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Association of CVD risk factors and probability of fatal cardiovascular events development with the amount of consumed alcohol in 42-44 years old patients

Detection of viable myocardium in patients with ischemic myocardial dysfunction: modern possibilities and practical value

Monitoring in cardiologic intensive care units

Acute Myopericarditis secondary to campylobacter jejuni enterocolitis

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CHINA HEART FEDERATION

GW-ICC

The 28th Great Wall International Congress of Cardiology

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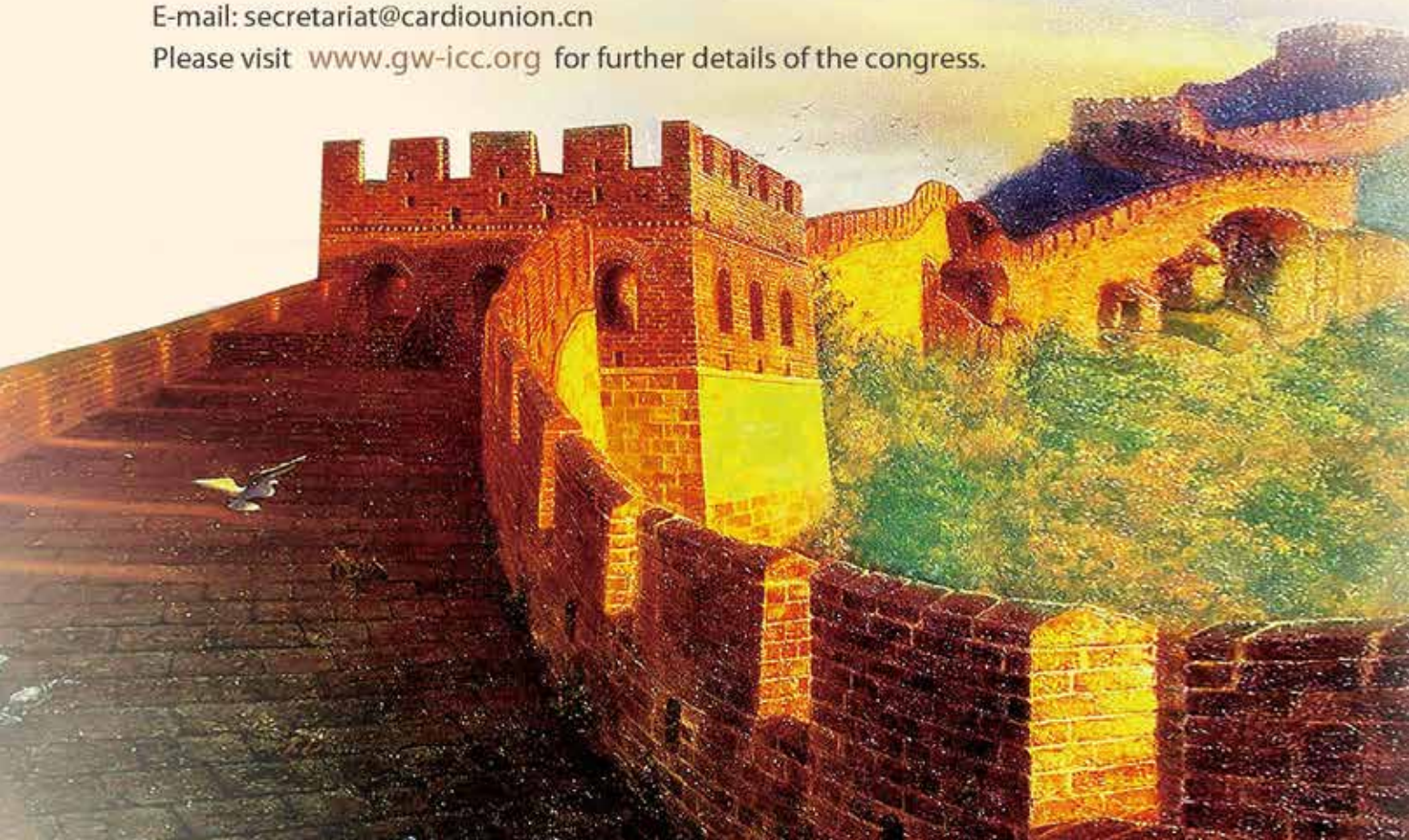

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Volume 4, Number 12, December 2016

Contents

Editor's Welcome

Dear colleagues!

In the 12th issue of the International Heart and Vascular Disease Journal, there are leading article, original article and review articles, clinical seminar and clinical case report.

The leading article was prepared by the group of authors from National Research Centre for Preventive Medicine and it is dedicated to the investigation of connection between the amount of consumed alcohol and cardiovascular disease risk factors. It has been identified, that increased alcohol is linked to increased frequency of abdominal obesity, arterial hypertension and atherogenic dyslipidemia.

Two articles are included into traditional «Review articles" section. The first of them discusses the practical value and possibilities of viable myocardium identification in myocardial ischemic dysfunction. The second article is dedicated to experimental medicine. It observes different aspects of atherosclerosis and analyzes separately lipoprotein transport systems in herbivorous and carnivorous animals.

The "Original articles" section is present with an article about optimization of management of patients with arterial hypertension and anxiety disorders. The authors propose a patented method of non-pharmacological treatment in addition to pharmacological therapy in order to increase patients' compliance to treatment.

New section "Clinical seminar" observes an article of Byelorussian authors about modern techniques of physiological parameters monitoring in patients of cardiologic intensive care units.

In this volume we published also the analysis of secondary myopericarditis associated with Campilobacter Jejuni clinical case. According with authors' results, this is the first bacterial etiology myopericarditis clinical case published in Lithuania.

I invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

International Heart and Vascular Disease Journal
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LEADING ARTICLE

Association of CVD risk factors and probability of fatal cardiovascular events development with the amount of consumed alcohol in 42–44 years old patients

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Objective

To estimate cardiovascular disease (CVD) risk factors (RF) association and the probability of fatal cardiovascular events development with the amount of consumed alcohol in 42-44 years old males.

Materials and methods

This study is the part of 32-years long prospective cohort observation of males starting from the childhood. 303 (30,1%) males have been observed. Observation included: obtaining patient's and family history, information about RF, bad habits, blood pressure (BP) changes, anthropometric characteristics, blood lipid profile, C-reactive protein (CRP), ureic acid, glucose, and insulin levels in blood serum. Males have been classified into three categories depending on alcohol consumption: nondrinkers, moderate drinkers, heavy drinkers. Then the total risk of CVD for the next 10 years has been estimated.

Results

The majority of observed men consume alcohol relatively rarely but in the amount exceeding the safe levels. Linear correlation between the frequency of abdominal obesity, arterial hypertension (AH), elevated total cholesterol (TC) and low density lipids (LDL) cholesterol levels and the amount of consumed alcohol. Systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, ApoA1, ureic acid and glucose in heavy and excessively drinking males were higher comparing with nondrinkers, and the difference in waist circumference (WC), high density lipids (HDL) cholesterol, LDL cholesterol, ApoB and HOMA-IR were observed only between nondrinkers and heavy drinkers. Heavy drinkers have the highest risk of CVD development. SBP impact on total risk is higher in heavy drinkers, and TC has stronger impact on total risk in moderate and heavy drinkers. The impact of smoking on total risk does not correlate with the amount of consumed alcohol. The probability of AH development in drinkers is 2,6 times higher than in nondrinkers.

Conclusion

The majority of males of 42–44 years consume alcohol, 40% of them consume dangerous for health amount of alcohol. The frequency of abdominal obesity, AH and atherogenic changes of blood lipid profile goes along with increased alcohol consumption. Alcohol has direct influence on SBP and DBP levels, TC, ApoA1, uric acid and glucose concentration. The value of total risk of CVD is mostly determined by other CVD RF like TC levels and smoking.

Keywords

Alcohol, middle-aged men, risk factors, cardiovascular diseases, total cardiovascular risk.

Excessive alcohol consumption is an important problem for the Russian federation and world population in general. Experts demonstrate increased alcohol consumption in all age groups starting from children and ending with older groups of able-bodied population. Beer and vodka forms of alcohol abuse become more spread, deviant behavior, somatic disorders and alcohol-dependent mortality become more common [1]. According with the study of World Health Organization "Global Status Report on Alcohol and Health", in 2014 per capita alcohol consumption in Russia reached 15,76 L in people above 15 years old [2]. This is one of the highest results in the world. According with the major cohort study, that had been performed in Russia in 2012, estimated number of deaths related to alcohol consumption was 231 900 (161100 for males and 70800 for females) per year and the number of years lost due to acquired disability (disability-adjusted life year, DALY index) was 13295000 (9625000 for males and 3 670 000 for females) [3].

33,4% of deaths related to alcohol consumption (6% of total amount of lethal cases in the world) are caused by cardiovascular diseases (CVD) and diabetes mellitus (DM) [4]. Impact of alcoholic beverages on cardiovascular mortality depends on two factors: amount of consumed alcohol and the pattern of alcohol consumption [5].

Excessive alcohol consumption has significant impact on several CVD risk factors (RF).Toxic doses of alcohol lead to essential hypertension development (EH), hypercholesterolemia, obesity (Ob), particularly in males, food behavior deviations, smoking [6–11].

Alcohol consumption in toxic doses is more typical for males than females. Percentage of lethal cases related to alcohol in the world between males is

7,6% of total death cases comparing with the 4% in females. Average total amount of consumed alcohol per capita measured as absolute alcohol volume between males and females in 2010 was >12,5 L and 8,9 L, respectively [12]. This difference can be considered significant.

At the same time, cardioprotective effects of alcohol in small amounts and their influence on antiatherogenic parameters of blood lipid spectrum are widely discussed in literature [13-15]. However the questions of impact of consumed alcohol amount on CVD RF and probability of fatal cardiovascular events (CVE) development in males still remain open.

The objective of this study was to estimate cardiovascular disease (CVD) risk factors (RF) association and the probability of fatal CVE development with the amount of consumed alcohol in 42-43 years old males.

Materials and methods

This study is the part of 32-years long prospective cohort observation of 1005 males starting from the childhood age (11-12 year). This study involved 303 males (30,1% of initial population sample).

This study has been performed according with the ethic regulations of Helsinki's Declaration and the National Standard of the Russian Federation "Good Clinical Practice (GCP)", State Standard R2379-2005.

This study included a survey according with the standard form (passport information, education, social position, personal and family history, information about physical activity (PA) and bad habits (smoking, alcohol consumption); triple blood pressure (BP) measurement, pulse estimation, body height (BH) and body weight (BW) estimation, abdominal skinfold (ASF), subscapular skinfold (SSF) and triceps skinfold (TSF) thickness, waist and thighs circumference (WC and ThC), total cholesterol (TC), high density lipids cholesterol (HDL Ch), triglycerides (TG), Apo-A1 and Apo-B lipoprotein (Apo-A1 and Apo-B, respectively), lipoprotein (a) (LPa), C-reactive protein (CRP), ureic acid (UA), glucose and insulin levels in blood serum. We used body mass index (BM) to estimate interrelation between BW and BH using the formula $BMI=BW(kg)/BH^2(m^2)$. Low density lipids cholesterol (LDL Ch) concentration was determined using formula LDL Ch=Ch – (HDL Ch+VLDL Ch), where VLDL Ch – very low density lipids cholesterol levels. TyG index was estimated using interrelation between TG (mg/dL) and glucose (mg/dL) concentration in blood serum. HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index of insulin resistance was quantified using the following formula (Matthews D.R. and coauthors, 1985): HOMA-IR=fasting glucose levels (mmol/L)* fasting insulin levels (μU/mL)/22,5. All measurement were performed using standardized methods with regular quality control.

Arterial hypertension (AH) group included persons with BP levels ⩾ 140/90 mm Hg. BMI ⩾ 25 and 30 kg/m^2 was considered as eBW and Ob, respectively. The group of abdominal (central) Ob included persons with WC>94 cm. Categories of blood lipid spectrum were formed according with the classification presented in the third report of the group of experts of the National Cholesterol Education Program (NCEP) for detection, estimation and therapy of high Ch levels in adults – Adult Treatment Panel III (ATP III). We used International Physical Activity Questionnaires (IPAQ) to estimate PA of participants [16]. PA categories were formed according with the IPAQ guidelines [17]. Men who smoked at least one cigarette per day were considered smokers. All men independently on their attitude to alcohol were classified into three categories: the first group (n=59) – non-drinkers, the second group (n=126) – moderate drinkers (consuming not more than 84 g of conventional absolute alcohol per week); the third group (n=118) of heavy drinkers consuming >84 g of conventional absolute alcohol per week [18].

Estimation of total fatal CVE development risk during the next 10 years was performed according with the SCORE (Systematic Coronary Risk Evaluation) scale for countries with the high risk of CVD, that include Russia. Total risk of fatal CVE development was classified as low (<1%), moderate (1-5%) and high (>5%) [19].

We used average value and median as the measure of central trend to describe obtained results, and we took standard deviation and quartile deviation as the measure of variability. Kolmogorov-Smirnov test was used for distribution normality testing in order to select statistical data for further analysis. Evaluation of connection between CVD Rf and the amount of consumed alcohol was performed using Pearson's chi-squared test (χ^2) for linear trend. We used Z-test with Bonferroni's correction for multiple comparisons for paired comparisons of proportions. To estimate the dependence of studied characteristics on the levels of alcohol consumption we used Kruskal-Wallis ANOVA dispersion analysis. Paired group comparisons for variables with not-normal distribution were made using Mann-Whitney U test with Bonferroni's

p-value correction for multiple comparison. Critical level of significance was set up for 95% for all statistical parameters (p<0,05). To describe power and direction of correlation between characteristics we used gamma(γ) coefficient of Goodman-Kruskall (Goodman-Kruskall's gamma). The size of the effect of consumed alcohol levels on investigated characteristics was made using eta-squared (η^2) values for non-parametrical Kruskal-Wallis test [20]: η^2=[H/(n–1)], where H is the value of Kruskal-Wallis test, n – number of observations. The size of the effect of consumed alcohol levels was estimated using the criteria suggested by Cohen (Cohen, 1988): small (η^2 = 0.01); medium (η^2 = 0.06) and big (η^2 = 0.14) effect [21]. Relative risk of AH development in the group of persons consuming alcohol was evaluated using logistic regression analysis. We quantified the odds ratio (OR) with 95% confidence interval (CI) and included non-drinker (OR=1.0) in the group of comparison.

Statistical processing of results was performed using IBM SPSS Statistics (Version 23.0) software.

Results

This analysis includes the results of observation of 303 male participants aged 42-44 years. The majority of examined men were married with specialized secondary or higher education (Figure 1). 74.6% of men had children. Divorced men consumed higher amounts of alcohol — 201.7±47.9 g per week comparing with married ones — 118.8±13.5 g per week and single ones — 141.2±46.2 g per week (p=0.012).

General characteristic of examined population sample is present in the Table 1. Average value of BMI exceeded common eBW criteria and average WC was higher than abdominal Ob criteria. Value of ASF and SSF indicate the excess of subcutane-

Table 1. **General characteristic of examined male patients**

Characteristic	M ± SD
Age, years	42.9 ± 0.5
Length of alcohol consumption	24.6 ± 0.2
BMI, kg/m^2	27.6 ± 4.8
WC, cm	94.2 ± 13.3
WC/ThC	0.93 ± 0.08
WC/BH	0.53 ± 0.07
ASF (left), mm	29.9 ± 9.4
SSF (left), mm	25.1 ± 9.8
TSF (left), mm	14.4 ± 6.9
SBP, mm Hg	122 ± 15
DBP, mm Hg	82 ± 11
Pulse, beats per minute	74 ± 10
TC, mmol/L	5.7 ± 1.2
HDL Ch, mmol/L	1.0 ± 0.3
TG, mmol/L	1.4 ± 0.9
LDL Ch, mmol/L	4.1 ± 1.2
Apo-A1, mg/dL	163.6 ± 30.6
Apo-B, mg/dL	103.1 ± 25.3
LP (a), mg/dL	29.6 ± 42.8
CRP, mg/dL	3.9 ± 3.8
UA, mg/dL	6.4 ± 1.4
Glucose, mmol/L	5.2 ± 1.2
TyG-index	8.5 ± 0.6
Insulin, μU/mL	9.0 ± 5.8
HOMA-IR index	2.13 ± 1.58
Total risk of fatal CVE (SCORE), %	1.2 ± 0.7
SBP impact on total risk, %	2.7 ± 11.9
TC impact on total risk, %	47.6 ± 44.2
Smoking impact on total risk, %	33.7 ± 41.3
Frequency of compromised family history of coronary heart disease, n (%)	22 (7.3)
eBW frequency, n (%)	117 (38.6)
OB frequency (based on BMI), n (%)	87 (28.7)
Abdominal OB frequency (WC>94 cm), n (%)	138 (45.5)

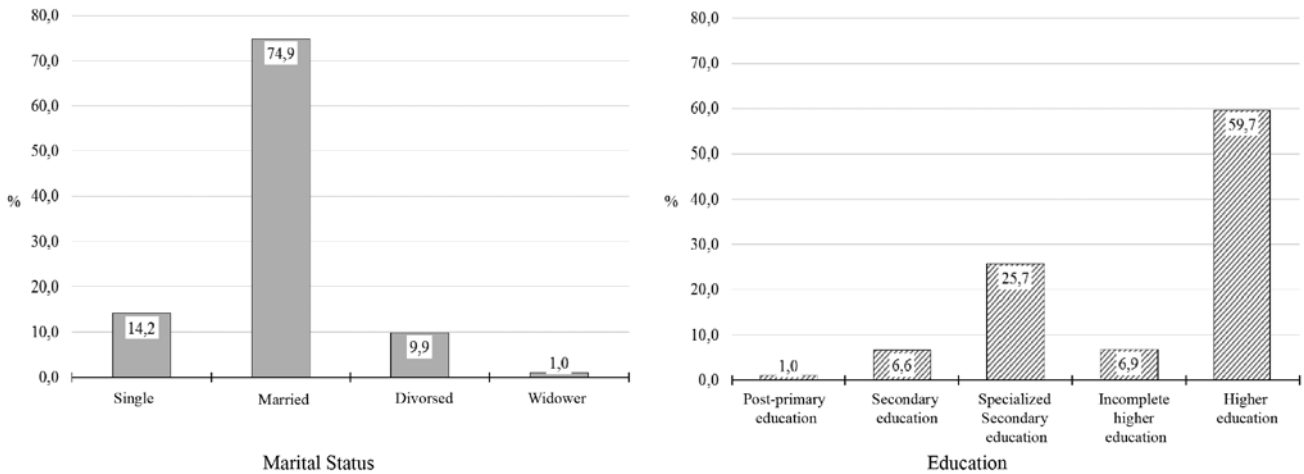

Figure 1. Marital status and education of patients

Table 1

Characteristic	M ± SD
Abdominal OB frequency (WC>102 cm), n (%)	87 (28.7)
AH frequency, n (%)	70 (23.1)
Hyper-TC frequency, n (%)	99 (32.7)
Hypo-HDL Ch frequency, n (%)	197 (65.0)
Hyper-TG frequency, n (%)	46 (15.2)
Hyper-LDL Ch frequency, n (%)	129 (42.6)
Smoking frequency, n (%)	128 (42.3)
Low PA frequency, n (%)	79 (26.1)

ous body fat deposits. 67.3% of examined men have eBW and Ob and more than the half of them have abdominal Ob. Average tC and LDL Ch levels reflect atherogenic trend of lipid blood spectrum. More than 40% of participants have dyslipoproteinemia (DLP). Average LP(a) levels in investigated population demonstrate prognostic potential corresponding to the low risk of CVD development and CRP levels in these males go along with high probability to develop CVD and their complications. 37.3% of male participants smoke regularly. 65% of examined people had ⩾2 RF. Average total risk of fatal CVE estimated with SCORE scale was moderate. TC and smoking have the biggest impact on total risk of CVE.

Almost all participants of this study, apart from the small exception, consumed alcohol with 30 days preceding this investigation (Table 2), mostly vodka and beer. The majority of them consumes alcohol enough rarely but in the amounts exceeding safe ones. Around 38,9% of people abuse alcohol (Figure 2).

Table 2. **Quantity and frequency of alcoholic beverages consumption by male patients during the last 30 days preceding the examination**

Characteristic	Value
Age of start of alcohol consumption, years; M (95% CI)	18.3 (15.0–24.0)
Did you consume alcoholic beverages during the last month, n (%):	
yes	246 (92.1)
not	21 (7.9)
Beer consumption frequency, n (%):	
every day	7 (3.7)
4 times for week	13 (6.8)
2 times for week	41 (21.6)
Once for week	42 (22.1)
2 times during last 30 days	34 (17.9)
Once during last 30 days	53 (27.9)
Total	190 (100.0)
Volume of beer normally consumed at once (mL), M (95% CI)	1025.7 (330.0–2500.0)
Volume of beer normally consumed per week (mL), M (95% CI)	1537.6 (116.7–5600.0)

Table 2

Characteristic	Value
Dry wine consumption frequency, n (%):	
every day	2 (1.5)
4 times for week	1 (0.7)
2 times for week	22 (16.1)
Once for week	26 (19.0)
2 times during last 30 days	28 (20.4)
Once during last 30 days	58 (42.3)
Total	137 (100.0)
Volume of dry wine normally consumed at once (mL), M (95% CI)	380.2 (100.0–750.0)
Volume of dry wine normally consumed per week (mL), M (95% CI)	692.5 (35.0–3733.3)
Fortified wine consumption frequency	
every day	0
4 times for week	0
2 times for week	1 (2.9)
Once for week	3 (8.8)
2 times during last 30 days	6 (17.6)
Once during last 30 days	24 (70.6)
Total	34 (100.0)
Volume of fortified wine normally consumed at once (mL), M (95% CI)	289.7 (50.0–1000.0)
Volume of fortified wine normally consumed per week (mL), M (95% CI)	113.9 (23.3–233.3)
Vodka consumption frequency	
every day	2 (1.0)
4 times for week	5 (2.5)
2 times for week	31 (15.7)
Once for week	37 (18.7)
2 times during last 30 days	53 (26.8)
Once during last 30 days	70 (35.4)
Total	208 (100.0)
Volume of vodka normally consumed at once (mL), M (95% CI)	263.6 (50.0–500.0)
Volume of vodka normally consumed per week (mL), M (95% CI)	242.1 (23.3–933.3)
Other alcoholic beverages consumption frequency	
every day	7 (3.7)
4 times for week	13 (6.8)
2 times for week	41 (21.6)
Once for week	42 (22.1)
2 times during last 30 days	34 (17.9)
Once during last 30 days	53 (27.9)
Total	190 (100.0)
Volume of other alcoholic beverages normally consumed at once (mL), M (95% CI)	1025.7 (330.0–2500.0)
Total volume of alcohol (in terms of absolute ethanol) consumed per week (g), M (95% CI)	162.6 (10.4–626.4)
Total volume of alcohol (in terms of absolute ethanol) consumed per week (g), (units UK), M (95% CI)	20.3 (1.3–78.3)
Total volume of alcohol (in terms of absolute ethanol) consumed per week (g), (units USA), M (95% CI)	11.6 (0.7–44.7)

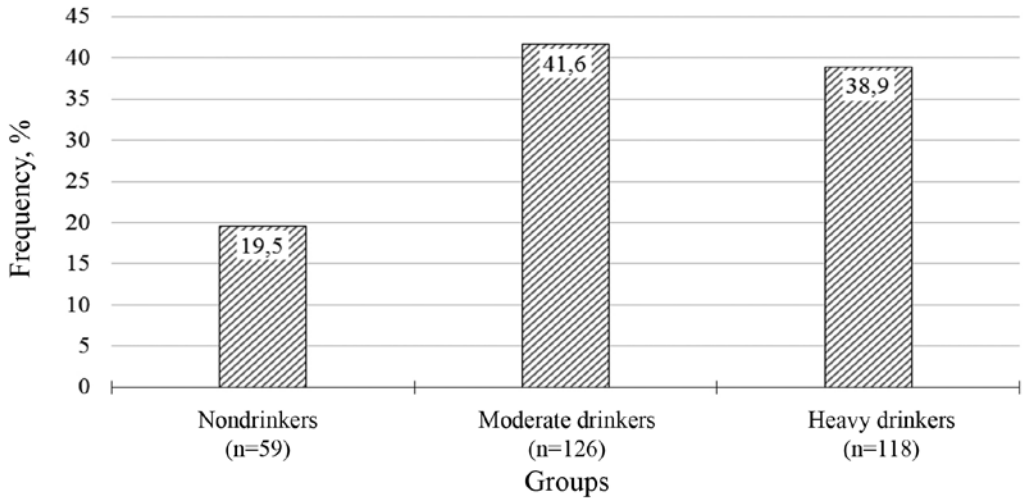

Figure 2. Distribution of patients according with the amount of consumed alcohol (n=303)

Results of χ^2 Pearson's test for linear trend (Table 3) evidence the presence of linear correlation between the frequency of abdominal Ob, AH, hypercholesterolemia (hyper-Ch), hyper-LDL-Ch and the levels of alcohol consumption. The percentage of people with abdominal Ob, AH, hyper-Ch and hyper-LDL-Ch goes up with the increase of alcohol consumption. Abdominal Ob, AH and hyper-Ch are more frequent in the group of heavy drinkers comparing with non-drinkers and/or moderate drinkers. There is a direct correlation between the increase of frequency of mentioned RF and the increase of consumed alcohol amount, it is proved by highly significant coefficients of Goodman-Kruskall' gamma rank correlation. The frequency of hyper-LDL-Ch is connected with increased alcohol consumption levels, but this correlation is weaker comparing with abdominal Ob, AH and hyper-Ch. Unidirectional trend between the frequency of smoking and amount of consumed alcohol was not found. The biggest number of smokers was present in the groups of moderate drinkers.

Table 3. **CVD RF frequency in groups of male patients with different levels of alcohol consumption**

RF	Groups			γ Goodman-Kruskal	χ^2 for linear trend
	Non-drinkers (1)	Moderate drinkers (2)	Heavy drinkers (3)		
Frequency of compromised family history of coronary heart disease, n (%)	4 (6.8)	9 (7.1)	9 (7.6)	0.040 p=0.829	χ^2=0.046 p=0.830
eBW, n (%)	17 (28.8)	51 (40.5)	49 (41.5)	0.138 p=0.158	χ^2=2.159 p=0.142
OB frequency (based on BMI), n (%)	16 (27.1)	33 (26.2)	38 (32.2)	0.098 p=0.360	χ^2=0.753 p=0.385
Abdominal OB frequency (WC>94 cm), n (%)	22 (37.3)	50 (39.7)	66 (55.9) [2]	0.264 p=0.005	χ^2=7.124 p=0.008
AH, n (%)	7 (11.9)	27 (21.4)	36 (30.5) [1]	0.325 P=0.003	χ^2=8.007 p=0.005
Hyper-TC, n (%)	9 (15.3)	41 (32.5) [1]	49 (41.5) [1]	0.345 p<0.001	χ^2=11.756 p=0.001
Hypo-HDL Ch, n (%)	46 (78.0)	78 (61.9)	73 (61.9)	−0.175 p=0.075	χ^2=3.417 p=0.065
Hyper-TG, n (%)	4 (6.8)	22 (17.5)	20 (16.9)	0.194 p=0.127	χ^2=2.320 p=0.128
Hyper-LDL Ch, n (%)	19 (32.2)	52 (41.3)	58 (49.2)	0.211 p=0.028	χ^2=4.746 p=0.029
Smoking, n (%)	30 (50.8) [2]	37 (29.4)	61 (51.7) [2]	0.121 p=0.218	χ^2=0.911 p=0.340
Low PA, n (%)	15 (25.4)	26 (20.6)	38 (32.2)	0.161 p=0.151	χ^2=1.813 p=0.178

Comment: Results of multiple comparison are based on two-sided tests with significance level of 0.05. For each significant pair number of group with smaller percentage of column is put into the group with higher percentage of column. For each pair comparison p-values were corrected according with Bonferroni method. Size of alcohol consumption levels' effect: a — big, b — medium, c — small.

