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Contents

Review of Organization and Availability of Reperfusion Therapy in Patients with ST- Segment Elevation Myocardial Infarction in the City of Kemerovo

V.I. Ganiukov[1] , R.S. Tarasov, O.V. Kovalenko, V.Yu. Kheraskov, G.V. Artamonova, G.V. Moiseenkov, O.L. Barbarash, L.S. BarbarashURAMS,
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Percutaneous coronary intervention (PCI) became an important component of treatment of acute and chronic coronary heart disease (CHD). In patients with chronic CHD, PCI improves the quality of life, while in patients with acute coronary syndrome, particularly with ST-segment elevation myocardial infarction (STEMI), PCI represents a lifesaving procedure. This article addresses the experience of countries, where the use of primary PCI in STEMI became the nation-wide practice, and the organization and availability of reperfusion treatment in Russia as exemplified by the city of Kemerovo.

Keywords: *ST-segment elevation myocardial infarction, percutaneous coronary intervention, organization of medical care.*

Objective: To review the experience of countries, where the primary percutaneous coronary intervention (PCI) is used in patients with ST-segment elevation acute myocardial infarction (STEMI), and the organization and availability of reperfusion treatment in Russia (as exemplified by the city of Kemerovo).

Relevance: Despite the absolute benefit of the primary PCI in STEMI patients is certain, the economic, territorial organizational, and social causes preclude the adherence to this standard in most European countries and in Russia as well.

Methods: Review of the literature on the experience of European countries in the treatment of STEMI within the "«Stent for Life» " Initiative launched by the European Association of Percutaneous Cardiovascular Intervention (EAPCI). The purpose of the initiative includes the assessment of national programs of PCI organization in acute coronary syndrome (ACS) and the development and implementation of measures to reduce acute myocardial infarction (AMI) related mortality in the territory of the European Union. The organization of medical care for STEMI patients in Kemerovo Region was analyzed based on the registry of the number and outcomes of ACS patients treatment in Kuzbass Cardiology Center, orders of Kuzbass Cardiology Center, governing the standards of care for STEMI patients in Kemerovo.

Conclusions:

1. In Russia, there is a reasonable need for further active promotion of the national program supporting primary PCI performing in STEMI patients.
2. The primary goals of timely high technology medical care for STEMI patients include:
   - qualification of primary PCI as an absolute priority of reperfusion treatment in STEMI patients on the national health care system basis,
   - conformity to the target treatment outcomes in STEMI patients, developed by the EAPCI,
3. «Closed cycle» technology, developed and introduced in Kuzbass Cardiology Center, may be used as a basis in the development of the organizational model of available reperfusion therapy for STEMI patients in Russia.

Abbreviations

PCI – percutaneous coronary intervention
AMI — acute myocardial infarction
ICU – intensive care unit
STEMI - ST-segment elevation myocardial infarction
ACS — acute coronary syndrome
TLT – thrombolytic therapy
ECS – Emergency Call Service
ECG – electrocardiogram
Ministry of HC and SD of RF – Ministry of Healthcare and Social Development of the Russian Federation
RSSC – Russian Scientific Society of Cardiology

INTRODUCTION

Despite the importance of treatment of STEMI patients with the use of modern techniques of reperfusion therapy (primary PCI, TLT), there is no comprehensive uniform national registry to record the state of medical care for patients with ACS in Russia. Although PCI is the most effective reperfusion treatment in STEMI patients, currently there are no regions in the Russian Federation where primary PCI in provided to all patients requiring this procedure (5). This problem is of complex nature and concerns not only the Russian Federation, but many other countries, which encour-

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aged the European «Stent for Life» Initiative in 2008. The purpose of this Initiative includes the introduction of the national programs of organization of PCI in ACS to reduce mortality. The national programs may have an individual pattern in any specific country, being based on the experience of countries with successive national programs developed with the implementation of three target parameters of the «Stent for Life» Iinitiative:

1. Primary PCI should be used in more than 70% of STEMI patients;
2. The rate of primary PCI should exceed 600 per 1 million of population annually;
3. PCI centers should provide primary PCIs to STEMI patients on a 24 hours- a-day, 7 days-a-week basis (1).

In addition to purely medical aspects, the solution of this problem requires the development of complex measures to improve public awareness of cardiac diseases through mass media; develop regional infrastructure; open new centers carrying out primary PCI on a 24 hours-a-day, 7 days-a-week basis; improve the activities of existing catheterization laboratories; optimize interactions between the hospitals performing PCI, ECS teams and hospitals that do not provide PCI, and develop obligatory and voluntary medical insurance system.

The **purpose** of this article includes the review of the experience of countries, where the primary percutaneous coronary interventions (PCI) are successfully used in patients with ST-segment elevation acute myocardial infarction (STEMI), and of the organization and availability of reperfusion treatment in Russia (as exemplified by the city of Kemerovo).

Medical care organization for STEMI patients in European countries

Five European countries with the most positive experience of treatment of STEMI patients with the use of primary PCI include Czech Republic, the Netherlands, Sweden, Denmark, and Austria. The successful implementation of the national reperfusion programs in STEMI patients is based on: the favourable geopolitical factors, stable economic situation and close interaction between the authorities, insurance companies, mass media and health care system. The area of the above countries varies from 41,500 km^2 (Netherlands) to 449,900 km2 (Sweden) (Table 1). The population of these countries varies from 5,000,000 (Denmark) to 16,000,000 persons (Netherlands) (Table 1). The unique feature of these five countries consists in relatively great number (in relation to the population) of the centers that carry out primary PCI for 24 hours-a-day, 7 days-a-week: from 5 centers in Denmark to 29 centers in Sweden (Table 1).

Table 1. Main characteristics of five European countries and of the city of Kemerovo

Country	Area (thousand km^2)	Population (millions)	Number of “24/7” centers
Czech Republic	78.8	10.4	22
Netherlands	41.5	16.5	21
Sweden	449.9	9.2	29
Denmark	43.1	5	5
Austria	83.8	8.3	23
Kemerovo	0.3	0.5	1

Currently, the Czech Republic has the highest rate of primary PCI: 92%. TLT is only used in 1% of STEMI cases (2).

Pre-hospital medical care for STEMI patients in the European countries

The mandatory requirement of the effective system of care for AMI patients in the above named European countries includes the commonly known emergency call number. Most countries provide the toll-free availability of these phone numbers for 24 hours-a-day, 7 days-a-week. These circumstances provide a relatively high (for Europe) percentage of AMI patients, who are transferred to the hospitals by ECS teams (about 80%). This rate is maintained due to the regular national information campaigns. The results of new clinical studies are reported on television and in the newspapers not less than once yearly. The public gets regular information about the necessity of ECS call in case of chest pain, including the notifications in the public places.

The emergency service teams include the specially trained paramedics or experienced nurses, less often – a physician. All ECS teams are equipped with 12-lead ECG apparatus, defibrillator and medication kit. Also oxygen supply and the assisted ventilation equipment are available (1). ECG recording is performed immediately after the first contact with the patient, then ECG record is sent to the PCI center or to the telemedicine center, where it is assessed, and the decision on further treatment strategy is made.

ECS generally transfers the patients immediately to the catheterization laboratory, by-passing centers, where primary PCI is unavailable. If a patient is transported to the center, where primary PCI is unavailable, and the diagnosis of AMI is made, he/she must be immediately transferred to the catheterization unit by the secondary transport. The ECS team must inform the staff of the laboratory of the upcoming arrival of the patient. The main cause of the delayed medical care in the European countries is still the delayed patients' referral (1).

In-hospital medical care organization for STEMI patients in the European countries

The organization of work of “24/7” catheterization units in the Czech Republic, the Netherlands, Sweden, Denmark, and Austria is generally similar, with a few differences. The experience of the Czech Republic, which is the leader in the organization of the reperfusion therapy in Europe, is of most interest. In 2001, the Czech Society of Cardiology submitted the national cardiac program, which was further approved by the government. This document coordinates the efforts of all participants of Czech health

care system in the creation of the effective system of treatment of patients with cardiovascular diseases. In particular, the information on the emergency care organization is represented. The necessity of immediate transportation of AMI patients to the primary PCI center is declared. This document establishes the number of primary PCI centers, number of the cardiac hospitals and staff regulations.

The team of catheterization unit (generally including one physician and one nurse) receives the aforehead information on the upcoming arrival of the patient. In some centers, the resident or one more nurse take part in the team's work. If necessary, the ICU physician may be engaged. The intervention cardiologist is on telephone duty and thus is able to arrive to the center within 30 minutes. The nurses of most catheterization units work on "24/7" schedule. The ECS team transfer a patient immediately to the radiology operating room, by-passing the emergency room and the admission unit.

Every PCI center has concluded a contract with non-PCI-capable hospitals, which regulates the order of management of AMI patients. Following the primary PCI, the patients are transferred to the ICU of the PCI center. The duration of patient's stay at PCI center is about 1 to 2 days, depending on the features of the procedure. Then the patient is transferred to the non-PCI-capable hospital. He/she is transported by the transport of the ECS. The expedite translocation of patients from the PCI centers is primarily due to their small bedspace and to the concernment of patient's return to the hospital that provides services to a specific district (1).

Table 2. Number of primary PCI in the five European countries and in the city of Kemerovo

Country	Number of primary PCI per year (% of the total number of PCI)	Number of the primary PCI per year per 1 million of population
Czech Republic	6,720 (31%)	657
the Netherlands	11,201 (31%)	683
Sweden	5,421 (20%)	600
Denmark	2,691 (26%)	481
Austria	3,500 (18%)	426
Kemerovo	308 (17.6%)	616

Based on the recent data (4), in 2008 6,720 primary PCI were performed in the Czech Republic, i.e. 31% of the total number of PCI (Table 2). A total of 657 primary PCI were carried out; one PCI center offers services to 464,943 persons (Table 3). The in-hospital mortality in STEMI patients following primary PCI was 6.7% (Table 4), with general mortality in STEMI patients being 8.6% (4). The time from symptom onset to first medical contact in Czech Republic is 150 minutes, and the time from first medical contact to the primary PCI is 120 minutes (Table 5) (4).

The number of primary PCIs in the Netherlands is 11,201 (31% of the total number of PCIs) (Table 2).

Table 3. Number of the PCI-capable centers and population of the five European countries and of the city of Kemerovo

Country	Total number of PCI centers	Number of centers performing the primary PCI ("24/7")	Population per 1 PCI center	Population per 1 primary PCI center ("24/7")
Czech Republic	22	22	464,943	464,943
the Netherlands	22	22	745,700	745,700
Sweden	29	13	311,417	694,699
Denmark	7	5	781,160	1,093,624
Austria	34	24	282,751	341,000
Kemerovo	1	1	550,000	550,000

The number of annual primary PCIs per 1 million of population is 683 (4). The population of 745,700 persons is serviced by one center that performs primary PCI ("24/7") (Table 3).

Few years ago in Sweden TLT was the predominant technique of reperfusion therapy in STEMI patients. The transition to the new treatment strategy became possible due to a number of cooperative efforts. PCI centers initiated an active discussion of reperfusion programs in AMI patients in the medical community and at the level of regional health care authorities. Eventually, the evidences of better outcomes of the primary PCI were obtained, thus convincing the physicians of the appropriateness of this new approach. In Sweden, the registry exists that summarizes the information on all ACS patients (3). The data from this registry are submitted to the politicians at regular intervals and serve as a basis for the possible optimization of the routine practice in order to improve the treatment quality. Nine quality criteria were developed, which assess the efficacy of the hospital activities in the treatment of AMI patients. One of these criteria is a percent of STEMI patients, who were treated with one of the reperfusion methods, Second criterion is the time delay to reperfusion.

The third criterion is the mortality rate. If the hospital's quality level is low, the plan of measures to improve the treatment efficacy is realized. The results of these assessments come into the public domain through the mass media.

In 2008 (4) 5,421 primary PCIs were performed in Sweden, i.e. 20% of the total number of PCIs (Table 2). A total of 600 PCIs per 1 million of population were carried out. One primary PCI center ("24/7") offers services to 694,699 persons (Table 3). The in-hospital mortality in STEMI patients following primary PCI was 3.8% (Table 4), with general mortality in STEMI patients being 6.2% (4). The time from symptom onset to first medical contact is 120 minutes, the time from first medical contact to primary PCI is 69 minutes (Table 5) (4).

In Denmark, there are five centers that carry out primary PCI and work on "24/7" schedule. The majority of population resides within 2-hour avail-

ability of PCI centers. There are several distant rural areas, where the timely transportation of patients to the catheterization laboratory is problematic. Even in these territories, primary PCI is considered preferable. The helicopters are used for transportation of patients who live in the islands.

In Denmark, 2,691 primary PCIs are performed annually, i.e. 26% of the total number of PCIs (Table 2). A total of 481 PCIs are carried out per 1 million of population annually. One primary PCI center ("24/7") offers services to the population of 1,093,624 persons (Table 3) (4).

In Austria, there are 23 centers that carry out primary PCI on "24/7" work schedule. The progression of the quality of medical care was achieved due to close interaction between the emergency call service, non-PCI-capable hospitals and primary PCI centers.

In 2008, 3,500 primary PCIs were carried out in Austria (i.e. 18% of the total number of PCIs) (Table 2). A total of 426 PCIs were performed per 1 million of population. One primary PCI-capable center ("24/7") offers services to the population of 341,000 persons (Table 3). The in-hospital mortality of STEMI patients following primary PCI was 5% (Table 4), with general mortality in STEMI patients being 12% (4). The time from symptom onset to first medical contact in Austria is 90 minutes, the time from first medical contact to primary PCI is 115 minutes (Table 5) (4).

Table 4. In-hospital mortality in AMI patients in the five European countries and in the city of Kemerovo (%)

Country	Total STEMI	STEMI with primary PCI	STEMI with TLT	Total AMI
Czech Republic	8.6	6.7	ND	6.3
Netherlands	ND	ND	ND	ND
Sweden	6.2	3.8	8.8	5.2
Denmark	ND	ND	ND	ND
Austria	12	5	8	ND
Kemerovo	ND	5.2	23.5	12

ND = no data

Table 5. Time delay of reperfusion treatment in the five European countries and in the city of Kemerovo (%)

Country	Time from symptom onset to first medical contact	Time from first medical contact to TLT	Time from first medical contact to primary PCI
Czech Republic	150	ND	120
Netherlands	ND	ND	ND
Sweden	120	40	69
Denmark	ND	ND	ND
Austria	90	30	115
Kemerovo	ND	ND	75±20

Economic aspects of the medical care for STEMI patients in the European countries

In most European countries that possess the health insurance system, the funding of hospitals does not represent any problem. The hospitals of these countries are sufficiently motivated to carry out primary PCI in all AMI patients. Moreover, there are the primary PCI programs under state patronage (1).

The health care system of the Czech Republic is an evident illustration of funding of medical care for AMI patients through the European medical insurance system, which is obligatory and is regulated by law. Any citizen has a possibility to choose between several health insurance companies. To assess the amount of financing, the international system, Refined Diagnosis Related Groups (DRG) is used. The specific code is assigned to any diagnosis and treatment. According to this code, the insurance company accomplishes the financial support. PCI center receives a fixed payment for AMI diagnosis and for PCI procedures, independent on the materials used (stents, balloons etc.). The territory hospitals get financing of the further in-patient stay. The sum of money does not depend on the time of admission (daytime, night, holiday). There are no limitations concerning the number of primary PCIs in STEMI patients. All procedures are fully compensated. Thus, primary PCI is financially attractive for PCI centers. The health insurance companies play an important role in this process. The "24/7" work schedule of PCI centers is a mandatory requirement for interaction with insurance companies. Thus, all primary PCI centers in Czech Republic work for 24 hours-a-day, 7 days-a-week (1).

Medical care organization for STEMI patients in Russia (as exemplified by the city of Kemerovo)

The territory of the Russian Federation is 17 millions 75 thousands and 260 km^2. The population of the country, as per January 01, 2009, is 141 million 900 thousand persons. About 60% of the territory of the Russian Federation fall on the Siberian and Far-East regions. The total number of the populated localities is 157,895. These circumstances make the optimization of the medical care for STEMI patients particularly difficult. In 2007, the incidence of AMI in Russia was 140.4 per 100,000 of adult population (5).

The problem of high-technology medical care for AMI patients in Russia is undoubtedly one of the priorities of the national health care system. However, due to the absence of the comprehensive national ACS registry in the Russian Federation, there is no possibility to assess the availability of reperfusion treatment in STEMI patients. Therefore, in this article we provide the results concerning the medical care organization for STEMI patients in the city of Kemerovo.

The area of the city of Kemerovo is 300,000 km^2. The population of Kemerovo is 520,000 persons (Table 1). Up to 30% of cardiovascular patients who reside in Kemerovo region receive medical care in Kemerovo.

In 2005, Kuzbass Cardiology Center (KCC) was founded in Kemerovo, which is a medical holding including the institutions of various forms of ownership. KCC includes:

Municipal Healthcare Institution Kemerovo Cardiology Dispensary, with 18 out-patient cardiology consultations, 384 full-time specialized beds and a 100-bed cardiology health resort for after-treatment of patients with myocardial infarction or after cardiac surgery,

Cardiovascular Scientific Research Institute, Siberian Branch of the Russian Academy of Medical Sciences, with 120-bed hospital (including 60 cardiosurgical) and endovascular laboratory.

There is the Department of cardiology and cardiovascular surgery of Kemerovo Medical Academy in the Center.

The main principles of the specialized care in AMI in Kemerovo are as follows:

1. Early hospitalization of any patient with suspected AMI to the single specialized hospital of Kemerovo.
2. Availability of primary PCI on "24/7" work schedule.
3. Uniform treatment ideology for ACS patients in Kemerovo based on the "closed cycle": out-patient clinic – admission unit – interventional radiology unit – urgent cardiology department – cardiac surgery department – rehabilitation health resort – out-patient clinic (6).

Prehospital medical care in STEMI patients in the city of Kemerovo

An important advantage of the prehospital medical care in the Russian Federation is the availability of the commonly known phone number "03" and the system of ECS stations (with estimated time of arrival to any point of the covered territory of 15-20 minutes). The existence of specialized cardiology teams makes possible the diagnosis and the start of the appropriate medical care at the early stages. The cardiology team of ECS includes the cardiologist skilled in the intensive care and resuscitation and two physician's assistants. The modern ECS cars are equipped with the 12-lead electrocardiogram recorder, defibrillator, resuscitation equipment and medications along with devices for central or peripheral intravenous administration.

The transportation of all AMI patients in Kemerovo is performed immediately to the admission unit of KCC. The distance of transportation does not commonly exceed 30 km. Due to the possibility of primary PCI on "24/7" schedule and to the transportation time not exceeding 20-30 minutes, no TLT is carried out at the ECS stage. ECG diagnosis and standard treatment are performed. The loading dose of clopidogrel (300-600 mg) is administered at the stage of ECS or in the admission unit of the cardiology center. The objectives of ECS physician in case of ACS include the determination of the indications for primary PCI, explanation the necessity of coronarography and PCI to a patient and obtaining the patient's informed consent to these procedures, notification of the admission unit on the upcoming arrival of STEMI patient. Thus, already at the first contact with the ECS physician the group of patients with increased risk of adverse events is identified, and the candidates for PCI are determined.

The physician of the admission unit coordinates the functions of the hospital services, which provide medical care in ACS. His/her functions include: acceptance of the notification of ECS on the transportation of ACS patient, gathering of the specialists of the hospital diagnostic units in the admission unit, notification of the radio-endovascular laboratory, confirmation of PCI indications and determining the extent of endovascular intervention.

The algorithm of interactions of the admission unit physician with ECS physician is approved by the joint order for Municipal Healthcare Institution Kemerovo Cardiology Dispensary and Municipal Healthcare Institution City Clinical Emergency Service Station. Uninterrupted informational interaction at the stages of the medical care is provided through the separate telephone line between the control rooms of the ECS station and hospital admission unit. The form of Accompanying sheet for ACS patients was developed and introduced, which superseded the form of medical documentation No. 114У, approved by the order No. 1030 of the Ministry of Healthcare of the USSR dated October 04, 1980.

In-hospital medical care in STEMI patients in the city of Kemerovo

KCC performs the 24-hour admission of all patients with urgent cardiology diseases in the city of Kemerovo. The primary hospitalization of the patients transported by the ECS, referred by the general practitioners and cardiologists from the city out-patient clinics, following independent patients' referral to the center and hospitalization of patients transferred from the city and regional hospitals is performed. More than three thousand ACS patients, including 32.1% of patients with confirmed AMI, receive the specialized care at KCC annually. The Center includes 10 cardiology departments, among them two Departments of Acute Coronary Diseases, Resuscitation and Intensive Care Unit (RICU), Interventional Radiology Diagnostic and Treatment Laboratory, Department of Cardiac Surgery, separate admission unit and diagnostic services.

The main features of the organization of KCC in-hospital medical care for ACS patients are as following: patients' hospitalization following the short stay at the admission unit; 24-hour and 7-day availability of the percutaneous coronary interventions; early rehabilitation of STEMI patients in RICU with subsequent stay at the Department of Acute Coronary Diseases.

The main purposes of the admission unit include the confirmation of the diagnosis and ACS patients' assignment in the groups of early invasive and non-invasive treatment. The admission unit is staffed

with medical team trained in cardiology, emergency medical care, internal diseases. The department contains the functional diagnostics room, ultrasound diagnostics room and the express laboratory. The algorithms of confirmation of the diagnosis of ACS and of patients' grouping into the arms of early invasive and non-invasive strategy were developed.

At the admission department, the treatment measures started at ECS stage continue; the follow-up ECG is recorded if necessary. The blood sample is drawn for testing the main clinical and biochemical parameters. Echocardiography is performed, then the patient is referred to the interventional radiology operating room by-passing RICU. This system has specific advantages compared to patient's immediate delivery onto the operating table by ECS team. Primarily, a more qualitative and informative patients' evaluation may be performed. Secondly, no time loss is present, as the team of interventional radiology unit begins the preparation of the interventions immediately following patients' delivery to the admission department.

The unit of interventional radiology of KCC includes the Department of interventional radiology, laboratory of interventional diagnostics and treatment and is equipped by three angiography apparatus; PCI is available on "24/7" schedule. The on-duty team of the unit of interventional radiology consists of one intervention cardiologist (intervention radiologist), anaesthesiologist, three nurses (scrub nurse, anaesthesiology nurse and radiological technician) and nurse's assistant. The presence of the staff anaesthesiologist allows the surgeon to concentrate on the intervention without unnecessary distraction for monitoring of vital signs and performing a complex of intensive care measures.

