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Contents

Significance of Factors Influencing Optimization of Stenting of the Left Main Coronary Artery

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Key words: CHD, stenting, left main coronary artery

List of abbreviations:
CABG - coronary artery bypass grafting
IABP - intra-aortic balloon pump
IVUS - intravascular ultrasound
CHD — coronary heart disease
LV – left ventricle
LCA – left coronary artery
MSCT – multispiral computed tomography
AMI — acute myocardial infarction
CVA – cerebrovascular accident
OTHT – orthotropic heart transplantation
EF – ejection fraction
CRF – chronic renal failure
PTCA – percutaneous transluminal coronary angioplasty

INTRODUCTION

During the initial era of implementation of angioplasty procedures into clinical practice, and especially for the left main coronary artery, this procedure was performed only if surgical treatment was refused. At that time it was due to insufficiently high effectiveness of balloon angioplasty: high rate of the left main coronary artery restenosis and considerably high level of procedure-related risk (1). Therefore, only single observations on the left main coronary artery PTCA were reported at that time. (2). However, with the improvement of the technique of endovascular treatment (implementation of stents and the development of drug-eluting stents), and the accumulation of experience in procedure performance, the effectiveness and number of the left main coronary artery stenting cases increased, and currently the left main coronary artery stenting is performed in many Russian clinics. Thus, competitive ability of the endovascular method versus CABG was demonstrated in the left main coronary artery lesion.

The basic problem of the left main coronary artery stenting seemed to be solved, but there are still some questions to be solved, and their solution might allow optimizing the usage of this method. These include: search of criteria allowing to determine the safe time of blood flow arrest in LCA, determination of indications for surgical or endovascular treatment of the left main coronary artery lesion, optimization of stenting technique, determination of the role of IABP in angioplasty, significance of concomitant pathology for the effectiveness of treatment, IVUS and MSCT role in diagnostics and assessment of the treatment efficacy in the left main coronary artery lesion.

This study was aimed to the search of solution for these problems.

CHARACTERISTICS OF THE EXAMINED GROUP OF PATIENTS

During the period from 1999 through 2007, PTCA of the left main coronary artery was performed in 88 patients. Distribution of procedures by year is shown in Figure 1.

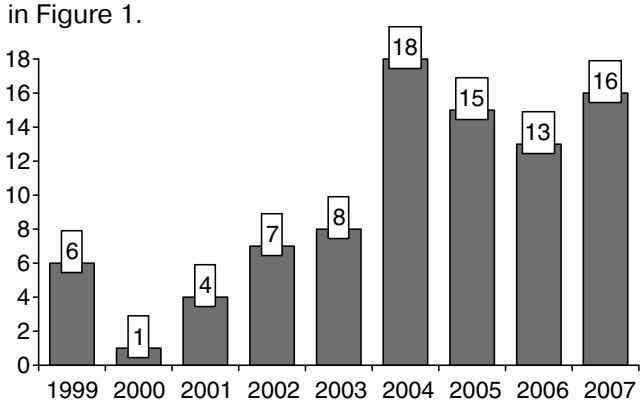

Figure 1. Number of interventions on the left main coronary artery by year.

Main clinical characteristics of patients are shown in Table 1.

As evident from the presented data, the majority of patients had risk factors for CHD development. Many patients were at high risk of surgical treatment (mean Euroscore of 5.81).

Clinical manifestations of CHD are shown in Table 2.

It should be noted that approximately one-third of patients had symptoms of unstable angina and AMI.

In two cases patients in the state of cardiogenic shock were transferred to the cathlab after CABG performed under extracorporeal circulation. We did not include these two cases in the examined group because we did not want to compromise the results of the left main coronary artery stenting, as we believed that death in these cases was caused by severe alterations in circulation, metabolism and myocardial function but not by complications of the left main coronary artery stenting. We paid attention especially to the fact that IABP use was not effective

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Table 1. Baseline clinical characteristics of patients.

Age (years)	59.96±9.98
Males, %	78.4
Diabetes mellitus, %	12.5
Arterial hypertension, %	73.9
Smokers, %	67.0
Hypercholesterolemia, (%)	55.7
EF,%	57.2±9.81
Main artery protected, %	9.1
Previous PTCA, %	9.1
Previous MI, %	67.0
Previous CVA, %	5.6
Cardiac failure, %	15.9
Peripheral artery lesion, %	5.7
Euroscore	5.81± 3.27

Table 2. Clinical manifestations of CHD.

Stable angina, %	68.76
Unstable angina, %	21.87
AMI, %	9.37

and did not improve hemodynamic parameters in these cases.

Most patients with stable angina were in functional class III-IV.

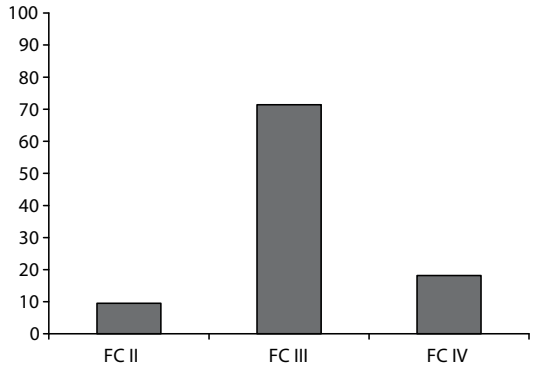

Figure 2. Patients distribution depending on clinical signs of stable angina.

Our study included 8 patients aged over 70 years, 4 patients with severe renal failure, 8 patients with EF <40%, 1 female patient with the transplanted heart.

Table 3. Concomitant pathology influencing the procedure.

Age over 70 years, %	9.1
Chronic renal failure (CRF)	4.5
EF < 40%	9.1
Orthotropic heart transplantation	1

The left main coronary artery lesion was revealed in 93.18% of patients during coronary angiography. The left main coronary artery dissection requiring its stenting occurred in 6 cases during PTCA of LCA branches. The left main coronary artery lesion localization is shown in Table 4.

Table 4. Localization of the left main coronary artery lesion.

Orifice, %	13.33
Middle third, %	23.33
Terminal segment, %	63.33
Dissection, % (n)	6

The analysis revealed the prevalence of patients with lesion of the terminal segment of the left main coronary artery.

In the majority of cases the left main coronary artery lesion was associated with other arteries' lesions. Distribution of patients depending on concomitant coronary lesions is shown in Table 5.

Table 5. Characteristic of coronary artery lesion by groups.

Isolated lesion, %	4.5
LCA + 1 CA, %	18
LCA + 2 CA, %	36.4
LCA k + 3 CA, %	41.1
RCA occlusion, %	18

Concomitant LAD lesion was the most frequently present (approximately in 85%).

CARACTERISTICS OF PROCEDURES

PTCA with stenting was performed in all 88 patients. Thirty three bare stents and 68 drug-eluting stents were implanted. Sirolimus-eluting stents were used in 56.36% of cases; paclitaxel-eluting stents were used in 43.63% of cases. Basic characteristics of implanted stents are shown in Table 6.

Table 6. Characteristics of performed stenting.

	Ordinary stents	DES	P
Mean stent diameter. mm	3.34 ±0.35	3.35±0.33	p>0.05
Mean stent length, mm	13.7±5.58	18.72±8.56	p<0.05
Number of stents per patient	1.03±0.18	1.21±0.41	p<0.05
Predilatation, %	78.12	85.71	p>0.05
Postdilatation, %	81.24	85.71	p>0.05
Bifurcation stenting using 2 stents, %	3.12	21.42	p<0.05

In bifurcation stenting different methods were used (see Table 7).

Intravascular ultrasound (IVUS) was used in order to assess the degree of stenosis in case of angiographically "ambiguous" lesions. Main criteria of lesion significance were not only percentage of artery narrowing but residual lumen area. Residual lumen

Table 7. Methods of bifurcation stenting used in the terminal segment of the left main coronary artery.

	Ordinary stents	DES
Culotte, n		4
Crush, n		4
Kissing, n	1	1
T-stenting, n		5

area of ⩾ 6 mm2 was considered sufficient for the left main coronary artery (Nishioka, 1999). Morphology of lesion, diameter and length of required stent were clarified, and the results of performed intervention were assessed by IVUS as well. IVUS was used in 10 procedures (11.4%). Intravascular manometry was performed during 2 procedures in order to assess hemodynamic significance of the lesion, particularly the lesion of the left main coronary artery, using Radi Analyzer device (Radi, Sweden).

Intra-aortic balloon pump (IABP) was used in 28 procedures (31.9%). In 22 (78.7%) out of these cases IABP was installed for preventive purposes prior to stenting procedure. In 6 cases (21.42%) IABP was installed during PTCA for indications in case of unstable hemodynamics or prolonged angina attack, refractory to medication.

Platelet IIb/IIIa receptor blockers were used in 8 procedures. The indications for their usage were signs of acute CA thrombosis development during the procedure.

IMMEDIATE RESULTS

Success rate of procedure was 98.86%. Extravasation of contrast agent requiring urgent CABG occurred in 1 case in the group of bare stents.

One patient in the "ordinary" stent group developed non Q-wave anterior myocardial infarction. One female patient from the same group and one female patient from the drug eluting stent group developed CVA. Vascular complications at the site of arterial access were revealed in 5 patients; subcutaneous hematoma developed at the puncture site have been treated conservatively.

LONG-TERM RESULTS

At the initial stage, from 1999 till 2003, patients were not followed up actively after stenting and appealed by themselves in case of symptoms recurrence. Later on, 52.2% of patients were followed up actively. Mean observation period was 18.7.1±9.1 months. Control coronary angiography was performed in 12 patients. In the group of bare stents restenosis of the left main coronary artery developed in 4 patients (13.33%). One patient (3.22%) underwent CABG in 1 year. In the drug-eluting stents group one patient (1.81%) died of non-cardiac complications at 1 month. One patient developed stent thrombosis in 4 months after intervention, non Q-wave AMI developed due to spontaneous plavix discontinuation. PTCA was performed; the postoperative period was uncomplicated. One female patient developed ostial restenosis of the CxB. PTCA was performed. One patient underwent CABG 14 months after the procedure due to appearance of new lesions. One patient developed spontaneous recanalization of the occluded artery 6 months after stenting without recanalization of the occluded LAD. PTCA with stenting was performed. The stent in the left main coronary artery was patent without signs of restenosis. No hemodynamically significant arterial stenosis was revealed in this patient. One patient in the "ordinary" stents group developed CVA 10 months after the left main coronary artery stenting.

MSCT was performed in 18 patients within 8 – 28 months. No changes in the left main coronary artery projection were revealed. In one female patient a de novo LCA branches lesion was revealed, which was confirmed angiographically; she underwent PTCA.

Thus, stenting of the left main coronary artery proved to be an effective and safe procedure. Patients showed significant improvement of clinical presentation of CHD and increase in physical tolerance. The use of drug-eluting stents allows to reduce the repeated interventions rate.

DISCUSSION

The analysis of 88 stenting procedures performed in the left main coronary artery allowed us to made some conclusions and assumptions as well as to raise some questions about the role of endovascular methods in the treatment of the left main coronary artery lesion and optimization of its performance. Certainly, the fact of the efficacy and safety of the left main coronary artery stenting (taking into consideration that approximately 30% of patients were denied surgical treatment due to severe myocardial and vascular lesion) is an important conclusion from the data obtained over 8 years.

The fact of discrepancies between our data and literature data about the influence of concomitant pathology on the effectiveness of the left main coronary artery stenting was important and somewhat unexpected for us. It was shown that patients with low ejection fraction, severe mitral regurgitation, renal failure, with previous CVA had worse immediate and long-term results of stenting compared to patients without associated pathology (3). In our opinion, this situation needs to be divided into two components: performance of stenting procedure itself and the severity of concomitant pathology.

In case of complications (occlusion or coronary artery dissection) occurring during the procedure and leading to a decrease in myocardial blood supply and ischemia development, a stenting procedure may be considered as a factor worsening organs' function and patient's condition.

In case of uncomplicated procedure, revascularization restores the heart blood supply and improves the patient's prognosis. In these situations the cause of fatal complications consists, in particular, in the severity of associated pathology.

The high 1-year mortality rate (up to 18%) in patients with severe concomitant pathology (4), in our opinion, should not limit PTCA performance, and questions of treatment and prevention should be solved together with revascularization.

Our little experience with the left main coronary artery stenting in 7 patients with ischemic cardiomyopathy allowed us to understand that it is necessary to perform PTCA using IVUS in such patients. The indices of EF and LV volume did not change, but patient's general condition and working capacity improved significantly; in our opinion, these was due to the increase of blood supply following PTCA, the presence of functioning but initially ischemic myocardium, and the increase of heart's functional reserve (6). 4-year follow-up of these patients allows to consider the left main coronary artery stenting to be effective in such cases.

In our opinion, one of limitations of the previous analyses of the results of endovascular intervention in the left main coronary artery consisted in the fact that the factor of initial severity of patient's condition was not taken into account. However, the findings of our study did not confirm the literature data. Seven patients aged over 70 years (8%), 4 patients with severe renal failure (4.5%) and 8 patients with EF<40% (9.1%) were included in our study. Immediate and long-term results in this group of patients did not differ from the results of other patients.

The search for the criteria of the safe duration of blood flow arrest in the LCA is a very interesting and important issue. We revealed that this time is 25-30 seconds for the cases with occluded RCA and the cases of severe myocardial damage, as judged by systolic and pulse blood pressure decrease by the end of blood flow arrest. With blood flow restoration the parameters of blood pressure returned spontaneously to the initial values (Figure 3).

Taking into consideration the importance of blood flow arrest in the LCA for the whole heart blood supply, in general, we revealed some technical features allowing to optimize the results of the LCA stenting.

Thus, in case of severe stenosis of the terminal segment of the main artery or of the orifices of its branches we consider it reasonable to introduce two guidewires and two balloon catheters into the distal third of the guiding catheter, and only after that to introduce them into the arteries so that to have a possibility of maximum fast kissing dilatation in case of lumen occlusion by the instruments, which reduces the duration of myocardial ischemia.

Furthermore, in severe lesion of the trunk and orifices of the RCA and the CxB we consider it reasonable to perform predilatation by balloons of small diameter (1.5 – 2.0 mm) which allows to improve blood flow in these segments to a certain extent and to increase the safety of subsequent stent positioning, on the one hand, and to avoid occluding dissection that may develop with the use of balloons with diameter of 2.5 mm and more.

We believe it is very important to have the instruments, which may be urgently needed during the intervention, available for the immediate use.

While considering a method of myocardial revascularization in patients with the left main coronary artery lesion, it is reasonable to define the criteria allowing to assess the situation limiting the use of PTCA. Our experience allows to define certain situations in which it would be preferable to use CABG for myocardial revascularization:

1. A lesion of the terminal segment of the left main coronary artery combined with ostial lesions of three and more significant branches arising from it. In such situation PTCA can lead to stenosis or occlusion of one of them. Furthermore, the presence of several branches originating from the left main coronary artery complicates the procedure and increases the risk due to difficulties with the visualization of the terminal segment of the LCA and its branches' orifices.
2. Eccentric stenosis of the left main coronary artery especially with calcium inclusions. Such arteries can be severely injured during stenting procedures (5). In this situation the stent also cannot adhere adequately to the arterial wall, thus increasing the risk of thrombosis and restenosis.
3. The CxB originating from the LCA at the angle of <90 degree that makes difficult to introduce an instrument into the CxB.
4. The left main coronary artery lesion and extended lesions of the proximal segments of the arteries combined with intact peripheral vessels.
5. Significant difference between the diameters of the left main coronary artery and originating branches.
6. Presence of chronic occlusions of the RCA and one of the LCA branches in the absence of real chances to perform successful recanalization.

In such cases, in our opinion, endovascular treatment is reasonable only when surgical treatment is refused.

In our opinion, IABP use is worth of detailed analysis, as still there are no clear indications for its use during stenting of the left main coronary artery. At initial stage we had no opportunity of its performance. Further we used IABP more widely because this method for blood supply support allows to increase the safety of procedure and to create more comfortable conditions of its performance both for patients and operator.

IABP is known to relieve severe clinical manifestations of myocardial ischemia by decreasing both preload and afterload which results in the improvement of myocardial perfusion and heart failure symptoms (7). Due to this fact IABP use in severe disorders of cardiac performance normalizes hemodynamic parameters. IABP is recommended in marked CHD symptoms or in acute heart failure, however manifestations of these conditions are typical for almost each patient with hemodinamically significant LCA stenosis.

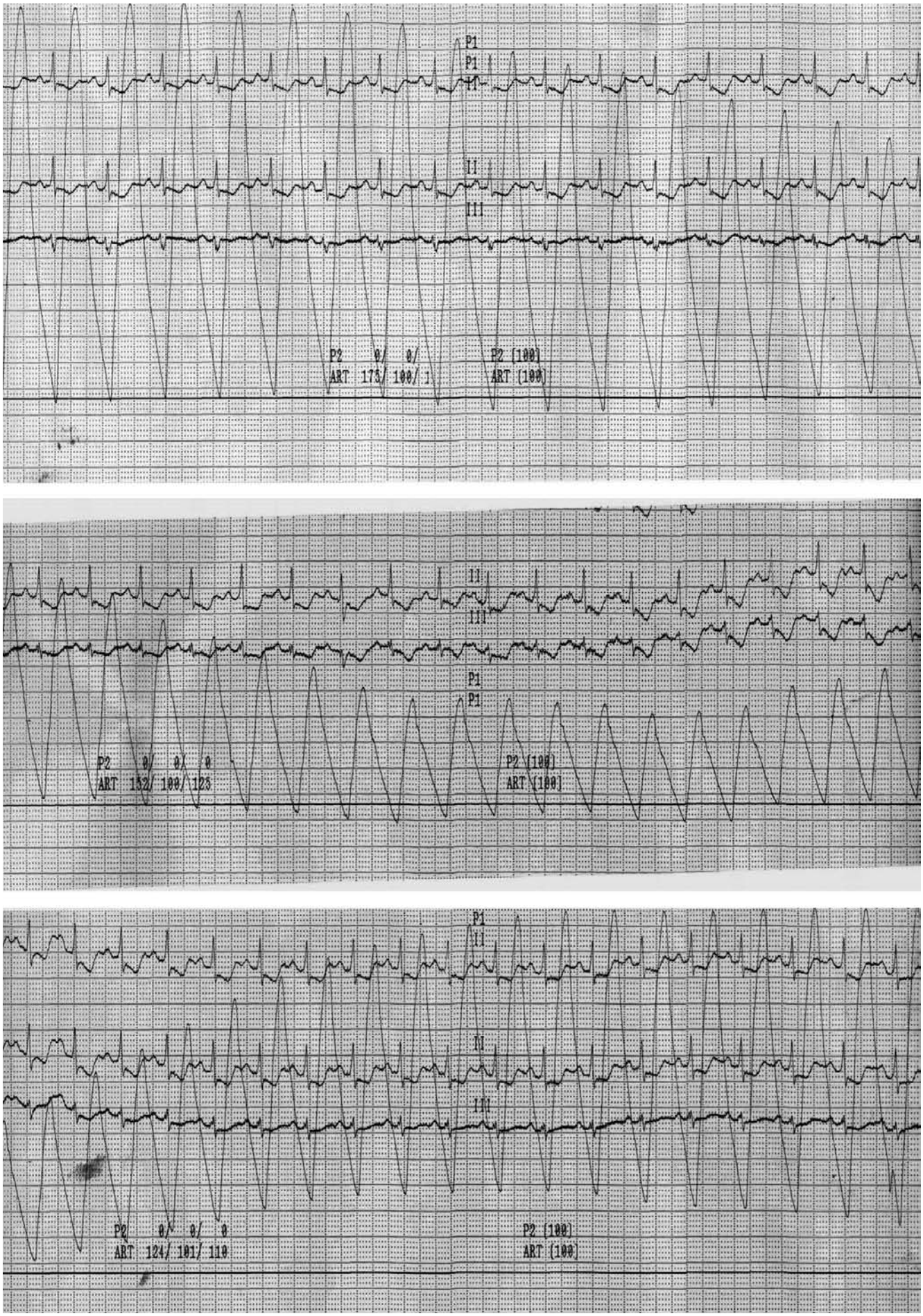

Figure 3. Change in systolic and pulse pressure during blood flow arrest in the LCA.

We used IABP rather widely not only if needed but with preventive purposes in patients with marked clinical manifestations of CHD, signs of heart failure, which can be increased or provoked by stenting procedure. This method allows to increase procedure safety, to create more comfortable conditions of procedure performance both for patient and operator, IABP can be used as a certain functional test for objective choice of treatment strategy especially in marked hemodynamic changes. Therefore, we perform preventive IABP before stenting in patients with severe coronary disease, especially when dealing with the single patent artery. IABP was used during stenting in 28 patients; in the left main coronary artery stenting we performed preventive IABP in 79% of cases and afterwards we started the procedure. In 21% of patients with less marked clinical manifestations we performed puncture of two femoral arteries with one arterial introducer left for urgent IABP placement, prepared IABP device to start its work rapidly within 5-7 minutes after appearance of indications. There was clear effect from IABP in all cases.

In our opinion, IABP can be used not only as for treatment purposes, but also as a functional test while considering the advisability of intervention in patients with severe myocardial damage. The reason for this hypothesis were two cases of the left main coronary artery stenting with lethal outcomes in patients with cardiogenic shock, marked disorders of coronary circulation, metabolism, and mechanical LV activity, admitted for PTCA following CABG. It was important that IABP performance practically did not improve hemodynamic parameters in these patients, and we qualified this as a total depletion of the heart functional reserve, that made us to put in question the necessity of stenting of the left main coronary artery in such patients. Even short term interruption in LCA blood flow (within 5-10 minutes) is worse tolerated by exhausted myocardium than in stable CHD and can be a decisive factor in such circumstances.

