THE EFFICACY OF RETROGRADE MYOCARDIAL PERFUSION IN ENDOVASCULAR CORRECTION OF SEVERE ANTERIOR CORONARY CIRCULATION DISORDERS IN PATIENTS WITH NON-ST-ELEVATION ACUTE CORONARY SYNDROME

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© **E.B. Shakhov,** PhD, Head of Experimental Medicine Laboratory[1];
D.V. Petrov, Radiologist, Surgeon, Head of the Department of Radiological Diagnostic and Treatment Methods[2];
D.V. Volkov, Emergency Physician[2];
A.S. Novikov, Anesthesiologist[2];
K.A. Kosonogov, Surgeon, the Department of Rhythm Disturbance Syrgery[2];
E.S. Timoschenko, Cardiologist, Chief of City Cardiologic Dispensary[2];
E.B. Petrova, PhD, Tutor, the Department of Radiodiagnosis, the Faculty of Doctors' Advanced Training[1];
B.E. Shakhov, D.Med.Sc., Professor, Head of the Department of Radiodiagnosis, the Faculty of Doctors' Advanced Training, Rector[1]

[1]Nizhny Novgorod State Medical Academy, Minin and Pozharsky Square, 10/1, Nizhny Novgorod, Russian Federation, 603005;
[2]City Clinical Hospital No.5, Nesterova St., 34, Nizhny Novgorod, Russian Federation, 603005

Patients with non-ST-elevation acute coronary syndrome (non-ST-elevation ACS) require emergency percutaneous coronary intervention in case of high risk of death or myocardial infarction development at hospital stage.

The aim of the investigation was to assess the efficacy of a new technique of retrograde perfusion support of coronary blood flow in the process of endovascular correction of severe anterior coronary circulation disorders in high-risk patients with non-ST-elevation ACS.

Materials and Methods. We studied the treatment results of 12 patients after X-ray endovascular intervention. Group 1 involved 6 patients with performed retrograde perfusion support of coronary circulation, group 2 — 6 patients without retroperfusion support.

Results. In group 1 we observed the significant decrease of ST depression in V_1–V_3 leads at the 60th second of antegrade blood flow deficiency in anterior coronary blood flow in the course of retroperfusion compared to angioplasty without coronary circulation support (with retroperfusion — –0.4±0.1 mm; without retroperfusion — –1.5±0.8 mm; p=0.027). In group 2 without retrograde perfusion support, in all patients at the 60th second of antegrade blood flow deficiency there was the significant ST depression increase in the same leads (–2.4±0.9 mm; p=0.027) compared to basic ECG-picture. The similar dynamics was observed in relation to arterial pressure indices.

Conclusion. Selective retroperfusion of the great cardiac vein can be used as an effective technique of intra-operative support of cardiohemodynamics in high-risk patients with non-ST-elevation ACS.

Key words: acute cardiac syndrome; retrograde perfusion; assisted perfusion; anterior coronary circulation disorder.

Patients with non-ST-elevation acute coronary syndrome (non-ST-elevation ACS) require emergency percutaneous coronary intervention in case of high risk of death or myocardial infarction (MI) development at hospital stage [1, 2]. The percentage of hospital case fatality and MI probability in non-ST-elevation ACS patients is directly related to the development of intraoperative fatal and non-fatal cardiac events, which,

For contacts: Shakhov Evgeniy Borisovich, e-mail: es-ngma@yandex.ru

in their turn, are due to the severity of coronary bed involvement [3]. Taking into consideration relatively high probability of fatal and non-fatal cardiac events in X-ray surgical correction of clinical determining complex disorders of the anterior coronary bed in non-ST-elevation ACS patients, leading world interventional cardiology centers are searching for safe endovascular interventional techniques for this group of patients [4, 5]. One of such methods is myocardial perfusion support. Its application is highlighted insufficiently in Russia as well as in European and American protocols of managing non-ST-elevation ACS patients.

The aim of the investigation was to assess the efficacy of a retrograde perfusion support of coronary blood flow in endovascular correction of clinical determining complex of anterior coronary bed disorders in non-ST-elevation ACS patients with high-risk of intra-operative fatal and non-fatal cardiac events.