Following the primary PCI the patient is transferred to the intensive care unit for 12 to 24 hours, which replaced the intensive care ward of the Myocardial Infarctions Unit. The foundation of RICU in 2006 allowed for the faster start and the increased volume of diagnostic and treatment care for ACS patients. RICU staff consists of cardiologists trained in resuscitation. The wards of RICU are spacially close and are connected to the interventional radiology operating room and the admission unit. The technique and the training of RICU medical staff provide the possibility of invasive haemodynamic monitoring in patients with ACS, the installation of the assisted circulation, the use of extrarenal homeostasis correction. Following the intensive care stage at RICU, the ACS patients continue their treatment at the Department of Acute Coronary Diseases. STEMI patients, who were admitted to the hospital lately (more than 12 hours after pain onset) also have the possibility to receive endovascular reperfusion, which is carried out with delay, at the stage of the Department of acute coronary diseases. In case when the endovascular procedure is impossible, in patients with multiple and critical coronary arteries impairment, the coronary bypass surgery is carried out at the hospital of the Cardiovascular Scientific Research Institute without discharge from the hospital. Following the in-patient treatment the patient is transferred to the rehabilitation unit, which is part of the KCC structure.

Economic aspects of the medical care for STEMI patients in the city of Kemerovo

The complex medical care provided in the Kuzbass Cardiology Center, is financed through the obligatory medical insurance system, regional and federal budget.

Treatment outcomes in STEMI patients in 2009 in the city of Kemerovo

In 2009, 308 primary PCIs in STEMI patients were performed in Kemerovo, amounting to 50% of the total number of patients with this disorder. The percentage of STEMI patients who underwent primary PCI, TLT or did not receive the reperfusion, was 50%, 13% and 37%, respectively. The "door-to-balloon" time was 75±20 minutes in average. The mortality of STEMI patients who received the primary PCI as a reperfusion therapy was 5.2%, while the total mortality in AMI patients was 12% (Tables 4, 5).

In 2009, the following target parameters according to the European standards were achieved in Kemerovo (Tables 2, 3):

1) Primary PCI was used in 50% of STEMI cases

2) The number of primary PCIs per 1 million of population was 616

3) Kemerovo has one PCI center with availability of primary PCI on "24/7" schedule. This center can cover the requirements of the city, but not of the entire Kemerovo Region with about 3-million population.

DISCUSSION

The formation of the national ACS registry and the implementation of the European standards of reperfusion treatment in STEMI patients in Russia represent significant difficulties related to geopolitical situation, geographic aspects and economic factors. However, the resolution of these problems is of particular importance due to a high morbidity and mortality in AMI patients which adversely affects the demographic situation in the Russian Federation (5).

Provided that the European standards of the treatment of STEMI patients (1, 2) are extrapolated to the Russian Federation, considering the population of 141,900,000, not less than 85,000 primary PCIs per year should be carried out. Considering the incidence of AMI, this number should be not less than 70,000. Thus, to meet the full requirements, 150 to 200 centers with primary PCI availability on "24/7" schedule are needed in the Russian Federation. According to B.G. Alekyan [9], in 2008 there were 96 centers in the territory of the Russian Federation, which performed only 13,000 PCIs in ACS patients, while the proportion of primary PCI in this number of procedures is unknown.

Realization of the goal of availability of primary PCI is possible in case of the close interaction between

the regulatory authorities at the regional and federal level, execution of the educational and informational campaigns for population through the mass media. Not only federal centers, which carry out primary PCI, but regional specialized medical institutions with potential of realization of such programs, as well, are of great importance for widening the use of reperfusion therapy in STEMI patients. Obviously, the Federal Program of optimization of medical care for patients with acute vascular diseases, which is currently implemented at the territory of the Russian Federation, will contribute to the achievement of these goals.

In Kemerovo, an exact algorithm for multiple-stage medical care for ACS patients is created and currently active. It provides the greater availability of primary PCI. Timely diagnosis at the ECS stage, urgent notification of the specialized center, prompt cooperation of the admission unit and radiology operating room reduce significantly the time of reperfusion. The "door-to-balloon" time in KCC is 75±20 minutes, resulting in a low mortality in the group of primary PCI.

The mortality in STEMI patients following primary PCI in 2009 was 5.2%; this is comparable to the outcomes of reperfusion in AMI in the EU countries (Table 4). Unhappily, relatively low rate of primary PCI (50%) in the total number of reperfusion procedures in AMI and rather high proportion of patients, who did not receive the reperfusion treatment (37%), result in high mortality (12%) in the total AMI group (Table 4).

Although one center is not sufficient to provide the optimal availability of reperfusion treatment to the population of the region, which is 2 mln 800 thousand persons, during the recent years several organizational measures aimed to improve the situation, were undertaken. In particular, in 2009 upon the initiative of the administration of Kemerovo Cardiology Center, the diagnostic and treatment department of interventional radiology was opened in Novokuznetsk on the basis of multi-field hospital. In 2010, this department will start its work within ACS setting. The mechanism of transportation of ACS patients with the use of air medical service in order to carry out urgent PCI between Kemerovo Cardiology Center and several hospitals in the districts of the region was developed.

The organizational technology of the "closed cycle" developed in Kemerovo Cardiology Center on the basis of the medical holding including the institutions of various forms of ownership, which provides the specialized medical care for AMI patients, is unique in Russia as well as in other European countries. This system allows to use all the potential of the center in the process of modern, high technology treatment of the patients, starting from the out-patient stage and ending by the specialized rehabilitation, on the basis of integrated treatment and diagnostic approaches.

CONCLUSIONS

1. In Russia, there is a reasonable need for further active promotion of the national program supporting primary PCI performing in STEMI patients.
2. The primary goals of the timely high technology medical care for STEMI patients include:
   - Qualification of the primary PCI as an absolute priority of reperfusion treatment in STEMI patients on the national health care system basis
   - Conformity to the target treatment outcomes in STEMI patients, developed by the European Association of Percutaneous Cardiovascular Interventions,
3. «Closed cycle» technology, developed and introduced in Kuzbass Cardiology Center, may be used as a basis in the development of the organizational model of available reperfusion therapy for STEMI patients in Russia.

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Predictors of In-Hospital Mortality in Patients with Acute Myocardial Infarction at the Heart Surgery Hospital

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While the modern heart surgery hospitals possess a diverse arsenal of methods for effective reperfusion and revascularization for patients with AMI (TLT, PCI, CABG), the mortality in these disorders is still high and sometimes exceeds 10%. The analysis of predictors of in-hospital mortality can facilitate improvement of organization of reperfusion treatment, selection of the optimal method of myocardial revascularization, and adjustment of treatment strategies and technique of surgical and endovascular methods in the assessment of causes of death in patients with AMI. This study concerns the demonstration of demographic, clinical, and angiographic predictors of in-hospital mortality in patients with AMI at the heart surgery clinic of Kuzbass Cardiac Center.

Keywords: *acute myocardial infarction, in-hospital mortality , myocardial revascularization, predictors.*

Objective: To demonstrate the predictors of in-hospital mortality in patients with acute myocardial infarction (AMI) in the setting of a heart surgery clinic.

Background:

Percutaneous coronary interventions (PCI) became an important component of treatment in acute forms of coronary heart disease. In AMI patients, particularly with ST-segment elevation myocardial infarction (STEMI), coronary stenting is a life-saving procedure. Unfortunately, even in the cohort of AMI patients, who were admitted to the heart surgery clinics with all methods of revascularization available (thrombolytic therapy [TLT], percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery), in-hospital mortality can exceed 10%. In spite of the importance of this problem, very limited information is available in the literature on such an aspect as predictors of in-hospital mortality in patients with AMI in modern heart surgery clinics.

Conclusion.

Based on the data provided in this study, the following parameters can be considered as predictors of in-hospital mortality in patients with AMI admitted to the heart surgery clinic:

1. Demographic factors: age above 70 years; female gender.
2. Clinical factors: time delay more than 12 hours from the onset of symptoms until hospital admission; history of myocardial infarction; recurrent AMI; diabetes mellitus; chronic left ventricular aneurism (LVA); left ventricular ejection fraction (LVEF) < 40%; severe acute heart failure (AHF) (Killip III-IV), chronic renal failure (CRF); non-performance of coronarography (CG) and PCI following hospital admission.
3. Angiographic factors: significant stenosis of the left main coronary artery combined with three-vessel coronary lesion (LMCA +3), impossibility of exact determination of the infarct-related artery (IRA).
4. PCI-related factors: unsuccessful intervention, circulatory arrest during intervention, «no-reflow» phenomenon during PCI.

Abbreviations

AH – arterial hypertension
LVA – left ventricular aneurysm
IABP – intra-aortic balloon pumping
CI – confidence interval
NSTEMI – non-ST-segment elevation myocardial infarction
IRA – infarct-related artery
STEMI – ST-segment elevated myocardial infarction
CG – coronarography
CABG – coronary artery bypass graft surgery
AMI – acute myocardial infarction
ACS – acute coronary syndrome
AHF – acute heart failure
OR – odds ratio
EMS – Emergency Medical Service
LMCA+3 – left main coronary artery lesion combined with three-vessel lesion
TLT – thrombolytic therapy
LVEF – left ventricular ejection fraction
CRF – chronic renal failure
PCI – percutaneous coronary intervention
ECG – electrocardiogram

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INTRODUCTION

The problem of treatment of AMI patients is still actual worldwide, despite improvement of organization, therapeutic, endovascular, and surgical approaches aimed at its solution. In Russia, the problem of AMI-related mortality has recently reached a catastrophic scale. In several well-equipped hospitals of the Russian Federation the in-hospital mortality reduced to 10-13%, while the average national mortality remains at the level of 17% to 27% (1). These data suggest the relevance of the problem of treatment of AMI patients.

Considerable part of literature on the in-hospital outcomes in AMI patients concerns the analysis of demographical and clinical factors that influence the short-term prognosis (2-16). However, the problem of determination of the predictors of in-hospital mortality in AMI patients in modern heart surgery clinics, which possess a complete set of interventional and surgical techniques of revascularization, is not resolved to date. The aim of this study was to reveal and review the complex of clinical, demographic, and angiographic predictors of in-hospital mortality in patients with AMI in a modern heart surgery clinic, as exemplified by the Kuzbass Cardiac Center.

MATERIAL AND METHODS

In 2009, 1008 patients with AMI were treated at the Kuzbass Cardiac Center: 716 patients (71%) with STEMI and 292 (29%) with NSTEMI. Mortality in the combined group of AMI patients was 12% (121 patients). All patients who died in the hospital during the year 2009, were included into Group 1 (n=121). Group 2 included 75 consecutive patients who underwent in-hospital treatment for AMI and were discharged from the hospital. The comparison of the study groups was performed on the base of the main demographic (sex, age) and clinical (time delay from the onset of the disease until the hospital admission, performance of CG and PCI following hospitalization, severity of AHF, history of myocardial infarction, recurrent AMI, presence of LVA, value of LVEF, diabetes mellitus, residual acute cerebrovascular accident, Leriche syndrome, CRF, AH, history of myocardial revascularization, ultrasound cardiac chamber dimensions, use of IABP) parameters.

A separate angiography analysis was performed in the group of patients who died (n=34) and in control patients (n=75). The angiography subgroups included all patients of the control group (i.e. in Group 2 coronarography was carried out in 100% of patients), while in Group 1 CG was performed only in 28% of cases (n=34). CG in Group 1 was not performed due to the following reasons:

1. Patient's death before CG (6%, n=7).
2. Late admission (> 12 hours) without severe AHF (6%; n=7).
3. Severe concomitant diseases (6%; n=7).
4. Age older than 75 years (49.6%; n=60).
5. Patient's refusal (0.8%; n=1).

During angiography analysis the subgroup comparison of the following parameters was performed: pattern of the coronary vessel lesions (one-, two-, three-vessel, LMCA+1, LMCA+2, LMCA+3), possibility of IRA determination and type of IRA.

A separate analysis of reperfusion approaches, PCI peculiar features and complications was carried out. The subgroups submitted to this analysis included patients who underwent PCI. The following parameters of patients who died (n=25) and control patients (n=61) were compared within the PCI subgroup: success of intervention, circulatory arrest during intervention, "no-reflow" phenomenon during PCI, stent thrombosis, and coronary artery dissection.

The determination of prognostic factors of the fatal outcome was based on the demographic, clinical, angiography and interventional (PCI) comparison of studied groups and subgroups. The discrete variables were presented as median and the continuous variables were presented as mean ± standard deviation. Qualitative parameters were compared with the use of X^2 test. In case of normal distribution, univariate analysis of variance (ANOVA) was used for primary data comparison between groups. $P<0.05$ indicated the statistical significance. To reveal predictors of in-hospital mortality multiple logistic regression analysis was used. Analysis results for each significant variable were characterized by the relative risk (RR), odds ratio (OR) and 95% confidence interval (CI). Study results were processed with the use of Statistica for Windows 5.0 (StatSoft Inc., USA) software package.

RESULTS

Results of analysis of demographic and clinical parameters

The mean age of patients who died (Group 1) was 73±10.9 years, in the control group (Group 2) 58±9 years ($p<0.05$). 86 from the Group 1 patients were older than 70 years (71%), in Group 2 only 11 patients were older than 70 years (OR 14.3; 95% CI) In Group 1 women predominated (58%; n=71), while in Group 2 the proportion of women was much lower (29%; n=22) ($p<0.05$) (OR 3.6; 95% CI). 77.3% of patients who died were admitted more than 12 hours after the onset of symptoms, while in the group of surviving patients only 28.1% were admitted more than 12 hours after the onset of disease ($p<0.05$; OR 1.8; 95% CI). 29% of patients in Group 1 were admitted with severe acute heart failure (AHF) (Killip III-IV), while in Group 2 the proportion of patients with severe AHF was much lower: 4% (n=3) ($p<0.05$; OR 9.7; 95% CI). The recurrent AMI was diagnosed in 51% of patients in Group 1 (n=62) and in 13% of patients (n=10) in Group 2 ($p<0.05$; OR 6.9; 95% CI). 42% (n=51) of patients in Group 1 and 17% (n=13) of patients in Group 2 had the history of myocardial infarction ($p<0.05$; OR 3.5; 95% CI). The mean value of left ventricular ejection fraction in Group 1 was 38.5±12.2%, in Group 2 – 54±21.9% ($p<0.05$), with

LVEF < 40% in 67 patients (55%) of the Group 1 and only in 8 patients (10.6%) of the Group 2 (OR 10.4; 95% CI) (Table 1 and Table 1.1).

Diabetes mellitus was diagnosed in 32% of patients (n=39) and 5.3% (n=4) in Groups 1 and 2, respectively (p<0.05; OR 8.5; 95% CI). Chronic left ventricular aneurysm (LVA) was revealed in 13% (n=15) of patients in Group 1 and in 2.6% (n=2) in Group 2, respectively (p<0.05; OR 5.6; 95% CI). CRF was reported in 15% and 2.7% of patients in Groups 1 and 2, respectively (p<0.05; OR 4.1; 95% CI). Residual signs of the acute cerebrovascular accident and Leriche syndrome occurred in 15% (n=18) and 9 (n=11) patients in Group 1. In Group 2 these disorders were present in 6.7% (n=5) and 4% (n=3) of cases, respectively (p>0.05). The comparison of the following clinical, angiographic and procedural parameters of Groups 1 and 2, respectively: arterial hypertension (98% vs. 83%), history of myocardial revascularization (7.44% vs. 4%), cardiac chambers dimensions (as per ultrasound examination) (end-diastolic diameter [EDD] 98±0.92 cm vs. 5.74±0.56 cm, end-systolic diameter [ESD] 4.8±1.02 vs. 4.18±0.7 cm), IABP use (4% vs. 1.33%) (p>0.05) did not reveal statistically significant differences between the groups (Tables 1 and 1.1)

Table 1. Comparison of the main demographic and clinical parameters in study groups.

Parameter	Group 1 (n=121)		Group 2 (n=75)		p
	абс.	%	абс.	%	
Age, years	73,1±10,9		58,45±9,1		<0.05
Females	71	58	22	29	<0.05
NSTEMI	32	26,5	23	31	NS
STEMI	89	73,5	52	69	NS
< 12 hours from the onset of disease	34	28,1	58	77,3	<0.05
AHF (Killip III-IV)	35	29	3	4	<0.05
IABP use	5	4	1	1,33	NS
Relapsed AMI	62	51	10	13	<0.05
Diabetes mellitus	39	32	4	5,3	<0.05
Arterial hypertension	119	98	62	83	NS
Ejection fraction (Echo-CG)	38,5±12,2		54±21,9		<0.05
EDD, cm	5,98±0,92		5,74±0,56		NS
ESD, cm	4,8±1,02		4,18±0,7		NS
Chronic renal failure	12	15	2	2,7	<0.05
History of myocardial infarction	51	42	13	17	<0.05
Residual signs of the acute cerebrovascular accident	12	15	5	6,7	NS
History of myocardial revascularization	9	7,44	3	4	NS
Leriche's syndrome	11	9	3	4	NS
Left ventricular aneurysm	16	13	2	2,7	<0.05

Table 1.1 . Significant clinical and demographic risk factors of in-hospital mortality in patients with acute myocardial infarction.

Parameter	OR (95% CI)
Age over 70 years	14.3
Females	3.6
More than 12 hours until the hospital admission	1.8
AHF (Killip III-IV)	9.7
Relapsed myocardial infarction	6.9
Diabetes mellitus	8.5
LVEF < 40%	10.4
Chronic renal failure	4.1
History of myocardial infarction	3.5
Left ventricular aneurysm	5.6

Results of the analysis of angiographic parameters, reperfusion approaches, peculiar features and complications of PCI in Group 1

Subgroup A of the Group 1 included patients who underwent CG. The comparison of angiographic parameters of this subgroup with Group 2 was carried out. One-vessel lesion of coronary arteries in subgroup A was revealed in 21% of patients (n=7); two-vessel lesion, in 18% (n=6); three-vessel lesion, in 35% (n=12); LMCA combined with one-vessel lesion (LMCA+1) and LMCA+2, in 3% each (n=1); LMCA+3, in 21% (n=7) (Table 2 and Table 3.1).

PCI was carried out in 25 patients of Group 1 (21%). In 48% of patients (n=12) the intervention was performed with the use of IABP. In seven patients (6%) PCI was not performed due to the multiple lesions of coronary vessels and/or technical infeasibility intervention (these patients were scheduled for urgent coronary bypass surgery). It should be noted that in 18 patients there were problems with determination of the infarct-related artery, while in 8 cases IRA was determined as left anterior descending artery (LAD), in 6 cases as right coronary artery (RCA), in 2 cases as circumflex artery (CxA) (Table 2). PCI was unsuccessful in 36% of patients in Group 1 (n=9). When considering only successful PCIs, the mean number of stents implanted per one patient was 1.5. The mean stent length was 23±6 mm, the mean diameter 3.2±0.5 mm (Table 3). In subgroup 1 of the Group 1 PCIs were accompanied by the following complications:

1.Patient's death during intervention (16%; n=4).
2.«No-reflow» syndrome (16%; n=4).
3.Coronary artery perforation (4%; n=1).
4.Stent thrombosis (4%; n=1).

Results of the analysis of angiographic parameters, reperfusion approaches, peculiar features and complications of PCI in Group 2

One-vessel lesion of the coronary arteries was revealed in 49% of patients (n=37); two-vessel lesion, in 23% (n=17); three-vessel lesion, in 21% (n=16); LMCA+3, in 3% (n=2). In three patients (4%) no morphological lesions of coronary arteries were

Table 2. Comparison of angiographic parameters between study groups.

Признак	Group 1 (n=34)		Group 2 (n=75)		p
	Abs.	%	Abs.	%	
Proportion of cases with CG carried out	34	28	75	100	<0.05
One-vessel lesion	7	21	37	49	NS
Two-vessel lesion	6	18	17	23	NS
Three-vessel lesion	12	35	16	21	NS
LMCA+1	1	3	0	0	NS
LMCA+2	1	3	0	0	NS
LMCA+3	7	21	2	3	<0.05
No lesions of coronary vessels	0	0	3	4	NS
IRA not determined	18	53	11	15	<0.05

Table 3. Comparison of PCI outcomes and complications between study groups.

Parameter	Group 1 (n=25)		Group 2 (n=61)		p
	Abs.	%	Abs.	%	
Unsuccessful PCI	9	36	3	5	<0.05
IRA could not be exactly determined	13	53	9	15	<0.05
No technical conditions for PCI	1	4	5	9	NS
Mean stent diameter, mm	3,2±0,5		3,17±0,42		NS
Stent thrombosis	1	4	0	0	NS
Coronary artery dissection	0	0	2	3	NS
Coronary artery perforation	1	4	0	0	NS
"No-reflow" syndrome	4	16	0	0	<0.05
Circulation arrest during PCI	4	16	0	0	<0.05

Table 3.1. Significant angiographic and procedure (PCI)-related risk factors of in-hospital mortality in patients with acute myocardial infarction.

Parameter	OR (95% CI)
LMCA+3 lesion	9.6
IRA not determined	6.5
Unsuccessful PCI	11.02

revealed. PCI was carried out in 61 patients of Group 2 (81%). In 5% of patients in Group 2 (n=4) PCI was unsuccessful. In seven patients (9%) the urgent coronary bypass surgery was scheduled. In 11 patients (14.6%) the infarct-related artery could not be determined, while in 29 cases IRA was determined as LAD, in 21 case as RCA, in 12 cases as CxA. In two cases (3%) stents were implanted in two vessels (LAD and CA). When considering only successful PCI, the mean number of stents implanted per one patient was 1.12. The mean stent length was 20.4±6 mm, the mean diameter 3.17±0.42 mm. In Group 2 PCI was complicated by coronary artery dissection in two cases (3%). Due to this complication the additional stents were implanted.

Comparison of angiographic and PCI parameters in Subgroup A of Group 1 and Group 2

It should be noted that the proportion of patients in Group 1 who underwent CG was significantly lower than in Group 2: 28% vs. 100%, respectively ($p<0.05$) (Table 2). The proportion of patients who underwent PCI in Group 1 and Group 2 considerably differed (21% and 81%, respectively [$p<0.05$]) (Table 3). During the analysis of PCI-related parameters the significant differences in the proportion of patients with LMCA+3 were revealed: 21% vs. 3% in Group 1 and Group 2, respectively ($p<0.05$; OR 9.6; 95% CI). IRA could not be determined in 53% and 15% of patients in Group 1 and Group 2, respectively ($p<0.05$; OR 6.5; 95% CI) (Table 2 and Table 3.1). The proportion of unsuccessful PCIs was 36% and 4% in Groups 1 and 2, respectively ($p<0.05$; OR 11.02; 95% CI). "No-reflow" phenomenon developed in 16% and 0% of patients in Groups 1 and 2, respectively ($p<0.05$) (Table 3). Circulation arrest during intervention ocurred significantly more often in patients of Group 1 (who died in course of hospitalization), compared with patients of Group 2 (16% vs. 0%, respectively) ($p<0.05$) (Table 3). No other significant differences between the study groups were revealed (Table 2, Table 3).

