,7 ± 8,2	18,5 ± 6,8	0,55	11,7 ± 5,2	12,4 ± 5,2	0,65
RD, mm	2,8 ± 0,3	2,9 ± 0,3	0,21	2,3 ± 0,2	2,4 ± 0,3	0,18
MLD, mm	0,7 ± 0,5	0,9 ± 0,4	0,24	0,7 ± 0,4	0,7 ± 0,3	0,61
% DS	72,9 ± 16,0	69,2 ± 12,8	0,35	68,3 ± 18,0	72,8 ± 12,3	0,40
Final						
In-Stent MLD, mm	2,8 ± 0,2	2,8 ± 0,4	0,60	2,1 ± 0,4	2,2 ± 0,4	0,46
In-Stent MLD, mm	2,3 ± 5,9	6,6 ± 8,4	0,07	9,6 ± 18,3	10,8 ± 14,7	0,80
In-Lesion	2,4 ± 0,3	2,5 ± 0,3	0,38	1,9 ± 0,5	2,0 ± 0,4	0,40
In-Lesion % DS	15,3 ± 5,4	17,7 ± 8,6	0,20	19,5 ± 13,9	19,1 ± 11,1	0,91

Values are expressed as mean ± 1SD (median). DS=diameter stenosis; MLD=minimum lumen diameter; MV=main vessel; RD=reference (vessel) diameter; SB=side branch; TLR=target lesion revascularization.

Discussion

Treatment of true coronary bifurcation lesions remain one of the most challenging technical endeavors in Interventional Cardiology. The controversy in the published literature has focused on whether bifurcation stenting (MV and SB stenting) is better or worse than provisional stenting (MV stenting and SB PTCA) for treatment of all patients with bifurcation lesions. Although this is an important theoretical question, the more clinically relevant issue is to better define a set of anatomic variables where each technique may have a unique advantage. The retrospective nature of the published literature, the un-measurable variability in bifurcation morphology among different studies, as well as the variability in

outcome ascertainment methods makes drawing scientifically valid conclusions impossible.

Most coronary bifurcation lesions can be treated with stent implantation of the MV and balloon dilatation of the SB, particularly if the SB is small, or have minimal or only focal disease. However, coronary bifurcation lesions that involve a large SB, particularly in the presence of severe ostial stenosis and / or severe angulation may need a strategy of bifurcation stenting (MV and SB stenting). In the "Randomized Study to Evaluate Sirolimus-Eluting Stents Implanted at Coronary Bifurcation Lesions" (4), 51% of patients crossed over from the provisional to the bifurcation stent arm due to suboptimal PTCA results in the SB. Despite this high rate of crossover, procedural success was achieved in only 77% of patients in the provisional arm versus 92% in the bifurcation stent arm.

While we cannot make any statement regarding the most suitable technique to treat bifurcation lesions (provisional stenting or stenting both branches), whenever two stents are needed the following conclusions can be drawn from this study: (1) bifurcation SES implantation using the crush technique can be performed with high procedural success rate and low incidence of in-hospital complications even in highly complex patient subsets; (2) stent thrombosis (1.7%) appears to be higher than that of a single stent technique, but similar or even lower than other bifurcation stent techniques; (3) compared to previous studies using two bare metal stents in bifurcation lesions (7-9), implantation of two SES is associated with a lower rate of repeat revascularization; (4) similar to historical results with "T" stenting or provisional stenting technique using SES stents, recurrence at SB ostium remains a problem; (5) in the current study, the use of final kissing balloon inflation did not impact stent thrombosis nor clinical restenosis, but that may be due to the very low number of patients who did not have final KB inflation (14 patients).

Safety of the "Crush" Stenting Technique

After introduction of the "crush" stenting technique, concerns were raised about the theoretical risks of stent thrombosis secondary to the high metal density at the site of the carina. In this study, 2 patients (1.7%) had stent thrombosis at 30-day follow-up and none thereafter. The first patient presented with chest pain and non-Q-wave MI 4 days after the index procedure (LAD/diagonal bifurcation intervention with final TIMI 2 in the diagonal branch). Angiography showed occlusion of the diagonal stent and the patient was referred to CABG. The second patient presented 27 days after the index procedure (LAD/diagonal intervention) to an outside hospital with anterior wall MI which was treated with thrombolytic therapy. Subsequent angiography showed patent LAD but under-expanded stent distal to the bifurcation. Repeat PTCA was performed to optimally expand the stents. Both patients were compliant with aspirin and clopidogrel. The rate of stent thrombosis

in the present study (1.7%) is similar to that reported with other bifurcation stent techniques using SES (1.5% to 3.5%) (4,10,11), but is higher than that reported with a single stent technique (0%) (4,11). Clearly, this difference is unlikely to reach statistically significance in any of these studies because they are underpowered to detect such an uncommon event. Nonetheless, this difference is clinically relevant and should be part of the clinical decision making process when the need arise for bifurcation stenting.

Durability of SES Using the “Crush” Technique

In the current study, TLR was needed in 13 patients (11.5%). Restenosis was focal in all patients and was confined to the SB ostium in 9 patients (69%), at both the SB ostium and the MV in 1 patient (8%), and only in the MV in 3 patients (23%). The rate of repeat revascularization in our study is similar to that reported in the double-stenting group of the “Randomized Study to Evaluate Sirolimus-Eluting Stents Implanted at Coronary Bifurcation Lesions” (9.5%) (4), where T-stenting was used, despite the higher complexity of our patient population. Similarly, Tanabe et al (10) and Colombo et al (11) reported an 8.6% and 8.9% TLR rate, respectively in a series of patients treated with various bifurcation stenting techniques (Crush, V, Culotte, T) using SES. A common feature among all the above bifurcation stenting studies is the location of angiographic recurrence at the SB ostium.

Limitations

This study has several limitations: 1) although this is a prospective registry it only reflects the experience of a single institution and it represents a consecutive non-randomized patient cohort; 2) due to the absence of a control group, this study can not provide answers to whether this technique is better or worse than provisional stenting or other bifurcation stent techniques. However, this is the largest prospective series of patients with highly complex bifurcation lesions undergoing SES implantation with the crush stenting in the USA.

Conclusions

The “crush technique” can be safely used by experienced operators to treat highly complex bifurcation lesions with SES. The safety profile of this technique is similar to that of other bifurcation stent techniques reported thus far. Nonetheless, despite excellent patency rates of the main vessel recurrence at the side branch ostium remains a problem.

References:

1. 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.
2. Moses J.W., Leon M.B., Popma J.J. et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N. Engl. J. Med.*, 2003,349,1315-23.
3. Schofer J., Schluter M., Gershlick A.H. et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet*, 2003,362,1093-1099.
4. Colombo A., Moses J.W., Morice M.C. et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*, 2004,109,1244-9.
5. Colombo A., Stankovic G., Orlic D. et al. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Catheter. Cardiovasc. Interv.*, 2003,60,145-51.
6. Lansky A.J., Popma J.J., Cutlip D. et al. Comparative analysis of early and late angiographic outcomes using two quantitative algorithms in the Balloon versus Optimal Atherectomy Trial (BOAT). *Am. J. Cardiol.*, 1999,83,1611
7. Reimers B., Colombo A., Tobis J. Bifurcation lesions. In: Colombo A, Tobis J, eds. *Techniques in Coronary Artery Stenting*. London, Martin Dunitz Ltd, 2000,171-204.
8. Yamashita T., Nishida T., Adamian M.G. et al. Bifurcation lesions: two stents versus one stent--immediate and follow-up results. *J. Am. Coll. Cardiol.*, 2000,35,1145-51.
9. Gobeil F., Lefevre T., Guyon P. et al. Stenting of bifurcation lesions using the Bestent: a prospective dual-center study. *Catheter. Cardiovasc. Interv.*, 2002,55,427-33.
10. Tanabe K., Hoye A., Lemos P.A. et al. Restenosis rates following bifurcation stenting with sirolimus-eluting stents for de novo narrowings. *Am. J. Cardiol.*, 2004,94,115-8.
11. Ge L., Tsalagou E., Iakovou I. et al. In-Hospital and Nine-Month Outcome of Treatment of Coronary Bifurcational Lesions With Sirolimus-Eluting Stent. *Am. J. Cardiol.*, 2005,95,757-760.

Transcatheter Alcohol Reduction of the First Septal Branch in the Treatment of Hypertrophic Obstructive Cardiomyopathy

A.G. Ossiev¹, M.A. Vereschaguin, I.V. Maletina, A.M. Karaskov

E.N. Meshalkin Science Research Institute of Circulation Pathology, Federal Agency for Healthcare and Social Development, Novosibirsk, Russia.

The treatment of patients with the symptoms of hypertrophic obstructive cardiomyopathy (HOCM) is aimed at the reduction of symptoms, improvement of functional capacity and the quality of life (1-2). This can be reached through the decrease of the pressure gradient in the left ventricular outflow tract (LVOT) and the improvement of its diastolic function. Agents possessing negative inotrope properties, such as β -blockers, Verapamil or Dizopyramide has always considered as the first line therapy. Unfortunately, at least 10% of patients with revealed LVOT obstruction have serious symptoms not responding to medical therapy (3). Surgical treatment with myectomy/myotomy was the main method of treatment in this group of patients for many decades. It assured long-standing symptomatic improvement in most patients, despite the reported mortality level of 1,5 - 10% (4-7). Percutaneous transluminal ablation of the ventricular septum through alcohol-induced occlusion of the septal branch is aimed at direct reduction of hypertrophied ventricular septum with stepwise enlargement of the left ventricular outflow tract and the decrease of pressure gradient in LVOT(8).

The idea of percutaneous ablation of the ventricular septum for the induction of local myocardial infarction through alcohol-induced occlusion of a septal branch was suggested in the 1980-ies, as a result of favorable hemodynamic and clinical results of surgical myectomy and the increasing experience with interventional procedures. Original technique of alcohol ablation has been described in 1989 (Berghoefer), after similar procedures of chemical septal branch ablation being used for the treatment of ventricular dysrhythmias (9). First experiments have shown that temporary balloon occlusion of the first septal branch leads to significant decrease of pressure gradient in the outflow tract in a small part of patients. Sigwart was the first to report successful non-surgical myocardial reduction after septal branch occlusion with the use of 96% alcohol (10).

Purpose of study:

The assess the effectiveness of the procedure of

alcohol reduction of the myocardium in patients with hypertrophic obstructive cardiomyopathy.

Material and methods:

From 2003 to 2006 we have performed 38 procedures of alcohol reduction of the myocardium for patients with hypertrophic obstructive cardiomyopathy. Mean age of the patients was $43 \pm 7,1$ years, there were 29 (76,3%) men. The main indications for the procedure of alcohol reduction of the myocardium were: ineffective pharmacological therapy, circulatory insufficiency of NYHA class III-IV, as well as of NYHA class II in the presence of syncopal states. Hemodynamic indications for the procedure performance were: LVOT pressure gradient > 30 mm Hg at rest and > 100 mm Hg at physical load.

According to EchoCG data, mean baseline thickness of the ventricular septum was $2,3 \pm 0,3$ cm, ejection fraction (EF) – $78,3 \pm 4,9\%$, LVOT pressure gradient – $77,3 \pm 8,6$ mm Hg. Direct measurement of LVOT pressure revealed mean pressure gradient of $81,4 \pm 7$ mm Hg.

While performing the procedure of alcohol ablation of the myocardium we follow the algorithm suggested by Lakkis N. et al. (14). All authors agree that temporary pacemaker should be placed in the right ventricle, as there is a risk for complete AV block development during ablation. In order to measure the pressure gradient in LVOT, the pressure is recorded simultaneously from the guiding catheter, placed in the ascending segment of the aorta, and from a special 5F catheter Pigtail with holes situated only in the distal part, placed in the apex of the left ventricle. Pressure gradient in LVOT is measured at rest and during provocative tests, such as Valsalva test, or after an extrasystole (Fig. 1a).

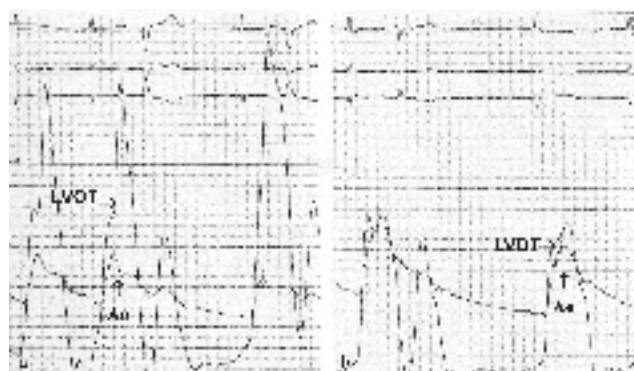


Figure 1

¹Ossiev A.G.
Center of X-ray diagnostics and interventional radiology
Acad. E. N. Meshalkin Novosibirsk Research Institute of Circulation Pathology
15, ul. Rechunkovskaya, Novosibirsk, 630055, Russia
e-mail: ossiev_ag@mail.ru
Manuscript received on June 19, 2006.
Accepted for publication on July 4, 2006.

Thromboembolic complications are prevented with body weight-adjusted heparin infusion. Besides, general anesthesia must be used in order to avoid pain syndrome during alcohol injection. After coronary angiography and detection of the septal branch blood-supplying the hypertrophied ventricular septum which participates in the obstruction (Fig. 2a), a 0,014-inch coronary guidewire is introduced in this

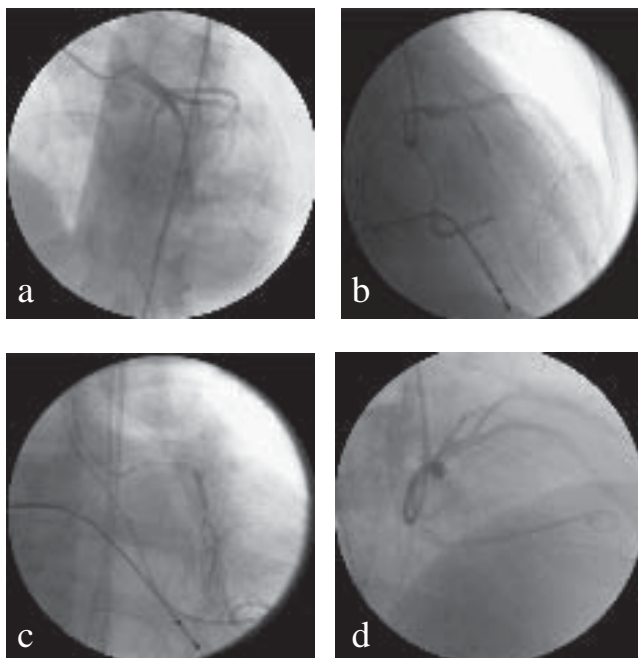


Figure 2

artery. It is necessary to use soft coronary guidewire so to not damage the anterior descending artery (ADA). After it a short (< 1 cm long) bi-lumen balloon catheter is introduced and inflated in the septal branch (Fig. 2b). In order to prevent alcohol entrance in the ADA the diameter of the balloon catheters should be somewhat bigger than this of the septal branch. Usually we use balloon catheters 1,5 - 3,0 mm in diameter (in one case, with a large septal we had to use 3,5 mm balloon catheter). Then a small amount of contrast (1-2 ml) is injected through the lumen of the inflated balloon catheter for angiographic determination of the territory of the septal branch blood supply and the exclusion of contrast reflux in the ADA (Fig. 2c). In order to determine the target septal branch and the exclude alcohol injection in other areas, such as papillary muscles or LV free wall, we perform contrast EchoCG examination (11-12) (Fig.3).

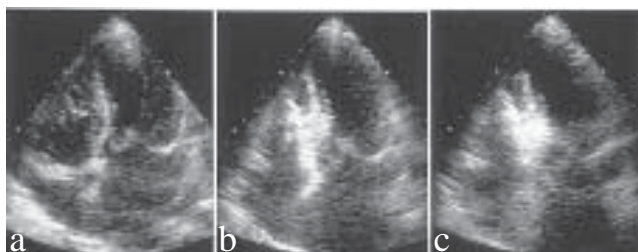


Figure 3. Echocardiographic examinations: a - baseline, b - with contrast injection, c- with alcohol injection.

Only after the fulfillment of all these criteria 1-2 ml of 96% alcohol are injected through the central lumen of the balloon catheter. It is extremely important to inject the alcohol under fluoroscopic control, in order to prevent eventual displacement of the balloon catheter. At least 10 minutes after alcohol injection, balloon catheter is deflated and pulled out, it is mandatory for the exclusion of alcohol entrance to the ADA (13). Control coronary angiography is carried out for the exclusion of ADA damage and confirmation of septal branch occlusion (fig. 2d), also control measurement of LVOT pressure gradient is performed (Fig. 1b). Hemodynamic indices and heart rhythm should be monitored in ICU for at least 48 hours.

Statistical analysis of the obtained data was carried out using «Microsoft Excel 2000», «Statistica 6.0» packages. Quantitative data are presented as $M \pm m$ (mean \pm SD), qualitative data – as a share of the set sample. Differences reliability was analyzed using Student's t-test for the samples with parametric distribution with $CD > 95\%$. The differences were considered as statistically reliable with $p \leq 0,05$. The differences with $0,1 > p > 0,05$ were considered as a tendency. With $p > 0,1$ the differences were considered as non-reliable.

Results and discussion.

Clinical and hemodynamical effectiveness of alcohol reduction of the myocardium was assessed in all 38 patients immediately and 6-24 months after the procedure.

Immediately after the procedure clinical improvement was noted in 100% of cases. Dynamics of clinical state is presented in Table 1.

Table 1. Dynamics of clinical state

n=38	Pre-Procedural	Post-Procedural	p
Dyspnea	38 (100%)	0	<0,01
Anginal pains	24 (63%)	19 (50%)	0,25
Prompt fatigue	32 (84%)	13 (34%)	<0,01
Syncopal states	10 (26%)	0	<0,01
Palpitations	32 (84%)	32 (84%)	ns

Direct tensiometry after alcohol reduction revealed mean intraprocedural gradient at the level of left ventricular outflow tract $11 \pm 7,2$ mm Hg. At day 1 after the procedure pressure gradient rose to $50,5 \pm 2,4$ mm Hg due to aseptic inflammation and edema of the infarcted septal area, by the moment of discharge gradient at the LVOT level was $21 \pm 1,6$ mm Hg in average and remained at that level thereafter (fig.4).