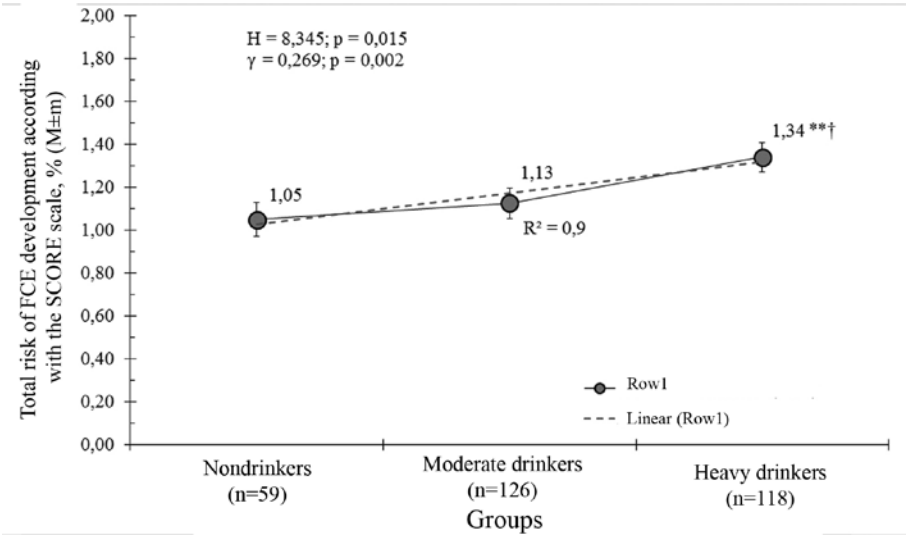

Figure 3. Total risk of FCE development during next 10 years in groups of male patients with different levels of alcohol consumption
Comment: R2 – coefficient of approximation significance, ** - p=0,008 vs the group of non-drinkers; † - p=0,017 vs the group of moderate drinkers; H – Kruskal-Wallis test; g – Goodman and Kruskal's rank correlation coefficient; paired comparisons have been performed using Mann-Whitney U-test (only the differences corresponding with the new critical level of significance corrected with the number of compared pairs 0,05/3=0,017 are shown).

Alcohol consumption length has the same duration independently on the levels of consumed alcohol. During analysis we paid attention not only on the fact of existence of differences between several groups, but also on the direction of changes in average RF levels (increase or decrease) moving from one group to another. Non-parametrical dispersion analysis (Kruskal-Wallis test) allowed detecting statistically highly significant differences of systolic BP (SBP), diastolic BP (DBP), TC, Apo-A1, UA, glucose, WC, HDL Ch, LDL Ch, Apo-B, HOMA-IR levels between the groups that proved the influence of the factor (in this case – the level of alcohol consumption) on dependent variables (mentioned above). At the same time we identified the growth of all mentioned characteristics' medians moving from the group of non-drinkers to the groups with the increased levels of alcohol consumption. Paired comparison revealed that SBP, DBP, TC, Apo-A1, UA and glucose levels in the groups of moderate and heavy drinkers were significantly higher than in the group of non-drinkers, and statistically significant differences in TC, HDL Ch, LDL Ch, ApoB and HOMA-IR existed only between the groups of non-drinkers and heavy drinkers. Statistically significant positive Goodman-Kruskal gammas also demonstrate the contingency of the majority of studied characteristics presented in the Table 4, excluding BH, ThC, pulse, LP(a) and CRP, with alcohol consumption levels. Alcohol influences many parameters listed in the Table 4, but alcohol have the biggest effect of moderate intensity on SBP, glucose and UA levels in blood.

Also the results of Kruskal-Wallis test demonstrate (Figure 3) that there are the differences of the value of total risk of fatal CVE between the groups ordered according with the increase of alcohol consumption levels. The highest total risk of fatal CVE development was present in the group of heavy drinkers comparing with the groups of non-drinkers and moderate drinkers. Linear trend line describes well enough the relation between total risk of fatal CVE and the levels of alcohol consumption. R^2 value = 0.9 indicates that the curve corresponds well with the obtained data. The higher probability of fatal CVE development in men with alcohol abuse comparing with non-drinkers and moderate drinkers can be proved with statistically significant Goodman-Kruskal gamma rank correlation coefficient. SBP impact on total risk of fatal CVE (Figure 4) is higher in the group of heavy drinkers comparing with non-drinkers and moderate drinkers, and the impact of TC on total CVE risk is higher in the groups of moderate and heavy drinkers comparing with non-drinkers, so it is not connected with the amount of consumed alcohol. The probability of AH development in male subjects consuming alcohol is 2,6 times higher than in non-drinkers (OR=2.6; 95% CI 1.1-5.9; p=0.029).

Discussion

In our study daily and weekly amount of consumed alcohol goes beyond the standard safe quantities of all alcoholic beverages [22-24]. Obtained results go along with the previously published data demonstrating that Russia is characterized with prevailed intake

Table 4. **Statistical average values of investigated characteristics in groups of male patients with different levels of alcohol consumption**

Characteristic	Statistical parameters	Groups			Gamma correlation	Kruskal-Wallis test	Multiple comparisons *
		Non-drinkers	Moderate drinkers	Heavy drinkers			
		(1)	(2)	(3)			
Age, years	M (SD)	43.1 (0.4)	42.9 (0.5)	42.9 (0.5)	— 0.109; p=0.041	H=8.204; p=0.017	p_{1-2}=0.009; p_{1-3}=0.009
	Me [25%-75%]	43.0 [42.8–43.3]	42.9 [42.6–43.2]	42.8 [42.6–43.2]			
Length of alcohol consumption	M (SD)	—	24.6 (3.4)	24.6 (2.8)	— 0.056; p=0.452	H=0.563; p=0.453	
	Me [25%-75%]	—	25.2 [23.4–26.6]	24.9 [23.0–26.4]			
BMI, kg/m^2	M (SD)	26.8 (5.0)	27.5 (4.7)	28.2 (4.7)	0.117; p=0.042	H=4.314; p=0.116	
	Me [25%-75%]	25.7 [23.5–31.6]	27.1 [24.0–30.2]	27.5 [24.8–31.3]			
WC, cm	M (SD)	91.9 (13.7)	93.2 (13.2)	96.5 (12.9)	0.148; p=0.010	H=6.806; [c] p=0.033	
	Me [25%-75%]	88.0 [83.0–106.5]	92.0 [84.0–102.0]	96.0 [87.0–104.0]			
WC/ThC	M (SD)	0.92 (0.08)	0.92 (0.09)	0.94 (0.07)	0.142; p=0.009	H=6.795; [c] p=0.033	p_{1-3}=0.016
	Me [25%-75%]	0.91 [0.86–0.97]	0.91 [0.87–0.99]	0.94 [0.89–1.0]			
WC/BH	M (SD)	0.51 (0.08)	0.52 (0.07)	0.54 (0.07)	0.149; p=0.008	H=6.996; [c] p=0.030	p_{1-3}=0.012
	Me [25%-75%]	0.50 [0.45–0.55]	0.52 [0.47–0.57]	0.54 [0.48–0.58]			
ASF, mm	M (SD)	28.3 (9.4)	29.2 (9.4)	31.4 (9.1)	0.144; p=0.012	H=6.290; [c] p=0.043	
	Me [25%-75%]	30.0 [20.6–37.0]	30.2 [23.0–38.4]	33.6 [26.0–40.0]			
SSF, mm	M (SD)	22.9 (10.0)	25.4 (9.7)	26.0 (9.7)	0.100; p=0.081	H=4.084; p=0.130	
	Me [25%-75%]	22.1 [14.3–29.7]	25.4 [17.4–32.1]	26.8 [18.4–33.7]			
TSF, mm	M (SD)	13.2 (6.8)	14.6 (6.9)	14.8 (6.9)	0.083; p=0.140	H=3.628; p=0.163	
	Me [25%-75%]	11.7 [8.0–17.1]	13.9 [10.0–17.8]	13.1 [10.3–18.0]			
SBP, mm Hg.	M (SD)	117 (12)	120 (14)	127 (16)	0.250; p<0.001	H=19.930; [b] p<0.001	p_{1-3}<0.001; p_{1-3}=0.001;
	Me [25%-75%]	117 [110.0–122.0]	119 [111.0–127.0]	124 [116.0–136.0]			
DBP, mm Hg.	M (SD)	79 (9)	81 (11)	85 (12)	0.204; p<0.001	H=13.737; [c] p=0.001	p_{1-3}<0.001; p_{1-3}=0.003;
	Me [25%-75%]	78 [74.0–84.0]	79 [73.0–87.0]	82 [77.0–91.0]			
Pulse, beats per minute	M (SD)	75 (9)	73 (10)	75 (10)	0.036; p=0.533	H=2.934; p=0.231	
	Me [25%-75%]	74 [68.0–88.0]	72 [68.0–80.0]	74 [68.0–82.0]			
TC, mmol/L	M (SD)	5.2 (1.0)	5.7 (1.1)	6.0 (1.4)	0.227; p<0.001	H=16.932; [c] p<0.001	p_{1-3}<0.001
	Me [25%-75%]	5.2 [4.4–5.7]	5.7 [4.8–6.5]	5.8 [5.1–6.7]			
HDL Ch, mmol/L	M (SD)	0.9 (0.3)	1.0 (0.3)	1.0 (0.3)	0.134; p=0.017	H=8.006; [c] p=0.018	p_{1-3}=0.006
	Me [25%-75%]	0.9 [0.7–1.0]	0.9 [0.8–1.2]	0.9 [0.8–1.2]			
LDL Ch, mmol/L	M (SD)	3.8 (1.0)	4.0 (1.1)	4.3 (1.3)	0.155; p=0.005	H=7.607; [c] p=0.022	p_{1-3}=0.010
	Me [25%-75%]	3.7 [3.1–4.4]	4.1 [3.3–4.7]	4.1 [3.4–5.1]			
TG, mmol/L	M (SD)	1.2 (0.7)	1.5 (1.0)	1.5 (1.0)	0.113; p=0.027	H=4.352; p=0.113	
	Me [25%-75%]	1.1 [0.8–1.5]	1.2 [0.7–1.9]	1.3 [0.9–1.7]			
Apo-A1, mg/dL	M (SD)	152.0 (22.4)	161.8 (26.6)	171.3 (35.8)	0.222; p<0.001	H=16.096; [c] p<0.001	p_{1-3}<0.001
	Me [25%-75%]	149.0 [136.0–163.0]	157.5 [143.0–178.0]	167.0 [149.0–190.2]			
Apo-B, mg/dL	M (SD)	98.8 (25.7)	100.9 (25.3)	107.7 (24.7)	0.166; p=0.002	H=9.094; [c] p=0.011	p_{1-3}=0.007; p_{1-3}=0.017;
	Me [25%-75%]	95.3 [83.0–111.0]	97.0 [84.8–116.0]	109.0 [91.0–124.3]			
LP (a), mg/dL	M (SD)	24.9 (35.1)	22.8 (32.7)	39.0 (53.0)	0.049; p=0.400	H=1.358; p=0.507	
	Me [25%-75%]	9.2 [5.3–21.9]	9.5 [5.4–21.4]	10.1 [4.9–64.1]			
CRP, mg/L	M (SD)	3.4 (3.2)	3.8 (3.7)	4.2 (4.1)	0.104; p=0.078	H=3.488; p=0.175	
	Me [25%-75%]	2.1 [1.6–4.8]	2.6 [1.9–4.2]	3.0 [2.1–4.5]			
UA, mg/dL	M (SD)	5.9 (1.2)	6.3 (1.4)	6.8 (1.3)	0.248; p<0.001	H=18.838; [b] p<0.001	p_{1-3}<0.001; p_{1-3}=0.003;
	Me [25%-75%]	5.9 [5.0–6.6]	6.1 [5.5–7.1]	6.8 [6.0–7.6]			
Glucose, mmol/L	M (SD)	4.8 (0.4)	5.2 (1.4)	5.4 (1.2)	0.305; p<0.001	H=27.166; [b] p<0.001	p_{1-3}<0.001; p_{1-3}=0.001;
	Me [25%-75%]	4.8 [4.6–5.2]	4.9 [4.7–5.3]	5.2 [4.9–5.7]			
TyG-index	M (SD)	8.3 (0.5)	8.5 (0.7)	8.6 (0.6)	0.161; p=0.001	H=8.672; [c] p=0.013	p_{1-3}=0.003
	Me [25%-75%]	8.4 [8.0–8.6]	8.5 [8.0–9.0]	8.6 [8.2–8.9]			
Insulin, μE/mL	M (SD)	8.2 (4.8)	8.6 (5.1)	9.9 (6.8)	0.118; p=0.039	H=4.296; p=0.117	
	Me [25%-75%]	6.9 [5.0–10.6]	7.2 [5.5–10.4]	8.1 [5.7–11.7]			
HOMA-IR	M (SD)	1.77 (1.11)	2.04 (1.39)	2.41 (1.91)	0.160; p=0.004	H=8.061; [c] p=0.018	p_{1-3}=0.008
	Me [25%-75%]	1.46 [1.05–2.17]	1.56 [1.16–2.50]	1.89 [1.37–2.71]			

Comment: * — Paired comparison was performed using Mann-Whitney test with p-values correction for multiple comparisons using Bonferroni method. Results of multiple comparison are based on two-sided tests with the new critical level of significance: 0.05/3=0.017. Size of alcohol consumption levels' effect: a — big, b — medium, c— small.

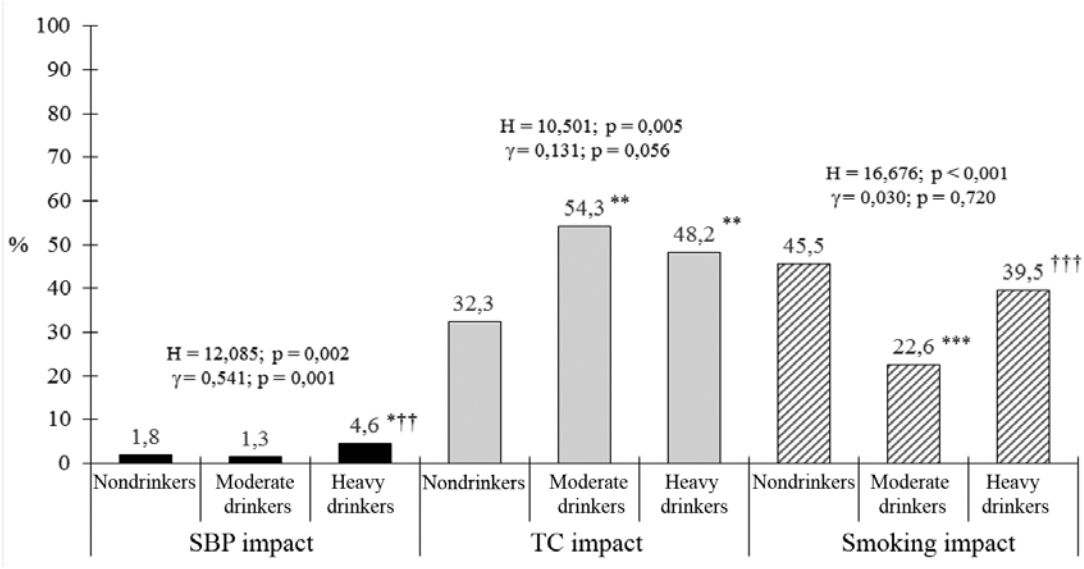

Figure 4. SBP, TC and smoking impact on total risk of FCE in groups of male patients with different levels of alcohol consumption. Comment: * - p=0,015 vs the group of non-drinkers; ** - p<0,01 vs the group of non-drinkers; *** - p<0,001 vs the group of non-drinkers; †† - p<0,01 vs the group of moderate drinkers; ††† - p<0,001 vs the group of moderate drinkers; H – Kruskal-Wallis test; g – Goodman and Kruskal's rank correlation coefficient; paired comparisons have been performed using Mann-Whitney U-test (only the differences corresponding with the new critical level of significance corrected with the number of compared pairs 0,05/3=0,017 are shown).

of strong alcohol drinks and beer – rarely but in big quantities [23, 24]. This fact is reflected in the results of big prospective study that had been performed in Russia during the last decade. It demonstrated that the major cause of premature death of adult RF population in the category of mortality due to external causes is the excessive alcohol consumption, vodka in particular [25].

It is interesting to mention the fact that the group of moderate drinkers in our study has the biggest number of smokers and the smallest levels of PA. Other works demonstrated that smoking becomes more intense and frequent according with the increase of amount of consumed alcohol [7]. This fact should be studied more precisely.

There is the correlation of AH frequency and hyper-Ch with alcohol consumption levels. These results are proved with international studies. The only difference is related to the fact, that several studies pointed out the positive influence of regular intake of small amounts of alcohol on TG and TC levels and that these works did not demonstrate the relation between DLP and amount of consumed alcohol drinks [6, 7, 15, 26].

Numerous studies demonstrate that there is the strong direct correlation between the patterns of alcohol consumption with WC and Ob, and this linkage is present particularly in males. The strongest correlation was identified for beer and strong alcohol drinks, whereas this correlation with wine has not been identified. There are some contradictory results demonstrating how different doses of alcohol influence the characteristics of carbohydrate metabolism, metabolic syndrome and DM 2 type development. The majority of the researchers agree that high doses of alcohol increase basal and postprandial glucose and insulin levels and also UA concentration, unlike the lower doses which can prevent DM 2 type development [7, 8, 27-29].

Impact of alcohol consumption on AH development is widely discussed in scientific literature. All works with no exception demonstrate correlation between AH and the mode of alcohol drinks consumption. Systematic alcohol drinks consumption in toxic doses causes the change of metabolic processes occurring in liver and oxidative stress that triggers a complicated cascade of reactions leading to liver cirrhosis, pancreatitis and HB. In particular, it is typical for young men [9-11, 30-32).

Talking about total risk of fatal CVE development, the majority of studies indicate that heavy drinkers have higher risk of CVD and non-infection diseases related mortality comparing with non-drinkers and moderate drinkers [5, 33-38]. This risk goes up along with the increase of consumed alcohol drinks amount, and hard periodic drinking does not increase total mortality, but it influences just the mortality due to alcohol-related causes and just in males [5] Excessive alcohol consumption influences mortality in males aged 70-89 years [34]. More than that, reduction of alcohol consumption by 18g of absolute ethanol per day allows decreasing mortality rate by 43%, and the higher was the initial amount of alcohol

consumption the more effective and useful for mortality rate reduction would be the effect of decreased alcoholic beverages intake [35,37].

Some studies demonstrate also the threshold amount of alcohol consumed per day (24 g) after exceeding which mortality risk starts to increase [18]. It is worth to mention that there are the studies that suggest that heavy drinkers have less mortality rate comparing with non-drinkers [38]. In our population average total risk of fatal CVE development increases along with the increase of amount of consumed alcohol drinks (from 1,1 to 1,4%). This risk had the smallest value in the group of non-drinkers and the highest value in the group of heavy drinkers (Figure 3).

During the last 30 years the question of cardioprotective effect of regular intake of alcohol in small amounts is widely discussed in literature. Numerous studies demonstrated inverse relation between moderate alcohol beverages consumption and the risk of fatal CVE development [5, 13-15, 36, 39-41]. In this study we identified also lower risk of fatal CVE (Figure 3) in the group of moderate drinkers comparing with the group of heavy drinkers.

As it has been previously shown, SBP, TC and smoking have the biggest impact on fatal CVE development. In the current study TC and smoking have the strongest impact on CVD mortality risk. In non-drinkers smoking had the strongest influence and TC had the least impact. The situation in moderate drinkers was directly opposite. Difference between these two groups is statistically significant. Although SBP has a small impact on fatal CVE risk formation in general, heavy drinkers are the most likely to develop fatal CVE due to increased SBP (Figure 3).

Conclusion

Results of this study demonstrated that the majority of male patients aged 42-44 years consume alcohol, at the same time around 40% of participants take alcohol beverages in quantities dangerous for health. It has been shown that the frequency of abdominal Ob, AH and blood lipid spectrum goes up with the increase of alcohol consumption. It has been identified that in males with the same length of alcohol consumption amount of consumed alcohol influences directly SBP, DBP, TC, ApoA1, UA and blood glucose levels. Alcohol has the most prominent effect on SBP, UA and glucose blood levels (medium level of effect). Though total risk of fatal CVE development is linked with the amount of consumed alcohol, its value depends more on other CVD RF like TC levels and smoking.

Conflict of interest: None declared

References

1. Ivanova AE, Korneshov AA. Tendencies and consequences of alcogol abuse among the population. Sotsial'nye aspekty zdorov'ya naseleniya [serial online] 2010; 14(2). Available from: http://vestnik.mednet.ru/content/view/187/30/lang,ru/ [accessed 16 July 2016]. Russian
2. World Health Organization. Global Status Report on Alcohol and Health, 2014. Available from: http://gtmarket.ru/ratings/rating-countries-alcohol-consumption/info [accessed 15 July 2016].
3. Shield KD, Rehm J. Russia-specific relative risks and their effects on the estimated alcohol-attributable burden of disease. BMC Public Health 2015;15:482. doi: 10.1186/s12889-015-1818-y.
4. McKee M, Britton A. The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms. J R Soc Med 1998; 91(8): 402-7.
5. Bobak M, Malyutina S, Horvat P, et al. Alcohol, drinking pattern and all-cause, cardiovascular and alcohol-related mortality in Eastern Europe. Eur J Epidemiol 2016; 31: 21–30.
6. Kwon YJ, Kim SE, Park BJ, et al. High-risk drinking is associated with dyslipidemia in a different way, based on the 2010-2012 KNHANES. Clin Chim Acta. 2016; 456: 170-5.
7. Schröder H, Morales-Molina JA, Bermejo S, et al. Relationship of abdominal obesity with alcohol consumption at population scale. Eur J Nutr. 2007; 46(7): 369-76.
8. Vadstrup ES, Petersen L, Sørensen TIA, Grønbaek M. Waist circumference in relation to history of amount and type of alcohol: results from the Copenhagen City Heart Study. Int J Obes. 2003; 27: 238–46.
9. Ansari RA, Husain K, Rizvi SA. Role of Transcription Factors in Steatohepatitis and Hypertension after Ethanol: The Epicenter of Metabolism. Biomolecules. 2016; 6(3). pii: E29.
10. Nadkarni A, Weiss HA, Naik A, et al. The six-year outcome of alcohol use disorders in men: A population based study from India. Drug Alcohol Depend. 2016; 162: 107-15.
11. Fan AZ, Li Y, Elam-Evans LD, Balluz L. Drinking pattern and blood pressure among non-hypertensive current drinkers: findings from 1999-2004 National Health and Nutrition Examination Survey. Clin Epidemiol. 2013; 5: 21-7.
12. WHO Media centre. Alcohol. Fact sheet Updated January 2015. Russian. Available from: http://www.who.int/mediacentre/factsheets/fs349/ru/ [accessed 16 July 2016]. Russian
13. Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits. BMJ. 1996; 312(7033): 731-6.
14. Gémes K, Janszky I, Laugsand LE, et al. Alcohol consumption is associated with a lower incidence of acute myocardial infarc-

tion: results from a large prospective population-based study in Norway. J Intern Med. 2016; 279(4): 365-75.
15. Kojima S, Ito H, Takashimizu S, et al. The Influence of Drinking Based on Data from Health Check-up. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2015; 50(3): 144-57.
16. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35(8): 1381-95.
17. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms – 2005. Available from: http://www.ipaq.ki.se/ [accessed 23 April 2016].
18. Alexandri AL, Konstantinov VV, Deev AD, et al. Alcohol consumption and its link with cardiovascular mortality in 40-59 year old males (data of a 21.5 year prospective study). Terapevticheskiĭ arkhiv 2003; 75(12): 8–11. Russian
19. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33: 1635–1701.
20. Vadasova B, Cech P, Smerecka V, et al. Overweight and obesity in Slovak high school students and body composition indicators: a non-randomized cross-sectional study. BMC Public Health. 2016; 16(1): 808.
21. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York, NY: Routledge Academic. 1988.
22. International Centre for Alcohol Policies. ICAP Reports 5. What is a "standard drink"? September 1998.
23. Zakharov VV. Alcohol abuse: neurological complications and current therapeutic approaches. Effektivnaya farmakoterapiya 2014; 8: 36-43). Russian
24. Ostroumova OD. Alcohol – friend or foe? Effektivnaya farmakoterapiya 2013; 49: 8-12. Russian
25. Zaridze D, Brennan P, Boreham J, et al. Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. Lancet 2009; 373(9682): 2201-14.
26. Vu KN, Ballantyne CM, Hoogeveen RC, et al. Causal Role of Alcohol Consumption in an Improved Lipid Profile: The Atherosclerosis Risk in Communities (ARIC) Study. PLoS One. 2016; 11(2): e0148765.
27. Sayon-Orea C, Bes-Rastrollo M, Nuñez-Cordoba JM, et al. Type of alcoholic beverage and incidence of overweight/obesity in a Mediterranean cohort: theSUN project. Nutrition. 2011; 27(7-8): 802-8.
28. Stoutenberg M, Lee DC, Sui X, et al. Prospective study of alcohol consumption and the incidence of the metabolic syndrome in US men. Br J Nutr. 2013; 110(5): 901-10.
29. Sun K, Ren M, Liu D, et al. Alcohol consumption and risk of metabolic syndrome: a meta-analysis of prospective studies. Clin Nutr. 2014; 33(4): 596-602.
30. Ostroumova OD, Saperova EV. Alcohol and arterial hypertension. Ratsional'naya farmakoterapiya v kardiologii 2014; 10(1): 79-82. Russian
31. Li Z, Bai Y, Guo X, et al. Alcohol consumption and cardiovascular diseases in rural China. Int J Cardiol. 2016; 215: 257-62.
32. Wellman RJ, Vaughn JA, Sylvestre MP, et al. Relationships Between Current and Past Binge Drinking and Systolic Blood Pressure in Young Adults. J Adolesc Health. 2016; 58(3): 352-7.
33. Wakabayashi M, McKetin R, Banwell C, et al; Thai Cohort Study Team. Alcohol consumption patterns in Thailand and their relationship with non-communicable disease. BMC Public Health. 2015; 15: 1297.
34. Almeida OP, McCaul K, Hankey GJ, et al. Excessive alcohol consumption increases mortality in later life: a genetic analysis of the health in men cohort study. Addict Biol. 2015 Dec 8. doi: 10.1111/adb.12340.
35. Rehm J, Roerecke M. Reduction of Drinking in Problem Drinkers and All-Cause Mortality. Alcohol Alcohol. 2013; 48(4): 509-13.
36. Sasaki S. Alcohol and its relation to all-cause and cardiovascular mortality. Acta Cardiol 2000; 55(3): 151-6.
37. Laramée P, Leonard S, Buchanan-Hughes A, et al. Risk of All-Cause Mortality in Alcohol-Dependent Individuals: A Systematic Literature Review and Meta-Analysis. EBioMedicine. 2015; 2(10): 1394-404.
38. Wannamethee G, Shaper A. G. Alcohol and sudden death. Br Heart J. 1992; 68(5): 443-448.
39. Klatsky AL. Alcohol and cardiovascular health. Physiol Behav. 2010; 100(1): 76-81.
40. Wandeler G, Kraus D, Fehr J, Conen A, et al; Swiss HIV Cohort Study. The J-Curve in HIV: Low and Moderate Alcohol Intake Predicts Mortality but Not the Occurrence of Major Cardiovascular Events. J Acquir Immune Defic Syndr. 2016; 71(3): 302-9.
41. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. Addiction. 2012; 107(7): 1246-60.