Observation of another patient who was denied stenting due to high risk (as we believed) of its performance, related with marked CHD manifestations, unstable hemodynamics and heart rate and absence of effect of IABP, in our opinion, proved this viewpoint. However, in approximately one day on the background of patient condition improvement and stabilization of hemodynamics with IABP use, successful PTCA with the left main coronary artery stenting was performed.

We understand that these single observations are rather supporting the need of studying of this question ut not any conclusions, and in our practice we start performing the left main coronary artery stenting only if clinical or hemodynamic effect of IABP is obtained, because currently we consider this criteria to be the only objective one for assessment of appropriateness of revascularization performance.

CONCLUSION:

In our opinion, a problem of determination of indications for one or another method for treating lesion of the left main coronary artery remains inadequately developed. Such factors as lesion localization, its morphology, number of branches originating from the left main coronary artery, character of coronary artery lesion, presence of concurrent pathology influences treatment strategy for the left main coronary artery. A small number of observations do not allow to develop the clear system of indications and contradictions for one or another method of treatment. However, the left main coronary artery stenting showed itself as the effective and safe method of treatment for the left main coronary artery lesion.

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Types of ST Segment Resolution during Thrombolytic Therapy in Patients with Acute Coronary Syndrome

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Reperfusion therapy is the basic treatment strategy for patients with acute coronary syndrome (ACS) and ST segment elevation (1, 2, 3). Choice of reperfusion treatment method is determined by time from onset of pain, patient's prognosis, thrombolytic therapy risk, availability of qualified laboratory for transluminal balloon angioplasty performance (1, 2, 3). Currently the thrombolytic therapy is the most widely used method of reperfusion therapy. According to Russian Scientific Society of Cardiology (RSSC) data, the use of thrombolytic therapy allows to save additionally 30 lives per 1000 patients treated during the first 6 hours after onset of disease, and 20 lives per 1000 patients treated within 7-12 hours after onset (3).

A coronarography with blood flow determination in the infarct-related artery according to TIMI score is the gold standard of the thrombolytic therapy efficacy assessment (4). In clinical practice the preference is given to indirect criteria including disappearance of pain, restoration of haemodynamical and/or electrical stability of the myocardium, changes in damage biomarker levels and resolution of ST segment on electrocardiogram (ECG) (2). The evaluation of ECG changes over time is the most available and informative indirect method of thrombolytic therapy efficacy assessment. The comparison of discrete ECG recordings before and after thrombolytic therapy is a method routinely used in clinical practice. The decrease of ST elevation by 50% from baseline is the generally accepted criteria for ECG changes evaluation (2, 3). However, the methodical aspects of the assessment of thrombolytic therapy efficacy by ECG criteria including number of leads used for evaluation, timing of control ECG registration, reference degree of ST decrease, and benefits of continuous ECG monitoring are discussed actively in literature (5, 6, 7). This study is dedicated to the investigation of the possibility of thrombolytic treatment efficacy assessment in patients with ACS using continuous 12-lead ECG monitoring.

MATERIALS AND METHODS

Patients with ACS with ST elevation and without contraindications to thrombolytic therapy, hospitalized within 6 hours after the occurrence of symptoms, were included in the study. Patients with bundle branch block and baseline scarry changes on ECG were not enrolled in this study. Investigation group consisted of 36 patients (25 male) aged from 36 to 71 (mean age 55±11 years). Patients were hospitalized in the intensive care unit in 25 to 360 minutes (mean 195±72) from pain onset. Forty four percent of examined patients had inferior AMI, 51% - anterior AMI, circular AMI was revealed in 4% of patients. Ejection fraction estimated by echocardiography using Simpson's method was within 33% to 64% (mean 50±9%). Heart failure (HF) (Killip FC II) was revealed in 41% of examined patients, FC III – in 2.7% of patients.

All patients received thrombolytic treatment with prourokinaza 6 mln U according to standard method (8). The efficacy of thrombolytic therapy was estimated using indirect criteria, control ECGs were recorded in 90 and 180 min after initiation of therapy. Continuous 12-lead ECG monitoring was performed using "Cardioteknika-04" (Inkart, Saint-Petersburg) cardiomonitor. ECG monitoring was started from the moment of patient's admission in the intensive care unit and continued throughout in-hospital period. ST calculation in recorded leads was performed automatically along with the mandatory visual medical control to exclude secondary repolarization changes. Results were statistically analyzed using standard Excel and Statsoft statistical programs.

RESULTS

Continuous monitoring allowed to reveal some types of ST segment changes over time during systemic thrombolysis. The ST segment decrease appeared to be non-monotonous in more than half of cases. Sharp increase in ST elevation appearing as a sharp-pointed peak was observed in 54% of patients in 37±30 minutes from the start of prourokinaza administration. Elevation increased by 140-500 (mean 203±83) percent from initial values. The increase in elevation was rapid – within 1-10 minutes (mean 5.1 ±3.6), then ST decreased immediately, reaching the baseline values within 1-15 (mean 10.1±4.5) minutes and continued to decrease further.

Typical character of ST changes over time with peak of increase in elevation is shown in figure 1. Initially, ST elevation in leads V3-V6 takes place; degree is maximal in lead V3. Sharp peak of increase in ST elevation is recorded in 15 minutes after initia-

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tion of thrombolytic therapy –ST elevation rises up to 160% from baseline within 9 minutes. Further ST-segment starts to decrease reaching the pre-peak values within 9 minutes, and in 95 minutes ST segment decreased staying at the same level within the next day. Development of the sharp peak of increase in ST-segment elevation in 15 minutes after thrombolytic administration was accompanied by the episodes of idioventricular rhythm with heart rate 58 to 78 beats per minute lasting up to 1 minute, which were considered to be the reperfusion arrhythmias.

The example of similar changes in ST-segment in inferior AMI is shown on figures 2, 3. A 59 years old patient diagnosed with the peracute phase of inferior AMI was hospitalized within 5 hours 20 minutes from the onset of first in life angina attack. Maximal degree of ST elevation was 180 uV and was observed in lead III. Thrombolytic therapy was started. In 20 minutes dramatic peak of increase in ST elevation to 280 uV was recorded, which corresponds to 155% of the baseline value. ST elevation raised to maximal values within 3 minutes, and then ST-segment decreased rapidly to baseline level within 7 minutes; and within 36 minutes ST was stabilized at 50 uV level remaining the same within the next day. STIII level was 50 uV on the control ECG recorded in 90 minutes after the drug administration, ST-segment decreased by 72% from baseline suggesting the effective thrombolytic therapy. Reperfusion arrhythmias were recorded in time period near the ST peak, in this patient the arrhythmias were manifested as episodes of severe sinus bradycardia up to 41 beats per minutes, frequent ventricular extrasystoles, and episodes of unstable ventricular tachycardia.

It is worth noting that there were no recurrent angina attacks at the moment of sharp-pointed ST peak recording in any patient.

Dramatic intermittent character of increase in ST elevation suggested an immediate relationship between the peak and reperfusion moment. The data from the experimental studies provided basis of this hypothesis. Thus, studies using intramyocardial electrodes described rapid hyperpolarization of cells during reperfusion, greater decrease in action potential duration compared to ischemia period that was accompanied by superficial ECG changes expressed as a positive shift of TQ, ST and T-wave peak (9).

If the observed sharp-pointed peak is caused by blood flow restoration in the infarct-related artery, then rapid decrease in ST level was to be expected. Indeed, when sharp reperfusion ST peak was recorded during thrombolytic therapy, ST level was normalized more rapidly in 79% of patients as compared to the group without specific peak (table 1).

In the group with peak, the ST-segment decreased fully and stabilized at the level close to the isoelectric line – within 100±51 minutes from the initiation of thrombolysis. On the contrary, in the group without "reperfusion" peak, the time of the ST-segment decrease was 220±149 minutes, but in 5 patients ST decrease was not revealed during 36 hours. In the group without typical sharp pointed peak, the time of ST decrease to isoelectric line was more than 140 minutes in 76% of patients, whereas in the group with peak – in 26% only (differences between groups p=0.00095 by Fisher method).

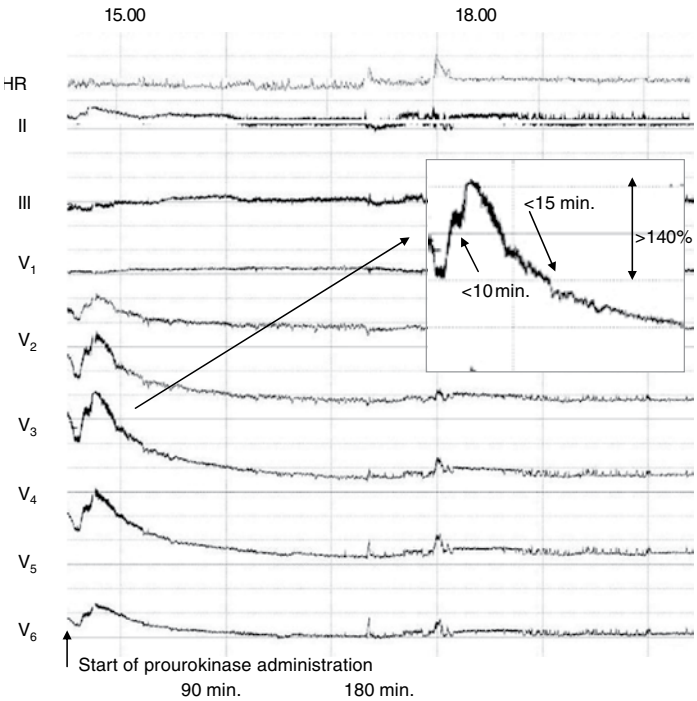

Figure 1. Typical character of ST changes over time with peak of increase in ST elevation during thrombolytic therapy. The arrow indicates the moment of prourokinasa administration. Typical ST pattern characteristics are shown on the magnified fragment of the diagram.

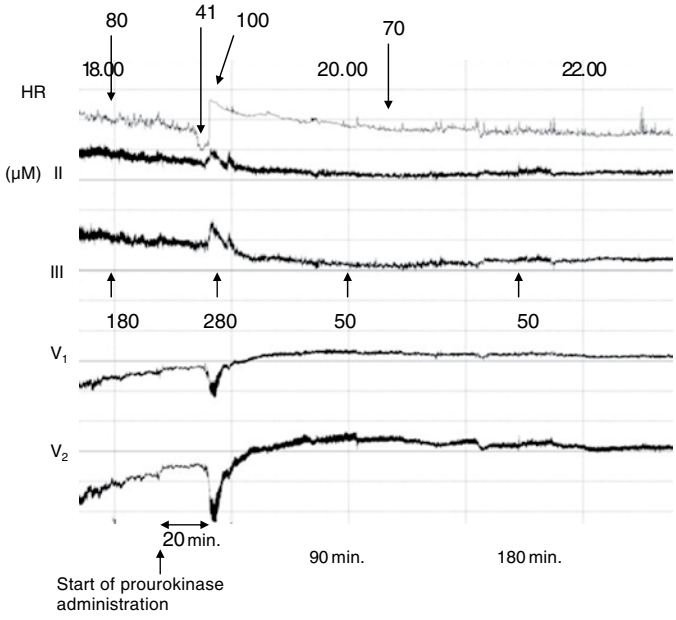

Figure 2. Example of ST changes over time with specific peak of increase in ST elevation in inferior AMI. The arrow indicates the moment of prourokinaza administration. See explanations in the text.

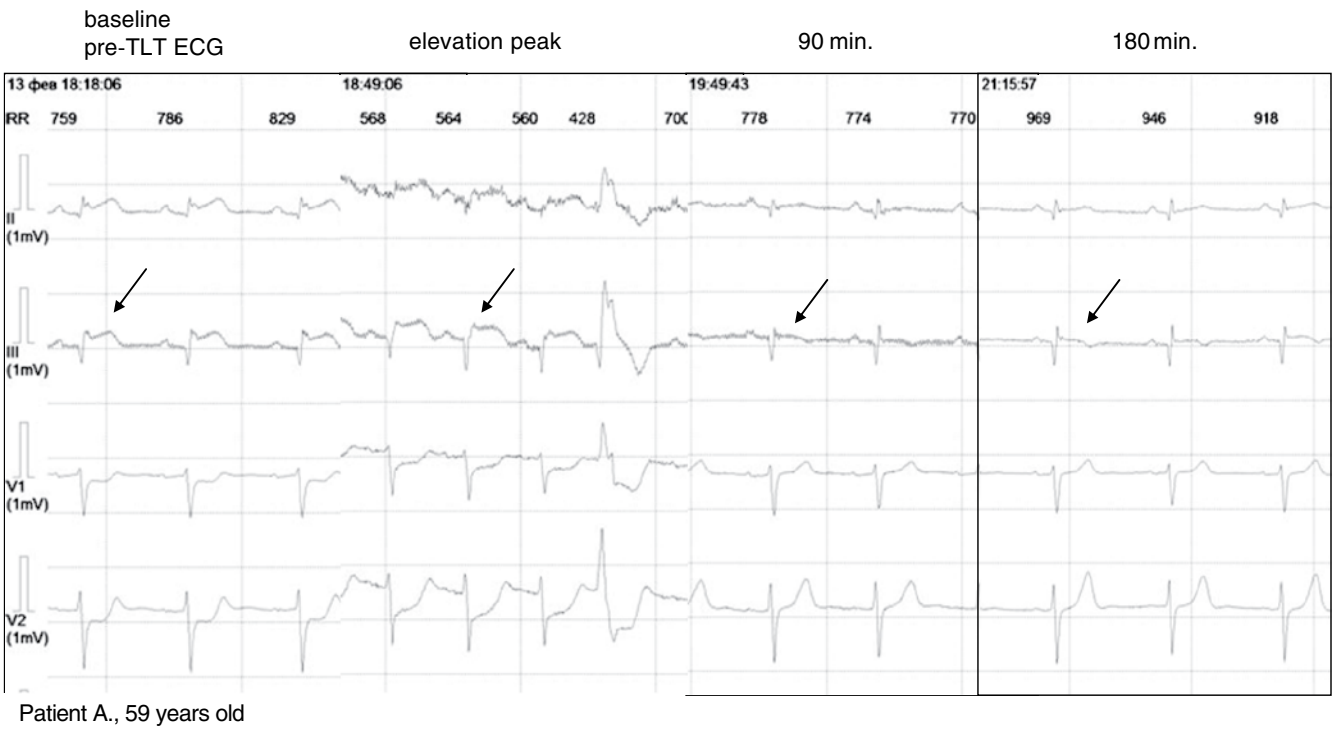

Figure 3. ECG examples during effective thrombolytic therapy in inferior AMI. Patient A., 59 years old. ECG: baseline, at the moment of maximal elevation, in 90 and 180 min. The arrows indicate the ST shift degree.

The example of absence of ST segment resolution during ineffective thrombolytic therapy is shown in figures 4, 5. Sixty years old patient C. was hospitalized in the intensive care unite within 4 hours 40 minutes after the onset of prolonged angina attack. Fig. 4 shows ST shift diagram from the moment of hospitalization, isoelectric line in leads V_1-V_3 is shown by dashed line. ST elevation is well seen in leads V_1-V_3, maximal – in lead V_2 – 600 uV (see ECG in fig.5). No peak of increase in ST elevation or decrease of ST elevation level is observed during thrombolytic therapy. In 90 and 180 minutes after initiation of therapy, ST segment remains at the same level: lead V_2 – 600 uV. The patient refused from coronary angiography; ST elevation was kept at the same level during the first day of observation, then ECG changes slowed, but later postinfarction aneurism developed.

On the stage of thrombolytic therapy the multiple dynamic painless episodes of ST shift were recorded in 13% of cases (Fig. 6). Probably, these series of episodes resembling ST shift of angiospastic origin can be explained by fluctuations in vessel tonus of the open infarct-related artery, or can be consequence of angiospastic reaction due to distal vessels embolization during thrombus fragmentation in thrombolytic therapy.

In 10% of patents recurrent ST elevation episodes were observed already after thrombolytic therapy completion. These episodes differed from reperfusion peak of increase in ST elevation as follows: absence of temporal association of episodes of recurrent elevation to the moment of thrombolysis start, there was no rapid reverse decrease in ST, segment; such episodes were often associated with recurrent angina attack in these patients.

DISCUSSION

The analysis of the degree of ST depression is a commonly accepted way of indirect assessment of the thrombolytic therapy efficacy. Comparison of two discrete electrocardiogram recordings is used most often. It is considered that ST decline by 50% and more in the lead with the maximal degree of initial elevation within 180 minutes after therapy initiation indicates the successful reperfusion (3). The approaches are also suggested that use assessment of changes over time not by one lead, but by calculation of the overall ST shift in all leads with initial elevation, or the overall ST shift in all leads where elevation is recorded and where the reciprocal ST depression is revealed (5).

In literature, the reference degree of ST decrease during thrombolytic therapy is discussed actively.

Table 1. Baseline characteristics, ST changes over time and reperfusion arrhythmias in patients with ACS depending on presence of "reperfusion" peak of increase in ST elevation.

	Age (years)	Localisation (% inferior AMI)	size of Baseline ST shift (uV)	Interval from pain onset to STL (min)	Reperfusion arrhythmias	Time to ST decrease (min)
Group 1 ("reperfusion peak")	54±8	63	343±222	220±81	68***	100±52**
Group 2 (no peak)	56±10	47	327±200	226±69	12	220±149

Note: **-p<0,005 ***-p<0,001

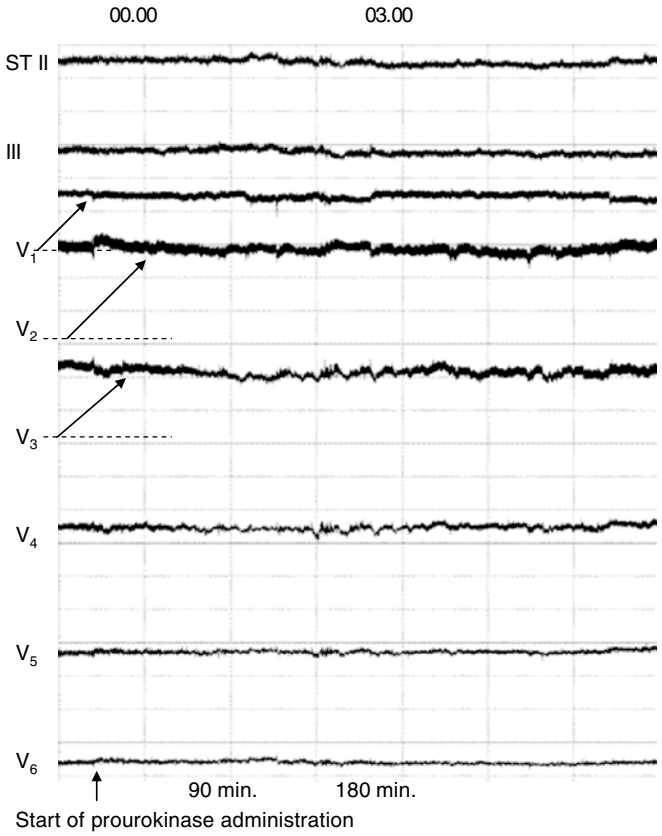

Figure 4. Absence of ST changes over time during ineffective thrombolytic therapy. Patient C., 60 years old. Diagram of ST segment shift during thrombolytic therapy. The dashed line indicates the isoelectric line in leads V_1, V_2, V_3.

Thus, there is an opinion that ST decline by 50% is sufficient in anterior infarctions, and decrease by 70% is optimal in inferior infarctions (5). G. Schroder suggested grading of ST resolution degree as total (⩾70%), partial (30% to 70%) and absence of decrease (ST changes over time less than by 30%) (7). It is well known that degree of ST decrease during reperfusion therapy is closely related to patients prognosis (6, 10).

Another relevant issue is the time of ECG recording in order to assess the changes over time. In HIT-4 study it was shown that in the group where streptokinase was administered as fibrinolytic, thrombolytic therapy efficacy criteria assessed in 90 minutes were achieved only in 25% of patents, whereas in the group of tissue plasminogen activators – in 35% of patients. Proportion of patients with successful thrombolysis assessed in 180 minutes was 50% in both groups (7). Thus, the time of ST decrease and the time interval for assessment of changes over time depends among others on the type of fibrinolytic drug used. Thrombolytic therapy efficacy assessment performed in 180 minutes provides more reliable results than that performed in 90 minutes and much less in 60 minutes.

