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Influence of 5-hydroxymethyluracil on the dynamics of angiogenic growth factors in the perioperative period of surgical myocardial revascularization: results of a randomized trial

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Aim. To evaluate the effect of 5-hydroxymethyluracil on the dynamics of angiogenic growth factors in the perioperative period of surgical myocardial revascularization.

Material and methods. This prospective, randomized, single-center study included two following groups: experimental group — 25 patients in the perioperative period of coronary artery bypass grafting (5 days before and 14 days after surgery) receiving 5-hydroxymethyluracil (at a dose of 500 mg 3 times a day) in addition to standard therapy; control group — 25 patients receiving standard therapy. The groups were comparable in terms of sex, age, main clinical and functional characteristics and features of surgical intervention. In patients, quantitative indicators of angiogenic growth factors in peripheral blood taken 5 days before and 14 days after surgery were studied by enzyme immunoassay: human vascular endothelial growth factor A (VEGF-A), human hepatocyte growth factor (hHGF), insulin-like factor growth 1 (IGF-1) and basic fibroblast growth factor (bFGF).

Results. In the experimental group of patients, while taking 5-hydroxymethyluracil, there was a significant increase in the peripheral blood concentration of following growth factors compared with the control group: VEGF-A by 26,90% (p=0,0246), IGF-1 by 44,89% (p=0,0011), bFGF by 60,0% (p=0,0006). The hHGF concentration also turned out to be higher by 19,90%, but did not reach the level of statistical significance (p=0,2836).

Conclusion. The use of 5-hydroxymethyluracil, a representative of pyrimidines, in the perioperative period of surgical myocardial revascularization leads to a significant increase in peripheral blood of such angiogenic growth factors as VEGF-A, IGF-1, and bFGF.

Keywords: coronary artery disease, coronary artery bypass grafting, angiogenesis, growth factors, pyrimidines.

Relationships and Activities: none.

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Key messages

- Coronary artery bypass grafting (CABG) is the treatment of choice for multivessel coronary artery disease.
- The clinical effect of the surgery is achieved not only by bypass, but also by collateral circulation, and by the release of factors with angiogenic properties.
- The study of pharmacological substances capable of stimulating angiogenesis process in CABG is of significant research and practical interest in terms of improving the surgery results.
- Pyrimidine representative 5-hydroxymethyluracil in the perioperative period of CABG leads to a significant increase in peripheral blood of angiogenic growth factors: vascular endothelial growth factor A, insulin-like growth factor 1, and basic fibroblast growth factor.

Coronary artery bypass grafting (CABG) is a method of surgical myocardial revascularization that can significantly increase the survival of patients with multivessel coronary artery disease (CAD) [1]. According to modern studies, this result is achieved not only due to improved myocardial blood supply due to bypass creation, but also due to collateral circulation, which can provide blood flow in the event of plaque rupture and bypass artery thrombosis [2]. The biological basis for collateral circulation is arteriogenesis and angiogenesis, and the main trigger for the growth and development of new blood vessels is myocardial ischemia. Thus, arteriogenesis and angiogenesis can be considered fundamental for survival in CAD [3, 4]. However, a number of studies have shown that myocardial revascularization with CABG can cause an independent angiogenic response [5]. Based on this, Gutterman DD, et al. [6] recently put forward a hypothesis, according to which CABG improves the myocardial ischemic environment, establishing "atherostasis" via endogenous release of factors with vasodilatory, anti-inflammatory, antithrombotic, and angiogenic abilities.

In this regard, of considerable scientific and practical interest is the revelation of mechanisms affecting the microcirculation development during surgical myocardial revascularization operations, as well as the search for pharmacological substances that can stimulate the process of angiogenesis and arteriogenesis during these operations [7].

The study aim was to evaluate the effect of 5-hydroxymethyluracil (5-hmU) on angiogenic growth factors in the perioperative period of surgical myocardial revascularization.

Material and mehods

This prospective, randomized, single-center study included 50 patients who underwent surgical myocardial revascularization at the Republican Cardiology Center (Ufa). Inclusion criteria were age 40 years and older, elective CABG, CCS class 3-4 exertional angina. The main exclusion criteria were severe valvular dysfunction in the presence of CAD, left ventricular aneurysm, acute period of myocardial infarction (MI), severe left ventricular systolic dysfunction (left ventricular ejection fraction <30%), severe carotid atherosclerosis (>70% stenosis).