In the follow-up period the thickness of the ventricular septum decreased from $2,3 \pm 0,3$ cm to $1,8 \pm 0,1$ cm. As for the LV EF, it was on average $78,3 \pm 4,9\%$ before the procedure, and at 6 months it decreased to $65 \pm 3,4\%$ in average (Table 2.)

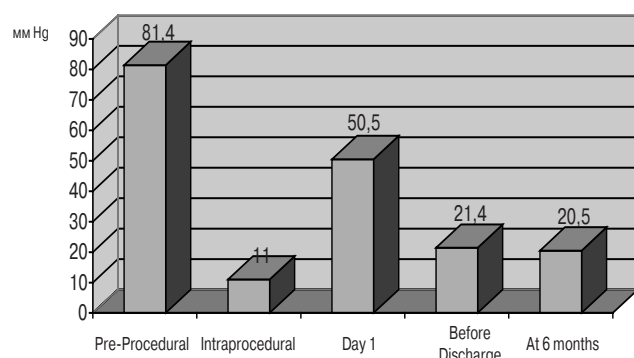


Figure 4. Dynamics of the changes of pressure gradient in LVOT.

Table 2. Dynamics of clinical state

	Pre-procedural (n=38)	Before discharge (n=38)	At 6 months (n=38)	p
VS thickness, cm.	2,3±0,3	2,2±0,4	1,8±0,1	ns
EF, %	78,3±4,9	75,8±4,1	65±3,4	0,07

VS = ventricular septum

No deaths occurred during the procedure and in the follow-up period. In one case (2,6%) transient AV block was noted after alcohol injection, which necessitated the use of temporary pacemaker; in the future the conduction resumed.

During the follow-up period 2 (5,3%) patients had disease recurrence with pressure gradient in LVOT increasing up to 64,5 mm Hg and 78,2 mm Hg, respectively. The first patient underwent repeated procedure of alcohol reduction of the myocardium with good clinical and hemodynamical result (pressure gradient in LVOT decreased to 23,7 mm Hg). With this we have performed alcohol reduction of a major second septal branch supplying hypertrophied portion of the ventricular septum. In the second case repeated alcohol reduction of the myocardium proved impossible. Coronary angiography showed the occlusion of the 1st septal branch, the opacification of the 2nd septal branch revealed that it did not participate in the blood supply of the hypertrophied portion of the ventricular septum. We decided not to perform the intervention.

Thus, our results suggest that the procedure of alcohol reduction of the myocardium contributes to significant decrease of the symptoms and improves the quality of life of the patients in the short-term and long-term follow-up.

Conclusions:

1. Alcohol reduction of the myocardium is a safe and effective method for the treatment of hypertrophic cardiomyopathy.
2. One must take into account the dynamics of systolic pressure gradient in the left ventricular outflow tract specific for this procedure.
3. In case of disease recurrence it is possible to repeat alcohol reduction of the myocardium in the presence of a septal branch supplying the hypertrophied portion of the ventricular septum.

References:

1. Wigle E.D., Rakowski H., Kimball B.P., Williams W.G. Hypertrophic cardiomyopathy: Clinical spectrum and treatment. *Circulation*, 1995, 92, 1680-1692.
2. Spirito P., Seidman C.E., McKenna W.J., Maron B.J. The management of hypertrophic cardiomyopathy. *N. Engl. J. Med.*, 1997, 336, 775-785.
3. Maron B.J. Appraisal of dual-chamber pacing therapy in hypertrophic cardiomyopathy: Too soon for a rush to judgment? *J. Am. Coll. Cardiol.*, 1996, 27, 431-2.
4. Schulte H.D., Gramsch-Zabel H., Schwartzkopff B. Hypertrophe obstruktive Kardiomyopathie: Chirurgische Behandlung. *Schweiz. Med. Wschr.*, 1995, 125, 1940-1949 (in German).
5. Robbins R.C., Stinson E., Daily P.O. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. *J. Thorac. Cardiovasc. Surg.*, 1996, 111, 586-594.
6. Heric B., Lytle B.W., Miller D.P. et al. Surgical management of hypertrophic obstructive cardiomyopathy: Early and late results. *J. Thorac. Cardiovasc. Surg.*, 1995, 110, 195-208.
7. Schoendube F.A., Klues H.G., Reith S. et al. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. *Circulation*, 1995, 92 (Suppl. II), 122-127.
8. Seggewiss H. Current status of alcohol septal ablation for patients with hypertrophic cardiomyopathy. *Curr. Cardiol. Rep.*, 2001, 3, 160-166.
9. Brugada P., de Swart H., Smeets J.L. et al. Transcatheter chemical ablation of ventricular tachycardia. *Circulation*, 1989, 79, 475-482.
10. Sigwart U. Non-surgical myocardial reduction of hypertrophic obstructive cardiomyopathy. *Lancet*, 1995, 346, 211-214.
11. Faber L., Seggewiss H., Gleichmann U. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: Acute and 3-months follow-up results with respect to myocardial contrast echocardiography. *Circulation*, 1998, 98, 2415-2421.
12. Faber L., Seggewiss H., Fassbender D., et al. Guiding of percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy by myocardial contrast echocardiography. *J. Interv. Cardiol.*, 1998, 11, 443-448.
13. Ruzyllo W., Chojnowska L., Demkow M. et al. Left ventricular outflow tract gradient decrease with non-surgical myocardial reduction improves exercise capacity in patients with hypertrophic obstructive cardiomyopathy. *Eur. Heart J.*, 2000, 21, 770-777.
14. Lakkis N., Kleiman N., Killip D. et al. Hypertrophic obstructive cardiomyopathy: alternative therapeutic options. *Gin. Cardiol.*, 1997, 20, 417-418.

Endovascular Surgery for Congenital Cardiovascular Pathology

*B.M. Shukurov¹, G.V. Kozlov, A.P. Dushkina, V.A. Nemchuk
Volgograd Cardiological Center, Volgograd, Russia*

Keywords: congenital cardiovascular pathology, embolization, Amplatzer device.

The article reviews our experience with endovascular therapy in patients with congenital cardiovascular abnormalities: 25 closures of atrial septal defects (ASD), 61 closures of patent ductus arteriosus (PDA), 11 embolizations of angiodysplasias of brachiocephalic arteries, 2 embolizations of coronary-cardiac fistulas. The questions of the effectiveness of indications and safety of endovascular approach in this population of patients are considered.

Introduction

Congenital cardiovascular defects have long been managed only by conventional surgery, while the endovascular techniques had auxiliary and investigative role being, on the one hand, one of the major diagnostic methods and, on the other hand, lacking therapeutic potential (1,2,3). However, the advances of technical and clinical research have lead to the occurrence of endovascular options with therapeutic impact (4,5,6,7,8). These were particularly crucial in children and infants, when high therapeutic potential and small surgical injury commonly determined the outcome, especially in critical care settings (9). Fortunately, recent years have brought increasing number of new options, which substantially widen the scope of endovascular therapy for congenital diseases of heart and vessels in various vascular territories. At the same time, currently developing novel non-invasive highly informative diagnostic and imaging methods will apparently replace invasive diagnostic techniques and make the endovascular surgery rather therapeutic than diagnostic discipline. Such transformation and the use of novel endovascular therapies have put the questions of indications, effectiveness, safety, etc. This report is an attempt to share our experience in this area and answer some questions arising with this method.

Endovascular closure of atrial septal defect (ASD) using the Amplatzer device

A total of 25 interventions for ASD with the use of Amplatzer device were performed in our Center. Indications were defined as the presence of secondary ASD anatomically eligible for endovascular repair (namely the presence of well-defined margin, central location, inadhesion to intracardiac structures, diam-

eter not exceeding 40 mm (10).

There were 21 male and 4 female patients aged 18 months to 38 years (mean 10.7 ± 5.2). Particular attention was given to the patients' weight, as the choice of surgical instruments was largely determined by this index. The smallest patient with ASD weighed 8.3 kg.

All patients presented with fatigue, decreased exercise tolerance, dyspnea. The majority of patients (20) had a history of frequent tracheo-bronchial respiratory infections, 5 patient previously had pneumonia.

Along with conventional clinical, laboratory and instrumental diagnostic methods, preoperative assessment included mandatory transthoracic and (where indicated) transesophageal echocardiography. We believe that these methods to a great extent determine the indications for surgery and are obligatory during procedures in the Department of Interventional Radiology.

All atrial septal defects were central and their diameter ranged from 12 to 36 mm (mean 23.7 ± 6.1). The upper edge was 2 to 15 mm wide (7.8 ± 2.6 mm), the lower edge - 7 to 13 mm (9.4 ± 0.7 mm). Pulmonary hemodynamic changes in the majority of cases ($n=20$) corresponded to grade II pulmonary hypertension as on the classification of V.I. Burakovsky and L.P. Plotnikova, 1978 (11). Pulmonary artery pressure ranged from 37 to 46 mm Hg (mean 37 ± 10 mm Hg). Systemic-pulmonary blood shunting varied from 38 to 53% (mean $41 \pm 8\%$).

In all patients ASD repair was performed under echocardiographic (transthoracic in 20 patients, transesophageal in 5) or fluoroscopic guidance. This double guidance is mandatory for safe and technically flawless procedures, preventing serious complications as demonstrated by our experience.

The choice of the method of echocardiographic control was made individually according to the quality and the amount of visual information showing the anatomy of heart defect. If the information obtained on transthoracic echocardiography was deemed insufficient, we used transesophageal approach; importantly, the choice of echocardiographic approach was made at preoperative assessment. Such method allowed for revision of indications for surgery in two female patients, who were initially considered candidates for endovascular repair according to the results of transthoracic study. However, the amount of data relating to the anatomy of defect proved insufficient and necessitated transesophageal assessment, which, in turn, showed

¹B. M. Shukurov,
Department of Interventional Radiology and Angiography
Volgograd Cardiological Center
Russia, 400008, Volgograd, Gornaya Poliana
Tel.: (8442) 46-09-83
Fax: (8442) 96-56-96
e-mail: bms@avtlig.ru

defects over 40 mm in diameter, thus making endovascular repair impossible; subsequently the patients were successfully managed by open surgery.

All endovascular interventions resulted in successful ASD closure (see Fig. 1 a,b). There were no complications related to technical imperfections.

Importantly, one must strictly follow the operative

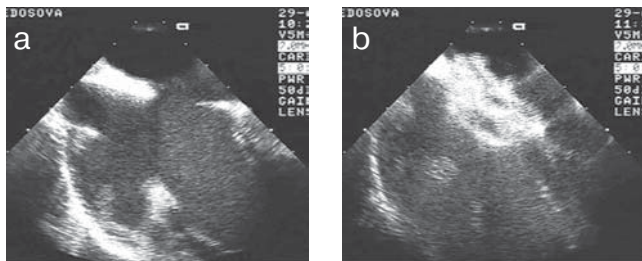


Figure 1: a – Patient F., 9 years. Ds: Congenital heart defect. ASD II. EchoCG before Amplatzer occluder implantation; b — EchoCG after Amplatzer occluder implantation.

technique and make adjustments when any uncertainties occur.

Thus, in one patient failure to perform echocardiographic guidance during ASD closure nearly caused a negative outcome (see below).

Postoperatively only 2 patients had minimal residual blood shunting during 1 and 3 months, respectively, which subsequently ceased.

All patients were clinically normal at the follow-up 6 to 18 months after the procedure.

Endovascular closure of patent ductus arteriosus (PDA)

A total of 61 patients underwent PDA closure, including 42 embolizations with Chigogidze coil (12) and 19 closures with Amplatzer device. Age distribution of patients is shown in Table 1.

Table 1. Age distribution of patients

Age, years	n
1-3	13
4-8	27
9-14	10
15-18	10
64	1
Total	61

PDA was 2 to 12 mm in diameter. In 42 cases the diameter was ≤ 3 mm, in 12 cases – 4-6 mm, in 4 cases – 7-10 mm, and in 3 cases – 11-12 mm.

Patient underwent comprehensive clinical and instrumental examination showing signs characteristic of PDA. On admission 15 patients had no complaints, 38 presented with fatigue, 8 had dyspnea induced by minor exercise, 6 had periodic palpitation, 24 had a history of frequent respiratory infections.

Isolated PDA was found in 53 patients, including 6

patients with duct recanalization after open ligation. PDA was accompanied by pulmonary artery stenosis in 3 patients, patent foramen oval in 2, restrictive VSD in 2, and grade I aortic insufficiency in 1. These associated defects were clinically and hemodynamically insignificant.

The method of repair was primarily determined by the size and the shape of PDA. Unfortunately, these could be only roughly estimated by echocardiography. Our first experience with preoperative endovascular assessment implied the use of magnetic resonance study yielding high informative value (12). With the experience growing and the Amplatzer device being introduced we started to use intraoperative aortography more frequently during closure of large PDA and the choice of proper device was made intraoperatively. We concluded, that PDA ≤ 3 mm in diameter can be safely closed with Chigogidze coil. For ducts ≥ 4 mm in diameter Amplatzer device would be more safe and convenient. Interventions were performed under general IV anesthesia and local anesthesia according to the established procedure comprised of the following steps:

1. Retrograde catheterization of the aorta.
2. Catheterization of right cardiac chambers.
3. Aortography to determine the location, size and shape of PDA.
4. Implantation of coil or occluder into the PDA (intravenous approach for Amplatzer device – see Figs. 2a, 2b, intraarterial approach for the coil of N.A. Chigogidze – see Figs. 3a, 3b).
5. Control angiography.

One patient had dislocation of coil into the left

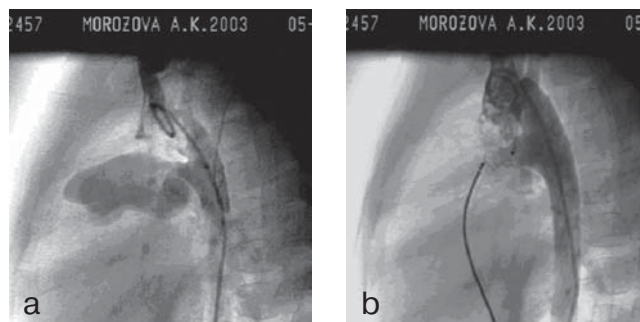


Figure 2: a — Patient M., 2 years. Ds: Patent ductus arteriosus (PDA). Thoracic aortography, lateral view. The blood shunting from the aorta (Ao) into the pulmonary artery (PA); b — Thoracic aortography, lateral view. Amplatzer device is implanted in the PDA. No shunt is seen.

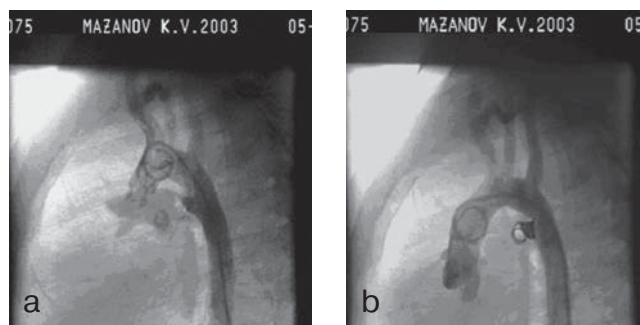


Figure 3: a — Patient M., 2 years. Ds: Congenital heart defect. PDA. Thoracic aortography, lateral view. Opacified blood is shunted to the PA through the PDA; b — Thoracic aortography. State after coil implantation. No shunt is seen.

lower lobe pulmonary artery and underwent repeated endovascular intervention using the Amplatzer occluder, which resulted in PDA closure. The 18-month follow-up showed no clinical or laboratory signs of aggravation. The use of coils and Amplatzer occluders was effective in all cases.

Control ultrasound study showed good adherence of all devices with no signs of pulmonary shunting. All patients were discharged 3 to 4 days postoperatively. Long-term evaluation at 1 to 5 years using echocardiography and X-ray study confirmed secure fixation of coils implanted with no signs of shunting.

Embolization of coronary-cardiac fistulas

Coronary-cardiac fistulas are classified among rare cardiac defects (13,14,15). Basic pathogenic factors that accompany this condition include shunting of blood through the fistula into right cardiac chambers causing coronary steal syndrome. The presence of fistula commonly results in extensive myocardial infarctions or pulmonary circulation disorders. Importantly, the world's priority in endovascular treatment of such conditions belongs to Yu.S. Petrossian – one of the founders of endovascular surgery in Russia (16).

A total of 2 embolizations of coronary-cardiac fistulas were performed in our Center: one for fistula between the circumflex branch of the LCA and the right ventricle, the other for fistula between the circumflex branch of the LCA and the right atrium. Arteries were 15 and 12 mm in diameter, respectively (8 and 6 mm at the site of narrowing). Blood shunting through the fistulas was significant. Embolization was performed using Chigogidze coils.

Both interventions were performed under IV anesthesia and included the following steps:

1. Catheterization of right cardiac chambers (for the assessment of right heart hemodynamics).
2. LCA and RCA angiography (to determine the anatomy and size of the fistula, as well as the presence of additional fistulas).
3. Implantation of coils was performed using Judkins angiography catheter in the narrowest site of the fistula.
4. Completion coronary angiography.

Six (6) coils were implanted in the first patient (see Fig. 4), 2 coils in the second. In the first patients shunting stopped intraoperatively 5 minutes after implantation of 6 coils. In the second patient 2 coils were implanted leaving insignificant shunting through the fistula. Completion angiography performed immediately after implantation of coils and reduction of shunting showed opacification of other large arteries and LCA side branches non-revealed previously, which suggested effective procedure.

Long-term follow-up (1-3 years) showed improvement of anatomical and functional values (normalization of right heart volumes, improvement of ECG- and EchoCG- pattern).

