The proposed algorithm relies on three principles:

1. Testicular torsion should be highly considered in males with acute scrotal pain until confidently excluded.

2. Scrotal US should be used in cases where spermatic cord torsion is suspected clinically.

3. In the absence of scrotal edema, the diagnostic value of clinical findings is higher than with US. The diagnostic value of US significantly exceeds the clinical examination when scrotal edema has developed.

Conclusions. In summary, the Doppler US is a highly sensitive preoperative diagnostic tool for scrotal pain. The sensitivity and specificity of physical examination signs of the acute scrotum in the absence of scrotal edema in children are higher than the US findings, but significantly drops after the onset of scrotal edema.

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PREVENTION OF NEW-ONSET ATRIAL FIBRILLATION AFTER DIRECT MYOCARDIAL REVASCULARIZATION SURGERY: RANDOMIZED COMPARATIVE STUDY

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ПРОФИЛАКТИКА ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ ПОСЛЕ ПРЯМОЙ РЕВАСКУЛЯРИЗАЦИИ МИОКАРДА: РАНДОМИЗИРОВАННОЕ СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ

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In order to investigate the effect of Omegaven on the risk of paroxysms of atrial fibrillation lasting for more than 30 seconds, and other complications in the early postoperative period after coronary revascularization surgery, an open randomized comparative study was performed, which included

73 patients with CAD aged 41–75 (mean age 55±7.1 years; 82.2% males) without valvular heart disease and a previous history of atrial fibrillation, hospitalized to undergo coronary artery bypass grafting under extracorporeal circulation. The main group included 33 patients treated with intravenous infusions of the Omegaven emulsion (100 ml / day, single dose) in the first 5–7 days after the surgery. The comparison group consisted of 40 patients who did not receive Omegaven.

The patients treated with Omegaven showed significantly lower rate of new-onset postoperative atrial fibrillation paroxysms (9.1% vs. 32.5%, $p<0.01$) and other life-threatening cardiac arrhythmias and conduction disorders (25.0% vs. 6.1%, $p<0.01$), also revealing a statistically significant reduction in the duration of postoperative period (14.1±2.21 days vs. 22.9±3.82 days, $p<0.05$). The decrease in the relative risk of atrial fibrillation in the group in question was 72%. The study detected no side effects typical for Omegaven. The data obtained suggest that Omegaven may be administered to prevent the development of atrial fibrillation in the early postoperative period after coronary revascularization surgery.

Key words: coronary artery bypass grafting, new-onset postoperative atrial fibrillation, prevention

С целью изучения влияния Омегавена на риск развития пароксизмов фибрилляции предсердий продолжительностью более 30 секунд и других осложнений в раннем послеоперационном периоде после хирургической реваскуляризации миокарда в открытое рандомизированное сравнительное исследование были включены 73 больных ИБС в возрасте 41–75 лет (средний возраст 55±7,1 года; 82,2% мужчин) без клапанной патологии сердца и предшествующей мерцательной аритмии, госпитализированных с целью выполнения коронарного шунтирования в условиях искусственного кровообращения. Основную группу составили 33 пациента, которым выполняли внутривенные инфузии эмульсии Омегавена в дозе 100 мл в сутки однократно в первые 5–7 дней после оперативного вмешательства. Группу сравнения составили 40 пациентов, не получавших Омегавен.

У пациентов, получавших Омегавен, достоверно реже возникали пароксизмы послеоперационной фибрилляции предсердий (9,1% против 32,5%, $p<0,01$) и другие жизнеугрожающие нарушения ритма и проводимости (25,0% против 6,1%, $p<0,01$), отмечено статистически значимое сокращение продолжительности послеоперационного периода (14,1±2,21 против 22,9±3,82 суток, $p<0,05$). Снижение относительного риска развития фибрилляции предсердий в данной группе составило 72%. В исследовании не было отмечено побочных эффектов, свойственных Омегавену. Полученные данные позволяют рекомендовать применение Омегавена с целью профилактики фибрилляции предсердий в раннем послеоперационном периоде хирургической реваскуляризации мокарда.