Standard treatment included antiplatelet (acetylsalicylic acid, clopidogrel), β-blocker (metoprolol, bisoprolol, carvedilol), angiotensin-converting enzyme inhibitor (enalapril, lisinopril, perindopril), statin (simvastatin, atorvastatin, rosuvastatin) therapy and, if necessary, short and long-acting nitrates (isosorbide dinitrate, isosorbide mononitrate). Patients with concomitant diabetes received adequate glucose-lowering therapy.

Randomization was carried out using the envelope method. Patients of the main group (n=25) received 5-hmU at a dose of 500 mg 3 times a day in addition to standard therapy 5 days before and within 14 days after surgery. The control group also consisted of 25 patients who received standard therapy. The study design is presented in Figure 1. Both investigators and patients were informed about the prescribed treatment.

The groups were comparable in terms of sex, age, disease duration, functional class of angina pectoris and heart failure, the number of affected vessels, clinical and functional parameters and features of surgical intervention (posteriori comparison using the Mann-Whitney test and Fisher's angular transform did not reveal significant differences (p>0,05)) (Table 1).

In all patients initially (before prescribing the drug) and 2 weeks after CABG, the quantitative assessment of the following angiogenesis growth factors was performed by enzyme immunoassay:

1. Human vascular endothelial growth factor A (VEGF-A) — Human VEGF-A BioLISA kit, Bender MedSystems, Austria.

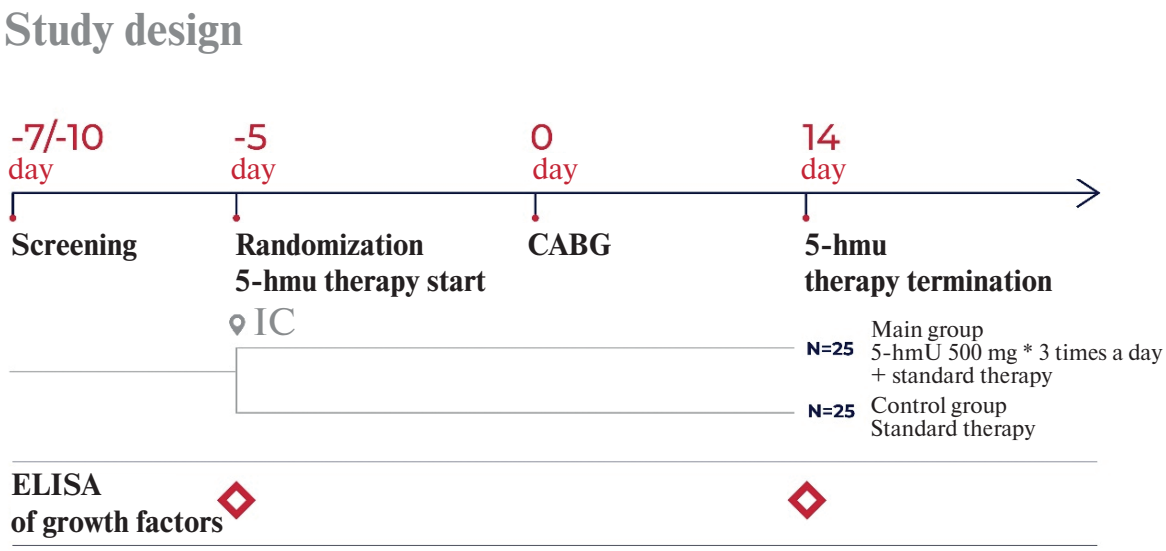

Figure 1. Study design.
Abbreviations: CABG — coronary artery bypass grafting, IC — informed consent, ELISA — enzyme immunoassay, 5-hmU — 5-hydroxymethyluracil.

2. Human hepatocyte growth factor (hHGF) — Human HGF test system, Biosource, Belgium.

3. Insulin-like growth factor 1 (IGF-1) — OCTEIA IGF-1 kit, Immunodiagnostic Systems Holdings Ltd, UK.

4. Human fibroblast growth factor-basic (bFGF) — Human FGF basic Quantikine ELISA kit, R&D Systems, Inc, USA.

The choice of analytes for the study was dictated by experimental studies conducted earlier by our author group on 5-hmU effect on the expression of growth factors in models of chronic and acute myocardial ischemia in rabbits, during which these factors was studied by real-time quantitative reverse transcription polymerase chain reaction [8].