However, if thrombolytic therapy fails, repeated administration of thrombolytic drug is not very effective, and such patients demand transluminal balloon angioplasty (3, 11). Since the volume of salvaged myocardium depends closely on the time from angina attack onset to coronary blood flow restoration, decision about “saving” PCI performance should be taken in shorter time. In the current guidelines this

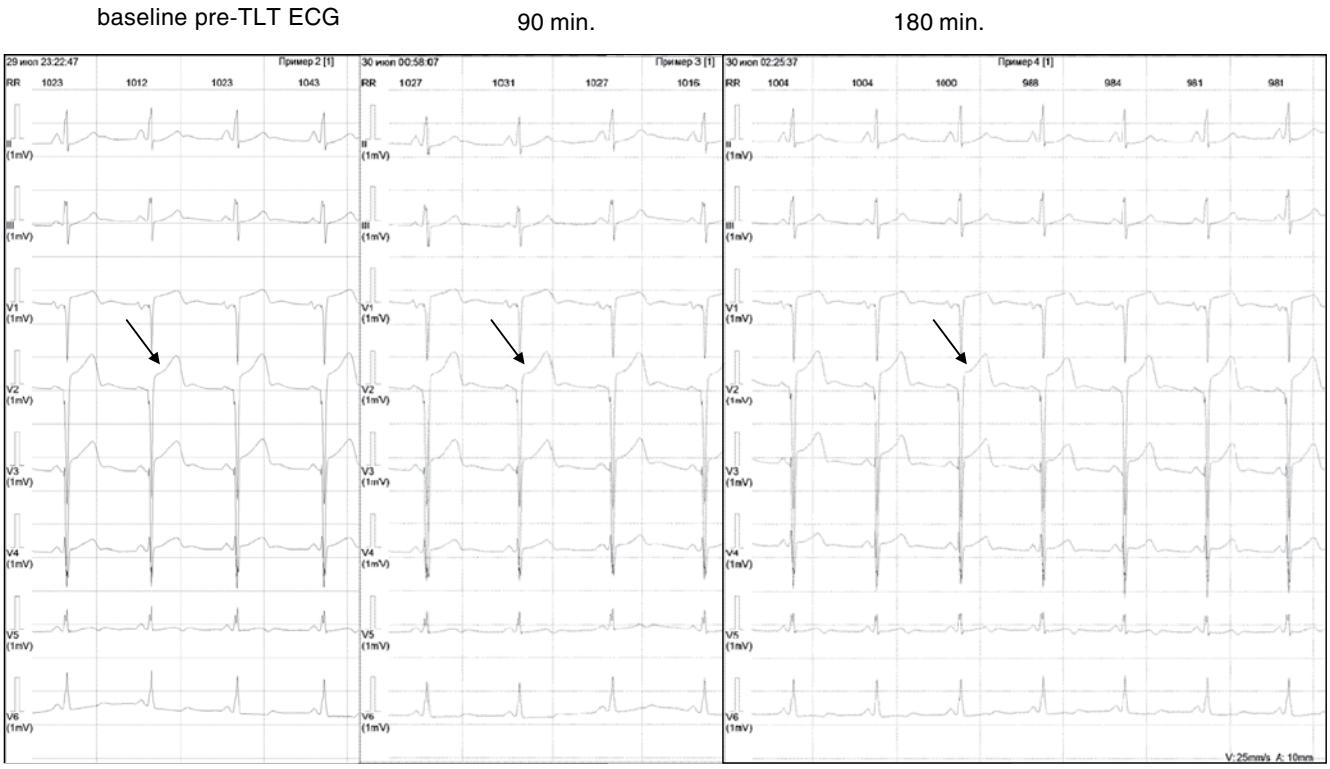

Figure 5. Examples of ECG recordings in Patient C performed before initiation of thrombolytic therapy and in 90 and 180 min. The arrows indicate the ST shift degree in leads with maximal elevation, there are no changes over time.

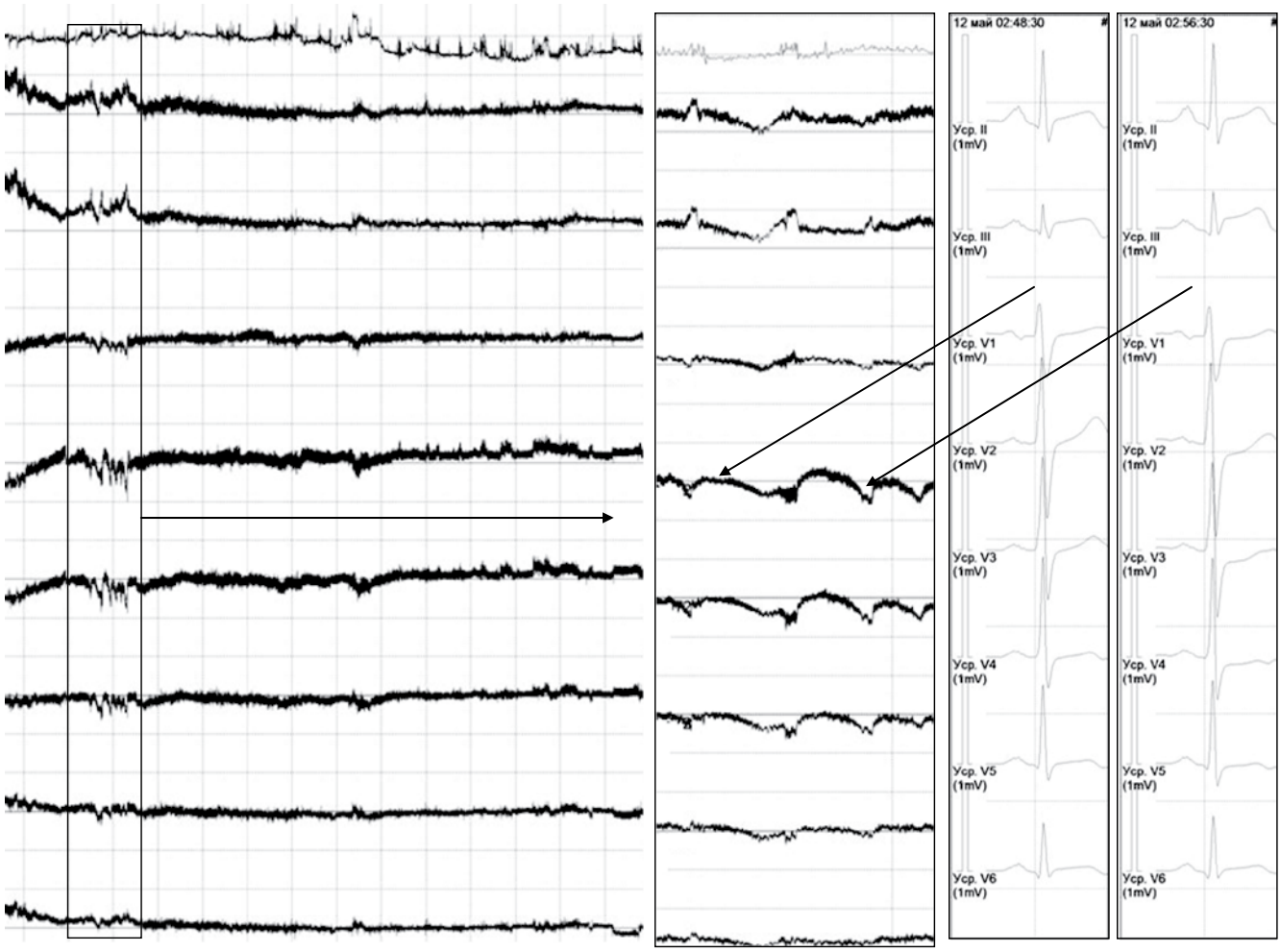

Figure 6. Dynamic episodes of ST shift on the stage of thrombolytic therapy completion. The decrease of ST elevation is clearly seen in leads II, III, the decrease of ST reciprocal depression in leads V_2, V_3, then series of painless episodes of ST shift are recorded (magnified fragment of the diagram and ECG examples during and outside the shift episode are shown).

time interval is defined as 60 minutes from initiation of thrombolytic therapy (3). There are no reliable electrocardiographic criteria allowing evaluation of the thrombolytic therapy efficacy in this time interval.

Our study showed that continuous ECG monitoring allows to reduce substantially the time of assessment of the thrombolytic therapy efficacy. In the examined group, the assessment of thrombolytic therapy efficacy defined as ST decrease by 50% and more on the basis of discrete ECG recordings, the therapy was considered to be successful in 33% of patients in 90 minutes, and in 63% of patients in 180 minutes. During continuous ECG monitoring it is possible to predict the efficacy of thrombolytic therapy after sharp-pointed peak recording followed by ST decrease. Using the analysis of ST changes pattern in the same patients, the conclusion about the efficacy of thrombolytic therapy could be made within up 90 minutes, and in 43% within up to 60 minutes.

Continuous 12-lead ECG monitoring with online ST shift assessment during thrombolytic therapy is used rarely in routine practice. However, there are descriptions of ST elevation increase during reperfusion therapy in literature (12, 13). In the cited works the vectorcardiography method was used for assessment of ST segment resolution, overall ST shift was calculated from orthogonal leads X, Y, Z. The episodes of ST elevation increase were considered to be a manifestation of the reperfusion syndrome contributing to formation of greater final focal area of necrosis (14). According to our data, patients with "reperfusion peak" of increase in ST elevation had shorter ST normalization time which was proved to be associated with better myocardial perfusion, better contractility preservation, lower mortality values and recurrent infarctions rate (15, 16). We believe that the specific peak is revealed more often in initially greater myocardial mass involvement in ischemia/reperfusion process, which can determine the resulting infarction area, but this hypothesis requires further investigations.

Aside from thrombolytic therapy efficacy assessment, continuous ECG monitoring allows to reveal recurrent ST shift episodes. Data about frequency and prognostic value of transient ischemic attacks in ACS without ST elevation are well known (17, 18, 19). The role of dynamic ST shift episodes, especially painless, in ACS is less studied. Further investigations of pathogenesis and prognostic value of series of dynamic ST shift episodes are needed on the stage

of systemic thrombolysis completion. Recording of the ST elevation recurrences during ECG monitoring after reperfusion therapy completion influences the choice of the further treatment strategy.

CONCLUSIONS

1. Detection of sharp-pointed peak of increase in ST elevation with rapid further ST depression is highly suggestive of the efficacy of thrombolytic therapy performed. Typical pattern is characterized by the following parameters: ST segment amplitude increase to 140% and more from baseline over time not exceeding 10 minutes and restoration to initial level in not more than 15 minutes.
2. Typical ST pattern recording during continuous ECG monitoring allows to reduce substantially the time of assessment of the reperfusion therapy efficacy – less than 90 minutes in all patients, less than 1 hour almost in half of patients.

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Five-Year Results of Coronary Stenting in Patients with Different Forms of CAD.

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The introduction of stents with antiproliferative drug-eluting coating into the clinical practice certainly reduced the rate of coronary restenoses (1-3). However with the accumulation of experience and the generalization of results several limitations to the use of these stents became evident. Firstly, some patients show hypersensitivity to their components. Secondly, in view of high risk for bleeding complications, prolonged use of double disaggregant therapy creates problems related to non-planned surgical interventions. Thirdly, several authors have shown that one year or more after the procedure the risk of thromboses development in stents with antiproliferative drug-eluting coating is higher than after the use of bare metal stents (4-8). Let us remind, that the endothelization of bare metal stents is achieved, as a rule, by six months, while the same process in the stents with antiproliferative drug-eluting coating is more time-consuming (9-10). Besides, according to some authors, in some cases the rate of restenosis development after the use of bare metal and drug-eluting stents is not significantly different (for example, in cases with non-complicated coronary lesions of types A or B1 according to AHA/ACC classification). For these reasons bare metal stents are still widely used in routine clinical practice. Thus, in the USA the share of stents without drug-eluting coating is about 50%. However only a careful analysis of long-term results of stenting procedure can give the final answer concerning the place of any given type of the stents in the treatment of coronary artery disease. Unfortunately, at present few works on this subject are available, and most of them deal only with clinical results, while angiographic results are poorly covered [11-15]. Meanwhile just the analysis of angiographic data can provide a real idea of the state of stents at different time spread after the treatment.

Taking into account, on the one hand, the relevance of the above-mentioned problems, and, on the other hand, a many years' experience with therapeutic procedures in Moscow City Center of Interventional Cardioangiology, we decided to conduct a retrospective study of the results of coronary arteries stenting with bare metal stents in patients with different forms of CAD at least five years after the implantation.

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DESIGN OF STUDY

We have studied long-term results of examination and treatment in 283 patients who underwent 353 procedures of coronary stenting in our Center from 1997 through 2002. The main conditions for patients' inclusion into the study were optimal immediate results and known six months' results of endovascular intervention.

208 patients out of 283 agreed to undergo control selective coronary angiography in five or more years' time after stenting; 39 refused in-hospital examination in view of absence of complaints and good physical tolerance (these patients hade been interviewed and their data were taken into account for the evaluation of their clinical state), and 36 patients died at different time spread after the procedure.

CHARACTERISTICS OF STUDIED PATIENTS AND METHODS OF INVESTIGATIONSTUDY

Some historical and clinical data of our patients are summarized in Table 1.

Table 1. Clinical and historical data of the studied patients.

Number of patients	283
Age, years	55.4±5.6
Males, %	77
History of MI, %	53.7
Duration of CAD, months	30.4±6.3

Before stenting 128 (45,2%) patients had exertional angina of functional class II-IV, another 37 (13,1%) had unstable angina of clinical form II, and 118 (41,7%) patients were within the first 24 hours after the onset of AMI (fig. 1).

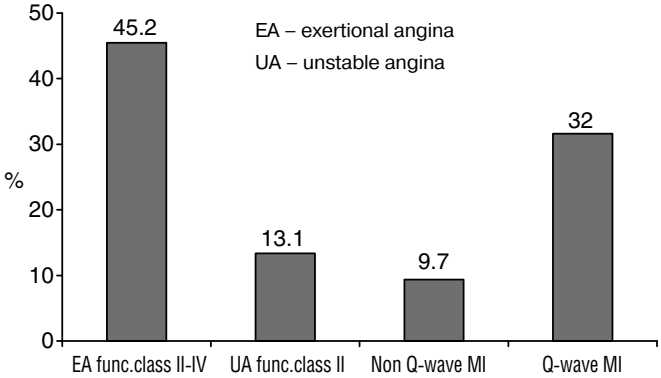

Figure 1. Patients' distribution depending on their initial diagnosis, %.

197 (68,6%) patients had the history of arterial hypertension, 172 (60,8%) had hypercholester-

olemia, 19 (6,7%) had diabetes mellitus. More than one of these risk factors for CAD were present in 54 (19,1%) patients.

24-hours ECG monitoring revealed the changes in the terminal portion of QRS complex (ST segment depression or elevation by over 1 mm, T wave inversion) in over 50% of patients.

Positive results of bicycle ergometry (development of typical anginal attack and/or ischemic changes on ECG) were obtained in 141 (85,5%) out of 165 patients, negative – in 13 (7,9%). The remaining 11 (6,7%) patients had non-informative stress test.

Left ventriculography and selective coronary angiography revealed left ventricular ejection fraction (LV EF) of 59,8 ±11,7%. The lesions affecting > 70% of one coronary artery lumen were seen in 79 (27,9%) patients, of two arteries – in 160 (56,6%), of three arteries – in 44 (15,5%). LAD lesion was revealed in 192 (67,8%) patients, CxB or OMB lesion – in 102 (36%) and RCA lesion – in 123 (43,5%) patients. No cases of left main coronary artery lesion were encountered (Table 2).

Table 2. Data of selective coronary angiography in the studied group before PCI performance.

Number of patients	283
LAD lesion	192 (67.8%)
CxB or OMB lesion	102 (36%)
RCA lesion	123 (43.5%)
Lesion of the proximal LAD	153 (54.1%)
True bifurcation lesion	28 (9.9%)
Major artery occlusion	62 (21.9%)

Before the PCI patients received, besides aspirin (125 mg daily), the following drugs: nitrates– 241 (85,2%), β-adrenoblockers – 232 (82%), Ca antagonists – 226 (79,9%) patients. Complex antianginal therapy was conducted in 178 (62,9%) patients.

Before the procedures all patients underwent routine complex examination, adopted in our Center, which included ECG, 24-hours ECG monitoring, EchoCG (stress-EchoCG in cases of necessity), bicycle ergometry – in the absence of contraindications.

All PCIs were performed in conformity with the generally adopted technique. In total, 283 patients received 353 bare metal stents: 187 (53%) in the LAD, 59 (16,7%) in the CxB or the OMB and 107 (30,3%) in the RCA. In the majority of cases we used MultiLink, CrossFlex, BiodYvisio, Bx Velocity, Bx Sonic and AngioStent stents.

Immediate angiographic results of the procedure were optimal in all patients. No cases of stent thrombosis were revealed during in-hospital stay. Complete myocardial revascularization (blood flow restoration in all major arteries and dominating side branches with ⩾ 70% lumen injury) was achieved in 229 (80,9%) patients. In most cases incomplete myocardial revascularization was due to pronounced diffuse lesion and/or chronic occlusion of one coronary artery.

Depending on the diagnosis patients were discharged at day 2-10 after the procedure (patients with AMI were followed in hospital for 10 days). The continuation of daily intake of aspirin (permanently) and ticlopidine (for 1 month at least) was an indispensable condition of treatment in all patients without exclusion.

According the protocol adopted in our Center, the first control examination was recommended in 6 months after the discharge. In cases of detection of coronary arterial restenosis or reocclusion, as well as of a de-novo lesion, repeated PCI have been performed, or surgical treatment was recommended.

Statistical analysis was performed using SPSS for Windows 10.0.5 software. P< 0,05 was considered significant. All data related to mean values are given as M ± m, where M is the arithmetic mean of the set sample, m – standard error of the mean.

RESULTS OF STUDY

283 patients were examined in 64,3 months on the average, that is, in over 5 years after stenting. By this time the survival was 87,3% (247 patients). Survival without MACE (AMI and ACVA) was 83,7% (237 patients).

During this period 36 (12,7%) patients died, among them 16 (5,7%) – from AMI, 8 (2,8%) – from ACVA, and 6 (2,1%) patients – from progressive cardiovascular failure. Mortality from other reasons (cancer, accident, renal failure) was 2,1% (6 patients).

Two (0,7%) of 16 patients dead from cardiovascular causes (Q-wave MI) died within the first 30 days after PCI from subacute occlusive in-stent thrombosis of the LAD, and 14 (4,9%) died later from occlusion of a non-stented coronary artery (in the majority of cases – the LAD or the RCA).

Non-fatal (in all cases Q-wave) myocardial infarction occurred in 10 (3,5%) patients. Among them 3 (1,1%) had MI in the territory of the stented artery (resulting from in-stent occlusive thrombosis in the LAD and the RCA), and 7 (2,9%) – in the territory of a native coronary artery (as a result of progressive lesion) (fig. 2).

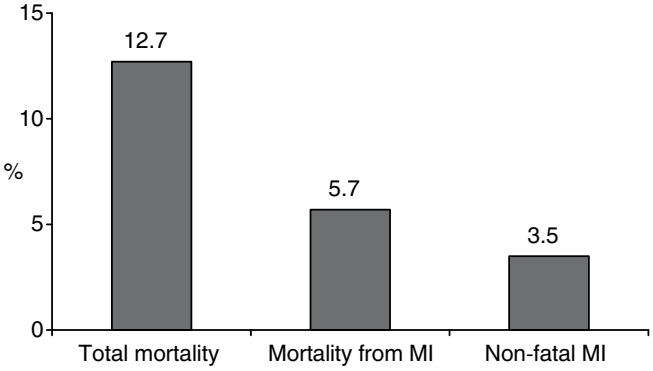

Figure 2. Mortality and the rate of MI on the average 64,3 months after PCI.

The cause of myocardial infarction was established in all cases on the base of clinical and laboratory studies, including control selective coronary angiography, or at autopsy. Herewith 4 out of 5 patients had stent occlusion within the first 30 days after the intervention, and 1 – after this period. Thus, the estimated rate of subacute in-stent thrombosis was 1,1%, of the late thrombosis– 0,3%.

By the moment of repeated control examination in the long-term follow up 113 patients (45,7%) out of 247 surviving patients (i.e., almost a half of the studied patients) were angina-free. Forty-nine among them (43,3%) previously (on the average, in 6 months after the first procedure) underwent repeated (in most cases endovascular) interventions for in-stent stenosis and/or progressive lesion of the native coronary arteries. Hence, angina was seen in 134 (54,2%) out of 247 patients, among them unstable angina of clinical form II – in 4 (1,6%), exertional angina (in most cases of functional class II) – in 130 (52,6%) (fig. 3).

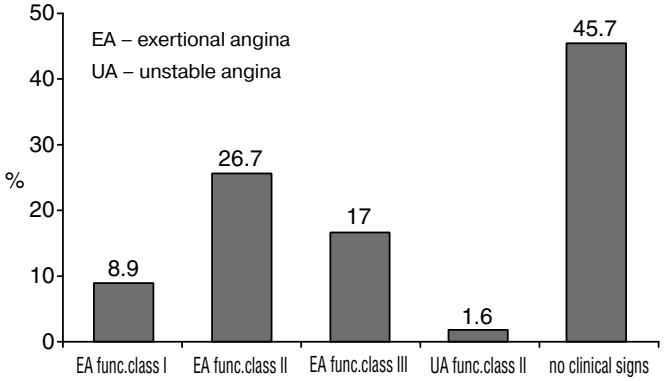

Figure 3. Distribution of patients depending on the diagnosis by the moment of control examination (64,3 months after stenting).

Probable causes of angina (as judged by the data of clinical and angiographic examination) in 122 (91%) out of 134 patients were progressive lesion and/or initially incomplete myocardial revascularization with the preservation of good results of previous endovascular interventions, while restenosis of the coronary artery was revealed only in 12 (8,9%) patients: for the first time – in 8 and repeatedly (in the site of PTCA performed in 6 months after the first PCI for in-stent stenosis) – in 4 patients.

The absence of angina or its equivalents, the decrease of the rate or of the intensity of anginal attacks, that is, the improvement of the quality of life in comparison with the baseline (before stenting) were noted in 201 (81,4%) out of 247 surviving patients, i.e., in the vast majority of the studied population. The state without significant dynamics in comparison with the baseline was seen in 32 (12,9%) patients, while a deterioration, mainly in the form of increased attacks frequency of decrease of physical tolerance – in 14 (5,7%) patients.

In the long-term follow up we noted a significant decrease of the amount of antianginal medications used (nitrates and Ca antagonists) in comparison with the baseline (Table 3).

Table 3. Changes of antianginal therapy.

Period	Before PCI (n=283)	At 5 years (n=247)	p
Nitrates	241 (85.2%)	115 (46.5%)	< 0.05
Ca antagonists	226 (79.9%)	68 (27.5%)	< 0.05
β-adrenoblockers	232 (82%)	176 (71.2%)	< 0.1

As one can see from this table, the change of the number of patients taking β-adrenoblockers was less significant, which can be explained by the fact, that these drugs had been prescribed not only for antianginal, but also for hypotensive purposes (most patients had history of arterial hypertension).

During bicycle ergometry performed in the long-term follow-up the criterion for the termination of study in 134 (64,4%) out of 208 patients was the achievement of sub-maximal HR without the development of anginal attacks and/or ischemic ECG changes. Positive results of bicycle ergometry were obtained in 74 (35,6%) patients. One has no note that before stenting positive results of stress testing were seen in 141 (85,5%) out of 165 patients ($p < 0,05$).