DISCUSSION

According to the literature, the main demographic predictors of in-hospital mortality in patients with AMI include: age older than 65-70 years (2-5) and female gender (7-11). This is due to the fact that AMI in women frequently occurs in advanced age, women are more predisposed to diabetes mellitus, and the treatment of women is often less aggressive compared with men. These data were confirmed in our study: the mean age of patients who died was 73.1±10.9 years, while in the group of survived, 58.2±9 ($p<0.05$). We also are prone to consider the female gender and age older than 70 years as demographic predictors of in-hospital mortality in AMI patients (Tables 1 and 1.1). The patient's age is most probably not only an independent predictor of AMI mortality, but is associated with an organization aspect, such as adherence to conservative treatment in patients older than 70-75 years. It results in low availability of endovascular or surgical revascularization for AMI patients of this category in many heart surgery clinics. Our analysis clearly demonstrated this situation: in the group of patients who died (n=121) with the mean age of 73.1±10.9 years, CG was performed in only 28% of patients (n=34) and PCI, in only 21% (n=25). The proportion of patients who underwent PCI in Group 1 and Group 2 also differed: 21% and 81%, respectively ($p<0.05$) (Tables 3 and 3.1). It should be mentioned that, besides age limitations of active endovascular or surgical strategy of patients' management, a high percentage of patients admitted more than 12 hours after the onset of symptoms (35%) and the proportion of patients with severe concomitant diseases (including cancer) (6%) remain a serious problem.

The time delay between the onset of symptoms and hospital admission more than 12 hours became one of the most significant predictors of in-hospital mortality : 77.3% vs. 28.1% in Group 1 and Group 2, respectively ($p<0.05$; OR 1.8; 95% CI). These results are quite consistent with literature data and closely associated with the volume of viable myocardium, contractility function of the left ventricle, severity of AHF, and possibility of the primary PCI.

Diabetes mellitus, often with concomitant multiple coronary vessels lesions, lipid disorders, and chronic kidney disease, is mentioned in the literature among clinical predictors of in-hospital mortality in AMI patients (6, 15, 16). Our study also confirmed this fact: the proportion of patients with diabetes mellitus in the group of patients who died was 32% (n=39), while in the control group it was 5.3% (n=4) ($p<0.05$; OR 8.5; 95% CI). In our study, there was a significant difference in the proportion of patients with CRF: 15% in the group of patients who died vs. 2.7% in the group of survived ($p<0.05$; OR 4.1; 95% CI) (Tables 1 and 1.1).

Other clinical predictors of the adverse in-hospital outcome, revealed in our study, included severe AHF (Killip III-IV) and poor contractile function of the left ventricle (Tables 1 and 1.1). The proportion of patients of Group 1 (who died) with signs of cardiogenic shock or pulmonary edema on admission was 29% (n=35), while in the control group, only 4% (n=3) ($p<0.05$; OR 9.7; 95% CI). The mean LVEF in the group of patients who died was 38.5±12.2%, compared with 54±21.9% in the control group ($p<0.05$). LVEF less than 40% was observed in 67 patients (55%) of Group 1 and only in 8 patients (10.6%) of Group 2 (OR 10.4; 95% CI). This characteristic is consistent with the data on the extent and depth of myocardial necrosis and is associated with relapsing course of AMI (51%, n=62 in Group 1 vs. 13% [n=10] in Group 2 [$p<0.05$]) and with the history of AMI (42%, n=51 in Group 1 vs. 17%, n=13 in Group 2 [$p<0.05$; OR 3.5; 95% CI]).

One of the principal distinctions of our study from the previously published similar data consists in the integrated approach to the analysis of in-hospital mortality in patients admitted to heart surgery hospitals. Most studies concerned the clinical predictors (1-11), while we tried to emphasize both the angiographic parameters and the factors associated with the availability of reperfusion treatment, particularly PCI. What stands out in our study is a very high proportion of unsuccessful PCIs in the group of patients who died (36%, n=9), compared with 5% (n=4) in the control group ($p<0.05$; OR 11.02; 95% CI). This fact can be partly explained by the severity of coronary lesions, manifested in multiple diffuse occlusive / stenotic lesions of coronary vessels, frequently associated with a certain degree of coronary calcification. In our study, in contrast to the literature data, the impossibility of exact determination of IRA was a significant predictor of in-hospital mortality due to AMI (53%, n=18 in Group 1 vs. 15%, n=11 in Group 2) ($p<0.05$; OR 6.5; 95% CI) (Tables 2 and 3.1). This situation generally occurred in cases of AMI without ST-segment elevated, in multiple significant coronary vessels lesions, and was frequently associated with technical infeasibility of PCI or reasonable indications for CABG.

Our analysis, in contrast to the previous studies, has revealed the lesion LMCA+3 (21% among patients who died vs. 3% in the group of survived patients) ($p<0.05$; OR 9.6; 95% CI) as a predictor of in-hospital mortality in patients admitted to the heart surgery clinic. This result intrinsically confirmed the fact that in patients with such coronarography characteristics CABG surgery is probably the optimal method of revascularization, as was shown in SYNTAX study for elective patients (19).

Our study made a special emphasis on the analysis of PCI complications, which were not adequately discussed in the modern literature. In our work, we revealed certain predictors of mortality associated with PCI complications, such as circulatory arrest during the intervention (16%, n=4) and «no-reflow» syndrome (16%, n=4), that were undoubtedly due to the extent of myocardial lesion, impaired local and global myocardial contractility, and severity of AHF. However, no significant differences were demonstrated in such PCI complications as stent thrombosis, dissection and perforation of coronary arteries (Table 3). Therefore, «no-reflow» phenomenon in IRA, frequently resulting from the massive thrombus, along with non-performed or unsuccessful PCI (appearing as TIMI 0 flow in IRA), represent very important predictors of in-hospital mortality in our analysis.

CONCLUSIONS

Based on the data provided in this study, the following parameters can be considered as predictors of in-hospital mortality in patients with AMI admitted to the heart surgery clinic:

1. Demographic factors: age above 70 years; female gender.
2. Clinical factors: time delay more than 12 hours from the onset of symptoms until hospital admission; previous myocardial infarction; relapsed AMI; diabetes mellitus; chronic left ventricular aneurism (LVA); left ventricular ejection fraction (LVEF) < 40%; severe acute heart failure (AHF) (Killip III-IV), chronic renal failure (CRF); non-performance of coronarography (CG) and PCI following hospital admission.
3. Angiographic factors: hemodynamically significant stenosis of LMCA+3, impossibility of the exact IRA determination.
4. PCI-related factors: unsuccessful intervention, circulatory arrest during intervention, «no-reflow» phenomenon during PCI.

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Endovascular Diagnostics and Treatment of Occlusive-Stenotic Lesions of the Unpaired Visceral Branches of the Abdominal Aorta.

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The article describes the results of examining patients with clinical manifestations of chronic abdominal ischemic syndrome, mainly caused by stenosis of the celiac trunk. The frequency and causes of visceral branches lesions were investigated. The structure of surgical correction methods in patients with chronic abdominal ischemia is shown. Short-term and long-term results of percutaneous endovascular angioplasty of the celiac trunk are presented. Clinical cases are presented.

Key words: *chronic abdominal ischemic syndrome, celiac trunk, superior mesenteric artery.*

Introduction: Syndrome of chronic abdominal ischemia (CAI) implies the insufficiency of digestive organs blood supply caused by lesions of the visceral branches of the abdominal aorta (1). The main causes of digestive organs ischemia are both intravascular (atherosclerosis, fibromuscular dysplasia, etc.) and extravascular (extravasal) factors (1, 2, 3).

Over the last four decades a certain experience was accumulated in diagnostics and treatment of disturbances in visceral territory blood supply. And though more than 150 years have passed since the first report about chronic occlusion of SMA (4) and 50 years since its successful reconstruction (5), this problem is far from its final settlement. It is explained by the rather low CAI incidence – in 3.2 % patients treated for chronic diseases of digestive organs in therapeutic departments (6, 7), the absence of pathognomonic CAI symptoms (1, 2, 3), and also the lack of physicians' awareness about this pathology. Development and implementation of contrast methods of investigation became the turning point in studying occlusive lesions of visceral branches. In 1959, stenosis of superior mesenteric artery was revealed and CAI was diagnosed for the first time with the help of angiography (8). Percutaneous endovascular angioplasty (PEA) has opened great opportunities for blood flow restoration in visceral branches due to its less traumatic effect, less blood loss, shortening of in-hospital stay compared with conventional surgical methods of treatment. During the last years the usage of PEA with stenting has contributed to a considerable increase of this method efficacy in patients with atherosclerotic lesions of visceral arteries (9, 10, 11, 12). This report describes our experience with endovascular diagnostics and treatment of occlusive-stenotic lesions of visceral arteries.

Material and methods: Endovascular investigations were performed in patients using the generally adopted method. Patient was prescribed antiaggregants (aspirin) in small doses 2-3 days before the investigation. The day before and on the day of surgery the ordinary preoperative management was conducted: purgative enema, shower, shaving of the operative site. Twenty–thirty minutes before the investigation 2 ml of 2% promedol solution and 1 ml of 1% dimedrol solution were administered subcutaneously.

Angiographic examination was performed in all patients on "Advantix LCV" (by "General Electric", USA) and "Alura Xper FD 10" (by "Philips", Holland) angiographic installations using digital subtraction technique of image processing. Contrast iodine-containing media "Omnipaque" ("Nicomed", Norway) were used, the contrast medium was administered by the automatic injector Angiomat Illumena. The image-taking speed varied from 1.3 to 8.3 shots per second. Standard angiographic investigation was performed in anteroposterior and lateral projections during the angiography of the terminal part of aorta. Images were registered on the hard disk after the digital processing that helped to evaluate peculiarities of the blood flow over time directly on the monitor, to examine static x-ray image later on, and to facilitate the archiving process. Endovascular interventions were performed via axillary and femoral approach by Seldinger technique. Further aortography in anterioposterior and lateral projections was performed with Cobra, Simmons, and Judkins catheters.

We analyzed 1848 initial aortographies made in the Center of endovascular surgery of A. A. Vishnevsky Central Military Clinical Hospital N 3 during 8 years. Lesions of visceral branches of the abdominal aorta, mainly the celiac trunk and its branches, were revealed in 136 (7.4%) examined patients (Table 1).

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Table 1. Lesion localization and degree of visceral artery stenosis according to the aortography results.

Stenosis degree	TC	SMA	IMA	TC+SMA	TC+ SMA+ IMA	CHA	SLA	LGA	Total
I	27	6		7			2		42
II	32	8		5		1			46
III	21	3	1	4		2	2	1	34
Occlusion	6	1	1	3	2	1			14
Total	86	18	2	19	2	4	4	1	136

TC – the celiac trunk; SMA – superior mesenteric artery; IMA – inferior mesenteric artery; CHA – common hepatic artery; A –splenic artery; LGA – left gastric artery.

At the same time 83 patients (61%) (mean age 64.1± 9.3) had radiographic signs of intravascular lesion of visceral arteries and 53 patients (39%) (mean age 42.9 ± 15.6) had extravascular lesions. Degree I stenosis was seen significantly more often in patients with intravascular lesions (30 patients, 36.1%) than in patients with extravascular lesions (12 patients, 22.6%) ($p<0.05$) (Table 2)

Table 2. Causes of lesions and degree of visceral arteries stenosis according to the aortography results

Stenosis degree	Intravascular stenosis (n=83)		Extravascular stenosis (n=53)		Total (n=136)
	N	%	N	%	
I	30	36.1	12	22.6	42(30,9%)
II	20	24.1	26	49.1	46(33.8%)
III	22	26.5	12	22.6	34(25%)
Occlusion	11	13.3	3	5.7	14(10.3%)

Further analysis of CAI causes with regard to the clinical stage in patients with hemodynamically significant stenosis showed that compensation stage was more often revealed in patients with intravascular stenosis, and decompensation stage, in patients with extravascular stenosis (Table 3).

Table 3. Causes of visceral arteries lesions according to the aortography results and clinical stages of CAI in patients with hemodynamically significant stenosis.

Stage	Intravascular stenosis (n=53)		Extravascular stenosis (n=41)		p
	N	%	N	%	
Compensation	15	28,3	1	2,4	p<0,01
Subcompensation	33	62,3	29	70,8	p>0,05
Decompensation	5	9,4	11	26,8	p<0,01

Endovascular angioplasty and stenting were performed via axillary and femoral approaches. After angioplasty and stenting, the control angiography was obligatory for documenting results, defining degree of residual stenosis, and revealing possible complications (intima detachment, embolism, or thrombosis). Compressing bandage was applied at the puncture area, and after that the patient was prescribed 24-hours bed rest, a lot of beverages (up to 2 liters), bandage monitoring (after the diagnostic procedure); Fraxiparin 0.3 twice a day, Aspirin 125.0 mg once a day, Plavix 75 mg a day were prescribed after angioplasty with stenting.

STUDY RESULTS

Percutaneous endovascular angioplasty, which is a promising treatment method for occlusive-stenotic lesion of abdominal aorta visceral arteries, was performed in 11 cases in 10 patients.

Angioplasty with stenting makes 18.6% in the structure of performed operations on visceral branches of abdominal aorta (Figure 1).

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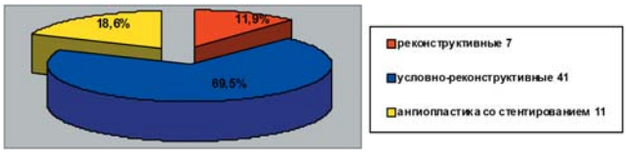
Fig. 1. The structure of surgical correction methods in patients with chronic abdominal ischemia.



More commonly angioplasty and stenting were performed for atherosclerotic lesion of the celiac trunk (Table 4).

Table 4. Reasons for performing percutaneous endovascular angioplasty and stenting.

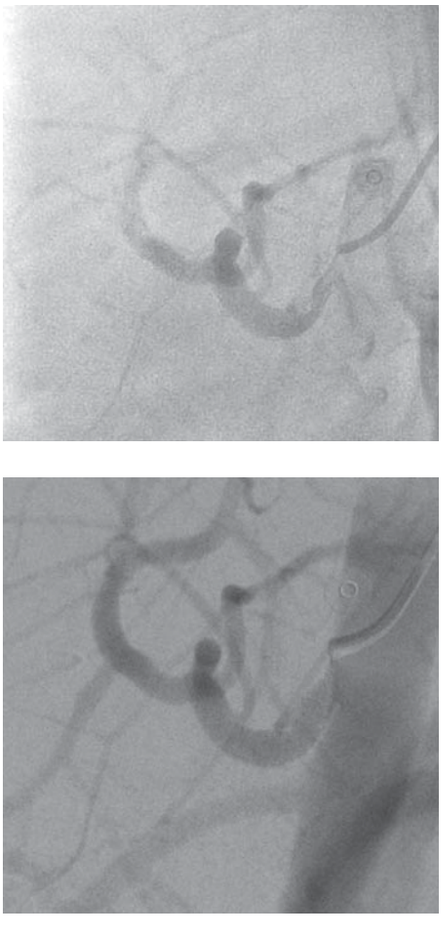
Reasons:	N
Intravascular reasons:	**8**
Atherosclerosis	8
Extravascular reasons:	**3**
Celiac ganglion, sickle-shaped ligament	2
Cancer of the pancreas head	1
Total:	**11**

Treatment results were evaluated on the base of clinical data and also on the results of instrumental methods of investigation (color duplex scanning of visceral arteries, CT-angiography). The immediate results of treatment were evaluated at the moment of discharging the patient from the hospital and in the long-term - 6 months and later. The immediate positive results of treatment were observed in 9 patients (81.8%). In two cases (20%) thrombosis of the the celiac trunk after balloon dilatation and stent migration to the aorta occurred. In both cases other methods of surgical correction were used. In the long-term abdominal pain and intestine dysfunction disappeared or considerably reduced in most of the patients, body weight has stabilized. Thus, good and satisfactory results were obtained in 7 patients (77.8%). Two patients (22.2%) had in-stent stenosis.

Clinical case # 1:

Patient N., born in 1955, case history # 17,981, was admitted to the A. A. Vishnevsky Central Military Clinical Hospital N 3 on September 9th, 2007. On admission he complained of the abdominal pain increasing after eating. According to the case history, the patient suffers from multifocal atherosclerosis for a long time and he had MI in 1996 and 1998. In 1997 the following surgical interventions were performed: aortocoronary bypass graft in the circumflex artery and right coronary artery, and mammary-coronary artery bypass with left anterior descending artery (LDA). In 2007 balloon angioplasty with stenting of the LDA was performed. During the last 3 years patient has suffered from the pain in epigastrium associated with eating; chronic ulcers of stomach and duodenum were diagnosed. Taking into consideration the complaints, the history of multifocal atherosclerosis, and systolic murmur in the projection of the celiac trunk, the CAI syndrome was suspected and confirmed by the aortography results. Due to the nearly 80% stenosis of the proximal third of the celiac trunk, MULTI-LINK ULTRA 5.0 * 28 mm stent was implanted into the stenotic area via direct stenting (double balloon dilatation , pressure 12-16 atm, duration 20 sec). Control angiogram confirmed the liquidation of stenosis (Figure 2 and 3).

Fig. 2 and 3. Patient N., 52 years old, 21.11.2007, case history # 17,981. Condition before and after direct stenting of the celiac trunk.



Clinical case # 2:

Patient B., born in 1941, case history # 11,641, was admitted to the A. A. Vishnevsky Central Military Clinical Hospital N3 on May 11th, 2009. On admission he complained of abdominal pain increasing after eating, and body weight loss. According to his history data, the patient has suffered from multifocal atherosclerosis for a long time. During the last 5 years the patient has suffered from the pain in epigastrium associated with eating; that was the reason why he was stinting himself in food. He reports progressive body weight decrease by 6 kg during the last 2 years. On admission, height 176 cm, weight 64 kg. Taking into consideration the complaints, the history of multifocal atherosclerosis, and systolic murmur in the projection of the celiac trunk, the CAI syndrome was suspected and confirmed by the aortography results and CT-angiography. Due to the nearly 75% stenosis of the proximal third of celiac trunk , the BALTON NEFRO 7.0 * 1.8 mm stent was implanted into the stenotic area via direct stenting (single balloon dilatation , pressure 15 atm, time 35 sec). Control angiogram confirmed the resolution of stenosis (Figure 4 and 5).

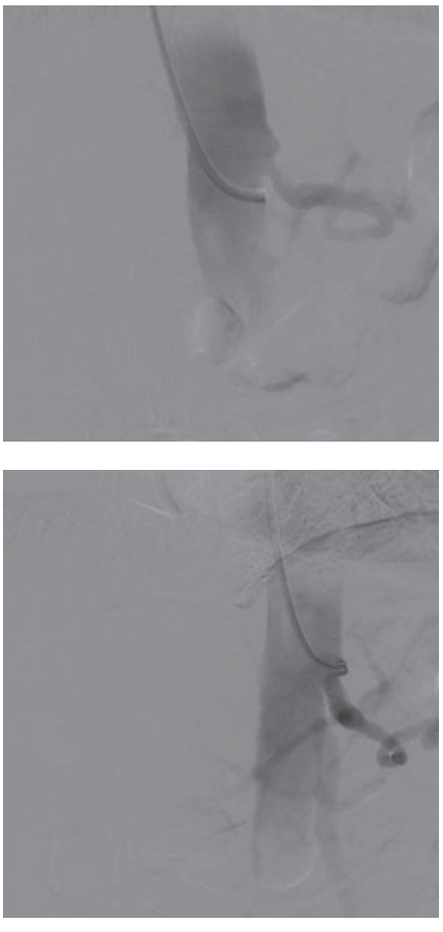


Fig. 4 and 5. Patient B., case history # 11,641. Condition before and after direct stenting of the celiac trunk.

At the follow-up examination significant improvement of general condition was observed: abdominal pain completely stopped and the patient gained 5 kg in 6 months. The patient received conservative treat-

ment that included enzyme drugs, statins, aspirin, and clopidogrel. Positive results of treatment were confirmed by instrumental investigations (Figure 6 and 7).

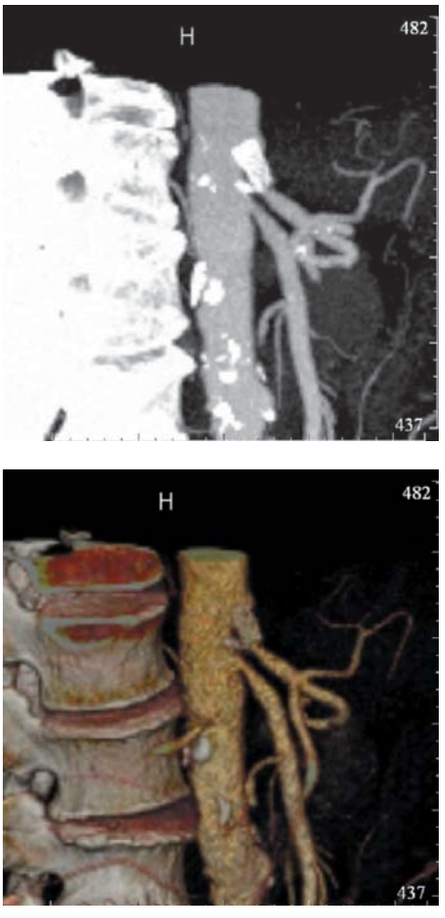


Fig. 6 and 7. CT-angiography of the patient B., 6.10.2009, case history # 23,478. Condition after stenting of the celiac trunk, its lumen is patent, stenosis up to 50% is more distal than the stent, stenosis of superior mesenteric artery ostium is 40%.