Materials and Methods. We studied the treatment results of 12 patients during the period from 25.04.2012 to 11.05.2014 admitted to City Clinical Hospital No.5, Nizhny Novgorod, who had undergone X-ray endovascular correction of complex disorders of anterior coronary circulation. Patients' age was from 41 to 75 years (mean age — 62.4±11.8 years), among them there were eight male and four female patients. When seeking medical advice for the first time, a provisional diagnosis of non-ST-elevation acute coronary syndrome was made to all patients.

For the purposes of the study all patients were divided into two groups. Group 1 consisted of 6 patients (50.0%), who had undergone endovascular correction of clinical determining complex disorders of the anterior coronary bed using retroperfusion support of coronary blood supply, group 2 — 6 patients (50.0%), who had undergone correction without assisted myocardial perfusion (Table 1).

The study complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)) and approved by the Ethics Committee of Nizhny Novgorod State Medical Academy. Written informed consent was obtained from all patients.

Clinically determining complex disorders of the anterior coronary bed were the following hemodynamically significant stenoses: stenoses of more than half of the main trunk of the left coronary artery (LCA); proximal bifurcation stenoses of 60–70% anterior descending artery (ADA) and diagonal branches (DB); ADA stenoses ≈80–90% in proximal and middle arterial segments (including subtotal stenoses) [6–8]. The stenoses of over 50% circumflex artery (CA), obtuse marginal branches (OMB) from circumflex artery and the right coronary artery (RCA) were considered to be associated hemodynamically significant disorders of posterior coronary bed [9, 10]. The severity of coronary bed disorders was estimated by SYNTAX scale [11].

Our study involved only patients with high risk of intra-operative fatal and non-fatal cardiac events. Lethality or MI risk at hospital stage was stratified using TIMI and GRACE scales [12, 13]. Relying on high probability of lethal outcome or MI at hospital stage, the instability of coronary hemodynamics with stable ischemic changes in V_1–V_6 leads on electrocardiograms, emergency invasive strategy was chosen for all patients under study [14]. Primary percutaneous coronary intervention was performed 90 min after admission to the hospital (mean time "door-balloon" in our study was 78.3±11.7 min). Diagnostic and therapeutic interventions were performed in X-ray operation rooms equipped by Innova 3100-IQ angiographic apparatuses (GE Medical Systems, France), where high risk non-ST-elevation ACS patients were brought from a reception ward or an intensive care unit. Before intervention the patients were

Table 1

Characteristics of coronary bed impairments in high risk non-ST-elevation ACS patients

Coronary bed disorders	Severity (scores) according to scale:		
	SYNTAX	TIMI	GRACE
Group 1 (n=6)			
Complex forms of anterior coronary bed disorders: ADA stenoses — 80–90% in proximal and middle arterial segments (n=4) LCA trunk stenosis (n=5) ADA and DB proximal bifurcation disorders (n=3) Associated hemodynamically significant disorders of posterior coronary bed — CA, OMB and RCA (n=6)	35.8±4.7	4.5±0.5	201.8±36.0
Group 2 (n=6)			
Complex forms of anterior coronary bed disorders: ADA stenoses — 80–90% in proximal and middle arterial segments (n=4) LCA trunk stenosis (n=5) ADA and DB proximal bifurcation disorders (n=2) Associated hemodynamically significant disorders of posterior coronary bed — CA, OMB and RCA (n=6)	35.5±9.9	4.3±0.5	197.0±18.5

given a loading dose of Clopidogrel at dose of 300 mg or Ticagrelor at dose of 180 mg, 10 000 U heparin was administered intravenously to achieve activated clotting time from 300 to 450 s.