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REVIEW ARTICLE

Detection of viable myocardium in patients with ischemic myocardial dysfunction: modern possibilities and practical value

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Summary

This article observes modern methods of viable myocardium detection in patients with ischemic heart disease. The article reviews diagnostic possibilities of positron emission tomography, single-photon emission tomography, cardiovascular magnetic resonance and stress echocardiography and describes the role of viability imaging in current clinical practice. Viability testing along with a number of clinical factors plays a key role in the treatment of patients with ischemic myocardial dysfunction. This article discusses the results of clinical studies dedicated to the study of evaluation of the viable myocardium before myocardial revascularization. The review observes literature data demonstrating that cardiac resynchronization therapy inefficacy might be related to the lack of viable myocardium at the segments targeted by the left ventricle lead.

Keywords

Ischemic myocardial dysfunction, myocardial viability, nuclear imaging, magnetic resonance, stress echocardiography.

Despite the progress of medical science, coronary heart disease (CHD) and myocardial dysfunction caused by it remain an important problem of modern cardiology [1, 2]. Myocardial dysfunction together with its structural remodeling and several neurohormonal systems activations are the key pathogenetic elements of heart failure progression and development [2].

It has been proved that myocardial contractility reduction is connected not only with scar changes but also with reversible myocardial dysfunction [3]. These myocardial areas contrain cardiomyocytes that do not contract actively but maintain minimal oxygen consumption and main cellular metabolism components, so they stay "alive", but at the same time are kept in reserve [4]. Therefore, influencing reversible dysfunction can become a promising direction of pharmaco-

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logical and surgical treatment [5]. This consideration makes it important to detect viable myocardium.

There are two forms of myocardial ischemic dysfunction with potentially reversible contractility reduction: hibernation and stunning [6, 7]. The difference between these variants appears after myocardial blood flow estimation: in hibernation blood flow in rest is reduced, whereas in chronic stunning the blood flow in rest can be preserved, but blood flow reserve is lowered [8].

In practice stunning and hibernation can coexist and it is not necessary to differentiate them, since both types of myocardial dysfunction are reversible, both when after blood flow is reestablished and after the normalization of balance between oxygen delivery and consumption by myocardium [9]. The presence of preserved cellular metabolism and contractility reserve allowed to unite the variants of reversible cardiac muscle dysfunction under the term "viable myocardium" [10].

Main viable myocardium characteristics (Table 1) like the presence of contractility reserve and metabolic activity, preserved perfusion and cardiomyocyte cell membrane integrity underlie its non-invasive diagnostics using various techniques of cardiovascular visualization [11]. It is also possible to detect viability of dysfunctional myocardium indirectly excluding nonviable (scar) tissue [12].

Table 1. **Viable myocardium diagnostic techniques**

Diagnostic principle	Diagnostic technique
Evidences of the presence of myocardial metabolic activity	Positron emission tomography (PET) of the heart with fluorodeoxyglucose
Estimation of myocardial perfusion and cardiomyocyte cell membrane integrity	Radioisotope heart scan – single photon emission computer tomography (SPECT) with ^{201}Tl and ^{99m}Tc-containing drugs.
Detection of myocardial contractility reserve	Stress-echography with dobutamine, dobutamine stress magnetic resonance imaging (MRI)
Evidence of the presence of viable myocardium excluding non viable (scar) tissue	Heart MRI with contrast use

Cardiac PET

Nowadays PET is taking the key role in viable myocardium diagnostics. PET is based on the use of radiopharmaceuticals (RP) tagged with isotopes – positron emitters [13]. Unlike traditional techniques of nuclear medicine, RP used in PET are made of isotopes of important biological atoms and molecules (oxygen, carbon, nitrogen, glucose) that are natural metabolites of organism [14, 15]. PET images reflect RP distribution in examined organ and allow to estimate cellular metabolism, blood flow and myocardial perfusion [15, 16]. Introduction of hybrid scanners that unite PET and computer tomography (CT) (PET/CT) and MRI (PET/MRI) can give additional opportunities for complex estimation of structural and functional heart changes in patients with coronary pathology [13].

18-fluorodeoxyglucose (^{18}F-FDG) is used as a RP for viable myocardium detection in PET [14]. Modern estimation of myocardial perfusion and glucose consumption in different myocardial segments allows to detect both nonviable myocardium areas (scar tissue) – lowered perfusion and glucose intake – and viable tissue – normal or elevated glucose consumption in lowered perfusion zone [16].

Estimation of perfusion in viable myocardium diagnostics

Radioisotope techniques of perfusion estimation can be used for viable myocardium detection (myocardial perfusion scintigraphy, SPECT) [17]. These methods are based on estimation of intravenously administered RP distribution in cardiac muscle that enters undamaged cardiomyocytes proportionally with coronary blood flow [11]. Myocardial parts with normal perfusion create the image of homogenous RP distribution, whereas myocardial zones with relative or absolute blood flow reduction due to ischemia or scar damage have lowered RP incorporation in place of perfusion defects [17]. RP distribution in myocardium depends on perfusion by itself, sarcolemma integrity and preserved cellular metabolism [11]. Nowadays thallium chloride (^{201}Tl) and technetium-based drugs (^{99m}Tc) are main RP for estimation of perfusion in SPECT [18].

Thallium chloride ^{201}Tl, biological analogue of potassium, that enters cardiomyocytes like potassium through Na+/K+ ATPase [18]. Early distribution pattern is proportional to blood flow, whereas late distribution pattern indicates the tissue with undamaged intra/extracellular gradient, which allows to differentiate viable and nonviable (scar) myocardium [11, 19].

Two separate injections are used for ^{99m}Tc-labeled RP since these drugs do not allow to determine redistribution in myocardium after single administration [18, 20]. Viable myocardium diagnostics in this case is performed using nitroglycerine test [21]. There are some data about possible use of ^{99m}Tc-labeled RP in SPECT combined with pharmacological dobutamine test [22].

Fatty acids labeled with iodine-123 (^{123}I) are considered to be another RP for viable myocardium detection [23]. Their mechanism of action, unlike perfu-

sion agents, is directed to myocardium metabolism estimation [24]. Normal myocardium metabolizes fatty acids instead of glucose, whereas myocardial segments with reversible dysfunction consume glucose that causes defects in fatty acids perfusion [25]. Combined use of RP for estimation of perfusion and metabolism allows detecting the difference between the condition of perfusion and metabolism in the same zones of the heart – so-called perfusion-metabolic discrepancy which corresponds with viable myocardium zones [24, 26].

Stress-echography in viable myocardium diagnostics

Examination of myocardial systolic function using echography in rest does not allow to determine if the segments with impaired kinetics can be considered as viable or scar tissure [27]. The only exception is improvement of viable myocardial segments contractility after postextrasystolic contraction [28, 29].

The presence of positive inotropic reserve that is expressed as increased contractility in response to inotropic stimulation is an important feature of reversible myocardial dysfunction [30].

This sign allows to stress-echocardiography for viable myocardium verification [11]. Unlike it, nonviable myocardium (scar) would not improve contractility (negative inotropic reserve) [31].

Tests with pharmacological agents that either increase contractility (dobutamine 5-10 μg/kg/min) or redistribute coronary blood flow causing coronary steal syndrome (dipyridamole 0.28 mg/kg) are used to identify viable myocardium during stress-echocardiography [11].

Techniques based on tissue dopplerography that analyze velocity of motion, deformation speed and myocardial deformation are used for regional myocardial kinetics estimation [32, 33, 34]. Despite obvious advantages comparing with semi-quantitative estimation of regional kinetics in echography, these techniques based on Doppler's effect have several limitations: their result depends on angle of scanning, movement of adjacent myocardial areas and heart movements by themselves cause errors in measurements [11].

During the last years the analysis of myocardial deformation with speckle-tracking technique is used in stress-echocardiography for quantitative estimation of myocardial kinetics [35]. This technique is not based on Doppler's effect, that's why it has no disadvantages of tissue dopplerography [36]. Several studies demonstrated high informativeness of this method for detection not only viable myocardium, but also scar tissue [37].

Heart MRI in viable myocardium diagnostics

Heart MRI with dobutamine test can be used for viable myocardium diagnostics [38]. Stress MRI with dobutamine test is based on the same principles of contractility reserve estimation as stress-echocardiography and is performed according with a similar protocol. At the same time stress MRI has the advantage of high spatial resolution and reproducibility comparing with stress-echocardiography [38].

Another way to distinguish reversible and irreversible myocardial damage using gadolinium chelates as contrast agents is MRI [39, 40]. In this case paramagnetic contrast agent based on gadolinium is accumulated in necrotic nonviable myocardium [12]. Possible cause of scar-changed myocardium contrasting can be the change of gadolinium kinetics due to increased volume of extracellular fluid because of damage of cardiomyocyte membreanes. High spatial resolution, possibility to obtain information without stress test and absence of radiation exposure are the advantages of contrast-enhanced MRI [40].

Viable myocardium diagnostics before revascularization operations in left ventricle (LV) ischemic dysfunction

Surgical myocardial revascularization is widely used in patients with CHD [41]. According with the modern guidelines, the decision about revascularization should be based on verification of significant coronary arteries stenosis, degree of ischemia caused by it and estimation of expected benefit for prognosis and/or improvement of clinical symptoms [42]. One of important predictors of coronary bypass grafting surgery (CBGS) efficacy is LV dysfunction [43]. It has been shown that CBGS promotes more significant improvement of CHD patients' survival in case of more severe manifestations and presence of LV dysfunction [42].

At the same time patients with severe LV dysfunction (LV ejection fraction <35%) and heart failure are the most difficult category of patients with CHD from myocardial revascularization point of view due to increased perioperative mortality [41]. Therefore, viable myocardium detection in these patients could in theory increase treatment efficacy. More than 100 nonrandomized studies that involved more than 3 thousands patients have proved it. Prognostic precision of

Table 2. **Prediction of global contractility improvement after revascularization using different viable myocardium diagnostic techniques (J.J. Bax andV. Delgado, 2015)**

Method	Number of studies	Number of patients	Sensitivity, %	Specificity, %
PET with ^{18}F-FDG	24	756	92	63
^{201}Tl	40	1119	87	54
^{99m}Tc	25	721	83	65
Stress-echocardiography with dobutamine	41	1421	80	78
Stress-MRI with dobutamine	9	272	74	82
Contrast-enhanced MRI	5	178	84	63

different viable myocardium diagnostic methods for improvement of global contractility after revascularization according with the results of main observation studies [44] is demonstrated in the Table 2.

Meta-analysis of 24 studies that involved in total 3088 persons with ischemic systolic LV dysfunction, demonstrated that patients with viable myocardium who took pharmacological treatment had the highest mortality rate between all subgroups. At the same time, if there was viable myocardium relative mortality reduction in case of revascularization comparing with pharmacological treatment was around 80%, and in case of its absence relative mortality reduction was 51% [45]. Other studies had similar results together with the possibility to detect viability for prediction of regional and global LV systolic function improvement and increased stress tolerance after revascularization [46].

However the results of major multicenter studies PARR-2 (The PET and Recovery Following Revascularization) and STICH (Surgical Treatment of IsChemic Heart failure) that estimated myocardium viability in patients with CHD were controversial.

Multicenter randomized trial PARR-2 involved 428 patients with LV ejection fraction <35% and suspected CHD that had been randomized into the groups where revascularization was planned according with viable myocardium diagnostics using PET with ^{18}F-FDG and where viable myocardium verification was not considered crucial for treatment tactics [47].

Results of PARR-2 study did not demonstrate significant reduction of cardiac events in patients for whom the decision about revascularization was based on results of viable myocardium tests comparing with the group of standard referral to vascularization. After one year the percentage of patients who survived one of endpoints (cardiac death, myocardial infarction, admission to hospital due to heart pathology) was 30% in "PET strategy" group versus 36% in "standard treatment strategy" group (relative risk 0.82%, 95% confidence interval (CI) 0.59-1.14; p=0.16) [47].

It is necessary to keep in mind that in this study there were deviations from treatment strategy based on PET results in 25% of cases [48]. In particular, the main reasons to renounce revascularization were cardiac events, comorbidity and renal failure [47].

At the same time PARR-2 study revealed significant differences of RR between patient referred and not referred to revascularization after PET diagnostics of viable myocardium (RR=0.62; 95% CI 0.42-0.93; p=0.019) [47]. More than that, significant reduction of cardiac death was obtained in the group of patients with LV systolic dysfunction referred for revascularization due to the presence of viable myocardium without preceding coronary angiography comparing with the patients who previously underwent coronary angiography. Patients who underwent viable myocardium diagnostics without coronary angiography were characterized with lower LV ejection fraction: 25.5±7.6 vs 27.5±7.7 (p<0.01) [47]. These results demonstrate that PET can be useful for optimal selection of patients with severe LV systolic dysfunction for revascularization and also to reduce the necessity of coronary angiography performing in case if there are no evidences of viable myocardium presence.

One of directions of multicenter randomized trial STICH was dedicated to the efficacy of viable myocardium evaluation for survival prognosis in patients with CHD and LV dysfunction before CBGS [44]. 1212 patients had been involved into this study, 601 patients underwent viable myocardium diagnostics using stress-echocardiography with dobutamine, SPECT or both techniques. These patients had been randomized into two groups: pharmacological treatment and CBGS (n=298) and only pharmacological treatment (n=303) [49].

As it was expected, mortality rate was significantly higher in patients without viable myocardium (51%) comparing with the patients who had viable myocardium (37%) (RR=0.64; 95% CI 0.48-0.86; p=0.003) [49]. However the connection between the presence of viable myocardium and mortality appeared to be non-significant (p=0.21) after the correction for other initial

parameters (LV ejection fraction, LV volumes, intensity of symptoms, signs of more severe disease) [49].

Although the STICH study had been organized in quite precise way, there were several features of its design that could have affected the results.

First of all, myocardial viability had been estimated not in all patients. Consequently, natural distribution of viable and non-viable myocardium zones could have been not respected in this category of patients.

In the second place, viable myocardium diagnostics has been performed using different methods: stress-echocardiography and SPECT with ^{99}Tc, they have different underlying principles and different diagnostic value. More than that, the most sensitive technique of viable myocardium diagnostics – PET with ^{18}F-FDG – and the most precise method of scar detection – contrast-enhanced MRI– have not been used.

Thirdly, this study took into account just the fact of viable myocardium presence and not its volume. Although the results indicating that global LV function can be restored only if liminal volume of viable myocardium is present are actively discussed nowadays.

Finally, the results of viable myocardium diagnostics in the STICH study did not influence on the choice of treatment method, unlike the PARR-2 study discussed above.

Taking into account all existing limitations of this study, its results cannot be considered as a sufficient reason to refuse viable myocardium diagnostics [44]. Absence of strong correlations between myocardium viability and CBGS benefit in this study can indicate that the choice of treatment tactics in patients with ischemic systolic LV dysfunction should be based not only viable myocardium diagnostics, but also on estimation of a wider range of factors (dimensions, LV shape, etc).

The results of performed multicenter and observation randomized studies allowed to the experts of European Society of Cardiology (ESC) and European Association for Cardio-Thoracic surgery (EACTS) to select myocardial revascularization in patients with CHD and LV systolic dysfunction (LV ejection fraction <35%) only in case of viable myocardium presence as a IIa class of recommendations with B level of evidence [41].

Viable myocardium diagnostics before cardiac resynchronization therapy

During the last years cardiac resynchronization therapy (CRT), an electrophysiological method of chronic heart failure treatment based on biventricular electrical cardiac stimulation, has become widespread. Numerous multicenter studies have proved the positive effect of CRT on hemodynamics, life quality, physical exercise tolerability and prognosis in patients with severe chronic heart failure (III-IV functional class) with low ejection fraction (<35%), enlarged LV and the presence of electrical dyssynchrony (QRS>120 ms) [50, 51].

However in case of standard selection of patients for CRT the efficacy of treatment of up to 30% of patients can remain low [52]. This is so-called category of patients not responding to this kind of heart failure treatment (non-responders). Because of this new approaches for selection of patients for CRT have been developed during the last years [53]. It has been shown that the electrode for LV electrical stimulation should be located in the place of the latest mechanical activation and outside the scar area [54]. Consequently, viable myocardium verification (lack of scar changes) in patients with cardiac failure of ischemic genesis can be an objective of patients' investigation before planned intervention.

Echocardiography estimation of myocardial deformation using speckle-tracking technique [54, 55] and myocardial perfusion analysis using SPECT [56, 57] are considered as techniques allowing to define optimal position of left ventricular electrode based on scar zones detection in patients who are supposed to be referred to CRT.

Conclusion

Viable myocardium detection in patients with LV ischemic dysfunction is an important problem of clinical medicine that has been reflected in European guidelines on myocardium revascularization. The presence of viable myocardium gives a chance for using such effective treatment methods like CBGS and CRT. At the same time the results of major studies make it possible to suggest individual decision on each patient individually taking into account other clinical factors.

Modern cardiology provides many highly informative techniques for viable myocardium detection. At the same time it is necessary to perform additional prospective clinical studies to find the role of these techniques in complex examination of patients with LV ischemic dysfunction.

Conflict of interest: None declared

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: A report from the American Heart Association. Circulation. 2015; 131(4): e29-322.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016. pii: ehw128.
3. Nikiforov VS, Nikitin AE, Tirenko VV, Svistov AS. Ischemic myocardial dysfunction. Moscow: APKiPPRO. 2005. Russian
4. Gowda RM., Khan IA, Vasavada BC, et al. Reversible myocardial dysfunction: basics and evaluation. Int J Cardiol. 2004; 97(3): 349-53.
5. Soman P, Udelson JE. Prognostic and therapeutic implications of myocardial viability in patients with heart failure. Curr Cardiol Rep. 2004; 6(3): 211-6.
6. Rahimtoola SH. Concept and evaluation of hibernating myocardium. Annu Rev Med. 1999; 50: 75-86.
7. Ambrosio G, Tritto I. Clinical manifestations of myocardial stunning. Coron Artery Dis. 2001; 12(5): 357-61.
8. Redwood SR, Ferrari R, Marber MS. Myocardial hibernation and stunning: from physiological principles to clinical practice. Heart. 1998; 80: 218-22.
9. Canty JM, Fallavollita JA. Chronic hibernation and chronic stunning: a continuum. J Nucl Cardiol. 2000; 7(5): 509-27.
10. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation and assessment of myocardial viability. Circulation. 2008; 117: 103-14.
11. Nikiforov VS. Methods of cardiovascular visualization for diagnostic of viable myocardium in patients with ischemic heart disease. Saint Petersburg.: KultInformPress. 2012. Russian
12. Yang T, Lu MJ, Sun HS, et al. Myocardial scar identified by magnetic resonance imaging can predict left ventricular functional improvement after coronary artery bypass grafting. PLoS One. 2013; 8(12): e81991.
13. Anagnostopoulos C, Georgakopoulos A, Pianou N, Nekolla SG. Assessment of myocardial perfusion and viability by positron emission tomography. Int J Cardiol. 2013; 167(5): 1737-49.
14. Ghesani M, Depuey EG., Rozanski A. Role of F-18 FDG Positron emission tomography (PET) in the assessment of myocardial viability. Echocardiography. 2005; 22(2): 165-77.
15. Gropler RJ, Soto P. Recent advances in cardiac positron emission tomography in the clinical management of the cardiac patient. Curr Cardiol Rep. 2004; 6(1): 20-6.
16. Mehta D, Iskandrian AE. Myocardial viability: nuclear assessment. Echocardiography. 2005; 22(2): 155-64.
17. Travin MI, Bergmann SR. Assessment of myocardial viability. Semin Nucl Med. 2005. 35(1): 2-16.
18. Won KS, Song BI. Recent trends in nuclear cardiology practice. Chonnam Med J. 2013; 49(2): 55-64.
19. Duncan BH, Ahlberg AW, Levine MG, et al. Comparison of electrocardiographic-gated technetium-99m sestamibi single-photon emission computed tomographic imaging and rest-redistribution thallium-201 in the prediction of myocardial viability. Am J Cardiol. 2000; 85(6): 680-4.
20. Barrington SF, Chambers J, Hallett WA, et al. Comparison of sestamibi, thallium, echocardiography and PET for the detection of hibernating myocardium. Eur J Nucl Med Mol Imaging. 2004; 31(3): 355-61.
21. Senior R, Kaul S, Raval U, et al. Impact of revascularization and myocardial viability determined by nitrate-enhanced Tc-99m sestamibi and Tl-201 imaging on mortality and functional outcome in ischemic cardiomyopathy. J Nucl Cardiol. 2002; 9 (5): 454-62.
22. Yamagishi H1, Akioka K, Hirata K, et al. Dobutamine stress electrocardiography-gated Tc-99m tetrofosmin SPECT for detection of viable but dysfunctional myocardium. J Nucl Cardiol. 2001; 8(1): 58-67.
23. Verani MS, Taillefer R, Iskandrian AE, et al. 123I-IPPA SPECT for the prediction of enhanced left ventricular function after coronary bypass graft surgery. Multicenter IPPA Viability Trial Investigators. 123I-iodophenylpentadecanoic acid. J Nucl Med. 2000; 41(8): 1299-307.
24. Soukhov VY, Nikiforov VS, Nikitin AE, et al. Predictive value of myocardial perfusion and metabolism studies for prognosis of surgical revascularization efficacy. Eur J Nucl Med Mol Imaging. 2005; 32(1): Suppl: S56.
25. Tamaki N, Yoshinaga K. Novel iodinated tracers, MIBG and BMIPP, for nuclear cardiology. J Nucl Cardiol. 2011; 18(1): 135-43.
26. Fujita K, Kasama S, Kurabayashi M. Serial dual single-photon emission computed tomography of thallium-201 and iodine-123 beta-methyliodophenyl pentadecanoic acid scintigraphy can predict functional recovery of patients with coronary artery disease after coronary artery bypass graft surgery. Nucl Med Commun. 2015; 36(2): 148-55.
27. Zaharova AI, Nikiforov VS, Svistov AS. Diagnostic possibilities of echocardiography in patients with ischemic heart disease. Regional hemodynamics and microcirculation. 2007; 6(4): 78-85. Russian
28. Scognamiglio R, Negut C, Palisi M. Spontaneous recovery of myocardial asynergic segments following acute myocardial infarction. The role of post-extrasystolic potentiation echocardiography in the predischarge evaluation. Eur J Echocardiogr. 2003; 4(2): 135-40.
29. Nikiforov VS. Postextrasystolic potentiation in viable dysfunctioning myocardium diagnostics. Ultrasound & Functional Diagnostics. 2008; 5: 49-56. Russian

30. Galatro K, Chaudhry FA. Prognostic implications of myocardial contractile reserve in patients with ischemic cardiomyopathy. Echocardiography. 2000; 17(1): 61-7.
31. Yao SS, Chaudhry FA. Assessment of myocardial viability with dobutamine stress echocardiography in patients with ischemic left ventricular dysfunction. Echocardiography. 2005; 22(1): 71-83.
32. Bountioukos M, Schinkel AF, Bax JJ, et al. Pulsed-wave tissue Doppler quantification of systolic and diastolic function of viable and nonviable myocardium in patients with ischemic cardiomyopathy. Am Heart J. 2004; 148(6): 1079-84.
33. Hoffmann R, Altiok E, Nowak B, et al. Strain rate measurement by doppler echocardiography allows improved assessment of myocardial viability inpatients with depressed left ventricular function. J Am Coll Cardiol. 2002; 39(3): 443-9.
34. Nikiforov VS, Nikitin AE, Yalovets AA, et al. Identification of the viable myocardium in patients after myocardial infarction by dobutamine stress echocardiography with tissue Doppler imaging. Vestnik Rossiiskoi Voenno-medicinskoi academii. 2005; Suppl. 2: C.97-9. Russian
35. Gong L, Li D, Chen J, et al. Assessment of myocardial viability in patients with acute myocardial infarction by two-dimensional speckle tracking echocardiography combined with low-dose dobutamine stress echocardiography. Int J Cardiovasc Imaging. 2013; 29(5): 1017-28.
36. Nikiforov VS, Marsalskaya OA, Novikov VI. Echocardiographic assessment of myocardial strain in clinical practice. Saint Petersburg.: KultInformPress. 2015. 28 p. Russian
37. Hutyra M, Skala T, Kaminek M, et al. Speckle tracking echocardiography derived systolic longitudinal strain is better than rest single photon emission tomography perfusion imaging for nonviable myocardium identification. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013; 157(1): 12-21.
38. Romero J, Xue X, Gonzalez W, Garcia MJ. CMR imaging assessing viability in patients with chronic ventricular dysfunction due to coronary artery disease: a meta-analysis of prospective trials. JACC Cardiovasc Imaging. 2012; 5(5): 494-508.
39. Glaveckaite S, Valeviciene N, Palionis D, et al. Prediction of long-term segmental and global functional recovery of hibernating myocardium after revascularisation based on low dose dobutamine and late gadolinium enhancement cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2014; 16: 83.
40. Gonzalez JA, Kramer CM. Role of imaging techniques for diagnosis, prognosis and management of heart failure patients: cardiac magnetic resonance. Curr Heart Fail Rep. 2015; 12(4): 276-83.
41. Windecker S, Kolh P, Alfonso F., et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014; 35(37): 2541-619.
42. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34(38): 2949-3003.
43. Shevtchenko YuL, Bobrov LL, Obrezan AG, Nikiforov VS. Some hemodynamic effects of correction of myocardial ischemia by methods of invasive revascularization. Kardiologiya. 2001; 41(7): 20-23. Russian
44. Bax JJ, Delgado V. Myocardial viability as integral part of the diagnostic and therapeutic approach to ischemic heart failure. J Nucl Cardiol. 2015; 22(2): 229-45.
45. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a metaanalysis. J Am Coll Cardiol 2002; 39: 1151-8.
46. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. Circulation 2008; 117: 103-14.
47. Beanlands RS, Nichol G, Huszti E, et al, for the PARR-2 Investigators. F-18-fluorodeoxyglucose positron emission tomography imagingassisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). J Am Coll Cardiol. 2007; 50: 2002-12.
48. Chareonthaitawee P, Gersh BJ, Panza JA. Is viability imaging still relevant in 2012. JACC Cardiovasc Imaging. 2012; 5(5): 550-8.
49. Bonow RO, Maurer G, Lee KL, et al., for the STICH Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med. 2011; 364: 1617-25.
50. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346: 1845-53.
51. Nikiforov VS, Didenko MV, Khubulava GG, Svistov AS. Cardiac resynchronization therapy is novel method of treatment of chronic heart failure. Rossiyskiy kardiologicheskiy zhurnal. 2005; 4: 87-93. Russian
52. Lebedev DS, Sedov VM, Nemkov AS, et al. Implantable electronic devices for the treatment of ventricular tachyarrhythmias and heart failure. Sankt-Petersburg.: S. n. 2005. Russian
53. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013; 34(29): 2281-329.
54. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy:

the TARGET study: a randomized, controlled trial. J Am Coll Cardiol 2012; 59: 1509-18.

55. Bakos Z, Ostenfeld E, Markstad H, et al. A comparison between radial strain evaluation by speckle-tracking echocardiography and cardiac magnetic resonance imaging, for assessment of suitable segments for left ventricular lead placement in cardiac resynchronization therapy. Europace. 2014; 16(12): 1779-86.
56. Adelstein EC, Tanaka H, Soman P, et al. Impact of scar burden by single-photon emission computed tomography myocardial perfusion imaging on patient outcomes following cardiac resynchronization therapy. Eur Heart J. 2011; 32: 93-103.
57. Bose A, Kandala J, Upadhyay GA, et al. Impact of myocardial viability and left ventricular lead location on clinical outcome in cardiac resynchronization therapy recipients with ischemic cardiomyopathy. J Cardiovasc Electrophysiol 2014; 25: 507-13.