The venous blood sampling with a volume of 10-12 ml in patients was carried out 5 days before CABG and 14 days after in the morning on an empty stomach using a Vacutainer system filled with a stabilizing agent. There were no complications associated with the procedure. The resulting blood samples were incubated for 5-10 min at room temperature, then centrifuged for 20 min at 1500 g and t +40° C. The resulting plasma was placed in 1,5 ml Eppendorf microtubes, after which the samples were frozen and stored in a medical freezer with -18° C.

When choosing control points for assessing angiogenesis biomarkers, we took into account the time of the maximum drug effect on nucleic acid metabolism and protein synthesis, which is in the range between 3 and 7 days [9] and corresponds to the start of administration — 5 days before surgery. The duration of admission (14 days after CABG) is due to the fact that the maturation of primitive blood vessels together with the walls and mesh structures occurs within 2 weeks after ischemic exposure; therefore, this time period is a promising target for therapeutic intervention [10].

Study endpoints. The primary endpoint was the change in the peripheral blood concentration of analyzed growth factors in patients 2 weeks after operation.

5-hmU is a derivative of pyrimidines, is a "minor" base, occurs in significant amounts in transfer RNA and DNA, and has a pronounced immunostimulating effect. In 2002, the use of 5-hmU under the trade name "Immureg" (FSP 42-0415-2777-02) was allowed. According to drug instructions for use, the registered indications for use are infectious and inflammatory diseases (as part of antibiotic therapy): respiratory diseases (pneumonia, chronic obstructive pulmonary disease, lung abscess), chronic pyelonephritis, as well as the prevention of infectious complications during chemotherapy for chronic lymphocytic leukemia.

Prior to inclusion in the study, written informed consent was obtained from each patient. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the local ethics committee at the Bashkir State Medical University.

Statistical processing was carried out using the Statistica 8.0 program. The sample size calculation was based on an expected frequency of primary endpoint (p) of 10%, with a reliability of inference of 95%, t=1,96, and a maximum error of Δ=5%.

Table 1

Demographic, clinical and functional characteristics of the study groups, Me (25%-75%)

Parameter	Main group (n=25)	Control group (n=25)	Statistical significance of differences, p
Main clinical and demographic characteristics			
Mean age, years	50,37 (42,93-66,41)	55,51 (46,84-63,88)	0,63
Male sex, %	92	96	0,60
CCS functional class of stable angina	3,00 (2,51-3,74)	3,34 (2,63-3,72)	0,88
NYHA functional class of HF	2,00 (1,54-2,40)	2,03 (1,66-2,22)	0,41
Disease duration, months	65,36 (55,00-72,08)	59,79 (48,84-69,82)	0,67
Comorbidities			
Old myocardial infarction, %	72	68	0,30
Hypertension, %	60	64	0,29
Diabetes, %	16	20	0,36
Characteristics of coronary system involvement			
Average number of affected arteries	2,62 (2,04-3,00)	2,55 (2,00-2,90)	0,44
Anterior interventricular artery involvement, %	100	100	1,0
Circumflex artery involvement, %	80	84	0,37
Right coronary artery involvement, %	84	80	0,37
Features of surgical intervention			
On-pump operation, %	64	64	1,0
Average duration of operation, min	235,86 (205,65-270,24)	252,00 (210,00-291,24)	0,68
Mean cardiopulmonary bypass time, min	102,18 (81,65-136,00)	111,40 (76,54-128,96)	0,89
Mean aortic cross-clamp time, min	60,76 (52,62-70,44)	55,48 (49,53-68,82)	0,39

Abbreviations: CCS — Canadian Cardiovascular Society, NYHA — New York Heart Association.

Taking into account that, according to Kolmogorov-Smirnov and Shapiro-Wilk test, the distribution was not normal. The nonparametric Mann-Whitney test and Fisher's transformation were used to identify statistical differences between independent samples. Data were presented as median Me and interquartile range (25-75%). Differences were considered significant at $p \leqslant 0,05$.

Results

Statistical analysis showed that the initial values of studied peripheral blood growth factors in the analyzed groups did not have significant differences.

At the next stage, we assessed studied growth factors with (main group) and without (control group) the use of 5-hmU.