Clinical case # 3

Patient Yu., born in 1937, case history # 12,675, was admitted to the A. A. Vishnevsky Central Military Clinical Hospital N3 on June 27th, 2009. On admission he complained of the pain in upper parts of the abdomen increasing after eating and during the nighttime. The analysis of his history case revealed that the patient suffers from the abdominal pain for two years. Stomach ulcer, chronic gastroduodenitis, and gastroesophageal reflux were diagnosed. In addition, the patient suffers from the multifocal atherosclerosis and atherosclerotic infrarenal aneurism of the abdominal aorta. Taking into consideration the complaints, the history of multifocal atherosclerosis, and systolic murmur in the projection of the celiac trunk, the CAI syndrome was suspected and confirmed by the aortography results. Therefore, the direct stenting surgery of the celiac trunk was performed. Genesis stent (6 * 18 mm) was implanted into the stenotic area and proximal third of the celiac trunk via double balloon dilatation (pressure 14-18 atm, duration 15-20 sec), the artery lumen was restored (Figure 8 and 9).

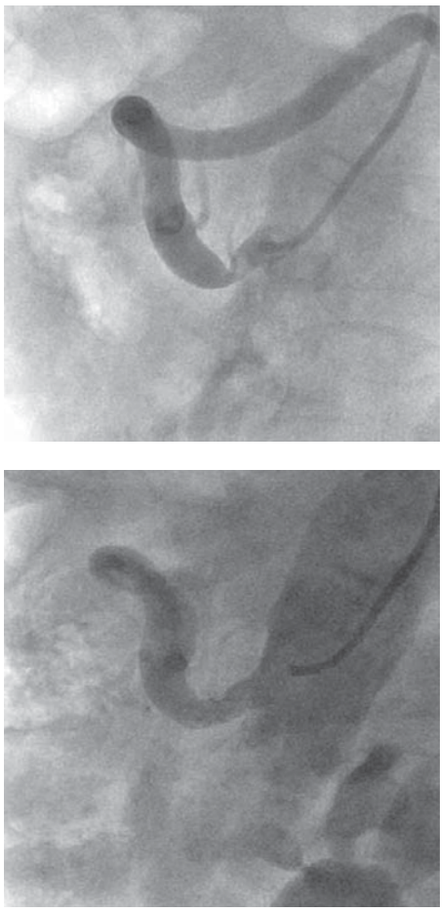


Fig. 8 and 9. Patient Yu., case history # 12675. Condition before and after direct stenting of the celiac trunk.

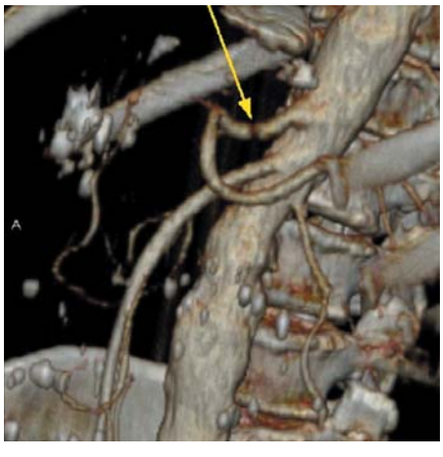


Fig. 10. CT-angiography of the patient Yu., 12.08.2008, case history # 16,908. Subtotal stenosis at the level of the distal part of the celiac trunk stent.

After the procedure the patient's condition improved, abdominal pain stopped, and the patient was discharged in a satisfactory condition. But in 3 months after the discharge abdominal pain recurred. During control examination performed in April 2006 (case history # 7,235), according to the aortography results, subtotal stenosis of the celiac trunk ostium was diagnosed. Due to the developed restenosis of the celiac trunk in June 2006 (case history # 9,857), resection and alloprosthetics of the celiac trunk with applying alloprosthesis "Ecoflon" was performed.

Early postoperative period was complicated by haematoma in the area of surgical intervention that required repeated puncturing and drainage. After that, the patient felt himself well enough, abdominal pain did not recur. In 2008, after the recurrence of abdominal pain, on the regular check-up restenosis of the celiac trunk was diagnosed once again (Figure 10).

In April 2009, the patient underwent repeated direct stenting of the celiac trunk . Stent EXPRESS VASCULAR 7.0 * 15.0 mm was implanted into the stenotic area using single balloon dilatation (pressure 16 atm, time 40 sec), artery's lumen was restored (Figure 11 and 12).

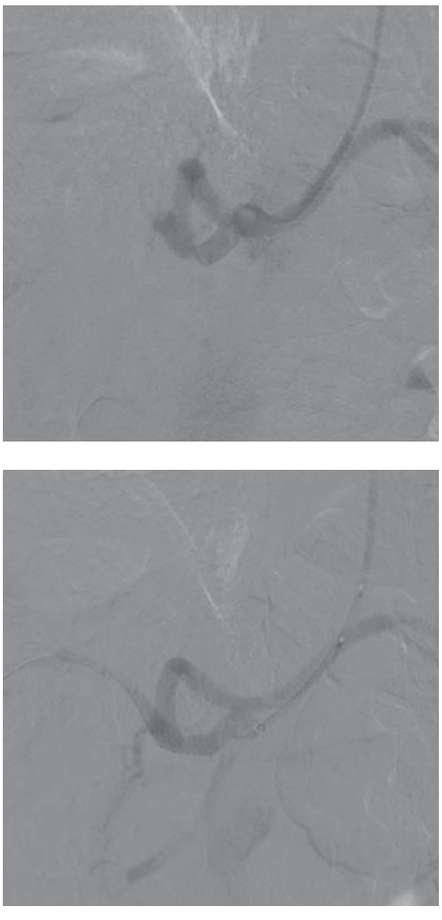


Fig. 11 and 12. Patient Yu.,3.04.2009, case history # 6,880. Condition before and after direct stenting of the celiac trunk.

After repeated angioplasty patient's condition has improved; short-term and long-term results of treatment are considered to be satisfactory. Patient received conservative treatment that included enzyme drugs, statins, aspirin, and clopidogrel. According to the color duplex scanning, no hemodynamically significant obstacle for the blood stream in the celiac trunk was revealed.

CONCLUSIONS

According to aortography data, the frequency of occlusive-stenotic lesions of impaired visceral arteries is 7.4%; they are mostly lesions of the celiac trunk in 85.3% of examined patients.

Atherosclerosis was the main cause of intravascular lesions of visceral arteries; these lesions were present as hemodynamically insignificant stenoses in 36.1% of our patients.

In patients with intravascular significant stenosis the chronic abdominal ischemia was at the compensation stage, or at the decompensation stage if the lesions were extravascular.

Endovascular angioplasty is an effective and minimally invasive method of treatment, and it can be used mainly for atherosclerotic lesion of the celiac trunk.

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Our First Experience with Endovascular Treatment for Ischemic Cerebrovascular Accident.

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Methods of endovascular treatment of ischemic cerebrovascular accident demonstrated their superiority over the systemic thrombolysis in clinical trials, but their use in routine practice is still limited. Four cases of endovascular treatment of ischemic cerebrovascular accidents were analyzed. As a result of intervention, cerebral blood flow (TICI 3) was restored in all patients. In early postoperative period there is a tendency to decreased severity of neurological deficiency by the NIHSS; a tendency to restoration of patients' functional independence (evaluated by Rankin scale) is observed. No deaths occurred during follow-up. Ultrasound control and MR angiography at discharge as well as in 30 and 90 days showed patent stents and cerebral blood flow within normal limits.

Keywords: *acute ischemic stroke, intra-arterial thrombolysis, mechanical thrombectomy, stenting.*

Objectives: To evaluate effectiveness and safety of endovascular treatment of ischemic cerebrovascular accident in early postoperative period.

Background: Methods of endovascular treatment of ischemic cerebrovascular accident demonstrated their superiority over systemic thrombolysis in clinical trials, but their use in routine practice is still limited.

Methods: 4 cases of endovascular treatment of ischemic cerebrovascular accidents were analyzed. All patients were males, patients' age varied from 52 to 69 years. Clinical manifestations of the stroke were evaluated by the NIHSS scale; on admission the total score was 14-22. Selective angiography of brachiocephalic artery revealed that the first patient had ostial occlusion of ICA, the second patient had occlusion of the petrous segment of the ICA, the third one had occlusion of the ICA supraclinoid segment, and the fourth one – critical stenosis of the basilar artery. Stenting of the affected vessel was performed in 3 patients; balloon angioplasty in 1 patient. Results were evaluated by the NIHSS scale after 24 hours, at discharge, after 30 and 90 days; a degree of patient functional dependence was evaluated by the modified Rankin scale (mRS) after 30 and 90 days. Stents patency and cerebral blood flow were evaluated by the TUS, TCDG, and MR angiography at discharge and after 30 and 90 days.

Results: Endovascular treatment resulted in TICI 3 cerebral blood flow restoration in all patients. Time from the moment of neurological deficiency appearance until the blood flow restoration was 75-280 minutes. In early postoperative period there is a tendency to decreased severity of neurological deficiency by the NIHSS; a tendency to restore patients' functional independence is observed. Ultrasound control and MR angiography revealed patent stents and a cerebral blood flow within normal limits.

Conclusions: After endovascular intervention, clear clinical improvement and restoration of functional independence is observed in all patients, but these techniques need to be further evaluated in multicenter randomized trials.

Abbreviations:

ICA	– internal carotid artery
MCA	– middle cerebral artery
ACA	– anterior cerebral artery
TUS	– triplex ultrasound
TCDG	– transcranial dopplerography
CT	– computed tomography
NIHSS	– the National Institutes of Health Stroke Scale
CVA	– cerebrovascular accident
mRS	– modified Rankin scale
MR angiography	– magnetic resonance angiography
IAT	– intra-arterial thrombolysis
TBA	– transluminal balloon angioplasty

In 1996, systemic thrombolysis by recombinant tissue plasminogen activator became the first method of treatment of the acute ischemic stroke that demonstrated its effectiveness in restoring cerebral blood flow (1). Nevertheless, despite of using systemic thrombolysis, the rate of stroke-related mortality and disability is 58% (2). In particular, systemic thrombolysis demonstrates limited effectiveness in proximal occlusions and strokes with total NIHSS scores ⩾10, where the occlusion after treatment persists in more than 80% of cases (3-5). These circumstances

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demanded further studies in the field of ischemic CVA treatment methods, especially of the strategies of endovascular recanalization in patients with severe neurological deficiency.

There are several types of endovascular interventions for treatment of ischemic cerebrovascular accident. The first one is intra-arterial infusion of thrombolytic agents directly to the occlusion area (6-8). The second type includes methods of mechanical recanalization and thrombus extraction (9-13). The third one is angioplasty and/or stenting (5). However, these techniques are generally used nowadays when systemic thrombolysis is impossible or contraindicated (2). Moreover, interventions are not a first-line therapy in patients eligible for systemic thrombolysis, despite of studies demonstrating superiority of endovascular techniques over the systemic thrombolysis when treating acute ischemic strokes (9, 11, 12).

We present our first experience with endovascular treatment of ischemic cerebrovascular accidents in the first hours from the onset of clinical signs.

MATERIALS AND METHODS

In 2010, in the Regional Vascular Center of Rostov Regional Clinical Hospital (Rostov-on-Don), endovascular interventions were performed in 4 patients with ischemic cerebrovascular accidents. Patients' age varied from 52 to 69 years, all patients were males. Clinical manifestations of the stroke were evaluated using the NIHSS scale; on admission the total score was 14-22. Three patients admitted to the emergency department underwent endovascular intervention within 90-190 minutes from the moment of neurological deficiency appearance. One patient developed CVA in the hospital; the interval from the manifestation onset till the intervention was 30 minutes. Two patients had a history of ischemic CVA with complete recovery of neurological manifestations; one patient – of transitory ischemic attacks; 1 patient had T2DM; 1 patient had atrial fibrillation; all patients were hypertensive and smokers. Computed tomography of the brain performed in all patients did not reveal hemorrhage focuses, while perfusion CT demonstrated the large area of ischemic but potentially viable brain tissue.

Systemic thrombolysis with Actilyse (Boehringer Ingelheim, Germany) in the dose of 0.9 mg/kg was performed in 1 patient without clinical effect.

According to the data of selective angiography of brachiocephalic arteries, the first patient had ostial occlusion of the left ICA, the second patient had occlusion of the ICA petrous portion, the third one had occlusion of the ICA supraclinoid segment, and the fourth one, critical stenosis of the basilar artery. During angioghaphy, 3 patients with occlusive lesions of ICA were infused 15 mg of intra-arterial Actilyse (Boehringer Ingelheim, Germany). As a result of selective thrombolysis, TICI 2 blood flow was reached in 2 patients; critical stenosis of petrous and supraclinoid ICA segments was revealed. In the patient with ostial occlusion of the ICA selective thrombolysis was ineffective; hence guide recanalization and mechanical thrombectomy were performed; as a result, TICI 1 blood flow was obtained, critical stenosis in the proximal third of the left ICA cervical segment was revealed.

Stenting of the affected vessel was performed in 3 patients, and balloon angioplasty was performed in one patient with critical stenosis of the right ICA supraclinoid segment. As a result of endovascular intervention, TICI 3 blood flow was restored in all patients.

After stenting all patients were given a loading dose of Clopidogrel 600 mg and also Aspirin 300 mg followed by treatment with Clopidogrel 75 mg and Aspirin 100 mg per day until the discharge. All patients were given IV heparin in doses of 5,000-10,000 units during the procedure to maintain activated clotting time at the level of 250-300 seconds.

Results of endovascular intervention were evaluated by the NIHSS scale after 24 hours, at discharge, and after 30 and 90 days; the degree of functional dependence was evaluated in patients using modified Rankin scale (mRS) after 30 and 90 days. Stents patentcy and cerebral blood flow were evaluated on the base of TUS and TCDG data (at discharge and after 30 and 90 days) and also by MR angiography after 30 days.

RESULTS

As a result of endovascular intervention, TICI 3 blood flow was achieved in all patients. According to the brain CT data, there were no haemorrhagic complications in the postoperative period. Ultrasound control and MR angiography demonstrated stents patency, without hemodynamically significant stenoses; cerebral blood flow was within normal limits. No deaths occurred during follow-up. Results of endovascular interventions in ischemic CVA are presented in the following clinical cases.

Patient R., 58 years old, was hospitalized via an ambulance 60 minutes after the onset of neurological deficiency in the territory of the right MCA. NIHSS score on admission was 18. According to the data of perfusion brain CT, there was a large focus of penumbra in the right temporal lobe. According to the data of selective angiography, an occlusion (TICI 0) of the right ICA was revealed in the supraclinoid segment with the right ACA and MCA opacification from the territory of the left ICA (Figure 1). Actilyse (Boehringer Ingelheim, Germany) was administered intra-arterially in a dose of 15 mg through a microcatheter into the occlusion area (Excelsior SL-10, Boston Scientific, USA). Control angiography showed critical stenosis of the right ICA in the supraclinoid segment with TICI 2 blood flow. An attempt to perform stenting in the affected segment was unsuccessful because of significant tortuosity of the intracranial part of ICA. Balloon angioplasty of the stenotic area was performed using Maverick2 coronary balloon catheter (Boston Scientific, USA) 3.0-15 mm; TICI 3 blood flow was obtained (Figure 2). The duration of pro-

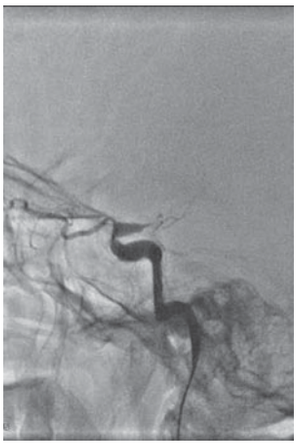

Fig. 1. Occlusion of the right ICA in the supraclinoid segment with TICI 0 blood flow.

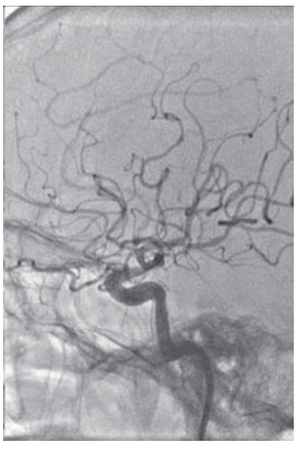

Fig. 2. Results of intra-arterial thrombolysis and balloon angioplasty in supraclinoid segment of the right ICA; TICI 3 blood flow.

cedure was 45 minutes. Time from the CVA beginning till the blood flow restoration was 2 hours and 15 minutes.

NIHSS score in 24 hours was 10;
at discharge – 6;
in 90 days – 2;
mRS score in 90 days – 2.

Patient V., 69 years old, was hospitalized via an ambulance 1 hour 45 minutes after the onset of CVA in the territory of the left MCA. At admission, NIHSS score = 10. A successful systemic thrombolysis with Actilyse (Boehringer Ingelheim, Germany) in a dose of 84.6 mg (0.9 mg/kg) was performed with complete regress of neurological manifestations (NIHSS=0 after 24 hours). On the 12th day of in-hospital stay the patient developed repeated ischemic CVA symptoms in the territory of the left MCA with NIHSS score 14. Selective angiography revealed an occlusion (TICI 0) of the left ICA with opacification of the left ACA and MCA from the territory of the right ICA (Figure 3). Actilyse was administered intra-arterially in a dose of 15 mg into the occlusion region. At control angiography, there was a critical stenosis on the boundary of occlusion in the left ICA petrous segment with TICI 2 blood flow (Figure 4). Liberte coronary stent (Boston

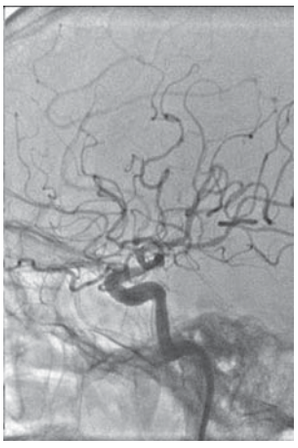

Fig. 3. Occlusion of the left ICA (arrow) with TICI 0 blood flow.

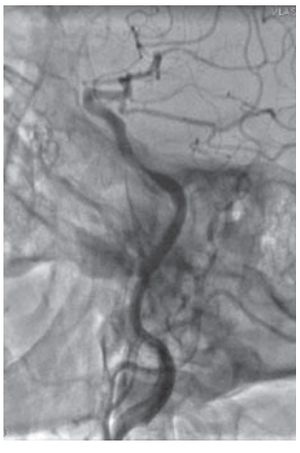

Fig. 4. After intra-arterial thrombolysis there is a critical stenosis of the left ICA petrous segment with TICI 2 blood flow.

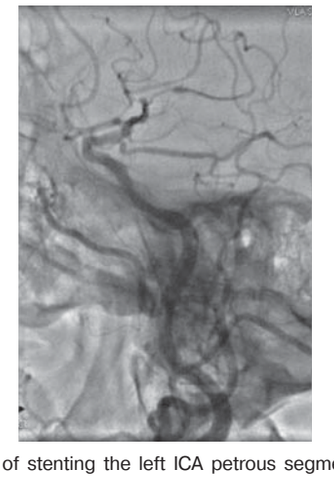

Fig. 5. Results of stenting the left ICA petrous segment, TICI 3 blood flow.

Scientific, USA) 3.5-17 mm was implanted into the stenotic area; TICI 3 blood flow was obtained (Figure 5). The duration of procedure was 1 hour and 10 minutes. Time from the CVA symptoms onset till the blood flow restoration was 75 minutes.

NIHSS score in 24 hours – 8;
at discharge – 4;
in 30 days – 2;
in 90 days – 0 points;
mRS score in 30 days – 1;
mRS in 90 days – 0.

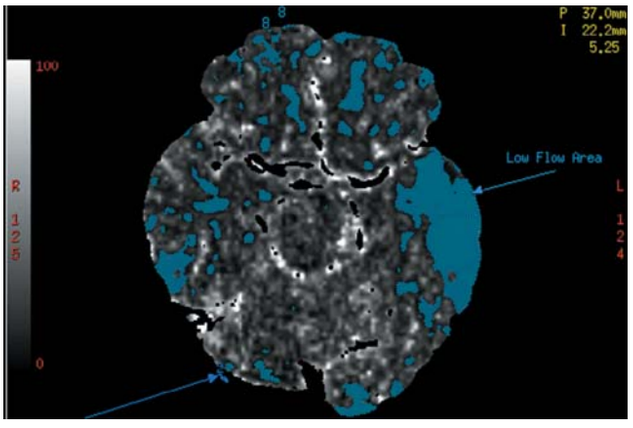

Fig. 6. Perfusion CT data demonstrate large ischemia focus in the left temporal lobe.

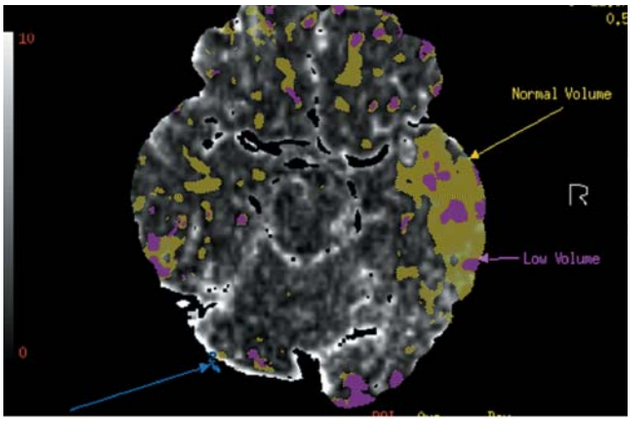

Fig. 7. Perfusion CT data demonstrate small dead brain tissue focuses (purple) and the large area of viable penumbra (orange).

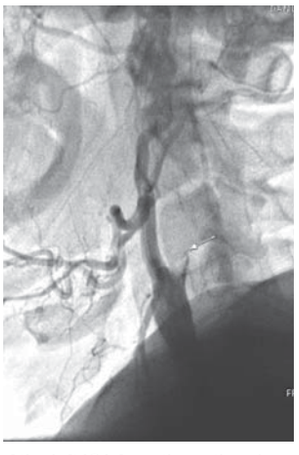

Fig. 8. Occlusion of the left ICA from the ostium (arrow) with TICI 0 blood flow.

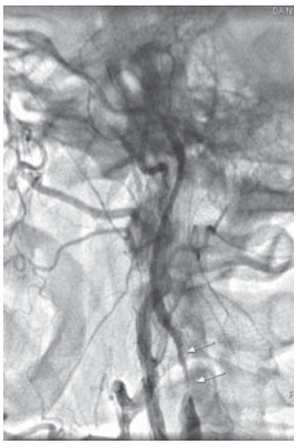

Fig. 9. After mechanical recanalization and thrombectomy TICI 1 blood flow was obtained; there is a critical stenosis in the proximal third of the left ICA cervical segment (arrows).

Fig. 10. Results of stenting of the left ICA; TICI 3 blood flow.