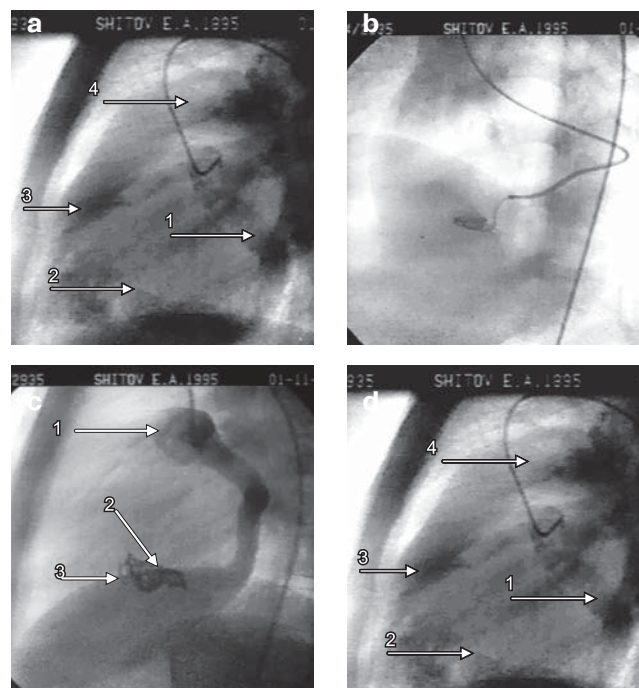


Figure 4: a — Patient Sh., 6 years. Ds: Congenital heart defect. Coronary-cardiac fistula (CCF).

1. Circumflex branch (CxB). 2. Coronary-cardiac fistula between the CxB and the right ventricle (RV). 3. RV outflow tract. 4. Pulmonary artery; b — The coil is being implanted in the CCF, c — The coils in the plane of the coronary-cardiac fistula. Six coils have been implanted; d — Control coronary angiography. 1. Opacification of the LAD. 2. Coils. 3. No blood is shunted to the RV.

Embolization of congenital angiodyplasias of brachiocephalic arteries

Embolization was performed only for congenital angiodyplasias involving the system of external carotid artery. We didn't perform interventions for angiodyplasias of internal carotid artery system, as this area is deemed very specific and requiring special approaches and skills. A total of 11 arteries in 8 patients were treated (see Table 2).

Five out of 8 patients were men. The age ranged from 29 to 61 years.

Table 2. The number of endovascular interventions

Intervention	Number of patients	Arteries treated
Embolization of carotid-cavernous fistula	4	5
Embolization of occipito-parietal hemangioma	2	4
Embolization of arteriovenous fistula between thyrocervical trunk and external jugular vein	2	2
Total	8	11

Long-term assessment at 1 - 2.5 years using ultrasound study showed secure fixation of coils at the implantation sites with the absence of blood shunting to venous system in 7 patients (Figs. 5 a,b; Figs. 6a,b,c). One female patient had signs of disease recurrence after embolization of arteriovenous fistula from the system of external carotid artery, later she successfully underwent open surgery.

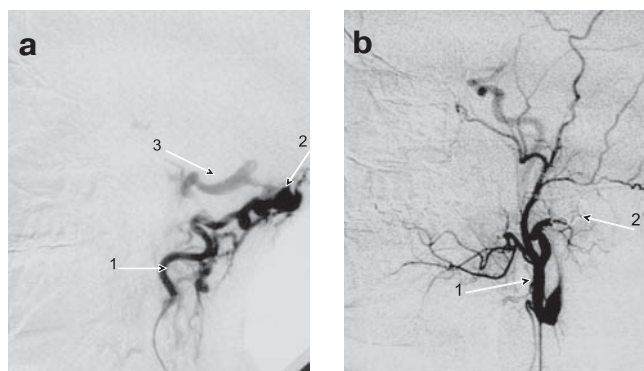


Figure 5: a — Patient Kh., 42 years. Ds: arterio-venous malformation between a.occipitalis and sinus transversus. 1. Right occipital artery. 2. Carotid-cavernous communication. 3. Transverse sinus. b — Selective angiography. 1. Right external carotid artery. 2. Carotid-cavernous communication is not opacified.

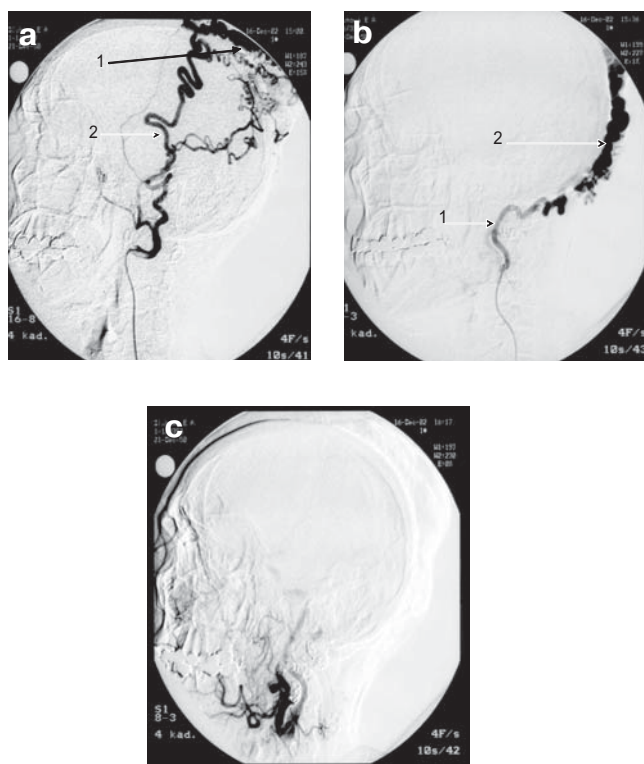


Figure 6: a — Patient G., 61 years. Ds: Arterio-venous malformation of the parietooccipital area. Selective angiography. 1. Temporal artery. 2. AV malformation; b — State after temporal artery embolization (malformation is opacified from the occipital artery). 1. AV malformation. 2. Occipital artery; c — State after occipital artery embolization (previously temporal artery had been embolized). No AV malformation is revealed.

Discussion

The results of endovascular therapy were positive. The effectiveness of interventions in these patients is nearly 100%, which is apparently encouraging. Analysis of our experience with the above methods for congenital cardiovascular abnormalities suggests that maximum therapeutic effect from all benefits of endovascular approach requires the following conditions to be observed.

1. Clear determination of indications for surgery.

This is achieved by clinical and instrumental pre-operative assessment providing complete information on the anatomy, physiology and resulting particularities of eventual intervention. In 2 patients planned for ASD the initial results of transthoracic

echocardiography were adjusted after transesophageal echocardiography, which determined the choice of conventional repair. We concluded, that planning of endovascular interventions necessitates maximum possible amount of diagnostic information from all imaging methods available, as this is even more important than in conventional surgery, when there's always a possibility to correct the mistake of pre-operative assessment. Unfortunately, interventional radiologists often have no such opportunity.

2. Strict adherence to the established surgical technique.

This approach proved successful in almost every patient, however, there was one case of technical fault during ASD repair with Amplatzer device, when the defect was measured with balloon catheter advanced under fluoroscopic guidance only (without additional echocardiographic assessment). Intraoperative measurements differed dramatically from those made preoperatively (namely were half as much), which made us doubt their exactness. Additional assessment with echocardiography showed, that the catheter was advanced through patent foramen oval adjacent to ASD and actually measured its diameter. The mistake was corrected and the procedure completed successfully. This episode clearly demonstrated that echocardiography is a major and the leading diagnostic method during endovascular closure of ASD and, therefore its replacement with other methods is currently risky and dangerous.

In one patient with PDA coil embolization the size of arterial duct was underestimated and the coil selected was only 50% larger than PDA diameter. Though the intervention was successful and there were no problem during it, dislocation of the coil into the left lower lobe pulmonary artery was revealed on the next day. Retrospective analysis of this complication suggested calculation error and the resulting improper selection of coil diameter. Importantly, this case is deemed to be the result of deviation from surgical technique, rather than the drawback of the used coil with securing element.

3. Use of the instruments ensuring safe intervention and leaving the way for correction.

All instruments used had constructive tools with securing elements, which prevented dislocation of occluders and coils after improper or incorrect implantation. This is particularly important in regions with difficult anatomy and unfavorable anatomy of PDA. The use of Chigogize coils allowed for convenient and safe embolization of PDA, arteriovenous malformations, as well as the coronary-cardiac fistulas, when the reliability of fixation and arranging of coils is most important. At the same time, we believe, that endovascular closure of PDA over 4 mm in diameter should be performed with Amplatzer device for its specific design and the wide range of diameters available.

Conclusions

1. Endovascular methods are highly effective in congenital cardiovascular abnormalities.
2. Complete preoperative assessment and proper indications for endovascular repair of ASD determine the success.
3. New endovascular devices increase safety of interventions and broaden the indications for endovascular therapy.
4. Strict adherence to surgical technique, on one hand, prevents complications and, on the other hand, provides high clinical efficacy of the endovascular intervention.

References:

1. N.A. Belokon, V.P. Podzolkov. Congenital heart defects. Moscow, Meditsina, 1991.
2. Yu.Ye. Berezov, I.E. Melnik, A.V. Pokrovsky. Aortic coarctation. Kishinev, 1967.
3. A.V. Pokrovsky. Clinical angiology. Moscow, Meditsina, 1979.
4. V.I. Prokubovsky, S.M. Kolody, V.S. Savelyev. Groudnyaya Khirurgia, 1988, 1, 42-47
5. I.Kh. Rabkin. Interventional radiology. Moscow, 1985.
6. Benson L. Catheter closure of the ductus arteriosus. In: Rao PS: Transcatheter Therapy in Pediatric Cardiology. New York, 1995, 321-333.
7. Perry S., Radtke W. et al, 1989: Coil embolization to occlude aorto-pulmonary collateral vessels and shunt in patient with congenital heart disease. J. Am. Coll. Cardiol., 13,100-108
8. L.A. Bokeria, B.G. Alekyan, V.P. Podzolkov. Endovascular and minimally invasive surgery of heart an vessels in children. Moscow, Publishing house of Bakoulev Center for Cardiovascular Surgery, 1999, 280 pages.
9. Rashkind WJ., Miller W.W. Creation of an atrial septal defect without thoracotomy. JAMA, 1966,196, 991-992
10. Richard W. Harper, Philip M. Mothrom, David J. Megaw. Closure of secundum Atrial Septal Defects with the Amplatzer Septal Occluder device. Techniques and problems. Catheteriz. Cardiovasc. Interv., 2002, 57, 508-524.
11. V.I. Burakovsky, L.A. Bokeria. Guidelines on cardiovascular surgery. Moscow, 1989.
12. B.M. Shukurov, N.A. Chigogidze, G.V. Kozlov. Endovascular Embolization of Patent Ductus Arteriosus by the New Type of Detachable Coils. International Journal of Interventional Cardioangiography, 2003, 1, 67.
13. I.N. Mitina, F.E. Abdullaev. The potential of echocardiography and Doppler study in the assessment of congenital coronary fistulas. Kardiologia, 1989, 6, 60-65.
14. Yu.S. Petrossian, F.E. Abdullayev, I.I. Lepikhova. Angiographic semiotics and pathophysiology of congenital coronary fistulas. Groudnyaya Khirurgia, 1989, 6, 23-31.
15. Upshaw C.R. Jr Congenital arteriovenous fistula. Report of a case with analysis of 73 reported cases. Amer. Heart J., 1962, 63, 399-404.
16. Petrossian Ju. S., Alekyan B.G. Percutaneous transluminal occlusion of congenital coronary fistulas. Abstract RIRCV 2. Toulouse, France, 1990.

Endovascular Approach to Arterial Injury

G.Ye. Belozеров¹, N.R. Chernaya, A.B. Klimov, S.M. Bocharov, S.M. Prozorov, G.A. Isayev.

Department of Endovascular Methods of Diagnostics and Treatment, N.V. Sklifosovssky Research Institute of Emergency Medicine, Moscow, Russia

Introduction

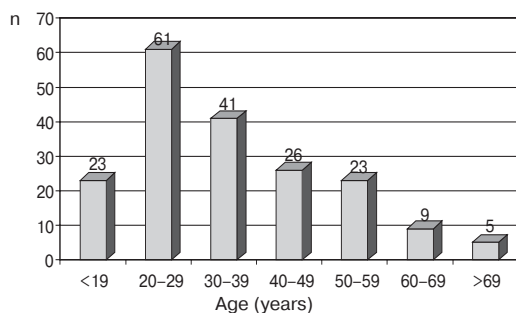
The growing incidence of road and domestic accidents in developed countries has led to the increased rate of injury to large arteries (1-5). Recently the road, domestic and occupational accidents had become the second most common cause of disability and mortality after cardiovascular diseases. Gunshot and explosive wounds characterized by large primary and secondary necrosis areas and concomitant injury of bones and nerves are becoming increasingly common in civil healthcare practice.

Endovascular diagnosis and therapy have been used for many conditions for a long time and are unreasonably uncommon in arterial injury. The search of injured arteries through conventional approach with subsequent open intervention is complicated by anatomic conditions: location (vertebral arteries lying in a bone channel), small diameter (muscular branches of the deep artery of thigh), the presence of extensive hematoma. Late post-traumatic arterial injury is frequently complicated by repeated extensive bleeding and wound infection occasionally accompanied by other organs' and tissues' lesions aggravating the patient's condition. Prolonged bleeding even due to injury of small arterial branches causes massive blood loss. Severe combined injuries aggravating the patient's condition lead to unfavorable outcome of open surgery and increase the rate of complications and mortality. Therefore, endovascular management of arterial injury is the only option in some instances when open surgery is impossible.

Materials and methods.

A total of 188 patients underwent angiographic study for arterial injury between 1995 and 2005. Indications to angiography were false aneurysm and arteriovenous fistula as suggested by ultrasound

Table 1. Age distribution of patients



¹G.E. Belozеров

Dept. of Endovascular Methods of Diagnostics and Treatment, N.V. Sklifosovssky Research Institute of Emergency Medicine, Russia, 129010, Moscow, B. Sukhrevskaya square, 3. Phone. (007 495) 280 45 79 Fax (007 495) 921-02-02

Manuscript received on May 16, 2006.

Accepted for publication on June 18, 2006.

Doppler study, post-traumatic pulse absence over large arteries, the need for more specific determination the site of arterial injury.

Patients were mostly young men (mean age 33.4 years) (see Table 1).

There were 109 patients with non-penetrating traumas and 79 patients with wounds. Wounds were mostly stab or incised, non-penetrating traumas were most commonly due to a road accident (see Table 2).

Table 2. Mechanism of arterial injury

Stab or incised wounds	47
Gunshot or missile wounds	25
Animal bites	1
Road accidents	55
Fall from a height	24
Domestic accidents	6
Iatrogenic injury	21
Compression	7
Electric trauma	2
Total	188

Angiography revealed signs of injury, such as the false aneurysm, arteriovenous fistula, arterial occlusion, soft tissue hematoma, intimal dissection (see Table 3).

Table 3. Arterial injuries revealed by angiography

False aneurysm	61
Arteriovenous fistula	11
Occlusion	57
Soft tissue hematoma	35
Intimal dissection	1
Normal findings	23

False aneurysms appearing as contrast medium extravasation had different size and shape (see Figure 1). Arteriovenous fistula appears as opacification of veins during early arterial phase (see Figure 2). The following changes of the vessel wall are encountered in closed injury due to its specific mechanism (concussion, compression, crushing or distension): intravascular hematoma, wall contusion causing rupture, intimal dissection and thrombosis causing occlusion (see Figure 3). Intimal dissection appears on the angiogram as an additional structure within the vessel lumen (see Figure 4).

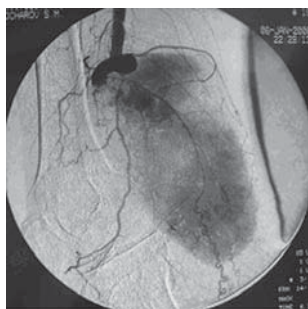


Figure 1. Lower limb angiogram showing false aneurysm of the popliteal artery (extravasation of the contrast medium)

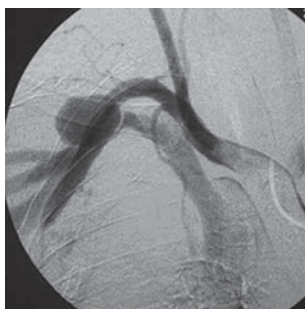


Figure 2. Brachiocephalic trunk arteriography showing an arteriovenous fistula of the right subclavian artery (venous shunting in early arterial phase)

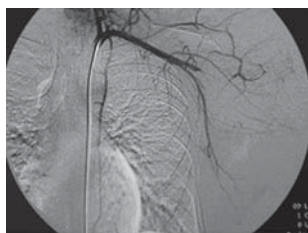


Figure 3. Upper limb arteriography showing occlusion of the subclavian artery

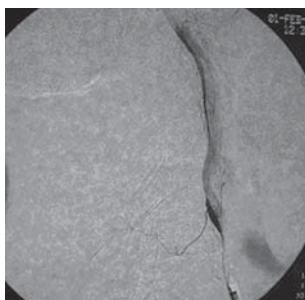


Figure 4. Arteriography of the right common carotid artery showing proximal intimal injury in the common carotid artery

A total of 28 patients underwent endovascular procedures: endovascular embolization of the damaged vessel in 22, stenting in 5, stent-graft placement in 1.

The following embolization materials were used: coils of various shape and size and from different manufacturers; calibrated microemboli preparations such as the Truefill or PVA.

Stents or a stent-graft were used for stenting.

Endovascular procedures were more commonly performed in the upper or lower limb arteries (see Table 4).

Table 4. Arteries treated with endovascular procedures

Common carotid artery	2
Upper limb arteries	6
Internal mammary artery	1
Vertebral artery	3
Superficial femoral artery	1
Deep artery of thigh and its branches	8
Internal iliac artery and its branches	4
Crural arteries	3

Below are the examples of clinical cases.