All high risk non-ST-elevation ACS patients involved in group 1 in order to support left ventricular (LV) myocardial perfusion in the course of a long correction of complex forms of anterior coronary bed disorders underwent selective retrograde perfusion of LV anterior wall according to an original technique. Subclavian vein puncture was performed on the right and followed by mounting a delivering system in coronary sinus orifice. Along a delivering system, selectively, in proximal part of the great cardiac vein with blood outflow from LV anterior wall there was placed a standard dual lumen retroperfusion balloon catheter (Swan-Ganz type, Germany). Alongside with selective catheterization of the great cardiac vein for arterial autoblood sampling we performed radial artery puncture on the right followed by placing a standard radial introducer in arterial lumen. During myocardial perfusion support the balloon was dilated at the end of retroperfusion catheter till complete occlusion of proximal segment of the great cardiac vein followed by connecting free internal catheter lumen to perfusion block BP-05 (Avangard, Russia). For arterial autoblood sampling, the perfusion block was connected to an arterial introducer. Retroperfusion time coincided with antegrade blood flow occlusion time when stenting (60 s). Retroperfusion rate in the process of antegrade blood flow occlusion along the anterior coronary bed did not exceed 40 ml/min. Considering the capabilities of selective catheterization of the great cardiac vain by means of which reverse blood supply of LV anterior wall was performed, retroperfusion was not synchronized with auxocardia but proceeded continuously till the recovery of adequate antegrade blood flow along the trunk of LCA, ADA and DB. The myocardial perfusion support technique we proposed is original (Application for a patent No.2014111410 dated 25.03.2014) and promotes effective selective retrograde perfusion of clinically dependent ischemic area of myocardium.

In order to evidence the efficacy of the suggested original technique, before stent implantation we performed preliminary catheter balloon dilatation of complex disorders of anterior coronary bed without retroperfusion support, the main cardiohemodynamic indices being studied at the 60th second of antegrade blood flow deficiency of LCA, ADA trunk or DB. After pre-dilatation a stent was implanted with retroperfusion support — central hemodynamic indices were recorded at the 60th second of antegrade blood flow deficiency along LCA, ADA trunk or DB. Further, we compared the basic cardiohemodynamic indices recorded during angioplasty without retroperfusion and stent implantation with retroperfusion in group 1 patients.

Group 2 patients, in a prolonged correction of clinically determining disorders of the anterior coronary bed, did not have LV myocardial perfusion support. When necessary, cardiohemodynamics was corrected by means of drug therapy.

During the coronary intervention we succeeded in maximum complete correction of atherosclerotic disease of coronary bed achieving 2–3 scores of antegrade blood flow along coronary arterial bed according to TIMI scale. The primary objective was to recover antegrade blood flow in clinically determining anterior coronary bed. During the intervention all hemodynamically significant involvements were corrected by implanting bare metal coronary stents and drug-eluting stents.

During the endovascular intervention the following parameters of intra-operative cardiohemodynamics in all patients in both groups were assessed: mean arterial pressure (MAP); systolic arterial pressure (APs); diastolic arterial pressure (APd); heart rate (HR). During the procedure we estimated ST-segment and T wave depth in six thoracic electrocardiograhic leads to control the efficacy of retroperfusion support and endovascular intervention. We studied hemodynamic parameters, as well as ECG-picture of the patients initially, during the correction of atherosclerotic involvements, and at the end of the surgery using a diagnostic unit GE Healthcare MacLab/SpecialsLab 6.8 (GE Medical Systems, USA) and intercompared them to determine the technique efficacy.

Subjective pain senses in patients at the moment of antegrade blood flow deficiency along the anterior coronary bed were assessed only in an early postoperative period using 10-score scale by the technique of R.L. Incorvati et al. [15].

The data were statistically processed using Statistica 8.0, the results being presented in the form of M±sd, where M — mean value, sd — standard deviation. For analysis of the findings we applied a nonparametric statistical analysis using a paired Wilcoxon test to compare two dependent variables, and Mann–Whitney U-test to compare two independent variables. If $p \leqslant 0.05$, the values were considered significant [16].

Results. Diagnostic coronography revealed multivessel coronary disease in all patients. Clinically determining involvements were localized in the anterior coronary bed (Fig. 1).

ADA stenoses ≈80–90% in proximal and middle arterial segments (including subtotal stenoses) were diagnosed in 4 cases among group 1 and group 2 patients. Hemodynamically significant trunk involvements were found in 5 patients in each group. Hemodynamically significant proximal bifurcation ADA and DB involvements were revealed in 3 cases in group 1 patients, and in 2 cases — in group 2. Bifurcation involvements were stenoses 60–70%, 1.1.1, 0.1.0 and 1.1.0 types according to Medina classification.

Associated hemodynamically significant involvements of the posterior coronary bed were found in all patients of both groups; stenoses of over 50% in RCA, CA and OMB prevailing.