Patient D., 52 years old, was hospitalized via an ambulance 1 hour 50 minutes after the onset of neurological deficiency. NIHSS score at admission was 16. According to the data of brain perfusion CT, there was a large focus of penumbra in the left temporal lobe (Figure 6, 7). Systemic thrombolysis performed with Actilyse (Boehringer Ingelheim, Germany) in the dose 77.5 mg (0.9 mg/kg) did not give clinical effect. Selective angiography revealed an occlusion (TICI 0) of the left ICA starting from the ostium, as well as the left ACA and the MCA opacification from the territory of the right ICA (Figure 8). Actilyse was infused intra-arterially in a dose of 15 mg into the occlusion region. Control angiography showed residual occlusion of the ICA from the ostium, and thrombotic masses are visualized in the ICA lumen. Mechanical recanalization of the occluded area was performed using a coronary guide; Catch system for mechanical thrombus extraction (Balt exstrusion, France) was placed distal from the occlusion area. Thrombectomy was performed and TICI 1 blood flow was obtained. Control angiography revealed critical stenosis in the proximal third of the left ICA cervical segment (Figure 9). Cristallo ideale stent 6–9 x 40 mm (Invatec, Italy) was implanted into the stenotic area; TICI 3 blood flow was obtained (Figure 10). The duration of procedure was 90 minutes. Time from the onset of CVA symptoms till the blood flow restoration was 4 hours and 40 minutes.

NIHSS score in 24 hours – 13;
at discharge – 8;
in 30 days – 6;
in 90 days – 2;
mRS score in 30 days – 2;
in 90 days – 1.

Fig. 11. Critical stenosis of the basilar artery (arrow); TICI 2 blood flow.

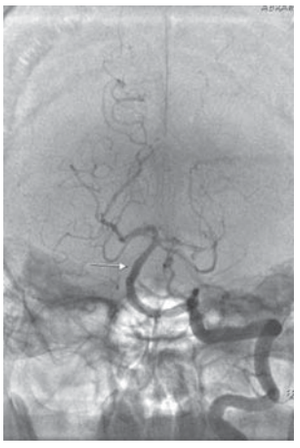

Fig. 12. Stenting results in the basilar artery (arrow); TICI 3 blood flow.

Patient A., 56 years old, was hospitalized via an ambulance 2 hour 15 minutes after the onset of ischemic CVA in the vertebrabasilar area, with NIHSS score of 16. Selective angiography of the brachiocephalic arteries revealed critical stenosis of the basilar artery with the TICI 2 blood flow (Figure 11). Coronary Multi-Link stent 2.75 x 18 mm (Abbott Vascular, Ireland) was implanted into the stenotic area; TICI 3 blood flow was obtained (Figure 12). The duration of procedure was 40 minutes. Time from the onset of CVA symptoms till the blood flow restoration was 3 hours and 25 minutes.

NIHSS score in 24 hours – 4;
at discharge – 0;
in 30 days – 0;
in 90 days – 0;
mRS score in 30 days – 0;
in 90 days – 0.

DISCUSSION

In 1996, NINDS study showed effectiveness of intravenous thrombolysis with recombinant tissue plasminogen activator in the treatment of acute ischemic stroke within 3 hours from the onset of symptoms. These fundamental findings opened a new era in the therapy of this dangerous disease (1). Later, ECASS-III study proved the effectiveness of systemic thrombolysis within 4.5 hours after the onset of the disease (14). At present, intravenous thrombolysis is included in the IA class of recommendations of many national associations (15, 16). The advantages of systemic thrombolysis consist in its relative simplicity and the possibility to start the treatment promptly, without need for any highly specialized equipment or technical skills. However, systemic thrombolysis is not a panacea for treating acute ischemic strokes. The frequency of recanalization achieved with systemic thrombolysis varies from 10% in cases of ICA occlusion to 30% in occlusions of MCA proximal segments (17). According to NINDS data, in order to get one good result it is necessary to perform systemic thrombolysis in 8 patients (18). Such factors as low effectiveness in proximal occlusions, narrow time bounds, and haemorrhagic complications required further research of acute ischemic stroke treatment methods, especially improved endovascular methods of blood flow restoration in brain vessels.

Endovascular methods of treating ischemic strokes are aimed at restoration of cerebral blood flow by means of dissolving, destructing, and/or extracting the thrombus; they include intra-arterial thrombolysis, mechanical recanalization and thrombectomy, mechanical destruction of the thrombus or thromborrhexis, and stenting.

References

Intra-arterial thrombolysis has some theoretical advantages over the systemic one. Tissue plasminogen activator can be delivered directly into the thrombus, and the dose for creating high thrombolytic concentration in the occlusion area is lower than with systemic thrombolysis; theoretically, this allows for more complete recanalization with lower total dose of thrombolytic agent (19). In theory, lower doses can decrease the rate of complications, including cerebral haemorrhage, observed during systemic fibrinolysis (19). For the same reasons time frame for endovascular interventions can be extended over 3 hours considered usually for systemic thrombolysis (19). This is of particular importance, as relatively few patients are admitted to the health care institution within the time limit allowing for the performance of systemic thrombolysis (20, 21). Besides, intra-arterial thrombolysis is characterized by higher frequency of recanalization than the intravenous one (22-24). In the trials on systemic thrombolysis, full recanalization of MCA occlusions was achieved approximately in 33% of cases, while IAT resulted in recanalization in 66% of cases, according to PROACT II (8, 17, 25-27). When occlusion is located in the vertebrobasilar territory, recanalization rate for intravenous thrombolysis is 53% and 65% for IAT (28).

Meta-analysis of PROACT I, PROACT II, and MELT studies including a total of 204 patients with acute ischemic stroke who underwent selective thrombolysis and 130 control patients demonstrated lower mortality and functional dependence rates in the long-term after IAT (58.5% versus 69.2%) (29).

However, these studies included patients with MCA occlusion. Acute strokes due to the occlusion of the terminal segment of the ICA are usually characterized by worse prognosis (30). Besides, effectiveness of intravenous thrombolysis in ICA lesion is considerably lower (17). At present, no randomized controlled studies including patients with ICA occlusion have been performed; therefore, all the data concerning the natural course and the results of endovascular intervention are obtained from small series of clinical cases. Arnold analyzed results of selective thrombolysis in 24 patients with occlusion in the ICA bifurcation and average NIHSS score of 19 within 237 minutes, on the average, from the onset of manifestations (31). Good results (mRS⩽2) in 3 months were observed in 16.6% of patients (31). Mortality rate was 41.7% (31). Partial recanalization of the intracranial segment of ICA part was achieved in 63% of cases, of MCA in 17% and of ACA in 33% (31). Sorimachi reported better outcomes at selective thrombolysis in cases of proximal occlusion of ICA (n=12; mRS⩽2, 75%), than in cases of distal occlusion (n=11; mRS⩽2, 36.4%) despite the same recanalization rates (100% versus 91%) (32).

Acute ischemic stroke as a result of isolated lesion of extracranial segment of ICA generally is associated with more favorable prognosis due to compensatory collateral blood flow from the ECA territory and/or the circle of Willis (30). However, patients with open circle of Willis or concomitant damage of intracranial segment of ICA/MCA often develop severe strokes and are candidates for emergency revascularization (30). Jovin reported a series of clinical cases of 25 patients with occlusion of extracranial segment of ICA and average NIHSS score 14 (33). After stent implantation, successful recanalization was obtained in 92% of patients (33).

The feasibility, the safety and the effectiveness of combined thrombolysis in patients with ischemic CVA were evaluated in several studies (34-36). This approach combines advantages of systemic (speed and simplicity of use) and intra-arterial (small doses, possibility of mechanical impact on the clot, higher recanalization rates) thrombolysis, thus increasing the speed and the probability of recanalization (30).

Main disadvantages of intra-arterial thrombolysis, as for other endovascular techniques, consist in relative complexity of the procedure, specific level of necessary technical skills, low availability of the method, delay in starting treatment, additional risks, and price of invasive intervention comparing to intravenous thrombolysis (19).

Methods of mechanical impact on the clot.

Methods of mechanical recanalization in ischemic cerebrovascular accidents can be used as primary ones or in combination with selective thrombolysis. These techniques decrease or completely exclude necessity of thrombolysis, thus reducing the risk of haemorrhagic complications and increasing time frames up to 6-8 hours (19). Mechanical clot fragmentation enlarges its surface area available for thrombolytic impact, facilitates fresh plasminogen inflow that, in its turn, accelerates the thrombolysis process (19). Finally, retrievers allow for quick recanalization and can be more effective in cases when occlusive material is resistant to plasminogen influence; for example, if the embolus consists of atherosclerotic plaque elements (19). Mechanical methods of blood flow restoration became the key ones for patients with contraindications for thrombolysis or in case of late admission (10, 37, 38). Besides, endovascular intervention can be necessary for completing successful thrombolysis, for example, for recanalization of proximal occlusion (39-41). Disadvantages of mechanical methods are technical difficulties when manipulating devices in cerebral vessels, possibility of vascular walls damage with potential risk of vasospasm, dissection, perforation, and rupture; probability of distal embolism of previously intact territories by pieces of fragmented thrombus. (19). However, the advantages of mechanical methods of blood flow restoration in acute ischemic strokes outweigh their risks and disadvantages.

Mechanical thrombectomy.

Mechanical thrombectomy allows for quick restoration of blood flow with lower probability of clot fragmentation and distal embolism in comparison with other endovascular techniques (19). Devices for thrombectomy differ depending on the point of force application to the thrombus: proximal approach with aspiration/capture of the clot or distal approach for devices that look like a basket or a loop (19). An example of Merci retriever can be provided as the first device approved for treatment of acute ischemic stroke; thus an era of mechanical thrombectomy was opened. Effectiveness and safety of this retriever was proved in MERCI and Multi MERCI trials (10, 38). MERCI trial involved 151 patients with neurological deficiency with NIHSS score 20.1±6.6, and TIMI 2-3 blood flow was obtained in 46% of patients with the help of retriever; additional IAT and mechanical clot destruction yielded recanalization rates of 60.3% (10). Clinically significant complications were observed in 7.1% of cases (10). In 90 days, mRS⩽2 was 46% and mortality 32% in the group with successful recanalization (10). In Multi MERCI trial, TIMI 2-3 blood flow was obtained in 55% of cases; additional IAT and mechanical methods of clot impact allowed recanalization to be achieved in 68% of cases (38). Clinically significant complications were observed in 5.5% of patients (38). In 90 days, mRS⩽2 was 49% and mortality 25% in the group with successful recanalization (38).

Aspiration thrombectomy.

Aspiration thrombectomy via the guide or microcatheter can be used in the new nonadherent thrombus (42-44). Aspiration devices more rarely cause embolism and vasospasm; however, their complex design frequently complicates navigation in brain ves-

sels (19). The most investigated is Penumbra System (Penumbra, Alameda, Calif). Penumbra Stroke Trial included 125 patients with NIHSS=17.3±5.2 (45). Complete or partial revascularization (TIMI 2-3) was obtained in 81.6% when using Penumbra System. Frequency of clinically significant complications was 3.2% (45). Symptomatic brain haemorrhage was observed in 11.2% of cases (45). Improvement by 4 and more NIHSS points was reported in 57.8% of patients at discharge (45). In 90 days, good results (mRS⩽2) were obtained in 25% of patients; mortality was 32.8% (45).

Thromborrhexis.

There are a few techniques of mechanical thrombus destruction. Microguides are most commonly used for these purposes (19). This technique is effective for intensification of thrombolysis (22). Alternatively, special loops can be used for thromborrhexis; they can also be applied for thrombus extraction in situations when the clot is dense or contains solid materials (13, 46).

A few trials demonstrated feasibility and high effectiveness of balloon angioplasty in acute ischemic stroke (47-50). Nakano analyzed the results of treating 70 patients with acute MCA occlusion who underwent direct TBA (34 patients) with further thrombolysis in 21 cases, or who underwent only thrombolysis (36 patients) (48). Complete or partial recanalization was achieved in 91.2% in the group of TBA and in 63.9% in the group of thrombolysis only; cerebral haemorrhage was observed in 2.9% of TBA cases versus 19.4% of thrombolysis cases; good results (mRS⩽2) comprised 73.5% in TBA group versus 50% in the thrombolysis group (48).

Balloon angioplasty is useful in atherosclerotic lesions when residual stenosis can lead to rethrombosis (39). Taking into consideration the risks of intraoperative complications, such as vessel rupture or distal embolism, TBA is generally used when more conservative methods cannot restore the blood flow (19). However, the technique became much safer with the use of more flexible low-pressure balloons (50, 51).

Stenting.

Stent implantation into the occluded area of intracranial vessels provides fast recanalization due to thrombus compaction between the stent and vascular wall (19). Further, it can result in thrombus dissolution by means of endogenous or pharmacological thrombolysis (19). Levy reported a series of clinical cases, where 19 patients with acute occlusion of the ICA terminal part, M1/M2 or basilar artery underwent stenting of the affected vessel (52). Recanalization with TICI 2-3 blood flow was achieved in 79% of patients; no symptomatic intracerebral haemorrhages were observed (52).

When treating acute ischemic stroke, self-expanding stents have several potential advantages over the balloon-expandable ones. They are more flexible and more easily guided through brain vessels; vasospasm rates are lower (53). As opposite to ACS, when the cause is the blasted plaque with the thrombus, most of intracranial vessel occlusions are caused by embolism without any pathology of vascular walls (19). For this reason angioplasty with high-pressure balloons and balloon-expandable stents is usually not required for recanalization; these devices can only increase the risk of severe complications such as vessel rupture or dissection (19). Self-expanding stents are less traumatic for endothelium; that is why early reocclusions or late in-stent stenoses are less common (19).

The necessity of aggressive antithrombotic therapy remains one of the main limitations of stents use for treating acute strokes (19). However, introduction of closed-cell stents allowed for stents removal after recanalization and eliminated the necessity of double antiplatelet therapy which potentially increases the risk of haemorrhagic transformation of infracted area (19). Also, this technique eliminates the risk of delayed in-stent stenoses (19). Kelly presented a clinical trial where partial implantation of Enterprise stent led to immediate recanalization of the occluded MCA refractory to intravenous and intra-arterial thrombolysis and also to mechanical impacts (54). The straightened part of the stent dosplaced the fragmented thrombus to the wall and acted as a temporary endovascular shunt, while Abciximab was additionally infused through the guiding catheter (54). Partially straightened stent was reassembled and removed in 20 minutes (54). Such manipulations theoretically can be conducted with other “folding” stents such as Leo or Solitaire/Solo (19).

Correlation between revascularization and favorable results was well showed in the meta-analysis by Rha and Saver (23). Recanalization rates and treatment outcomes in acute ischemic strokes were analyzed in all the articles published in 1985–2002 (23). The analysis included 53 trials with 2066 patients enrolled (23). Recanalizaiton rates depending on treatment methods were as follows: spontaneous recanalization (24.1%), intravenous thrombolysis (46.2%), IAT (63.2%), intravenous thrombolysis + IAT (67.5%), and mechanical methods (83.6%) (23). Good clinical results and lower mortality were more common in the group of patients with successful recanalization (23). However, the relation between clinical outcomes and reperfusion in strokes is not necessarily linear due to effects on treatment outcomes of such factors as ischemia size and duration, initial stroke severity, presence and degree of collateral blood supply, cerebral perfusion pressure, lesion localization and length. That is why reperfusion can develop according to different clinical scenarios including neurological improvement, deterioration, and even death due to the reperfusion cerebral edema and/or haemorrhage (24).

CONCLUSIONS

A small sample size of our clinical observations precludes making statistically grounded conclusions; however, it is necessary to note clear posi-

tive dynamics in patients' clinical condition after endovascular treatment in all four cases and restoration of functional independency in patients with severe stroke in whom predicted lethal outcome and deep disability without treatment makes 16-55% and 40-60%, respectively (55). In Russian publications we did not find other examples of mechanical thrombectomy and stenting of carotid arteries after ischemic cerebrovascular accidents. Endovascular techniques of blood flow restoration in acute ischemic stroke require further research in multicenter randomized trials.

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A Case of CP Stent Migration after the Correction of Aortic Coarctation

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Introduction: Our clinic possesses quite a sound experience with the correction of aortic coarctation by the method of balloon angioplasty; more than 100 interventions have been performed over fifteen years. Personal observations reliably confirm literature data: in cases of coarctations with significant aorta hypoplasia distal to the left subclavian artery origin and in cases with bifurcation involvement into the coarctation, after the intervention recoarctations and saccular aneurysms in the area of angioplasty can occur (1, 2, 3). The availability of a special Cheatham Platinum (CP) stent at the Russian market made the prognosis of treatment of these anatomically unfavorable variations significantly more optimistic (4, 5, 6). It is due to the fact that the stent has considerable flexibility, its diameter can be enlarged in proportion to the child's growth, and it can safely reinforces the plasty area pressing down the sites of dissection. Stents with double balloon by the same manufacturer are especially convenient and safe.

Our personal experience in aortic coarctation stenting by CP stents comprises 7 cases in patients of different ages (from 2 to 18 years old, weight from 12 to 67 kg). All interventions earlier performed with the implantation of similar devices were characterized by simple positioning and reliable fixation of the stent that was being made easier by using double balloon (balloon in balloon, BIB) with its uniform inflation excluding "sand-glass" effect and deformation during the implantation (1).

Clinical case: Patient G., male, 26 years old (168 cm, 65 kg) was admitted to the neurosurgical department of Chelyabinsk Regional Clinical Hospital with a history of hemorrhagic episode in the territory of right internal carotid artery and complaints related to hypertension up to 220/120 mmHg. He had a concomitant HIV infection (without clinical manifestations). On palpation, femoral arterial pulse was weak. During retrograde catheterization through the right femoral artery it proved impossible to move the catheter in the area of aortic isthmus. At aortograms performed with the help of catheter placed through the right brachial artery, the coarctation of the aorta was revealed with narrowing of its diameter up to 1mm (Figure 1). Anatomically it was a preductal type with hypoplasia of the aorta from the left subclavian artery ostium and with dramatically expanded collateral network (Figure 2). Selective cerebral angiography confirmed saccular aneurysm of the right internal carotid artery.

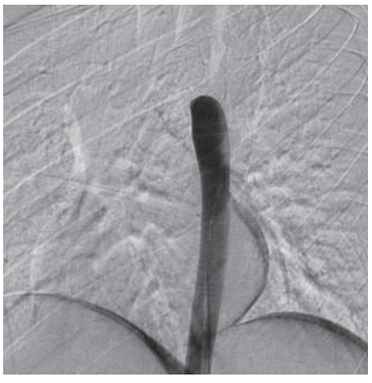

Fig. 1. Retrograde aortogram.

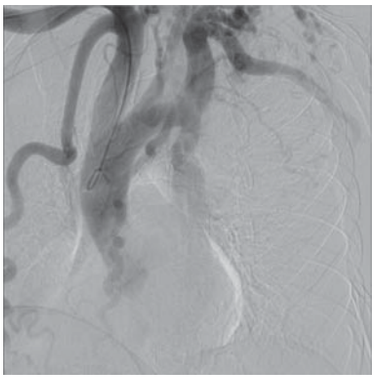

Fig. 2. Antegrade aortogram.

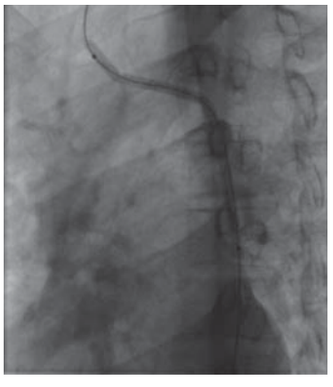

Fig. 3. Predilatation by the 5 mm balloon.

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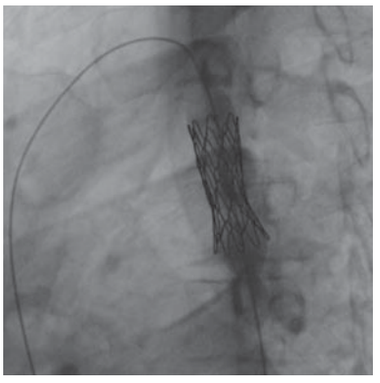
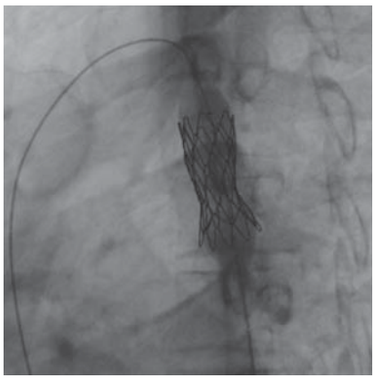
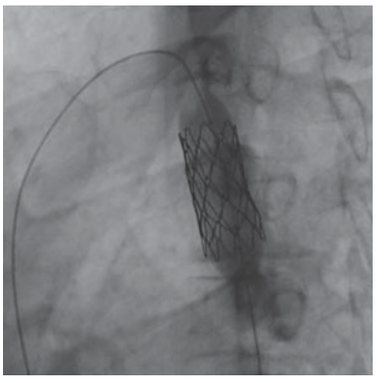

Fig. 4, 5, 6. Sequential inflation of BIB balloon.

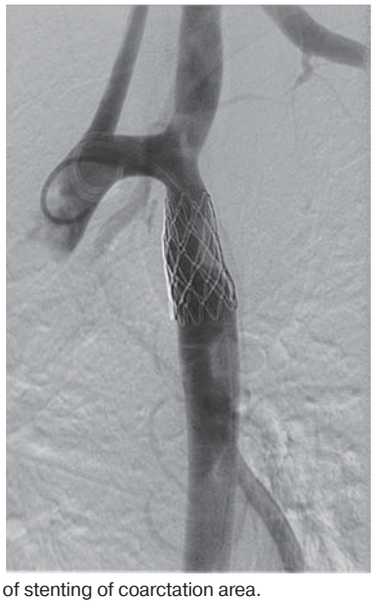

Fig. 7. Result of stenting of coarctation area.

Fig. 8. Stent migration, conic shape is preserved.

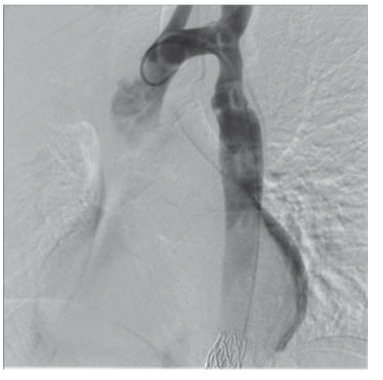

Fig. 9. Coarctation area after stent migration, there are no signs of dissection.