VEGF-A in the control group of patients showed a significant increase as follows: the median increased from 204,50 (117,50-297,50) to 420,63 (338,54-563,58) pg/ml — by 105,68% ($p<0,0001$) (Figure 2).

Changes of VEGF-A in the main group of patients after surgical myocardial revascularization with simultaneous administration of 5-hmU was more pronounced as follows: the increase was 184,29% (from 187,50 (101,00-338,54) to 533,05 (435,26-612,03) pg/ml, $p<0,0001$) (Figure 2). At the same time, in the main group, the final level of VEGF-A was significantly higher than in the control group by 26,90% ($p=0,0246$). The result obtained, in our opinion, is associated with a cumulative beneficial effect on the angiogenesis processes of coronary bypass surgery and the use of 5-hmU.

The HGF concentration in the control group was characterized by a downward trend (from 1413,00 (817,50-1912,00) pg/ml in the preoperative period to 1402,00 (937,50-2174,50) pg/ml 2 weeks after CABG ($p=0,4153$)) (Figure 3).

HGF changes in patients of the main group, on the contrary, was positive, but did not reach statistical significance. There was an increase in the median by 6,12% from 1584,00 (1062,00-1965,00) pg/ml in the preoperative period to 1681,00 (1244,50-2179,00) pg/ml ($p=0,2481$) 2 weeks after CABG. At the same time, the differences between the HGF concentration in the control and main groups 14 days after surgical myocardial revascularization also turned out to be insignificant ($p=0,2836$), which indicates a limited beneficial effect of 5-hmU on angiogenesis processes.

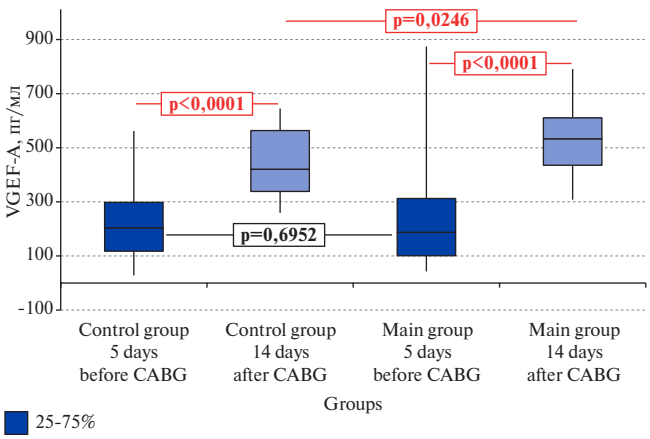

Figure 2. Dynamics of vascular endothelial growth factor A (VEGF-A) blood concentration in patients of the control (n=25) and main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney test).
Abbreviations: CABG — coronary artery bypass grafting, VEGF-A — human vasculoendothelial growth factor A.

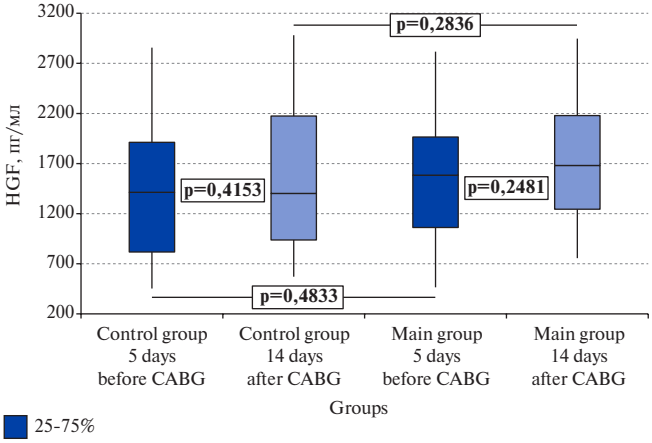

Figure 3. Dynamics of hHGF blood concentration in patients in the Control (n=25) and Main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney criterion).
Abbreviations: CABG — coronary artery bypass grafting, hHGF — human hepatocyte growth factor.

Content of IGF-1, in contrast to the two previous analyzed factors, significantly decreased in the control group from 117,50 (88,00-193,00) pg/ml in the preoperative period up to 98,00 (75,00-143,00) pg ml 2 weeks after surgery (by 19,89%, p=0,0177) (Figure 4).