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REVIEW ARTICLE

Common etiology, different pathogenesis and basics of atherosclerosis and atheromatosis prevention. Marked differences in lipoprotein-mediated fatty acids transport in blood of herbivores and carnivores.

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Summary

According to the phylogenetic theory of general pathology, increased consumption of meat by herbivorous animals always leads to the development of atherosclerosis and arterial intima atheromatosis. The following etiological factors of atherosclerosis and atheromatosis have been developed during phylogenesis: a) cellular uptake of fatty acids (FA) with ApoB-100 low density lipoproteins; b) human cells do not convert exogenous palmitic saturated FA (SFA) into oleic monounsaturated FA (MFA), instead in vivo they enter non-physiological palmitic pathway of FA metabolism and c) phylogenetically late monocytes→macrophages hydrolyze with low efficiency polyenic FA esterified with cholesterol (CL). Environmental influence, impaired biological function of trophology (nutrition) and impaired biological reaction of food consumption, including non-physiologically high content of palmitic SFA and CL in diet, are pathogenic factors of atherosclerosis and atheromatosis. Formation of circulating ligandless palmitic very low density lipoproteins (VLDL) is the key step of atherosclerosis and atheromatiosis pathogenesis. Several problems arise under these conditions: a) how to utilize in vivo big amount of ligandless palmitic VLDL which affect the biological function of endoecology and the biological reaction of inflammation, thus creating pathogenetic basis for atheromatosis and b) how can cells maintain their function if it is impossible to uptake polyenic FA from the extracellular medium, which creates the basis for atherosclerosis, impairs biological function of adaptation and biological reaction of compensation. Physiological diet of Homo Sapiens consists mostly from

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carbohydrates, palmitic SFA synthesized de novo from glucose, insulin converts it to oleic acid that subsequently undergoes highly effective oxidation in mitochondria. At low dietary content of palmitic FA insulin promotes an optimal oleic pathway of FA metabolism providing high "kinetic parameters" of the organism and efficient ATP production. According with common pathogenesis of atherosclerosis and atheromatosis, it is necessary to prevent the formation of ligandless palmitic VLDL. Their absence will make impossible the development of atherosclerosis and atheromatosis.

Keywords

Fatty acids, cholesterol, atherosclerosis, atheromatosis, biological function of endoecology.

Starting from the times of R. Virchow and N.N. Anichkov during the last one hundred years minds of researchers, experimentalists and medical doctors are concentrated on cholesterol theory of atherosclerosis. Being based on this theory, during the XX century we haven't been able to understand neither etiology nor pathogenesis of atherosclerosis and atheromatosis and haven't worked out the principles of their effective prevention.

Hypolipidemic drugs statins can be estimated from the point of view of atherosclerosis pathogenesis, from biological point of view these compounds are not very effective [1]. They normalize impaired biological function of trophology (nutrition), their action balances on the edge of toxicity, more than that, these drugs do not reduce coronary heart disease (CHD) related mortality [2]. Despite to doubts in cholesterol theory of atherosclerosis, every day we measure cholesterol (Ch) concentration in lipoproteins (LP) of thousands of patients. Why?

During the last years researchers pay more and more attention to the role of non-physiological amounts of consumed food and in vivo concentrations of fatty acids (FA) in the pathogenesis of atherosclerosis. first of all, it can be applied to C16:0 palmitic saturated FA (SFA) and trans-forms of monounsaturated FA (MFA) like trans-C18:1 elaidic MFA. But these things lead to another theory of FA and different atherosclerosis and atheromatosis pathogenesis. During phylogenesis course and life spent in the depth of the world ocean, despite the fact that each animal cell synthesizes in situ de novo palmitic SFA quantum sates, its amount in food and in vivo does not exceed 20% of total FA concentration in vivo, and trans-oleic MFA is present in trace quantities.

Oleic MFA prevails between all FA in vivo in normal physiological conditions of Homo Sapiens. FA role in atherosclerosis, atheromatosis and CHD pathogenesis is realized in two separate non-physiological disorders of biological function of trophology (nutrition): a) excessive amount of palmitic SFA in food and b) alimentary deficiency, low amount of ω-3 and ω-6 essential poly-unsaturated FA (PUFA) [3].

Excessive amount of palmitic SFA in very low density lipids LP (VLDL LP), in low density lipids (LDL) has the major impact on atheromatosis pathogenesis. Though etiological factors of atherosclerosis and atheromatosis are the same, their pathogenetic mechanisms differ.

Experimentalists haven't found the answer still to the questions about the model of exogenous hypercholesterolemia of N.N. Anichkov which allows reproducing aorta atheromatosis in rabbits and makes it impossible for mice and rats? Why is it necessary to make knock-out of ApoE gene to perform so fast modeling of aorta atheromatosis in mice?

Phylogenetic development of consequent PUFA transporting together with HDL and LDL lipoproteins in herbivorous animals

Several years before, 150 years after R. Virchow and his cellular theory of general pathology we created another one – phylogenetic theory of general pathology [4]. This theory allows understanding of biological functions development through evolution of biological functions and reactions including biological function of homeostasis, trophology function (nutrition), biological function of endoecology ("purity" of intercellular environment), adaptation function, biological function of reproduction. Phylogenetic theory of general pathology observes in detailed way phylogenetically late function of locomotion (movement due to the contraction of cross-striated myocytes) and the last one – cognitive function, regulatory of nervous system in vivo. Intellect is the highest step of biological cognitive function.

Phylogenetic theory of general pathology allowed estimating several things from biological and physicohemical point of view: unite non-physiological role of Ch, SFA excess and the lack of PUFA in atherosclerosis pathogenesis; b) identify common etiological factors and c) pathogenesis of atheromatosis and

atherosclerosis is combined but separate at the same time. Discussing the role of environmental factors in atherosclerosis pathogenesis, we will put aside for a while all inherited conditions with impaired FA transport with LP, all hyperlipoproteinemias (HLP) [5], including their different phenotypes [6].

Taking a precise look into the results of comparative anatomy and physiology, using the physicochemical and biochemical detection techniques, it is possible to discuss consciously the development of FA transport consequently as the part of different LP classes. Apolipoprotein (Apo) ApoAI is an evolutionally early protein binding lipids that binds them non specifically and can be associated with low-polarity and non-polar lipids. In intracellular environment ApoAI transfers: a) all FA MFA+SFA, unsaturated FA (UFA) with two-three double bonds (DB); and b) PUFA with 4-6 DB as the phospholipids (PL); c) MFA and SFA as di- and monoacylglycerols; and d) Ch, a polar nonesterified alcohol.

All cells absorb FA from HDL passively changing FA between PL of HDL and PL of plasma membrane, this system has been working for millions of years and hasn't lost its importance up to date. With time HDL function has become more complicated, HDL, together with the FA delivery to the cells started to transfer Ch synthesized by cells from them. To make Ch transfer more effective, etherification of Ch with oleic MFA started to happen in HDL, and it became easier to pack formed mono-unsaturated cholesterol esters (mono-ChE) and cholesterololeat into HDL.

With the course of time passive FA absorption became insufficient, and the next step of evolution has led to formation of their active receptor mediated uptake. ApoB100 has formed LP from non-polar lipids from triglycerides (TG) in hepatocytes; cells started to consume non-polar TG actively using receptor-mediated endocytosis. Unlike earlier HDL, ApoB-100 as the part of LDL started to bind MFA+UFA+SFA in the form of non-polar TG; cells started to uptake LDL using ApoB-100 mediated endocytosis. for this ApoB-100 forms ligand-domain in LDL; cells expose ApoB-100 on their membrane. Thus cells started to absorb actively MFA+UFA+SFA; and PUFA absorption had been performed passively for a long time. With the course of time passive uptake became insufficient.

During later evolutional steps, during the establishment of biological function of locomotion, when the quantity of FA transported to cross-striated myocites has increased; insulin expressed directed (vector) transfer of MFA+SFA to all insulin-dependent cells as the part of a new LP class – very low density lipoproteins (VLDL). For this reason insulin-dependent cells started to synthesize and express ApoE/B-100 receptors on their membrane, and VLDL started to form ApoE/B-ligands. Cells absorb all oleic and palmitic VLDL using ApoE/B-100 endocytosis. Neither palmitic nor oleic VLDL do not turn into LDL, after ligand formation they are absorbed by insulin-dependent cells. After it cells have developed active PUFA absorption with Apo-B-100 LDL in the way similar with ApoB-100-mediated endocytosis of MFA+UFA +SFA. To achieve it HDL started to re-etherify PUFA from polar PL to non-polar, more hydrophobic poly-cholesterol esters (ChE), PUFA etherified with Ch. Cells perform active PUFA intake through several steps:

- in HDL esterase (aminophospholipid-cholesterol-aciltransferase) catalyzes re-etherification of PUFA from polar PL to poly-ChE; then
- newly synthesized protein – polyene cholesterylester transfer protein (PCETP) started to create in blood triple association (HDL+PCTP+LDL) where non-polar poly-ChE transfer from HDL to LDL; then
- more hydrophobic lipids like poly-ChE that are transferred from HDL to VLDL they displace TG from their association with ApoB-100, forming LDL with lower hydrated density and smaller dimensions, then ApoB-100 in association with poly-ChE changes its steric conformation, exposing ApoB-100 ligand-domain on the surface of LDL; in the end
- cells take in PUFA in the form of polyChE as the part of LDL via ApoB-100 mediated endocytosis.

Thus all phylogenetically early herbivorous animals developed consequent FA transfer to cells: at first LDL bring MFA+UFA+SFA in the form of TG to cells; then they transfer PUFA to cells in the form of poly-ChE. PUFA percentage is relatively low (several %) comparing with the amount of MFA+UFA+SFA transferred with LDL.

Carnivorous animals have formed parallel transport of MFA+UFA+SFA as the part of LDL and PUFA as the part of HDL

It is possible to suppose that during the course of evolution carnivorous animals who started to consume animal food particular FA composition of which (high contents of palmitic SFA) promoted formation of PCETP null mutation. After this 95% of animal population became extinct, the rest of them have acquired adaptations to this mutation fulfilling biological function of adaptation. It happened by in vivo formation of parallel, separate absorption by cells (opposite to the

mechanism observed in herbivorous animals) of: a) MFA+SFA+UFA in the form of TG via LDL; and b) PUFA in the form of poly-ChE via HDL where they have been synthesized. Thus carnivorous animals (rats, mice, dogs) have developed parallel and not consequent transport of PUFA in HDL via new ApoE/A-I endocytosis during the process of evolution.

LDL in the blood of herbivorous animals bring consequently to cells MFA+SFA+UFA in the form of TG at the first turn and then PUFA in the form of polyChE; cells absorb all FA via Apo-B100 endocytosis. In carnivorous animals LDL transfer only MFA+SFA+UFA to cells which in their turn take them in via Apo-B100 endocytosis. HDL transport PUFA to cells which absorb them using another mechanism – ApoE/A-I endocytosis.

Differences of FA transport to cells in carnivorous animals are so much significant, that whatever high was the concentration of palmitic SFA in food it would not interfere with parallel independent absorption of PUFA by cells. At the same time in herbivorous animals having consequent transport of PUFA excessive amount of palmitic SFA in food blocks consequent absorption of PUFA by cells reducing its bioavailability for cells and initiating clinical manifestations of atherosclerosis.

Carnivorous animals who due to different reasons entered the condition of starvation and have to consume food typical for do not demonstrate abnormal HDL-mediated PUFA transport and their cellular intake. If herbivorous animals start to consume excessive amount of animal food, high concentration of palmitic SFA there blocks MFA+SFA+UFA into VLDL and blocks also PUFA absorption by cells with LDL via Apo-B100 endocytosis. It always leads to atherosclerosis and arterial intima atheromatosis development.

Characteristic biochemical and physiological tests of herbivorous animals are: a) prevalence in blood during fasting period ApoB-100 LDL; b) oleic TG and oleic VLDL prevalence in blood; c) low concentration of ApoE in HDL; d) high PCETP concentration in blood plasma e) oleic variant of FA metabolism in cells. In this case PCETP pharmacological inhibition is totally non-physiological and non-biological.

Carnivorous animals are characterized by the opposite results of these tests: a) HDL prevalence in blood during fasting period; b) palmitic TG and palmitic VLDL prevalence in blood; c) high concentration of ApoE in HDL; d) trace quantities of PCETP in blood plasma; e) partially palmitic variant of FA metabolism. It is worth to mention that 8% of people from Japanese population demonstrate HDL prevalence in blood during fasting period (physiological hyperalphaproteinemia) due to increased poly-ChE concentration in HDL, at the same time blood levels of PCEPT are reduced.

Carnivorous animals cells of whom absorb PUFA as poly-ChE as the part of HDL using ApoE/A-I endocytosis do not develop atherosclerosis and atheromatosis in the model of exogenous hypercholesterolemia. All herbivorous animals cells of whom absorb PUFA as poly-ChE as the part of LDL via Apo-B100 mediated endocytosis develop atherosclerosis and atheromatosis of arterial intima in the model of exogenous hypercholesterolemia. It creates the block of bioavailability and of possibility of palmitic VLDL absorption by cells, it creates pathogenetic basis for arterial intima atheromatosis. Block of PUFA absorption by cells by excess of palmitic SFA in food underlies the pathogenesis of atherosclerosis. Transport of MFA+SFA+UFA and then PUFA by the same type of LP – LDL and their absorption by the same ApoB-100 mediated endocytosis is an etiological factor of atherosclerosis and atheromatosis also in Homo Sapiens. In carnivorous animals MFA+SFA+UFA are transported to cells by LDL and PUFA – by HDL.

According with the phylogenetic theory of general pathology, atherosclerosis is a syndrome of PUFA deficiency in cells, thus to develop atherosclerosis and atheromatosis in rats, mice and dogs it is necessary to block PUFA absorption by cells. This situation occurs in case of ApoE gene knock-out in animal models [7]. ApoE gene knock-out in rats and mice turns them into herbivorous animals, similar with the ones that they used to be during early stages of phylogenesis. Mice with ApoE gene knock-out (like herbivorous animals) develop intima atheromatosis in the model of exogenous hypercholesterolemia like rabbits [8]. There is no other way to activate atherosclerosis and atheromatosis in the model of exogenous hypercholesterolemia in rats, mice, dogs. At first they should be turned into herbivorous animals like Homo Sapiens or rabbits.

During evolution Homo sapiens has become an herbivorous animal

If we use the criteria that characterize herbivorous animals (LDL prevalence in blood, prevalence of oleic TG and VLDL, high concentration of PCETP in blood plasma) it is possible to suppose that Homo sapiens during phylogenesis has developed as an herbivorous animal. Like all herbivorous animals, human has

long intestine, its length is 12 times bigger than the length of the body; in carnivorous animals intestine is 3-4 times shorter. Carbohydrate assimilation in vivo is more long process than protein assimilation. Herbivorous animals have 10 times lower acidity of gastric juice and activity of positionally specific pancreatic lipase (TG hydrolase) in small intestine than predators. Saliva of carnivorous animals is acid and contains proteases for protein hydrolysis, it lacks of amylase that is responsible for initial steps of polysaccharides hydrolysis. Human saliva is alkaline.

Hepatocytes of carnivorous animals synthesize 10-15 times more ureic acid, it occurs because of necessity to excrete bigger amount of nitrogen derived from animal food. Urine of carnivorous animals is quite acid, physiologically human urine is slightly alkaline. Though anthropologists affirm that humans are omnivorous from time immemorial, this period seems to be a short episode comparing with the duration of evolution. And humans do not consume raw meat, it is biologically impossible.

It is difficult to say anything distinct about atheromatosis development in the Neanderthal men, since there are no evidences and their lifespan was significantly shorter comparing with the modern people. There is no doubt that environmental conditions sometimes made Homo sapiens use animal food, but it was not raw meat consumption normal for carnivourous animals. It was normal for phylogenetically herbivorous human to consume raw phylogenetically early fish and eggs of phylogenetically early birds; with time it has become inhabited. By land only the eggs of birds contain optimal for human amount of ϕ-6 C20:4 arachidonic essential PUFA, vegetable oils do not contain optimal for human amount of arachidonic PUFA

Anatomical structure of human (teeth, jaws, digestive system) are not optimal even for all types of vegetable food, people cannot eat young bark of the trees, plant roots, young sprouts and branches, many root crops; it is necessary to boil them before people can eat them. Carl Linnaeus, the founder of binomial nomenclature, used to say that "comparative analysis of inner and outer structure of human and animal body proves that fruits and vegetables are natural food for people". from phylogenetic point of view, human can be considered frugivorous (from the word fruit) and not carnivorous (from the root carn- staying for meat). Anthropoid apes demonstrate that human hand is more adapted for tree-climbing and taking fruits.

Locus minoris resistentia, atherosclerosis and atheromatosis pathogenesis in herbivorous animals and Homo sapiens

To understand main physicochemical and biochemical mechanisms which are responsible for atherosclerosis and atheromatosis pathogenesis after consumption of meat by herbivorous animals, we suggest in the beginning understanding: a) features of exogenous FA assimilation by human, synthesis of positionally specific TG in hepatocytes; b) secretion of functionally different VLDL by hepatocytes into bloodstream; c) VLDL absorption mostly by insulin-dependent cells; d) small percentage of VLDL to LDL conversion in blood during FA transport and their absorption by cells.

Depending on FA type that is etherified in the second (middle) position (sn-2) of triatomic alcohol glycerol of TG molecule that cannot be hydrolyzed by extracellular lipases, TG are subdivided into palmitic, oleic, linoleic, linolenic acid. More than 80% of all TG in vivo are palmitic and oleic. Evidently different steric form of TG positional isomers (PI), especially if they are etherified with UFA underlies separate structuring of TG by ApoB-100 into palmitic, oleic, linoleic and linolenic VLDL in hepatocytes. The more lipids derived from animal food contain palmitic SFA the more hepatocytes synthesize palmitic TG and the more palmitic VLDL are formed from them with ApoB-100.

Physiologically neither oleic nor palmitic VLDL don't turn into LDL in blood. Oleic and palmitic VLDL form ApoE/B-100 ligand binding it with their receptors, insulin-dependent cells absorb all oleic and palmitic VLDL. Physiologically only linoleic and linolenic VLDL transform into LDL. All PUFA in the form of poly-ChE move into linoleic and linolenic VLDLfrom HDL in physiological conditions under PCETP action, transforming VLDL into linoleic and linolenic LDL.

Experiments on laboratory animals and clinical observations demonstrate that if quantity of animal food in herbivorous animals exceeds optimal and physiologically acceptable one, the following thing happens: a) palmitic VLDL prevail over physiological oleic VLDL in blood; b) development of HLP IIb type occurs with the increase of TG and Ch concentration in blood plasma; c) LDL-Ch.

The place of palmitic SFA excess action, the locus minoris resistentate is common in all herbivorous animals and human. This is the block of palmitic TG hydrolysis in palmitic VLDL; if VLDL do not form ApoE/B-100 ligand and do not expose it on their sur-

face, these VLDL cannot be absorbed by insulin-dependent cells via ApoE/B-100 endocytosis.

Herbivorous animals consume MFA+SFA+UFA as the part of oleic, palmitic VLDL, and PUFA as the part of linolenic, linoleic VLDL turning to LDL

VLDL are the latest from phylogenetic point of view lipoproteins, they have been formed during establishment of biological function of locomotion – movement due to contraction of skeletal muscle. VLDL formation by hepatocytes is stimulated by insulin. Biological role of this hormone is to provide substrates for energy production in all cells that realize the locomotion function. VLDL transport FA in blood pointedly for further energy production, adenosine triphosphate (ATP) production. In herbivorous animals VLDL transport mostly exogenous+endogenous C18:1 MFA oleic acid to the cells and much less exogenous palmitic SFA. More than 80% of VLDL are oleic+palmitic, together they transport MFA+SFA just to insulin-dependent cells [9].

Insulin-dependent cells are present by: a) cross-striated, skeletal myocytes; b) cardiomyocyte syncytium; c) periportal hepatocytes; d) hypodermal adipocytes; e) Kupffer cells – resident liver macrophages. Visceral adipose cells of omentum do not have insulin receptors on their membrane, their FA metabolism does not depend on insulin. Insulin-dependent cells have several features of their plasma membrane: a) insulin receptors; b) phylogenetically late insulin-dependent glucose transporters Glut4. VLDL transport to insulin-dependent cells is determined by the fact that just these cells express on their membrane ApoE/B-100 receptors. Cells bind VLDL ligand with their receptors, in herbivorous animals VLDL transport mostly oleic and to less extent palmitic TG [10].

When person consumes vegetable food and seafood that contain mostly oleic MfA, hepatocytes secrete mostly palmitic VLDL into the bloodstream. In case of non-physiological prevalence of animal food with high contents of palmitic SFA hepatocytes secrete in blood mostly palmitic VLDL. But the difference of TG PI of oleic and palmitic VLDL hydrolysis velocity in blood catalyzed by post-heparine lipoprotein lipase (LPL) is very high.

TG position isoforms are substrates for hydrolysis in blood as the part of VLDL under post-heparin lipoprotein lipase action

If we put all PI of palmitic (P) and oleic (O) TG in the order of increasing velocity constant of their hydrolysis in blood under post-heparin LPL action, we observe the following "spectrum" of TG in blood plasma:

PPP - PPO - OPP - POP - OPO - OOP - POO - OOO.

66,4 - - 35,2 22,0 18,2 - 5,5 °C

We put melting temperature as the main physico-chemical parameter under positional isoforms. We did not include linoleic and linolenic TG due to their relatively low abundance. We used the method of "shift" to the right and to the left for estimation of TG positional isoforms diagnostic value.

Shift to the left in the side of palmitic PI is functionally undesirable, it happens due to: a) animal food (beef) consumption; b) consumption of fat cow milk; c) cheese consumption, since they contain high amount of palmitic SFA and TG. Intake of this FA with food can significantly exceed physiological amount (15-20% of all food FA) and reach the level of 40-60% of all FA consumed with food. In case of in vivo development of insulin resistance (IR) syndrome the majority of food carbohydrates is transformed into endogenous palmitic SFA by hepatocytes and further etherified into palmitic TG with excessive secretion of VLDL into the bloodstream.

Cells of herbivorous animals including Homo Sapiens cannot transform physiologically exogenous palmitic SFA into endogenous oleic MFA. During stages of phylogenesis animals did not synthesize palmitoyl-CoA-elongase enzyme in the metabolism of exogenous palmitic SFA. Cells of Homo Sapiens synthesize only palmitoyl-CoA-desaturase and can transform exogenous C16:0 SFA only into C 16:1 palmitoleic UFA. If human consumes animal food, palmitic VLDL, high VLDL-Ch and low HDL-Ch prevail in blood, and the concentrations of ApoE and ApoC-III are high. Formation of low-effective palmitic variant of FA metabolism always occurs in case of shift to the left in vivo. Constant deficiency of macroergic ATP in all cells is typical for this variant, so TG positional isoforms shift to the left is always undesirable.

Shift to the right in the direction of oleic TG position isoforms is desirable from pathogenetic and preventive point of view. It occurs in case of: a) Mediterranean diet, low dietary contents of beef and fat cow milk products, abundant consumption of fish, seafood and olive oil, optimal carbohydrate consumption; b) physiological action of insulin; and c) high levels of physical activity, optimal realization of biological function of locomotion. Physiological TG concentration in VLDL goes along with low values of LDL-Ch, high levels of HDL-Ch, physiological plasma concentrations of ApoE and ApoC-III [11].

Melting temperature of palmitoyl-palmitoyl-palmitate glycerol, tripalmitate (PPP) is 49 ºC and oleyl-oleyl-oleate, trioleate (OOO) melting temperature is -15ºC; the difference of this physicochemical parameter between these two TG is more than 60 ºC. TG melting point is a physicochemical parameter of each substrate, it determines the velocity of individual TG hydrolysis under the action of pancreatic lipase, post-heparin LPL, hepatic glycerol hydrolase and hormone-sensitive lipase. It occurs in case of: a) phylogenetically early, not sensitive to insulin visceral adipose cells of omentum; and b) in phylogenetically later, insulin-dependent hypodermal adipocytes.

During late stages of phylogenesis humoral mediator insulin formation has happened because of necessity to regulate the metabolism of MFA+SFA and provide skeletal myocytes with adequate ATP quantity. According with the experiments , previously performed by our group in vitro, oleic MFA ω-9 C18:1 oxidation with ozone has reaction velocity constant significantly higher than in case of palmitic SFA oxidation [12].

Mitochondria take in phylogenetically early SFA with the velocity many time higher than the velocity of palmitic SFA transport through the outer membrane. It occurs despite the presence on specific transporter for palmitic SFA, carnitinepalmitoyl acyltransferase on outer mitochondrial membrane. Mitochondrial productivity is equally dependent on substrate; ATP production occurs many times faster in case of oleic MFA oxidation comparing with palmitic SFA. Biological role of insulin is the increase of organism's kinetic potential. Insulin expresses the synthesis off such substrate, this FA, oxidation of which makes mitochondria produce maximal ATP amount for the unit of time and hives them high productivity. This is a necessary condition for fast in vivo realization of all biological functions and reactions.

According with the phylogenetic theory of general pathology, biological role of insulin, first of all, consists of transforming all endogenous palmitic SFA synthesized by hepatocytes into -9 C18:1 oleic MFA. Insulin promotes the expression of conjugated biochemical reactions:

- endogenous C 16:0 palmitic SFA transformation into C 18:0 stearic SFA under the action of palmitoyl-CoA-elongase; then
- stearyl-CoA-desaturase turns stearic SFA into ω-9 C18:1oleic MFA. Oleic acid is the one that can be oxidized in mitochondria with the highest reaction velocity constant, with high productivity producing maximal ATP amount [10].

The key step of atherosclerosis pathogenesis: MfA+SFA transport in palmitic VLDL in the form of TG and PUFA in the form of poly-ChE

According with the phylogenetic theory of general pathology, the formation of insulin-dependent VLDL and ApoE/B-100 ligand-receptor formation by hepatocytes had happened during late steps of phylogenesis. The later systems have been formed in phylogenesis, the more functionally unstable they are. That gives the explanation to the fact that it is impossible to find a patient with primary HDL pathology. Only familial hypercholesterolemia is known among primary LDL pathologies. Hypertriglyceridemia that seems to be so common in diagnostics of metabolic pandemias is the pathology of VLDL transport in intercellular environment and their absorption by insulin-dependent cells.

Non-physiological action of external environment factors is the main reason of high atherosclerosis and atheromatosis frequency in the population of phylogenetically herbivorous Homo sapiens. It is the impairment of biological function of trophology, nutrition function, biological function of exotrophy – external feeding. The factors mentioned below underlie the pathogenesis of atherosclerosis and atheromatosis:

a) consumption of big amount of animal food containing a lot of SFA, mainly palmitic SFA, prevalence of palmitic TG and VLDL in blood;

b) increased dietary content of trans-fatty acids; their metabolic parameters are very similar with SFA;

c) increased amount of Ch in animal food;

d) alimentary deficiency of ω-6 and ω-3 PUFA [13]. In case of physiological food intake the amount of oleic TG and VLDL in blood plasma exceeds significantly the amount of palmitic TG and palmitic VLDL.