Comparative analysis of baseline and control bicycle ergometry performed in the long-term follow-up revealed that the increase of physical tolerance by at least one step occurred in over 50% of cases. On the average its value increased from 60,6±26 at baseline to 83,4 ±27 Wt ($p < 0,05$) (fig. 4).

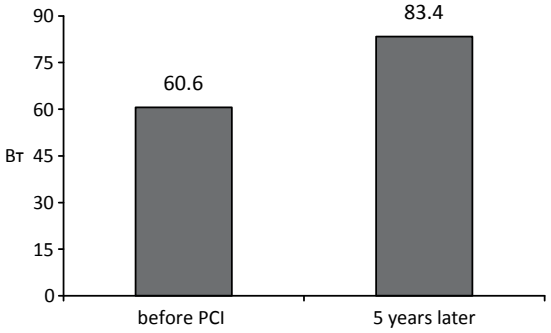

Figure 4. Dynamics of physical tolerance in studied patients.

Thus, control examination revealed the increase of physical tolerance by at least one step in comparison with the baseline in the majority of patients. Physical tolerance increased on the average by over 20 Wt.

The results of control left ventriculography performed in the long-term follow-up revealed general decrease of the ejection fraction in comparison with the baseline from 62,8 ±12,8 to 54,4 ±11,7% ($p > 0,05$), which theoretically can be explained by several causes. Firstly, before PCI the majority of patients with AMI had compensatory hyperkynesis of the intact portions of the left ventricle, which was neutralized after some time (with scar development and redistribution of myocardial functions). Secondly, some patients had myocardial infarction after stenting, which also could contribute to the decrease of ejection fraction indices in the whole group. Besides,

one cannot exclude the natural process of progressing of coronary arterial lesions in some patients; this process could affect left ventricular function as a result of so called atherosclerotic cardiosclerosis.

The increase of LV EF on the average from 56,5% to 62,4% ($p < 0,05$) was seen only in patients with good results of previous endovascular procedures and without signs of progressive stenotic-occlusive lesions of the coronary arteries by the moment of control study (fig. 5).

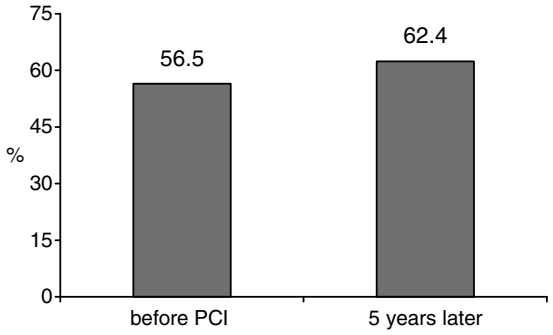

Figure 5. Dynamics of total LV EF in patients with good results of previously performed PCIs and without signs of progressive coronary arterial lesions by the moment of control study.

DATA OF SELECTIVE CORONARY ANGIOGRAPHY IN THE LONG-TERM PERIOD OF FOLLOW-UP

In the long-term follow-up control coronary angiography was performed in 208 patients. As a result, the state of 258 stents was evaluated. The preservation of the optimal state of the stented segment for the whole follow-up duration was noted in 176 (68,2%) cases, unsatisfactory results of the procedure were seen in 82 (31,8%) cases: restenosis ⩾ 50% – in 72 (27,9%) and occlusion within the stent or in the stented segment of the coronary artery – in 10 (3,9%) cases (fig. 6).

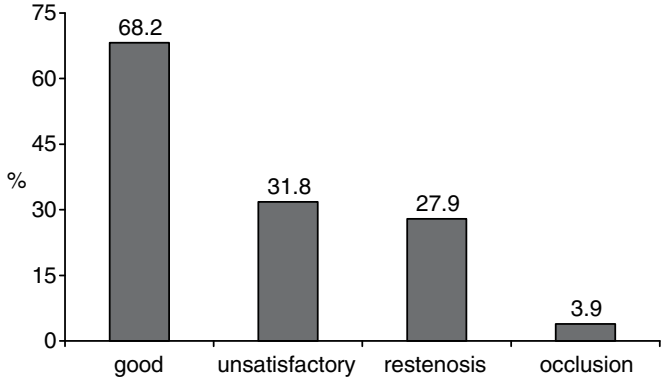

Figure 6. Angiographic results of coronary stenting in 5 years (on the average 64,3 months) after the procedure.

On the average in 6 months after the procedure, that is, during the first control coronary angiographic examination, good results of stenting were seen in 184 (71,3%) out of 258 cases. In 176 (95,7%) out of these cases angiographic results were preserved in the long-term, while in the remaining 8 (4,3%) cases restenosis ⩾ 50% was revealed. No cases of in-stent occlusion (provided good six months' results of stenting) were seen in the long-term follow-up.

Unsatisfactory angiographic results of stenting at 6 months were seen in 74 (28,7%) out of 258 cases: restenosis ⩾ 50% - in 64 (24,8%) and in-stent occlusion – in 10 (3,9%) cases. Balloon angioplasty within the stent was performed in 64 cases with optimal immediate angiographic results, in the remaining 10 cases in view of concomitant multiple coronary lesions and/or high risk of endovascular treatment surgical myocardial revascularization was recommended. In the long-term follow-up good angiographic results of in-stent balloon angioplasty were seen in 60 (93,8%) cases, unsatisfactory results – in 4 (6,2%) cases: restenosis ⩾ 50% - in 2 (3,1%) and reocclusion in 2 (3,1%) cases.

Thus, the preservation of good results of coronary stenting for 5 years was seen in the great majority of patients (almost in 70% of cases). The rate of so called late restenosis (6 months and more after stenting) was less than 4,5%, the rate of repeated restenosis (in the site of in-stent balloon angioplasty) – 6,2% (including reocclusion rate – about 3% of cases).

Hemodynamically significant de novo coronary lesions were seen in 83 (39,9%) patients. Herewith within the first 6 months progressive atherosclerotic lesions were revealed only in 2 (0,96%) patients, while in later periods – in 81 (38,9%). In 10 (4,8%) cases a newly formed > 50% stenosis of the left main coronary artery was found at control examination. It is worth noting that the patients in the group with progressive atherosclerotic lesions received hypolipidemic agents (statins), significantly less frequently that in the group without signs of progressive lesions – in 36% and 81% of cases, respectively ($p < 0,01$). Meanwhile the number of patients with baseline dyslipidemia in these groups was similar

Surgical myocardial revascularization was recommended to 24 (28,9%) out of 83 patients with newly formed hemodynamically significant coronary lesions, repeated endovascular interventions – to 46 (55,4%), and 13 (15,7%) patients (with distal coronary lesions, absence of clinical signs of angina or exertional angina of func. class I) received the recommendations for conservative therapy with mandatory prescription of hypolipidemic agents.

Repeated myocardialum revascularisation. During the follow-up period (on the average - 64,3 months) repeated interventions had been recommended to 146 (51,6%) out of 283 patients: surgical myocardial revascularization – to 32 (11,3%) (in most cases for progressive lesions) and endovascular interventions – to 114 (40,3%) (in 68 cases for in-stent restenosis or reocclusion and in 46 cases – for the lesions of native coronary arteries) (fig. 7).

Within the first six months after stenting the main indication for repeated interventions was restenosis, after that – progressive atherosclerotic lesions of native coronary arteries (fig. 8).

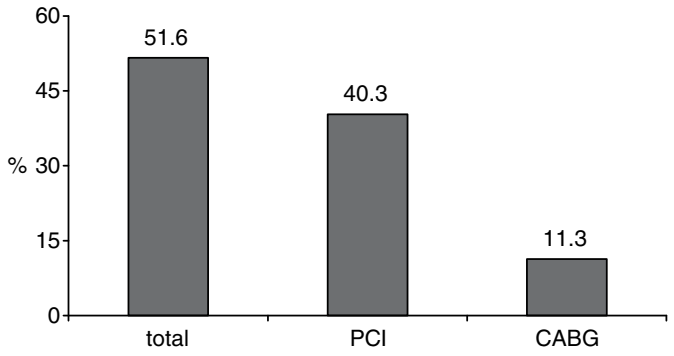

Figure 7. Rate of repeated interventions on the average in 64,3 months after coronary stenting.

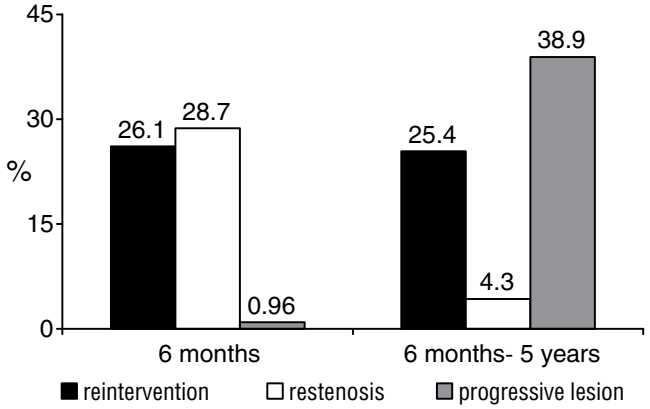

Figure 8. Relation of the rate of repeated interventions to the rate of restenosis and progressive lesions at different follow-up periods.

CONCLUSION

Thus, stenting of the coronary arteries is a clinically effective and safe method for the treatment of CAD, providing high 5-year survival and low rate of cardiovascular complications.

During 5 years good angiographic results of stenting are preserved in almost 70% of cases, restenosis is revealed in about 30% (among them in-stent occlusion – in less than 4%). Herewith in the vast majority of patients restenosis develops within the first six months after the procedure, while the probability of restenosis development in later follow-up periods (provided good results of stenting at six months) is under 4,5%.

In the vast majority of patients it is possible to eliminate restenosis by in-stent balloon angioplasty, without recurring to surgical methods. In doing so, in over 90% of cases the results are preserved for many years.

In the whole, within 5 years about 50% of patients need repeated myocardial revascularization. Endovascular procedures can be performed in the vast majority of them with good clinical effect. Within the first six months after stenting the main indication for repeated myocardial revascularization is restenosis, while in later follow-up periods – progressive atherosclerotic lesions of native coronary arteries.

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Assessment of the Degree of Myocardial Revascularization in Patients with Coronary Heart Disease

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Kew words: Coronary heart disease, cumulative parameter of coronary lesion, myocardial revascularization, degree of revascularization, revascularization index.

Abbreviations
CHD – coronary heart disease,
MI – myocardial infarction,
CABG – coronary artery bypass grafting,
MCBG – mammary coronary bypass grafting,
PTCA – percutaneous transluminal coronary angioplasty
LV – left ventricle,
EchoCG — echocardiography,
SCG – selective coronarography,
CA – coronary arteries,
ADA – anterior descending artery,
CA – circumflex artery,
RCA – right coronary artery,
LCA – left coronary artery,
EF – ejection fraction,
DD – diastolic dysfunction,
AV – aortic valve,
MV – mitral valve,
LCII – local contractility impairment index

Currently, surgical restoration of coronary blood flow is the basic therapeutic modality in CHD patients (1). Surgical revascularization is aimed mainly at the restoration of cardiac muscle function, since in the absence of coronary blood flow improvement the remaining areas of viable myocardium will be inevitably necrotised (2). Surgical techniques of treatment in CHD patients are being improved continually; the new approaches to the myocardial reconstruction and revascularization are being developed (3). The most important methods of MI and CHD treatment are CABG, MCBG, PTCA and stenting. Endovascular intervention on coronary vessels was proven to be non-inferior to CABG (4, 5). In these cases the efficacy criteria for coronary stenting and bypass grafting are the completeness of blood flow restoration in involved arteries and improvement of the left ventricle functional parameters leading to the improvement of clinical manifestation of the disease.

In many scientific works attention is paid to complete and incomplete myocardial revascularization (6, 7, 8), as well as to its influence on LV function changes, however, there is no objective criterion reflecting the degree of revascularization in available literature.

Thus, the aim of this study is to develop the objective criterion for the assessment of myocardial revascularization after endovascular intervention on coronary arteries and to demonstrate the importance of this parameter for the assessment of changes of LV myocardial function over time.

MATERIAL AND METHODS

We analyzed the results of treatment of 94 CHD patients hospitalized in Nizhniy Novgorod Regional Specialized Cardiosurgery Clinical Hospital, including 14 (15%) women and 80 (85%) men aged from 35 to 73 (mean age 54.1±0.9 years).

Ain addition to physical examination, all patients underwent electrocardiography, Doppler and echocardiography as well as stress echocardiography and selective coronary angiography.

Doppler and echocardiography were performed using SonoAce 8000 EX system (Korea), with transducers 3.5 MHz and 7 MHz. The echocardiographic end-volumes were examined by standard methods, LV ejection fraction, LV local contractility impairment index, vE/vA parameter describing the severity of LV diastolic dysfunction were determined as well.

Selective coronary angiography as well as therapeutic endovascular procedures were performed in cathlabs equipped with Angioscop – 3D angiography systems (Siemens, Germany).

All patients underwent myocardial revascularization using instruments for coronary angioplasty (Cordis, Medtronic, Occam, Terumo).

For a quantitative assessment of coronary arteries the cumulative parameter of coronary lesion was calculated (9, 11).

We were first to implement the conception of "revascularization degree" for objective assessment of coronary vessels after blood flow correction (Patent No. 2322188 dated April 20, 2008).

The known way of determination of cumulative parameter of coronary lesion was chosen as a prototype of prospective method for the assessment of

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coronary arteries after endovascular correction (10). The scores for affected arteries were determined using a scale specially developed at the A.N. Bakulev Scientific Center for Cardiovascular Surgery under the direction of professor Yu.S. Petrosyan. Further, after the intervention the scores were summated so that only treated arteries were included in this sum.

The ratio of the sum of operated arteries scores to absolute maximal sum of all arteries scores (240) represents the parameter we proposed to call "revascularization index".

$$\text{Revascularization index} = \frac{\text{Sum of operated arteries scores}}{240}$$

The ratio of revascularization index to preoperative total score of coronary lesion is expressed as percentage and represents the indicator of the degree of revascularization.

$$\text{Degree of revascularization} = \frac{\text{Revascularization index}}{\text{Total score of coronarylesion}} \times 100$$

Thus, the method we have suggested allowed to assess the efficacy of endovascular treatment in CHD, and to determine a plan of further treatment in cases of incomplete revascularization.

STUDY RESULTS AND DISCUSSION

The following results were obtained during performed study.

One hundred seventy nine (83%) out of 216 coronary lesions were corrected. Stenting of 154 stenoses was performed, among these 114 (74%) stenoses were eliminated by direct stenting, 40 (26%) – by indirect stenting. Eighteen (12%) antiproliferative drug-eluting stents (Cypher, Axion) were implanted.

Twenty five (60%) out of 42 occlusion lesions were eliminated by stenting with predelatation.

Correction of 20 (9%) stenoses and 17 (40%) occlusions failed due to different reasons.

Analysis of the relation between the LCII, EF, DD and the degree of revascularization in all operated patients at 24 months after stenting showed that the best results for myocardial contractility restoration and normalization of diastolic function and ejection fraction were obtained with complete revascularization (67%, 66%, and 82% of patients, respectively). Similar results were obtained with the revascularization degree of more than 80% (64%, 67%, 75% of patients, respectively). With the revascularization degree of 50-80% LCII improved in 36% of cases, EF improved in 33%, and diastolic function improved in 57% of patients. With incomplete revascularization of less than 50% the positive changes in LCII over time were revealed only in 11% of patients, in EF – in 25%, and in diastolic function – in 44% of patients (Fig.1).

Thus, in incomplete restoration of coronary blood flow, the more pronounced positive changes over time in the main functional parameters were achieved with the degree of revascularization of more than 80%.

LCII, EF, DD normalization depending on the degree of revascularization in Q-wave and non Q-wave MI patients in long-term follow-up after stenting

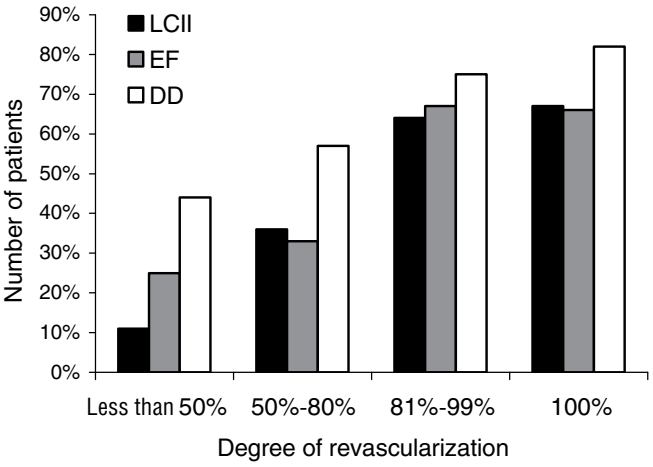

Figure 1. LCII, EF, DD improvement depending on the degree of

CONCLUSIONS

Conception of the degree of revascularization, proposed for the first time in this work, and its quantitative characteristics allow to assess the efficacy of endovascular treatment in CHD patients.

Calculation of this parameter after surgical intervention allows for the determination of the strategy of further patient treatment.

With the degree of revascularization of 80% and more, the changes in LV myocardial functional parameters over time are comparable with those of 100% coronary blood flow restoration.

When complete correction of coronary atherosclerotic lesion is impossible, achievement of partial luminal restoration in coronary arteries (with the degree of revascularization of at least 80%) should be reasonably considered as suboptimal result of surgical intervention.

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Electrical Impulses Attenuate Atherosclerotic Progression

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INTRODUCTION

A large body of research has been aimed at the finding of the most effective way to manage atherosclerosis, and yet, as a cause of stroke and 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 drugs to reduce 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 with the early 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 used different voltage (2, 3, 4 V) and different rate of impulses (30, 60, 120 impulses per minute). Best results we obtained when 3V and 30 impulses per minute were used. The present study evaluates the effect of EI on different stage of atherosclerosis.

METHODS

Animal studies in this investigation were approved by our institution's Animal Care Committee, 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. We used New Zealand White Rabbits divided into seven different series.

Study Population

Series 1 (6 rabbits): 8 weeks of high cholesterol diet (HCD) without electrical impulses (EI).
Series 2 (6 rabbits): 11 weeks of HCD without EI
Series 3 (6 rabbits): 8 weeks of HCD, followed by 8 weeks of normal diet (ND)
Series 4 (6 rabbits): 8 weeks of HCD, followed by 8 weeks of ND with EI
Series 5 (6 rabbits): 11 weeks of HCD with EI
Series 6 (6 rabbits): 11 weeks of HCD, followed by 8 weeks of ND
Series 7 (6 rabbits): 11 weeks of HCD, followed by 8 weeks of ND with EI

High Cholesterol Diet (HCD) and blood sampling.

All rabbits were put on a 2% cholesterol diet and were fed the same quantity of food at the same time. Blood samples (series 2, 6, and 7) were taken prior to implant and prior to painless sacrifice to assess blood cholesterol, triglyceride and iron levels. Blood was taken from the peripheral artery of the ear.

OPERATIVE TECHNIQUE

Prior to surgery, rabbits were anesthetized with a mixture 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 via mask. Then they were given Buprenorphine (0.05 mg/kg IM) for pain (one-thirds of the 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 postoperative treatment of infection. Incision sites were checked at least once daily for any abscess formation. Appropriate action, including drainage, additional sutures, and antibiotic treatment were taken as necessary under the direction of a veterinarian. No infections or erosion of pacers or leads occurred

Stimulator and lead implantation

Surgery (series 4, 5, and 7) was performed using strict sterile technique. After induction of anesthesia, a Lateral incision was made and the stimulating lead implanted into the left Psoas Major muscle close to the upper part of abdominal aorta. The lead was tunneled behind the vertebral column on the right side and connected to the pacemaker (Thera 8966, Medtronic), which was implanted between the right Psoas Major muscle and the Abdominal Oblique muscle, close to the upper part of the abdominal aorta. The pacemaker was programmed to 30 contractions per minute, 0.5 Hz and 3 V for 24 hours/day. The incision was closed in layers.

PATHOLOGICAL STUDIES

Iron and cholesterol investigations

The spectrophotometry method was used to investigate the iron in blood. Cholesterol and triglyceride

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in the blood were measured using the enzymatic rate method; these investigations were performed at Marshfield Laboratories, Marshfield, Wisconsin.

Evaluation of surface area affected 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 photographed with a digital camera. ADOBE PhotoShop was used to calculate the atherosclerotic area and its percentage of involvement in the aorta. The aorta was divided into two segments: thoracic and abdomen. Total pixel numbers for each area were calculated using the rectangular marquee tool. From "SELECT" tool bar ("COLOR RANGE"), the eyedropper tool was used to choose the intermediate color in the segment that we selected. We adjusted the fuzziness to 200 in order to calculate pixels for the entire segment. To calculate pixel numbers we used the "IMAGE" tool bar and selected "HISTOGRAM", using channel "LUMINOSITY". Atherosclerotic area was calculated for each segment by using the pixel number of the atheroma and pixel number of whole segment. We calculated the percentage surface area of the 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 if $p<0.05$ using t- test analysis in comparing the mean between the two groups (control and experimental).