Patient C., male, aged 55, was referred to the Sklifossovsky Research Institute of Emergency Medicine from the City Hospital N 51 for false aneurysm of the right common carotid artery accompanied by venous shunting. Circumstances of the injury

were unknown. The patient presented with edema of the right neck region and the right hemithorax, severe pain in the injured area, weakness, dizziness. Examination revealed hematoma of the right neck region extending to the chest. Wound 0.5x1 cm above the right common carotid artery with scanty hemorrhagic discharge. Pulsation at the wound level with systolic and diastolic murmur. On admission: BP 130/80 mm Hg, HGB 126 g/l. ECG showed LV hypertrophy, moderate myocardial changes. Duplex ultrasound study revealed 6 mm defect of the lateral wall of the right common carotid artery; blood is shunted through the defect into a false aneurysm 25x25 mm in size with solid capsule, which, in turn, has 2.5 mm defect allowing for blood shunting into the internal jugular vein. Angiography entirely confirmed the ultrasound diagnosis. The results were discussed with vascular surgeons and, considering the high risk of open surgery, the endovascular therapy – right common carotid artery stenting – was attempted. Under local anesthesia using right femoral approach a stent-graft 38 mm in length and 7 mm in diameter was advanced and implanted in the fistula. Control angiography showed stent covering the fistula. There were no signs of opacification of the arteriovenous fistula and the false aneurysm, right CCA was patent. The patient was discharged in normal condition for further outpatient surgical follow-up.

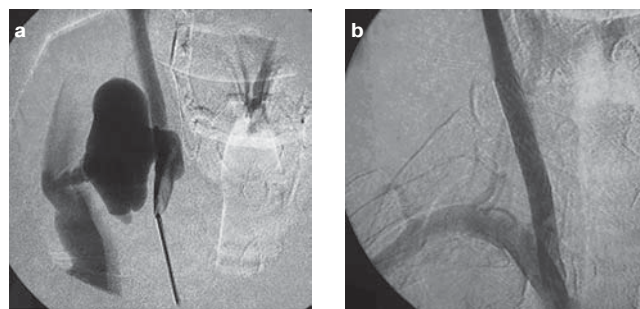


Figure 5. Arteriography of the right common carotid artery. a – false aneurysm and arteriovenous fistula of the common carotid artery; b – implanted stent-graft, the study doesn't show false aneurysm cavity or arteriovenous shunting

Blunt arterial injury can cause intimal rupture without any exterior damage to the vessel, and as a result, intimal dissection and thrombosis can develop. Such injuries are commonly accompanied by musculoskeletal trauma, such as fractures or joint dislocation adjacent to vessels, which are therefore stretched. According to the published findings, blunt injury is the cause of damage to large vessels in 6.8 to 50% of cases.

Patient L., male, aged 47, was admitted to the Sklifossovsky Research Institute of Emergency Medicine for combined injury including closed craniocerebral injury, rib fracture and chest concussion due to a road accident. The patient presented with pain the right hemithorax and the right neck region. Examination revealed hematoma of the right hemithorax extending to the neck. Ultrasound study

showed right hemothorax. Doppler ultrasonography of the neck revealed intimal dissection in the right internal carotid artery. Due to the high risk and complexity of open intervention an endovascular procedure – stenting of the right internal carotid artery – was attempted. Under local anesthesia using right femoral approach a stent was implanted into the right internal carotid artery. Completion angiography showed no signs of additional structures within the vessel lumen and normal blood flow through the right internal carotid artery.

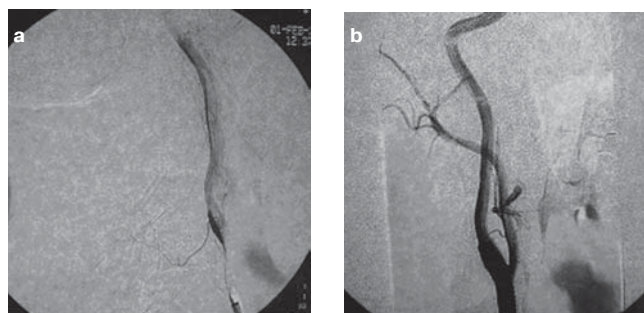


Figure 6. Angiographic study of the right internal carotid artery. a – intimal dissection in the proximal portion of the internal carotid artery; b – stent in the arterial lumen, normal blood flow through the internal carotid artery

Introduction of novel osteosynthesis systems and minimally invasive endovascular methods into routine surgical practice has resulted in the occurrence of complications, which haven't been encountered before.

Patient P., male, aged 21, was admitted to the Sklifossovsky Research Institute of Emergency Medicine for right forearm fracture, left hip fracture, brain contusion due to a road accident. Skeletal traction was used to reduce the left hip fracture. At day 10 osteosynthesis of the right hip bone was performed using a nail. The patient developed chest pain during postoperative period. In order to exclude pulmonary embolism, ultrasound study of the lower limbs was performed. No signs of venous lesions were found. However, the study revealed a mass with arterial blood flow (false aneurysm) in the middle third of the hip. Angiography showed false aneurysm perfused from the branches of the deep artery of thigh. Transcatheter coil implantation into the vessel was carried out. Completion angiography showed no signs of false aneurysm.

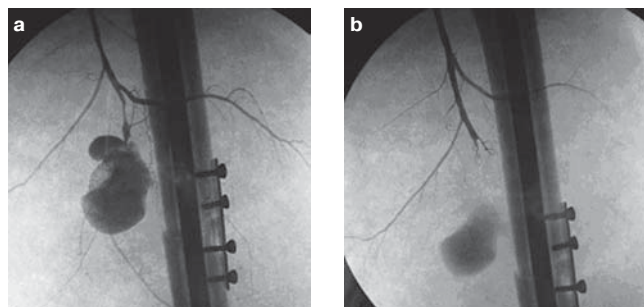


Figure 7. Lower limb arteriography. a – false aneurysm of the deep artery of thigh; b – after embolization: coils in the arterial lumen

Conclusion.

The analysis of the above studies allowed for the following conclusions: angiography is one of the most informative diagnostic methods for arterial injury, particularly as regards to small branches. It provides reliable data concerning the type and location of vascular injury, allows for the evaluation of collateral circulation's compensatory potential as well as for rapid passage from the diagnostic stage to endovascular intervention. Endovascular embolization and stenting of the injured arteries are very effective, have minimum complications and should be preferred in severe combined injuries and severe general condition. In certain instances this method is the only possible option to treat arterial injury.

References:

1. V.L. Lemenev, Yu.M. Koshelev, B.I. Nikulin. Injury of large vessels in a metropolis. *Vrach*, 1998, 4, 16-17.
2. I.Kh. Rabkin, A.L. Matevosov, L.N. Gotman. *Interventional radiology*. Moscow, Meditsina, 1987, 416.
3. V.I. Prokubovsky, V.A. Cherkasov, S.G. Dubovik. Percutaneous transcatheter embolization to treat arterial injury and its complications. *Angiologia i Sosuistaya Khirurgia*, 1997, 1, 39-43.
4. D.A. Korotkov, D.V. Mikhailov. Endovascular occlusion of pulsatile hematoma and false aneurysm. *Angiologia i Sosuistaya Khirurgia*, 1998, 1, 134-136.
5. Waigand J, Uhlich F, Gross C., Thalhammer C, Dietz R. Percutaneous treatment of pseudoaneurysms and arteriovenous fistulas after invasive vascular procedures. *Catheter Cardiovasc Interv.*, 1999, June, 47(2), 157-164

Intravenous Stent-Filter to Prevent Pulmonary Embolism

S.A.Kapranov¹, A.G.Zlatovratsky, V.F.Kuznetsova, A.N.Balan, A.A.Khachaturov

Faculty Surgery Department, Russian State Medical University,

Federal Center of Interventional Radiology, Russian Federation Ministry of Health, Moscow, Russia.

Keywords: Thromboembolism, pulmonary artery, vein, thrombosis, catheter, prevention, cava-filter, stent-filter

Introduction

The objective of pulmonary embolism (PE) prevention in patients with deep venous thrombosis of the lower limbs and pelvis (DVTLL) is among the leading problems of modern surgery. Most commonly used method is percutaneous implantation of a vena cava filter (VCF) into the inferior vena cava (IVC) (11). However, despite the apparent benefits of the endovascular intervention, particularly its minimal invasiveness and high clinical efficacy (7, 8), this technique of PE prevention has a number of major drawbacks, including:

1) frequent development of total occlusion of infrarenal IVC (1, 9) or its perforation with the cava filter wiring (13) in late post-implantation period;

2) inability to use standard VCF in infrarenal IVC in cases of anatomic variations of the renal veins' entry (6) or "giant" floating thrombi in the IVC with apex extending to the intra- or suprarenal portion of the vessel (3, 12).

These negative events somewhat compromise the benefits of endovascular PE prevention forcing the surgeon to reject their use in some cases.

To eliminate the above drawbacks of endovascular PE prevention an original stent-filter (SF) device to be implanted into iliac veins and the IVC (2, 4) (Russian Federation Patent N2143246 registered 03.06.1999) has been developed and clinically implemented by the members of Faculty Surgery Department of the Russian State Medical University (headed by V.S. Savelyev, Professor, member of Russian Academy of Sciences) together with specialists from «KOMED» company (Russia) (5).

Materials and methods

The stent-filter (SF) (see Fig. 1) is manufactured from nickel-titanium (nitinol) as a braided structure with diamond-shaped cells forming a cylinder with one end tapered as a cone and tipped with a metallic hook. The stent-filter is secured to the vessel wall with its cylindrical part due to the self-expanding effect of the shape memory metal. This is accompanied by self-centering ability facilitating the filtration of blood through the vessel and preventing emboli

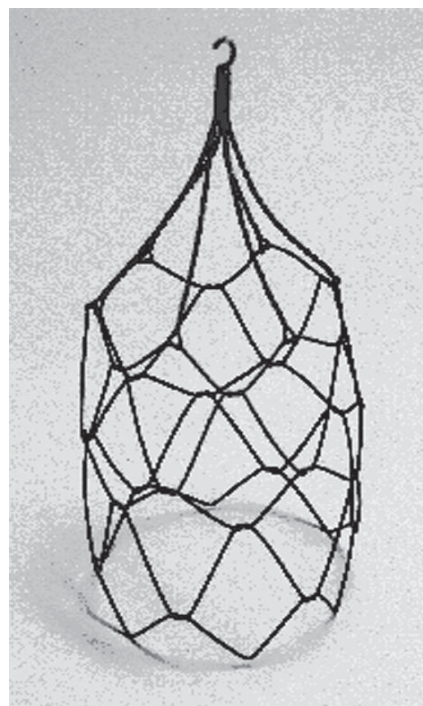


Figure 1. Nitinol stent-filter.

from migration. The closed design of SF together with the absence of any hook-shaped fixing elements avoid perforation of the vessel wall.

Between 1999 and 2006 a total of 28 consecutive patients with DVTLL (age 19 to 68, mean 49.7 years) underwent stent-filter implantation to prevent PE in the Faculty Surgery Department of Russian State Medical University.

Indication to PE prevention was the presence of floating thrombus in the deep veins of lower limbs or the IVC in all patients, including 4 patients with a history of PE (14.3%). All patients received adequate anticoagulation and disaggregation therapy with proper laboratory control of hemostasis parameters.

Comorbidities compromised the clinical situation in 16 patients (57.1%) and included cancer in 3 (10.7%), abdominal aortic aneurysm or deviation in 2 (7.1%) and fractures of pelvic or lower limb bones in 11 (39.3%) patients.

The apex of floating thrombus was located in popliteal or femoral vein in 18 (64.3%) patients and the iliac vein in 10 (35.7%) patients as suggested by ultrasound and/or radiological study.

The stent-filter was implanted into the external iliac vein in 8 patients (28.6%), common iliac vein in another 8 patients (28.6%) and the inferior vena cava in 12 patients (42.8%).

Endovascular procedures involved right iliac veins in 5 patients (17.9%) and left iliac veins in 23 patients (82.1%).

¹S.A.Kapranov

Faculty Surgery Department, Russian State Medical University,
Federal Center of Interventional Radiology,
8, bld. 1, Leninsky prospect,
117049, Moscow, Russia
e-mail: DrKapry@mail.ru

Manuscript received on May 15, 2006.

Accepted for publication on June 6, 2006.

Depending on the level of thrombosis, anatomic parameters of stent implantation site in the external iliac, common iliac vein or the IVC, the devices of three basic sizes (diameter-length) were used: 15x20 mm, 25x30 mm and 30x35 mm.

Stent-filters were implanted via left subclavian approach in 26 (92.8%) patients, right internal jugular vein in 1 (3.6%) patient, femoral vein also in 1 patient (3.6%).

Long-term assessment 7 to 68 months post-operatively (mean 31.4 months) was performed in 21 patients (75%). Five patients (17.9%) refused to undergo evaluation, 2 patients (7.1%) died from underlying cancer.

Results

The efficacy of PE prevention using a stent-filter was absolute. No patient developed primary or recurrent pulmonary embolism.

Long-term assessment revealed no complications, such as perforation of iliac veins and inferior vena cava, retroperitoneal haematoma, SF migration or destruction.

Total thrombotic occlusion of the stent-filter was found in 3 (10.7%) patients following its implantation into the external iliac vein (1), common iliac vein (1) or inferior vena cava (1).

Thrombus growth above the SF implanted into the common iliac vein was found only in 1 patient (3.6%) necessitating repeated endovascular intervention with permanent cava filter implantation.

All patients with stent-filter occlusion occurring within 2 to 5 (mean 4.1) weeks postoperatively had signs of early recanalization of the obstructed distal venous territory.

Removal of the SF from iliac veins was attempted in 2 patients. The stent-filter was removed 11 days after endovascular intervention in 1 patient. In the other patient SF removal was infeasible due to its tight fixation to the iliac vein.

Factors limiting SF removal in other patients were persisting embologenic nature of the thrombus or progression of thrombosis despite medical antithrombotic therapy, as well as the late ambulation (the so-called «uncontrolled patient behavior»).

It should be noted that 2 patients (7.1%) underwent intraoperative SF reposition because of inadequate implantation resulting from underestimation of iliac vein or inferior vena cava anatomy.

Discussion

Stent-filter implantation into iliac veins

Stent-filter implantation into iliac veins was used to treat unilateral DVTLL where the use of standard cava filters was impossible or associated with increased risk of complications predominantly in young patients, in whom thrombosis development was related to benign conditions (mostly the trauma), potentially non-threatening with thrombus growth or recurrence, as well as in cases of adequate labo-

ratory response of hemostasis system to anticoagulation and antithrombotic therapy.

The major reason to use a stent-filter in this population, in addition to reliable PE prevention, was the reduction of negative long-term consequences associated with permanent cava filters, namely the eventual IVC occlusion. The use of a stent-filter implanted into the iliac venous segment eliminates the possibility of such a complication, as even in case of SF occlusion the thrombosis doesn't extend to infrarenal IVC and doesn't provoke descending deep veins thrombosis in the contralateral leg.

Finally, this method allows for dramatic decrease of disability level in patients after endovascular PE prevention, which is particularly important in young patients who underwent filter implantation for floating thrombi of the deep femoral or pelvic veins occurring after trauma of the lower limbs.

Moreover, in case of left-sided injury of pelvic or the lower limbs' veins, SF implantation at the site of anatomic stenosis of the common iliac vein inducing or aggravating the May-Thurner syndrome (10) eliminates hemodynamic pathology, thus facilitating restoration of cylindrical shape of the vessel and positively affecting regional blood flow volume, as well as the degree of recanalization in distal venous territory.

Long-term assessment of patients 9 months after iliac stent-filter implantation revealed mild chronic venous failure of the lower limbs in 68.8% of patients, which is nearly one third of the number of such patients after superficial femoral vein ligation, IVC plication or implantation of IVC cava-filters.

An additional factor ensuring the benefits of unilateral iliac SF implantation for DVTLL is the fact, that even migration of thrombus into the stent-filter or its in situ thrombosis doesn't lead to the well-known syndrome of «low inflow» to the right heart resulting in some cases in death after endovascular PE prevention.

One of the common situations when the use of conventional cava filters is undesirable or impossible, is encountered in 30% of patients and represents anatomical variations of renal veins entry - their duplication, ring-shape or extremely low localization (6). This is connected with the risk of impaired venous outflow from the kidneys resulting in renal failure due to IVC thrombosis, the risk of «bypass» pulmonary embolism or the extension of thrombus above the cava filter, which ultimately decrease the efficacy of endovascular PE prevention.

Implantation of an iliac stent-filter is apparently the only way to protect patients from pulmonary embolism in such circumstances.

Importantly, the above benefits of SF implantation into the iliac veins depend on the surgical technique. It is preferable to have the apex of a stent-filter located in the outflow area of contralateral common iliac vein (with SF implantation into a common iliac vein) (Fig. 2 a-b) or of the internal iliac vein (for devices located in the external iliac vein) (Fig. 3 a-d).

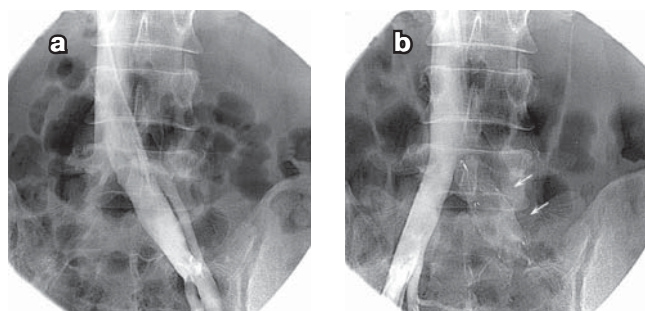


Figure 2. Phlebograms before (a) and after (b) stent-filter implantation (arrows) into common iliac vein

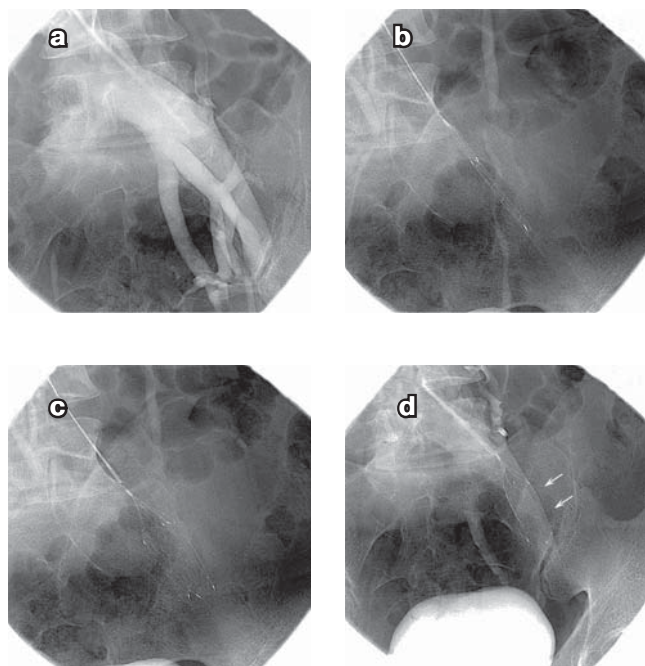


Figure 3. Stages of stent-filter implantation (arrows) into external iliac vein: a – baseline phlebography, b – folded SF is advanced through a cannula, c – opening and fixation of SF in the vein, d – angiography after implantation

An indisputable benefit of the stent-filter is the possibility to remove it. However, this requires strict adherence to the established procedure, which, in the majority of cases, determine relatively low rate of endovascular removal of a filter device: 1) elimination of the embolic threat, 2) adequate response of coagulation system to the treatment, 3) absence of the long-term risk of recurrent thrombosis or PE, 4) strict adherence to the timing of possible stent-filter removal.