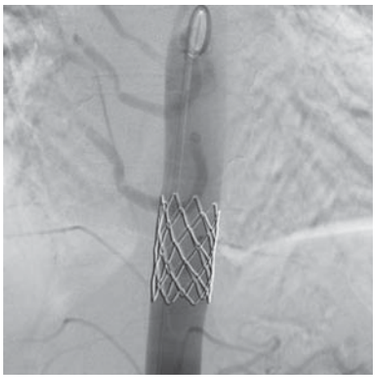

Fig. 10. Results of stent dilatation after its migration.

The board of physicians with participation of neurosurgeon and vascular surgeon decided to perform endovascular treatment of the newly diagnosed aortic coarctation allowing treatment of internal carotid artery aneurysm to be performed at the earliest date. The elimination of aortic coarctation also decreased the risk of repeated intracranial hemorrhage. Considering intensity of coarctation and disease duration (considerable fibrosis and eventual high risk of excessive dissection), it was decided to perform stenting.

Hydrophilic guide 0,035”x260 mm was introduced through the severe narrowing in the area of coarctation by the brachial artery access, where we managed to place and expand a balloon 5 mm in diameter (Figure 3). This stage allowed us to place diagnostic guide to the aortic arch through 14 F introducer by the femoral access and locate a 34 mm long CP stent, assembled on BIB balloon 8 x 25 mm, 16 x 40 mm in diameter into the predilated coarctation. Preliminary measurement of aorta diameter revealed approximately 12 mm above coarctation and 17 mm below coarctation.

Positioning was performed in such a way that 2/3 of the stent fell in the area of aortic arch hypoplasia for adjust the difference in diameters of the arch and post-stenotic area of the thoracic aorta. During the implantation internal and external balloons were successively inflated (Figure 4, 5, 6); only with 10 Atm pressure (maximal for this balloon) it became possible to put the stent into the most anatomy-corresponding shape with a smooth change of diameter, continuity with the aorta in the distal part, and some overinflation that can be seen at the control aortograms (Figure 7). There were no signs of aorta's dissection (contrast leakage). The catheter and guide were removed from the stenting area under fluoroscopic control.

The patient tolerated the intervention rather well; he reported painful sensation at the moment of stent implantation and for the short period of time after this.

Control chest radiography performed rays four days after the stenting on February 19, 2010, revealed atypical position of the aortic stent and, therefore, emergency aortography was performed.

Pulse of femoral arteries in the groin was full. Aortography showed CP stent migration from the area of isthmus to the diaphragm level (above the level of celiac trunk origin). The stent preserved its conic shape set during implantation, and hence there was a gap about 4-5 mm at the upper edge (Figure 8). At the coarctation area magistral blood flow is registered, the contours are irregular without signs of dissection (Figure 9).

As the coarctation angioplasty area was in satisfactory condition, it was decided not to perform repeated stenting and to adapt stent's configuration to the aorta in the region of its migration. Additional dilatation of the stent with a 18 x 40 mm balloon at the 9-atm pressure was performed setting its cylindrical shape, up to the size corresponding to the aorta's diameter for eliminating the risk of migration (Figure 10).

In a week the patient underwent endovascular embolization of internal carotid artery aneurysm during which a stable position of CP stent in the thoracic aorta was confirmed. Coarctation angioplasty area almost did not interfere with conducting neurosurgical intervention.

Conclusions: We have to state the possibility of spontaneous CP stents migration from the implantation region, not described in previous publications.

The specific reason for such migration cannot be defined with certitude, so just some guesses can be made:

1) The stent is made of polished platinum wire of circular section which probably contributes to worse fixation in comparison with ordinary stents from laser cut metal tubing.

2. Possibly, within a relatively short time period of implantation a hypertensive crisis (without clinical manifestations) took place that led to increased aorta pulsation and shifting of the stent to distal parts of the aorta.

In order to prevent migration, perfect similarity between CP stent shape and patient's anatomy probably should be avoided. Considering the fact that in adults aortic wall in the coarctation area have increased rigidity, preserving the minimal constriction when placing the stent could possibly provide its additional fixation. Stent material allows removing constriction by means of postdilatation in 6-8 months after supposed endothelization of the stent. Apparently, regular control radiography during the first two-three weeks after stenting should become a necessary component of managing such patients.

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Influence of Electrical Impulses Delivered into the Vena Cava Inferior on Development of Atherosclerosis in Thoracic and Abdominal Aorta

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Previous investigations revealed positive impact of electrical field created around the aorta or its branches on the process of atherosclerotic plaques formation. Being applied simultaneously with high-cholestrol diet this field decelerated the process of plaques formation. Atherosclerotic changes develop far more slowly when high-cholesterol diet is replaced by the diet with normal lipid content. In our study the electrical field was created by the impulses delivered from a special catheter introduced into the inferior vena cava, that is located in immediate proximity to the abdominal aorta. Rabbit model of atherosclerosis was chosen. Control and experimental groups received the diet with 2% cholesterol content for 11 weeks. At week 12 this diet was stopped (as a rule marked coronary arterial atherosclerosis developed). Simultaneously with high-cholesterol diet experimental rabbits received electrical stimulation. The areas of thoracic and abdominal aorta situated in close proximity to the lead were virtually free of atherosclerotic plaques. In whole the plaques-covered surface both in thoracic and abdominal aorta was fivefold smaller than in the control group. Our study showed that low-frequency impulses directed toward the aorta from the inferior vena cava significantly reduced the degree of atherosclerotic process.

Keywords: *atherosclerosis, electrical impulses, electrical field, iron ions.*

Background: In our previous investigations, the application of low frequency electrical impulses (EI) in rabbits was performed resulting in different stages of atherosclerosis throughout the aorta; this may inhibit intima thickening, affect newly-formed atherosclerotic plaque in the intima of the vessels, and decrease the extent of previous pathologic damage in these structures. Previous works were focused solely on the effect of EI on atherosclerotic plaques, with electrical stimulation applied to psoas major muscle close to the upper portion of the abdominal aorta. The present study evaluates the effect of EI in rabbits with 11 weeks of high-cholesterol diet (HCD) and with EI delivered from a catheter placed into inferior vena cava close to the border between thoracic and abdominal aorta.

Methods: New Zealand White Rabbits were divided into two different series: intravenous electrical impulses (Series 1) and Control (Series 2). All rabbits were put on a 2% cholesterol diet during 11 weeks. A standard bipolar pacing lead was used. The tip of lead was positioned at the level of the first lumbar vertebra (in the upper part of abdominal aorta). In Series 1, the pacemakers were programmed to a pacing rate of 30 pulses per minute, 0.5 ms and 3.0 V for 24 hours/day. In Series 2, the pacemakers were at end of life with no output. Serum cholesterol, triglyceride and iron levels were investigated prior to surgery, every two weeks after surgery and prior to sacrifice. After the sacrifice, the percentage of surface area involved in the atherosclerosis process was calculated in the thoracic and abdominal aorta using pixel count method which allows for differentiation between stained atherosclerotic and normal aortic endothelium.

Results: In Control rabbits, the surface area of the aortic arch covered by atherosclerotic lesions was 60.2±18.1% vs. 22.3±21.4% in the Paced rabbits (p=0.0078). In Control rabbits, the area involved in atherosclerosis in thoracic aorta was 32.0±19.9% vs. 6.8±5.2% in the Paced rabbits (p=0.0135). In Control rabbits, the area involved in atherosclerosis in abdominal aorta was 27.3±18.4 % vs. 5.7±1.8% in the Paced rabbits (p=0.0168). In Control rabbits, the area involved in atherosclerosis in all aorta was 32.5±21.2% vs. 10.5±5.6% in the Paced rabbits (p=0.0339).

CONCLUSION

Our study showed that when applied intravenously through blood flowing conduits, such as the inferior vena cava, low-frequency electrical impulses decrease atherosclerotic plaques deposition in the surrounding or target tissues; i.e. the thoracic and abdominal aorta.

INTRODUCTION

A large body of research has been devoted to finding the most effective way to manage atherosclerosis, and yet, as a cause of stroke, carotid stenosis and

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myocardial infarction, it remains one of the leading causes of mortality and morbidity in the western world (1). Current recommendations include medical management and/or an interventional procedure. Medical management relies on drugs that inhibit intima thickening to reduce the luminal narrowing of the vessel (2) and on dietary restrictions and/or medications aimed at the reduction of plasma low-density lipoprotein (LDL) concentration. Patients requiring mechanical intervention undergo percutaneous balloon angioplasty with stent placement, coronary atherectomy, or bypass grafting of arteries. Our previous investigation showed that the application of low frequency electrical impulses (EI) and the subsequent creation of an electrical field in rabbits at different stages of atherosclerosis, may inhibit intima thickening, affect newly-formed atherosclerotic plaque in the intima of the vessels, and decrease the extent of previous pathologic damage in these structures (3, 4, and 5). We demonstrated that after 8 weeks of a high-cholesterol diet (HCD), followed by continuous application of EI to psoas major muscle close to the abdominal aorta for the next 8 weeks, there was a significant decrease in atherosclerotic deposition in the aorta beyond that achieved with normal diet in the absence of EI (5). Our previous work focused solely on the effect of EI in rabbits with electrical stimulation applied to psoas major muscle close to the abdominal aorta. However, the EI across the psoas major muscle caused muscle stimulation. The present study evaluates the effect of EI in rabbits with 11 weeks of HCD and with EI delivered from a catheter placed into inferior vena cava (IVC) close to the border between thoracic and abdominal aorta. Direct muscular or vascular stimulation was avoided and the contractions of muscle around aorta were eliminated with IVC catheter placement.

METHODS

Animal studies in this investigation (12 rabbits, six in each series) were approved by institution's Animal Care Committee (Aurora Sinai Medical Center, Milwaukee) , which is in compliance with the "Principles of Laboratory Animal Care" formulated by National Society for Medical Research "AHA position", and to all federal laws. All animal studies were conducted in a full AAALAC-accredited research facility. All experiments were performed in Cardiology Research Laboratory in Milwaukee Heart Institute at Aurora Sinai Medical Center We used New Zealand White Rabbits divided into two different series.

Study Population :

Series 1. Intravenous electrical impulses – 6 rabbits.

Series 2. Control – 6 rabbits

High-cholesterol Diet (HCD) and blood sampling.

All rabbits were on a 2% cholesterol diet and were fed the same quantity of food at same time. Blood samples were taken prior to surgery, every two weeks after surgery and prior to sacrifice. Serum cholesterol, triglyceride and iron levels were investigated. Blood was taken from the peripheral vein of the ear.

Animal preparation:

Prior to surgery, rabbits were anesthetized with a cocktail of Ketamine (25 mg/kg IM), Acepromazine (1 mg/kg IM), and Glycopyrrolate (0.02 mg/kg IM). Once sedated, rabbits were placed on a semi-open, non-rebreathing ventilation system, with Halothane gas (0.75–2%) mixed with 2–3 L O2. Rabbits were given Buprenorphine (0.05 mg/kg IM) for pain (one-third dose after induction of anesthesia, and two-thirds after surgery). Additional pain medication was given as needed (Buprenorphine 0.02–0.05 mg/kg BID). Chloramphenicol Succinate (30 mg/kg IM SID for 10 days) was given for prophylactic post-operative treatment of infection. Incision sites were checked at least once daily for any abscess formation. Appropriate measures, including drainage, additional sutures, and antibiotic treatment were undertaken as necessary under the direction of a veterinarian

Stimulator and lead implantation:

Surgery was performed using strict sterile technique. After induction of anesthesia, a small incision was made above the left femoral vein. The vein was mobilized and a standard bipolar pacing lead was advanced into inferior vena cava (ATS Medical, Minneapolis, Minnesota). The tip of lead was positioned at the level of the first lumbar vertebra (in the upper part of abdominal aorta). The position was the same in all rabbits and confirmed by x-ray. A subcutaneous pocket was created in the lower left area of the abdomen. The pacemaker and the proximal portion of the lead were placed in this pocket. In Series 1, the pacemakers were programmed to VOO mode, at a pacing rate of 30 pulses per minute, 0.5 ms and 3.0 V for 24 hours/day. In Series 2, the pacemakers were at end of life and had no output. The incision was closed in layers.

Pathology Investigations

Iron and cholesterol investigations

The spectrophotometric method was used to investigate the iron in blood. Blood cholesterol and triglyceride were evaluated using the enzymatic rate method; these investigations were performed at Marshfield Laboratories, Marshfield, Wisconsin.

Evaluation of surface area occupied by atherosclerosis

Aortas were opened longitudinally, stretched onto a piece of mounting board and fixed using 10% formalin. Following fixation, samples were immersed in 70% ethanol for 24 hours. Samples were stained using 70% ethanol and 2 gm Sudan IV for 24 hours and rinsed using 70% ethanol. The rabbit's aorta was

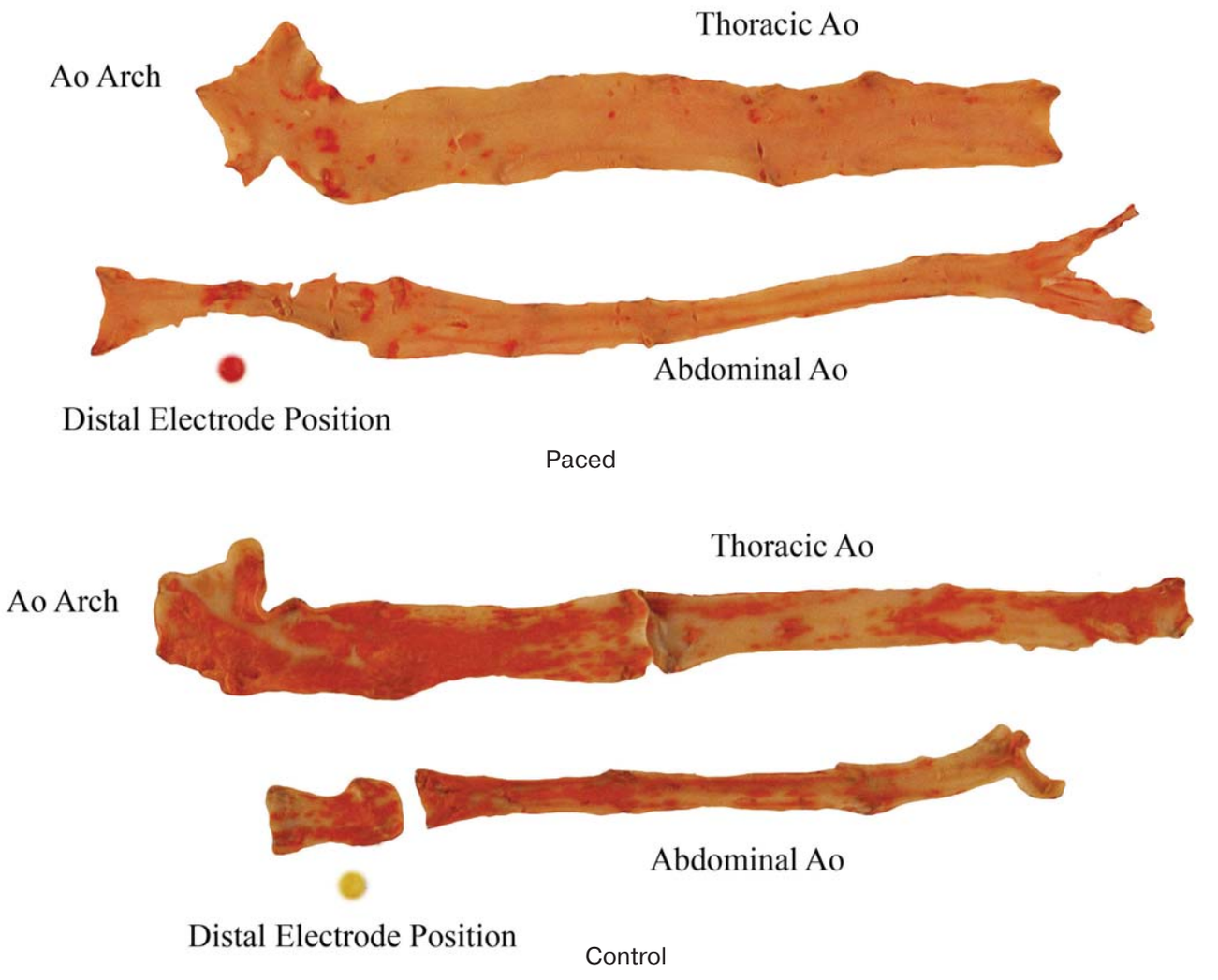

Figure 1.

photographed with a digital camera (fig 1). Adobe® PhotoShop CS2 was used to calculate the atherosclerotic area and its percentage of involvement in the aorta using a pixel count method. The aorta was divided into five segments: arch, upper thoracic, lower thoracic (two cm above the tip of catheter), upper abdomen (two cm below the tip of catheter), and lower abdomen. Atherosclerotic area was calculated for each segment by using the pixel number in the atheroma and pixel number in the whole segment. We calculated the percentage surface area of atherosclerosis by dividing the atheroma's pixel number by the whole segment's pixels. These steps were repeated for all segments of all rabbits in the study.

Statistical Analysis

The results are expressed as the mean ± standard deviation of the mean. All analyses were performed with appropriate software (SAS Institute, Inc, Version 8.0, Windows application). Resultant fraction was found to be significant at $p<0.05$, using t test analysis for the comparison of the mean between the two groups (control and experimental).

RESULTS

No animal lost weight. In Control rabbits, without electrical stimulation, before HCD, baseline weight was 3.5±0.1 kg and 3.6±0.2 kg after 11 weeks of HCD. In Paced rabbits, baseline weight was 3.6±0.0 kg and 3.7±0.2 kg after 11 weeks of HCD. All changes in weight were statistically insignificant ($p>0.05$). No infection or erosion of pacers or leads occurred..

Weight of Heart, Liver and Spleen.

Weight of heart, liver, and spleen were measured after euthanization.

Weight of the heart in the Control group was 6.5±0.4g versus 6.2±0.6g in the Paced group ($p>0.05$). Weight of liver was 152.9±19.9g (Control) versus 141.7±15.1g (Paced) ($p>0.05$). Weight of spleen was 2.3±0.5g (Control) versus 2.2±1.0 (Paced) ($p>0.05$).

Level of cholesterol and triglyceride in blood

Serum cholesterol at baseline was 36.7±10.7 mg/dL in Control rabbits and 29.0±6.9 mg/dL in Paced rabbits. This increased to 1621.7±133.1 mg/

dL (p<0.001) after 11 weeks of HCD in Control rabbits and to 1580.0±422.2 mg/dL (p<0.001) in Paced rabbits. There was no difference between two series after 11 weeks of HCD (p>0.05). Serum triglyceride at baseline was 55.7±12.2mg/dL in Control rabbits and 43.8±15.5mg/dL in Paced rabbits. After 11 weeks of HCD this increased to 129.0±52.9 mg/dL in control (p<0.05 vs. baseline), and to 127.0±22.2 mg/dL in Paced rabbits (p <0.05 vs. baseline) (p>0.05 Ctl vs. Paced)

Level of iron in blood

Baseline iron level in the blood was 206.3±29.6 ug/dL in Control and 220.3±31.6 ug/dL in Paced rabbits. After 11 weeks of HCD, iron level in the blood decreased but was not significantly different: (180.0±9.7 ug/dL in Control, and 177.8±22.7 ug/dL in Paced p>0.05).

Atherosclerotic Area

Aortic arch

In Control rabbits, the surface area of the aortic arch covered by atherosclerotic lesions was 60.2±18.1% vs 22.3±21.4% in the Paced rabbits (p=0.0078). In three of six Paced rabbits, less than 10% of the surface area of aortic arch was involved. In all Control animals, the lesion surface area was greater than 38%, and in three of them it was more than 68%.

Thoracic aorta

In Control rabbits, the area involved in atherosclerosis was 32.0±19.9% vs. 6.8±5.2% in the Paced rabbits (p=0.0135). In all control rabbits, this area was more than 13.6% (13.7%-61.5%). In three of six Paced rabbits, the area involved in atherosclerosis was less than 3.4%. In four of six Paced rabbits there was no (0%) atherosclerosis in lower part of thoracic aorta (2 cm above the tip of electrode).

Abdominal aorta

In Control rabbits, the area involved in atherosclerosis was 27.3±18.4 % vs 5.7±1.8% in the Paced rabbits (p=0.0168). In all Control rabbits, the area involved was more than 7.7% (7.8%-54.8%). In all Paced rabbits, the area involved was less than 7.4% (2.8%-7.3%). In one of six paced rabbits there was no lesion in upper part of abdominal aorta (level corresponding to the tip of the electrode). A summary of the atherosclerotic area can be seen in Figure 2.

Total aorta

In Control rabbits, the area involved in atherosclerosis was 32.5±21.2% vs. 10.5±5.6% in the Paced rabbits (p=0.0339) (fig 3). In five of six Control rabbits, the area of atherosclerosis was more than 18% (14.8%-63.1%). In all Paced rabbits this area was less than 18% (3.4%-17.7%). One Paced rabbit had an interesting distribution of atherosclerosis: 62.3% in aortic arc and a completely clean thoracic and abdominal aorta.

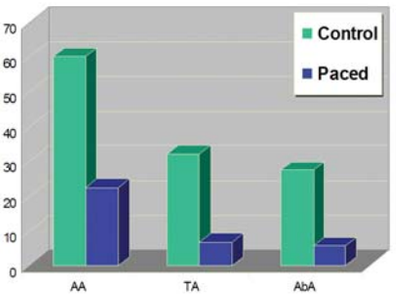

Figure 2. Atherosclerotic Area

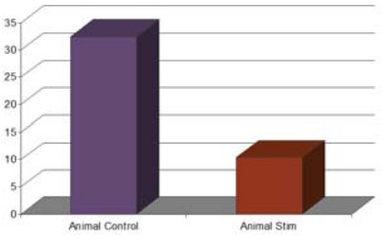

Figure 3. Mean Area: 32% Control vs 10% Stim P = 0.03

DISCUSSION

In the present study we evaluated the effect of EI in rabbits with 11 weeks of HCD and with EI delivered from a catheter placed into IVC eliminating the stimulation of muscle around aorta which was present in our previous studies. This study yielded very similar and promising results. In the thoracic aorta of Paced rabbits, only 6.8±5.2% of the area was involved versus 32.0±19.9% in Control rabbits. Similar evidence of effectiveness of electrical impulses is shown in the abdominal aorta: 5.7±1.8% (Paced) versus 27.3±18.4 % (Control). In the area closest to the pacing electrode, four of six Paced rabbits had no (0%) atherosclerotic lesions in lower part of thoracic aorta (2 cm above the tip of electrode) and in one of six Paced rabbits there was no atherosclerosis lesion in upper part of abdominal aorta (at the level of the electrode tip). Both methods created the same electrical field around the aorta and we believe this is the reason that both methods gave the same good results. However, the method of introduction of catheter into vena cava inferior (or into jugular vein for decreasing of atherosclerosis in carotid artery) is better for the clinical use than implantation of electrode in the skeletal muscle near the aorta, using surgical approach.