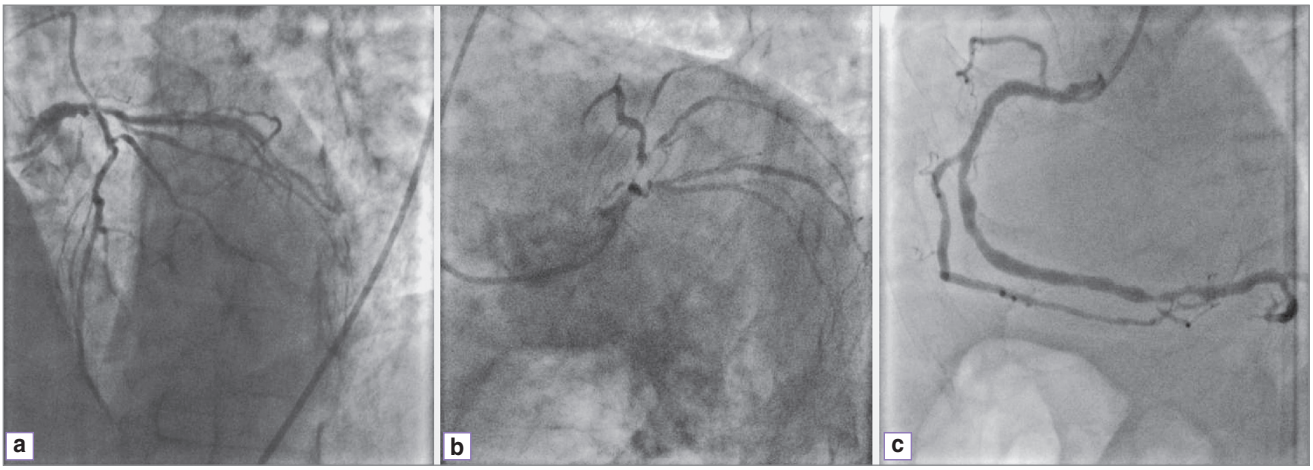

Fig. 1. Multivessel coronary disease: clinically determining stenoses of left coronary (*a*); anterior descending trunk arteries and diagonal branches (*b*); associated stenoses of the right coronary artery (*c*)

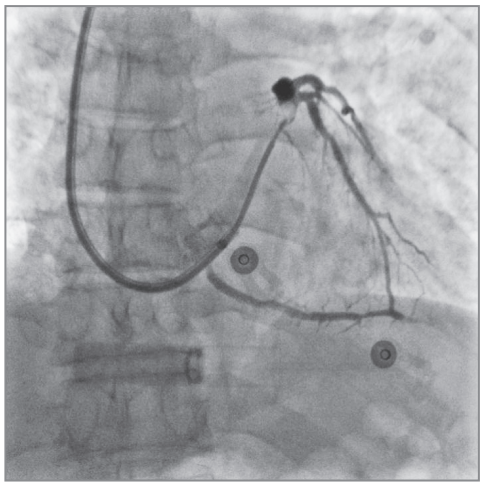

Fig. 2. Selective catheterization of the great cardiac vein

Initial antegrade blood flow along the anterior coronary bed was not more than 1–2 scores according to TIMI scale (TIMI 1–2), along the posterior coronary bed — not more than TIMI 2.

In the course of X-ray endovascular intervention all patients in both groups were performed a successful X-ray endovascular correction of clinically determining anterior coronary involvements and hemodynamically significant posterior coronary involvements. Antegrade blood flow along the anterior and posterior coronary beds after endovascular intervention in all patients under study significantly increased up to TIMI 3 (p=0.002).

Selective catheterization of the great cardiac vein and myocardial retroperfusion support were successfully performed in 6 patients of group 1 (Fig. 2).

Mean time of selective catheterization of proximal segment of the great cardiac vein in subclavian approach was 12.9±2.5 min. There were no complications in the catheterization of cardiac venous system and retroperfusion support.