One patient (patient C, aged 32, case history N4474) underwent stent-filter implantation for floating thrombus in the femoral vein occurring after multiple self-performed intravenous injections. Following endovascular therapy accompanied by conventional medical therapy the apex of the thrombus acquired an obstructive shape posing no threat of PE. The SF was removed from the iliac vein 11 days postoperatively using endovascular approach (Fig. 4 a-c). The 46-month follow-up revealed no signs of recurrent thrombosis or PE. Moreover, there were no symptoms of ipsilateral chronic venous failure.

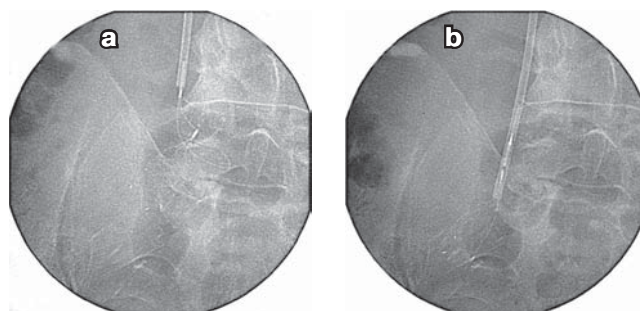
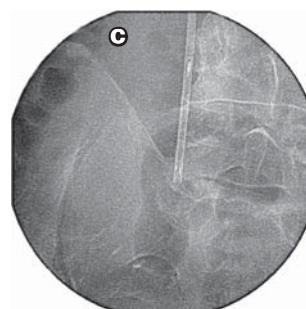


Figure 4. Removal of an intravenous stent-filter: a – metal loop is fixed around the filter hook, b – SF folding stage, c – stent-filter completely pulled into the cannula and removed.



Failure of endovascular stent-filter removal from the iliac vein 28 days after primary intervention was encountered in a patient after SF implantation for embologenic thrombus in the common femoral vein resulting from splintered fracture of the tibial bone. After transformation of the thrombus apex into occlusion excluding PE and followed by early recanalization of the distal venous territory SF removal was attempted. However, despite the correct capture of SF hook with a metal extractor, the stent couldn't be folded or removed due to neointimal ingrowth and extremely solid fixation to the vessel wall.

The only exclusion as regards to efficacy of PE prevention after iliac SF implantation was patient K, aged 32 (case history N25071), who underwent stent implantation for floating thrombus in the femoral vein after shin injury necessitating reposition and immobilization of the left lower limb. The patient underwent implantation of a stent-filter into the left common iliac vein and discharged while receiving medical therapy with recommendations to assess coagulation system.

However, after being discharged, the patient discontinued medical therapy and didn't perform recommended tests. Somewhat later edema of the lower limb increased. Ultrasound study performed 4 days later showed total thrombosis of the sub-filter space with floating thrombus extending to infrarenal IVC.

The patient was repeatedly hospitalized, radiological study showed total occlusion of the left common iliac vein containing the SF with a floating 5 cm IVC thrombus extending from its origin (Fig. 5). In addition, detailed coagulation assay revealed congenital deficit of coagulation factors. The patient underwent corrective replacement infusion therapy and the

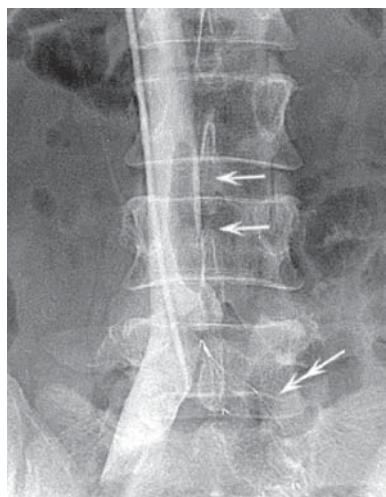


Figure 5. Floating thrombus (arrows) extending above the stent-filter (double arrows)

implantation of an umbrella-shaped cava filter to prevent PE.

Stent-filter implantation into the inferior vena cava SF implantation into IVC was used for DVTLL, when the use of conventional cava-filters was impossible or associated with an increased risk. This could be due to the small diameter of inferior vena cava and the threat of its perforation with SF wiring, vessel tortuosity or atypical IVC entry.

Small diameter and tortuosity of the infrarenal IVC can be due to anatomical variations, as well as external compression by tumors in lymph nodes or retroperitoneal space, or the presence of abdominal aortic aneurysm/deviation.

The above factors, besides the external compression, mostly cause pulsation of IVC walls at the site of implantation, substantially increasing the risk of perforation with wiring of conventional cava-filters.

Indication to PE prevention in a female patient L, aged 80 (case history N21303), was the presence of a floating thrombus over 10 cm in length in the external iliac vein. Lower cavography performed prior to cava-filter implantation showed external compression of infrarenal IVC. Simultaneous indirect subtraction aortography revealed atherosclerotic deviation of the abdominal aorta as the cause of compression. Considering the potential risk of IVC perforation with wiring of conventional SF models, the patient underwent SF implantation into IVC (Fig. 6 a-d). The technique and strategy of endovascular PE prevention eliminated any negative consequences and ensured the desired clinical outcome.

It has to be noted that additional positive aspects of SF implantation into IVC for external compression are the restoration of normal geometry of the vessel and improvement of regional hemodynamics, which largely determine the long-term patency of IVC and prevent thrombosis of the sub-filter portion affecting veins of the contralateral limb.

Finally, in some cases, SF implantation into IVC is the only possible method of endovascular PE prevention.

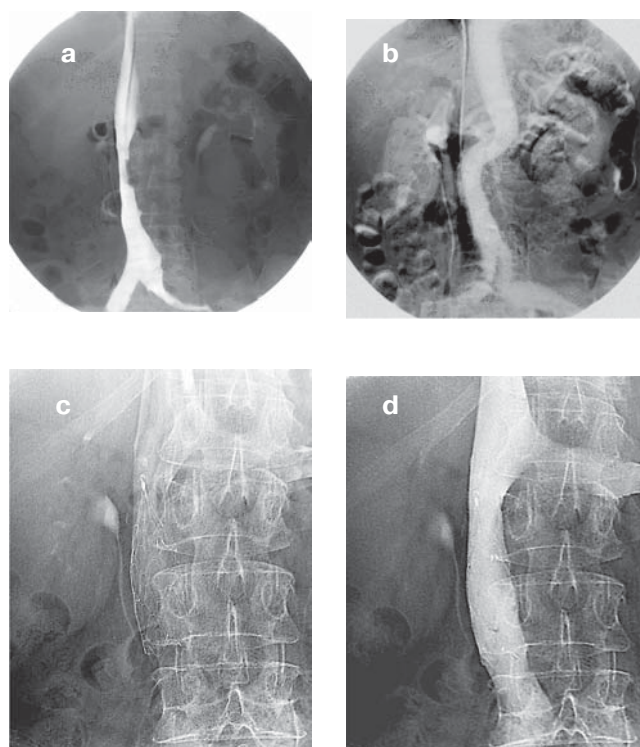


Figure 6. Implantation of a stent-filter into the inferior vena cava (see comments in the text): a – external compression of IVC, b – atherosclerotic deviation of aorta, c – SF fixation in IVC, d – recanalization after stent-filter implantation

Patient Kh., aged 64 (case history N7505), with recurrent PE and a floating thrombus in the right common iliac vein was found to have atypical anatomy of the IVC, which was located to the left of the spine, falling into the azygos vein and, subsequently, into the superior vena cava forming a sharp angle. In addition, the IVC contained a floating thrombus with its apex located 3 cm below the origin of the right renal vein.

In view of the above anatomical particularities of the venous system, retrograde implantation of the most commonly used cava-filters via subclavian, jugular or right femoral approach was virtually impossible. The only possible approach was via the left femoral vein, which, together with the particularities of renal veins' anatomy also precluded the use of conventional intravenous filter devices. Therefore, a stent filter with original design was implanted via antegrade approach (Fig. 7 a-c). The endovascular intervention provided the desired PE prevention and excluded the long-term negative consequences associated with the risk of renal vein thrombosis.

It must be emphasized, that implantation of a stent-filter into the inferior vena cava requires strict control of the procedure: the SF hook must be located opposite the renal veins's ostia at the site of active outflow, thus ensuring normal circulation in the infra-renal IVC and preventing occlusion of the vessel.

Conclusions

Intravenous stent-filter implantation:

- 1) is an effective way to prevent PE,

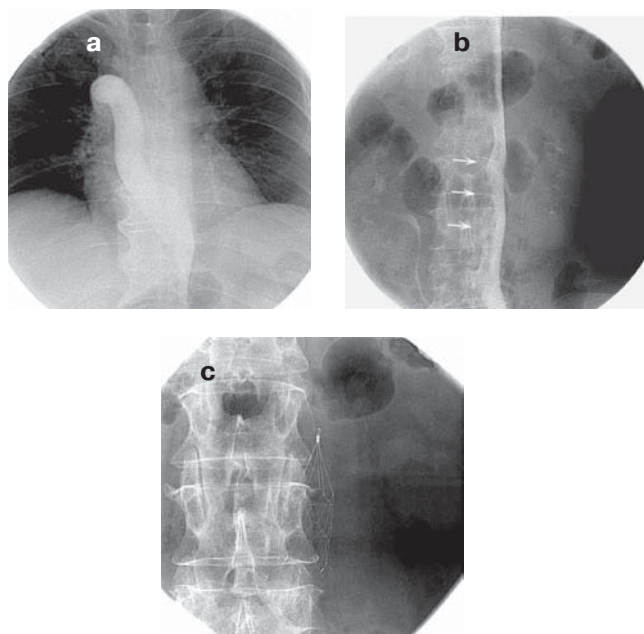


Figure 7. Sharp-angle confluence of the left-sided inferior vena cava and the azygos vein (a), infrarenal floating thrombus (arrows) (b), stent-filter implanted (c)

- 2) minimizes the risk of usual complications associated with conventional cava-filters,
- 3) in a number of cases is the only possible method of endovascular PE prevention,
- 4) can be used both as a temporary or a permanent method to prevent PE.

References:

1. Zlatovratsky A.G., Kapranov S.A. Analysis of the causes for thrombotic inferior vena cava occlusion after cava-filter implantation, International Congress of Surgery «New Technology in Surgery», Rostov-on-Don, October 5-7, 2005, 281-282.
2. Kapranov S.A., Kuznetsova V.F., Zlatovratsky A.G. Removable stent-filter to prevent pulmonary embolism, International Journal of Interventional Cardioangiography, 2005, 7, p. 44.
3. Kapranov S.A., Prokubovsky V.I., Burov V.P. Endovascular catheter thrombectomy from inferior vena cava and iliac veins: review of 115 procedures, International Congress of Surgery «New Technology in Surgery», Rostov-on-Don, October 5-7, 2005, 287-288.
4. Kuznetsova V.F., Kapranov S.A., Zlatovratsky A.G. Stent-filter in endovascular prevention of pulmonary embolism, «New Technology in Surgery», Rostov-on-Don, October 5-7, 2005, 297.
5. Prokubovsky V.I., Kapranov S.A., Savelyev M.C., Balan A.N. Zashcherinskaya N.A., Lomkov S.S., Nikitina A.V., Polikarpov O.V., Polikarpov I.V. «Intravascular stent-filter», Russian Federation patent N 2143246, priority 03.06.1999.
6. Prokubovsky V.I., Kapranov S.A., Moskalenko Ye.P. Anatomical and hemodynamic changes in the inferior vena cava associated with prevention of pulmonary embolism. Angiologia i Sosudistaya Khirurgia, 2003, 2, 9, . 51-60
7. Ballew K.A., Philbrick J.T., Becker D.M. Vena cava filters devices. Clin. Chest Med., 1995, 16, 295-305.
8. Becker D.M., Philbrick J.T., Selby J.B. Inferior vena cava filters. Indications, safety, effectiveness. Arch. Intern. Med., 1992, 152, 10, 1985-1994.
9. Coccheri S., Palareti G. Prevention and treatment of deep venous thrombosis: prevention of pulmonary embolism. Cardiologia, 1994, 39,12, Suppl 1, 341-5.
10. Heijmen R., Bollen T., Duyndam D. et al. Endovascular venous stenting in May – Thurner syndrome. J. Cardiovasc. Surg., 2001, 42, 1, 83 – 87.
11. Reckers J.A. Mechanical thrombectomy and vena cava filters. Cardiovasc. Intervent. Radiol., 2000, 23(Suppl. 1), 54-55.
12. Solonko A., Kapranov S., Bobrov B. Endovascular prophylaxis of pulmonary embolism in patients with giant floating thrombi in inferior vena cava. International Angiology, 2001, 20, June, suppl. 1 to issue № 2, 320.
13. Tagliabue M., Merati I., Crivellaro M. Computerized tomography in the follow-up of inferior vena cava filters. Radiol. Med. (Torino), 1991, Sep., 82,3, 315-21.

Diagnostic and Therapeutic Radiology in Oncology

B.I. Dolgushin¹

N.N. Blokhin Russian Oncological Scientific Centre, Russian Academy of Medical Sciences

Interventional radiology (IR) is a young developing branch of medical science that is rapidly taking leading positions in different fields of medical practice including clinical oncology. IR does not only considerably enlarge potentialities of multiple view radiodiagnostics by extending this routine method with modern and constantly developing minimally invasive techniques. Due to this beneficial contribution the 'good old' evolutionary developing diagnostic method that has not had any fundamental ideological changes for a hundred of years is currently undergoing far more serious alterations that radically transform its very essence. The distinction between diagnostic and therapeutic areas in this field of medical practice has been erased. Now we can notice the appearance of a new category of specialists who are able to find effective solutions to diagnostic and therapeutic tasks using IR techniques, thus sparing patients from severe surgical interventions that formerly were inevitable. In a short period of time IR conceptually changed radiodiagnostics which has developed from routine non-invasive diagnostic technique into an effective minimally invasive method, from a technique without any therapeutic potential into a broad range of minimally invasive treatment procedures that are performed as a part of one or several methods of radiodiagnostics.

First IR interventions were performed in the early 1970-es.

Minimally invasive approach used in IR techniques requiring no general anesthesia, providing considerably lower rate and less severity of possible complications and therefore lower post-operative mortality, shorter period of hospitalization, decrease in treatment costs, more effective rehabilitation aiming to restore everyday activity, occupational and social rehabilitation associated with these techniques determine their more and more frequent use comparing to that of traumatic surgical procedures. Compared to traditional surgery, IR has such additional advantages as substantially fewer contraindications to its use and easy repeatability of IR-procedures without increase in risk associated to these interventions. There are often no alternatives to radiological methods as general anesthesia required for traditional surgical interventions can not be performed in severe and debilitated patients to whom these procedures

are indicated. These methods can also be used to treat severe preoperative homeostasis disorders caused by the underlying disease that limit potentialities of the surgical treatment. Therefore, IR has indisputable appeal both as a separate method of treatment and as an effective method used to create certain conditions required for surgical procedures in patients considered to be inoperable so far as well as a method of effective treatment of surgical and IR complications.

A number of different IR procedures currently used in oncological practice can be classified as follows:

A. Puncture/needle methods:

- Biopsy (aspiration biopsy, forceps biopsy),
- Drainage of pathological and physiological fluid accumulations (leakages, hematomas, abscesses, intraductal biliary hyperpression, urosthesis, hydropericardium, etc.),
- Vertebroplasty (procedure of strengthening vertebral bodies that have been affected by a lytic tumor with a special cement),
- Radiothermoablation (precise thermal destruction of a neoplasm with the help of the special electrode punctured into the tumor under X-ray guidance),
- Neurolysis (procedure producing relief of chronic pain by special spot radiation of nerve plexes),
- Gastrostomy, laparocentesis and thoracocentesis performed by puncture techniques.

B. Methods that enable to regain patency of hollow organs and tubular anatomic structures:

- Lumen dilatation (dilatation of strictures of gastrointestinal, respiratory, biliary and urinary tracts),
- Stenting of tubular structures (bile ducts, trachea, ureters, gastrointestinal tube),
- Anastomotic procedures (compressive anastomoses with special magnetic elements and puncture anastomoses).

C. Intravascular procedures:

- Tumor embolization and embolotherapy (tumor tissue exposure to ischemizing conditions or chemical agents in order to stop its growth or lysis),
- Preliminary inserting of cava filters for prevention of the pulmonary artery embolism during and after extensive operations in severe cancer patients,
- Retrieval of intravascular foreign bodies (torn-off IR-catheters, guidewires, etc.),
- Hemostasis or hemorrhage prevention (transcatheter embolization of bleeding vessels and vascular fistulas of decaying tumors, in case of post-operative hemorrhages or hemorrhages occurring as a complication of IR-procedures, or the same procedures performed to prevent anticipated massive hemorrhages).