In this regard, interesting data were obtained in patients of the main group, who, instead of decreasing, showed a trend towards an increase in IGF-1 level with 5-hmU use as follows: median increased from 128,50 (75,00-198,00) pg/ml in the preoperative period up to 142,00 (93,00-173,00) pg/ml for 14 days, after CABG, or by 10,5% (p=0,7649). And, most importantly, statistical significance of differences in IGF-1 postoperative levels in the main and control groups of 44,89% (p=0,0011), indicates a clear advantage of 5-hmU in maintaining normoglycemia in the perioperative period.

The bFGF is one of the main regulators of angiogenesis processes. In our studies, it demonstrates a statistically significant increase during CABG in the control group from 3,40 (2,15-6,95) pg/ml to 5,70 (4,65-7,65) pg/ml (p=0,0336), or by 67,64% (Figure 5).

The bFGF level in the main group (against the background of 5-hmU use) showed even more impressive changes than in the control group — from 4,70 (2,70-6,45) pg/ml in the preoperative period to 8,35 (5,30-10,70) pg/ml 14 days after CABG, or by 77,65% (p=0,0006). When comparing the final bFGF levels (14 days after CABG) in the control and main groups, its values were significantly higher in the main group (by 60%, p=0,0006).

Discussion

In connection with the theory of surgical collateralization during CABG formulated in recent years, the study of pyrimidine derivatives as proangiogenic agents is of scientific and clinical interest. This class of drugs has long been used in wide medical practice in various fields due to the wide variety of clinical effects. The effect of pyrimidine derivatives on angiogenesis is also quite well studied in [11, 12], and its effect on angiogenesis is comparable in efficiency with the introduction of VEGF [13].

For 5-hmU, as for all representatives of pyrimidines, there are two proven mechanisms of angiogenic action — antioxidant activity [14] and the ability to accumulate adenosine [15].

The effect of reactive oxygen species on postischemic angiogenesis is associated with local suppression of angiogenic growth factors in the ischemic area. It has been reliably established that reactive oxygen species can inhibit NO directly and through inhibition of endothelial nitric oxide synthase, blocking its effect on the vascular system [16]. Thus, suppression of myocardial oxidative stress by the use of pharmacological substances with antioxidant activity naturally leads to angiogenesis stimulation.

An increase in adenosine content (by disrupting its reuptake) due to the use of pyrimidine nucleotides, as well as the ability to increase the concentration of cyclic adenosine monophosphate, is associated with inhibition of phosphodiesterase enzyme [15]. According to modern data, adenosine activates 4 different subtypes (A1, A2A, A2B, and A3) of receptors, stimulates capillary development in the

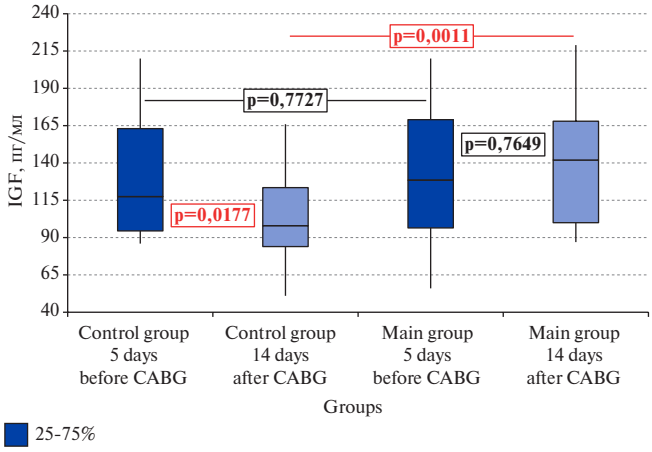

Figure 4. Dynamics of IGF-1 blood concentration in patients in the Control (n=25) and Main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney test).
Abbreviations: CABG — coronary artery bypass grafting, hHGF — human hepatocyte growth factor.