Ключевые слова: коронарное шунтирование, послеоперационная фибрилляция предсердий, профилактика

The postoperative period after coronary artery bypass grafting (CABG) is commonly complicated with atrial fibrillation (AF), which happens yet despite the improving quality of anesthetic and surgical treatment [1]. Postoperative atrial fibrillation (POAF) often comes along with life-threatening disorders in the central and systemic hemodynamics, contributes to the development of cardioembolic strokes, longer hospitalization term, increased cost of treatment, as well as brings up the early and delayed postoperative mortality statistics [1, 4, 38]. The research focusing on prevention of POAF investigated the effectiveness of Beta-blockers (BB), amiodarone, sotalol, statins, corticosteroids, magnesium sulfate, and some other drugs.

BB are effective and safe for a wide range of patients yet may get complicated with severe bradycardia, persistent hypotension, and non-fatal stroke. Preventive use of amiodarone is reasonable only in cases of high cardiovascular risk. Besides, neither BB nor amiodarone have an impact on postoperative mortality rates [9, 14, 36]. Meta-analyses show that statins mostly prove effective in preventing POAF provided they are administered in a daily dose above that considered average therapeutic, 10–14 days prior to the surgery [22, 40], which cannot be easily implemented in reality. There has been no sufficient evidence supporting clinical use of magnesium sulfate and corticosteroids [31, 39]. Any attempts to use angiotensin converting enzyme inhibitors for the up-stream preoperative therapy resulted in an increased postoperative mortality rate, as well as complications affecting kidneys and cardiovascular system, including POAF [6]. In view of the things said above, the search for ways to improve outcomes of CABG stands out as an urgent issue.

Literature contains data confirming positive effect of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) in terms of preventing of cardiovascular events in coronary artery disease (CAD). Recently there has been a connection revealed between relatively low levels of cardiovascular diseases with higher serum concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) against large consumption of seafood rich in ω-3 PUFAs [28]. In a large-scale (18,645) randomized JELIS study targeted use of EPA (1.8 g/day) for 4.6 yrs combined with statins resulted in a further reduction in the number of sudden deaths, fatal myocardial infarction, and non-fatal cardiovascular events in patients with hypercholesterolemia. Besides, the EPA effect was independent of the impact it has on the level of low density lipoproteins

[33]. There is a report stating a decrease in the total content of EPA and DHA (ω-3-index) in erythrocytes of patients with acute coronary syndrome [21]. The GISSI-Prevenzione study demonstrated that adding ω-3 PUFAs (1 g/day) to the diet and standard drug therapy offered to myocardial infarction survivors was accompanied with a reduction in all-cause mortality and, especially, in cases of sudden cardiovascular death [26]. Therefore, there is obvious ground for evaluating the potential of ω-3 PUFAs in improving the outcomes of surgical treatment for patients with CAD. The authors of the pilot study published in 2005 reported reduced incidence of postoperative AF (down by 54.4%) and shortened hospitalization in cases of ω-3 PUFAs administration at the dosage of 2 g/day prior to the CABG [10]. However, the meta-analysis of randomized clinical trials produced contradictory information regarding the benefits of oral ω-3 PUFAs for preventing POAF, reducing the frequency of its recurrences and postoperative mortality, yet supported its safety [12, 7, 19, 16].

Lately, there has been experimental and clinical evidence for the antiarrhythmic effect of PUFAs when used in combination with antioxidants [16, 35].

The purpose of the study was to investigate the effect that ω-3 PUFAs and tocopherol contained in Omegaven – a fat emulsion for parenteral nutrition, have on the risk of AF and other complications in the early postoperative period after CABG in patients without valvular heart disease and history of atrial fibrillation.

Material and Methods. The open randomized comparative study involved 73 patients with CAD aged 41–75 (mean age 55±7.1; 82.2% males), hospitalized to further undergo elective direct myocardial revascularization surgery. The exclusion criteria were documented episodes of AF in past medical history, mitral stenosis, replaced valves, and contraindications to the Omegaven treatment.

Before the surgical treatment, all the patients underwent laboratory and instrumental examination, including coronary angiography (CAG). According to CAG, lesion of the anterior descending artery was revealed in 64 (87.7%) selected patients; the right coronary artery lesion – in 53 (72.6%) patients; lesion of the circumflex artery – in 52 (71.2%) of the selected body of patients. Lesion of three or more coronary vessels was registered in 34 (46.6%) patients. 61 (83.6%) of the patients had received, before admission, continuous cardiotropic medication, including BB – 53 (72.6%) patients, inhibitors of the renin-angiotensin-aldosterone system – 48 (65.8%), nitrates – 54 (73.97%), statins – 29 (39.7%) patients.