Oleic, palmitic, linoleic and linolenic VLDL that are secreted into the bloodstream by hepatocytes do not make ligands. They are functionally overloaded with TG; it makes impossible ApoE/B-100 ligand's active position. Physiologically oleic TG of oleic VLDL undergo fast hydrolysis under the action of post-heparin LPL and its cofactor ApoC-II. When the quantity of oleic TG bound with ApoB-100 become optimal ApoB-100 takes active conformation (steric, spatial form) and expose ApoE/A-100 ligand on the surface of oleic VLDL. Insulin-dependent cells bind it fast with appropriate receptors and absorb all oleic VLDL.

Physiologically excessive TG content in linoleic and linolenic VLDL is hydrolyzed by another, phylogenetically earlier hepatic glycerolhydrolase andApoC-III

cofactor. Poly-ChE activate lipolysis in linoleic and linolenic VLDL; they leave HDL under the action of PCETP and go into linoleic and linolenic VLDL. In this case more hydrophobic poli-ChE displace TG from their bond with ApoB-100 and form linoleic and linolenic VLDL, exposing ApoB-100 ligand on the surface. Binding it with appropriate receptors, cells absorb actively linoleic and linolenic VLDL with all PUFA transported with them.

When hepatocytes secrete in blood steam mostly palmitic TG as the part of VLDL with the same, TG hydrolysis occurs non-physiologically slowly, and excessive TG amount remains linked with ApoB-100. ApoE/B-100 ligand almost does not form in palmitic VLDL. Ligandless palmitic VLDL circulate in blood initially after consumption of food with high palmitic SFA content and then constantly promoting the development of HLP IIb type. Palmitic VLDL slowly transform into palmitic LDL forming the fraction of palmitic VLDL→LDL [14].

Then PUFA in the form of poly-ChE and HDL enter big pool of ligandless palmitic VLDL→LDL instead of being associated with a small pool of linoleic and linolenic VLDL. Linoleic and linolenic VLDL are almost not formed in blood, cells have nothing to intake via ApoB-100-mediated endocytosis. In case of low bioavailability of linoleic and linolenic LDL for cells, PUFA absorption by cells almost comes to stop, and cells acquire PUFA deficiency.

Depending on the duration of persistence in blood, palmitic VLDL→LDL can undergo modifications. These modifications include biochemical reactions of glycation, sialylation, acylation, up to the formation of autoantibodies for ApoB-100 of VLDL→LDL. In case of long non-physiological circulation in blood palmitic VLDL→LDL that didn't manage to form ApoE/B-100 ligands transform to small, dense and the most atherogenic palmitic LDL [15]. It is possible to distinguish them between physiological and non-physiological LDL using nuclear magnetic resonance spectroscopy. When we measure VLDL-Ch concentration, for real we detect Ch content in non-physiological palmitic VLDL→LDL.

Two consequences of ligandless palmitic VLDL→LDL formation in blood

Ligandless palmitic VLDL→LDL formation in blood in vivo results in two abnormalities that require activation of biological function of adaptation, biological reaction of compensation, biological function of endoecology and biological reaction of inflammation.

How can cells deprived from the opportunity to intake essential ω-6 and ω-3 PUFA can maintain their function, how can they synthesize aminophospholipids and provide plasma membrane parameters, how can they synthesize phylogenetically early humoral mediators eicosanoids, prostacyclines, prostaglandins, thromboxanes and leukotriens?

How to get rid of big amount of ligandless palmitic VLDL→LDL, from endogenous biological "waste" with high molecular weight? Since enodogenous phlogogens with high molecular weight are impossible to excrete from organism [16], organism has to utilize them in situ. It is possible to realize it only with biological function of endoecology, biological reaction of inflammation. According with the phylogenetic theory of general pathology, biological function of endoecology is responsible for in vivo utilization of "biological waste" with low and high molecular weight (maintaining of "purity" of intercellular environment).

Elimination of low molecular weight (<70 kDa, albumin weight) catabolites from intravascular, local intercellular pool is performed by biological reaction of excretion. Biological reaction of inflammation in situ utilizes endogenous phlogogens with high molecular weight (> 70 kDa). All consequences of the block of PUFA cellular intake and consequent PUFA cellular deficiency are smoothed by biological function of adaptation, biological reaction of compensation.

Impairment of biological functions and reactions that occurs during in vivo utilization of ligandless palmitic VLDL→LDL underlie clinical manifestations of atheromatosis of intima of elastic and mixed type arteries. In case of the same pathogenesis there is no atherosclerosis without atheromatosis and atheromatosis without atherosclerosis. And at the same time it is better not to use the expression "coronary artery atherosclerosis" since the phrase "coronary artery atheromatosis" is more correct. At the same time platelet hyperaggregation and increased rigidity of cellular plasma membrane in vivo are the symptoms of atherosclerosis.

Biological function of adaptation compensates PUFA deficiency in the synthesis of biologically active eicosanoids

During the millions of years of life in the water of three world oceans ω-3 C20:5 eicosapentaenoic acid (eicosa) and C22:6 docosahexaenoic (docosa) PUFA became the substrates for in vivo synthesis of phylogenetically early, biologically active humoral mediators

– eicosanoids [17]. These families of prostacyclines, prostaglandins, thromboxanes and leukotrienes are humoral regulators of metabolism, in particular of the biological reaction "metabolism↔microcirculation" (M↔M), local abnormalities of which occur the most frequently in vivo. Cells of loose connective tissue (LCT) starting from the level of paracrine communities (PC) of cells synthesize eicosanoids using eicosa PUFA as a predecessor. Docosa is the main form of PUFA storage in cellular organoids' monolayer membranes [18].

Cells synthesize the most active eicosanoids (eicosa means twenty in Greek) from eicosa; molecules of these prostacyclines, prostaglandins, thromboxanes and leukotrienes have three double bonds (DB), they are classified as the group of biologically active eicosanoids-3. Neither one animal cell can synthesize PUFA, in the ocean eicosa and docosa are produced by cyanobacteria that are further consumed by fish. During the Permian period when animals exited the ocean and entered the ground where plants did not synthesize neither eicosa nor docosa, more than 95% of animal population had become extinct. Small part of them has adapted to eat plants that synthesized ϕ-6 C20:3 γ-linolenic UFA, carnivorous animals started to use it for ϕ-6 C20:4 arachidonic synthesis. They used it as the substrate for eicosanoids synthesis. Molecules of these eicosanoids had two DB, so they were called eicosanoids-2. Their functional activity is lower than the one of eicosanoids-3, but it was enough for maintaining their function in vivo [19].

When during atherosclerosis normal cellular absorption of ϕ-3 and ϕ-6 PUFA is blocked, cells compensatory synthesize eicosanoids from endogenous ϕ-9 C20:3 dihomo-γ-linolenic PUFA. Eicosanoids synthesized from this PUFA have one DB in the molecule, they are called eicosanoids-1. And if eicosanoids-2 are just less active than eicosanoids-3, the action of prostacycline-1, thromboxane-1, prostaglandin-1 and leukotrien-1 is evidently non-physiological. Instead of causing dilation of muscle type arterioles simultaneously with the action of NO, prostacyclines-1 inhibit biological reaction of endothelium-dependent vasodilatation and lead to abnormal M↔M reaction. Thromboxane-1 promotes platelet aggregation instead of its inhibiting. Leukotrienes-1 activate biological reaction of inflammation in non-physiological way.

Aminophospholipides form a zone of less hydrophobic aminophospholipids around each of integral cellular proteins in the membrane: they have PUFA etherified at the sn-2 position of glycerol. Aminophospholipides create functional, less hydrophobic environment for each receptor, change the activity of cation and anion transporters, GLUT4 in hydrophobic bilayer of phosphatidylcholine membrane [20]. PUFA deficiency in the membrane impairs cellular communication with the environment and other cells.

Impaired metabolism regulation and biological reaction M↔M that cannot be neutralized locally at the level of eucosanoids' action on the level of single cells, PC, organs, systems of organs should be eliminated at the level of neurosecretary hypothalamus, spinal bulb, and even organism level [21]. Atherosclerosis is the impairment of metabolism regulation in each cell in vivo, in each PC, in each organ and organ system due to lack of PUFA in cells.

Ligandless palmitic VLDL→LDL in biological reaction of inflammation in arterial intima

All ligandless palmitic VLDL→LDL that litter intravascular and intercellular environment in vivo should be taken and utilized thus realizing biological function of endoecology and biological reaction of inflammation. The purpose of biological reaction of inflammation is to maintain purity of intercellular environment by: a) collection; and b) utilization ov endogenous phlogogens (endogenous initiators of inflammation), collection and utilization of VLDL→LDL [22]. Biological reaction of inflammation is mostly realized by the cells of LCT: a) endothelial monolayer and biological reaction of transcytosis; b) phylogenetically early, resident, regional macrophages; c) specialized Kupffer macrophages in the liver; and d) phylogenetially later monocytes derived from blood, in tissues they turn to macrophages (monocytes→macrophages) [23].

Many cells participate in the realization of biological reaction of inflammation in vivo: endothelial monolayer, neutrophils, humoral opsonization system, resident macrophages, bone marrow monocytes and monocytes→macrophages derived in situ. LCT cells perform these functions in tissues, in situ where the biological reaction M↔M is often impaired; cells commit apoptotic death accumulating endogenous phlogogens as apoptotic bodies. According with the phylogenetic theory of general pathology, greater circulation closing united two different parts of arterial system: a) phylogenetically early distal part of arterial system – muscle type arterioles that do not have intima; and b) phylogenetically more recent proximal

arteries. They include heart, aorta and elastic type arteries having well-defined intima that is the structural component of arterial wall [24].

According with the phylogenetic theory of general pathology, intima of elastic type arteries is the place of endogenous phlogogens, exogenous pathogens, xenobiotics, bacteria, viruses from the local pool of intravascular and intercellular environment collection and utilization. All endothelial cells excrete these compounds into intima where link them with glycosaminoglycans of matrix, thus realizing biological reaction of transcytosis. Phlogogens' liberation from matrix occurs through the realization of early biological reaction of extracellular digestion by phylogenetically early macrophages.

Ligandless VLDL→LDL in blood, biological reaction of transcytosis, phlogogens absorption by resident intima macrophages

Before taking ligandless palmitic VLDL→LDL from bloodstream it is necessary to physiologically denaturate them. Neutrophils realize this reaction; they produce reactive oxygen species (ROS) through the reaction of respiratory burst. ROS serve for physiological denaturation of ApoB-100, for antigen determinants formation on the surface of ligandless LDL. Then Toll-like receptor-4 estimate blood protein molecules according with the principle "self-non self" and if they find denaturated ApoB-100 (its antigenic determinant) they consider this LP as a foreign one determining its elimination. In this case LP FA (lipid) peroxidation is more likely to be just a collateral process.

Then palmitic LP undergo opsonization-opsonin adsorption on their surface, they optimize transcytosis and further phagocytosis reactions. Both phylogenetically early resident macrophages of arterial intima and more phylogenetically recent hepatic Kupffer's cells absorb LP. According with the phylogenetic theory of general pathology, phylogenetically early resident macrophages started to realize biological reaction of inflammation before the others, being the part of PC of LCT. It happened according with the following mechanism:

1. Cells of endothelial monolayer physiologically excrete ligandless VLDL→LDL, antigen-antibody complexes, bacterial lipopolysaccharides , lipopolysaccharide-binding protein, enzymes and other molecules from vascular lumen to the matrix of elastic arteries' intima through biological reaction of transcytosis [25].

2. Phylogenetically early resident macrophages utilize endogenous phlogogenes through biological reaction of inflammation realizing biological function of endoecology. Resident macrophages secrete proteolytic enzymes metalloproteinases that have Zn2+ ion in their active center into intima. Proteinases cause matrix glycosaminoglycanes' proteolysis together with palmitic VLDL→LDL bound by them; further macrophages uptake all phlogogens together with matrix proteoglycans.

3. Macrophages use scavenger receptors to absorb hydrolyzed molecules. Cells hydrolyze actively all lipids including TG, PL, mono-ChE and poly ChE in lysosomes and peroxisomes, maintaining "cleanness" of elastic arteries intima and intravascular pool of intercellular environment. Then smooth muscular cells of media change their phenotype from contractive to secretory and restore intima integrity by producing matrix components [26].

There are not so many resident macrophages in arterial intima of herbivorous animals; bioavailability of endogenous phlogogens for macrophages is physiologically restricted. During phylogenesis endothelial cells did not form mechanisms of biological reaction of transcytosis activation. Ligandless LDL utilization by macrophages requires a lot of energy. Resident macrophages produce it in the form of ATP oxidizing FA produced after LP TG hydrolis in mitochondria. We suppose that C-reactive protein is functional vector of directed FA transport in the form of TG as the part of VLDL for production of energy by the cells that realize biological reaction of inflammation.

The following factors activate biological reaction of transcytosis through endothelial monolayer during late stages of phylogenesis starting from organism level: elevated blood pressure (BP) in the proximal part of arterial system and in the arteries of elastic type and hydraulic punching of vesicles that transport LP using endocytosis+exocytosis=transcytosis [27]. When phlogogenic palmitic VLDL→LDL are accumulated inside the vessels, BP in proximal parts of arterial system gets elevated on the organism level in order to activate physically biological reaction of transcytosis.

During phylogenesis herbivorous Homo Sapiens started to consume big amount of animal food that contains more palmitic SFA. In its turn it increased formation of ligandless palmitic VLDL→LDL in blood, and macrophages were unable to utilize big numbers of these LP. Specialized Kupffer cells were formed in liver to fulfill biological function of endoecology [28].

The question of their role in collection and utilization of ligandless palmitic LP from intravascular pool still requires profound investigation.

The particular characteristic of Kupffer cells is that these cells managed to overcome anatomically and functionally the barriers underlying low bioavailability of endogenous phlogogens for their absorption by resident macrophages of arterial intima. for this reason venous vessels of portal system form wide sinusoids [29], having spaces of Disse under the monolayer of fenestrated endothelium where resident macrophages (Kupffer cells) have direct contact with blood; scavenger receptors of Kupffer cells easily bind and uptake palmitic VLDL→LDL. It is not necessary for Kupffer cells to realize biological reactions of transcytosis and extracellular digestion mediated by metalloproteinases. Though Kupffer cells have big possible opportunities, we suppose that their formation during phylogenesis had happened after the development of closed circulatory system and appearing of resident macrophages in arterial intima. Probably resident macrophages of arterial intima continue to be the main place for collection and utilization of LP that did not manage to form ligand in blood.

Not only palmitic VLDL→LDL can become ligandless in blood, also oleic VLDL having non-physiological phenotype ApoE-E2/E2 can be ligandless. In this case ApoE2/B-100 ligand-receptor affinity is not more than 2-3% of physiological E3/E3 phenotype activity [30].

Though the phenotypes of smooth muscle cells and endothelial monolayer of aorta, carotid and femoral arteries are different, we can have an opinion that all mesothelial cells realize biological reaction of inflammation during collection and utilization of endogenous phlogogens using the same algorithm. If palmitic ApoE/ApoB-100 VLDL become ligandless, arterial intima develops inflammatory destructive atherothrombotic lesions. Resident macrophages make soft plaques in intima that have a tendency to rupture with further atherothrombosis formation in coronary arteries. Ligandless palmitic VLDL→LDL form atheromous plaques in intima [31].

It is reasonable to suppose that formation of the system responsible for collection and utilization of endogenous phlogogens from local intravascular pool of intercellular environment occurred due to consumption of mostly vegetable food by animals. In this case during millions of years formation of ligandless palmitic VLDL was small and there were no problem of their utilization by small number of resident macrophages of arterial intima.

During the stages of phylogenesis resident macrophages became insufficient for ligandless palmitic VLDL→LDL utilization after increased animal food consumption by herbivorous animals. In this conditions resident macrophages started to produce and secrete humoral mediators chemoattractants. Chemokines (chemotactic cytokines) are proinflammatory cytokines initiating monocyte migration in tissues along a concentration gradient. Secreting chemoattractants, resident macrophages attract and recruit monocytes of hematogenic origin from the bloodstream to arterial intima.

Monocytes, attracted by chemokines action, exit intravascular space and per diapedesis move into intercellular environment of intima. Within a few days they pass initial specialization and become monocytes-macrophages and start to utilize in situ ligandless palmitic VLDL→LDL. It makes the impression that monocytes turning to macrophages are unable to acquire all necessary specific functions during this short period of time, in particular, they do not express poly-ChE hydrolase in lysosomes, they cannot liberate PUFA from non-polar poly-ChE environment, they cannot hydrolyze poly-ChE [32]. Total functional incapability of phylogenetically late monocytes→macrophages comparing with phylogenetically early resident macrophages is the third atheromatosis etiological factor – foam cell (labrocyte) formation. They are filled mostly with poly-ChE, they finish their cellular fate with necrotic death and form atheromatosis and atherosclerosis intima lesions.

According with the phylogenetic theory of general pathology, non-physiological influence of external environment factors, excessive dietary contents of animal Ch and palmitic SFA in the food of herbivorous animals are the main factors of atherosclerosis and atheromatosis pathogenesis. Both factors act in the same direction and position initiating ligandless palmitic VLDL formation in blood. In case of high dietary contents of Ch and palmitic SFA:

- polar lipids (phosphatidylcholine+Ch) monolayer with high Ch concentration that covers TG in VLDL practically uncouples the enzyme in hydrophilic environment of bloodstream and its substrate – hydrophobic TG in VLDL.
- the presence of low-permeable monolayer with high Ch concentration blocks TG, the substrate for enzymatic hydrolysis, bioavailability.

Even in case of physiological concentration of polar Ch in phosphatidylcholine+Ch monolayer of VLDL, palmitic TG cannot be considered as the optimal substrate for hydrolysis under the action of post-heparin LPLI [34]. As the result of impaired lipolysis, ApoB-100 does not acquire specific conformation and does not expose ApoE/B-100 ligand on the surface of palmitic VLDL. Arterial intima atheromatosis is the result of impaired utilization of palmitic VLDL turning to LDL in biological function of inflammation.

Phylogenetic theory of general pathology, atherosclerosis and atheromatosis prevention

From the phylogenetic theory of general pathology point of view characteristics mentioned below are the etiological factors of atherosclerosis and atheromatosis, formation of which had happened separately with the difference of million years:

- cells of herbivorous animals absorb PUFA in the form of poly-ChE as the part of ApoB-100 LDL, at second turn after MFA+SFA+UFA intake; impaired MFA+SFA+UFA absorption blocks PUFA intake, this thing does not occur in carnivorous animals;
- herbivorous animals, Homo sapiens cannot turn exogenous palmitic SFA into oleic MFA; it leads to the formation of palmitic variant of FA metabolism with ATP deficiency that is ineffective from energetic point of view;
- insufficient function of evolutionally late cells like monocytes and macrophages; they cannot utilize fully ligandless palmitic VLDL and their derivatives LDL and to hydrolyze poly-ChE.
- hostile influence of external environment and impairment of biological function of exotrophy (impaired external feeding). It is expressed in non-physiologically high consumption of animal food and meat with high palmitic SFA and Ch contents by herbivorous animals and humans.

Formation of ligandless palmitic VLDL and their derivatives LDLD is the key step of atherosclerosis pathogenesis; simultaneously it leads to impairment of several biological functions: a) how to utilize in vivo huge amount of ligandless palmitic VLDLD, that is pathogenetic base of atheromatosis; b) how would cells continue their function if it was impossible to uptake PUFA from intercellular environment, it is the base of atherosclerosis.

To reduce the frequency of CHD, myocardial infarction, lethality and increase human lifespan it is necessary to perform primary prevention, that means taking out hostile environmental factor of excessive amount of animal food consumed by phylogenetically herbivorous animals and humans. It is necessary to restrict beef, fat cow milk, cheese, acid cream, cream cheese and other animal food fats consumption. They contain the biggest amount of palmitic FA, Ch and palmitic TG [35].

Talking about the restriction of consumed animal food amount, it is necessary to decrease use of pork and mutton, keeping bird meat and bird eggs since just them contain PUFA in the form of poly-ChE. It is necessary for patients who don't eat fish. Fish of cold seas is an obligate substitution of beef. Cognitive function of brain cortex is the fundament of atherosclerosis prevention and, according with the Chinese principle of losing weight called "small plate", one should begin to lose weight starting from his head [36].

Carbohydrates are the main food substrate of all herbivorous animals and humans, insulin-dependent cells stimulated by insulin turn all newly synthesized palmitic SFA into oleic MFA. This FA in its turn is the fastest one and the most effective one to be oxidized by mitochondria. In vivo insulin creates physiologically optimal oleic variant of FA metabolism and provides high kinetic parameters of organism [37, 38].

It is important to reduce the quantity of consumed food, maintaining its diversity and keeping body weight at the lower border of physiological values and adding to body weight normalization constant optimal amount of physical exercises, biological function of locomotion and cognitive biological function. Primary prevention of atherosclerosis and atheromatosis should not be based on pharmacological methods. Small doses of statins are pathogenetically reasonable drugs for secondary prevention of atherosclerosis and atheromatosis. Physicochemical action of statins cannot be evidently effective and reduce significantly Ch content in lipid monolayer of VLDL. If statins decrease significantly Ch levels in some patients, it occurs due to changes of other Ch fractions on the edge of their toxic action and only if biological reaction of compensation is working well.

Phylogenetic theory of general pathology eliminated dualism of atherosclerosis pathogenesis, it united two ambient parameters with non-physiological action: excessive amount of SFA in food and Ch. It creates a united theory of atherosclerosis and atheromatosis. In the majority of patients without genetic abnormalities it is forbidden to allow formation of ligandless palmitic VLDL turning to LDL. If we were be

able to follow it, the problem of atherosclerosis and atheromatosis would be solved. There is no other way of atheromatosis and atherosclerosis prevention, it is impossible to propose anything else for abnormal biological function of trophology and biological reaction of exotrophy.

At this point we can make a pause in the discussion of causes underlying high cardiovascular mortality of Homo Sapiens in many countries due to environmental hostility, coronary atherosclerosis and myocardial infarction. It is necessary to organize effective atherosclerosis and atheromatosis prevention based on St.Peter's diet stated in the Holy Bible. Everything new is actually well-forgotten old. And only after it we can proceed with understanding of more difficult problems of inherited HLP, secondary atherosclerosis and atheromatosis. Tertium non datur.

Conflict of interest: None declared.

References

1. Titov V.N., Osipov G.A., Tararak E.M., Godkov M.A.. Fatty acids tissue in the carotid arteries and atheroma lipid stains. Unity of the pathogenesis of atherosclerosis syndrome and its symptoms - atheromatosis of the intima of the arteries. Patologicheskaya fiziologiya i eksperimental'naya terapiya. 2015; 59(3): 4-17. Russian
2. Dombrowskiy AL, Sergienko IV, Rvacheva AV, et al. Influence of atorvastatin therapy in different doses on endothelial progenitor cells and angiogenesis factors in patients with coronary heart disease. Ateroscleroz i dislipidemii. 2015; 2: 56–68. Russian
3. Titov VN. Phylogenetic theory of general pathology. The pathogenesis of metabolic pandemics. Diabetes. INFRA-M. M. 2014. 222 p. Russian
4. Musunuru K, Kathiresan S. Surprises from genetic analyses of lipid risk factors for atherosclerosis. Circ Res. 2016; 118(4): 579-85.
5. Nurnberg ST, Zhang H, Hand NJ, et al. From Loci to Biology: Functional Genomics of Genome-Wide Association for Coronary Disease. Circ Res. 2016; 118(4): 586-606.
6. Whitman SC, Hazen SL, Miller DB, et al. Modification of type III VLDL, their remnants, and VLDL from ApoE-knockout mice by p-hydroxyphenylacetaldehyde, a product of myeloperoxidase activity, causes marked cholesteryl ester accumulation in macrophages. Arterioscler Thromb Vasc Biol. 1999; 19(5): 1238-49.
7. Stachowicz A, Olszanecki R, Suski M, et al. Mitochondrial aldehyde dehydrogenase activation by Alda-1 inhibits atherosclerosis and attenuates hepatic steatosis in apolipoprotein E-knockout mice. J Am Heart Assoc. 2014; 3(6): e001329.
8. Lopez S, Bermudez B, Pacheco YM, et al. Dietary oleic and palmitic acids modulate the ratio of triacylglycerols to cholesterol in postprandial triacylglycerol-rich lipoproteins in men and cell viability and cycling in human monocytes. J Nutr. 2007; 137(9): 1999-2005.
9. Titov VN, Rogkova TA, Amelushkina VA. Fatty acids, triglycerides, hypertriglyceridemia, hyperglycemia, and insulin (pathogenesis, diagnosis, prevention, treatment foundations). M. INFRA-M. 2015. 197 p. Russian
10. Sanders T, Berry S, Miller GJ. Influence of triacylglycerol structure on the postprandial response of factor VII to stearic acid-rich fats. Am J Clin Nutr. 2003; 77(4): 777-82.
11. Titov VN, Lisizin DM. Fatty acid. Physical chemistry, biology and medicine. M. – Tver': LLC «Izdatel'snvo «Triada». 2006. 672 p. Russian
12. Anand SS, Hawkes C, de Souza RJ, et al. Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the Workshop Convened by the World Heart Federation. JACC. 2015; 66(14): 1590-614.
13. Nielsen S, Karpe F. Determinants of VLDL-triglycerides production. Curr Opin Lipidol. 2012; 23(4): 321-6.
14. Wildgruber M, Swirski FK, Zernecke A. Molecular imaging of inflammation in atherosclerosis. Theranostics. 2013; 3(11): 865-84.
15. Gentek R, Molawi K, Sieweke MH. Tissue macrophage identity and self-renewal. Immunol Rev. 2014; 262(1): 56-73.
16. Riccioni G, Sblendorio V. Atherosclerosis: from biology to pharmacological treatment. J Geriatr Cardiol. 2012; 9(3): 305-17.
17. Goode GK, Garcia S, Heagerty AM. Dietary supplementation with marine fish oil improves in vitro small artery endothelial function in hypercholesterolemic patients: a double-blind placebo-controlled study. Circulation. 1997; 96(9): 2802-7.
18. Libby P, Bornfeldt KE, Tall AR. Atherosclerosis: Successes, Surprises, and Future Challenges. Circ Res. 2016; 118(4): 531-4.
19. Shaikh SR, Kinnun JJ, Leng X, et al. How polyunsaturated fatty acids modify molecular organization in membranes: insight from NMR studies of model systems. Biochim Biophys Acta. 2015; 1848(1 Pt B): 211-9.
20. Qi K, Seo T, Jiang Z, et al. Triglycerides in fish oil affect the blood clearance of lipid emulsions containing long- and medium-chain triglycerides in mice. J Nutr. 2006; 136(11): 2766-72.
21. Abramov VV, Ershov OV, Filatenkov EV. Patterns of migration and circulation of immune cells: fundamental and applied aspects. Uspekhi sovremennoy biologii. 2007; 127(3): 257-66. Russian
22. Dushkin M.I Macrophage / foam cells as an attribute of inflammation: mechanisms of formation and functional role. Biokhimiya. 2012; 77 (4): 419-32. Russian
23. Zenkov NK, Chechushkov AV, Kozhin PM, et al. Macrophage and mycobacterium: war without beginning or end. Uspekhi sovremennoy biologii. 2015; 135 (6): 554-74. Russian

24. Shapiro MD, Fazio S. From Lipids to Inflammation: New Approaches to Reducing Atherosclerotic Risk. Circ Res. 2016; 118(4): 732-49.
25. Tabas I, Bornfeldt KE. Macrophage Phenotype and Function in Different Stages of Atherosclerosis. Circ Res. 2016; 118(4): 653-67.
26. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2016; 118(4): 547-63.
27. Nguyen-Lefebvre AT, Horuzsko A. Kupffer cell metabolism and function. J Enzymol Metab. 2015; 1(1): 101-15.
28. Knolle PA, Wohlleber D. Immunological functions of liver sinusoidal endothelial cells. Cell Mol Immunol. 2016; 13(3): 347-53.
29. Sorci-Thomas MG, Thomas MJ. Microdomains, Inflammation, and Atherosclerosis. Circ Res. 2016; 118(4): 679-91.
30. Maeda S, Nakanishi S, Yoneda M, et al. Associations between small dense LDL, HDL subfractions (HDL2, HDL3) and risk of atherosclerosis in Japanese-Americans. J Atheroscler Thromb. 2012; 19(5): 444-52.
31. Bie J, Zhao B, Marqueen KE, et al. Macrophage-specific transgenic expression of cholesteryl ester hydrolase attenuates hepatic lipid accumulation and also improves glucose tolerance in ob/ob mice. Am J Physiol Endocrinol Metab. 2012; 302(10): E1283-91.
32. Yuan Q, Bie J, Wang J, et al. Cooperation between hepatic cholesteryl ester hydrolase and scavenger receptor BI for hydrolysis of HDL-CE. J Lipid Res. 2013; 54(11): 3078-84.
33. Pedersen TR. The Success Story of LDL Cholesterol Lowering. Circ Res. 2016; 118(4): 721-31.
34. Domanski MJ, Fuster V, Diaz-Mitoma F, et al. Next Steps in Primary Prevention of Coronary Heart Disease: Rationale for and Design of the ECAD Trial. JACC 2015; 66(16): 1828-36.
35. Titov VN. Based on primary prevention of atherosclerosis. Klinicheskaya medizina. 2014; 12:19-29. Russian
36. Shnol S.E Physical and chemical factors of biological evolution. M. Nauka, 1979. Russian
37. Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. Cochrane Database Syst Rev. 2015; 3: CD008226.
38. Paynter NP, Ridker PM, Chasman DI. Are Genetic Tests for Atherosclerosis Ready for Routine Clinical Use? Circ Res. 2016; 118(4): 607-19.