However, the matter is far from resolved. If we consider atherosclerosis as the lumen narrowing resulting from growth of intima (6); beneficial effects should be expected from any treatment that inhibits intima thickening by means of inhibiting collagen synthesis. In this regard, calcium channel blockers (7), derived dextrans (8), tranilast (9), protamine (10), halofugione (11), and L-minosine (12) have a proven effectiveness. Before adding EI to this list additional studies are necessary needed to confirm

its efficacy. After our first investigations with electrical stimulation delivered to psoas major muscle, we suggest that effect of decreasing the area of atherosclerotic plaques onto the surface of the aorta might be explained by excitation of the muscle or nerves. However, this current investigation with EI delivered from catheter placed into the inferior vena cava (and with the same effect on atherosclerosis area) showed, that the stimulation of the muscle or nerves around the aorta may not explain this effect.

Another possible mechanism is the change in level of cholesterol and iron ions in the blood serum or aortic wall. Iron is known to stimulate low-density lipoprotein and membrane lipid peroxidation (13) and its transition metal ions are present in atherosclerotic lesions in sufficient quantities to catalyze this reaction (14) Duffy et al (15) reported that non protein-bound iron may directly inactivate nitric oxide and iron may be mobilized from ferritin by superoxide (16), which is increased in atherosclerosis. Therefore, we suggested, if deferoxamine decreases the atherosclerotic lesion with iron chelation (17,18), low frequency EI, by creating an electrical field around the target vessels, may also decrease atherosclerotic lesions or even prevent their development by removing the iron ions from the target vessels. We had our own experimental data with another iron chelator, deferoxamine, which considerably increased angiogenesis in severe ischemic skeletal muscle (19). If the chelation of iron is needed to accelerate angiogenesis and inhibit atherogenesis, is it possible to speculate that electrical impulses change the distribution of iron in the vessel walls and lead to a reduction in atherosclerotic lesions? However, at present, in our current investigation we could not show any differences in level of iron in serum between paced and control animals (180.0±9.7 ug/dL in Control, and 177.8±22.7 ug/dL in Paced $p>0.05$). We realize that it is more important to investigate the iron deposition in aortic wall to make any conclusion and will do it in future. We also did not see any differences in cholesterol level: this increased to 1621.7±133.1 mg/dL after 11 weeks of HCD in Control rabbits and to 1580.0±422.2 mg/dL in Paced rabbits.

The other possible explanation for the obtained results could be due to the changes in calcium ion concentration. Atherosclerotic lesions have calcium granules that are intracellular and set free through cell death. Extracellular granules combine and grow to form large structures among the vast quantity of extracellular lipid droplets and cell remnants that form the core of the lesion (20). In 1999, a large cohort study was conducted in 139,849 patients in northern California. The investigators found evidence that aortic calcification was independently related to coronary heart disease risk (21). Shaw et al. (22) in a large observational data series including 10,377 patients who underwent coronary calcium screening with electron-beam CT scan, saw that coronary calcium provided independent incremental risk in addition to traditional risk factors in the prediction of all-cause mortality. Kondos et al. (23) confirmed this and posited calcification of the atheroma caused instability and rupture. However, an autopsy series done on 20 human coronary lesions by Huang et al (24) showed conflicting results. Based on their findings, the investigators concluded that calcification does not increase fibrous cap stress in typical ruptured or stable human coronary atherosclerotic lesions nor decrease the mechanical stability of the coronary atheroma. In contrast, other investigators documented the presence of calcification of the arterial wall in ruptured plaques, as well as in plaques showing superficial erosion (25, 26, and 27). Wayhs et al. (28) theorized that, though calcification might not affect the stability of a single atheroma; it might indicate the extent of the disease or some other systemic process, e.g. “inflammation.” The presence of calcification might indicate an individual’s predisposition to thromboembolic and ischemic events.

We may propose that in response to the application of EI, the calcium ions may travel out from the atheroma and stabilize the inflammation process. This process may reflect the mechanism of regression of the atherosclerosis. A future additional study is needed on this topic, measuring the influence of EI on calcium content in the atheroma.

Our study did provide evidence that EI helps preventing atherosclerosis progression and may be useful in treating atherosclerosis or peripheral vascular disease. It can be applied regardless of the degree of vessel patency or the number of involved vessels, and it does not traumatize the inner wall of the vessel. Electrodes can be implanted intramuscularly or intravenously close to target vessels, and/or externally through the use of patch electrodes.

LIMITATIONS

A limitation of this study is that we have yet to clarify the mechanism by which EI prevents atherosclerosis plaque formation and fat deposition. The assumption that EI changes iron ions concentration in the aortic wall requires to be confirmed through histological and biochemical investigations of the aortic wall. We also realize that it is necessary to investigate cholesterol deposition in the aortic wall in areas within the electrical field.

CONCLUSION

Our study showed that, within the environment of applied electrical impulses, whether applied to surrounding muscle or intravenously, low-frequency electrical impulses decrease, and even prevent, atherosclerotic deposition of aorta despite continuation of a high-cholesterol diet. These results continue to build upon previous studies and provide good rationale and belief a new treatment for such a wide spread disease may be possible.

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Complex Approach and New Aspects of Primary Disease Prevention in Children with Hereditary Risk Factors for Early Atherogenesis.

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For the first time in Russia a complex clinical functional examination of 50 children aged from 5 to 15 years from the hereditary "risk group" of early atherogenesis has been held. A group was strictly formed according to the presence of one- or two-vessel atherosclerotic coronary disease confirmed by coronarography in fathers of these children, for which they underwent endovascular procedures in young age (till 44 years) (Prof. D.G. Iosseliani). A high incidence of behavioral risk factors (pro-atherogenic and/or imbalanced diet, low motion activity, active and passive smoking) was revealed in children that were correlated to lipid profile abnormalities, clinical signs and laboratory indices of secondary immune deficiency. Significantly higher incidence of the heart's connective tissue dysplasia in form of minor cardiac abnormalities, especially of the aortic root and valve, has been determined (which was completely absent in the control group). In 8% of observations a decrease in exercise tolerance and "myocardial reserve" were objectively confirmed by cycle ergometry. A program of primary prevention and rehabilitation has been suggested with the account of family history, revealed risk factors, prenosological changes of lipid profile and immune disorders.

Keywords: *Atherosclerosis, early atherogenesis, primary prevention, heredity, immune aspects of atherogenesis, stress tests in children of "risk groups", minor cardiac abnormalities, connective tissue dysplasia.*

The priority of the strategies of primary prevention of atherosclerosis and necessity of their accomplishment in children and adolescents (WHO Technical Report Series "Prevention in childhood and youth of adult cardiovascular diseases: time for action", 1990) were established more than 3 decades ago, and subsequently confirmed by documentary evidence (1, 2, 4, 8, 14, 21, 22, 31, 32, 41, 43). The early prevention of CHD is based on the prediction of early atherogenesis in children of "risk groups" and especially in the hereditary "risk group of early atherogenesis", i.e. in children of the young patients with CHD, atherosclerosis (AS) confirmed by coronarography, or the ones who had a history of Q-wave myocardial infarction under 44 years of age (4, 8, 19, 40).

Researches unanimously supported initiation of correction of such controlled behavioral AS risk factors as hypokynesia, active and passive smoking, psychoemotional and physical overstrain (that later form the "stress-coronary behavior profile" of the adults) in childhood (29, 30, 35, 37, 39, 44, 45, 46, 50). After many years of discussions, the normalization of pro-atherogenic imbalanced dietary habits was considered to be effective enough way to reduce classic cardiovascular risk factors: arterial hypertension, dyslipidemia, hyperinsulinemia and obesity. Multicenter studies confirmed the role of increasing dietary intake of folates and vitamin B6 in the reduction of hyperhomocysteinemia risk (16, 17, 19, 21, 22, 25, 26, 27, 28, 29, 36, 49).

In recent years the investigations of immune and infectious aspects off atherogenesis have got a "second wind", since only half of patients suffering from coronary heart disease can associate the disease with the main known risk factors (age, gender, hypercholesterolemia, hypertension, diabetes mellitus, smoking and heredity). According to the modern concept the main importance in atherogenesis is attributed to endothelial dysfunction, which may be initiated by lipid and immune complexes, infectious agents, herpes virus, cytomegalia virus, influenza virus, adenoviruses and other respiratory viruses, Chlamydia and campylobacter infections (5, 11, 12, 13, 15, 24, 34, 42, 47).

The existing data suggest the role of cytomegalovirus in pathogenesis of myocardial infarction and restenosis after balloon angioplasty. It was found that viruses are able to increase atherogenicity of low-density lipoproteins by stimulating the lipid peroxidation, suppressing anticoagulant properties of endothelium, reducing the activity of lysosomal and cytoplasmic enzymes hydrolysing cholesterol ethers (13, 15, 38). Many studies confirmed that atherogenesis is associated with the chronic inflammation and that immunopathological processes in blood vessels act in synergy with known risk factors, especially with hyperlipidemia. Correlation of immune disorders with the degree of endothelial damage, platelet and coagulation shifts is being discussed. However, increase

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in the lipid peroxidation (LP) and immune disorders such as depression of phagocyte function – the most important factor of the congenital immunity that reflects the integrative abilities of immunobiological defence, immunocomplex and cell-mediated immune damage of vessels, and activation of the complement system – are considered to be the main damage mechanisms. The new importance is attached to smoking in the aspect of the endothelial dysfunction initiation and the indirect effect on atherogenesis through increased levels of atherogenic lipids with reduction of their elimination. It was determined that all mentioned processes promote the development of atherosclerosis even in moderate hyperlipidemia and in case of family history they can become a critical factor for atherogenesis acceleration (10, 12, 13, 15, 24, 32, 34, 38, 41, 42).

According to the hypothesis called “response to injury” (R. Ross, J. Glomset, 1973), just the endothelium injury of any genesis with blood clot formation, growth factors release, proliferation of media smooth muscle cells and their translocation into the intima is the basic trigger mechanism of atherosclerotic process development and open entry for secondary lipoprotein penetration into the arterial intima (5, 10, 24, 48). T.Bonnet et.al. (1988) have showed that one of the leading roles in the pathogenesis of atherosclerosis is played by the involvement of the connective tissue structures being the component of atherosclerotic plaque, vessel wall, valve apparatus, and correlating in people with coronary pathology with phenotype manifestations of undifferentiated connective tissue dysplasia of the skin, its derivatives, musculoskeletal system and facial skull (9). Studies confirmed that turbulent blood flow that occurs in presence of heart connective tissue dysplasia, including disorders of valve closing function or alterations of outflow tract, i.e. outflow ways from the heart ventricles, also plays a role in pathogenesis of lipid spots being the earliest manifestations of atherogenesis.

The objective of this study was to evaluate the cumulative “risk factors” (including behavioral and immunological disorders and phenotypic features) in children with family history of early atherogenesis to support the complex program of primary prevention, rehabilitation and immunorehabilitation.

Material and methods.

Fifty children (32 boys and 18 girls) from 35 families with history of early atherogenesis were examined and followed up, 30 children from 15 families were siblings at the age from 5 to 15 years (mean age 11.4± 3.2). Fathers of these children have been hospitalized to the Moscow City Centre of Interventional Cardioangiology (Director - Professor D.G. Iosseliani, Chief Cardiologist of the City of Moscow) with chronic coronary hear disease, exertional angina of CCS class I-II (in 93%) and acute Q-wave myocardial infarction (in 7%) at the age from 29 to 44 years (mean age 39.2 ± 5.6). All patients underwent endovascular procedures (balloon angioplasty and/or coronary artery stenting) for to one-vessel disease in 73% (with LAD lesions making 64% of the total) and two-vessel disease in 27%, which was revealed by coronary angiography.

Behavioral risk factors (rational diet, daily physical activity, active and passive smoking) were evaluated using modified by us the WHO expert group questionnaires and by our own questionnaires (4, 6, 17, 20, 21, 22, 44, 45). The children were considered to be "trained" if they were practicing intensive physical exercises during the leisure time and in sport sections not less than 6 times per month; “healthy untrained” were those practicing physical exercises 1-2 times per week during the leisure time or at school, but not in sports clubs; “inactive” or “sedentary” were the children not practicing “active physical exercises leading to increased perspiration and hurried breathing equivalent to jogging, i.e. more than walking for 60 minutes" (Duke Activity Status Index, 1989; WHO expert group questionnaires, 1981-1998, recommendations of L.V. Petrunina, 1996, 2000). Frequently ill children (FIC) (in terms of ARVI) are those who get ill > 8-10 times per year (WHO, 1999). Plasma lipid profile and immune disorders were assessed according to the WHO Level II tests (1983) at the laboratories of the Institute of Immunology of the Russian Academy of Medical Science. Quantitative characteristics of immunocompetent cells were assessed by standard technique (Boym A.) using monoclonal antibodies on a FACScan flow cytofluorometer (Becton Dickinson, USA). Functional activity of the immunocompetent cells was assessed by blast-transformation reaction (BTR) on the standard polyclonal mitogens: concanavalin A (Con A), phytohemagglutinin (PHA) and pokeweed mitogen (PWM) using the technique of Bicker K. et.al. (1983). The echocardiography on ACUSON-128-XP10 machine and cycle ergometer test (CET) with incremental work load (Watt/kg body weight) and impedancemetric monitoring of the myocardial pump and contractile functions were conducted (G.I. Kassirskiy, E.A. Degtiareva, 1998 (6, 7). The evaluation of phenotypic features and signs of connective tissue dysplasia included: genealogical analysis, evaluation of physical development and its harmonicity using Stewart percentile scales, mass-height index (MHI) connecting centile assessment of patient’s mass and height [MHI = (A/B) *100, where A – ratio of actual body mass (kg) to the 50th percentile of body mass corresponding to given age and sex, and B – ratio of actual body length (cm) to the 50th percentile of body length] and Cole indices, evaluation of minor developmental abnormalities (MDA) and minor cardiac abnormalities (MCA) with revealing Mass-phenotype or CSC phenotype (cutis, skeleton, cranium) which are markers of abnormal structure of collagen, elastic fibers and vasculature (4, 9). The data of 50 children from 48 families were compared to data received in the control group of 20 healthy children of the same age from 20 families where the parents didn’t have a history of cardiovascular pathology.

Statistical processing of the results was conducted using parametric and non-parametric statistics using Student's t-test, non-parametric Pearson's X^2-test with known number of degrees of freedom (df), significance of differences between groups was evaluated using Fisher's (F) test at a significance level a=0.05 and with known number of degrees of freedom.

Results.

In the group of children with family history of early atherogenesis there was a high incidence of "behavioral risk factors". Only in 15 (30%) children family eating habits clearly tended to be anti-atherogenic. In 19 (38%) the diet was imbalanced in important anti-atherogenic components of food, especially in fiber-containing food products, B6 and folates (daily folate intake was less than 100-200 mg/100 g and daily vitamine B6 intake was less than 0.8-1.8 mkg/100 g according to the questionnaire). Clear pro-atherogenic diet, i.e. excessive intake of food rich in animal fat and cholesterol along with insufficient intake of plant fiber and important anti-atherogenic components of food was observed in 16 (24%).

When interpreting results of smoking survey 50 (100%) children appeared to be passive smokers, their relatives started smoking at the age of 16 years in 57%, best friends were smokers in 67%. Thirty two percent of children were active and passive smokers, all started to smoke at the age of 12-14 years, 22% smoked 8-10 cigarettes per day. The answer to the question about the probability of future smoking was definitely positive in 16 (32%) children, probably positive in 18 (36%) and definitely negative in only 10 (20%) children.

The analysis of the results of children's daily physical activity in "risk group" for early atherogenesis showed that 6 (12%) children were "inactive", 19 (38%) - healthy untrained and 25 (50%) children were trained. The comparison of data on physical activity from questionnaires and objective quantitative data on physical performance (W) from stepwise incremental cycle ergometry test (CET) with work load in Watt/kg of patient's weight showed that W was high in the subgroup of trained children with mean of 2.5 ± 0.7 Watt/kg. In healthy untrained children W was 1.92 ± 0.25 Watt/kg in 66.3% of observations, i.e. did not differ significantly from that in the control group of children without hereditary taint (2 Watt/kg), and W was reduced up to 1.5 Watt/kg in 33.7% of observations. Among "inactive children" W was reduced to 1.5 Watt/kg in 66.7% and to 1.0 Watt/kg among the others. Therefore, children assigned to the "inactive" group according to the questionnaire data in most cases have objectively decreased exercise tolerance and need to undergo compulsory CET for prescribing optimal training regimens. It is important to note that one "behavioral risk factor" was noticed in 30% of our observations, two factors – in 52% and 3 - in 18%, thus confirming the necessity of "life style" correction in families of children from the hereditary "risk group" of early atherosclerosis development.

Evaluation of classical risk factors revealed that body mass index was normal for age in all cases, none of the children had increased BP values at rest, diabetes mellitus or decreased glucose tolerance. Nineteen (38%) children presented with cardiac complaints; 9 (18%) with heart pain, 34% of children with palpitation, 5 (10%) – with cardiac "intermissions". We confirmed vegetative dysfunction with arterial hypotension in 5 (10%) children. No major cardiovascular disorders were revealed during objective examination.

The analysis of mean lipid parameters in the group of children with family history of early atherogenesis showed, in general, a tendency ($p>0.05$) to increased total cholesterol (TC), low-density lipoproteins (LDL) and atherogenic index and significant ($p>0.05$) increase in very low-density lipoproteins (VLDL) and decrease in high-density lipoproteins (HDL) compared to that of healthy children from the control group. When analyzing individual results, normal blood lipid profile parameters were recorded in 30 (60%) children. Pro-atherogenic shift in blood lipid profile due to significant increase in two or three pro-atherogenic fractions of serum lipids (total cholesterol, very low-density lipoproteins, low-density lipoproteins, triglycerides and apolipoprotein B) compared to normal parameters ($p<0.05$) was revealed in 15 (30%) children from young fathers with two-vessel coronary disease (Table 1).

Table 1. Parameters of blood lipid profile in groups of children with hereditary risk factors for early atherogenesis

Parameters	Pro-atherogenic dyslipidemia	Reduction of anti-atherogenic HDL fraction	Normal lipid profile	P_{1-3}
	N=15 (30%)	N=5 (10%)	n=30 (60%)	
TC (mmol/L)	5,80±0,19	3,38±0,23	3,86±0,10	<0,05
VLDL (mmol/L)	0,44±0,04	0,47±0,07	0,37±0,10	>0,05
LDL (mmol/L)	4,02±0,19	1,97±0,18	2,15±0,10	<0,5
HDL (mmol/L)	1,38±0,04	0,98±0,03	1,43±0,06	<0,5
TG (mmol/L)	1,20±0,12	1,26±0,37	0,93±0,07	<0,5
Apo A1(mg/dl)	169,47±6,37	140,6±6,97	151,57±3,26	<0,05
ApoB (mg/dl)	70,40±3,68	54,40±4,83	52,37±2,17	<0,05
B/A1(mg/dl)	0,42±0,03	0,38±0,03	0,35±0,06	<0,05

In 5 children (10%) a significant ($p<0.05$) decrease in HDL anti-atherogenic fraction was revealed in spite of significantly younger age compared to children with normal blood lipid profile, 10.2±3.8 and 13.6±2.4, respectively; $p<0.05$. Nine among 15 children (60%) with pro atherogenic blood lipid profile shift had moderate hypercholesterolemia, in which, according to accepted criteria, blood cholesterol concentration varies from 5.2 to 6.5 mmol/L, and 6 (40%) children had a severe hypercholesterolemia with TC of more than 6.5 mmol/L.

Two-way intra-group analysis revealed that normal lipid profile was recorded in 58% of children on an anti-atherogenic diet.

In the group of patients with significant pro-atherogenic lipid profile shift, the number of children on pro-atherogenic diet was 3-fold higher than that in the group with normal lipid profile (73.33% and 13.34%, respectively; p<0.05), and the number of children on diet imbalanced in folate and B6 content was 3-fold lower (26.6% and 43.33%, respectively; p<0.05). In children with high fat intake (total score > 27 according to questionnaires) serum LDL level was the highest, and the values of anti-atherogenic HDL fraction were significantly lower (p<0.05) compared to children with minimal total score for animal fat intake. In children with low rate of vegetable and fruit intake the blood TG level was higher by 0.27±0.09 mmol/L compared to children with moderate intake of vegetable products.

In all children with pro-atherogenic dyslipidemia family traditions of prophylactic anti-atherogenic diet (0% and 43.33%, respectively; p<0.05) were completely absent.

Table 2. Correlation of eating habits and lipid disorders in children with hereditary risk factors for early atherogenesis

Lipid profile parameters/ Eating habits	Pro-atherogenic diet n=16	Anti-atherogenic diet n=15	Differences	P
ОХС (ммоль/л)	5,44±0,23	3.68±0,14	t=5,86	<0,001
ЛПОНП (моль/л)	0.43±0,05	0,35±2,03	-	>0,05
ЛПНП (ммоль/л)	3.62±0,19	2,03±0,13	t=5,78	<0,001
ЛПВП (ммоль/л)	1.39±0,03	1,34±0,07	-	>0,05
ТГ (ммоль/л)	1.19±0.14	0.85±0,26	t=1,79	>0,05
Апо А1 мг/дл	158,12±6,19	159,12±5,16	-	>0,05
Апо В мг/дл	66,50±3,13	52,4±3,12	t=3,20	<0,01

Therefore, pro-atherogenic diet violations had significant impact on the pro-atherogenic changes in blood lipid profile in at least 30% of children with family history of early atherogenesis, increasing the risk of pathology manifestation. The latter is consistent with the opinion of authors, who deem the correction of diet violations as an important tool of primary prevention of atherosclerosis and its clinical consequences and a way for mortality reduction (21, 23, 25, 26).

Comparison of the degree of motion activity versus blood lipid profile parameters showed that in the group of children with pro-atherogenic lipid profile shift compared to children with normal lipid profile, there were significantly more “inactive” children (26.67% and 6.67%, respectively; p<0.05) and 5-fold lower number of “trained” children (13.33% and 66.67%; p<0.05).

In “trained” children attending sports clubs and practicing intensive physical exercises during the leisure time, TC, TG and LDL levels were significantly lower, and mean anti-atherogenic HDL fraction level was higher. In “healthy untrained” children TC and LDL levels were almost normal and were significantly lower than that in children with “sedentary lifestyle”.