Table 2

Basic indices of central hemodynamics of group 1 patients with and without retroperfusion support

Hemodynamic parameters	Antegrade blood flow deficiency during angioplasty/stenting at the 60th second		p
	with retroperfusion	without retroperfusion	
HR, per min	68.0±7.9	63.8±5.2	>0.05
MAP, mm Hg	100.5±15.2	80.2±19.7	**0.027**
APs, mm Hg	136.3±26.9	103.0±28.1	**0.027**
APd, mm Hg	88.8±14.6	74.0±12.2	**0.027**

Group 1 patients were revealed to have a significantly favorable effect of myocardial retroperfusion support on basic cardiohemodynamic indices. MAP, APs and APd significantly increased in patients with endovascular correction with retroperfusion support compared to angioplasty without myocardial perfusion support. There was also the tendency for HR increase during the retrograde perfusion (Table 2).

The comparison of the main cardiohemodynamic indices at the beginning and at the end of endovascular correction of clinically determining complex forms of the anterior coronary bed disorders in group 1 revealed no significant differences between them. There was only observed the tendency for a slight HR increase and some decrease of MAP, APs, APd at the end of the surgical intervention (Table 3).

At the 60th second of antegrade blood flow deficiency along the anterior coronary bed, group 2 patients were found to have significant decrease of MAP, APs and APd compared to the same indices taken just before the balloon catheter inflation, there being the tendency for HR decrease (Table 4).

Comparing the basic cardiohemodynamic indices at the beginning and at the end of endovascular correction of clinically determining complex forms of the anterior

Table 3

Basic indices of central hemodynamics in group 1 patients at the beginning and at the end of endovascular correction, p>0.05

Hemodynamic parameters	Beginning of the operation	End of the operation
HR, per min	68.6±8.8	69.5±4.2
MAP, mm Hg	101.5±20.4	94.5±15.9
APs, mm Hg	132.7±28.6	125.0±17.1
APd, mm Hg	84.5±17.5	84.2±13.5

Table 4

Basic indices of central hemodynamics of group 2 patients during angioplasty without retroperfusion support

Hemodynamic parameters	Initial	Antegrade blood flow deficiency at the 60th second	p
HR, per min	73.3±6.7	66.9±16.8	>0.05
MAP, mm Hg	117.8±23.9	96.7±17.2	**0.002**
APs, mm Hg	168.3±36.4	141.9±19.7	**0.002**
APd, mm Hg	91.1±15.3	72.3±14.4	**0.002**

Table 5

Basic indices of central hemodynamics of group 2 patients at the beginning and at the end of endovascular correction

Hemodynamic parameters	Beginning of the operation	End of the operation
HR, per min	73.3±6.7	75.2±10.0
MAP, mm Hg	117.8±23.9	116.3±22.2
APs, mm Hg	168.3±36.4	159.6±29.5
APd, mm Hg	91.1±15.3	88.0±16.5

Table 6

ST segment and T wave amplitude dynamics on intra-operative ECG in group 1 patients with and without retroperfusion support

ECG leads	Antegrade blood flow deficiency during angioplasty/stenting at the 60 second				p
	without retroperfusion		with retroperfusion		
	ST	T	ST	T	
V_1–V_3	–1.5±0.8	–6.6±4.4	–0.4±0.1	–3.8±2.3	**0.027**
V_4–V_6	–2.3±0.8	–5.2±3.1	–0.3±0.1	–2.1±1.0	**0.027**

coronary involvements in group 2, we revealed no significant differences between them either. There was just a tendency for slight increase of HR and slight decrease of MAP, APs, APd values at the end of the operative intervention (Table 5).

The analysis of an intra-operative electrocardiogram taken in thoracic leads in group 1 patients showed that at the 60th second of antegrade blood flow deficiency along the anterior coronary bed under retroperfusion support there was significant decrease of ST segment and negative T wave amplitude depression compared to ECG-picture without retroperfusion (Table 6).

Group 1 patients showed no significant differences in segment ST and negative T wave amplitude depression at the end of the operation compared to ECG-picture at the beginning of the intervention (Table 7).

The analysis of an intra-operative electrocardiogram in group 2 patients revealed significant increase of ST segment and negative T wave amplitude depression at the 60th second of antegrade blood flow deficiency along the anterior coronary bed compared to the initial ECG-picture (Table 8).

Group 2 as well as group 1 patients showed no significant differences in the value of ST segment and negative T wave amplitude depression at the end of the intervention compared to ECG-picture at the beginning of the procedure (Table 9).