¹Boris I. Dolgushin
Dept. of Radial Diagnostics and Endovascular Methods of Treatment
N.N. Blokhin Russian Scientific Center of Oncology, RAMS,
Russia, 115478, Moscow,
Kashirskoye shosse, 24
Phone: (007 495) 324-63-60; 324-44-96
E-mail: dolgushinb@mail.ru
Manuscript received on May 23, 2006
Accepted for publication on June 26, 2006

D. Occlusion of pathological fistulae

- Occlusion of pathological fistulae by inserting special stent-based occluders using IR methods.

Navigation and Guidance Systems Used in IR Procedures

IR procedures are performed under fluoroscopic, ultrasound or X-ray CT-guidance or using the combination of these methods. The method of choice is usually the one that ensures better visualization of the pathological focus and allows to choose the optimal route to it. When radiological imaging methods are of equal informational value, the interventional radiologist chooses the one that is cheaper and simpler or the one he is most familiar with.

Fluoroscopy

Fluoroscopy is preferred in case of biliary drainage, nephrostomy, tumor biopsy, cyst emptying or abscess drainage; in these cases fluoroscopy is performed using fluoroscopic arc-system, while the use of ordinary single-view X-ray diagnostic device is usually sufficient to provide guidance in these procedures.

Ultrasound and X-ray CT-imaging

Compared to X-ray CT, ultrasound guidance allows to decrease the duration of puncture IR procedures; it is cheaper, more available and 'flexible' in urgent situations. However, X-ray CT in contrast to US-imaging allows to visualize the puncture needle within lung and bone tissues. Due to its high sensitivity in detecting fluid accumulations, ultrasound imaging is the method of choice in controlling the results of IR treatment of cysts and abscesses. Doppler mapping under ultrasound guidance is a very sensitive technique to differentiate pathological fluid accumulations from normal blood flow, which allows to prevent choosing wrong route for the insertion of the puncture needle and therefore to avoid serious complications associated with this event. Technical development of X-ray CT allows to obtain images of better quality in shorter periods of time increasing therefore the precision of needle placement. The latest generation spiral computer tomography apparatus characterized by large gantry aperture and possibility to obtain several scans by one rotation of the X-ray tube provide the interventional radiologist with additional opportunities up to possibility of obtaining real-time images (X-ray CT-fluoroscopy).

Combination of fluoroscopy, ultrasound and X-ray CT-imaging

When the clinic possesses all the equipment required for all above mentioned methods of radiological guidance it is possible to use them in different combinations when necessary. On the one hand, that allows to use IR approach to the "zone of interest" with greater degree of precision, and on the other hand such combinations provide possibility to visualize the instrumental manipulations inside the pathological lesion and to control adequacy of these procedures. In practice this procedure is performed

as follows: the pathological focus containing fluid (an abscess, a cyst, a hematoma, etc.) is punctured under US- or X-ray CT-guidance, while placement of the drainage and insertion of its working part into the pathological cavity is performed under fluoroscopy guidance. Thus, some major manufactures of medical diagnostic equipment have started the production of combined apparatus providing the opportunity to perform IR procedures under double guidance (US and fluoroscopy or X-ray CT and fluoroscopy).

Analgesia

Successful performance of interventional radiological procedures requires adequate analgesia. Many aged cancer patients have severe concomitant diseases resulting in such real somatic condition that excludes not only the possibility of surgical treatment but also, not infrequently, the performance of complicated IR procedure. This reason as well as others determines multiple stage performance of most of IR procedures that helps to provide natural continuation and logical completion of rationally scheduled multiple stage IR treatment without any risk to the patient. The right choice of analgetic agents with the account of their known advantages and disadvantages can guarantee the patient an adequate degree of analgesia and relatively comfortable conditions throughout the procedure as well as provide the interventional radiologist with more optimal conditions for the performance of the procedure.

The important condition for the successful performance of an IR procedure is effective patient premedication aimed primarily at the relief of psychoemotional stress. The interventional radiologist requires the patient to be quiet, not to be afraid of the upcoming procedure, to be able to cooperate with the doctor, to do required actions, for example to hold his or her breath, to breath in or out deeply, to change his or her position on the operating table. The second objective of premedication is to reduce pain caused both by the disease and by performance of the IR procedure.

IR procedures performed on an outpatient basis are usually brief and cause little pain that is why premedication for these interventions is rarely required. They are performed after overnight fast provided the patient is accompanied by a capable person. In most cases out-patient IR procedures are performed in the first half of the day to provide the possibility of required post-procedure follow-up during 1-3 hours in the interventional radiology office setting.

In all cases additional local infiltrative anesthesia using 0.25-0.5% Novocaine solution is performed in the zone of IR approach.

Biopsy

Nowadays treatment of cancer patients is impossible without prior morphological confirmation of the tumoral nature of the lesion. There are many differ-

ent methods of obtaining material for morphological examination during IR procedures: brush biopsy for cytological examination, aspiration biopsy for cytological examination of the centrifugate or native samples of physiological and pathological fluids; forceps biopsy, and needle biopsy. In all cases the samples of material for morphological examination are obtained under radiological guidance (US, X-ray CT, fluoroscopy). When interventional radiology procedures are performed in combination with endoscopy, morphological samples are obtained using endoscopic instruments under direct optical visualization. Diagnostic effectiveness of biopsy amounts up to 85%.

Drainage of Abnormal Fluid Accumulations

Surgical treatment in thoraco-abdominal oncology is often complicated by purulent and septic conditions. According to D.P. Chukhrienko and Ya.S. Bereznitski, the rate of postoperative mortality associated with surgical treatment of solitary and multiple liver abscesses is 29% and 98%, respectively [1]. Due to the development of interventional radiology and wide implementation of X-ray computed tomography into clinical practice, we have acquired the real possibility to obtain precise images of abscesses and to perform percutaneous drainage of these lesions under adequate guidance.

Percutaneous therapeutic catheterization for treatment of abscesses that are not complicated by fistula formation usually takes 3-16 days (on average 1 week). In these cases temperature normalization, reduced level of intoxication and improved general state of the patient can already be observed within the first 24 hours after the drainage procedure. IR treatment of complicated abscesses sometimes takes 4-12 weeks. Over the four last years percutaneous drainage and treatment of abscesses of the thoracic and abdominal cavity have been performed in more than 400 patients at the N.N. Blokhin Russian Scientific Oncological Centre of Russian Academy of Medical Sciences. Complications directly related to IR-drainage were reported in 12.2% of cases and mortality rate associated with these complications was 1.1%. The average hospitalization period was 16 days compared to 28 days in case of conventional surgical treatment of this complication [2].

Basing on our experience we can affirm that postoperative abscesses in 85-90% of cancer patients after thoraco-abdominal interventions can be effectively treated by IR method under radiological guidance without using traditional surgical methods and general anesthesia.

In cancer patients with tumors of biliopancreatoduodenal zone, surgical treatment at the peak of jaundice is associated with high rate of postoperative mortality (20-40%) [3]. Therefore, nowadays at the N.N. Blokhin Russian Scientific Oncological Centre of Russian Academy of Medical Sciences as well as

at most large clinics percutaneous transhepatic biliary drainage is performed as a preliminary procedure in all patients with mechanical jaundice to achieve decompression and to provide subsequent restoration of physiological bile flow. We have experience of treatment of more than 800 cancer patients with mechanical jaundice.

The use of percutaneous transhepatic endobiliary approach with the possibility of manipulations inside the ducts under fluoroscopy guidance has created background for a fundamentally new approach in diagnostics and treatment of tumors of biliopancreatoduodenal zone. It includes the possibility of controlled decompression in patients with mechanical jaundice, treatment of cholangitis that often accompanies bile drainage problems, precise detection of the location and the length of the tumorous stricture; obtaining of biopsy samples from stenosing tumors of the bile ducts, bougienage, and restoration of physiological bile flow into the duodenum, the possibility of precise topometric planning, positioning of intraductal applicators (endostats), performance of intraductal radiation therapy, duct stenting, postoperative monitoring and prevention of failure of enterobiliary anastomoses, performance of compression choledochoduodenal anastomoses using special magnetic elements, performance of cholangiogastral anastomoses using puncture technique, and other IR methods that enable to improve quality of remaining life if specific antitumor treatment is impossible.

A single method of interventional radiology is represented by minimally invasive therapeutic procedures in patients with urostasis caused by mechanical obstacle in the upper urinary tract. This group includes first of all patients with ureteral blockade caused by bladder, uterine, ovarian, intestinal tumors and non-organ cancers. Another group consists of patients with mechanical urostasis resulted from the previous antitumor treatment. Primarily, these are patients with complications of radiation therapy, less frequently with intraoperative injuries, and far less frequently with scarry changes in the area of tumor localization that occurred after effective antitumor drug treatment and involve the ureter. In all above mentioned cases patients require urgent urinary diversion. During last years specialists of N.N. Blokhin Russian Scientific Oncological Center of Russian Academy of Medical Sciences perform urinary diversion under fluoroscopy and ultrasound guidance using percutaneous puncture technique. Nephrostome placed with the use of this technique provides the possibility of performing diagnostic and therapeutic procedures on the upper urinary tract such as monitoring and correction of position of nephrostomy catheters and their replacement, biopsy, balloon dilatation of strictures, placement of J-J stents and meshed metal stents to provide physiological drainage of urine. We have performed over 1000 such procedures [4].

Vertebroplasty in Patients with Lytic Lesions of Vertebral Bodies

Metastatic skeletal tumors occur two to four times more often than primary lesions with the skeleton being the third most frequent location of tumor metastases after lung and liver. Most frequently metastatic lesions are observed in the spinal column (up to 70%). Patients with metastatic lesions in the skeletal system have the largest number of musculoskeletal complications associated with the treatment.

In 75% of cases pain is the first clinical sign of bone affection, although pathological fractures of long tubular bones occur in 5-10% of these patients (Dijkstra P.D.S., 2001) [6]. About one third of patients with metastatic skeletal lesions have different complications, such as pathological fractures, hypercalcemia, and spinal cord compression (R. Coleman, 2001) [7].

At present percutaneous vertebroplasty has become widely used in the treatment of patients with lytic lesions of the spinal column. This procedure is mainly performed in patients with hemangiomas and metastatic lesions of the spinal column, as these diseases very often lead to reduction of bone density, therefore considerably increasing risk and rate of pathological fractures.

The indication for vertebroplasty is pain syndrome in patients with pathological fractures resulted from destructive osteolytic tumor lesion of the spinal column.

Before this procedure all patients should undergo clinical examination, including assessment of their general condition and neurological status (before and after vertebroplasty), interpretation of laboratory results, standard X-ray examination of the spinal column in two planes, magnetic resonance imaging (MRI) and X-ray computed tomography (X-ray CT).

The IR procedure of vertebroplasty is performed under computed tomography guidance with simultaneous real-time fluoroscopy guidance at the stage of the insertion of bone cement. The average duration of the procedure is about 1 hour. The requirements for vertebroplasty are similar to those for all interventional procedures with obligatory adherence to the rules of asepsis and antiseptics. In 10% of patients vertebroplasty was complicated by postoperative increase in radicular pain that was relieved by conservative treatment.

Complete or considerable pain relief was reported in 80% of patients. The onset of analgetic effect was observed within the first 48 hours. All patients (78) resumed activity on the following day [8].

Radiofrequency Thermoablation of Liver Tumors

Over the last years interventional radiology techniques have been also used in treatment of tumor of parenchymatous organs, soft tissues and bones.

Radiofrequency (RF) method becomes more and more popular among all percutaneous ablation methods producing direct effect on the tumor lesion.

This method is based on the effect of the energy of radiofrequency current that causes tumor heating. A special electrode emitting RF current is placed in the tumor under radiological guidance (ultrasound scanning, CT or MRI). Radiofrequency current makes electrically charged particles of intracellular structures (ions) oscillate with the same frequency. Energy produced by these oscillations causes heating and coagulation of cell proteins. RF ablation can cause coagulation of lesions measuring up to 2.5-3 cm in diameter. The most high-power modern RF generators can be successfully used for treatment of tumors up to 5-7 cm in diameter. Percutaneous RF ablation is performed under local anesthesia with intravenous sedation.

RF ablation is indicated in case of not more than 4-5 tumoral nodes in the liver measuring not more than 5 cm in diameter each that are located at least 1 cm away from the portal vein or hepatic veins.

In most cases RF ablation is performed through percutaneous approach under local, intravenous or spinal anesthesia. All manipulations are performed under real-time US or X-ray CT guidance.

The average duration of one procedure is 13 minutes. The number of electrode applications depends on the lesion size. Thus, for example a tumor lesion measuring 3 cm in diameter is cured on average in 3 sessions. At the N.N Blokhin Russian Scientific Oncological Centre of Russian Academy of Medical Science this technique has been used in treatment of 71 patients [9]. In one patient only the procedure was complicated by hemorrhage, which required performance of laparotomy.

Immediate results show that radiofrequency ablation causes an effective destruction of tumoral nodes in the liver. The development of this technique in Russia can provide effective medical help to a large number of patients with metastatic lesions in liver considered to be inoperable at the moment of detection of these lesions.

RF generator can be used not only for ablation of hepatic metastases but also for treatment of small primary hepatocarcinomas as well as of kidney, lung, bone, thyroid and parathyroid gland tumors.

Dilatation of Scarry Stenosing Strictures of Hollow Organs Occurred as Complications of Antitumor Treatment

Scarry strictures of hollow organs can complicate antitumor treatment and its outcomes regardless the method of therapy, although they more frequently occur after surgical procedures. Resection procedures of any extent associated with performance of interorgan anastomoses (operations performed on the esophagus, small and large intestine, organs of hepatopancreatoduodenal zone, urinary tract, etc.) are sometimes complicated by stenosing scarry strictures that occur for various reasons. Such strictures have a pernicious course, are poorly amenable to endoscopic recanalization and can recidivate even

after a successful procedure. In such cases it is possible to perform balloon dilatation of the scarry stricture under local analgesia and fluoroscopy guidance. Positioning and placement of the special balloon is performed using Seldinger's technique. The balloon is filled with radioopaque contrast agent, and a special device is used to create excessive pressure sufficient for dilatation of the scarry tissue. Radioopaque content of the balloon allows to provide radiological guidance of the balloon position, to control the degree of compressive effect on the stricture and to access its results. In contrast to endoscopic bougienage, balloon procedure causes less damage to the mucous lining of hollow organs and the lumen is dilated due to the straining of the deep layers of the wall and the scar tissue. The procedure is fairly well tolerated by patients and can be easily repeated. IR balloon dilatation is of significant importance in those cases when the location of these strictures makes the performance of endoscopic balloon dilatation impossible.

Specialists have gained first promising experience with multistage balloon dilatation of radiation-induced bronchial strictures. Although this method is only being implemented into clinical practice we have already some data that allow to characterize it as a promising technique.

IR-Stenting of Mechanical Strictures of Hollow Organs with Meshed Metal Stents

Esophageal or cardiac cancer leads to progressive dysphagia and, in absence of treatment, to starvation that is usually fatal in such cases. This problem can be properly managed by a surgical intervention one of the effects of which is restoration of physiological food passage. But even after the surgery almost 20% of patients have either symptoms of dysphagia or a newly formed stricture at the site of anastomoses caused by persistent growth of the tumor. Radiation therapy is reported to be effective in 60-80% but significant improvement of dysphagia occurs only within 4-6 weeks after the treatment was initiated. Moreover, in 25% of patients radiation therapy causes scarry stenoses in the irradiated area. Lack of access to the deep layers of the wall of the organ affected by the tumor as well as to the tumor's extraorgan component limits the use of endoscopic diathermal or laser recanalization of tumor strictures. These procedures are also associated with high risk of perforation of the organ's wall and hemorrhage from damaged vessels, while the effect of the intervention does not last long. Esophageal replacement using meshed metal stents placed at the site of stenosing stricture is an appealing, easy, fast and available method of treatment of dysphagia caused by cancer.

Esophageal stenting is also indicated in patients with pathological esophagorespiratory fistula between the esophagus and the trachea or esophagomediastinal fistula that can occur due to the

tumor decay or be a result of effective treatment (radiation, chemoradiation or drug therapy). Meshed metal stents covered by special plastic film are placed at the site of abnormal fistula. There they act as obstacles to food passage from the esophagus to the respiratory tract or to the mediastinum, thus preventing continued contamination of these areas and as a result obstruction of the respiratory tract due to aspiration, etc.

We have performed esophageal stenting in 63 patients with grade 3-4 dysphagia. In 60% of cases stenting resulted in complete disappearance of dysphagia and in 40% dysphagia improved to grade I [10].

Meshed metal stents have recently been used for restoration of patency of other gastrointestinal organs. Placement of these stents can be promising in patients with tumors of the left colon complicated by intestinal obstruction to obtain temporary restoration of passage and to provide optimal conditions for the delayed one-stage surgical procedure. Meshed metal stents for treatment of tumor and scarry strictures can also be placed in other gastrointestinal organs that can be visualized by IR technique (stomach, duodenum, gastrointestinal anastomoses).

At present advisability of stenting in patients with inoperative tumor strictures of bile ducts is obvious. This method allows to achieve restoration of physiological bile flow and to ensure satisfactory quality of life.

Current complex treatment of tumors of intra- and extrahepatic bile ducts including surgical treatment and combination (remote and intraductal) radiation therapy has promising long-term results. In this connection we have some observations of scarry strictures of bile ducts resulting from such treatment in patients practically cured from cancer, these strictures were successfully treated by IR implantation of meshed metal endoprostheses.

The options of IR that we have investigated allow to perform not only interductal anastomoses but also ductogastral, ductoduodenal, and ductoenteral anastomoses ensuring satisfactory quality of life and the possibility of better occupational and social rehabilitation. However, if these IR anastomoses are not strengthened from inside, they will be rather vulnerable due to potential obliteration caused by natural reparative processes. For these purposes we successfully use meshed metal stents implanting them at the site of the described anastomoses using IR technique. At the N.N Blokhin Russian Scientific Oncological Centre of Russian Academy of Medical Science we have successfully implanted 62 stents into bile ducts (as well as in ductogastral, ductoduodenal IR-anastomoses) in 42 patients. Recurrence of mechanical jaundice was observed only in one third of these patients and was successfully treated by IR procedures.

First promising results of ureteral stenting have been reported.