Surgical myocardial revascularization procedure was performed under extracorporeal circulation (EC). The surgery volume depended on the degree of coronary lesion. The echocardiographic parameters showed no significant dynamics after the surgery; left ventricular ejection fraction (LVEF) went down from 53.5±6.8% to 51.1±7.6%.

The main group included 33 patients treated with intravenous infusions of Omegaven emulsion (100 ml/day, single dose) in the first 5–7 days after the surgery.

Omegaven is based on highly purified fish oil containing a complex of mostly ω-3 and ω-6 polyunsaturated fatty acids, 0.150–0.296 g of dl-α-tocopherol acetate and a number of other ingredients (egg yolk phospholipids, glycerol, etc.) [3]. The average daily dose of Omegaven was 1–2 ml/kg of body weight, which corresponded 100–200 mg of fish oil/kg. The medication was infused into the central or peripheral vein. The infusion rate did not exceed 0.5 ml/kg/h, which was equal to 50 mg of fish oil/kg of body weight per hour. The size and biological properties of the lipid globules administered together with Omegaven are identical to those for physiological blood chylomicrons. During the infusion of the fat emulsion, the content of serum triglycerides was assessed, which was not to exceed 3 mmol/l in order to avoid a metabolic overload. There was regular monitoring of blood glucose, acid-base balance, fluid and electrolyte balance, general clinical blood test, as well as bleeding time, if necessary.

The comparison group included 40 patients who did not receive Omegaven and matched the main group in terms of gender, age, clinical and anamnestic characteristics, echocardiographic parameters, the drug therapy received, and intraoperative characteristics (Table 1).

The primary endpoint was considered to be paroxysms of AF that lasted over 30 seconds for 7–10 days after surgery, secondary endpoint – the development of other fatal and non-fatal postoperative complications, as well as the duration of hospital stay.

Through the work with the patients The Declaration of Helsinki was followed. The study was approved by the local Ethics Committee. Each of the patients provided a documented voluntary consent to join the study.

The statistical analysis was performed using IBM SPSS Statistics 21 for Windows (IBM SPSS Inc., USA). To evaluate the distribution of quantitative characters the Kolmogorov-Smirnov test was employed. Under normal distribution the signs were presented as arithmetic mean and standard deviation (M±σ), while the differences between the groups were evaluated using one-way ANOVA test with the calculation of Fisher criterion. In the case of abnormal distribution the data were expressed as median and interquartile range (Me (Q1-Q3)), and to analyze the differences between groups the Mann-Whitney U Test was performed. The qualitative characteristics were presented as absolute values and percentages. When comparing the shares, Pearson's chi-squared test (χ^2) and Fisher's exact test were used. To evaluate the impact of Omegaven treatment on the likelihood of achieving the endpoints, the relative risk (RR) with 95% of the confidence interval and relative risk reduction (RRR) were calculated. The differences were considered as statistically significant at $p<0.05$.