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Optimized management of hypertensive patients with anxiety: focus on non-pharmacological approaches

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Resume

Objective

To optimize the management of patients with hypertension and anxiety in order to increase the adherence to treatment by non-pharmacological approaches in addition to basis therapy.

Materials and methods

The study involved 209 patients with arterial hypertension and anxiety. Adherence to drug therapy was estimated by Moriski Green's questionnaire. Anxiety was diagnosed by the Hospital scale of anxiety and depression. The subjectively perceived stress was estimated by a visual analogue scale of stress at work and at home.

Results

We investigated 149 factors and determined factors influencing the adherence to treatment in this cohort of patients. Based on selected factors, the procedure of prediction of non-adherent behavior in patients with AH and anxiety using the results of binary logistical regression has been created. The authors have developed "Non-pharmacological approach" (Patent №2525736) based on works investigating progressive muscle relaxation and controlled mental visualization. The research for assessment of adherence to treatment dynamics after the cycle

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of lessons in the "School of Health" with the standard program and using the "non-drug method of influence" (Patent №2525736) has been performed in 104 and 105 patients with AH of I and II groups respectively
It has been demonstrated, that progressive muscle relaxation exercises and controlled mental visualization (patent № 2525736) normalize blood pressure levels and increase patients' adherence to treatment, maintaining achieved results during 24 month observation.

Key words
Arterial hypertension, anxiety, non-pharmacological approach.

Anxiety is a personal feature, characteristic of temperament, caused by weakness of nervous processes and characterized by predisposition to frequent and intence experiencing of uneasiness [1]. According with numerous Russian and international studies , anxiety worsens the course of many somatic diseases and creates conditions for polytherapy [2]. Anxiety is diagnosed in 12-46% of arterial hypertension (AH) cases [2-5]. The presence of anxiety leads AH patients to violation of therapeutic regimen or even makes them refuse take drugs [6]. Studies of compliance to therapy in this category of patients are quite general [7, 8]. There are no data about the degree of distinct factors' impact on compliance, and up to date no techniques of non-compliant behavior prognosis have been developed in this cohort of patients.

Additional of non-pharmacological anxiety correction and formation of self-regulation skills to somatic disease treatment is one of variants to optimize the management of patients with AH allowing augmentation of therapy efficacy without increasing the number of prescribed drugs [2-9]. Relaxation techniques are more efficient, they reduce anxiety manifestations being used as a part of a complex approach for treatment of several diseases [10].

Behavioral methods reducing anxiety include progressive muscle relaxation developed by Jacobson E. and directive mental imagery devised by Simonthon C., Simonthon S. and Rossman M [9].

Methods directed on creation of positive mental images have been described just in elderly AH patients not receiving antihypertensive drugs exclusively with mental images of "heaviness" and "warmth" during autogenic training [10].

We developed "Non-pharmacological approach using progressive muscle relaxation, controlled mental visualization for treatment of patients with arterial hypertension" (Patent № 2525736, hereinafter "Non-pharmacological approach") based on Jacobson's method of progressive muscle relaxation and directive mental imagery worked out by Simonthon and colleagues [9]. "Non-pharmacological approach" provides blood pressure (BP) normalization, anxiety levels reduction by means of consequent, specially selected exercises for contraction and relaxation of particular muscle groups , creation of mental images in mind in addition to basis antihypertensive therapy. This "non-pharmacological approach" is quite topical in terms of the World Health Organization (WHO) guidelines on reduction of cardiovascular disease (CVD) development and progression risk factors influence.

The aim of this study was to optimize the management of patients with AH and anxiety to increase their compliance to treatment using non-pharmacological approach in addition to pharmacological therapy.

This study has been performed in two phases. The first stage was designed as a "case-control" study involving 209 patients into the group, the second stage was characterized as a prospective crossover observation of previously formed cohort of patients.

Materials and methods

209 patients with AH and anxiety that have been separated into two groups (n=104 and n=105) using envelope method participated in this study. Number of males in the first group was 48.1% (n=50) and in the second one – 44.8% (n=47). Number of females in the first group was 51.9% (n=54) and in the second one – 55.2% (n=58). Median of age in the first group was 45(41; 50) years and 47 (43; 51) in the second group. Necessary number of observations was quantified using Lopez Gemenes formula and Boyarskiy tables [11]. The protocol of this study has been approved by local ethic committee of Omsk State Medical University. Every patient received detailed information about ongoing study and signed informed consent form.

Inclusion criteria for this study: 1) males and females aged 40-55 years; 2) verified AH of I, II, III stage diagnosis; 3) presence of anxiety according with the HADS questionnaire; 4) patient's consent to participation in the study.

Exclusion criteria for this study: 1) symptomatic AH in endocrine system diseases, kidney diseases, disorders of renal vessels and central nervous system,

other symptomatic hypertensions; 2) excessive alcohol consumption; 3) patients with acute diseases and exacerbation of chronic diseases; 4) patient's refusal from participation in the study;

Patients' adherence to pharmacological treatment in this cohort of patients was estimated using Morisky-Green questionnaire. Anxious disorders were diagnosed using Hospital Anxiety and Depression Scale. Intensity of subjectively perceived stress as estimated using visual analogue scale of stress at home and at work, life quality was assessed using SF-36 questionnaire. 24-hours ambulatory BP monitoring (ABPM) was peformed using "Valenta" gadget (limited liability company "Neo", Saint Petersburg, Russia).

Statistical estimation of results was performed with descriptive statistics and graphic analysis methods using standard . Microsoft Excel 2003 and Statistica 8.0 software. Results didn't have normal distribution, thus their quantitative estimation was performed using non-parametric methods and obtained results are presented as median, upper and lower quartile – Me, (P25, P75), absolute values (n) and percentage±error of the proportion (%±m). Mann-Whitney test (Z) was used for comparison of two independent groups, Wilcoxon (z) test was performed for comparison of two linked groups. The x^2 test was used for comparison of categorical data. Correlation between variables was evaluated with Spearman's rank correlation coefficient. Analysis of correlation between several variables was assessed using univariate and binary logistic regression analysis. The technique of non-compliant behavior of patients with AH and anxiety prediction has been created using regression equation. Results were considered significant if p-value was <0.05 [11].

In the beginning of the study only one fifth part of patients of both groups were adherent to pharmacological therapy of AH. These numbers are less by 9-17% comparing with the patients without comorbid anxiety [12].

Results

We investigated 149 factors and determined factors influencing compliance in this cohort of patients. These factors have been subdivided into three groups: socio-demographic and psychological, features of patients' behavior, patients' condition and prescribed therapy.

The first group of factors included: marital status, level of anxiety/depression, subjective attitude to stress, role functioning, caused by emotional condition, psychical health [3; 13].

The second group of factors included features of patients' behavior in terms of modifiable risk factors: addition of salt to food, smoking status, physical activity [14].

The third group consisted of: AH manifestations intensity, presence of concomitant pathology, BP values measured during ABPM, examples of treatment refusal in the past [15-18].

Spearman's rank correlation analysis revealed statistically significant negative correlations between characteristics of compliance to pharmacological treatment and several factors in patients with AH and anxiety. The majority of studied factors are linked directly, it restricts their use for further analysis in order to create the technique of non-compliant behavior prediction.

We selected four factors, correlation between which was not statistically significant. Then regression coefficients have been quantified (degree of each factor's impact on the model).

Parameters of binary logistic regression and their estimation are present in Table 1.

The factor of treatment refusal in the past was the most important one between factors participating in non-compliant behavior formation. The risk of non-compliant behavior in this case was 2.34 times higher than in case of this factor's absence. The probability of non-compliant behavior in anxious patients with AH in case of absent complaints during treatment is

Table 1. **Contingency criteria value and relative risk of non-compliant behavior according with the results of univariate logistic regression**

Factor	Regression coefficient, β	Wald's test	Level of significance
Constant, β_0	1,79		
Lack of a partner	2,06	12,56	0,043
Addition of salt to food	0,91	1,38	0,924
Low physical activity	0,76	2,65	0,563
Smoking	1,92	10,04	0,042
Persistent complaints during AH therapy	2,29	15,27	0,023
Examples of treatment refusal in the past	2,34	17,39	0,000

2.29 times lower than the same value in patients with preserved complaints during pharmacological AH treatment. Smoking and lack of a partner increased the risk of non-compliant behavior twice.

We created a technique of non-compliant behavior of patients with AH and anxiety based on selected factors and results of binary logistic regression [6]. Logistic regression equation (1):

$$Y = \frac{\exp(-1,79 + 2,34 \times X_1 + 2,29 \times X_2 + 2,06 \times X_3 + 1,92 \times X_4)}{1 + \exp(-1,79 + 2,34 \times X_1 + 2,29 \times X_2 + 2,06 \times X_3 + 1,92 \times X_4)}$$

where

Y – probability of non-compliant behavior expressed as decimal fraction;

X_1, X_2, X_3, X_4 – (predictors) factors influencing non-compliant behavior;

B_0 – absolute term (regression coefficient). Constant.

β_1, β_2, β_3, β_4 – regression coefficients for X_1, X_2, X_3, X_4 predictors;

exp – a power function, e – natural logarithmic base, approximately equal to 2.72.

Comorbid somatic pathology was present in 36.4±3.3% (n=76) of patients involved in this study. The majority of patients with comorbid somatic pathology had diabetes mellitus (DM) 2 type(68.4±5.3%). Patients with DM 2 type had more evident deviations of 24 hours BP profile during ABPM in comparison to patients without DM 2 type (Figure 1). Differences between these groups are statistically significant (χ^2=2.093, p=0.043).

After selection of patients and their division into groups we performed a randomized prospective cohort crossover study with control examinations after 2, 12, 14 and 24 months after the beginning of the study to estimate the changes of compliance of patients with AH and anxiety in the first group (n=104) and the second group (n=105) after a cycle of lessons at the School of Health using standard program [19] and "Non-pharmacological approach".

According with the study design, patients of the second group attended standard lessons at the School of Health during first months, and patients of the first group attended the same lessons during 13 and 14 month after the beginning of observation. Education was performed according with the study guide for doctors "School of health for patients with arterial hypertension" [19]. Patients of the first group attended the School of Health lessons where "Non-pharmacological approach" was introduced during first months, and patients of the second group attended the same lessons during 13 and 14 month after the beginning of observation.

After two months of weekly education to perform exercises of "Non-pharmacological approach" patients received recommendations how to make the same exercises at home every week during 6-10 months. Exercise regimen was regulated taking into account how much busy were patients. Once in every two months patients of the first group (3-12 months of study) and patients of the second group (15-24 months of study) had to call the researcher and report their general state and BP dynamics. In parallel patients of the first group (3-12 months) and patients of the second group (15-24 months) were supervised once in 3 months by physicians and general practitioners in outpatient setting (according with the law of USSR Healthcare ministry from 30.05.1986 №770 "About the order of mass healthcare examination". Information about the treatment was obtained dur-

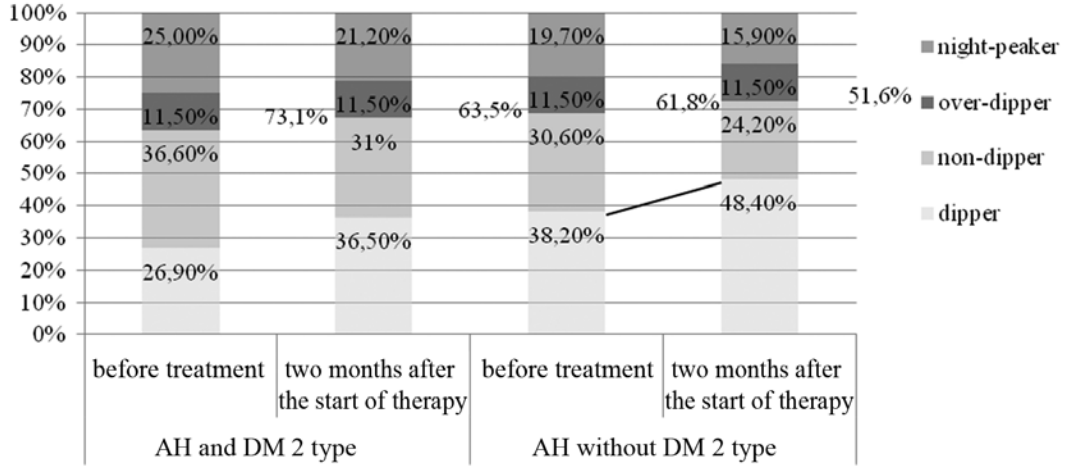

Figure 1. 24-hours BP profiles in patients with concomitant DM 2 type and without DM 2 type in the beginning of the study and 2 months after the start of "Non-pharmacological approach" use.

Table 2. **Dynamics of subjective attitude to stress at work and presence of evident anxiety in patients with AH and anxiety during 24-years observation**

Factors	Subjective attitude to stress at work			Anxiety with evident symptoms		
Time interval	Group I	Group II	Mann-Whitney test	Group I	Group II	Mann-Whitney test
	Abs	Abs.	Z; p	Abs	Abs	Z; p
0 months (start of the study)	76	77	0,219; 0,746	76	76	0,286; 0,732
2 months	29	59	8,913; 0,000	0	38	9,531; 0,002
12 months	21	62	8,734; 0,000	0	42	7,392; 0,003
14 months	17	15	0,903; 0,089	0	0	
24 months	15	14	0,841; 0,108	0	0	

ing personal talk 12 months after the beginning of the study because the majority of patients refuse to follow the treatment at this time [7].

Control examinations were performed 2, 12, 14 and 24 months after the beginning of the study.

Patients demonstrated the levels of compliance to antihypertensive therapy increased by 35.4±3.3% after the end of education in the "School of health" using "Non-pharmacological approach" . In comparison patients who attended standard lessons at the Health School increased compliance by 13.4±2.4%. 12 months after the beginning of observation 64.6±3.3% of patients who followed the lessons of the School of health with the addition of "Non-pharmacological approach" remained compliant to pharmacological treatment of AH, whereas only 46.9±3.5% of patients who followed standard lessons remained compliant.

After the cycle of lessons in the School of health with addition of "Non-pharmacological approach" the levels of subjectively perceived stress at work reduced by 45% and clinically evident anxiety was smoothed over (Table 2). Achieved results had been maintained until the end of the study in the first group and in the second one until 12 months of observation.

After obtaining statistically significant positive dynamics of compliance, reduction of subjectively perceived stress and anxiety levels we estimated BP changes during ABPM in this cohort of patients.

By the end of the cycle of lessons in the School of Health with addition of "Non-pharmacological approach" patients demonstrated reduction of average daily BP levels.

Optimization of management of patients with arterial hypertension and anxiety disorders after the education in the School of health with addition of "Non-pharmacological approach" in compliant patients of the first group was characterized with significant positive dynamics of average daily systolic BP (SBP), by its reduction. Achieved results had been maintained until the end of the study. Compliant patients of both groups after the education in the School of health with addition of "Non-pharmacological approach" demonstrated reduction of average daily BP: in the first group by 7 mm Hg (Z=8.2369; p≤0.01) and in the second group by 6 mm Hg (Z=8.4976; p≤0.01) .

Average daily diastolic BP (DBP) values reduced in compliant patients of both groups after the education in the School of health with addition of "Non-pharmacological approach", DBP decreased by 5 mm Hg in the first group . (Z=8.5072, p < 0.01) and by 4 mm Hg. in the second group (Z=7.9364; p≤0.01).

Patients with DM 2 type, selected during the first stage of the study from the patients with comorbid somatic pathology were characterized with more evident deviations of 24-hours BP profiles. As patients without DM 2 type, patients with comorbid DM 2 type demonstrated decrease of number of 24-hour BP profile deviations (figure 1) after the education in the School of health with addition of "Non-pharmacological approach", differences between groups are statistically significant (x^2=2.164, p=0.047).

Discussion

This study allowed to select factors that influence the most the compliance of patients with AH and anxiety independently on the presence of comorbid somatic pathology: socio-demographic factors: lack of a partner (R=-0.493, p<0.05; R=-0.506, p<0.05); factors reflecting patients' behavior: smoking (R=-0.478, p<0.05; R=-0.473, p<0.05); factors reflecting the course of disease - examples of AH treatment refusal in the past (R=-0.519, p<0.05; R=-0.523, p<0.05) and persistent complaints during antihypertensive treatment (R=-0.431, p<0.05; R=-0.363, p<0.05. We created the method of non-compliant behavior prediction in patients with AH and anxiety.

These results demonstrate that education of patients with AH and anxiety in the School of health with addition of "Non-pharmacological approach"

increases the levels of compliance to pharmacological treatment of AH by 35.4±3.3% comparing with the standard education program (x^2=8.96; p=0.049).

Use of "Non-pharmacological approach" smoothed over clinically evident anxiety (χ^2=8.93; p=0.008) and reduced subjective perception of stress at work 45.0±3.4% (χ^2=6.74; p=0.047), obtained results had been maintained during 24 months of observation.

It is necessary to notice that optimization of management of patients with AH and anxiety after education at the School of Health using the "Non-pharmacological approach" was accompanied with the reduction of average daily SBP by 7 mm Hg. in compliant patients of the first group (Z=8.2369; p≤0.01) and by 6 mm Hg. in the second one (Z=8.4976; p≤0.01); daily average DBP reduced by 5 mm Hg in compliant patients of the first group (Z=8.5072, p < 0.01) and by 4 mm Hg – in the patients of the second group (Z=7.9364; p≤0.01); it was also characterized by the reduction of deviations in 24-hours BP profile according with the ABPM results independently on the presence of comorbid somatic pathology from 61.8±3.9% to 51.6±4.0% in patients without DM 2 type and from 73.1±6.2% to 63.5±6.7% in patients with DM 2 type.

Thus, progressive muscle relaxation and controlled mental visualization "Non-pharmacological approach" exercises normalize BP values, increase the degree of patients' compliance to antihypertensive treatment, maintaining achieved results for 24 months of observation.

Conflict of interest: None declared

References

1. Large psychological dictionary. M.: Prime EVROZNAK. Ed. BG, Meshcheryakov, VP Zinchenko, 2002. 633s. Russian
2. Garganeeva NP, Belokrylova MF The main symptom and conditions of formation of neurotic and affective disorders in patients with cardiovascular disease. Siberian Medical Journal. 2009; 4: 11-7. Russian
3. Boitchov SA The structure of the factors of cardiovascular risk, and the quality of their prevention efforts in the primary care setting and Russia in European countries (according to the results of research EURIKA). Cardiovascular therapy and prevention. 2012; 11 (1): 11-6. Russian
4. Smulevich AB, Sirkin AL. Mental disorders in general medical practice. Psihokardiologiya. 2007; 4: 4-9. Russian
5. Bogner HR, de Vries HF. Integration of Depression and Hypertension Treatment: A Pilot, Randomized Controlled Trial. Ann Fam Med. 2008;6:295-301.
6. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. Am J Cardiol. 2010;105(10):1495-501.
7. Mazzaglia G, Ambrosioni E, Alacqua M, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation. 2009; 120(16):1598-605.
8. Trukhan DI, Pozdnyakov YM Actual aspects of rational pharmacotherapy in cardiology. Pros and cons of fixed and arbitrary combinations of antihypertensive drugs. Consilium Medicum. 2016; 1: 25-31. Russian
9. Linden W, Moseley JV. The efficacy of behavioral treatments for hypertension. Appl Psychophysiol Biofeedback. 2006;31:51-63.
10. Ostir GV, Berges IM, Markides KS, et al. Hypertension in Older Adults and the Role of Positive Emotions. Psychosom Med. 2006;68:727-33.
11. Khalafyan AA. STATISTICA 6. Statistical analysis of the data. 2nd ed. M.: OOO "Bean-Press", 2010. 528 p. Russian
12. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. Am J Cardiol. 2010;105(10):1495-501.
13. Vorobyov OV. Stress and adjustment disorders. Russian Medical J. 2009; 11: 789-93. Russian
14. Jones DE, Carson KA, Bleich SN, et al. Patient trust in physicians and adoption of lifestyle behaviors to control high blood pressure. Patient Educ Couns. 2012;89(1):57-62.
15. Black HR. Controlling Hypertension: From Mechanisms to Management CME/CE. CME/CE Released: 06/15/2010. Available from: html://www.medscape.org/viewarticle/723061.
16. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008 Jun; 31(3):213-24.
17. Kettani FZ, Dragomir A, Cote R, et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. Stroke. 2009; 40(1):213-20.
18. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005 (353): 487-97.
19. Chukaeva II, Orlova NV, OA Kislyak, et al. Health Schools for patients with cardiovascular diseases. Tutorial. M.: Russian State Medical University, 2011. 149 p. Russian

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Monitoring in cardiologic intensive care units

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Summary

The article examines main modern methods of physiological parameters monitoring in patients of cardiologic intensive care units: pulse oximetry, ECG, invasive blood pressure monitoring, cardiac output monitoring. Clinical monitoring is continuous monitoring of patient's condition, based on the registration of biological signals and evaluation of organism's diagnostic characteristics in order to detect deviations from normal values, to prevent risks and complications arising during treatment. Methods of physiological processes investigation that are used in clinical monitoring equipment should provide continuous registration of biological signals in real time together with high diagnostic value of parameters derived from processed signals.

Keywords

A*cute coronary syndrome, sudden cardiac death, arrhythmias, monitoring.*

The first in the world intensity care units (ICU) for patients with acute coronary syndrome (ACS) have been organized in the beginning of the sixties in the USA (Kansas, Miami, Philadelphia, New-York). American cardiologist Bernard Lown had made a significant description of the difference in patients' management before and after ICU introduction [1].

Before this time all intensive care units in the Peter Bent's hospital had been mostly oriented to resuscitation after sudden cardiac arrest. Monitoring had been performed before the start of ventricular fibrillations. Electronic monitor was the main device that controlled constantly the heart rate and gave the signal in case of any deviations. Well-educated nurses had been constantly alert in order to start resuscitation if it was necessary. All this reminded of fire-fighting units where everyone is waiting for warning alarm.

But when there was an alarm, superior medical staff started to take care of the situation. If patient had cardiac arrest, a lot of interns, trainees, residents, students, laboratory assistants and duty doctors started to make a fuss over him. Excited voices were ringing, the atmo-

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sphere was getting unbearable. Unlike nurses, doctors did not have distinct plan of actions, but they felt obliged to have overall charge. All procedure was accompanied with endless shouts, fuss and nervousness.

There was a popular joke at that time. Patient with the heart attack is admitted to the intensive care unit. He is frightened, agitated and wants to know what will happen to him. All medical staff is busy saving the life of another patient and does not answer to his questions. Patient is connected with different devices and he, entangled in wire, can hear his loud heartbeat and see the paling lines on the screen of oscillograph.

The evening is coming. Patient starts to think about future disability or death. Charwoman enters the room and starts to wash the floor. Patient turns his face on her and asks: "What will happen with me after?" – "I don't know but I can say this. Can you hear "Beep-beep-beep"? The most important thing is not to let it fell silent. If it happens, a dozen of people with white scrubs will rush into the room and they will wring this "beep" from you by all means".

When the intensive care department was opened in Peter Bent's hospital in 1965, I stopped immediately this disgrace. The main goal remained the same – the rescue of patients with acute myocardial infarction who had cardiac arrest. We used new oscillographs to identify the moment of ventricular fibrillations' start, that were connected with screens on nurses' area. Now they were allowed not to stay nearby patients waiting for arrhythmia to start, but to take care about patients under their charge from their duty stations.

Our department was organized in the way allowing to put as few psychological pressure on patients as possible. The light was dim, patients were able to listen to the radio using headphones, to keep silence was an unalterable rule. Since the surgeons always speak too much loud, we put the plate with the words "Surgeons should knock before entering!" on the door of our department. We tried to achieve the maximal privacy of all patients, but at the same time they could constantly see nurses, and they in their turn could always look after them. I always highlighted the necessity to protect patients from everything that can bring him anxiety in my endless instructions for medical staff. One can hear a faint moan or a heavy thigh only in silence.

Thus, active cardiac rhythm monitoring with the possibility of defibrillation became one of the main reasons of dramatic decrease of mortality in patients with ACS together with the prevention of fatal arrhythmias with lidocaine and the development of reperfusion techniques (thrombolysis and endovascular interventions).

As a half a century ago, nowadays prevention, early detection (another common name of these units – intensive observation units – is derived from here) and treatment of ACS complications including ventricular arrhythmias as the most frequent one, remain the main functions of ICU.

Modern ICU should have not less than six beds. The optimal way is to place a patient in a separate ward, the dimensions of which are enough to put all the necessary equipment like electrocardiograph, electric defibrillators, ventilator, ultrasound machine, counterpulsation device, portable X-ray machine etc, and to leave enough space for 3-4 persons working simultaneously. Wards should be equipped with water supply, oxygen delivery systems and vacuum system. According with international standards, the square of a ward should be not less than 25 m^2.

ICU are equipped with monitors, using which it is possible to control not only electrocardiogram (ECG) but also central hemodynamics parameters. Monitoring system usually has automatic alarm that turns on when controlled characteristics go beyond the normal values. Apart of bedside monitor, there is a central monitor in the area where medical staff stays that collects the information about all patients. The bedside console has a panel with an alarm button, which patient can easily push in case of slightest discomfort. Apart of this, in ICU there are the rooms for staff, equipment storage, making laboratory assays etc.

A team of qualified doctors and nurses is in 24-hour attendance at the ICU: for each 6 patients there is one doctor, 2-3 nurses and one junior nurse [2].

Since monitoring has a great importance in survival statistics of patients with ACS, further we will observe main techniques like ECG monitoring, peripheral oxygen saturation (SpO_2), CO_2 concentration, invasive blood pressure monitoring and cardiac output monitoring.

Pulse oximetry, ECG

Physiological parameters' monitoring is an important part of intensive care complex and it can promptly indicate the aggravation of ICU patient's condition and also evaluate the efficacy of treatment. Despite their high efficacy and importance of instrumental techniques of monitoring, it is necessary to remember that they are addition and not substitution of clinical estimation of heart rate, blood pressure, capillary

filling time, respiratory rate, neurological status and diuresis rate.