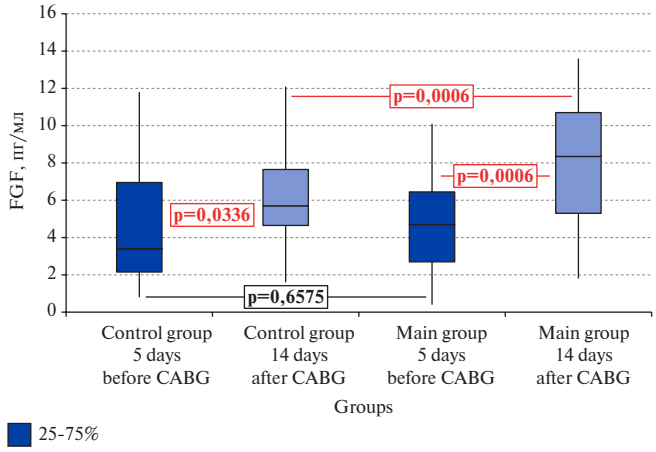

Figure 5. Dynamics of bFGF blood concentration in patients in the Control (n=25) and Main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney criterion).
Abbreviations: CABG — coronary artery bypass grafting, bFGF — basic human fibroblast growth factor.

ischemic heart, and induces the production of pro-angiogenic factors [17, 18].

The most pronounced concentration changes in the peripheral blood among the growth factors analyzed by us with the 5-hmU use was recorded in VEGF-A, as a key factor in angiogenesis in the myocardial hypoxia [10]. A number of clinical studies have shown that an elevated VEGF-A level promotes the proliferation of vascular endothelial cells, improves vascular permeability, and restores endothelial integrity and vascular function, which is a compensatory mechanism in the development of myocardial ischemia [19, 20]. An analysis of the databases of scientific sources showed that the drug impact on VEGF-A is a promising target for the treatment of cardiovascular diseases. For example, hydroxysafflor yellow improved endothelial progenitor cell function and increased VEGF-A concentration in mice with MI through the HO-1/VEGF-A/SDF-1α signaling cascade, which significantly restored ischemia-induced cardiac dysfunction and improved animal survival [21, 22]. *Pueraria* and *Salvia miltiorrhiza* extracts stimulated angiogenesis by activating the VEGF/VEGFR2 pathway, thereby preserving the myocardium of MI rats [23], and salidroside increased HIF-1α expression and then VEGF levels to inhibit necrosis and apoptosis of cardiomyocytes induced by hypoxia [24].

At the same time, the pronounced changes of pre- and postoperative bFGF values against the background of 5-hmU, which increase was similar to VEGF-A, is noteworthy, which is a natural consequence of the inextricable relationship between FGF-2 and VEGF-A in angiogenesis [25]. The decrease in peripheral blood IGF-1 concentration in control group patients recorded in our study is associated with the activation of catabolic processes after surgical myocardial revascularization, and the depth of this decrease reflects the severity of the surgical injury and, consequently, the catabolism degree after surgery [26]. And, on the contrary, the stabilization of this growth factor in the main group of patients against the background of 5-hmU use is extremely important for maintaining glucose homeostasis in the perioperative period of surgical myocardial revascularization [27].

Previously, the effectiveness of 5-hmU as an angiogenesis stimulator, as well as possible mechanisms of action, were experimentally studied by V. V. Plechev, B. A. Oleinik and R. Yu. Risberg in 2012 on a model of acute MI in rabbits. Thus, in an experiment on 112 male chinchilla rabbits with irreversible myocardial ischemia, the authors demonstrated that 5-hmU contributes to a significant increase in the level of expression of *FGF2* gene by 26%, *HGF* gene by 60%, and *VEGFa* gene by 131% [8], and also leads to an increase in vascular density in the myocardium [28] at the border of ischemic zone, which is generally consistent with this clinical study and, to a certain extent, suggests a similar relationship in patients with CAD against the background of perioperative drug use. At the same time, we realize the need to obtain not indirect, but direct evidence of 5-hmU effectiveness in stimulating angiogenesis processes in the myocardium and take into account the objective difficulties in performing histological studies due to the need for intravital myocardial biopsy.

Therefore, promising tasks of our scientific group will be to conduct modern non-invasive methods imaging, such as single photon emission computed tomography with Tc^{99} [29] and positron emission tomography with angiogenesis radiotracers [30] in patients of this group.

Study limitations. The limitations of this study are the small sample size and short follow-up period.

Conclusion

The use of 5-hydroxymethyluracil, a representative of pyrimidines, in the perioperative period of surgical myocardial revascularization leads to a significant increase in peripheral blood of such angiogenic growth factors as VEGF-A, IGF-1, and bFGF.

Relationships and Activities: none.

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