Table 1

Clinical and anamnestic data and echocardiographic parameters

Index	Main group (n=33)	Comparison group (n=40)
Age, yrs	56.4±6.5*	54.8±5.9
Males	27 (81.8)**	33 (82.5)
BMI, kg / m^2	29.5±4.3*	29.2±3.6
History of CAD, yrs (Me (Q1-Q3))	5.1 (2.3; 9.2)	4.0 (1.9; 7.8)
Exertional angina (NYHA classes III and IV)	22 (66.7)**	26 (65.0)
Postinfarction cardiosclerosis	22 (66.7)**	27 (67.5)
PCI in past medical history	3 (9.1)**	4 (10.0)
Stage 3 arterial hypertension	23 (69.7)**	29 (72.5)
Diabetes mellitus	4 (12.1)**	6 (15.0)
Burdened familial history	21 (63.6)**	23 (57.5)
Heart rhythm and conduction disorders in past medical history except AF	23 (69.7)**	27 (67.5)
Drug therapy:		
ASA	29 (87.9)**	37 (92,5)
Statins	13 (39.4)**	16 (40,0)
Beta-blockers	24 (72.7)**	28 (70,0)
Calcium channel blockers	12 (36.4)**	16 (40,0)
ACE inhibitors	13 (39.4)**	17 (42,5)
Angiotensin II receptor blockers	9 (27.3)**	11 (27,5)
TC, mmol / l	5.0±0.84*	5.1±1.2
Triglycerides, mmol / l	1.59±0.72*	1.62±0.91
LDL, mmol / l	3.1±0.78*	3.25± 0.81
HDLS, mmol / l	1.1±0.24*	1.16±0.22
VLDL, mmol / l	1.63±0.34*	0.72±0.32
LVEDD, cm	5.6±0.65*	5.47±0.42
LVESD, cm	3.91±0.62*	3.75±0.37
LVPW, cm	1.01±0.06*	1.05±0.1
IVSd, cm	1.19±0.16*	1.12±0.14
LA, cm	4.26±0.52*	4.43±0.71
EF, %	57.67±4.8*	55.1±6.3
The total number of grafts, n	2.8±0.84*	2.6±0.68
Mean time of the EC, min	83.8±28.7*	80.8±27.6
Mean time of aortic occlusion, min	47.1±16.3*	46.1±15.1
Average blood loss, ml	156.3±51.6*	152.7±53.8

* – data presented as (M±σ),
** – data presented as n (%).
Abbreviation used: BMI – body mass index; PCI – percutaneous coronary intervention, ASA – acetylsalicylic acid, ACE – angiotensin-converting enzyme. TC – total cholesterol, LDL – low-density lipoproteins, VLDL – very low density lipoproteins, HDLS – high density lipoproteins. LVEDD – left ventricular end-diastolic diameter, LVESD – left ventricular end-sistolic diameter, LVPW – left ventricle posterior wall, IVSd – interventricular septum in diastole, LA – left atrium, EF – ejection fraction.

Results. Postoperative AF developed in 16 (21.9%) patients. At the same time, the occurrence of POAF in the main group was 3.6 times as low as in the comparison group (p<0.01) (Table 2). All paroxysms were tachysystolic with an average frequency of ventricular contractions of 131.7±13.2 beats per minute. About half of the cases (47.1%) were asymptomatic. The peak of rhythm disorders came on the second and the third postoperative day. The dynamics of AF episodes frequency must be related to intraoperative myocardial injury and reperfusion syndrome, which are known to be stopped by day 6–7 after the surgery [34, 38].

The average sinus rhythm recovery time was 5.2 hrs (1; 49) and proved significantly shorter in the main group (Table 2). In 7 (43.8%) patients the reverse of AF paroxysm occurred spontaneously, including all the patients of the main group and 4 (30.8%) out of the 13 patients with AF in the comparison group. In other cases intravenous infusion of amiodarone was performed in order to restore the sinus rhythm. 16 (94.1%) patients underwent prophylactic therapy with oral BB, 3 (17.6%) – a combination of BB with amiodarone, while 1 (5.9%) patient had amiodarone monotherapy administered. 6 out of the 13 patients with POAF in the comparison group showed recurrences of POAF on the background of antiarrhythmic therapy. A stable form of AF developed in 2 (15.4%) patients. The main group showed no POAF recurrences.

Other life-threatening cardiac arrhythmias and conduction disturbances, including high-grade ventricular premature beats, paroxysmal ventricular tachycardia, ventricular fibrillation, second- and third-degree transient atrioventricular block, also appeared significantly more often in the comparison group (p<0.01) (Table 2). Besides, in the first 10 days after the CABG there were cases of pericarditis, hydrothorax, non-fatal myocardial infarction, and 1 case of transient ischemic attack registered. No statistically significant differences in the frequency of the adverse events listed above were detected in the groups under comparison. Neither were there fatal postoperative complications. Uncomplicated postoperative period was significantly more often to be registered in the main group (p<0.01). The duration of the postoperative period in patients that received PUFAs proved significantly shorter than in the comparison group (p<0.05).