ECG, SpO_2 estimation require the presence of power supply and, in general, some active storage like pulse oximetry sensors or electrodes. More than that, it is necessary to provide maintenance service and monitor repair if necessary. All these aspects make it difficult to use these techniques under conditions of less-developed healthcare system.

There are several advantages of monitor system use:

• **Additional clinical information.** ECG, SpO_2, CO_2 monitoring provide important clinical information about the condition of cardiac and respiratory function. This information constantly enters the system in real-time mode that gives it particular importance in critical conditions.

• **Non-invasiveness.** These monitoring approaches are not invasive and well-tolerated by patients.

• **Early alarm system.** Alarm limits of each monitor can be regulated in the way allowing determining deviations of the most important parameters from the permissible level thus providing well-timed notification about changes of physiological characteristics. Careful analysis of the character of these deviations allows warning the doctor about early signs of deterioration.

Pulse oximetry (SpO_2)

If anesthesiologists were able to choose the only monitoring technique, the majority would choose pulse oximetry. It demonstrates how much important and useful can be the information obtained with this technique. The majority of pulse oximeters are separate units requiring battery. Pulse oximeter can also be a part of complex multipurpose systems. It consists of sensing element that is put on patient's finger and visual display reproducing obtained information.

Which information gives pulse oximeter?

The most important information that can be obtained with this technique is the value of peripheral oxygen saturation (SpO_2) reflected in percentage terms. Healthy patient breathing atmospheric air has SpO_2 value around 96-100%. SpO_2 of smokers and patients with chronic pulmonary diseases is reduced to 92-95. Patients in critical condition with primary (for example pneumonia) or secondary (for example acute respiratory distress-syndrome) pulmonary lesion are characterized with impaired gas exchange and lowered saturation. Target saturation levels that are reached by oxygen administration and ALV should be established on the basis of initial respiratory system condition [3]. For example, for the patient with concomitant chronic pulmonary disease complicated with infection it is reasonable to set up the lower limit of alarm for SpO_2 as 88%.

The majority of SpO_2 monitors quantify the heart rate (HR) that is accompanied with the sound. The pitch of tone varies according with the change of SpO_2, although it is enough difficult to estimate SpO_2 using just this signal. The change of volume is the sign for a doctor indicating that it is necessary to pay attention on monitor's reading.

Displays of several types of monitors demonstrate pulse wave that gives information about the quality of a signal and indicates how low is the real SpO_2 value. SpO_2. Good quality of the signal means that perfusion in the measuring area is not impaired. This sign has additional meaning in the conditions when limb perfusion can be impaired, for example, after injury or vascular operation. Weak or absent signal should urge the doctor to estimate patient's perfusion and blood pressure (BP). Signal can temporally disappear during cuff inflation on the limb for BP measurement.

Which information pulse oximeter does not provide?

SpO_2 reflects just partially the delivery of oxygen (DO_2) to tissues, because this characteristic depends also on hemoglobin(Hb) concentration and cardiac output (CO) value. Patient with Hb levels 35 g/L can have SpO_2 100%, but low oxygen arterial blood concentration (CaO_2), and therefore low DO_2 [3].

SpO_2 value is determined by ventilation efficacy, so by pulmonary pumping function, and by gas exchange through alveolar-capillary membrane. But ineffective ventilation (for example due to upper airways obstruction, opioid overdose, weakness after muscle relaxant use) can lead to the development of the second type of respiratory insufficiency that is characterized with CO_2 accumulation. Pulse oximetry does not provide information about CO_2 levels in arterial blood. Weakened patient can have promisingly normal SpO_2 levels especially during oxygen therapy, but it will be accompanied with evident respiratory acidosis with arterial blood CO_2 levels > 75 mm Hg and high risk of vascular collapse development [4].

Several specifics of pulse oximeter use

Bright artificial light source and bright sunlight can interfere with signal detection. Bright light effects

can be minimized closing the limb and the sensor with dark tissue. Patient movements can lead to noises and instability of measurements. This problem is quite important for agitated and aggressive patients. It is possible to fix the sensor on patient's finger using plaster and allowing them to move together.

Nowadays several types of sensors are available. All sensors are based on the same working principle; the difference is just in the size of patient and sensor's position on patient's body. Ear clip and pediatric sensors are smaller. If special pediatric sensor is absent, it is possible to put sensor for adult patients on the limb of a child. Quite often pediatric sensor is made as a sticker that can be attached on child's arm or leg. If it has been used for a short time, it is possible to reuse it after cleaning its adhesive surface. After all, these self-adhesive sensors can be effectively used during transportation of adult patient providing reliable fixation of sensor to finger [4].

It is reasonable to use central censor in patient with hypothermia or shock. It is possible to place finger sensor in the mouth of patients, making the measurements through cheek, nose or auricle. Small ear clip sensor can be also put on cheek, lip or nostril.

Electrocardiographic monitoring

ECG monitoring in ICU usually includes observation of a single, usually II lead and measurement of heart electric activity in longitudinal left axis. It is necessary to put three electrodes: the first one (usually red) on the right shoulder, the second one (yellow) on the left shoulder and the third one (usually green) on the left part of the chest. Using II lead it is possible to register the majority of arrhythmias, and it is the most important role of ECG-monitoring in ICU.

Which information gives ECG?

Monitor quantifies HR averaging the number of complexes during fixed period of time. If patient has arrhythmias like atrial fibrillation it is necessary to use the period of time as much long as it is possible for this monitor in order to estimate HR correctly.

Arrhythmias are diagnosed more often with the adjustment of upper and lower alarm signals in order to detect tachi- and bradyarrhythmias. Default alarm settings can be appropriate for healthy patient during manipulations under anesthesia, but they are not correct to be used in patients in critical condition. Patient with sepsis can have HR 120 beats per minute that will be higher than upper alarm signal. All alarm signal levels can be set up manually, making them significantly different from actual patient's parameters.

Several monitors allow to set up upper and lower alarm limits making them 10% different from actual value of parameter measured in patient. Several more advanced monitors can detect arrhythmia's character, although in general medical doctor should be responsible for detection of arrhythmia's cause (artefacts of movement, trembling that are often taken as ventricular fibrillation). It is very useful to use ECG and pulse oximetry together. The development of tachycardia with wide QRS complex together with the extinction of signal from pulse oximeter indicates ventricular tachycardia without pulse that is an urgent situation [5].

Often it can be useful to print registered ECG to study precisely cardiac rhythm (for example, to detect P wave). It is also possible to "freeze" the screen pushing the pause in order to perform more detailed ECG analysis. Frequently several ECG-monitor signals can be interpreted in a false way. For example, high T waves can be evaluated as separate QRS complexes that doubles measured HR. It is possible to use pulse oximetry to solve this problem, comparing HR and pulse oximeter readout. Multiple channel monitors including ECG, pulse oximetry (and the possibility of invasive BP measurement) demonstrate HR according with ECG analysis as the default, but these settings can be changed and HR value can be taken from another channel.

Bad quality of ECG-monitor signal can be the consequence of unsatisfactory contact between electrodes and patient's skin (sweat, dirt). If patient is shivering or moving, some background noise resembling arrhythmia can appear on the screen.

What ECG-monitor cannot estimate?

In case of myocardial ischemia development ECG can demonstrate the presence of morphological changes only if the ischemia has appeared in the area of corresponding lead. Otherwise ischemic changes would be impossible to see. In case of suspected myocardial ischemia doctor should make detailed ECG in 12 leads in order to check all parts of myocardium. Normal ECG does not always indicate normal patient's condition, in case of pulseless electrical activity (PEA), previously called electromechanical dissociation, and cardiac arrest there will be no CO, but ECG will demonstrate normal sinus rhythm. It is always necessary to compare monitor's readout and real clinical manifestations [5].

Conclusions

Pulse oximetry and ECG-monitoring use can be an useful addition to the management of patients in ICU increasing safety and optimizing therapeutic schemes. It is necessary to remember that all monitors are as much good as the people who use them, so it is necessary to think what is measured, set up alarm levels correctly and always use monitoring together with clinical estimation of patient's condition.

BP invasive monitoring

Invasive (intra-arterial) BP monitoring is widely used in ICU and in operating rooms. This technique considers catheter insertion in the lumen of appropriate bacteria with consequent displaying of arterial wave on the screen of monitor. The most frequent indication for invasive BP monitoring is the necessity to obtain information about hemodynamics condition for "each heartbeat".

Advantages of invasive BP monitoring:

• continuous BP measurement "with every heartbeat" is reasonable in case of patients who have sudden and unpredictable BP changes (like in case of cardiac and vascular operations) and when invasive BP control is prescribed. BP should be measured invasively in patients who receive inotropic and/or vasopressive agents (like adrenalin);

• this technique allows to measure BP precisely and accurately even for its low values for example in shock condition;

• prevents accidents due to constant cuff inflation who need long-term BP monitoring;

• intravascular volume status can be estimated according with the shape of BP curve or by visual estimation or by mathematical analysis of pulse wave shape (circuit);

• BP invasive monitoring can be used in patients in whom non-invasive BP measurement is not prescribed, for example, in case of evident peripheral edema or morbid obesity;

• fixed arterial catheter can be used for blood sampling and consequent analysis, for example, for gas composition estimation [6];

• Thus, there are several reasons for arterial catheter insertion.

Disadvantages of invasive BP monitoring:

• Arterial catheter is a potential infection source, although it is less prone to be infected comparing with venous catheters.

• Catheter staying in the lumen of artery can cause local thrombosis that in its turn can cause the formation of emboli migrating in vascular lumen or arterial occlusion. This complication occurs rarely if catheter is cleaned regularly and puncture position has been chosen correctly. Radial, femoral and axillary artery or foot arteries like posterior tibial artery and dorsal artery of foot can be used for catheter insertion. If it is possible it is better to avoid brachial artery catheterization. It is a terminal vessel and has no collateral connection, it means that brachial artery occlusion will lead to termination of forearm blood supply.

• All agents inserted in arteries can be crystallized and cause critical limb ischemia. Thiopental sodium and antibiotic can be the examples of the drugs that act in the same way. All arterial tubing should be signed accurately, and all tubing should have a red mark in order to prevent mistakes. You should not put the drugs inside the arterial catheter insertion!

• Arterial catheter insertion can be complicated in patients in shock condition, that can distract doctor from solving of more important problems that appear during the treatment of this patient.

• Equipment for monitoring, catheter and tubing are enough expensive, especially comparing with standard non-invasive monitoring technique.

• Invasive BP monitor requires external power supply, this can restrict its use in some cases [6, 7].

Invasive monitoring components and principles

Invasive monitoring components can be subdivided into three parts: detection system, transducer (signal transducer) and monitor.

Invasive BP monitoring precision

The following characteristics of measuring instruments will convince doctor that BP measurement precision is maximal.

• arterial catheter should be short and ad much wide as possible;

• normal saline solution column, so the length of the tubing, should be as much short as possible;

• catheter and tubing should be as much hard as possible;

• transducer diaphragm should be as much rigid as possible;

Settings and possible problems during work

Radial artery is a typical localization for catheter insertion. Radial artery advantage is that it is situated superficially, easy to palpate, it is also important that hand has collateral blood supply from ulnar artery. It is recommended to perform Allen's test to estimate the adequacy of hand's collateral blood supply with ulnar artery, although this test has some mistakes and it can be performed only in unconscious patients [8].

Alllen's test:

Patient is asked to clench his fist, doctor should push on patient's radial and ulnar arteries with his thumbs.

Patient is asked to unclasp his hand, the palm remains pale.

As soon as doctor removes his finger from patient's arm, patient's palm turns red, if the blood supply is functioning adequately.

It is not recommended to insert arterial catheter in brachial artery, because there is no collateral blood supply. If necessary, femoral artery, ulnar artery, foot and ankles arteries and even axillar artery can be used. Whatever artery has been used for catheter insertion, distal part of the limb should be checked regularly to exclude embolism or ischemia signs.

Arterial catheter insertion

This procedure should be performed in aseptic conditions. Wrist should be disinfected with chlorhexidine alcoholic solution before cannulation. It is necessary to infiltrate the skin of conscious patients with 1% lidocaine solution. The limb should be abducted in anatomical position and the hand should be overstraightened in order to facilitate cannulation (radial artery lays superficially and subcutaneously and limb movement lead to its shift during catheterization). More often assistant provides limb's correct position. If there is no assistant, it is possible to use plaster that allows to fix fingers on some surface (like container with infusion solution). Nowadays there are many rigid and short arterial catheters. Some of them are designed in the shape of "catheter on needle", reminding normal intravenous cannula, others should be inserted using catheter guide with Seldinger's technique. Artery is catheterized with a needle, catheter guide should be inserted though this needle and it should be used for catheter introduction. It is better to use the catheters with which doctor is well-acquainted. Ideally cannula should be connected with injection port in order to prevent unintended intra-arterial drug administration. If arterial cannula has injection port, it should be closed and the catheter by itself should be marked clearly as an arterial one [8].

It is important to fix arterial catheter firmly in necessary position, and do not allow bending the catheter. Sometimes it is useful to fix catheter to skin with several stitches.

Arterial catheter should be connected with tubing, and transducer should be fixed on heart level and previously "zeroized", that means it should be closed in the direction of patients and open "for air" to obtain information about atmospheric pressure (taken as 0). Often it is convenient to fix the transducer on patient's shoulder using plaster to make it stay on the heart level.

Practical advices and solution of appearing problems

• Reach-through puncture occurs frequently when it is impossible to find artery (sometimes doctors consciously use this technique): *needle is extracted, and cannula is pulled slowly, in parallel aspiration with a syringe should be performed. As soon as catheter tip enters again arterial lumen, blood starts to enter syringe under pressure. Cannula should be moved slowly from this position, possibly, with a bit of rotation in the direction of vascular axis. This insertion technique leads to positive result and successful artery catheterization more frequently than the others.*

• In case of successful insertion of a needle in the artery but unsuccessful catheterization it is useful to change the hand, arterial spasm develops very often after unsuccessful catheterization and it makes it very difficult to proceed with the catheterization.

• Catheter insertion into artery in patients in shock condition is complicated. Medical stuff should not lose time for retries, it is much more important to perform urgent interventions.

• After connection of catheter and tubing filled with normal saline solution it is necessary to make sure that air bubbles in the system are absent before the start of washing.

• Sudden elevation of BP values can signify that transducer fell on the floor.

• If wave on monitor's screen disappeared or became too much smooth it can mean that catheter is bent or blocked with blood clot, otherwise it can be the sign of air bubbles presence in the system.

Pulse wave form analysis

Useful information can be obtained during observation of arterial wave on the monitor.

• High amplitude or peak amplitude variation of systolic BP going along with the respiratory cycle can demonstrate the presence of hypovolemia in patient.

• Conscious patients due to evident changes of intrathoracic pressure can have significant fluctuations of arterial pulse wave.

• Narrow, high amplitude peaks combined with tachycardia can indicate hypovolemia.

• Arterial wave slope angle can give information about myocardial contractility; steep slope indicates more evident pressure change during unit of time and higher contractility. In practice this characteristic can roughly and approximately estimate myocardial contractility [9].

Conclusions

Invasive BP monitoring is very useful since it allows to examine BP dynamics in ICU patients. More than that, presence of arterial catheter facilitates arterial blood sampling for further estimation of its gas compositions and other characteristics. It is important to understand the main measuring principles to optimize the efficiency of monitoring systems and solve successfully appearing problems.

Cardiac output (CO) monitoring

Studies that have been performed since 1980 have proved that oxygen delivery optimization (that is the product of CO and oxygen concentration in blood) prevents the development of polyorgan insufficiency and improves survivability in high risk patients. Although neither one of the studies did not provide obvious evidences, their total impact demonstrates that therapy directed to improve oxygen delivery (task-oriented therapy) should be the priority. It has been proved that patients with hypovolemia should undergo infusion therapy to optimize oxygen delivery, whereas excessive infusion therapy can be harmful [9].

The only limiting factor in this area was the search of reliable and precise monitoring technique that could have helped to control volume and velocity of infusion therapy. Measurement of heart "filling" is not an easy task. We are trying to use a Frank-Starling law in that part when heart efficiency grows with the stretching of ventricular muscle fiber up to certain point, after which further stretching impairs heart productivity. To use this principle it is necessary to know end-diastolic volume of the left ventricle (LV) and observe its changes during ongoing infusion therapy. Its best characteristic measured in case of presence of Swan-Ganz catheter is pulmonary wedge pressure (PWP) that gives an idea about BP inside the left atrium, which, in its turn, defines LV end-diastolic volume, that is a "surrogate" of LV end-diastolic volume (in case of normal LV extensibility. These characteristics do not reflect correctly enough heart chambers filling during ALV and when catheter's tip passes through pulmonary artery small branches. Thermodilution with Swan-Ganz catheter use allows obtaining precise CO values, that can be changed constantly when all necessary equipment is available.

Nowadays the attention of researchers and technologies has moved into the direction of less invasive monitoring, risk of complications is reduced in case of its use. In wide understanding, these techniques using Doppler-based analysis of aorta blood flow velocity (in case of sensor's position inside the esophagus). or methods analyzing pulse wave curve [10,11]. In some monitors that analyze pulse wave shape to measure CO, it is possible to perform simultaneously the dilution of cold indicator or dye used to obtain reliable CO values that, in their turn, can be used after for machine calibration and following continuous measurement of this characteristic using pulse wave shape transmitted with arterial catheter. To facilitate this process, several monitors calibrate pulse wave using population data obtained from healthy volunteers and that have not been validated for patients with changed vascular resistance that, undoubtedly, affects the precision of quantifiable characteristics like CO. Thransesophageal Doppler ultrasound also uses population data to estimate the size of aorta cross-section.

Even if one is skeptical about absolute values obtained with these monitors, they still can be useful to estimate CO changes and efficacy of infusion therapy. The key question is the answer to the question: "Will patient respond to infusion load?" Otherwise, will the introduction of liquid bolus increase the productivity of cardiovascular system (like CO) and, consequently, oxygen delivery? The possibility to "respond" to infusion load indicates the movement "above" along Starling's curve.

Areas of present and future development include the use of systolic volume variability and pulse pressure variability measured using arterial wave. Observations demonstrated that hypovolemia can lead to evident fluctuations of systolic BP during respiratory cycle. These characteristics are expressed in percentage and not in absolute values and are used for prediction of sensitivity to infusion load.

Below we observe three methods of CO evaluation the most frequently used in Russian Federation: echocardiography (EchoCG), transesophageal EchoCG, right heart chambers catheterization with PWP estimation and thermodilution technique.

Echocardiography

Transthoracic EchoCG

EchoCG is an ultrasonic heart examination that can be used for CO estimation using direct heart visualization in real-time mode. EchoCG has become widespread being one of the most safe and available ways to perform CO monitoring in patients in critical condition.

EchoCG can be performed within minutes and can be helpful to determine the cause of unstable hemodynamics. 4 observation positions(sensor position) are available for transthorachic EchoCG: parasternal long axis, parasternal short axis, apical and subcostal positions, it is possible to evaluate ventricular function and heart chambers size [7].

Transesophageal EchoCG

Theoretical premises

Specific sensor is inserted into esophagus allowing to obtain ultrasound image of high resolution in real-time mode. 2-D square measurement of cross-section, Doppler-based flow velocity measurement and HR estimation allow to estimate CO qualitatively and quantitatively.

Practical use

Multiaxial transducer can be inserted into esophagus or stomach allowing to obtain images in different planes.

Advantages

A lot of information is available apart from CO measurement (Table 1).

Disadvantages

Sensors are quite expensive and equipment is heavy. Working experience is necessary, and it takes time and money to obtain it. Complete observation can require up to 20 minutes. Patient should be sedated; otherwise local pharynx anesthesia should be performed to provide successful sensor insertion. There is a risk of injury with the sensor, but it is lower in patients without esophageal pathology. Sensors can lead to the heating of tissues that makes their long-term use impossible. Further development of technologies and reduction of its price can lead to even more frequent use of transesophageal EchoCG in ICU and operation rooms.

Swan-Ganz catheter

Swan-Ganz catheter use is widely discussed during last years, and the frequency of its use in the majority of countries is not high. The PAC-Man study did not demonstrate improved survivability of patients comparing with the control group where catheter has not been used [12].

Theoretical premises

Flexible catheter with the balloon on its tip, directed with the blood blow (flotation catheter) is introduced through central venous catheter with big lumen (introducer). Catheter "floats" through right atrium and ventricle and enters pulmonary trunk. In this position if the balloon is inflated catheter can occlude one of pulmonary artery branches.

Using this catheter it is possible to measure several characteristics, and additional variables can be calculated.

Measured characteristics are: pulmonary artery pressure, PWP, CO and mixed venous blood saturation. CO is traditionally measured using termodilution and introducing 10 ml of cooled solution through proximal (central venous) catheter's port. Change of blood temperature decrease after introduction of indicator and its passing through the distal catheter's tip allows to estimate right ventricle CO and, consequently, LV CO. Semi-continuous CO measurement is available in case of use of catheter with heating spiral

Table 1. **Transesophageal EchoCG technical characteristics**

Characteristic	Desciption	Interpretation
Peak height	Peak velocity	The highest, recognizable flow velocity in aorta can be used for afterload, vascular resistance and contractility.
Angle of slope	Average acceleration	Contractility measure
Basement width (Ejection time)	Duration of flow	LV contraction time (duration of blood flow in aorta). Being corrected for HR it can be used for preload index quantification (if the basement is narrow it is possible to suspect hypovolemia).
Area under wave curve	Systolic distance	Length of blood column that is moved through aorta during each heart beat
Systolic distance	Systolic volume	Aortic cross-section
Afterload	Systemic vascular resistance	Is estimated using peak height and basement width reduction

that is built-in into the part of catheter staying in the right ventricle. Consequent heating of spiral together with analysis of obtained blood temperature changes allows to estimate average CO value after a short period of time.

Practical use

Catheter is inserted under the control of pressure curve shape change appropriate for each heart chamber and pulmonary artery and also controlling wedge position. Sometimes it is necessary to make several attempts to insert the catheter correctly, and this procedure is more difficult to perform in patients with low CO.

Advantages

The most frequent parameter obtained with flotation catheter is CO that allows estimating the efficacy of medical treatment. During PWP interpretation as the characteristic of preload it is necessary to take into account a big number of assumptions that lowers its reliability. Sometimes mixed venous blood saturation can be used as an universal tissue perfusion characteristic and it is obtained by slow aspiration of blood from pulmonary artery.

Limitations

Pulmonary artery catheterization is a highly invasive monitoring technique linked with several potential complications. The PAC-Man study has identified non-lethal complications in 10% of Swan-Ganz catheter insertion. Apart of typical complications that can occur during central venous catheter insertion, pulmonary artery catheterization can lead to the development of arrhythmias, blockade and rupture of right parts of heart or pulmonary artery, thromboembolism, pulmonary infarction, heart valves damage and endocarditis [12, 13].

Conclusion

Currently there is no ideal system, but each one of the monitors mentioned above can help a medical practitioner in case of doubts related to the management of patients in critical condition. Obtained information should be interpreted taking into account possible limitations of the used technique and particular patient's situation. Only in this case it can be safely used for control and modification of intensive care.

Conflict of interest: None declared

References

1. The Lost Art of Healing. Boston, MA: Houghton Miflin, 1996. New York City: Ballantine Books (paperback), Bernard Lown, 1999.
2. Zègre-Hemsey JK, Garvey JL, Carey MG. Cardiac Monitoring in the Emergency Department. Crit Care Nurs Clin North Am. 2016 Sep;28(3):331-45.
3. Schröder T. Hemodynamic monitoring – Basic monitoring. Anasthesiol Intensivmed Notfallmed Schmerzther. 2016 Oct;51(10):610-615.
4. Langton JA, Hutton A. Respiratory gas analysis. Contin Educ Anaesth Crit Care Pain. 2009; 9 (1): 19-23.
5. Carey MG. Acute Coronary Syndrome and ST Segment Monitoring. Crit Care Nurs Clin North Am. 2016 Sep;28(3):347-55.
6. Engelmann L, Kunig S, Kunig H. Blood pressure monitoring – Status quo and future : A contribution to the personalized medicine. Med. Klin. Intensivmed Notfmed. 2016 Oct;111(7):610-18.
7. Bauchmuller K, Faulds M. Care of the critically ill patient. Surgery. 2015 apr;33(4):165-71.
8. Monnet X, Cipriani F, Camous L et al. The passive leg raising test to guide fluid removal in critically ill patients. Ann Intensive Care. 2016 Dec;6(1):46.
9. Brown Z, Gupta B. Electrical signals and their measurement. Update in Anaesthesia 2008
10. Vincent JL. Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? No. Intensive Care Med. 2016 Nov;42(11):1778-80.
11. Aya HD, Cecconi M, Hamilton M, Rhodes A. Goal-directed therapy in cardiac surgery: a systematic review and meta-analysis. Br J Anaesth. 2013 Apr;110(4):510-7.
12. Davey R, Raina A. Hemodynamic monitoring in heart failure and pulmonary hypertension: From analog tracings to the digital age. World J Transplant. 2016 Sep 24;6(3):542-7.
13. Cooper AS. Pulmonary Artery Catheters for Adult Patients in Intensive Care. Crit Care Nurse. 2016 Apr;36(2):80-2.

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CLINICAL CASE

Acute Myopericarditis secondary to campylobacter jejuni enterocolitis

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Summary

Myo(peri)carditis is a rare condition that can mimic an acute coronary syndrome. Infective myocarditis is most commonly due to viral infections while bacterial etiology is extremely rare. There are only a few case reports of** Campylobacter jejuni **associated myocarditis. We present a case of previously healthy young adult male who de-

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veloped myopericarditis shortly after infectious gastroenteritis caused by** Campylobacter jejuni**. To our knowledge this is the first reported case of Campylobacter jejuni myopericarditis in Lithuania.

Keywords
Campylobacter, enterocolitis, myocarditis.

Introduction

Myo(peri)carditis is a rare condition that can mimic an acute coronary syndrome. Infective myocarditis is most commonly due to viral infections, while bacterial infection is extremely rare. [1] *C.jejuni* is the most common bacterial cause of enterocolitis in developed countries [2]. There are only a few case reports on *Campylobacter jejuni* associated myocarditis [3, 4]. Patients with C.jejuni associated myo(peri)carditis are usually young and previously healthy adult males. In most cases it ended with no sequel. [5] We present a case of previously healthy 23 year old adult male who developed myopericarditis shortly after infectious gastroenteritis caused by *Campylobacter jejuni*. With aspirin and antibiotics his condition improved within few days.

Case presentation

A 23-year old male, Italian citizen studying in Lithuania, was admitted to the Emergency department of Infectious diseases and tuberculosis hospital on December 1st, 2013, with a history of high fever (38.5 °C) for four days, abdominal pain and profuse watery diarrhea (up to 10 times per day). He did not have any recent travel history, nor contact with other sick people. On examination, patient was haemodynamicaly stable with medium signs of dehydration. After intravenous fluid infusion, the patient was released home with prescription of ciprofloxacin 500 mg BID for 5 days. On December, 5th *Campilobacter jejuni* infection was identified in coproculture analysis. At that point patient had no fever, yet he noticed blood in his stools. Azithromycin 500 mg QD for 3 days was administered. On December, 6th patient developed high fever (38.5 °C), chest pain and difficulty to breathe. After the evaluation at the Emergency department of Infectious diseases hospital patient was referred to the Emergency department of Vilnius University Hospital Santariskiu klinikos. He referred pressure like left chest pain no radiating, increasing with a change of posture and during deep breathing. The chest pain used to subside when sitting upright.