Subjective pain senses in group 1 patients during the 60-second antegrade blood flow deficiency along coronary bed were minimum — 0.5±0.5 scores, while in group 2 — 2.2±0.4 (U=0.0; Z=–1.9; p=0.049). Despite a high risk of intra-operative fatal and non-fatal cardiac events resulted from highly technical and prolonged

Table 7

Electrocardiographic picture in group 1 patients at the beginning and at the end of surgery

ECG leads	Beginning of the operation		End of the operation	
	ST	T	ST	T
V_1–V_3	–0.4±0.1	–3.1±1.6	–0.4±0.2	–2.8±1.5
V_4–V_6	–0.1±0.1	–2.8±1.7	–0.1±0.1	–1.9±0.8

Table 8

ST segment and T wave amplitude dynamics on intra-operative ECG in group 2 patient during angioplasty without retroperfusion support

ECG leads	Initial		Antegrade blood flow deficiency at the 60th second		p
	ST	T	ST	T	
V_1–V_3	–0.5±0.3	–1.3±0.6	–2.4±0.9	–4.2±1.9	**0.027**
V_4–V_6	–0.8±0.7	–3.2±2.2	–1.8±0.2	–5.9±3.9	**0.027**

Table 9

Electrocardiographic picture in group 2 patients at the beginning and at the end of the intervention

ECG leads	Beginning of the operation		End of the operation	
	ST	T	ST	T
V_1–V_3	–0.5±0.3	–1.3±0.6	–0.4±0.2	–1.0±0.7
V_4–V_6	–0.8±0.7	–3.2±2.2	–0.6±0.6	–3.1±2.2

manipulations, none episodes of marked hemodynamics failure were recorded. There were revealed no episodes of cardiac arrest, LV fibrillation, marked bradycardia or any other arrhythmic complications.

Subjective pain senses in group 2 patients during the 60-second antegrade blood flow deficiency along coronary bed were more significant — 2.2±0.4 scores. There was an episode of degree II atrioventricular block during the antegrade blood flow deficiency along coronary bed in one patient, and in one case there occurred ventricular fibrillation that required urgent resuscitation.

Discussion. Applicability of circulatory support systems in non-ST-elevation ACS patients is being under constant discussion by cardiologists. However, according to American Heart Association researchers, myocardial circulation support plays a core role during endovascular intervention in patients with impaired coronary hemodynamics and high risk of intra-operative fatal and non-fatal cardiac complications [17–22]. In present study we succeeded in demonstrating clinical efficacy of proper modification of the technique consisting in forming a retrograde flow of arterial autoblood in the system of the great cardiac vein in patients with high risk of non-ST-elevation ACS. The efficacy of the suggested method was assessed by comparing the basic indices of intra-operative cardiohemodynamics in subjects with and without retroperfusion.

MAP in all patients who underwent retroperfusion support during an endovascular intervention was significantly higher compared to angioplasty without myocardial perfusion support (100.5±15.2 and 80.2± 19.7 mm Hg, respectively; p=0.027). Similar dynamics was observed in relation to other AP indices as well. Significant decrease of ST segment depression was observed at the 60th second of retroperfusion support compared to endovascular angioplasty without myocardial perfusion support (ST in V_1–V_3 leads in retroperfusion was –0.4±0.1 mm; without retroperfusion — –1.5±0.8; p=0.027). Taking into account a high risk of invasive treatment strategy of non-ST-elevation ACS patients, as well as hemodynamic significance of the anterior coronary bed involvement, we may assume that intra-operative cardiohemodynamic improvement under retroperfusion support is due to a cardioprotective effect of retrograde perfusion and does not depend on ischemic myocardial preconditioning during angioplasty [23].

All the patients without retroperfusion support at the 60th second of antegrade blood flow deficiency along the anterior coronary bed were found to have significant decrease of MAP compared to its value recorded before angioplasty (MAP at the 60th second of antegrade blood flow deficiency — 96.7±17.2 mm Hg; initially — 117.8±23.9 mm Hg; p=0.002). Similar dynamics was observed in relation to other arterial pressure indices as well.