Table 2

Specific issues in postoperative period

Index	Main group (n=33)	Comparison group (n=40)
POAF, n (%)	3 (9.1)	13 (32.5)*
Sinus rhythm recovery time, hrs (Me (Q1-Q3))	4.3 (1; 36)	6.9 (1; 54)*
POAF recurrences, n (%)	–	6 (46.2)
Other life-threatening cardiac arrhythmias, n (%)	2 (6.1)	10 (25.0)*
Cardiac conduction disorders, n (%)	5 (15.2)	16 (40.0)
Transient ischemic attack, n (%)	–	1 (2.5)
Non-fatal myocardial infarction, n (%)	1 (3.1)	3 (7.5)
Pericarditis, n (%)	5 (15.2)	6 (15.0)
Hydrothorax, n (%)	6 (18.2)	7 (17.5)
Uncomplicated postoperative period, n (%)	16 (48.5)	11 (27.5)*
Duration of postoperative period, days (M±σ)	14.1±2.21	22.9±3.82*

* – differences between groups are statistically significant.

Based on Table 3, the reduction in the relative risk of POAF in the patients who received Omegaven was 72%, which was statistically significant. There was a clear downward trend revealed in the relative risk of developing other life-threatening cardiac arrhythmias and conduction disturbances.

Table 3

Effect of Omegaven on risk of complications in early postoperative period after coronary artery bypass grafting

Index	RR (95% CI)	RRR, %
POAF, n (%)	0.28 (0.09; 0.89)	72.0
Other life-threatening cardiac arrhythmias and conduction disorders, n (%)	0.24 (0.06; 1.03)	75.8
Non-fatal myocardial infarction, n (%)	0.4 (0.04; 3.7)	59.6
Pericarditis, n (%)	1.01 (0.34; 3.02)	1.0
Hydrothorax, n (%)	1.04 (0.39; 2.79)	3.9
Uncomplicated postoperative period, n (%)	0.64 (0.33; 1.25)	35.8

The study showed no side effects typical for Omegaven (prolonged bleeding time, «fish taste» in the mouth) and fat emulsions in general (increase in body temperature, anorexia, gastric dyspepsia, anaphylactic reactions, symptoms of metabolic overload, etc.).

Discussion. The pathophysiological mechanisms of postoperative AF still remain unclear. There is an opinion that oxidative stress, local and systemic inflammatory response to the factors of surgical stress (intraoperative myocardial injury, reperfusion syndrome, contact of blood components with the surface of cardiopulmonary bypass machine, swelling of the right atrium after cannulation, etc.) combined with unfavorable background like ischemia and/or fibrosis of the atrial myocardium develop morphological and electrophysiological substrates for initiation and maintenance of AF in the early postoperative period [25].

The experimental and clinical data available serve evidence to the fact that there is direct antiarrhythmic effect of PUFAs on cardiomyocytes [30]. Apart from that, the pleiotropic effects of the PUFAs manifested as reduced severity of oxidative stress, enhanced anti-inflammatory and anti-fibrotic activity, taken together, will obviously mediate additional antiarrhythmic effect [23, 21].

The mechanisms of anti-arrhythmic and antioxidant actions of PUFAs are interlinked and include modification in the eicosanoids system, modification of the fatty acid composition of membrane phospholipids, direct influence of nonesterified fatty acids on myocardium, impact on innozitol lipid cycle and signaling systems, as well as ion transport systems [20].

When in physiological concentrations, DHA and EPA will block potassium channels of the two types (K (V) 1.5 and K (v) 11.1), reduce the value of ionic currents caused by activation of Na (V) 1.5 and calcium channels. There is an opinion that modulation of the L-type calcium channels activity in sarcolemma of cardiomyocytes under the influence of PUFAs averts the increase in cytosolic calcium levels and ensures leveling of atrial dispersion of refractoriness [2]. However, such effects on sodium and calcium channels, in theory, are supposed to shorten the action potential of cardiomyocytes. At the same time, due to the blockade of potassium channels lengthening of the action potential should be expected. Indeed, in the experiment the effect of marine ω-3 PUFAs on the action potential duration and, consequently, on the risk of heart rhythm disorders depended largely on the mode of administration, animal model and background heart disease [29].

When released from the cell membranes under the influence of phospholipases, ω-3 PUFAs turn into eicosanoids with less remarkable inflammatory properties. Besides, ω-3 PUFAs reduce the production of inflammatory mediators – inflammatory cytokines: tumor necrosis factor-α, interleukin-1β and interleukin-6, transcription factor kB and reactive groups, as well as they increase the synthesis of anti-inflammatory mediators – rezolvins. The anti-inflammatory activity of highly purified ω-3 PUFAs was seen in case of administering these (2 g/day) prior to carotid endarterectomy surgery, which resulted in a decrease in the activity of interleukin-6 and the levels of metalloproteinases in the plaques removed during endarterectomy [5, 30].