Placement of self-expanding steel and nitinol stents produced by Russian and foreign manufacturers is an effective and safe procedure that allows to treat obturation of different hollow and tubular organs and thereby to rehabilitate cancer patients and significantly improve quality of their life. Russian nitinol stents are as effective as foreign analogues and can be made with the account of individual parameters.

Magnetic Anastomoses in Treatment of Tumor and Non-Tumor Strictures of Bile Ducts

New approach to restoration of internal bile drainage as a part of complex palliative treatment of mechanical jaundice of tumoral etiology with the occluded segment located not above the orifice of the common bile duct has been implemented by combining performance of compression biliodigestive anastomoses using X-ray endoscopic technique and implantation of specially constructed magnetic elements. In patients with non-resectable tumors of the terminal segment of the common bile duct causing its occlusion and in patients with high operative risk this technique allows to perform cholecystogastral, cholecystoduodenal, hepatoduodenal or hepatojejunal anastomoses.

The procedure suggests the insertion of two magnets into the cavity of two organs to be anastomosed. Then the magnets are approached to each other under radiation guidance up to the moment of their interaction is detected. Constant compression of the tissue captured between the two magnets results in ischemic necrosis of the anastomoses. Then the magnets are removed or eliminated in a natural way.

This method of restoration of internal bile drainage combines the advantages of surgical method (big diameter of the biliodigestive anastomosis) with considerably lower traumatism, similar to that in endoprosthesis placement. The absence of sutures and ideal repositioning of the layers of the organs that are being anastomosed decreases the risk of scarry obliteration of this anastomosis. All the described methods used for restoration of internal bile drainage can be included into the range of methods of palliative treatment in patients with high operative risk.

Regional Chemotherapy, Embolization and Embolotherapy

Trying to find effective methods of treatment of inoperable tumors of different localizations interventional radiologists have offered to use technical options of selective catheterization of arterial vessels supplying the tumor for precise injection of antitumor drugs and insertion of emboli into these vessels to produce ischemizing effect. In practice this idea has been implemented by the following procedures:

- Intraarterial regional chemotherapy,
- Ischemic embolization of arterial vessels sup-

plying the tumor,

- Chemoembolization, i.e. a procedure of insertion of oil emboli resulting in temporary blood flow deceleration in the tumor vessels which ensures sustained exposure of the tumor tissue to antitumor drugs dissolved in the emboli.

In contrast to system (intravenous) chemotherapy, regional (intraarterial) chemotherapy provides the possibility to deliver an antitumor drug to the affected organ in higher concentration. Regardless the sensitivity of the tumor tissue to antitumor drugs regional chemotherapy is highly justified in patients with tumors located in organs and tissues with the same source of blood supply. First of all these are tumors of bones and soft tissues of lower extremities. This technique is widely and successfully used at the N.N Blokhin Russian Scientific Oncological Centre of Russian Academy of Medical Science where specialists have experience of use of intraarterial chemotherapy as a part of antitumor regimen in treatment of more than 1000 patients. Accessing the effectiveness of this approach to antitumor treatment using intraarterial chemotherapy suffice it to say that 5-year survival has increased from 36% to 68%.

Taking into consideration long-term experience with chemoembolization of different liver carcinomas, we can assume that best results of this method were observed in patients with highly vascularized tumors (hepatoblastoma, hepatocellular carcinoma, carcinoid) and in patients with liver metastases of breast cancer. Thus, partial regression of primary liver cancer was observed in 15% and stabilization of tumor disease was observed in 35% of patients. In patients with liver metastases of breast cancer partial effect of the treatment was achieved in 10% and stabilization of tumor disease was seen in 40%. Median survival was two times longer in both groups. Chemoembolization of hepatic arteries to achieve long-term antitumor effect can be repeated several times.

In practice the interventional radiologist can encounter the situations when he or she must stop arterial blood flow for different reasons. It can be necessary in cases of hemorrhage from hepatic vessels occurring as a complication of puncture or drainage procedure and in cases of bleeding tumors of kidneys, bladder, uterus, and other organs in extremely debilitated patients. Surgical procedures that are performed to arrest such hemorrhages often turn into a very complicated operation with poorly predicted consequences. Therefore, selective embolization of the damaged vessel is a method of choice for hemostasis. A catheter is inserted through femoral or axillary artery and placed in the bleeding vessel. The embolizing material is then gradually delivered in under visual guidance. Angiography confirms the occlusion of the damaged vessel or the vessel supplying the bleeding tumor. Cessation of bleeding indicates the effectiveness of hemostasis

performed by this technique. IR procedure is performed under local analgesia and can be repeated in case of recurrent bleeding.

At the N.N Blokhin Russian Scientific Oncological Centre of Russian Academy of Medical Science selective intrahepatic embolization of hepatic arteries aiming to arrest hemorrhage has been performed in 16 patients, none of which required general anesthesia. Selective hepatic angiography by Seldinger's approach through the femoral artery performed at the first stage to detect the source of bleeding was followed by highly selective catheterization and hemostatic embolization of the affected artery. This method of hemostasis was effective in 100%.

Selective embolization of vessels supplying the tumor may be a method of preparation of patients for the subsequent surgical intervention aiming at intraoperative hemorrhage reduction in case of giant highly vascularized and deeply located tumors of different sites. We have successfully performed selective vascular embolization for this purpose in 45 patients. In oncology vascular embolization can also be used for re-direction of blood flow. In portal vessels this procedure is performed before the scheduled hemihepatectomy to accelerate blood circulation and regeneration of the lobe to be preserved (18 successful observations). In arterial vessels this procedure aims to reduce resorptive effect of antitumor drugs before the scheduled chemoembolization of vessels supplying the tumour of the head of the pancreas (12 successful observations).

Placement of Vena Cava Filters for Prevention of Pulmonary Artery Embolism

During the last decade special meshed intravascular devices have been used in practical surgery to prevent pulmonary artery embolism. They are developed to catch torn-off clots from large venous trunks of the lower extremities and pelvis that are moving to central venous collectors, which is extremely important in oncological practice. Elderly patients confined to bed for a long time experience some conditions predisposing to formation of venous clots. Tumors of pelvic organs adversely affect hemodynamics and can cause clot formation. During extensive surgical procedures or in the postoperative period clot masses can tear off and cause pulmonary artery embolism. Special vena cava filters that permit free blood passage and catch emboli are used to prevent these severe and often life-threatening complications. These devices are inserted under X-ray guidance through subclavian or jugular vein under local analgesia. There are temporary and constant filters. Temporary filters are withdrawn when the threat of embolization is removed. Temporary filter is also removed by IR procedure through the same veins without tissue dissection. For this purpose we have placed over 130 vena cava filters. None of the procedures was accompanied by thromboembolic complications.

Occlusion of Postoperative Bronchopleural Fistulas

Treatment of bronchopleural fistulas that occur after pneumonectomy in cancer patients is a very difficult task especially in case in infection of the pleural cavity. Most of these patients have little chance to be cured as spontaneous occlusion of such fistulas occurs rarely and surgical procedures on infected tissues are not very effective.

Specialists of the Russian Scientific Oncological Centre have developed a priority X-ray endoscopic technique of occlusion of bronchopleural fistulas by using metallopolymer composites that are implanted under fluoroscopy and endoscopy guidance and can be placed both from the side of the trachea and that of the pleural cavity. The procedure is performed under general anesthesia with suppression of spontaneous breathing [11]. The first procedures gave promising results, however, in order to be recommended for wide implementation this method needs thorough advanced investigation through more extensive clinical experience.

Complications of Interventional Radiology Procedures

Surgical component of interventional radiological methods is consistent with conventional surgical concepts. Tasks set by clinicians to the interventional radiologist should be solved taking into consideration patient's safety. Therefore, improvement of IR method suggests not only its intensive development but also finding ways and methods of prevention intra- and postoperative complications. All manipulations should always be performed under close radiological guidance with all surgical principles to be regarded. Main life-threatening complications during abdominal interventional procedures result from direct injury of parenchymatous organs, vessels, and decaying and infected tumors by instruments used for intervention radiology procedures. While intraabdominal hemorrhage and acute peritonitis can be fatal if urgent measures are not taken, bacteriemia and septic shock can be and should be treated using intensive methods of treatment including antibiotic and infusion therapy and detoxication. It should be remembered that intraprocedural septic shock can have severe complications; therefore it is very important to take appropriate measures before and during IR interventions in patients with fever and patients with specific changes in the hemogram to prevent infection and septic complications. Every time there when is a possibility of complications of interventional procedures the doctor should be ready to use active surgical and resuscitation supporting facilities. Adherence to these principles and sufficient experience of the interventional radiologist allow to minimize the rate and the severity of different complications of IR procedure or to treat them effectively in case they occur (Table 1).

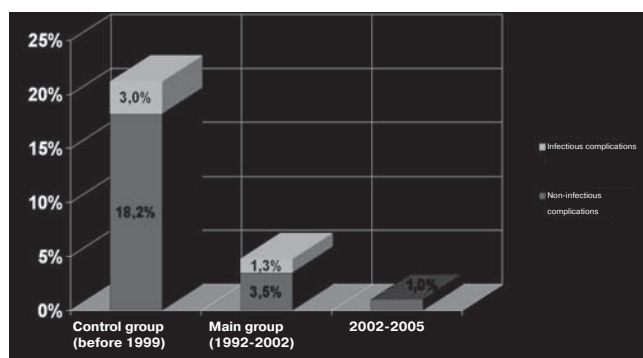


Table 1. Dynamics of decrease in mortality rate associated with IR procedures performed on biliary tract in cancer patients with mechanical jaundice over the last 15 years

In conclusion it should be noted that interventional radiology combining precise radiological guidance and delicate surgical options has promising future in oncology. Interventional procedures are better tolerated by patients, have fewer complications, can be easily repeated and cost far less compared to conventional surgical procedures. Along with the development of technical options radiology will find more and more new clinical applications.

References:

1. D.P. Chukhrienko, Ya.S. Bereznitski. Intraabdominal abscesses and phlegmons. Kiev, Zdorovie publishing house, 1977, 135 pages.
2. O.A. Pankratenko. Puncture interventional radiological methods in treatment of postoperative surgical complications in thoracic oncology. Avtoreferat ... PhD in Medicine, Moscow, 2006.
3. B.I. Dolgushin, Yu.I. Patutko, A.M. Nechipai, A.V. Kukushkin. Antegrade endobiliary interventions in oncology. Moscow, MIA publishing house, 2005. 175 pages.
4. B.I. Dolgushin, I.A. Trofimov. Percutaneous needle nephrostomy in oncology. International Journal of Interventional Cardioangiology, 2005, 7, 18. Abstracts of the 2nd Russian Congress of Interventional Cardioangiology, Russia, Moscow, 2005.
5. A.K. Valiev, B.I. Dolgushin, M.D. Aliev et al. Vertebroplasty: a method of choice in treatment of pain syndrome in patients with tumors of the spinal column. Proceedings, 3rd CIS Congress of Oncologists and Radiologists. Minsk, 2004, 255.
6. Dijkstra P.D.S. Pathological fractures of long bones due to bone metastases. 2001
7. Coleman R. Bone metastases from breast cancer and other solid tumors. ASCO 2001
8. A.K. Valiev. Vertebroplasty in treatment of patients with tumors of the spinal column. Avtoreferat ... PhD in Medicine, Moscow, 2006.
9. B.I. Dolgushin, V.N. Sholokhov, V.Yu. Kosirev. Complications of radiofrequency thermoablation of tumors. Proceedings of the Conference "New Technologies in the Diagnostics, Interventional Radiology and Surgery of the Pancreas". June 8-10, 2005. 89.
10. B.I. Dolgushin, M.I. Nechushkin, V.A. Cherkassov et al. Restoration of patency in strictures of tubular organs with

meshed metal prostheses in elderly cancer patients with inoperable disease. Klinicheskaya gerontologiya. 2005, 11, 6, 15-25.

11. B.I. Dolgushin, A.M. Nechipai, V.A. Cherkassov et al. Implantation of the original occluder: a method of treatment of postoperative bronchopleural and tracheopleural fistulas. International Journal of Interventional Cardioangiology 2005, 7, 18. Abstracts of the 2nd Russian Congress of Interventional Cardioangiology, Russia, Moscow, 2005.

LOZAP (Angiotensin-1-Receptor Antagonist) vs PRESTARIUM (ACE inhibitor) for the Treatment of Hypertension Prior to Endovascular Procedures

I. Ye. Chernysheva, O. V. Zakharova¹, N. V. Kuchkina, M. V. Diagileva, D. G. Iosseliani
Moscow City Center of Interventional Cardioangiologiy, Moscow, Russia

Hypertension is known to be one of the leading risk factors for stroke, coronary heart disease (CHD) and terminal renal failure (1,2). It affects approximately one out of four adults. Despite the detailed diagnostic strategy and the wide range of effective hypotensive agents, medical therapy provides the desirable outcome, i.e. the controlled hypertension, only in 17.5% of hypertensive women and 5.7% of men (3). This value varies with the country, ranging from 29% in USA and 17% in Canada to as low as 10% in Europe (4, 5).

Since recently hypertension has been successfully treated with selective AT₁-antagonists eliminating pressor, humoral and proliferative effects of angiotensin II (6, 7). Efficacy and safety of AT₁-antagonists in hypertensive patients was studied in large international clinical trials. AT₁-antagonists are effective hypotensives with organ-protecting action. They provide high patient compliance due to convenient dosage scheme (1 time daily) and virtually no undesirable events. Unfortunately, one of the major drawbacks of these agents is the high cost of treatment, which makes them unavailable for the majority of patients. Until recently there were no generic AT₁-antagonists in Russia. The first generic losartan in Russia was the Lozap (Zentiva, Czechia). Moderate cost of Lozap and its fixed combination with hydrochlorothiazide (Lozap Plus) substantially extends the number of patients who can afford AT₁-antagonists on a permanent basis.

The purpose of the study was to compare the hypotensive efficacy and safety of an AT₁-antagonist Lozap (Zentiva, Czechia) with those of an ACE (angiotensin-converting enzyme) inhibitor Prestarium (Servier, France) in hypertensive patients at the stage of preparation to endovascular procedures.

The study enrolled 38 hypertensive patients (26 women) with blood pressure (BP) within the range of 150-180/95-110 mm Hg. All patients were candidates for PTCA. Exclusion criteria were symptomatic hypertension; history of stroke or myocardial infarction within the last 6 months; grade 3-4 hypertensive encephalopathy; congestive heart failure; unstable angina or angina at rest; bradycardia with HR below 60 bpm; sick sinus syndrome; grade II-III sinoatrial

or atrioventricular block; type I diabetes mellitus; moderate or severe renal failure; hepatic failure or transaminases over 2 times above the normal range or bilirubin over 1.5 times above the normal range; history of angioedema; history of malignancy within the last 5 years; alcohol or drug abuse; impossibility to withdraw the therapy; Parkinson's disease.

Depending on the agent used, all patients were divided between two groups. Group I included 18 patients taking Lozap 25 – 100 mg daily. Group II included 20 patients taking Prestarium 2 - 4 mg daily. The dose was determined by eventual BP below 140/90 mm Hg. The mean age of patients in group I was 57.2±8 years vs 59.4±8.5 years in group II. Seventeen (17) patients in both groups (8 in group I vs 9 in group II) had various grades of angina (grade I-III). The majority of patients in group II had grade II hypertension (83.3%), another 16.7% had grade III hypertension (according to the classification of Russian Society of Cardioangiologists, 2004) (8). The mean duration of hypertension in group I was 15.2±4 years. In group II 95% of patients had grade II hypertension, while 5% had grade III hypertension. The mean duration of hypertension was 8.25±5.5 years.

The study began in January 2005 and lasted 12 weeks. During this period all patients were receiving a single morning dose of Lozap or Prestarium. At week 4, if the hypotensive effect was insufficient, the dose was increased in both group I (up to 50-100 mg Lozap) and group II (up to 4 mg Prestarium). The mean dose of Lozap was 48.6 mg daily. The mean dose of Prestarium was 2.3 mg daily. Patients from both groups were taking aspirin. Statins were used in 83.3% of patients in group I vs 85% of patients in group II. Beta-blockers were administered to 67.7% of patients in group II vs 85% of patients in group I. Calcium channel blockers were used in 50% of patients in group I vs 25% in group II. A single weekly dose of diuretics was administered to 50% of patients in group I vs 25% of patients in group II.

Blood pressure was measured after a 10-minute rest. Three measurements were made on the same arm with 2-min intervals after complete cuff deflation. A standard 12-lead ECG was taken in all patients.

A standard 24-h BP monitoring was performed using portable GE system (USA). Mean 24-h, daytime and night-time systolic (SBP) (mSBP₂₄, mSBP_d, mSBP_n, respectively) and diastolic (DBP) (mDBP₂₄, mDBP_d, mDBP_n, respectively) blood pressure were

¹Boris I. Dolgushin

Dept. of Radial Diagnostics and Endovascular Methods of Treatment
N. N. Blokhin Russian Scientific Center of Oncology, RAMS,
Russia, 115478, Moscow,
Kashirskoye shosse, 24
Phone: (007 495) 324-63-60; 324-44-96
E-mail: dolgushinb@mail.ru

Manuscript received on May 23, 2006

Accepted for publication on June 26, 2006

assessed. The circadian index (CI) of SBP and DBP was calculated using the formula: $CI\ SBP = (mSBP_d - mSBP_n) \times 100\% / mSBP_d$, $CI\ DBP = (mDBP_d - mDBP_n) \times 100\% / mDBP_d$. Analysis of the clinical BP rhythm was performed using normal and disturbed circadian rhythm: Dipper – patients with normal night-time decrease of BP, CI 10-20%; Non-dipper – patients with insufficient BP decrease, CI below 10%, Over-dipper – patients with excessive night-time decrease of BP, CI over 20%, Night-piker – night-time BP values exceed the daytime BP values. SBP variability was calculated on the basis of the standard deviation from the mean 24-h value, daytime and night-time BP. Normal SBP variability was defined as the change below 15.5 mm Hg at daytime vs 14.8 mm Hg at night-time.