RESULTS

No animal lost weight. In control rabbits, without electrical stimulation, before HCD, weight was 3.6±0.3 kg. After 8 weeks of high cholesterol diet (HCD) without electrical impulses (EI)

weight was 3.7 ±0.2 kg (series 1); after 11 weeks of HCD without EI – 3.6±0.4 kg (series 2); after 11 weeks of HCD with EI – 3.5±0.1 kg (series 5); after 8 weeks of HCD followed by 8 weeks of ND – 3.7±0.2 kg (series 3); after 8 weeks of HCD followed by 8 weeks of ND with EI – 3.5±0.3 kg (series 4); after 11 weeks of HCD followed by 8 weeks of ND – 3.6±0.1 kg (series 6); and after 11 weeks of HCD followed by 8 weeks of ND with EI-3.7±0.3 kg (Series 7) (all $p>0.05$)

Weight of Heart, Liver and Spleen

Weights of heart, liver, and spleen (series 2, 6, and 7) were measured after sacrifice of the animals. Weight of the heart after 11 weeks of HCD (series 2) was 7.0±0.4 g, after 11 weeks of HCD, followed by 8 weeks of ND (series 6) – 6.9±0.3 g ($p>0.05$) and after 11 weeks of HCD followed by 8 weeks ND with EI (series 7) – 6.3±0.2 g ($p<0.05$). Weight of liver after 11 weeks of HCD (series 2) was 152.9±9.3 g ; after 11 weeks of HCD followed by 8 weeks of ND (series 6) – 149.7±7.4 g ($p>0.05$); and after 11 weeks of HCD followed by ND with EI (series 7) – 136.7±5.1g ($p<0.05$) Weight of spleen after 11 weeks of HCD (series 2) was 2.9±0.3 g ; after 11 weeks of HCD followed by 8 weeks of ND (series 6) – 3.1±0.4 g ($p>0.05$) and after 11 weeks of HCD followed by ND with EI (series 7) – 2.9±0.5 g ($p>0.05$).

Level of blood cholesterol

Level of blood cholesterol was investigated in series 2, 6 and 7. Serum cholesterol at baseline was 71.8±32.4 mg/dL for all rabbits. This increased to 1449.6±419.1 mg/dL ($p<0.001$) after 11 weeks of HCD (series 2). In series 6 rabbits, after additional 8 weeks of a normal diet, cholesterol decreased to 501.8±196.3 mg/dL ($p< 0.001$ vs. after 11 weeks of HCD). In series 7 rabbits after additional 8 weeks of a normal diet with EI cholesterol decreased to 208.4±47.8 ($p< 0.001$ vs. 11 weeks of HCD only, series 6; and $p<0.05$ vs.11 weeks of HCD followed 8 weeks of ND, series 2)

Level of blood iron

Level of iron in blood was investigated in series 2, 6, and 7. Baseline blood iron level was 165.2±27.8 ug/dL. After 11 weeks of HCD (series 2), blood iron level was not significantly different (154.4±28.5 ug/dL, $p>0.05$). In series 6 rabbits with normal diet after HCD, iron level was not significantly different (163.0±16.7 ug/dL, $p>0.05$). However, in series 7 rabbits with 8 weeks of normal diet and EI, the iron level in the blood decreased to 116.0±16.4 ug/dL ($p<0.001$ vs. baseline, $p<0.05$ vs. 11 weeks HCD and vs. series 2 and 6).

Level of iron in the aortic wall

Level of iron in the aortic wall was investigated in series 2, 6, and 7. Our findings in relation to the level of iron ion in the wall of the aorta in the area of electrical field were more enlightening. We investigated pieces of aorta just between thoracic and abdominal parts to calculate the iron levels. In a previous study, 5 rabbits on normal diet had an iron level of 220±59.5 ug/g in the same segments of their aorta (unpublished data). In our current study, after 11 weeks of HCD (series 2) the iron level decreased to128.8±57.5 ug/g. In series 6 rabbits after on a 8-weeks normal diet after 11 weeks of HCD diet , the iron level was not significantly different (145.2±34.6 ug/g). In series 7 rabbits with 8 weeks ES and normal diet after 11 weeks of HCD, the iron level decreased to 82.8±34.5 ug/g ($p<0.05$ vs. series 6).

Atherosclerotic area

Thoracic aorta

After 8 weeks of HCD (series 1) area covered by atherosclerotic plaque was 46.9±7.5%. After 11 weeks of HCD (series 2) this percentage increased to 57.5±5.0% (p>0.05). When electrical stimulation was applied simultaneously with HCD (series 5), after 11 weeks there was 6 times less atherosclerotic plaques in thoracic aorta (**7.6±7.2% vs.** 57.5±5.0%, p < 0.0001). When normal diet was applied for 8 weeks after preliminary 8 or 11 weeks of HCD, there was no statistically significant decrease in atherosclerotic area. In series 3 this area decreased to 40.6±6.1% (vs. 46.9±7.5%., p>0.05), and in series 6 to 49.1±7.9% (vs. 57.5±5.0%, p>0.05).

The results completely changed when electrical impulses were applied. In series 4 (8 weeks of HCD after 8 weeks of ND plus EI) the surface covered by atherosclerotic plaque decreased to **18.4±6.3% (p<0.001 vs. series 1 and 3), and in series 7 (11 weeks of HCD after 8 weeks of ND plus EI) – to 31.0±5.8% (p<0.001 vs. series 2 and 6).**

Abdominal aorta

After 8 weeks of HCD (series 1) the surface area in abdominal aorta, covered by atherosclerotic plaque was 24.7±3.7%, and after 11 weeks of HCD (series 2) 32.5±4.2% (P<0.05). When electrical impulses were applied simultaneously with HCD, atherosclerotic area was 10 times less (**3.0±2.2%, p<0.0001**). When normal diet was used for 8 weeks after 8 weeks of HCD (series 3) surface area covered by atherosclerosis was statistically smaller than after HCD only (13.3±2.3% vs. 24.7±3.7%, p<0.05). However, the results were better when electrical impulses were added to normal diet (series 4): 3.0±2.9% vs. 13.3±2.3% (p<0.001).

The same was observed when 8 weeks of normal diet only (19.6±4.8 vs. 32.5±4.2%, p<0.05) or normal diet with EI (10.1±2.9% vs. 19.6±4.8%) were applied.

DISCUSSION

The main purpose of our investigation consisted in the evaluation of the influence of electrical impulses on atherosclerotic process. First question concerned the changes in blood cholesterol levels.

As expected, this level increased by more than 10 times up to 1449.6±419.1 mg/dL after 11 weeks of HCD. Also, as expected, when diet was reverted to normal, the level of cholesterol dropped to 501.8±196.7 mg/dL during 8 weeks. We may speculate that the continuation of normal diet would led to complete normalization of level of cholesterol in blood. More important, electrical impulses increased the speed of normalization of blood cholesterol level.

This difference (208.4±47.8 vs. 501.8±196.7) was statistically significant. It is first very objective evidence of influence of electrical impulses on atherosclerosis process. Data in the literature showed the same results with reversion of cholesterol level to normal values after low cholesterol diet (6, 7, 8, and 9). However, nobody except us used the electrical impulses for acceleration of this process.

In an attempt to define the mechanism by which application of EI affects the atherosclerotic area, we tested our hypothesis that a change in the aortic wall's ions (e.g. iron), caused by electrical field, affect the progression of the atheroma. HCD has been found to cause hemolytic anemia in rabbits (10, 11). This, in turn, can stimulate the bone marrow to produce more red blood cells and deplete iron storage. In our experiment, the level of iron in blood was statistically lower in paced rabbits versus nonpaced animals (116.0±16.4 ug/dL vs. 163.0±16.7 ug/dL). Similar data were received for the level of iron ion into aortic wall (82.8±34.5 ug/g vs.145.2±34.6 ug/g). Iron is known to stimulate low-density lipoprotein and membrane lipid peroxidation (12, 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, if deferoxamine (iron chelator) decreases the atherosclerotic lesion with iron chelating (17), low frequency electrical impulses, 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. The data received in our study are very impressive, but we must check them in another series of experiments.

The other possible explanation for the results obtained, could be due to change in calcium ions concentration. Atherosclerotic lesions possess 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 (18, 19, 20, and 21). In response to the application of electrical impulses, the calcium ions may travel out from atheroma and stabilize the inflammation process. This process may reflect the mechanism of regression of atherosclerosis. Additional study is needed on this topic, measuring the influence of EI on calcium content in the atheroma.

Yet more interesting data have been received after evaluation of the weight of liver. It was the same after 11 weeks of HCD and after 11 weeks of HCD followed by 8 weeks normal diet. However, when EI was added to normal diet, weight of liver became statistically lower (136.7±5.1 g vs. 152.9±9.3 g). We are careful to do any conclusion, but we may speculate, that more biochemical and morphological investigations are needed to explain the influence of electrical field (localized just near the liver) on lipid metabolism in the liver.

Morphological investigations of surface area covered by atherosclerotic plague were more informative and confirmed some very well known knowledge about atherosclerosis in rabbit, and also supported our hypothesis that electrical impulses may prevent the development of atherosclerosis or decrease the size of already existing moderate or advanced plaques.

In all series (paced and non-paced animals) surface area covered by atherosclerosis every time was large in thoracic aorta in comparison with abdominal aorta. Surface area covered by plaques was the largest after 11 weeks of HCD in comparison with 8 weeks of HCD. Surface area decreased in all cases when HCD was changed to normal diet. However, the speed of elimination or decreasing in size of atherosclerotic plaques in abdominal aorta was greater than in thoracic aorta. Here are data from thoracic aorta. Surface area was 46.9±7.5% after 8 weeks of HCD and decreased to 40.6±6.1% (minus 6.3%) after 8 weeks of normal diet. Surface area was 57.5±5.0% after 11 weeks of HCD and decreased to 9.1±7.9% (minus 6.4%) after 8 weeks of normal diet. In both series here was the same speed of elimination of plaques.

Here are the data from abdominal aorta. Surface area covered by atherosclerosis was 24.7±3.7% after 8 weeks of HCD and decreased to 13.3±2.3% (minus 11.4%) after 8 weeks of normal diet. After 11 weeks of HCD, surface area covered by atherosclerosis was 32.5±4.2% and decreased to 19.6±4.8% (minus 12.9%) after 8 weeks of normal diet. In both series, the speed of elimination of atherosclerosis was mostly the same and near two times higher than in thoracic aorta. These data support the opinion, that atherosclerotic plaques in rabbit after HCD are more stable and more difficult eliminated under influence of normal diet in thoracic aorta than in abdominal aorta.

Electrical impulses have been shown to markedly influence the decrease and even the elimination of atherosclerotic plaques. When electrical impulses were applied in the same day with HCD, after 11 weeks, only 7.6±7.2% of surface of thoracic aorta and 3.0±2.9% of surface of abdominal aorta were covered by atherosclerotic plaques (versus 57.2±5.0% and 32.5±4.2% without EI, respectively). These data let us to consider that electrical impulses prevent the development of atherosclerosis.

When electrical impulses were applied after 8 weeks of HCD (moderate atherosclerosis) for another 8 weeks, the surface area covered by atherosclerotic plaque was 18.4±6.3% in thoracic aorta and 3.0±2.9% in abdominal aorta (versus 46.9±7.5% and 24.7±3.7% after HCD only, respectively). These data led us to conclude, that in case of moderate, non stable atherosclerotic process electrical impulses may almost completely eliminate atherosclerotic plaques in abdominal aorta and considerably decrease their number and size in thoracic aorta. As we mentioned previously, the plaques are more stable in thoracic aorta, but we must also consider, that in our experiments the site of electrical impulses applications was more close to abdominal than to thoracic aorta.

When electrical impulses were applied after 11 weeks of HCD (advanced atherosclerosis) for another 8 weeks, the surface area covered by atherosclerotic plaque was 31.0±5.8% in thoracic aorta and 10.1±2.9% in abdominal aorta (versus 57.5±5.0% and 32.5±4.2% without EI, respectively). The surface area continue to be larger than after 8 weeks of HCD followed by 8 weeks EI, but atherosclerosis was more advanced. Maybe, in this case 8 weeks of EI are not enough for complete elimination of atherosclerosis in rabbits. We believe, that continuation of EI for additional several weeks will contribute to more effective cleaning of the aortic surface from atherosclerotic plaque. New experimental investigations are needed to confirm this suggestion.

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-ion concentration in the aortic wall requires 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.

Although this is not strictly a limitation, but an indication for future works, some questions remained to be solved: does EI affect macrophage and leukocyte deposition in the aortic intima , does EI prevent accumulation of lipid material, cholesterol clefts, cellular debris, lipid-laden foam cells, fibrin, and thrombi, does EI increase the permeability of the endothelium to plasma lipids, thus preventing the adherence of blood monocytes and platelets to the endothelial surface, does EI prevent smooth muscle cells from migrating from the media to the intima, does EI depress LDL receptors so that they no longer can recognize and find LDL?

We also realize that our approaches (even with intravenous catheter application) is still far from being completely suitable for clinical application. Furthermore, it needs to be determined whether EI can just as effectively be applied transcutaneously.

Another limitation is that it is difficult to apply this method in patients who suffer from coronary atherosclerosis. We have started to study the effect of EI on coronary atherosclerosis, but have only preliminary results.

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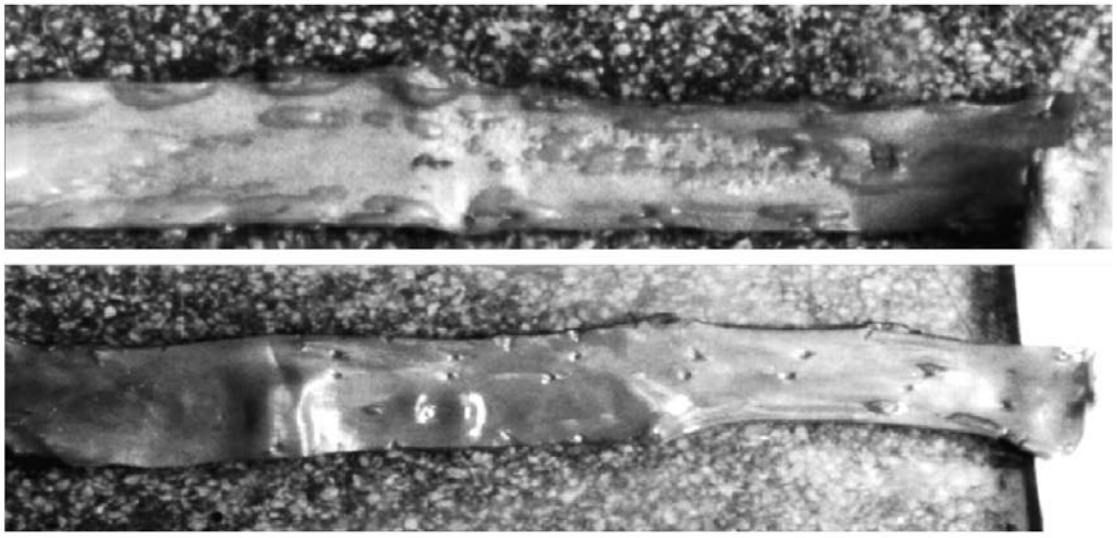
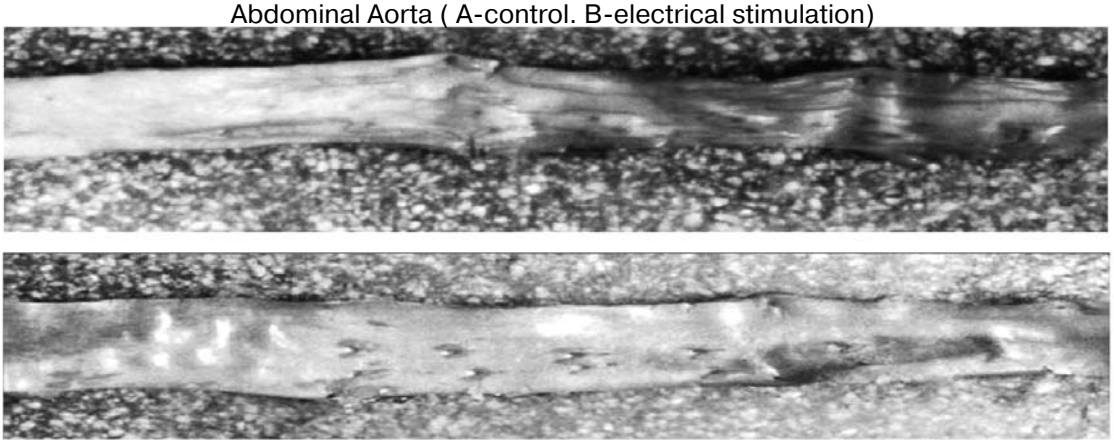
8 weeks HCD: Surface Involved in Atherosclerosis
Abdominal Aorta (A-control. B-electrical stimulation)



11 weeks HCD: Surface Involved in Atherosclerosis
Abdominal Aorta (A-control. B-electrical stimulation)



Electronic Case History for Cardiological Clinics

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INTRODUCTION

Modern cardiological clinic is a high-technology medical institution comprising multiple departments and services aimed at enhancement of diagnostic and therapeutic care using the newest methods. It comprises outpatient and rehabilitation departments. The purposes of medical information system (MIS) in such clinic are to ensure concerted functioning of all these departments, exclusion of information doubling and minimization of medical staff routine job, providing access to the results of examinations for physicians whatever department they are located at, using of uniform regulatory system. Benefit and necessity of such systems development seems nowadays to be obvious. Convenience and efficacy of working with electronic case histories (ECH), which are created using MIS, are already acknowledged by physicians from many countries worldwide. Hundreds of enterprises abroad and in our country work on developing of complexes and facilities for keeping of electronic CHs. If there was a necessity to convince physicians of the expediency of adoption of electronic CHs as early as 10-15 years ago, then National Standard "Electronic Case History. General Provisions" (GOST R 52636 – 2006) has come into operation since January 01, 2008. It binds medical institutions over mandatory use of such systems.

Main advantages of ECHs were mentioned above. However, ECH has some fundamental peculiarities for cardiological clinics:

- Medical information system, which provides keeping of electronic CH in cardiological clinic, should be designed for large flow of patients requiring planned and urgent hospitalization. Door-to-treatment time should be minimized in acute cardiovascular diseases. Sometimes every minute counts for successful treatment, and a patient should be registered, physician should examine him/her and make decision concerning therapeutic approach and policy of treatment during this time. It is virtually impossible to achieve this without powerful informational support, including physician insight into patient's history and results of previous examinations.
- Angiography is one of the important examination methods in patients suffering from cardiovascular diseases. The last 20 years were marked with wide spreading of surgical and endovascular methods of cardiovascular diseases treatment. Thus far, angioplasty and stenting as well as coronary artery bypass grafting became leading methods for coronary heart disease management. More than 2 million of angiographic procedures and interventions are performed annually worldwide, their use became popular by its nature, thus determining the expediency and in many instances even the necessity of automation of the whole diagnostic and treatment process, which is characterized by the necessity of processing, analyzing and storing of large volumes of video data.
- Along with the above-stated, the necessity to perform diagnostic procedures in large quantities, including the performance and the analysis of the results of different clinical examinations, X-ray, CT scan etc. is an important aspect of treatment of cardiovascular and other diseases
- At any time of the day cardiologist and/or cardiac surgeon should be able to look through all the set of the angiographic scenes obtained during examination at any clinic and in any time period. This imposes additional requirements to the construction of medical information system archive and to the creation of specialized subsystems of procurement and conversion of angiographic data during the performance of both a study itself and an examination of a patient referred from another clinic. Similar requirements are imposed on ability of reviewing and analysis of X-ray and tomographic images, results of clinical analyses and other data.
- Many examinations have to be repeated again and again when a patient is transferred from one clinic to another. Treatment cost increases significantly. Moreover, many examinations are not harmless for the organism. Therefore, a possibility to repeatedly refer to primary results of diagnostics, irrespective of clinic and time they were obtained, seems to be important.
- Cardiological patients need long-time follow-up at the outpatient or rehabilitation department post-treatment. During this follow-up physicians should have a possibility to not only control their current condition using their diagnostic equipment and other facilities, but also to compare the results of previous examinations.

All these peculiarities are taken into consideration by medical information system, DIMOL-IK, which is installed in a number of largest cardiological clinics

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of Moscow. Below we will focus on the principles of building of DIMOL-IK complexes, which are intended for diagnostics and management of cardiovascular diseases and provide keeping of electronic case history and electronic outpatient's cards in hospitals and outpatient departments. It will be demonstrated how the activities of several cardiological clinics including those geographically remote from each other were successfully combined into a common informational space on the basis of DIMOL-IK complexes using information and telecommunication technologies.

DIMOL-IK complex, which is suggested in this paper, provides complex automation and computation of medical technologies in the cardiological and cardiosurgical clinics, provides keeping of full electronic case history in hospitals, and outpatient's card in outpatient departments, permits exchanging digital data with different domestic and foreign specialists. A patient is given a disk, which can be read on any computer, containing case records and results of main examinations.

Structure and principles of functioning of complex DIMOL-IK STATSIONAR

Complex DIMOL-IK STATSIONAR provides complex automation of all diagnostic and treatment processes including:

- registration of patients;
- creation and keeping of electronic case histories;
- availability of uniform regulatory system and automated system of classification and coding of medical information;
- Obtaining and processing of diagnostic data (angiography, X-ray, CT scan, EchoCG, ECG, ECG-Holter etc.)
- generation of output documents;
- performing of statistical analysis;
- input, transfer, storing, processing and displaying video information (angioscenes, X-ray, tomographic images etc.)

Structure of complex and principles of its functioning are demonstrated at diagrams presented on Fig. 1 and Fig. 2.

The complex consists of workstations (PC) installed in different rooms of the clinic and integrated through network means into an unified system of hardware and software resources. The server provides work of the complex database and processing of requests for provision of information to network abonents. Hierarchical archive system is used for storing and operative issue of data, dynamic and static images, obtained during performing of diagnostic procedures and surgical interventions. Functional workstations are intended for automation of functioning of physicians of corresponding specialties. These PCs permit work with full case history, angiographic movies, X-ray and tomographic images. Possibility of analysis and processing of dynamic images, generating of reports according to the results of angiographic and other examinations and procedures is provided.

PC “Director” is installed at the workplace of director or head physician of a clinic. PC “Director” possesses the same features as any other functional PC and has access to the administrative subsystems of the complex. The most important feature of PC lies in providing to the director of a clinic the possibility to follow the course of angiographic procedure “online” not leaving his/her office and to interact with operating crew of in the mode of video conference.