We can suggest that introducing PUFAs into standard therapy can reduce the frequency of POAF after CABG due to launching and/or interaction of the two or more of the mechanisms described. Yet, the authors of the most recent meta-analysis (11 randomized controlled trials; 3,137 participants) do not confirm the benefits of ω-3 PUFAs in the prevention of POAF [16].

While discussing the result of this meta-analysis note to be made that, first of all, POAF development may be contributed to by perioperative factors like damage and ischemia of the atrial myocardium, electrolyte imbalance, volume overload, the use of drugs with positive inotropic effect, and the duration of the EC [14]. At the same time, PUFAs do not have a direct impact on the factors mentioned.

Second, the effectiveness of PUFAs regarding POAF may depend on the duration of preoperative use and the method of administration (oral, parenteral). In their experimental study, R. G. Metcalf et al. discovered that maximum inclusion of PUFAs into the membrane structures of atrial cardiomyocytes in humans takes place appr. by Day 30 of their oral intake [27]. It was shown that it was longer (over a month) intake of fish oil that results in a significant increase in the EPA and DHA

as part of the serum phospholipid fraction, and a reduction in the frequency and duration of the AF paroxysms [23]. N. Sao et al. in their meta-analysis confirmed a significant reduction in the resumption of arrhythmia in case of using PUFAs for at least four weeks prior to cardioversion and maintaining the intake after the procedure [11]. Most of the research that X.-Y. Guo et al. included into their meta-analysis show that the duration of oral PUFAs did not exceed five days prior to the surgery [16]. In one research only PUFAs were administered three weeks before the surgery [15]. There is every reason to conclude that PUFAs levels in plasma and atrial tissue grows also in case of short-term oral administration; yet, the concentration may prove insufficient for ensuring maximum antiarrhythmic and anti-inflammatory effects as the severity of inflammation and oxidative stress is at peak in the early postoperative period.

Third, the protective effect that the drug containing fatty acids has in relation to POAF may depend on the EPA and DHA ratio as well as on ω-3 and ω-6 PUFAs. Even though EPA and DHA are largely similar, yet they are different in the chain length and number of double bonds. In the work by U. Benedetto et al., the EPA/DHA index of 1:2 ensured a higher effect in terms of preventing POAF [8]. R. De Caterina et al. showed in their study that DHA has a greater impact on the severity of inflammation, if compared with EPA [13]. A laboratory experiment revealed a higher effectiveness of DHA in reducing the atrium vulnerability to the occurrence of AF and remodeling prophylaxis [32]. The meta-analysis performed by X.-Y. Guo et al. contained a subgroup analysis with a different EPA/DHA ratio. The combined data suggest that PUFAs with an index of EPA/DHA equal to 1:2 had a positive effect while of lower DHA had no significant influence on POAF [16]. A certain balance of EPA and DHA may be an important element in antiarrhythmic efficacy of the drug containing PUFAs; however, mention to be made here that two studies with the EPA/DHA index of 1:2 that are part of the said meta-analysis were open [10, 37], so their results need further verification. As for the ratio of ω-3 and ω-6 in the drug, an experiment conducted on healthy dogs showed that plasma fatty acid profiles are only determined with the total dose of PUFAs administered [17].

Fourth, finally, it cannot be excluded that PUFAs alone are not able to resist the active inflammatory process and intense oxidative stress after CABG. This suggestion seems to gain support from the conclusion made by the authors of the earlier mentioned large-scale meta-analysis [16] concerning a 68% decrease in the frequency of the new-onset and recurrent AF and an increase in the time prior to the AF development in the early period after CABG in case of administering a combination of PUFAs with vitamins C and E. Earlier, L. Harling et al. in their meta-analysis obtained proof to a significant (by 57%) reduction in POAF frequency in case of prophylactic use of vitamins C and E before an open heart surgery [18].