The statistical analysis of combined “behavioral" risk factors revealed that the dietary habits in trained children were significantly more often anti-atherogenic (X^2 (df = 1.29) = 3.2; p< 0.05) compared to inactive children who were on pro-atherogenic diet in 67% of cases. Thus, the degree of daily motion activity and training in children with hereditary taint affects the extent of dyslipidemia which is consistent with the data from several trials in adults (18, 21).

The comparison of blood lipid profile parameters and the incidence and pattern of smoking revealed that 53.33% of children from the group with pro-atherogenic blood lipid profile shift were active and passive smokers, while in the group of children with normal lipid profile, the number of active and passive smokers was significantly, almost 2 fold lower (26.67%). Low motion activity along with smoking initiated significant pro atherogenic shift in lipid profile (p< 0.05). In addition, significant increase in the incidence of intercurrent morbidity in the group of actively smoking children with pro atherogenic lipid profile shift was revealed.

Therefore, our data confirmed the presence and combined influence of “behavioral” risk factors in the families of children with family history of early atherogenesis and the necessity of forming a healthy lifestyle in terms of primary prevention. Multivariate analysis of the dependence of lipid profile changes on smoking and type of motion activity revealed normal lipid profile in trained children regardless of the smoking factor. At the same time, in case of combined influence of active and passive smoking factors and low motion activity a significant pro-atherogenic lipid profile shift was revealed (F(2.44), p<0.05).

Taking into consideration the available data on synergistic influence of immunopathological disorders and hyperlipidemia on early atherogenesis, we have compared the incidence of intercurrent diseases, i.e. clinical manifestations of secondary immune deficiency in children of “risk group”, versus blood lipid profile parameters.

It was determined that in general 18 (36%) children were “FICs” (more than 8-10 periods of illness per year), 10 (20%) had ARVI 5-8 times per year, and only 22 (44%) children - less than 5 times per year. The intercurrent ARVI morbidity pattern in these children with high incidence of subfebrile temperature (in 68%), bronchial obstruction (in 30%), pneumonias during the first year of life (in 30%), further exacerbation of chronic tonsillitis (in 34%) indicated the reduction of overall and immunological reactivity. In the group of children with pro-atherogenic lipid profile shift compared to children with normal lipid profile, ARVI morbidity was significantly higher (66.66% and 16.66%; respectively; (p=0.04), the incidence of pneumonia was significantly higher (p=0.032) at the age till 1 year old (in 73.33% and 6.66 %, respectively) as well as incidences of bronchial obstruction in ARVI (73.33% and 6.66%; p=0.0015), sore throat (73.33% and 6.66%; p<0.05) and exacerbations of chronic tonsillitis (93.33% and 0 %, p<0.05).

Evaluation of the correlation between the immune and lipid disorders revealed that total T-lymphocytes (CD3) counts and absolute counts of main subpopulations of immunocompetent cells did not differ depending on the presence or absence of pro-atherogenic lipid profile shift (p>0.05). At the same time, significantly higher phagocyte activity of neutrophils (p=0.049) was observed in children with normal lipid profile, and the functional activity of T-lymphocytes in the spontaneous blast-transformation reaction to standard mitogens (LBTR) was significantly (p=0.05) almost 2-fold higher, than in the group of patients with pro-atherogenic lipid profile shift (Table 3).

Analysis showed significant correlation of total serum cholesterol level with index of spontaneous FHA activation (r=0.67; p=0.015), triglyceride level and regulatory CD8 cell counts (r=-0.58; p=0.045). The above correlations are consistent with the data concerning the role of lipids and their cytotoxic fractions in membrane processes, their adverse impact on lymphocyte membrane structure with further interference with immunocompetent cell activation. Our data confirm the possibility of interdependent dyslipidemic disorders and changes in the number and functional activity of immunocompetent cells that possibly accelerates formation of pro-inflammatory mediators including oxidized low-density lipoproteins and endothelial dysfunction.

The primary causative role of immune and lipid disorders in the “risk groups” is undoubtedly ambiguous, most probably diverse and requires further studying. However, the obtained results are consistent with the conception of authors who believe that the pathogenesis of well-known “risk factor” such as lipid disorders may be of secondary importance in immune disorders, and in some cases the disorders caused by immunological imbalance could become the leading factors of pathology.

Considering the documented role of connective tissue dysplasia in disturbances of intermediary (basal) metabolism, immune disorders and atherogenesis, we have analyzed the incidence of CSC phenotype, reflecting an undifferentiated collagenopathy, which is a marker of one of the mechanisms of atherogenesis acceleration in persons with coronary pathology (9). The assessment of physical development of children by centile tables showed that disharmonious development occurs significantly more often in the main group, in 60% of observations. The signs of connective tissue dysplasia syndrome were observed in 70% of cases (in 35 out of 50 children) compared to 20% in the control group (in 4 out of 20 children; p⩽ 0.05). The incidence of physical development abnormalities correlated with the incidence of minor developmental abnormalities (MDA). The analysis of anamnestic data did not reveal correlation of unfavorable factors in pregnancy with the incidence of MDA in the examined group, while this correlation was obvious in the control group. This allowed us to assume that increase in the incidence of external MDA along with minor cardiac abnormalities (MCA) and signs of connective tissue dysplasia syndrome in children from the parents with early atherosclerosis are related to polygenic, multifactorial nature rather than to pathogenic effects in ontogenesis.

Table 3. Functional activity of T-B-lymphocytes in children with hereditary risk factors for early atherogenesis in comparison with lipid disorders.

Parameters	Pro-atherogenic dyslipidemia (1) N=15	P_{1-3}	Reduction of anti-atherogenic HDL fraction (2) n=5	Normal lipid profile (3) n=30
Spontaneous LBTR, counts per minute (CPM)	637,58±103,31	*	607,00±212.20	920±118,16
FHA stim. / LBTR, CPM	101938,00± 33585,97	**	61758,67±33196,72	105157,0±23511,66
Index of activation of FHA / PD, CPM	155,17±36,43	**	99,98±28,95	114,5±15,44
ConA stim. / LBTR, CPM	67402,83± 10045,56	**	63403,45±21837,05	65102,1±6799,04
Index of activation of Con A / PD, CPM	128,55±25,57	**	109,07±25,04	81,2±8,45
RWM stim. LBTR, CPM	61194,58± 1729,20	**	54622,67±14198	57548,5±5633,72
Index of activation of	70,40±3,68	54,40±4,83	52,37±2,17	<0,05
RWM / PD, CPM	90,68±14,29	**	93,85±11,40	75,0±9,36
Activity of NK, cytotoxity index, %	60,25±4,16	**	51,33±11,84	59,2±2,87
Phagocytosis, %	16,83±2,14	***	16,67±6,17	21,7±1,50

* p = 0,049, ** p > 0,05, *** p = 0,049

Table 4. Phenotypic particulars in families of children with hereditary risk factors for early atherogenesis

	Main group n=50	Phenotypic signs of CTD
Looking like fathers	29 (57%)	
Girls	10	6.1±0.8 signs of CTD
Boys	19	11.3±2.3 signs of CTD
Looking like mothers	29 (57%)	
Girls	10	Absent
Boys	19	6.5±1.4 signs of CTD

In the comparative within-family analysis (child-father, mother-child) phenotypic similarity was seen significantly more often between children and their fathers. The degree of stigmatization in boys of this group was the highest (mean 11.3 ± 2.3 stigmata) and almost 2-fold higher than that in girls (mean 6.7 ± 1.2 stigmata). In 13 boys who demonstrated phenotypic similarity with mothers, stigmatization was lower (mean 6.5 ± 1.4 stigmata), than in those who looked like their fathers, but significantly exceeded this parameter in 10 girls with phenotypic similarity with mothers in whom stigmatization was absent. (Table.4).

In the group of children with family history of atherogenesis a higher incidence of minor cardiac abnormalities (MCA) was revealed: 1-2 MCA in 32% and 3 and more MCA in 68% of children compared to controls (p⩽ 0.05). The incidence of phenotypic manifestations of CTD correlated directly with the incidence of cardiac stigmatization (Table 5). The incidence of cardiac stigmatization increased significantly from 50% to 90.5% of children (2-3 MCA) with

increase in the number of phenotypic manifestations of CTD (from 2-4 to 10-12).

Pathology of mitral valve (mitral valve prolapse with moderate regurgitation and abnormalities of subvalvular apparatus) (68.8%), dilatation of the pulmonary artery with moderate regurgitation (68.5%), aortic root and valve abnormalities (37.5%) in the form of borderline wide or borderline narrow aortic root, bicuspid aortic valve, aortic valve leaflet asymmetry; additional trabecules and abnormal chords in the left ventricular outflow tract in 33.3% were the most common abnormalities. In general, the incidence of the aortic root and valve MCA was higher in boys (in 13 boys and in 8 girls, respectively), and borderline wide aortic root (28.1%) was the most common MCA (in 9 boys). No minor abnormalities of aortic valve were revealed in patients of the control group ($p \leqslant 0.05$).

The turbulent blood flow that occurs in presence of valve closing function or alterations of the outflow tract, i.e. outflow ways from the heart ventricles, plays the role in the pathogenesis of "lipid spots" being the earliest manifestations of atherogenesis. The latter is well consistent with the hypothesis called "response to injury" (R. Ross, Glomset J., 1973), assuming that exactly the endothelium injury is the trigger mechanism of the development of inflammatory changes and in imbalance of agents with vasoconstrictive and vasodilatory properties, atherogenic modification of lipids, activation of the migration factors and proliferation of smooth muscle cells (9, 10, 47).

Table 5. Incidence of phenotypic manifestations of CTD and MCA in children with hereditary risk factors for early atherogenesis.

Number of MCA	Number of phenotypic manifestations CTD (n=50)		
	2-4 (n=12)	5-8 (n=17)	10-12 (n=21)
1-2	6 (50%)	5 (33.4%)	2 (9.5%)
2-3	6 (50%)	12 (66.6%)	19 (90.5%)

Table 6. Minor abnormalities of aorta in children with hereditary risk factors for early atherogenesis

Minor abnormalities of the aortic valve aortic valve and root	Основная группа (n=50)		
	Boys n=32	Girls n=18	Total n=50
1. Borderline narrow aortic root	2 (6%)	1 (5,5 %)	3 (6%)
2. Borderline wide aortic root	9 (28,1%)	4 (22,2%)	13 (26%)
3. Bicuspid aortic valve	2 (6%)	1 (5,5%)	3 (6%)
4. Asymmetry of the aortic valve leaflets	4 (12,5%)	2 (11,1%)	6 (10,7%)
5. Prolapse of the aortic valve leaflets	2 (6%)	2 (11,1%)	4 (8%)
6. Deformation of LV outflow tract due to systolic thickening of IVS	1 (3,1%)	-	1 (2%)
7. Regurgitation 1+ at the aortic valve	7 (21,8%)	3 (16.67%)	10 (20%)

In the presence of MCA in the form of additional trabecules and abnormal chords in the outflow tract of LV, patent foramen ovale, dilatation of the pulmonary artery, the mean exercise tolerance (W) in the examined children was not significantly lowered compared to the control group of healthy untrained children (1.87±0.7 and 2.2±0.5 Watt/kg, respectively; $p \geqslant 0.05$) and did not differ depending on the type and number of minor cardiac abnormalities listed above. The mean reduction of W up to 1.66±0.3 Watt/kg was observed in children with mitral valve prolapse, MCA of the aortic root and valve and additional trabecules and chords in the medium third of LV. An adequate linear growth of CI consistent with classical conception of increase in the cardiac output and oxygen consumption proportionally to the workload was observed on exertion in only 40% of MCA observations. In 60% of examined persons a "plateau" or inadequate increase in the cardiac index (CI) was observed at one of the workload increment steps before reaching submaximal heart rate, i.e. so called "myocardial reserve" was quantitatively determined. These met functional criteria for latent systolic (44%) and diastolic (36%) myocardial dysfunction (reduction of the contraction index, inadequate increase in the stroke index (SI), inadequate change in LV filling pressure).

In view of the fact that no pathology of aortic valve was revealed in the control group of patients, the increase in the external stigmatization incidence can be considered an additional "risk marker" of early atherogenesis in children with risk factors for early atherogenesis, because it reflects the involvement of connective tissue structures and correlates with the incidence of minor abnormalities of the aortic valve and root where the early manifestations of atherogenesis are seen most early (r=0.62).

According to the study results it was determined that 60% of children required correction of behavioral risk factors, 70% – of diet violations, 50% – of the motion activity, 100% – of pernicious habits, 40% – of pro-atherogenic lipid disorders, and 36% required correction of clinical manifestations of secondary immune deficiency (SID).

Based on the conducted studies we developed a program of primary prevention and rehabilitation of children from the hereditary "risk group" for early atherogenesis, that includes organizational aspects, investigation of "behavioral" risk factors and immunobiochemical screening to support the primary prevention approach and pathogenetically grounded rehabilitation methods.

In the presence of latent myocardial dysfunction according to the results of exercise tests, individual regimens of motion activity were developed (L.V. Petrunina, O.A. Mukhanov). Considering the favorable influence of the diet correction on dyslipidemia and pre-nosological nature of secondary immune deficiency, we did not use immunotropic and lipotropic agents. In 100% of observations correction included 2 agents. Nutraceutical phytocom-

plexes and antioxidants with the strength of biologically active substances of no more than 1/6 of the pharmaceutical analogue according to Federal Regulations and preparations containing potentiated biologically active substances of vegetable origin in low doses were used. In part of children (in 40% of observations) cardioprotectors (succinate-containing drugs) and agents for correction of collagenopathies (ascorbic acid, glucosamine and chondroitin preparations, phytoantioxidants) were used.

Correction for 6 months in children from the hereditary "risk group" of early atherogenesis resulted in the significant decrease in TC, TG and LDL cholesterol over time compared to baseline examination.

Children with initial pro-atherogenic dyslipidemia demonstrated the most evident (p<0/05) reduction of 2-4 parameters of pro-atherogenic fractions of TC, LDL cholesterol, TG and atherogenic index (Table 7).

Comparative evaluation of the immune status change over time in children with initial pro-atherogenic shift in lipid profile revealed significant (p<0.05) increase in quantitative values of CD3, CD4 and phagocytosis and decrease in D16 and CD19 counts, significant increase (p<0/05) in functional activity of NK-cells compared to baseline.

These changes confirmed improvement of cellular immunity parameters with relative decrease in humoral and cytotoxic immunity level. In children with initially normal blood lipid profile the similar changes of immune status parameters over time were observed, i.e. positive changes of immune status in children of "risk group" of early atherogenesis was recorded regardless of the presence or absence of the initial pro-atherogenic shift in lipid profile (Table 8).

During 3 months of observation in the course of active primary prevention and pathogenetically grounded correction in the spring period (March – April – May) mild ARVI (rhinitis) was observed only in 2 children (4%), and it was 8-fold lower than that in the similar period of the previous year (32%).

Our study and developed on its basis program of primary prevention and rehabilitation in children from the hereditary "risk group" of early atherogenesis support differentiated approaches and possibility of sufficiently effective achievement of positive clinical and laboratory results in behavioral, lipid and/or immune disorders.

Table 7. Change over time in pro-atherogenic dyslipidemia before and after the correction course over 3 months.

Parameters (mmol/L)	Baseline examination n=15	After correction n=15	P
TC	5,80±0,19	4,10±0,30	< 0,001
VLDL	0,44±0,04	0,37±0,04	>0,05
LDL	4,02±0,19	2,26±0,30	<0,001
HDL	1,38±0,04	1,48±0,13	>0,05
TG	1,20±0,12	1,02±0,10	>0,05
AI	2,91±0,75	1,52±0,23	<0,05
Apo A1mg/dl	169,47±6,37	167,80±18,79	>0,05
ApoB mg/dl	70,40±3,68	64,80±4,45	>0,05
B/A1mg/dl	0,42±0,03	0,41±0,07	>0,05

Table 8. Change over time of immunological parameters and phagocytosis in 15 children with pro-atherogenic dyslipidemia

Parameters			P
	Before correction	After correction	
CD3%	58,50±2,31	69,01±1,26	<0,05
CD4%	29,58±0,85	39,80±0,20	<0,05
CD8%	27,25±0,99	29,8±1,20	>0,05
CD16%	21,08±0,54	13,20±1,06	<0,05
CD19%	18,96±0,96	16.01±1,20	>0,05
CD4 / CD 8%	1,03±0,04	1,00±0,04	>0,05
Spontaneous LBTR, CPM	637,58±103,31	640,40±48,83	>0,05
FHA stim. LBTR, CPM	101938,01± 33585,97	106337,10±498,69	>0,05
Index of activation of FHA / PD, CPM	155,17±36,43	171,90± 20,73	<0,05
ConA stim. / LBTR, CPM	67402,83±10045,56	96335,60±6232,78	>0,05
Index of activation of Con A / PD, CPM	128,55±25,57	139,80±18,49	>0,05
RWM stim. LBTR, CPM	61194,58±1729,20	51036,40±5012,42	>0,05
Index of activation	169,47±6,37	167,80±18,79	>0,05
of RWM / PD, CPM	90,68±14,29	84,30±15,46	>0,05
Activity of NK cytotoxity index, %	60,25±4,16	54,80±3,20	>0,05
Phagocytosis, %	16,83±2,14	20,40±2,60	=0,049

CONCLUSIONS

1. The compex program of primary prevention and rehabilitation in children with hereditary taint of "early" atherogenesis should be based on the objective information obtained through complex functional examination taking into account the relationship between hereditary, behavioral, hyperlipidemic, immune and infectious disorders in early atherogenesis.
2. Forty percent children from the hereditary "risk group" require correction of pro-atherogenic lipid disorders. Degree of pro-atherogenic shift in blood lipid profile in children with hereditary taint of early atherogenesis correlates significantly with pro-atherogenic diet, hypodinamia and smoking, and increases when several "behavioral" risk factors are combined.
3. Immune disorders are observed in 60 % of children with hereditary taint of "early" atherogenesis and are more marked in the presence of pro-atherogenic blood lipid profile shift.
4. Immunoregulatory dysfunction in children

with hereditary taint of early atherogenesis is characterized by the phagocytosis impairment, quantitative imbalance of T-lymphocytes, B-lymphocytes and natural killers and is accompanied by the differently directed changes of immunocompetent cell activity.

5. Significant increase in the incidence of heart connective tissue dysplasia and especially in the incidence of minor cardiac abnormalities of the aortic valve and root in boys with hereditary taint of early atherogenesis who phenotypically look like their fathers needs special observations of child cardiologists and pediatricians.
6. Studying the hemodynamical adaptation to exertion allows to identify the risk group for myocardial dysfunction in patients with hereditary taint of early atherogenesis and to objectify recommendations on physical activity.

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JUBILEE

Elena Degtiareva

On October 8, 2010 the colleagues have congratulated the Chief Physician of Moscow Pediatric infective clinical hospital N6 Elena Degtiareva on the occasion of her jubilee.

In 1974 Dr Degtiareva graduated cum laude from the pediatric faculty of the 2nd Moscow State medical institute named after N.I. Pirogov. From 1976 through 1981 she has worked in Pediatric clinical hospital N6 as a physician in the intensive care ward. From 1981 through 1997 she has worked in Bakoulev Scientific Center for Cardiovascular surgery of Russian Academy of Medical Sciences, where she made her way from a cardiologist to the leading research worker. From April 1998 to 2001 Dr. Degtiareva was Deputy Director for scientific work in Moscow City Center of Interventional Cardioangiology. From December 2001 till now she is Chief Physician of Moscow Pediatric infective clinical hospital N6.

Dr. Elena Degtiareva received the highest certification category as the pediatrician, the cardiologist and the organizer of healthcare.

In 1987 she defended her Ph.D. thesis on cardiology under the scientific direction of Professors Guenrikh Kassirsky and Anatoly Malashenkov. The subject of this thesis was “Evaluation of the efficacy of patients rehabilitation after aortic replacement on the base of the data on myocardial pumping and contractile functions”. In 1996 she upheld her Doctor thesis on the subject “Significance of non-surgical factors in surgical treatment of congenital heart diseases”. This thesis, prepared under scientific guidance of Academician of Russian Academy of Medical Sciences Vitaly Boukharin, summarized the authoring, immunological, bacteriological and functional aspects of postoperative complications in cardiac surgery.

Dr Degtiareva steadily combines medical, consultative and organizational work with research and pedagogical activities. From 2003 she is Academician of Russian Academy of Natural Sciences, and in 2008 she obtained the title of Professor.

Dr. Degtiareva participates in lecturing cycles of post-graduate medical education for pediatric cardiologists and cardiologists under the auspices of Research Institute of Pediatrics and Pediatric Surgery, Moscow City Center of Interventional Cardioangiology and Russian University of Nations Friendship, holds an elective course on pediatric cardiology at Moscow faculty of Russian State Medical University. She is member of Scientific Dissertation Council of Moscow City Center of Interventional Cardioangiology.

From 2001 till 2007 Dr. Degtiareva was President of pediatric section of Russian Scientific Society of Cardiology, from 2006 till now she is Vice-President of the Association of pediatric cardiologists of Russia, from 2009 - President of pediatric section of Russian Society of cardiosomatic rehabilitation. She actively participates in the work of Moscow Society of Pediatricians and is a member of the Executive Committee of Russian Homeopathic Society. From 2000 she is a member of the Organizing Committee and co-chairperson of the sessions of congresses “Pediatric Cardiology”, Russian National congresses of cardiologists, congresses “New Technologies in Pediatrics and Pediatric Surgery”, scientific and practical conferences on sports medicine.

Dr. Degtiareva is the author of over 110 published works, methodical recommendations, chapters in textbooks, 4 books (issued in 1998, 2000, 2005, 2009), top-priority research works in the fields of infective and immune aspects of cardiac pathology, rehabilitation in pediatric cardiology; she was the initiator of the study of problems of pathological “sportsman heart” transformation in pediatric cardiology.

In 2006 she won the competition “Woman-Director of the Year” in the field of healthcare led by the Government of Moscow. She received several certificates of Merit from the Ministry of Healthcare and Social Development of RF (2005, 2010.), Department of Healthcare of the Northern administrative district of Moscow (2008), Head Office of Emergency Ministry for Moscow (2010).

From 2010 Dr. Elena Degtiareva is a member of the Community Council at the prefecture of the Northern administrative district of Moscow. The same year Russian Academy of Natural Sciences awarded to Dr. Degtiareva a Silver Ivan Pavlov medal for her merits in the field of healthcare