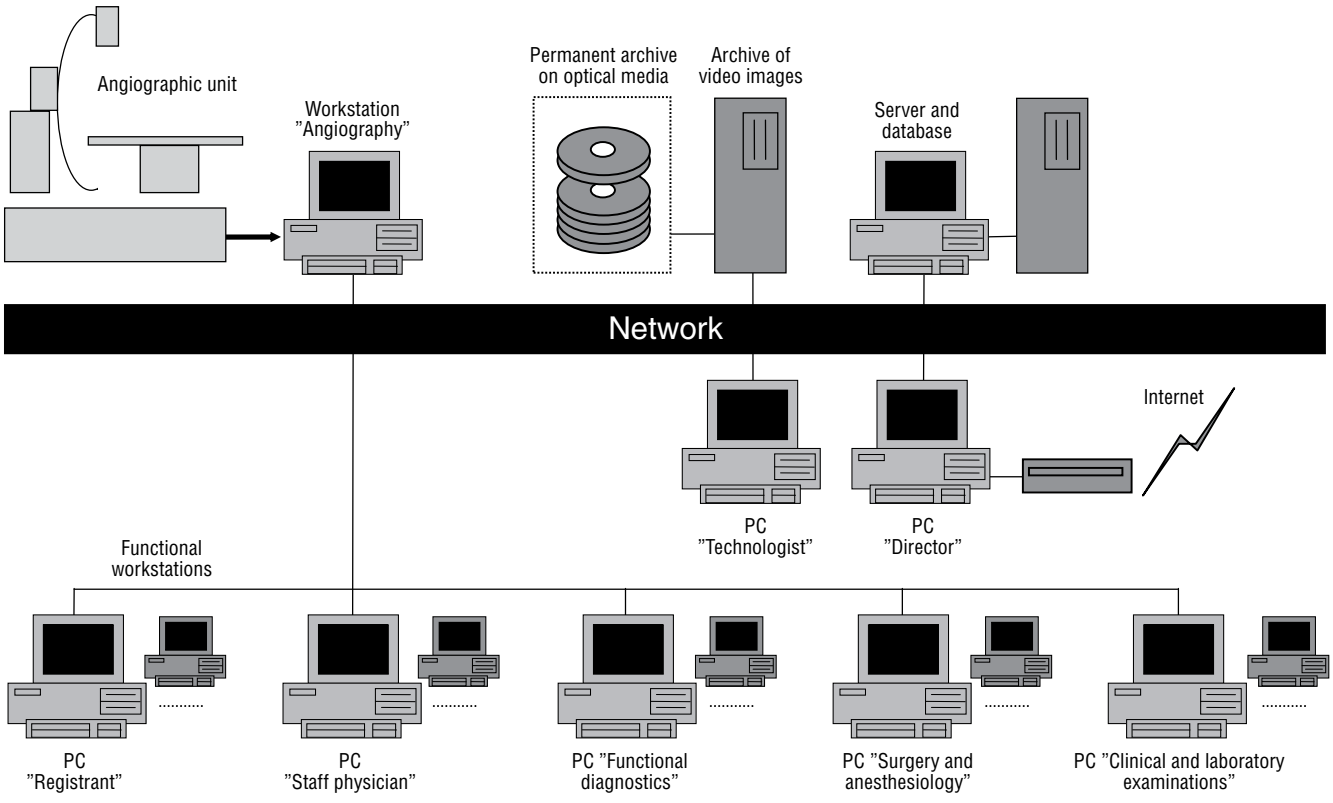

Figure 1. Structural diagram of the “DIMOL-IK STATSIONAR” complex.

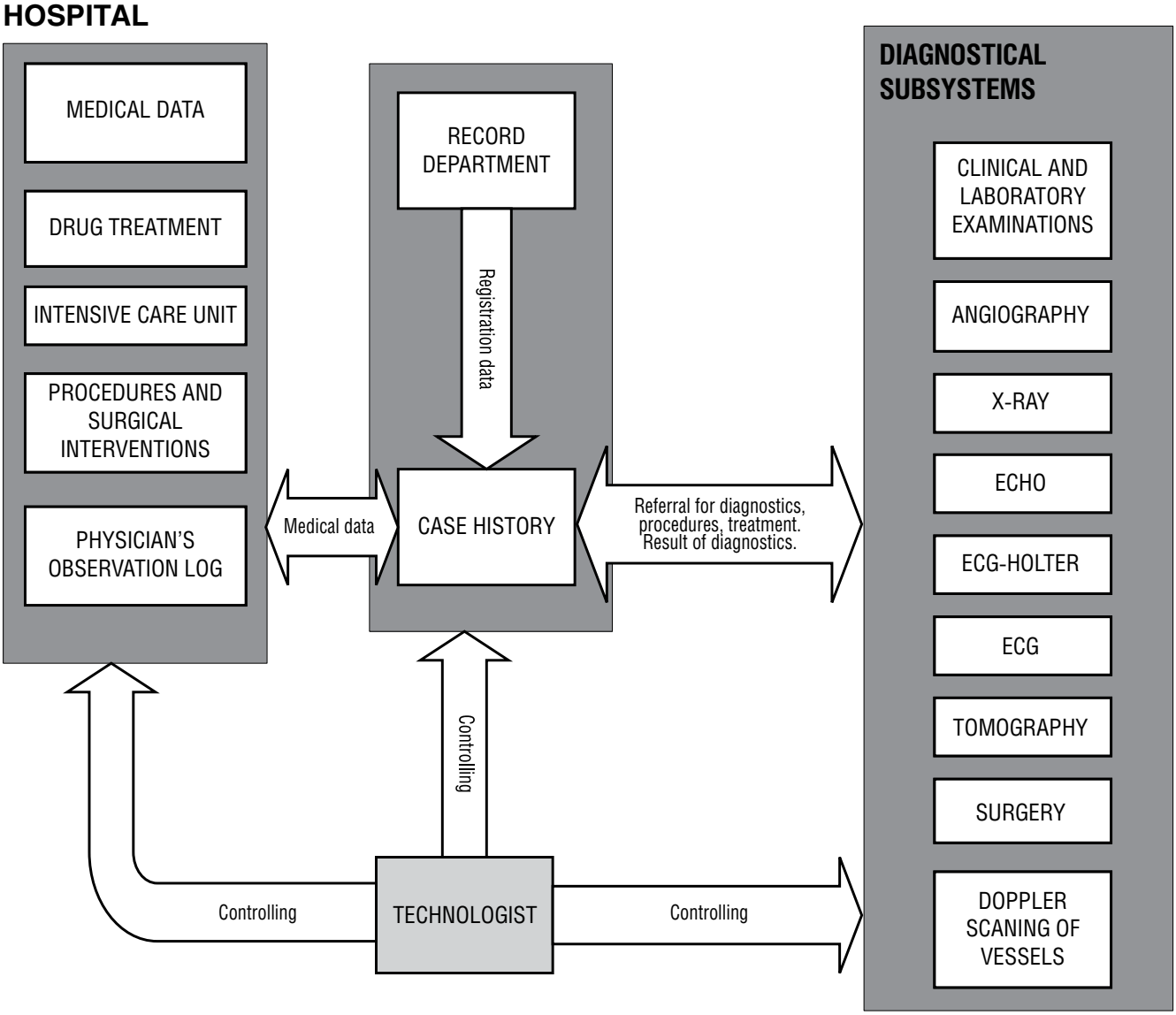

Figure 2. Functional diagram of the complex "DIMOL-IK STATSIONAR".

PC "Technologist" is the workplace of the complex administrator. The complex includes printers for printout of patient case histories, including the most informative diagnostic images.

Possibility of communication and information exchange using specifically organized protected channels with the complexes DIMOL-IK POLIKLINIKA, DIMOL-IK REABILITATSIA and other similar complexes at any medical institutions is provided by the "DIMOL-IK STATSIONAR" complex.

All the complex workstations are built on the basis of IBM-compatible personal computers combined in a local area network with a capacity 100 Mbit per second. Central control complex is built on the basis of two high-end servers. Two Raid-controllers in each server are connected with corresponding Raid-massive rack intended for archiving of all medical and administrative information. Recordable CD-RW, DVD-RW and additional Hard-driver are used for permanent archive. Three "Angiography" PC, which can work with devices having both analogous and digital output, workstations "X-Ray" and "Computed tomography" are included in the complex. General software includes Windows 2000 at servers and Windows XP at workstations. Applied mathematical software is designed using products of Sybase company and programming language C++ as well.

WORKSTATION "ANGIOGRAPHY"

PC "Angiography" works in two main modes: «on-line» and «off-line». In "on-line" mode "live" image, which comes to its input from X-ray operative room, can be viewed on PC display. PC adjustment, compression and recording of angioscenes to hard disk and viewing of movies during monitoring and recording can be performed in this mode. Possibility of data entry to system from VCR or compact disc is provided by PC for viewing and analyzing of previously recorded angiographic movies.

"Off-line" mode permits following:

- Viewing of video films using video blaster both at the point of input and at the point of output – viewing of digitized video films recorded on PC hard disc.

- Cyclic viewing with adjustable speed including manual step-by-step mode.
- Viewing of a sequence of film frames in the mode of multiimage.
- Simultaneous viewing on the display of 2 and more frames from different angioscenes.
- Hardware and software decompression of movies (scenes).
- Mathematical processing of angioscenes.

Following main algorithms are realized in the PC "Angiography":

- Quantitative measurements within separate frames, changing of their contrast and edge enhancement.
- Subtraction (different variants) of the angiographic movie.
- Calculations needed for determination of the extent of the coronary vessels narrowing.
- Ventriculographic examinations, needed for evaluation of the left ventricle function, calculation of total and segmental ejection fraction.

Methods and algorithms of processing are divided into general-purpose and special. The general-purpose algorithms are as follows:

- Calculation of area within closed contour on the image.
- Calculation of the given area focal point coordinates on the image.
- Generating of the given area contrast histogram.
- Enhancement of image contrast and smoothing of image brightness.
- Edge enhancement and sharpening.
- Smoothing contours and curvature calculation.

Algorithms of special-purpose, realized in the PC "Angiography" are as follows:

- Subtraction.
- Contouring of coronary vessels, accentuation and counting of stenotic segments of vessels.
- Determination of the left ventricle volumes in different phases of cardiac cycle and ejection fraction, both total and segmental.
- Calculation of area enclosed within closed contour on the image.
- Calculation of the given area focal point coordinates on the image.
- Generating of the given area blackening histogram.
- Enhancement of image contrast etc.

Prepared report based on the results of angiographic examination is automatically entered in electronic case history and corresponding section of summary. Examples of angiographic frames and results of their subsequent mathematical processing obtained using complex "DIMOL-IK" during angiographic procedures in real patients of a clinic are presented in Fig. 3-5. Machine form for generating of report for one of angiographic examinations is shown in Fig. 6. Results of ventriculographic analysis and calculation of ejection fraction are presented in Fig. 7. Possibilities of image subtraction algorithm realized in the DIMOL-IK complex are demonstrated in Fig. 8.

ARCHIVE SYSTEM

Archive system of the complex "DIMOL-IK" is built according to hierarchical approach. There is a local data archive on each workstation which is necessary for routine work of physician. Current archive includes all registration and medical data (including angiographic movies, X-ray and tomographic images over the last 10 years). Current archive allows to obtain necessary information on a patient, which is now being treated or has whenever been treated in the clinic, at any moment and nearly instantaneously. Permanent archive provides reliability of the whole archive system by doubling of current archive data on optical media. Data deleted from current archive are stored in permanent archive as well.

Archive system plays the most important role in information support of a clinic. Facing the patient admitted with an acute complication of cardiovascular disease, the physician has only a few minutes to find a unique appropriate solution concerning the approach and policy of treatment. If this patient has been already treated in a hospital equipped with electronic archive system, then his/her data are stored in global archive. Request and receiving of

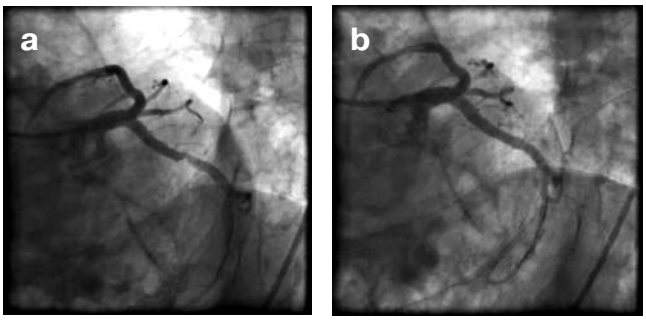

Figure 3. The circumflex artery before (a) and after (b) PTCA.

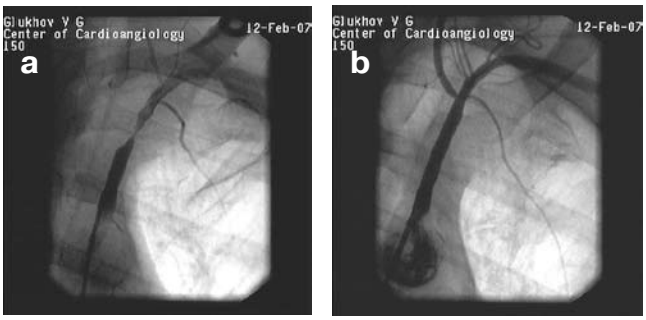

Figure 4. The left subclavian artery before (a) and after (b) PTCA.

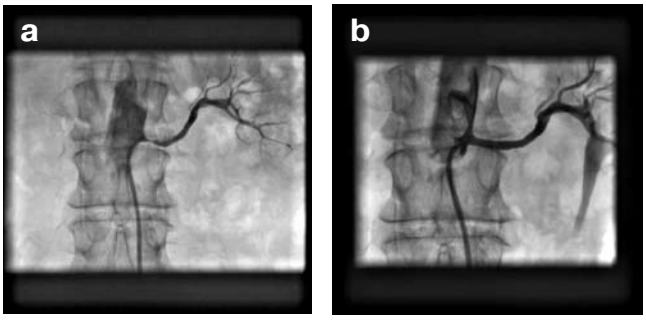

Figure 5. The renal artery before (a) and after (b) PTCA.

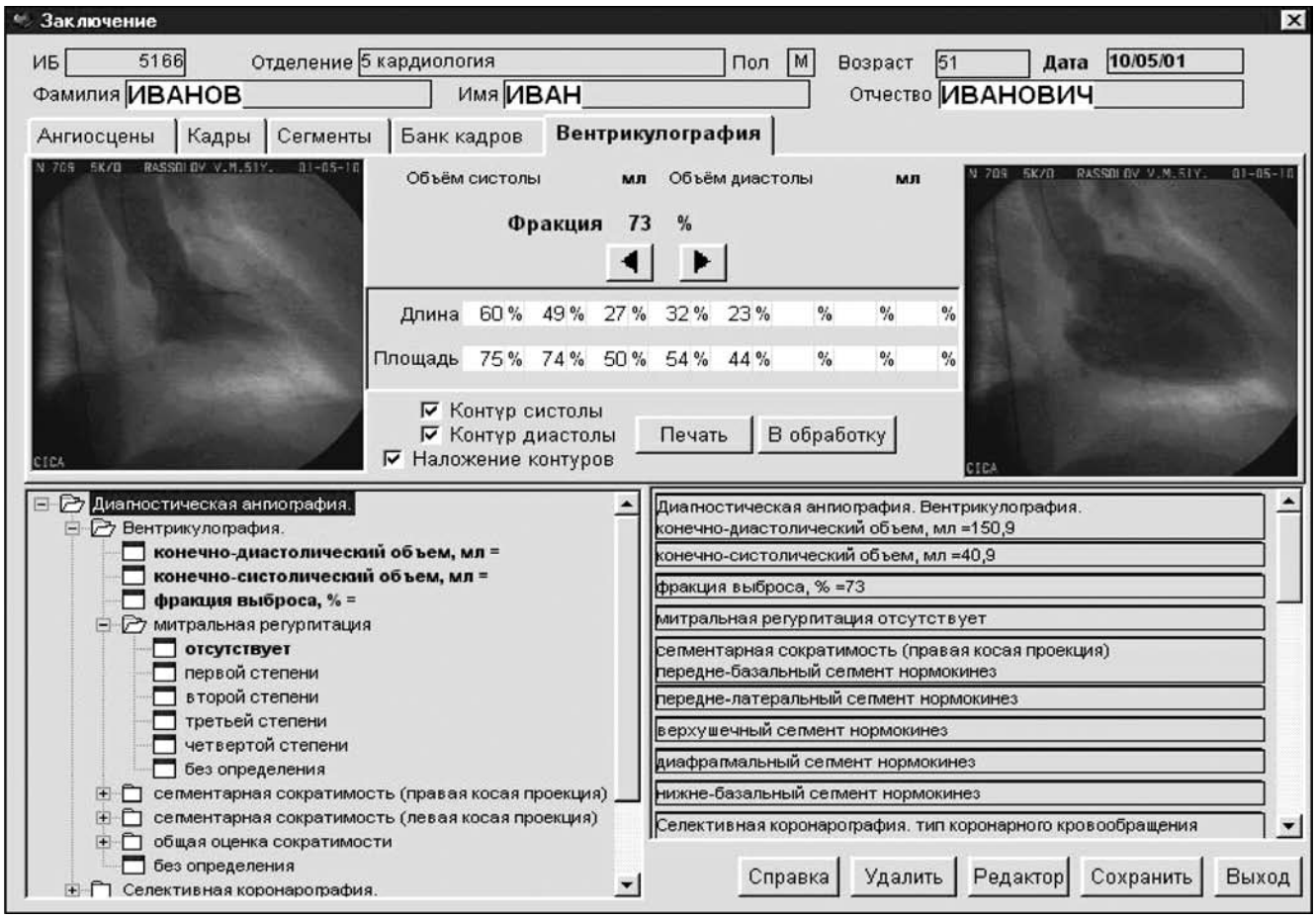

Figure 6. Generating of reports according to the results of ventriculography.

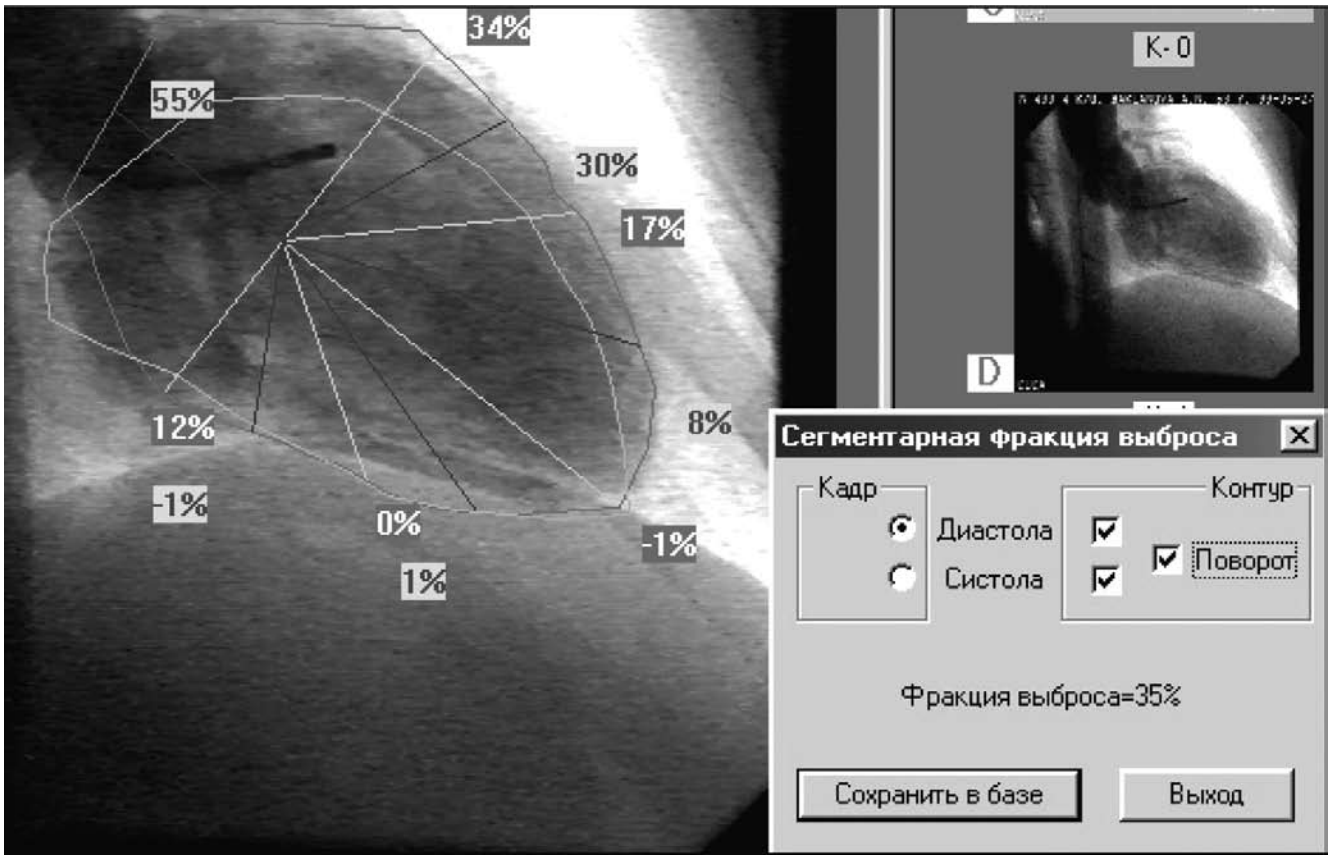

Figure 7. Calculation of ejection fraction and segmental characteristics.