On the admission the patient had high fever (39.1 °C) and was haemodynamicaly stable (blood pressure 116/86 mm Hg, heart rate 96 beats/min.). Palpation of the thorax and abdomen did not show any painful areas and bowel sounds were normal.

Laboratory tests revealed high troponin I (0.993 mkg/l, reference <0.03mkg/l), total white cell count (10.56 $x10^9$/l, reference <9 $x10^9$/l), C-reactive protein (18.3 mg/l, reference <5mg/l) and procalcitonin (0.15 mkg/l, reference <0.05 mkg/l). Potassium level was abnormal (3.7 mmol/l, reference >3.8 mmol/l). CK-CM was normal (2.95 µg/l, reference <5.2 µg/l). Erythrocyte sedimentation rate, haemoglobin level and platelet count were normal.

An electrocardiogram showed sinus rhythm with ST-segment elevation on leads I, II, V4-V6 (Fig. 1).

Echocardiography showed normal myocardial function.

Given the history of recent diarrhea, chest pain, fever, elevated troponin I 0.993 mg/l, CRP 18.3 mg/l, procalcitonin 0.25 mkg/l, ECG changes, the patient was diagnosed with acute perimyocarditis secondary to C*ampylobacter jejuni* infection and was admitted to Department of Cardiology.

He was started on aspirin 100mg QD and amoxicilin with clavulanic acid 1.2g TID i/v. Within the treatment course CRP increased from 18.3 to 107 mg/l, troponin increased from 0.993 to 11.005 mkg/l and CK-MB from 2.95 to 33.78mkg/l. On the 3rd day of hospitalization patient was commenced on Gentamicin 80 mg x TID i/v and clarithromycin 500 mg BID i/v. Urinary and blood cultures were negative.

Colonoscopy showed turgid mucosa of sigmoid intestine. Biopsy revealed chronic active colitis likely of infectious etiology.

Within the course of antibacterial treatment the patient's condition improved. His temperature settled and inflammatory markers decreased. He was discharged on 7th day of the hospitalization.

Discussion

Myocarditis is an inflammatory disease of cardiac muscle. The exact prevalence of the myocarditis is not known, though evidence of myocardial inflammation is foud in 5% of post mortem examinations.[6] Infective myocarditis is most commonly due to viral infections – coxsackie A and B viruses, echovirus and adenovirus. Myocarditis due to a bacterial infection is

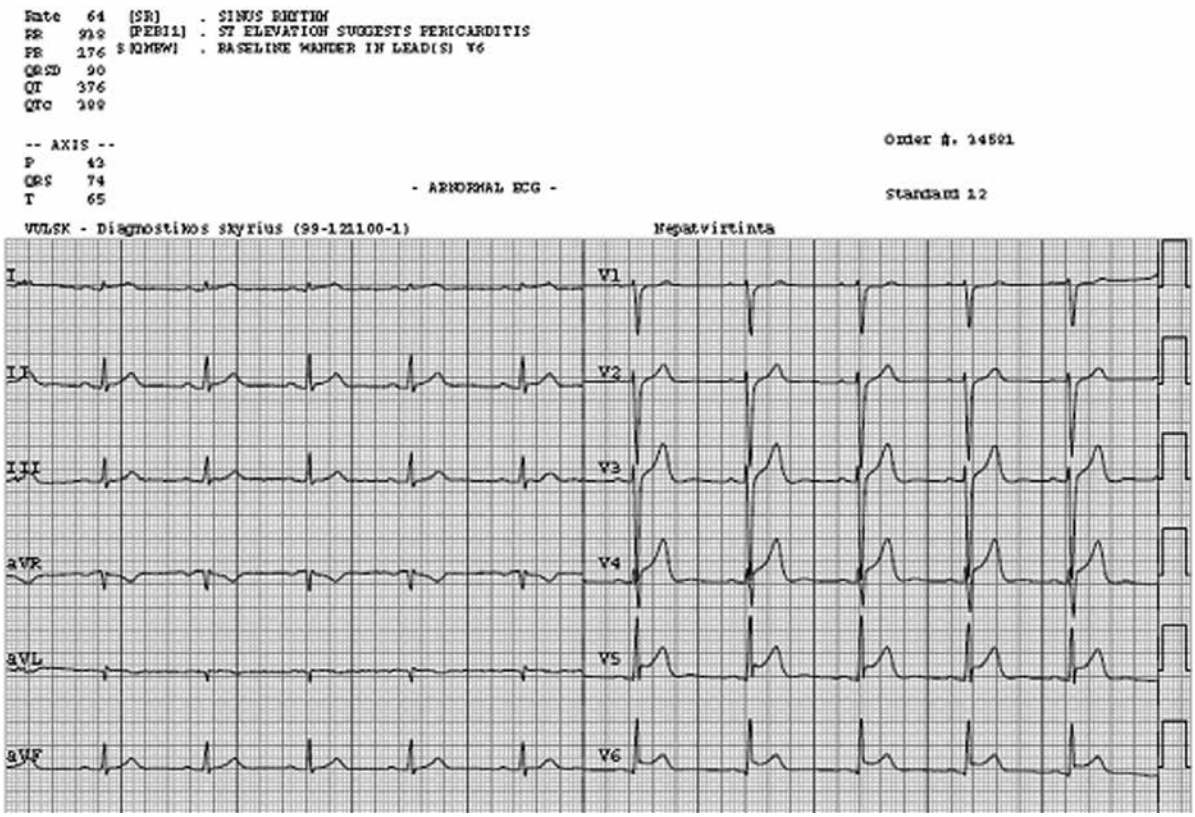

Fig. 1. ECG showed ST-segment elevation on leads I, II, V4-V6

rare. Bacterial pathogens associated with myocarditis include Streptococci, Staphylococci, Pneumococci, Neisseria, Legionella, Coxiella, Pneumophilus, Mycobacterium tuberculosis.[7] Enteric pathogens cause myocarditis in extremely rare cases, with most of them associated with Salmonella and Shigella. To this day only a few cases of C.jejuni associated myocarditis have been reported in the literature, most of them being young adult males.[5, 8-13] Myocarditis can progress to a chronic cardiomyopathy and is a leading cause if sudden death in adults under 40 years old [14].

Epidemiological studies showed that Campylobacter was the cause of diarrheal illness more than 2-7 times as frequent as infections with Salmonella, Sheila species or Escherichia coli O157:H7. Extraintestinal manifestations of Campylobacter infection are quite rare and may include meningitis, endocarditis, septic arthritis, osteomyelitis and neonatal sepsis. The most common postinfectious complication of C.jejuni infection is the Guillain –Barre syndrome. People with the HLA-27 histocompatibility antigen are prone to the development of reactive arthritis several weeks after infection with Campylobacter. Other postinfectious complications are rare and include uveitis, hemolytic anemia, hemolytic uremic syndrome encephalopathy and myocarditis [15].

The pathophysiologic mechanism by which Campylobacter causes myo(peri)carditis remains uncertain. It may be caused by direct bacterial invasion of cardiac tissue, bacterial toxins, circulating immune complexes, or cytotoxic T-cells. Direct bacterial involvement is documented in Campylobacter fetus cases, were pathogen was isolated from blood in almost all cases. But in C.jejuni associated cases the organism was isolated only in one case. PCR studies were negative when performed with myocardial tissues in one fatal case of C.jejuni associated myocarditis in USA – thus supporting toxin induced myocardial injury theory.[10] Although C.jejuni is known to produce a variety of exotoxines with cytotoxic, haemolytic and hepatotoxic effects, but none is known to cause cardiotoxicity. [16] There were few reports on patients with longer interval between enterocolitis and cardiac complications and arthritis, both occurring at the same time. These cases suggest immunological involvement.

Diagnosis of myo(peri)carditis is primary clinical. Clinical features observed in this patient are as reported in the literature. Elevated cardiac biomarkers and acute phase reactants can be detected. Troponin I has high specificity (89%) but limited sensitivity (34%) in the diagnosis of myocarditis (elevated in a minority of patients with acute myocarditis) that coupled

with transient ECG ST-segment elevations or T wave inversions are important to recognize heart disease. Cardiac enzymes are initially elevated but decline promptly as right medication are given even though the efficacy of antimicrobial therapy still lacks evidence. [17, 18] The 12 lead ECG may mimic the changes of an ACS or it may show tachy or bradyarrhythmias. In patients presenting with chest pain, ECG abnormalities and a raised cardiac biomarker, diagnostic coronary angiography needs to be performed to exclude obstructive coronary artery disease. There is no clear relationship between the clinical, laboratory and ECG findings in patients with myocarditis and no validated diagnostic criteria are used in daily clinical practice.

Gold standard for diagnosing myocarditis is endomyocardial biopsy (EMB). EBM usually shows inflammatory cellular infiltration with or without necrosis. However, these criteria are unreliable due to possible infiltration tissue sampling error, therefore cell-specific immunoperoxidase stains for surface antigens, such as anti-CD3, anti-CD4, anti-CD20, anti-CD68, and anti–human leukocyte antigen should be performed and may have prognostic value. Due to lack of sensitivity and the invasive nature of the procedure it is not commonly performed at many medical centers. [19, 20]

Noninvasive methods are primarily used for diagnosis of myocarditis. Recent studies have shown that cardiac magnetic resonance with gadolinium enhancement provides an accuracy of 78%. [21] Gadolinium accumulates in areas of inflammation so that the hyperintense areas observed on T2-weighted images are due to increase in myocardial free water content due to lymphocytic infiltration and myocytolysis. [8] Cardiac MRI is more sensitive than echocardiography. [22]

The clinical efficacy of antimicrobial treatment for C.jejuni associated myo(peri)carditis is unknown. Treatment of myocarditis is usually supportive. Patients with heart failure should be started on diuretics and angiotensin-converting-enzyme inhibitors. Once stabilized, beta-blockers should also be initiated in patients with left ventricular systolic dysfunction.[23] Aspirin may be given if concomitant pericarditis is suspected, however, other nonsteroidal anti-inflammatory agents, including ibuprofen and indometacin, have been shown to worsen myocarditis in animal studies.[7]

Conclusion

In summary, despite being a rare complication, *C. jejuni* associated myopericarditis should be suspected when chest pain appears shortly after or during an episode of diarrhea and fever. This condition usually affects young adult male patients and has a favorable prognosis. Cardiac enzymes are initially elevated but decline promptly. ST-segment elevations and/or T wave changes are concurrently observed, but they rapidly normalize. Cardiac magnetic resonance can be more sensitive and helpful than echocardiography, showing focal enhancement with gadolinium during the first days of evolution. Identification of *C. jejuni* in stools requires special culture media though efficacy of antimicrobial therapy still lacks evidence.

Conflict of interest statement

The authors of this case report that have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Feldman AM, McNamara D. Myocarditis. N Engl J Med, 2000. 343(19): p. 1388-98.
2. Allos BM. Campylobacter jejuni Infections: update on emerging issues and trends. Clin Infect Dis, 2001. 32(8): p. 1201-6.
3. Rafi A, Matz J. An unusual case of Campylobacter jejuni pericarditis in a patient with X-linked agammaglobulinemia. Ann Allergy Asthma Immunol Oct 2002;89(4):362–7.
4. Nowakowski MLD, Freeman SR. Pericarditis associated with Campylo- bacter jejuni enterocolitis. Hosp Physician Jan. 2002:39–42.
5. Turley AJ, Crilley JG, Hall JA. Acute myocarditis secondary to Campylobacter jejuni enterocolitis. Resuscitation, 2008. 79(1): p. 165-7.
6. Burlo P, Di Giola V, Passarino G et al. Adult myocarditis in a general hospital: observations on 605 autopsies. Pathologica, 1995(87(6)): p. 646-9.
7. Maisch B, Seferović PM, Ristić AD et al. Guidelines on the diagnosis and management of pericardial diseases executive summary: the task force on the diagnosis and management of pericardial diseases of the European Society of Cardiology. Eur Heart J, 2004(25): p. 587-610.
8. Panikkath R, Costilla V, Hoang P. Chest pain and diarrhea: a case of campylobacter jejuni-associated myocarditis. J Emerg Med, 2013(46(2)): p. 180-183.

9. Alzand BSN, Ilhan M, Heesen WF et al. Campylobacter jejuni: enterocolitis and myopericarditis. Int J Cardiol, 2010. 144(1): p. e14-6.
10. Pena LA, Fishbein MC. Fatal myocarditis related to Campylobacter jejuni infection: a case report. Cardiovasc Pathol, 2007. 16(2): p. 119-21.
11. Mera V, Lopez T, Serralta J. Take traveller's diarrhoea to heart. Travel Med Infect Dis, 2007. 5(3): p. 202-3.
12. Fica A, Seelmann D, Porte L et al. A case of myopericarditis associated to Campylobacter jejuni infection in the southern hemisphere. Braz J Infect Dis, 2012. 16(3): p. 294-6.
13. Cunningham C, Lee CH. Myocarditis related to Campylobacter jejuni infection: a case report. BMC Infect Dis, 2003. **3**: p. 16.
14. Drory Y, Turetz Y, Hiss Y et al. Sudden unexpected death in persons less than 40 years of age. Am J Cardiol 1991;68(13):1388—92.
15. Allos BM. Campylobacter jejuni Infections: Update on Emerging Issues and Trends. Clini Infect Dis, 2001(32): p. 1201-6.
16. Wassenaar TM. Toxin production by Campylobacter spp. Clin Microbiol Rev, 1997. 10(3): p. 466-76.
17. Roongsritong C, Warraich I, Bradley C. Common causes of troponin elevations in the absence of acute myocardial infarction: incidence and clinical significance. Chest, 2004. 125(5): p. 1877-84.
18. Smith, SC, Ladenson JH, Mason JW et al. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation, 1997. 95(1): p. 163-8.
19. Herskowitz A, Ahmed-Ansari A, Neumann DA et al. Induction of major histo- compatibility complex antigens within the myocardium of patients with active myo- carditis: a nonhistologic marker of myo- carditis. J Am Coll Cardiol 1990;15:624- 32.
20. Maisch B, Portig I, Ristic A et al. Definition of inflamma- tory cardiomyopathy (myocarditis): on the way to consensus: a status report. Herz 2000;25:200-9.
21. Elamm C, Fairweather D, Cooper LT. Pathogenesis and diagnosis of myocarditis. Heart 2012;98:835–40.
22. Yelgec NS, Dymarkowski S, Ganame J et al. Value of MRI in patients with a clinical suspicion of acute myocarditis. Eur Radiol, 2007. 17(9): p. 2211-7.
23. Magnani JW, D.G., Myocarditis: current trends in diagnosis and treatment. Circulation, 2006(113): p. 876-90.

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Report on the results of VI Caucasus scientific and educational conference of cardiology and internal medicine

VI Caucasus scientific and educational conference of cardiology and internal medicine was successfully held in Grozny, Russia, on October 25-26, 2016. This event was organized by the Ministry of Healthcare of the Russian Federation, Russia President Plenipotentiary Representative Office in the North Caucasian Federal district (NCFD), Head of the Administration and Government of the Chechen Republic, the Ministry of Healthcare of the Chechen Republic, Chechen State University, Russian society of Cardiology and the foundation for advancement of cardiology "Cardioprogress".

The minister of healthcare of the Chechen Republic Elkhan Suleimanov made a speech during the opening ceremony and noted that participation in professional conferences of such scale is a good opportunity to improve the knowledge level of primary healthcare practitioners and public health officials. The minister expressed his deep gratitude for active participation in the conference to leading scientists, colleagues and all guests from other regions. The head cardiologist and cardiac surgeon of NCFD spoke with an annual report about cardiologic service organization and secondary care for patients with cardiovascular diseases.

More than 700 doctors and delegates from NCFD and different cities of 5 federal districts of the Russian Federation (RF) participated in the conference.

Scientific program included more than 120 presentations and lectures of leading experts from 26 cities of RF and CIS countries. The congress had been hold in parallel in four assembly halls of Chechen State University. Subject area of the Conference included questions of prevention, prevalence, pharmacological and surgical treatment, rehabilitation for cardiovascular and other somatic diseases, comorbidity in clinical practice and healthcare management problems. Master class of functional diagnostics and echocardiography was organized during the conference. Organization of mass health examination was one of important and debatable topics. Main aspects of new European guidelines and results of international clinical trials in cardiology had been present during the congress.

Lectures of the leading experts: the honorable president of Russian Society of Cardiology, president of the "Cardioprogress" Foundation, RAS academic Rafael G. Oganov, Professor Zh.D. Kobalava, Professor F.T. Ageev, head doctor of Astrakhan federal Cardiovascular Center Dmitry Tarasov, Professor M. N. Mamedov, etc, have attracted great interest. for the first time experts from different regions of Russia (Urals, Siberia, cities like Saratov, Rostov-na-Donu, St. Petersburg) and Kazakhstan took part in the scientific part of the conference. Together with this, around 60% of all presentations were made by specialists from different regions of the North Caucasus including the Chechen Republic. It is pleasant to notice that eight leading cardiologic institutions, cen-

ters and universities organized their own workshops on different directions of cardiology and therapy. Four workshops of interventional cardiology and cardiac surgery involving specialists from different NCFD and RF federal centers became a new element of the scientific program of the conference this year. Two workshops with participation of 10 young scientists were included into the scientific program of the conference. All presentations were accompanied with active discussions.

Collection of scientific works (300 abstracts from 60 cities of Russia and CIS countries) was published in supplementary materials of the "Cardiovascular therapy and prevention" journal.

An exhibition of medicines and medical devices manufacturers was organized during the conference. Delegates received medical literature, information booklets and CDs with international clinical guidelines.

The department of culture of Grozny prepared a concert program involving important artists of Chechen Republic. Participation, registrations of delegates, coffee-breaks and ceremonial party were free of charge.

After the conference delegates received academic certificates reflecting new model of continuous medical education with 12 credit hours.

Five doctors received awards for their impact in the development of cardiology service. During the first day of the conference the minister of healthcare of the Chechen Republic invited 15 leading expert from the North Caucasus and other regions of Russia and Kazakhstan into the Ministry of Healthcare and expressed the gratitude on the behalf of the head of the Chechen Republic for their contribution to medical education in the Chechen Republic and adjacent regions. Press-conference with leading professors was organized during the congress. Later the head of the Chechen Republic Ramzan Kadyrov received 5 eminent Russian scientists and the president of Kazakhstan associations of therapists. Scientists expressed their willingness to help to prepare specialists for the Chechen Republic healthcare system.

The conference was widely covered by federal and regional mass-media, In particular, state TV channel "Grozny" has prepared special news block, several reportages and interviews giving information about the work of the conference. This information was published in news blocks of the Russian News Agency TASS, "Vesti Kavkaza" (Caucasus News), "Rambler News", information agency "Grozny inform" and in profiled mass-media and official websites of NCFD healthcare ministry. Leading Russian scientific journals "Kardiologiia"(Cardiology), Cardiovascular Therapy and Prevention, Rational pharmacotherapy in cardiology and "International heart and Vascular Disease Journal".

Next VII Caucasus scientific and educational conference of cardiology and internal medicine with international participation will be held in two Dagestani cities Makhachkala and Derbent in the end of October 2017. Detailed information, photos and videos about the conference can be found on the official website of the "Cardioprogress" Foundation www.cardioprogress.ru

International Heart and Vascular Disease Journal
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Journal of the Cardioprogress Foundation

Guidelines for authors

International Heart and Vascular Disease Journal
Requirements for Submission and Publication

The requirements for submission and publication in the **International Heart and Vascular Disease Journal** are based on the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the *International Committee of Medical Journal Editors* (ICMJE), which can be found at www.ICMJE.org

These requirements form the basis for relations between the Editors of the **International Heart and Vascular Disease Journal**, further called "the Editors", and an author who submits a manuscript for publication, further called "the Author".

The **International Heart and Vascular Disease Journal** publishes reviewed articles that cover all aspects of cardiovascular diseases, including original clinical research, experimental research with clinical relevance, reviews on current problems in cardiology, and clinical case studies. Usually 4 issues are published annually (one issue every 3 months).

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1. Submission requirements and publishing policy

1.1. A manuscript should be submitted to the following e-mail address: submissions.ihvdj@gmail.com

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1.14. The Editors recommend that submitted manuscripts conform with the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the *International Committee of Medical Journal Editors* (ICMJE), and available on the **International Heart and Vascular Disease Journal** website www.cardioprogress.ru, in the 'For Authors' section.

1.15. Adhering to the standards outlined in this document will lead to faster reviewing, editing, and publishing of manuscripts accepted for publication. Manuscripts submitted outside the standards on design and formatting for this journal may not be accepted by the Editors.

2. General recommendations for submission of original scientific works

2.1. The Editors recommend that results of randomized controlled trials conform to the 'Consolidated Standards of Reporting Trials' (CONSORT) guidelines. Information on these standards are available on the CONSORT website: www.consort-statement.org

2.2. A manuscript should be typed using the Times New Roman font (12 points, double spacing; with 2 cm at the top, bottom, left and right margins). The length of a manuscript, including references, schedules, drawings and tables, should not exceed 12 standard typewritten pages (1 page is 1800 letters or symbols, including spaces). A case study should not exceed 6 standard pages. Reviews and lectures should not exceed 25 standard pages.

2.3. Manuscripts should be organized as follows: 1) title page; 2) structured summary and keywords; 3) list of abbreviations; 4) text; 5) acknowledgements (if applicable); 6) references; 7) names and legends of pictures, tables, graphics, and photocopies in the order they appear in the manuscript; 8) drawings, tables, graphics, and photocopies should be submitted on separate pages in the order they appear in the manuscript. Numeration of pages should begin from the title page.

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2.5. Manuscripts based on reviews of original research works should contain the following sections: Introduction (reflecting the urgency of a problem and research goals); Material and methods; Results; Discussion of the obtained results and Conclusion. The text should be clear, brief and without repetition.

3. Publication of uncontrolled trials results

3.1. An uncontrolled trial is a research without a control group.

3.2. Manuscripts based on uncontrolled trials results will be accepted for publication in the 'Practical Experience' column only if the uncontrolled design of the study is described in the Material and methods and Discussion sections. It is important not to exaggerate the significance of results in the Conclusion' section.

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of "good clinical practice". Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The «Material and methods» section must contain details of the process of obtaining participants informed consent, and notifica-

tion that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

4.2. Patients have the right to privacy and confidentiality of their personal data. Therefore, information containing pictures, names, and initials of patients or numbers of medical documents should not be presented in the materials. If such information is needed for scientific purposes, it is necessary to get written informed consent from the research participant (or their parent, their trustee, or a close relative, as applicable) prior to publication in print or electronically. Copies of written consent may be requested by the Editors.

4.3. Animal trials must conform to the 'International Guiding Principles for Biomedical Research Involving Animals', adopted by the *Council for International Organizations of Medical Sciences* (CIOMS) in 1985.

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5.1. Each author should significantly contribute to the work submitted for publication.

5.2. If more than 4 authors are indicated in the author's list, it is desirable to describe the contribution of each author in a covering letter. If the authorship is attributed to a group of authors, all members of the group must meet all criteria for authorship. For economy of space, members of the group may be listed in a separate column at the end of the manuscript. Authors can participate in the submitted manuscript in the following ways: 1) contributing to the concept and research design or analyzing and interpreting data; 2) substantiating the manuscript or checking the intellectual content; 3) providing final approval for the manuscript. Participation solely in collection of data does not justify authorship (such participation should be noted in the Acknowledgements section). Manuscripts should be submitted with a covering letter containing the following information: 1) the manuscript has not been submitted to any other media; 2) the manuscript has not been published previously; 3) all authors have read and approved the manuscript's content; 4) the manuscript contains full disclosure of any conflict of interests; 5) the author/authors confirm responsibility for the reliability of the materials presented in the manuscript. The author responsible for the correspondence should be specified in the covering letter.

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6.1. It is desirable for authors to disclose (in a covering letter or on the title page) any relationships with industrial and financial organizations, which might be seen as a conflict of interest with regard to the content of the submitted manuscript. It is also desirable to list all sources of financing in a footnote on the title page, as well as workplaces of all authors (including corporate affiliations or employment).

7. Manuscript content

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7.1.1. It should include the name of the article (in capital letters); initials and last names of the authors; the full name of the institution which supported the manuscript, together with the city and country, and full mailing address with postal code of that institution.

7.1.2. A short title of the article (limited to 45 letters or symbols).

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7.1.5. The manuscript (or the covering letter) should be signed by all authors.

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7.2. Summary

7.2.1. Summary (limited to 300 words) should be attached to the manuscript. It should include the full title of the article, last names and initials of the authors, the name of the institution that supported the manuscript, and its full postal address. The heading of the summary should contain the international name(s) of any drug(s) mentioned.

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7.2.3. 5-6 keywords of the article should be given at the end of the abstract.

7.3. List of abbreviations and their definitions

7.3.1. To conserve space in the journal, up to 10 abbreviations of general terms (for example, ECG, ICV, ACS) or names (GUSTO, SOLVD, TIMI) can be used in a manuscript. List of abbreviations and their definitions should be provided on a separate page after the structured summary (for example, ACS – aortocoronary shunting). Only words generally accepted in scientific literature should be used.

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7.4.1. Original studies should be structured as follows: Introduction, Material and methods, Results, Discussion and Conclusion.

7.4.2. Case studies, reviews and lectures may be unstructured, but it is desirable to include the following paragraphs: Discussion and Conclusion (Conclusions and Recommendations).

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Periodicals

Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.

Sources in Russian with transliteration:

Baevskiy RM, Ivanov GG, Chireykin LV, et al. Analiz variabel'nosti serdechnogo ritma pri ispol'zovanii razlichnyh jelektrokardiograficheskih sistem (metodicheskie rekomendacii) [Analysis of heart rate variability using different ECG systems (guidelines)]. Vestnik aritmologii. 2002;24:65-86. Russian.

Please provide initials after the last names of authors. Last names of foreign authors are given in the original transcription. Names of periodicals can be abbreviated. Usually such abbreviations are accepted by the Editors of those periodicals.

These can be found on the Publisher's site or in the list of abbreviations of Index Medicus.

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If the total number of authors exceeds four people, please provide the names of the first three authors and put "et al." afterwards. If there are not more than 4 authors, the full list of authors should be provided

Chapters in a book

Swanton RH, Banerjee S. Cardiac Failure. In: Swanton RH, Banerjee S., editors. Swanton's Cardiology: A concise guide to clinical practice. 6th ed. Oxford: Blackwell Publishing; 2008. p. 255-309.

Sources in Russian with transliteration:

Belenkov YuN. Kardiomiopatii [Cardiomyopathies]. In.: Chazov EI, Belenkov YuN., editors. Racional'naja farmakoterapija serdechno-sosudistyh zabolevanij: Rukovodstvo dlja praktikujushhih vrachej [Rationale for drug therapy of cardiovascular diseases: A guide for medical practitioners]. Moscow: Litterra; 2006. p. 431-452. Russian.

Reference to a book chapter should be arranged in the following order: authors of the corresponding chapter; name of the chapter; «In:»; editors (title authors) of the book; name of the book; number of issue, publisher; city of publishing; year of publishing; pages of the corresponding chapter. Punctuation should be considered. There are no quotation marks.

Books

Sources in Russian with transliteration:

Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaja nervnaja sistema i arterial'naja gipertenzija [The autonomic nervous system and hypertension]. St. Petersburg (Russia): Meditsinskoe izdatel'stvo; 2008. Russian.

Websites

Websites should be provided in the list of references, but not in the text. References to websites should be made only when original text is not available. References should be provided in the following way:

WHO. Severe Acute Respiratory Syndrome (SARS) [Internet]. [place unknown: publisher unknown]; [updated 2010 June 1; cited 2010 June 10]. Available from: http://www.who.int/csr/sars/.

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