Following the official user's guide, Omegaven has immunomodulatory and anti-inflammatory effects and can be used for treating postoperative conditions, cancer, inflammatory bowel disease, sepsis, burns and other acute conditions involving potent systemic inflammatory response. Despite the lack of the claimed antiarrhythmic action in relation to POAF, there are reasons to expect such effects in Omegaven. In our research, the use of the drug in the early postoperative period after CABG came along with a statistically significant reduction in the relative risk of postoperative AF and a much lower duration of the postoperative period, as well as was associated with shorter sinus rhythm recovery time, frequency of other life-threatening cardiac arrhythmias and conduction disturbances, and was safe.

Such effects have several explanations behind them. First, Omegaven contains a combination of fatty acids, mostly ω-3 and ω-6 PUFAs, where the largest share belongs to EPA (up to 28 g) and DHA (up to 31 g). Second, parenteral administration must be responsible for prompt and high intensity in launching the drug's therapeutic effect, while most of the beneficial effects attributable to oral administration of PUFAs manifest themselves only after the peak concentrations in plasma and tissues are reached, which occurs by the 4th week of administration [27]. The size and biological properties of the lipid globules used together with Omegaven are identical to those of physiological chylomicrons. In healthy male volunteers the half-life of triglycerides administered intravenously with Omegaven is 54 minutes. Obviously, in case of intravenous administration the increase in concentration of the drug components in blood and atrial tissues, their utilization, PUFAs inclusion into the structure of cardiomyocytes' cell membranes, effect on signaling pathways and inflammatory responses in the myocardium, all these happen much faster and in a more active fashion, if compared to oral use. It is parenteral formulation that ensures effective resistance to local and systemic inflammatory response to numerous factors of surgical stress, providing a reduction in inducibility and duration of the AF paroxysms through the early postoperative period. This is especially relevant given the current clinical conditions where cases of prolonged regular use of PUFAs oral medications in the preoperative period by patients with CAD are just few. M. C. Heidt et al. in their prospective randomized study showed that perioperative infusions of fish oil (100 mg/kg/day) would reduce the frequency of POAF after CABG and lead to a reduced duration of stay in the ICU and in the in-patient department [20]. This conclusion, however, runs contrary to the data obtained from a double-blind placebo-controlled study wherein episodes of POAF were

recorded with an implantable heart monitor Reveal®, where intravenous PUFAs (200 mg/kg/day) 24 hours prior to anesthesia, and further use of it (100 mg/kg/day) for 7 days helped reduce the frequency of POAF in the ten days of the early postoperative period and also within the two years of follow-up [24]. Note to be made here that the research projects focusing on the efficacy and safety of perioperative parenteral use of PUFAs in preventing POAF are scarce, which is also to be kept in mind when interpreting their results.

Second, the antiarrhythmic effect of PUFAs may get enforced due to a combination with an antioxidant – vitamin E. Oxidative stress is the main inevitable consequence of the ischemia/reperfusion cycle during cardiac surgery. The results of a high concentration of active oxygen species are inflammation, cell death (apoptosis/necrosis), and myocardial fibrosis. There is data available that stand serious proof to the involvement of active oxygen species in POAF pathogenesis [34]. Vitamin E suppresses the enzymatic production of reactive oxygen species thus contributing to the removal of free radicals and limiting free radical interactions [34]. ω-3 PUFAs, in turn, also activate the survival mechanisms of myocardium under ischemic conditions enhancing myocardial expression of antioxidant enzymes, which is due to the ability to modify enzyme systems and receptor functioning in the membranes [34]. Therefore, the presence of significant amounts of ω-3 PUFAs and vitamin E in Omegaven must ensure a comprehensive synergistic therapeutic and preventive effect related to postoperative oxidative stress and, consequently, to POAF, through strengthening of the antioxidant protection and an increase in the anti-apoptotic capacity of the myocardium.

The outcomes suggest a need for further comprehensive investigation into drugs based on PUFAs and antioxidants, and may serve a ground for a large-scale prospective study aiming at evaluating the efficacy and safety of Omegaven in prevention of cardiac arrhythmias after direct myocardial revascularization.

Conclusions. The study has shown, for the first time, that Omegaven used early after surgical revascularization helps reduce significantly the relative risk of new-onset postoperative AF and shorten the post-operative period.

Any limitations of the study are due to the relatively small number of patients.

This study contains no conflict of interest.

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