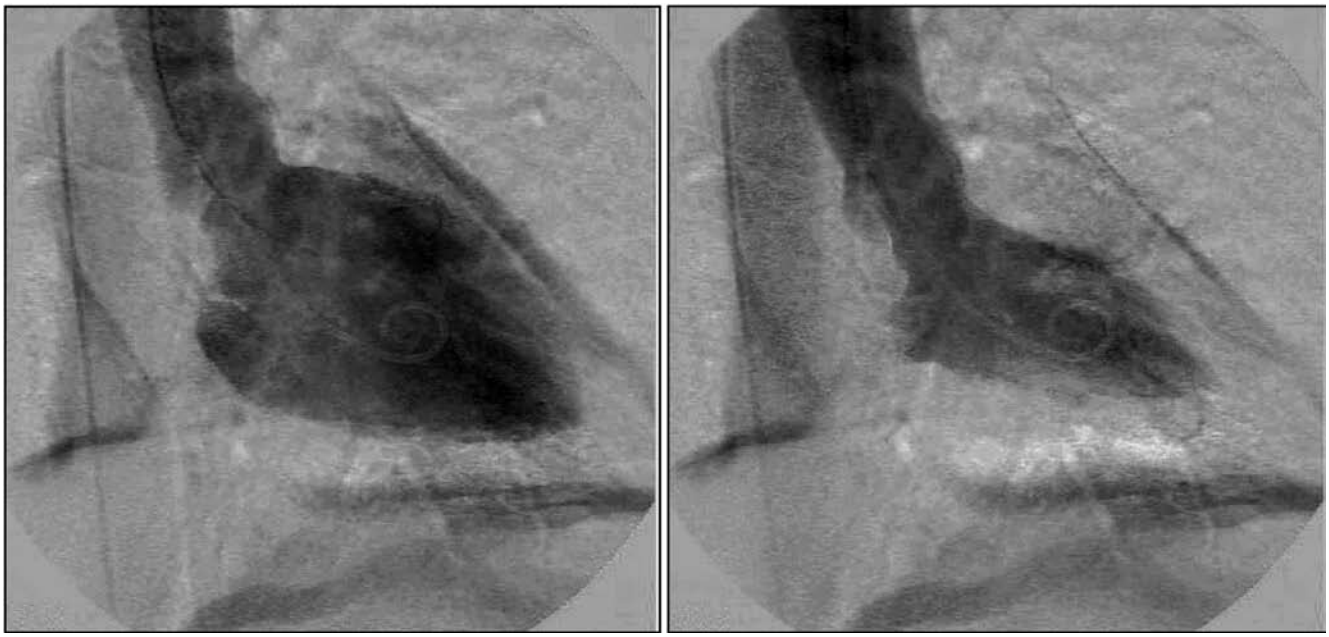

Figure 8. Subtraction of images obtained in diastole and systole.

The structure of the workstation "ANGIOGRAPHY" and chart of its interaction with different subsystems of the complex is presented in Fig. 9.

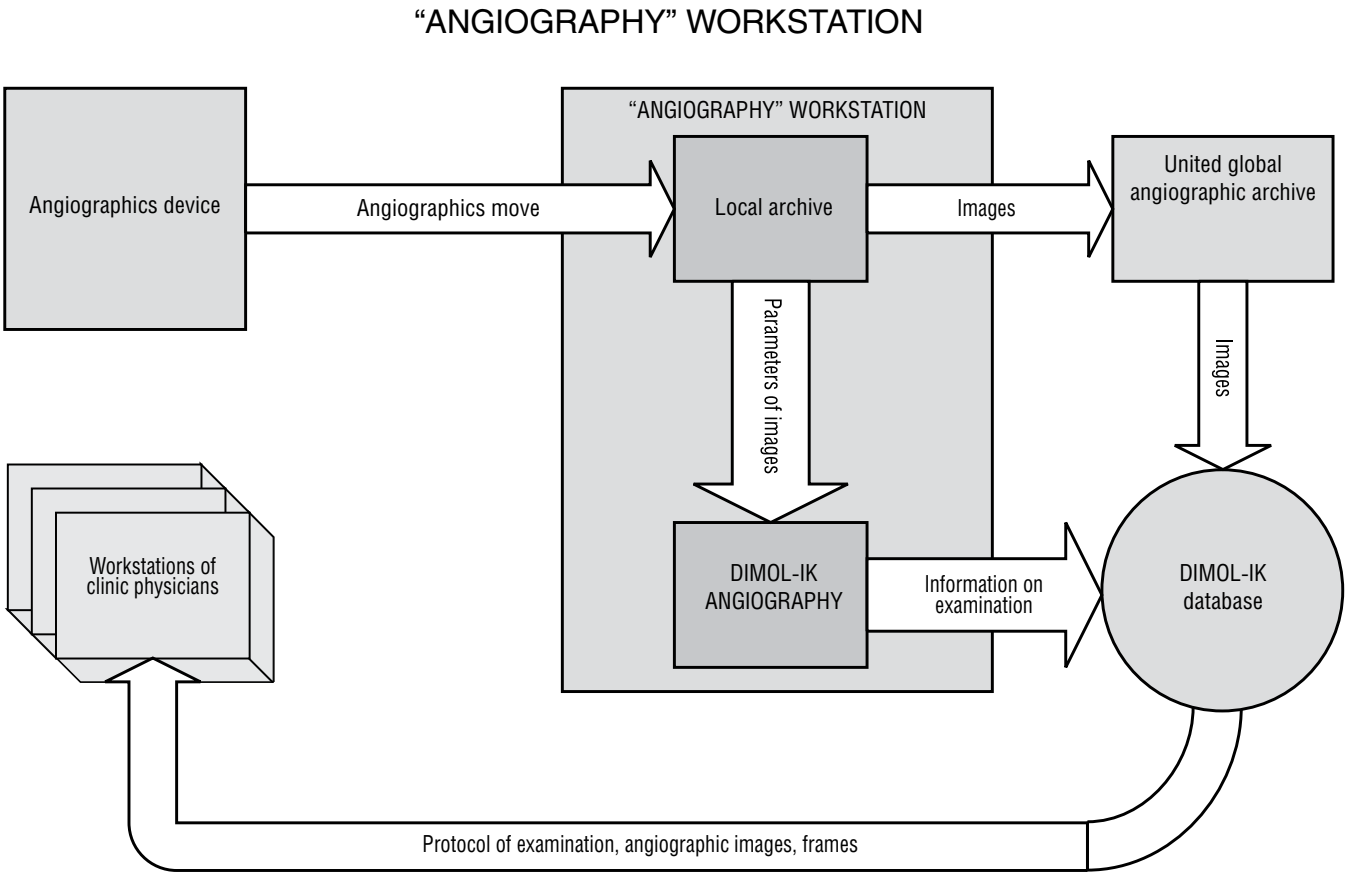

Figure 9. Chart of interaction of the PC "ANGIOGRPHY" with subsystems of the complex.

them require only several minutes or even seconds. In such a case, physician obtains systematized and generalized information, sees data of all previous functional examinations, can judge on objective condition of the cardiovascular system at the time of patient's previous stay at the hospital. The possibility to view angiographic films demonstrating heart performance and vessels' condition in details is of special significance. The physician can select an optimal schedule for further examinations after analysis of the results stored in archive only. In case of need, there is a possibility to return to analysis of previously obtained angiographic data.

The advantages of the electronic archive system consist in the fact that it allows to perform the researches on the basis of rich factual material. If research assistants of a clinic have formerly spent many months for search and selection of necessary data, now it takes minutes or tens of minutes.

Technology of digital archiving realized in the "DIMOL-IK" complex combined with workstations located in different rooms of a clinic allows to perform an operative and repetitive detailed analysis and processing of obtained angiographic data. Patient capacity of a clinic and the effectiveness of the use of expensive angiographic equipment are significantly increased due to parallel work of operative team and physicians performing the analysis of the results of examinations, while the time spent for searching and analysis of required information decreases sharply.

SYSTEM OF CLASSIFICATION AND CODING OF MEDICAL INFORMATION

Automated system of classification and coding of medical information is an important element of the "DIMOL-IK" complex. The system of classification and coding allows creation of digital classifiers for different examinations based on common international and domestic practice. Collection of classifiers and coding tables represents a medical regulatory system which includes main types of diagnostics and treatment as follows:

1. Examination (catheterization).
2. Procedures (catheterization).
3. Interventions (catheterization).
4. Complications (catheterization).
5. Diagnoses (referring, underlying, surgical).
6. Medicinal remedies (surgery and anesthesiology).
7. Procedures and surgical interventions (surgery and anesthesiology).
8. Duplex scanning of vessels.
9. Clinical and laboratory examinations.
10. Drug treatment.
11. Referral for clinical and laboratory examinations.
12. Complications.
13. ECG-Holter monitoring.
14. 12-lead electrocardiography.
15. Veloergometry.
16. Ergonovine test.
17. Echocardiography.

Due to introduction of the system of classification and coding, report generation is performed by physician via selection of variants from a tree of conjugate alternatives. Such work technology provides uniformity of regulatory system used by physicians and accuracy of information entry. Information retrieval system integrated in the "DIMOL-IK" complex allows to find any classified data concerning examinations performed in any time period in a matter of seconds. Thus, physicians got the possibility to carry unique researches on the basis of materials actually collected in digital archive.

STRUCTURE AND PRINCIPLES OF FUNCTIONING OF THE DIMOL-IK POLIKLINIKA COMPLEX

The structure and principles of functioning of the DIMOL-IK STATSIONAR and DIMOL-IK POLIKLINIKA complexes are similar. Therefore, we will dwell on some peculiarities of complex work in outpatient department.

Functional diagram of the complex is presented in Fig. 10.

Outpatient services equipped with workstations of the "DIMOL-IK POLIKLINIKA" complex are demonstrated in Fig. 10.

Main form for completing electronic outpatient's card is shown in Fig. 11.

The "DIMOL-IK POLIKLINIKA" complex can function both stand-alone and together with the "DIMOL-IK STATSIONAR" complex. Complex automation of diagnostic and treatment process in outpatient department is provided under stand-alone mode. Work of the record department is significantly simplified. Cardiologists are permitted to work with electronic outpatient's card; a process of statistical card keeping and other functions are automated.

However, the main advantages of the complex are evident during its work together with the "DIMOL-IK STATSIONAR" complex. In this case, the technology of outpatient department work appears to be as follows.

Patient's electronic outpatient card is initiated during his/her initial visit. If hospitalization is required according to the results of examination doctor puts a patient on a waiting list and if free place is available he/she presses function key "Hospitalization". In this case, all registration and medical data including examination results are automatically transferred to hospital. On patient's admission to the hospital, case history with the results of his/her examination in outpatient department is automatically generated. Hospitalization process for such patients takes several minutes. There is also a mode of urgent hospitalization from outpatient department, which is similar to that described above.

Taking into consideration that cardiological patients need outpatient follow-up after being discharged from the hospital there is a mode of automated generating of outpatient card for such patients. At the time of discharge, registration data

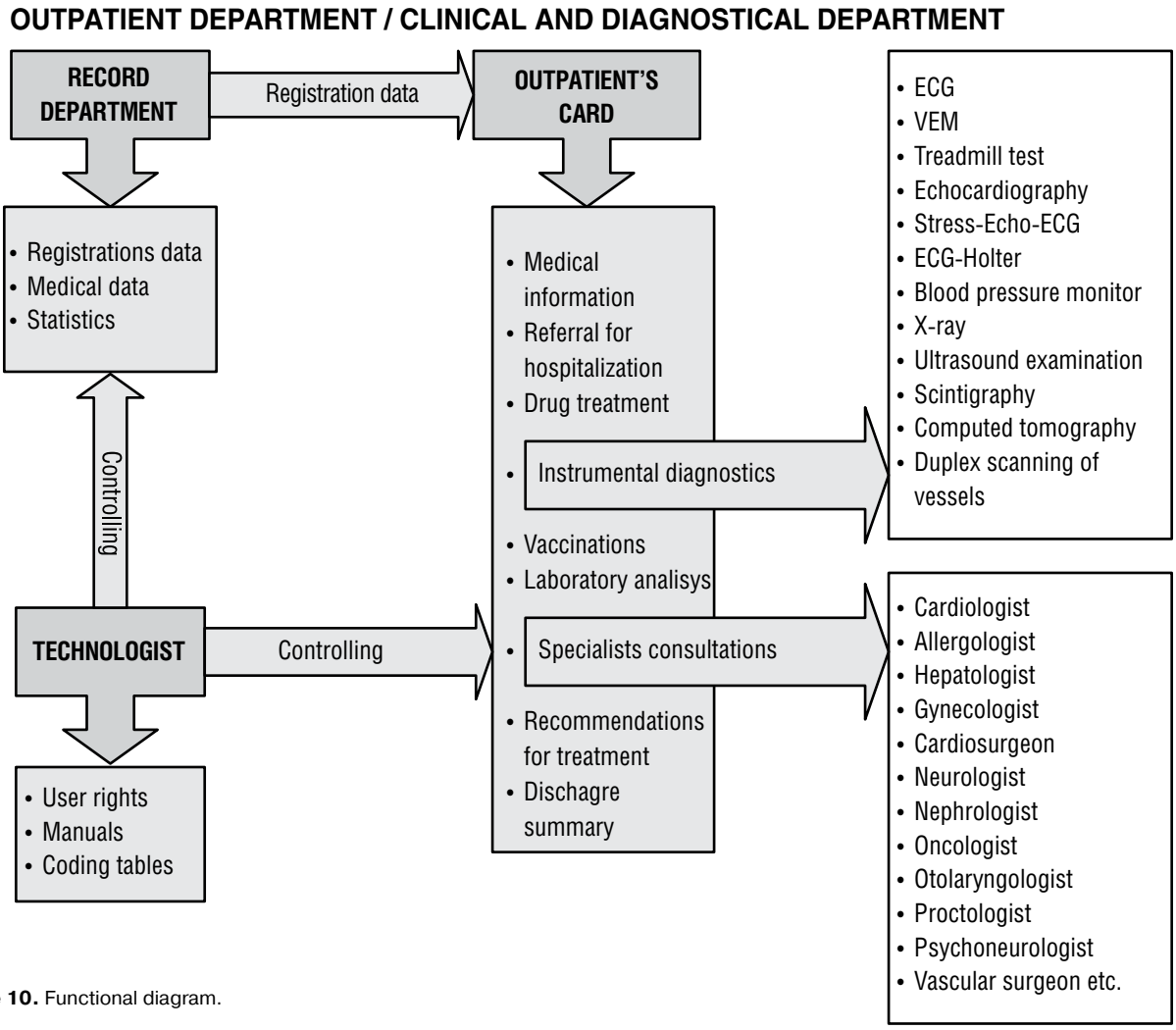

Figure 10. Functional diagram.

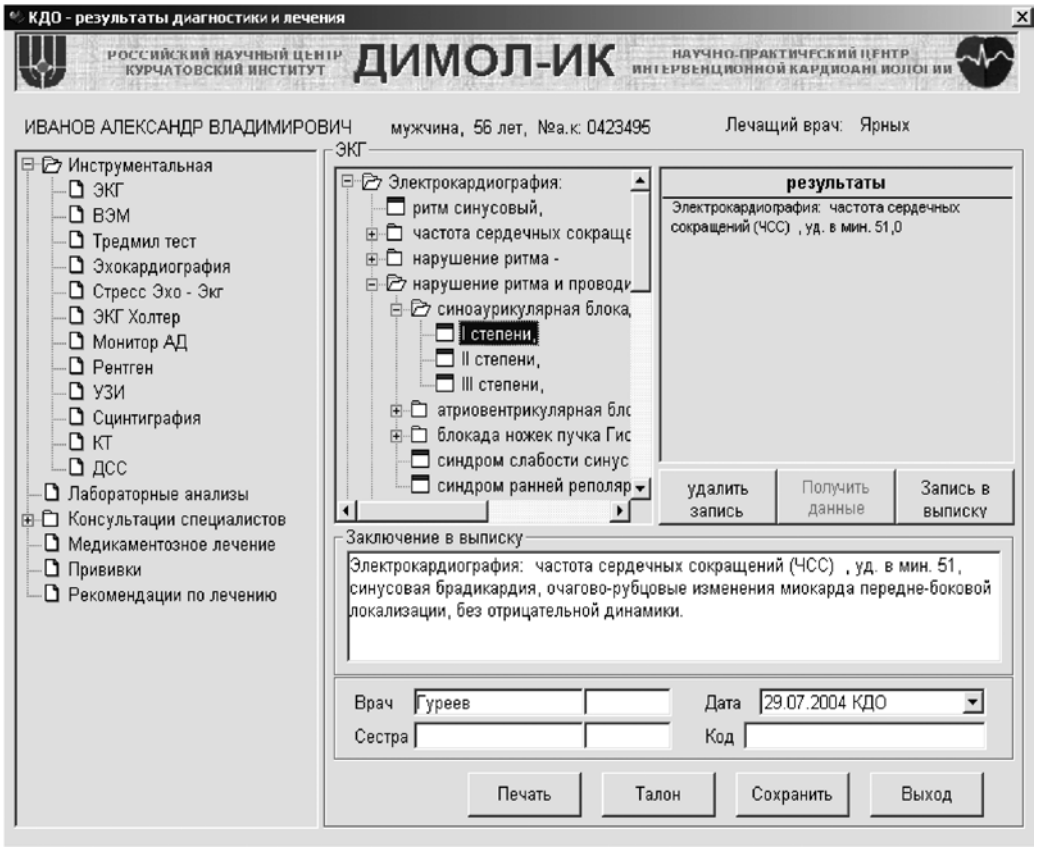

Figure 11. Form for completing electronic outpatient's card.

and patient's discharge summary are automatically transferred to the outpatient department. If a patient has earlier attended outpatient department, then he/she already has an outpatient card, to which discharge summary is pasted. If a patient did not visit outpatient department earlier, then outpatient card with discharge summary is automatically generated for him/her. Hence, when a patient comes to outpatient department, completed outpatient card already "waits" for him/her. Such a technology is worked up and proved itself useful in Moscow City Center of Interventional Cardioangiology.

Similar technology is realized upon referral of patients from Moscow City Center of Interventional Cardioangiology to rehabilitation department "Bykovo".

RESULTS OF COMPLEX EXPLOITATION

Treatment of more than 70,000 patients with cardiovascular diseases was performed during exploitation of the "DIMOL-IK" complex in the Center of Interventional Cardioangiology. The number of incorrect diagnoses is minimized – occasional cases. The mortality from myocardial infarction is approximately 4-5%, with the average level for Moscow being 22-23%. The number of PCIs increased to 2,000 per year. The information about all patients who underwent treatment at any department of Moscow City Center of Interventional Cardioangiology (hospital, outpatient department, rehabilitation department) is operatively available from archive of the "DIMOL-IK" complex. This information includes full case histories, diagnostic images and angiographic films. This means that all patients' data over any period of time can be obtained by physician in a matter of seconds.

Heterophil Anti-Cardiac Antibodies and Cardiovascular Changes in Children with Viral Infections

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Kew words: herpes infection, Epstein-Barr virus, cytomegalovirus, human herpes virus type 6, respiratory viruses, anti-cardiac antibodies to endothelium, conduction system, cardiomyocytes, smooth myocytes.

Abbreviations

DCMP– dilated cardiomyopathy
IM – infectious mononucleosis
EBV – Epstein-Barr virus
CMV – cytomegalovirus
HHV-6 – human herpes virus type 6
HI – herpes infection
ACAB – anti-cardiac antibodies
AB – antibodies
CTD – connective tissue dysplasia
MCM – minor cardiac malformations
ELISA – enzyme-linked immunosorbent assay
PCR – polymerase chain reaction
IFA – immunofluorescence assay
TIC – toxic and infectious cardiomyopathy

Cardiovascular function disturbances during acute infectious diseases are observed in 50-95% patients, according to various authors' data; they are most common in patients with burdened premorbid grounds or cardiological family history (1, 2, 3). In most cases these changes are not permanent, however, the infections may cause myocarditis, pericarditis, endocarditis, heart contractile and conductive disturbances, and endothelial cell damage (4, 5, 6).

It is known that viruses, especially enteroviruses, are the most cardiotropic ones. However, over the last years herpes viruses are considered more commonly as the causes of cardiovascular lesions in clinical practice. They are wide spread pathogens and, along with enteroviruses, are able to persist in the body for a long time. The role of herpes in development of DCMP, coronary vasculitis, and early atherosclerosis, left ventricle dilatation and heart rhythm disturbances (4, 7, 8, 9, 10, 11, 12) is being investigated. The Herpes family viruses possess a number of properties that allow them to be a cause of chronic cardiovascular pathology with altered endothelial cells, smooth muscle cell proliferation, various immunopathological shift, including polyclonal humoral activation, morphological changes in the cardiomyocytes (13, 14, 15).

The data appeared on possible role of the respiratory viruses in development of cardiovascular pathology, by direct cardiomyocytes damage associated with myolysis and increased levels of cardiotropic enzymes (16), by toxic or immune-mediated effects, involving the mechanisms of generalized inflammatory process (17) appeared

The viral infection in children may result in persistent morphologic and functional changes in the cardiovascular system 3-7 times more frequently than in adults. Thus, biopsy performed in a multicenter study evaluating the efficacy of treatment for chronic myocarditis in children showed myocarditis to be a cause of DCMP in 30% patients, and in 4.3-10% of adult patients (18, 19).

One of potential mechanisms of cardiac structure damage in viral and bacterial infections may be an effect of specific and non-specific antibodies resulting in different heart function disturbances including dissociation of electromechanical myocardial coupling (20, 21). Increased titers of anti-cardiac auto-antibodies, heterophil anti-cardiac antibodies are observed not only in rheumatic patients but in patients with myocarditis, Kawasaki disease, cardiomyopathies, coronary heart disease, and myocardial infarction as well (22, 23).

It has been shown that increased titers of anti-cardiac antibodies are observed not only during the ongoing inflammation but during myocardial dystrophy, myocardial remodeling of various genesis,

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including stress-induced remodeling in sport of highest progresses (24, 25).

The PURPOSE of the present study consisted in integrated evaluation of the state of cardiovascular system and the spectrum of heterophil anti-cardiac antibodies in children with acute respiratory viral infections and herpes viral infections.