Echocardiography was performed on Vivid 7 GE unit (USA) and included measurement of LV posterior wall (LVPW) and interventricular septum (IVS), end-systolic (ESD) and end-diastolic (EDD) LV diameters, left atrium (LA) anteroposterior diameter. Systolic LV function was assessed on the basis of the ejection fraction (EF).

AST, ALT, LDH, glucose, creatinine, urea, uric acid, cholesterol, triglycerides, potassium, sodium were assessed in all patients.

Descriptive statistical methods were used for the sample analysis, measurement of the mean values and dispersion of the mean (Student test). The level of type I error for the assessment of significance was defined as $p < 0.05$.

Results and discussion

Clinical and laboratory findings in patients from both groups are summarized in Table 1.

Table 1. Clinical and laboratory findings in patients from both groups

Parameter	Group I Lozap	Group II Prestarium	P
Age (years)	57,2 ± 8	59,4 ± 8,5	NS
Men/women	3 (16.7%) / 15 (83.3%)	10 (50%) / 10 (50%)	
Angina of effort	8 (44,4%)	9 (45%)	NS
Grade I	2	4	
Grade II	4	2	
Grade III	2	3	
Smokers	6 (33,3%)	4 (20%)	NS
Type 2 diabetes mellitus	4 (22,2%)	1 (5%)	NS
Dislipidemia	14 (77,8%)	17 (85%)	NS
2A	4	5	
2B	10	12	
Maximum SBP (mm Hg)	208,9 ± 32,5	178,3 ± 23,7	NS
Maximum DBP (mm Hg)	115,3 ± 21,6	99,5 ± 10,5	NS
Mean SBP (mm Hg)	132,2 ± 14,3	126,8 ± 9,5	NS
Mean DBP (mm Hg)	82,8 ± 9,6	82 ± 6,2	NS
LVEF (%)	66 ± 6,7	63,4 ± 7,9	NS
ESD (cm)	3,2 ± 0,7	3,4 ± 0,6	NS

Parameter	Group I Lozap	Group II Prestarium	P
EDD (cm)	4,9 ± 0,7	5,2 ± 0,5	NS
IVS (mm)	12,1 ± 3,3	10,6 ± 1,9	NS
LVPW (mm)	11,9 ± 3,6	10,8 ± 1,6	NS
LV hypertrophy (ECG)	11 (61,1%)	10 (50%)	NS
Cholesterol, mmol/l	6 ± 1,3	6 ± 1,3	NS
Triglycerides, mmol/l	2,4 ± 1,2	1,8 ± 0,6	NS
Glucose, mmol/l	5,9 ± 0,8	5,8 ± 1,4	NS
Uric acid, mmol/l	321,8 ± 70,5	294 ± 124	V

During the entire study period patients from group I had sustained decrease of both systolic and diastolic BP – the decrease of mean 24-h SBP became significant as soon as 4 week after the onset of therapy (from 135.9±15.9 to 130.9±14.6 mm Hg, $p=0,001$) (see Table 2). Significant differences in DBP were also detected 4 weeks after the onset of therapy (decrease from 87.3±14 to 81.7±10.4 mm Hg, $p<0,001$). At 3-months follow-up visit patients from group I had mean 24-h SBP of 127.3±12.6 mm Hg ($p<0,001$) and mean 24-h DBP of 80.2±10.4 mm Hg ($p<0,001$). After 4 weeks of Lozap therapy normal mean 24-h SBP was achieved in 72.2% of patients vs 88.9% of patients with normal 24-h DBP.

Patients from group II had significant decrease of both mean 24-h SBP (from 136.5±9.1 to 134±9.7 mm Hg, $p=0,047$) and mean 24-h DBP (from 89.4±9.5 to 86.1±6.5 mm Hg, $p=0,008$) at 4 weeks (see Table 2). Target level of SBP according to the 24-h monitoring was achieved at 4 weeks in 70% of patients on Prestarium, target DBP was achieved in 75% of patients. There were no significant difference between the study groups ($p=0,36$ for the mean 24-h SBP, $p=0,17$ for the mean 24-h DBP).

Table 2. Mean 24-h BP in groups I and II at baseline and during therapy at 1 and 3 months

	baseline		1 month		3 months	
	mSBP	mDBP	mSBP	mDBP	mSBP	mDBP
Lozap	135,9 ± 15,9	87,3 ± 14	130,9 ± 14,6; $p=0,001$	81,7 ± 10,4; $p<0,001$	127,3 ± 12,6; $p<0,001$	80,2 ± 10,4; $p<0,001$
Prestarium	136,5 ± 9,1	89,4 ± 9,5	134 ± 9,7; $p=0,047$	86,1 ± 6,5; $p=0,008$	132,8 ± 9,6; $p=0,01$	84,7 ± 5,9; $p=0,002$

Results of the study were quite comparable to those obtained by Veterans Affairs Cooperative Study collaborators, where the target DBP level was below 90 mm Hg at 12 weeks and below 95 mm Hg at 1 year in 54-72% of the 1292 male patients randomized to receive monotherapy with a diuretic; non-hydropyridine calcium channel blocker; beta-blocker; ACE inhibitor; alpha-2-agonist or alpha-blocker (9). At the same time, only 37% of 6264 patients reached target DBP below 90 mm Hg in HOT study (10).

In groups I and II there was a significant decrease of the mean daytime DBP at 4 weeks (group I: from

88±14.8 to 84.3±10.8 mm Hg, $p=0.02$; group II: from 89.4±9.5 to 87.7±6.8 mm Hg, $p=0.01$) (see Table 3). The mean daytime DBP also significantly decreased at 12 weeks in both groups (group I: from 88±14.8 to 81.6±10 mm Hg, $p<0.001$; group II: from 89.4±9.5 to 85.8±6.5 mm Hg, $p=0.001$).

Table 3. Mean daytime BP in groups I and II at baseline and during therapy at months 1 and 3

	Baseline		1 month		3 months	
	mSBPd	mDBPd	mSBPd	mDBPd	mSBPd	mDBPd
Lozap	138 ± 16,1	88 ± 14,8	133,9 ± 15,1; $p=0,002$	84,3 ± 10,8; $p=0,02$	129,2 ± 12,1; $p<0,001$	81,6 ± 10; $p<0,001$
Prestarium	138,2 ± 9,7	89,4 ± 9,5	136 ± 9,3; $p=0,07$	87,7 ± 6,8; $p=0,01$	134,5 ± 10,4; $p=0,02$	85,8 ± 6,5; $p=0,001$

Patients on Lozap had significant decrease of the mean daytime SBP at months 1 and 3 (from 138±16.1 to 133.9±15.1 mm Hg, $p=0.002$; from 138±16.1 to 129.2±12.1 mm Hg, $p<0.001$, respectively) (see Table 3). Target level of the mean daytime SBP was achieved in 77.8% of patients at 12 weeks of Lozap therapy, whereas in the INVEST study only 64% had SBP below 140 mm Hg regardless of the treatment strategy (11).

Patient on Lozap had significant decrease of the mean night-time BBP at months 1 and 3 (from 78.3±13.7 to 74.7±11.9 mm Hg, $p=0.04$; from 78.3±13.7 to 73.7±11.7, $p=0.02$, respectively) (see Table 4). Similar results were obtained by Ruilope L. et al, who observed 9 and 11 mm Hg decrease of DBP at 12 weeks of therapy with losartan (50 mg) or hydrochlorthiazide (12.5 mg, 25 mg), respectively (12). In patients taking on Prestarium the mean night-time SBP decreased significantly at months 1 and 3.

Table 4. Mean night-time BP in patients from groups I and II at baseline and during therapy at months 1 and 3

	Baseline		1 month		3 months	
	mSBPd	mDBPn	mSBPd	mDBPn	mSBPd	mDBPn
Lozap	120,1 ± 30,5	78,3 ± 13,7	120,9 ± 14,3 $p=0,33$	74,7 ± 11,9 $p=0,04$	113,3 ± 11 $p=0,32$	73,7 ± 11,7 $p=0,02$
Prestarium	130,1 ± 11,3	86,3 ± 9,8	126,9 ± 9,8 $p=0,02$	84,2 ± 7,2 $p=0,08$	126,2 ± 9,5 $p=0,01$	83 ± 6,4 $p=0,03$

According to the circadian index (CI) of SBP the variants of 24-h SBP profile were defined in patients from both groups at baseline and at 12 weeks of therapy (see Table 5).

Table 5. Circadian index of the systolic BP in both groups

	CI SBP at baseline	CI SBP at 12 weeks	P
Lozap			0,03
Dipper	8 (44,4%)	12 (66,7%)	
Non-dipper	8 (44,4%)	6 (33,3%)	
Over-dipper	0	0	
Night-piker	2 (11,2%)	0	
Prestarium			0,11
Dipper	3 (15%)	6 (30%)	
Non-dipper	16 (80%)	14 (70%)	
Over-dipper	0	0	
Night-piker	1 (5%)	0	

Interestingly, the normal type of SBP circadian rhythm («dipper») was detected only in 44% of patients in group I vs 15% of patients in group II. In group II the «non-dipper» type with insufficient night-time decrease of the SBP was predominant (80%). Two patients in group I (11.2%) and one patient in group II (5%) had higher night-time SBP as compared to the daytime SBP – the «night-piker» variant. In the majority of patients from group I taking Lozap (66,7%) had normal «dipper» circadian SBP profile at 12 weeks ($p=0.03$). In group II, the share of «non-dipper» patients non-significantly decreased to 70% at 12 weeks of Prestarium therapy ($p=0.11$).

Analysis of the baseline circadian rhythm of DBP showed, that only 33.3% of patients in group I and 15% of patients in group II had normal daytime and night-time distribution of this value corresponding to «dipper» profile (see Table 6). The «non-dipper» type was observed in 50% of patients in group I vs 80% of patients in group II, «night-piker» - in 5.6% (group I) vs 5% (group II), «over-dipper» - in 11.1% of patients in group I characterized by excessive decrease of DBP at night-time. In the majority of patients (61.1%) therapy with Lozap resulted in normalization of the circadian rhythm ($p=0.46$). The per cent of «dipper» patients on Prestarium increased from 15% to 40% at 12 weeks ($p=0.09$).

Table 6. Circadian index of the diastolic BP in both groups

	CI DBP at baseline	CI DBP at 12 weeks	p
Lozap			0,46
Dipper	6 (33,3%)	11 (61,1%)	
Non-dipper	9 (50%)	7 (38,9%)	
Over-dipper	2 (11,1%)	0	
Night-piker	1 (5,6%)	0	
Prestarium			0,09
Dipper	3 (15%)	8 (40%)	
Non-dipper	16 (80%)	12 (60%)	
Over-dipper	0	0	
Night-piker	1 (5%)	0	

Significant decrease of the daytime and night-time SBP variability was detected at 12 weeks in both groups (see Table 7). In group I the daytime value decreased from 14.7±2.9 to 7.5±4.6 mm Hg compared to the decrease of the night-time value from 14±3.6 to 7.1±2.8 mm Hg ($p<0.0001$). In group II the daytime SBP variability decreased from 14.7±1.95 to 8.9±4.6 mm Hg compared to the night-time decrease from 13.3±4.8 to 7.5±3.9 mm Hg ($p<0.0001$). This was due to normalization of BP variability in patients with increased variability at baseline.

The results obtained seem important as numerous evidences suggesting high predictive value of several BP monitoring values in hypertensive patients has been observed. Particularly, direct correlation was found between the mean 24-h values of BP, increased variability and the degree of changes in the target organs (myocardial hypertrophy, retinal angiopathy and nephropathy) (13, 14, 15). The significant effect of Lozap on the BP monitoring parameters studied is supposed to have a direct

action on the cardiovascular remodeling processes in hypertensive patients.

Table 7. Daytime and night-time variability of the systolic BP (VSBP) in patients from both groups

	Baseline		3 months		p
	VSBPd	VSBPn	VSBPd	VSBPn	
Lozap	14,7 ± 2,9	14 ± 3,6	7,5 ± 4,6	7,1 ± 2,8	p<0,0001
Prestarium	14,7 ± 1,95	13,3 ± 4,8	8,9 ± 4,6	7,5 ± 3,9	p<0,0001

Assessment of several biochemical values characterizing the carbohydrate, lipid, nitrogen, purine and electrolyte metabolism showed, that the patients studied had increased total cholesterol (Chol) (group I: 6±1.3 mmol/l; group II: 6±1.27 mmol/l), triglycerides (TG) (group I: 2.4±1.2 mmol/l; group II: 1.82±0.6 mmol/l), whereas other mean values were normal. Five patients in both groups (4 patients in group I) had moderate type 2 diabetes mellitus. Therapy with Lozap and Prestarium was associated with significant decrease of the mean total cholesterol, triglycerides, uric acid (UA) (see Table 8). We believe, that normalization of the lipid profile was associated with parallel treatment with statins in over 80% of patients in both group I and group II.

Table 8. Biochemical values in both groups

	At baseline			At 3 months			P
	Chol	TG	UA	Chol	TG	UA	
I	6 ± 1,3	2,4 ± 1,2	321,8 ± 70,5	4,8 ± 0,6	1,4 ± 0,7	200,7 ± 38,1	<0,001
II	6 ± 1,27	1,82 ± 0,6	294,3 ± 124	5,1 ± 0,8	1,2 ± 0,3	239 ± 87,9	<0,001

Nakashima et al. were first to report, that losartan strengthened the excretion of uric acid (16). ACE inhibitors and calcium channel blockers increase the excretion of uric acid, however, this moderate effect is not clinically relevant. Other AT1-antagonists don't show uricosuric action of losartan (17). In a double blinded randomized study Wurzner G. Et al compared the effect of two AT1-antagonists (losartan 50 mg daily, 1 month cycle followed by 50 mg BID, 1 month cycle vs irbesartan 150 mg daily, 1 month cycle followed by 150 mg BID, 1 month cycle) on the serum level of uric acid in hypertensive patients (17). Losartan significantly decreased the serum level of uric acid, whereas irbesartan had no effect on these values (14). Our study showed, that Lozap more markedly decreased the level of uric acid as compared to Prestarium (see Table 8).

At 12 weeks the patients were recommended to stay on therapy. All patients were invited to a follow-up visit at 3 months to assess the treatment efficacy and compliance. The tolerance of Lozap and Prestarium was good in all patients, there were no difference in tolerance between the groups. No adverse or undesirable effects were detected during the 12 weeks.

Conclusions

Therapy with Lozap provides stable and smooth 24-h hypotensive effect and has multidimensional corrective action on circadian profile of BP in patients during preparation to endovascular procedures: significant decrease of mean 24-h SBP, DBP, mean daytime SBP, DBP, mean night-time DBP, SBP variability at daytime and night-time. The per cent of patients, who achieved target BP at 4 weeks was higher in Lozap group. At 12 weeks the amount of SBP dips on Lozap significantly increased.

Lozap and Prestarium were characterized by good tolerance. No adverse or undesirable effects were observed in either group.

Lozap is an effective hypotensive agent showing unique potential to decrease the level of uric acid. The potential of Lozap to decrease the level of uric acid can be particularly useful for the treatment of hypertensive patients with hyperuricemia.

The results obtained will undoubtedly contribute to the extension of the clinical use of Lozap (losartan) and re-consideration of the existing approaches to the treatment of hypertension.

References:

1. Franco O.H., Peeters A., Bonneux L., de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis. *Hypertension*, 2005, Aug., 46(2), 280-6.
2. Eberly L.E., Neaton J.D., Thomas A.J., Yu D. Multiple Risk Factor Intervention Trial Research Group. Multiple-stage screening and mortality in the Multiple Risk Factor Intervention Trial. *Clin. Trials*, 2004, 1(2), 148-61.
3. Shalnova S.A., Deev A.L. et al. Prevalence of hypertension in Russia. Information distribution, treatment, control. Профилактика неинфекционных заболеваний и укрепление здоровья, 2001, 2, 3-5.
4. Wolf-Maier K., Cooper R.S., Kramer H. et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension*, 2004, Jan., 43(1), 10-7.
5. Banegas J.R., Segura J., Ruilope L.M. et al. CLUE Study Group Investigators. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. *Hypertension*, 2004, June, 43(6), 1338-44.
6. Mancia G., Seravalle G., Grassi G. Tolerability and treatment compliance with angiotensin II receptor antagonists. *Am. J. Hypertens.*, 2003, 16 (12), 1066-73.
7. Wogen J., Kreilick C.A., Livornese R.C. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J. Manag. Care Pharm.*, 2003, 9 (5), 424-9.
8. Guidelines for prevention, diagnosis and treatment of hypertension. Instructions for Russia (second revision). Expert Committee of the Russian Research Society of Cardiologists. Hypertension section. Moscow, 2004.
9. Materson B.J., Reda D.J., Cushman W.C. Department of veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Am. J. Hypertens.*, 1995, Feb., 8(2), 189-92.

10. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment randomized trial. *Lancet*, 1998, 351, 1755-1762.
11. Pepine C.J., Handberg E.M., Cooper-DeHoff R.M. et al. INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*, 2003, Dec., 3, 290(21),2805-16.
12. Ruilope L., Simpson R., Ton J. et al. Controlled trial of losartan given concomitantly with different doses of hydrochlorothiazide in hypertensive patients. *Blood Press.*, 1996, 5, 32 - 40.
13. Oshchepkova Ye.V., Rogoza A.R., Varakin Yu.A. Variability of blood pressure (according to the daily monitoring) in mild hypertension. *Terapevtichesky Arkhiv*, 1994, 8, 70-73.
14. Devereux R.B., Pickering T.G., Harshfield G.A. et al. Left ventricular hypertrophy in patients with hypertension: importance of blood pressure response to regulary reccuring stress. *Circulation*, 1998, 68, 447-76.
15. Meredith P.A., Perloff D., Mancia G. et al. Blood pressure variability and its implications for antihypertensive therapy. *Blood Press.*, 1995, 4, 5-11.
16. Nakashima M., Uematsu T., Kosuge K., Kanamaru M. Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur. J. Clin. Pharmacol.*, 1992, 42(3),333-5.
17. Wurzner G., Gerster J.C., Chiolerio A. et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J. Hypertens.*, 2001, Oct., 19(10), 1855-60.