Significant increase of ST segment depression was revealed at the 60th second of antegrade blood flow deficiency along the anterior coronary bed compared to ECG-picture recorded in thoracic leads before angioplasty start (ST in V_1–V_3 leads at the 60th s of antegrade blood flow deficiency — –2.4±0.9 mm; initially — –0.5±0.3 mm; p=0.027). The findings can be explained by the growth of ischemic changes in myocardium occurring in the course of a long antegrade blood flow deficiency along the clinically determining anterior coronary bed [23].

Comparative intergroup analysis of intra-operative cardiohemodynamics revealed no significant difference between its basic indices recorded at the beginning and at the end of the endovascular correction of complex involvements of anterior coronary bed. Both groups were found to have only the tendency for an insignificant increase of HR and an insignificant decrease of AP indices at the end of the surgery (See Tables 3, 5). The results of the comparative assessment of intra-operative ECG-picture observed at the beginning of the operative intervention and at the end of endovascular correction appeared to be unreliable either. In both groups there was some reduction of the negative wave T amplitude in V_1–V_6 leads. However, minimum tendency of segment ST towards an isoline was observed only in patients without retroperfusion (See Tables 7, 9).

No reliable differences between cardiohemodynamic indices recorded at the beginning and at the end of the surgery are consistent with the findings of researches [21]. In the authors' opinion, variability of HR, MAP, Ads and APd depends on many factors including medical support of a patient, and has no direct relationship with the effect of local circulatory support systems. Unreliable changes of ECG-picture observed at the end of endovascular correction can be explained by the investigations of I.S. Yavelov [24]. According to Yavelov, ischemic changes on ECG in non-ST-elevation ACS patients and multivessel coronary bed involvement frequently persist within a long period of time after percutaneous coronary intervention. Acute ischemic myocardial changes without ST-elevation on ECG occurring in patients with complex anterior coronary bed involvements and associated atherosclerotic changes in RCA, CA and their branches result from exacerbations of chronic metabolic and functional myocardial dysfunction, and frequently lead to irreversible changes of myocardium [25, 26]. Therefore, having performed a successful urgent operation in patients with clinically determining complex forms of coronary bed involvement we reduced myocardial damage area, and by that minimized the risk of fatal and nonfatal cardiac complications; however, this does not exclude the possibility to preserve local, functionally non-active parts of myocardium [27].

Our findings coincide with the results of the studies carried out by J.M. Gore et al. [22]. According to J.M. Gore et al., retroperfusion support contributes to reliable improvement of HR, MAP, APs and APd indices, as well as ECG-picture only at acute myocardial

ischemia supplied by anterior coronary bed. Therefore, the use of retroperfusion has no effect on functional activity of myocardium after the recovery of an adequate antegrade blood flow along the trunk of LCA, ADA and DB, and should be used only in balloon angioplasty or stent implantation.

The researches [28, 29] have shown that local and systemic coronary blood flow support techniques have no significant effect on patients' survival rate in a medium- and long-term period after myocardial revascularization. However, the results we obtained suggest myocardial retroperfusion to reduce significantly the risk of nonfatal intra-operative cardiac complications (group 1 — no complications; group 2 — two complications) and decreases pain senses in the course of antegrade blood flow deficiency along the anterior coronary bed (pain senses in group 1 — 0.5±0.5 scores; in group 2 — 2.2±0.4 scores; U=0.0; Z=–1.9; p=0.049).

Conclusion. It is reasonable to use percutaneous temporary retrograde myocardial perfusion in X-ray endovascular correction of clinically determining complex forms of the anterior coronary bed involvements in patients with non-ST-elevation acute coronary syndrome with high risk of intra-operative fatal and nonfatal cardiac events.

Selective retroperfusion of the great cardiac vein can be used as an intra-operative cardiohemodynamic support technique in high risk non-ST-elevation ACS patients only during a long deficiency of antegrade blood flow along the anterior coronary bed in the course of angioplasty and stenting.

Retroperfusion support in operations on the trunk of the left coronary artery and the anterior descending artery with its branches enables to reduce the risk of ischemic myocardial changes associated with the risk of nonfatal intra-operative cardiac complications.

Significantly reducing the incidence of subjective pain senses in the course of endovascular intervention, retroperfusion support has no direct effect on early postoperative arterial pressure indices and ECG-picture of non-ST-elevation ACS patients.

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