MATERIAL AND METHODS OF STUDY

Over the period from 2000 through 2006, 66 patients (38 boys and 28 girls) aged from 3 to 14 years with various viral infections were followed up at the Isolated Ward Infectious Department No.22 of the Morozovskaya Children City Clinical Hospital. Group I included 44 children with infectious mononucleosis (IM), group II – 22 patients with severe complicated acute respiratory viral infections (ARVI).

Complex examination included clinical and functional assessment of the cardiovascular system using electrocardiography, echocardiography, evaluation of vegetative status by variation pulsometry at rest and in orthostatic test (R.M. Baevsky, 1984), phenotypic assessment of connective tissue dysplasia (CTD) by Milkovsky Dmitrova criteria (1982) along with identification of infectious agent and determination of heterophil anti-cardiac antibodies.

Viral DNA was determined by PCR, and specific antibodies to herpes Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus type 6 (HHV-6) were determined by ELISA (Research Institute of Immunology of the Russian Academy of Medical Science) for identification purposes in patient's serum. These herpes viruses are currently considered as an etiologically significant pathogen in development of infectious mononucleosis within conception of the polyetiology of this disease (26, 27) Early and late cytomegalovirus antigens were determined in peripheral white blood cells by IFA using monoclonal antibodies (pp72 - protein of the early replication stage, pp65 – late structural protein). EBV diagnosis was based on the diagnostic level of specific antibodies to VCA capsid antigen (IgM 1:10; IgG 1:320) and early EA antigen (IgM 1:10; IgG 1:20). CMV diagnosis was based on determination of diagnostically significant levels of IgM 1:2700 and IgG 1:8100, HHV-VI diagnosis was based on the levels of antibody titers of IgM 1:100 and IgG 1:800. The serum titers of IgM and IgG antibodies to type I and II herpes viruses were determined in children with infectious mononucleosis. Respiratory viral infections and enteroviruses were diagnosed using paired serum in complement fixation and hemagglutination inhibition tests when titers were increased more than 4 times.

Electrocardiographic tests included 12-lead electrocardiography (supine, upright, after physical exercises, according to the indications, in medication tests) and cardiointervalography (CIG). Echocardiography (Echo-CG) was performed using ACUSON 128XP/10 (USA) by standard method assessing morphometric parameters, minor cardiac malformations (MCM), pericardium status on Days 7-14 after admission.

Determination of heterophil anti-cardiac antibodies (ACAB) to endothelial cells, cardiomyocytes, conduction system, and smooth myocytes was performed at the Federal State Institution Research Institute of Transplantology and Artificial Organs (Laboratory of Transplantation Immunology, Head of Laboratory - V.Yu. Abramov) by indirect immunofluorescence assay on bovine myocardium slices on Days 10-14 after admission in 18 children with HI and in 22 children with ARVI. When assessing obtained ACAB titers, the values of $\leqslant$1:40 were considered as normal; titers of 1:80 were considered as median values for population; titers 1:160 – as limited values, and titers 1:320 – as clinically significant values (22, 25, 28). The reverse titers were used for determination of mean antibody values, i.e. absolute values of corresponding dilutions (40; 80; 160; 320).

STUDY RESULTS AND DISCUSSION

Combined infection by two and more types of herpes viruses was observed in all children with IM. Infection with only etiologically significant pathogens of infectious mononucleosis (EBV, CMV and HHV-6) in different combinations was determined in 28 children (63%), additional infection with type I and II herpes viruses was found in the remaining 16 children (37%).

Viral etiology was confirmed and decoded in 17 (77%) children from group II. Four-fold increase of the titer of antibodies to influenza virus was found in 9 (53%) children, including antibodies to influenza type A1 virus in 4 children, antibodies to influenza type A2 virus in 3 children, and antibodies to influenza type B virus in 2 children. Adenovirus was revealed in 5 (29%) children, parainfluenza virus – in 3 children (18%). One child had combination of the influenza type A2 and adenovirus, and another child had 4-fold increase in he titer of antibodies to Koksaki B virus.

Analysis of historical data revealed unfavorable course of the ante- and intranatal periods in 41% (9) children with ARVI and in 34% (15) with herpes infection (HI). High infection index was more common in children with HI (23% and 15%, respectively) In these children the burden family cardiovascular history was almost 2 times more frequent (in 34% (15) children with HI and 18% (4) children with ARVI, respectively). In 10 out of 15 children with HI, there was (coronary heart disease, angina pectoris, essential hypertension, congenital heart defect, heart rhythm disturbances, vegetative dysfunction syndrome). In a half of cases the pathology was observed in two or more nearest relatives.

Chronic pathology of ENT-organs was 2-fold more frequent in children with ARVI (ARVI – 68%, HI – 31%). Contamination with group A β-haemolytic streptococcus (confirmed by laboratory tests) was revealed in 45% patients with HI and in 27% patients with ARVI.

Cardiac complaints (palpitation, heart irregularity, cardiodynia) were more frequently observed in children with ARVI (27% (6) children), and children with HI – 2.5 times less frequently (11% (5) patients). On physical examination, heart area was not changed in any child. The borders of relative heart dullness were insignificantly displaced to the left (0.5-1.0 cm) in 2 (5%) children with HI and in 6 (27%) children with ARVI.

Physical cardiovascular changes observed in acute period were common in children with ARVI and were characterized with moderately muffled apical first sound (10-45% and 13-30%, respectively). In a half of observations, in 21 (48%) patients with HI and in 12 (55%) children with ARVI, systolic murmur was heard at point V (third intercostal space) and/or left parasternal region, which was possibly due to increasing hemodynamical significance of minor cardiac malformations on the background of acute infectious toxicosis and changes in hemorheology parameters (3).

Various changes were revealed on the initial ECG recordings within first three days after admission in all children. Sinus node dysfunction (atrial rhythm, pacemaker migration and/or significant bradycardia with the episodes of sinoatrial block) was recorded in 46% patients with ARVI and in 31% patients with HI. In children with ARVI there was a greater trend towards more fast recovery of sinus node function with 2.2-fold decrease in the incidence of significant bradycardia, 3-fold decrease in the incidence of atrial rhythm, and 1.3-fold decrease in the incidence of pacemaker migration on Days 10-14 simultaneously with disappearance of intoxication symptoms. In children with HI there was a similar decrease in the incidence of atrial rhythm (3 fold), but pacemaker migration rate was higher in 1.5 times, and there was no change over time in bradycardia incidence (23%). Change in atrio-ventricular conduction (PQ prolongation or shortening) was found during acute period with similar incidence both in children with ARVI and in children with HI (32%). There was more evident normalization of AV conduction over time in children with ARVI (9%) with 3.5-fold decrease in the incidence of conduction disturbances as compared to patients with HI (20%). Intraventricle conduction disturbances were observed in 39% of children with HI during acute period and in 43% patients over time. In patients with AVRI these changes were characterized with evident positive changes over time with almost 2-fold decrease in their incidence during recovery period (50% and 28%, respectively). Repolarization abnormalities on the initial ECG recording occurred totally in one third of patients with viral infections regardless of the etiology. In children with ARVI, evident marked positive changes over time in the end part of QRS with 3-fold decrease in the incidence of ST-T changes were observed during recovery period. In children with HI, the repolarization abnormalities were characterized with more significant stability, these were observed in 34% children on the initial recordings and persisted over time till Day 14 in 30% patients.

Thus, during acute period of viral infections the ECG changes including combined changes were found more often in children with ARVI and were characterized with evident positive changes during recovery period with more than 3.5 fold decrease in their incidence. This may suggest a favorable prognosis for cardiovascular changes occurring in children with infectious toxicosis. In children with HI, the ECG changes were more persistent and there were no positive changes over time in a number of parameters.

Analysis of vegetative homeostasis revealed the signs of vegetative dysfunction, generally of one-way pattern in 82% of children with ARVI, and in 89% children with HI (Table 1). In a half of children, baseline vegetative tone was characterized with sympathicotonia, with hypersympathicotonia dominating in children with ARVI. Change in the vegetative provision of activity with absolute domination of insufficient provision was observed in one third of children. Disturbance of the vegetative reactivity was more typically for children with HI (83%), they had similar incidence of asympathicotonic reactivity and hypersympathicotonia; the latter is unusual for recovery period.

Table 1. Characteristics of vegetative homeostasis in children with viral infections during recovery period.

Children groups	BVS				VAP			VR		
	E	V	S	HS	Norm	Insuf	Exc	Norm	Asymp	HSR
HI (n=18)	28%	16%	28%	28%	67%	33%	-	17%	50%	33%
ARVI (n=22)	36%	18%	14%	32%	64%	32%	4%	32%	45%	23%

Note: BVS – baseline vegetative tone (E – eutonia, V – vagotonia, S – sympathicotonia, HS - hypersympathicotonia), VP – vegetative activity provision (Norm – normal provision, Insuf – insufficient; Exc - excessive), VR – vegetative reactivity (Norm – normal reactivity; Asymp – asympathicotonia; HSR – hypersympathicotonic reactivity)

Disturbances of adaptive resources of the vegetative nervous system observed in the majority of examined children (68% - ARVI, 77% - HI) were characterized with the prevalence of central nervous regulation of vegetative homeostasis with adaptation exertion in 80% of children.

The evaluation of mean morphometric echocardiographic parameters in children with viral infections showed no significant deviations from the reference data taking into account age, sex, and body surface area. Minimal dysfunction of the left ventricle, i.e. moderate increase in cardiosystolic and cardiodiastolic dimensions and volumes and/or decreased ejection fraction, was revealed in 26% (6) of children with HI and in 14% (3) of children with ARVI. Minimal pericardial effusion with separation of the pericardial sheets at the level of papillary muscles (up to 3-4 mm) was observed in 18% (4) of patients with ARVI and in 9% (2) of patients with HI. These changes

being more evident in children with HI were considered by us to be manifestations of toxic and infectious cardiomyopathy.

Comparative assessment of CTD and MCM grades showed almost 2-fold lower level of significant general (grade II-III CTD) and cardiac stigmatization in patients with ARVI as compared with children with HI (Table 2).

Table 2. Comparative characteristics of connective tissue dysplasia rades and rates of minor heart malformations in children with viral infections.

Children groups	CTD grade				MCM	Combined MCM
	0-I	II	III	II-III		
HI (n=23)	57%	39%	4%	43%	73%*	39%*
ARVI (n=22)	77%	18%	5%	23%	41%*	5%*

*- significant difference ($p<0.05$)

A number of studies revealed decreased immunological reactivity in patients with malformations, multiple stigmatization reflecting connective tissue dysplasia (29, 30, 31). Thus, higher degree of general connective tissue dysplasia and cardiac stigmatization in children with HI may indicate the immunological involvement of patients from this group and confirm the presence of burdened premorbid cardiovascular status in children with herpes infection.

Seventy two measurements of anti-cardiac antibodies (ACAB) to endothelial cells, cardiomyocytes, conduction system, and smooth myocytes were performed in 18 children with HI. Normal titers (1:40) of various antibodies were found in 41.6% (30) measurements; marginal and clinically significant increase in ACAB titers (⩾1:160) was found in 39% measurements; clinically significant increase was found in 18% measurements (Table 3).

Table 3. Distribution of anti-cardiac antibody titers in all measurements performed in children with herpes infection.

Antibody titers				
ACAB type	1:10-1:40	1:80	1:160	1:320
To endothelium	11 (15,3%)	3 (4,2%)	2 (2,8%)	2 (2,8%)
To cardiomyocytes	7 (9,7%)	2 (2,8%)	4 (5,6%)	5 (7%)
To conductive system	6 (8,3%)	2 (2,8 %)	7 (9,7%)	3 (4,2%)
To smooth myocytes	6 (8,3%)	7 (9,7%)	2 (2,8%)	3 (4,2%)
Total measurements: n=72	77%	18%	5%	23%

In 22 children with ARVI, 88 measurements of ACABs to four cardiac antigens were performed. Normal titers of various antibodies were obtained in 45.5% (40) measurements; antibody titer increase above the median population values were observed in 54.5% (48) measurements among these marginal and clinically significant values were revealed in 21.5% (19) measurements, and clinically significant values - in 4.5% (4) measurements (Table 4).

Table 4. Distribution of anti-cardiac antibody titers in all measurements performed in children with ARVI.

Antibody titer				
ACAB type	1:10-1:40	1:80	1:160	1:320
To endothelium	9(10,2%)	4(4,5%)	7(8,0%)	2(2,3%)
To cardiomyocytes	10(11,4%)	10(11,4%)	1(1,1%)	1(1,1%)
To conductive system	13(14,8%)	4(4,4%)	4(4,5%)	1(1,1%)
To smooth myocytes	8(9,1%)	11(12,5%)	3(3,4%)	-
Total measurements: n=72	40(45,5%)	29(33,0%)	15(17,0%)	4(4,5%)

Thus, positive ACAB titers were determined almost in a half of measurements both in children with ARVI and in children with HI. However, clinically significant titers were observed 4-fold more frequently in children with HI (18.0% and 4.5%, respectively).

When assessing ACAB titers to different heart structures in children with HI, marginal and clinically significant increases in titers of antibodies to conduction system (14%), cardiomyocytes (12.6%) were found more frequently and antibodies to endothelium (5.6%) - less frequently. On the contrary, in children with ARVI positive titers (>1:80) to endothelial cells (14.8%) were found more frequently, and increased titers (>1:160) to cardiomyocytes (2.2%) and conduction system (5.6%) were revealed less frequently than in children with HI. More frequent determination of positive ACABs to endothelial cells in children with ARVI may be explained by known endotheliotropism of influenza virus, which was the cause of respiratory infection in a half of patients from this group.

Among 10 children with HI having marginally high and/or clinically significant titers of antibodies to conduction system, had simultaneous increase in the titers of antibodies to cardiomyocytes was revealed in 6 children. Among these children minimal dysfunction of left ventricle by EchoCG was observed 2 times more often than in the total group. ECG changes were characterized with intraventricle and/or atrioventricle conduction disturbances in 8 out of these10 patients. Combination of high titers of ACABs to conduction system and cardiomyocytes was associated with marked tendency toward increase in the incidence and degree of repolarization abnormalities.

Comparative analysis of mean reverse titers of ACAB in children with HI showed that the mean values of all ACAB parameters including mean total titer (112.8±19.9) exceeded mean population values (1:80) (Table 5).

Mean reverse titers of antibodies to cardiomyocytes, conduction system, and smooth myocytes were statistically significantly higher than that in children with ARVI. Only mean titers of antibodies to endothelial cells were close to mean population values in patients with HI (82.2±23.0).

Table 5. Mean reverse titers of ACAB in children with viral infections.

ACAB type	Groups of children with viral infections	
	HI (n=18)	ARVI (n=22)
To endothelium	82.2±23.0	107.3±19.0
To cardiomyocytes	147.8±27.6*	72.9±13.5*
To conductive system	134.4±24.3*	79.0±15.4*
To smooth myocytes	112.8±4.3*	74.0±8.9*
Total titer	112.8±19.9	83.3±14.3

* - significant difference ($p < 0.05$)

In children with ARVI, total ACAB titer was practically equal to mean population level (83.3±14.3), and titers of antibodies to cardiomyocytes, conduction system, and smooth myocytes were lower than mean population levels (Table 5).

CONCLUSION

Thus, high ACAB production levels, mainly of antibodies to conduction heart system and cardiomyocytes, were observed in children with herpes infection. In a quarter of patients, his was associated with the minimal changes in the morphometric parameters of the left ventricle and in more than a half of children with HI – with conduction and repolarization disturbances on ECG.

In children with ARVI, the levels of anti-endothelium Abs were higher than that in children with HI; it may be attributed to influenza virus endotheliotropism. On the contrary, titers of antibodies to other heart structures were lower than that in children with HI. In children from this group it was combined with less burdened cardiovascular familial history, less evident general and cardiac stigmatic signs, rare detection of the left ventricle dysfunction signs and evident positive ECG changes over time as compared to children with HI.

Conclusions:

1. High incidence of cardiovascular changes (premorbid pre-existing constitutional dysplastic features (MCM), vegetative disorders, toxic and infectious cardiomyopathy occurring in more than a half of patients) was revealed in children with viral infections, especially with herpes infection.
2. The signs of vegetative dysfunction in children with viral infections have generally one-way pattern with prevalence of sympathicotonia in baseline vegetative tone with insignificant activity provisions and asympathicotonic reactivity.
3. Toxic and infectious cardiomyopathy in patients with herpes infection is characterized with more prolonged course, signs of minimal left ventricle dysfunction, persistence of ECG changes over more than 14 days, and high mean titer of anti-cardiac antibodies.

   The features of clinical and immunological status in children with herpes infection are as follows: high values of anti-cardiac antibodies to conduction system and cardiomyocytes in combination with persistent conduction and repolarization disturbances on ECG.
4. In 70% of children with ARVI, toxic and infectious cardiomyopathy was only observed during infectious toxicosis and was characterized with favorable prognosis, rapid positive changes over time as assessed by clinical and instrumental methods, absence of formation of anti-cardiac antibodies to the heart's conduction system and cardiomyocytes, activation of development of antibodies to endothelial cells due to endotheliotropism of influenza viruses.

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A JUBILEE

Vladimir Podzolkov

On November 15, 2008, the eminent Russian cardiac surgeon, Professor, Honored Worker of Science of Russian Federation, Academician Vladimir Podzolkov turned 70.

Vladimir Podzolkov was born on November 14, 1938, in the city of Voronezh, both his parents were physicians. In 1961 he finished Krasnoyarsk State Medical Institute, and after that passed his residency on the Institute of Radiology affiliated with the Academy of Medical Sciences (1961-1963).

After that V. Podzolkov began to work in Bakoulev Institute for Cardiovascular Surgery that was headed by Academician V.I. Bourakovsky. There he passed his way from a post-graduate student to the junior, then senior scientific worker. In 1966 Vladimir Podzolkov defended his Ph.D. thesis on the subject "Duration of right ventricular contraction phases in patients with atrial and ventricular septal defects", and in 1974 – his Medical Doctor thesis "Congenital defects of an abnormally positioned heart". In 1979 he was appointed Head of the Department congenital heart diseases. In 1983 Dr. Podzolkov was given the title of Professor, and in 1998 he was awarded the a honorary title of Honored Worker of Science of Russian Federation. From 1995 V. Podzolkov simultaneously worked as Deputy Director for Scientific Problems of Bourakovsky Institute for Cardiac Surgery at Bakoulev Scientific Center for Cardiovascular Surgery, and from 2001 he is Deputy Director for Scientific Problems of Bakoulev Scientific Center for Cardiovascular Surgery.

Professor Vladimir Podzolkov was at work upon the most important problems of pediatric cardiac surgery. He paid particular attention to the elaboration and the introduction into the clinical practice of new optimal method of surgical correction in patients with complex congenital heart defects. He was the first in Russia to perform several operations on heart and vessels, among them: radical correction of single left ventricle with sinistro-transposition of the aorta; hemodynamical correction of mitral atresia associated with pulmonary arterial stenosis; radical correction of partial and total anomalous pulmonary venous drainage to the coronary sinus and the inferior vena cava; radical correction of single or additional left superior vena cava draining into the left atrium; reconstruction of right ventricular outflow tract with conduit in pulmonary arterial atresia; reimplantation of the left coronary artery arising from the pulmonary trunk into the aorta; Fontan operation in the modification of total cavapulmonary anastomosis, as well as extracardiac tubular graft and many others. V.Podzolkov elaborated and successfully used in clinical practice a revolutionary approach to surgical treatment of complex in "criss-cross" heart.

Scientific investigations concerning hemodynamical correction of congenital heart diseases performed by Vladimir Podzolkov, enriched the knowledge on circulatory physiology and pathology and have been summarized in monographs. He has accumulated an invaluable experience with heart valves replacement in children.

Fundamental studies carried out under the guidance of professor Podzolkov allowed for an enlargement of contingence of patients operated on for complete and corrected transposition of the great arteries, pulmonary arterial atresia, origin of the great arteries from the right and left ventricles through the introduction of valved homoaortic and homopulmonary grafts.

Vladimir Podzolkov is the author and co-author of over 450 scientific works published in Russia and abroad, including 14 monographs. The most important among them are: "Anomalies of Intrathoracic Heart Postion " (1979), "Aorto-Pulmonary Septal Defect" (1987), "Manual on Cardiovascular Surgery" (1989), "Intervascular Anastomoses in Surgical Treatment of Complex Congenital Heart Diseases" (1989), "Congenital Heart Diseases" (1991), "Hemodynamical Correction of Congenital Heart Diseases" (1994), "Extracardiac Conduits in Surgical Treatment of Complex Congenital Heart Diseases" (2000), "Pulmonary Arterial Atresia with Ventricular Septal Defect" (2003), "Ebstein's Anomaly" (2005), "Surgical Treatment of Congenital Heart Diseases using the Method of Hemodynamical Correction" (2007), " Tetralogy of Fallot" (2008). He possesses two inventor's certificates, is the author of guidelines and of an educational film "Hemodynamical Correction of Tricuspid Valve Atreisa".

V. Podzolkov is an active promulgator of Russian scientists' achievements. He made multiple presentations on surgical treatment of complex congenital heart diseases at international congresses.

Vladimir Podzolkov conducts an active scientific and educational work, he dedicates his time to the training of high-skilled professionals in the field of cardiovascular surgery. Seventeen Doctor of Medicine's and 56 Philosophy Doctor's theses had been prepared and defended under his guidance.

In 1997 Vladimir Podzolkov was elected Corresponding Member, and in 2000 – Academician of Russian Academy of Medical Sciences. He is the fellow of Russian Association of Cardiovascular Surgeons, of European Association of Cardiothoracic Surgeons, member of Editorial Board of the Russian journal "Annals of Surgery".

In 1988 Vladimir Podzolkov was awarded State Prize of the USSR for the elaboration and introduction into the clinical practice of new reconstructive methods for the treatment of complex congenital heart defects. He has been decorated with the orders of Badge of Honor and of Friendship.