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Arterial pressure and left ventricular geometry in heavyweight athletes

The assessment of inflammatory diseases of periodontium as cardiovascular disease risk factor

Anticoagulative therapy after stroke in patients with atrial fibrillation

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Contents

Editor's Welcome

Dear colleagues!

In the 23d issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles.

The leading article section presents the study of arterial pressure and left ventricular geometry in heavyweight athletes. The results of the study on the association between BP and heart geometry disturbances in heavyweight athletes may be used as the scientific basis for organizing preventive programs with the main focus on risk groups.

Four articles are published in the «Original articles» section. The first article presents the study on the effect of antihypertensive, lipid-lowering and metabolic therapy on hemodynamic parameters and life quality in patients with arterial hypertension and chronic kidney disease. The second article included 528 patients and was dedicated to the association between chronic kidney disease and cardiovascular risk factors in patients with diabetes mellitus. It was found that 8% of patients had decreased glomerular filtration rate, 36% - microalbuminuria. Researchers also assessed its general and individual risk factors that can be used for preventive measures. The third article is dedicated to the association between inflammatory diseases of periodontium and cardiovascular diseases in patients with different cardiovascular risk. The authors concluded that specialists of related disciplines need to evaluate the prognostic significance of risk factors when assessing subclinical atherosclerosis and periodontium condition in order to perform preventive measures. The fourth article assesed the efficacy and cardiovascular safety of sildenafil in men with stable coronary artery (CAD) disease and erectile dysfunction (ED). The investigation showed that course therapy with low doses of sildenafil as part of complex therapy can be used for ED treatment in patients with CAD with low and moderate risk according to Princeton Consensus.

The "Review article" section presents the analysis of anticoagulative therapy possibilities in stroke patients with atrial fibrillation as well as indications, dosing and administration recommendations of oral anticoagulants.

We 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

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LEADING ARTICLE

Arterial pressure and left ventricular geometry in heavyweight athletes

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Objective. *To study arterial pressure and left ventricular geometry in heavyweight athletes.*

Materials and methods. *We examined 645 heavyweight athletes (weightlifters, powerlifters, bodybuilders) with candidate to master of sports, master of sports and international master of sports qualifications with average body weight of 102.7±6.4 kg. All patients underwent general examination, standard electrocardiography, double BP measurement and transthoracic echocardiography.*

Results. *The results of investigation showed that 248 (37%) athletes had increased BP (systolic BP — 157,4±5,6, diastolic BP– 91,2±5,3) and left ventricular (LV) geometry impairment. The following heart parameters increased in athletes with hypertension compared with normotensive athletes: diastolic interventricular thickness by 0,1 mm (p<0,01), left ventricular posterior wall thickness by 0,2 mm (p<0,01), right ventricular diameter by 4.2 mm (p<0.01), LV myocardial mass by 32, 2g (p<0,01), LV myocardial mass index by 17,8 g/m^2, LV relative wall thickness by 0,08 mm (p<0,01). LV end-diastolic volume was 0,2 mm (p<0,05) lower in hypertensive athletes.*

Conclusion. *Thus, the results of the study on the association between BP and heart geometry disturbances in heavyweight athletes may be used as the scientific basis for organizing preventive programs with the main focus on risk groups.*

Key words: *arterial pressure, arterial hypertension, sport, athlete heart, sudden cardiac death, myocardial hypertrophy, heart remodeling.*

Conflict of interests: none declared.

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Introduction

Most people associate physical exercises and sports with health and increased life expectancy. Therefore, cases of sudden cardiac death (SCD) in highly-qualified athletes always attract great attention. Cardiovascular diseases (CVD) are the leading cause of death among athletes. It is also remarkable that SCD is more frequent in men (from 0.46 to 0.75 cases for 100000 athletes per year) compared with women [1]. John Longhurst et al. [2] were the first researches of cardiovascular system (CVS) in heavyweight athletes, who observed increased arterial pressure (AP) and CVS vulnerability among them, that were later supported by other researches [3, 4]. This can be associated with additional heart hemodynamic stress during exercises due to larger static component [5] or higher AP [6]. It increases the development of cross-bridges according to Frank-Starling law and activates the neurohormonal mechanisms to enhance heart contractility that leads to its compensatory hypertrophy. According to Laplace's law, the voltage on the wall of the left ventricle (LV) is proportional to the multiplication of the pressure and LV radius and inversely proportional to the thickness of LV wall. In order to maintain normal values of intramyocardial tension during AP and LV size increase, it is necessary to rise myocardial wall thickness. Therefore, an pressure due to increased power load can be compensated by rise of LV wall thickness. Since concentric hypertrophy develops during pressure overload, peak systolic wall tension is thought to be its stimulus, because it causes parallel replication of sarcomeres [7].

Unlike isokinetic, isometric exercises, that we call strength training, are characterized by increased peripheral vascular resistance and normal, or slightly increased cardiac output. This increase of peripheral vascular resistance causes transient conditions with potential risk of hypertension and increased afterload [8]. LV wall tension increase, for example, caused by hypertension induced by increased afterload, stimulate myocyte hypertrophy, the formation of collagen and fibroblasts, and, thus, leads to myocardium remodeling with disproportionate increase of fibrous tissue. These changes subsequently decrease LV compliance, that leads to diastolic dysfunction. Increased LV wall tension is the main mechanical factor of the LV hypertrophy (LVH) development, and BP — of LV mass. But some additional hemodynamic factors also play an important role in the development and maintenance of LVH, for example, volume overload also contribute to the development of heart hypertrophy. Total vascular resistance can also contribute to the increase of arterial stiffness. Systolic blood pressure (SBP) contributes to the development of myocardial hypertrophy, while diastolic blood pressure (DBP) is associated with LV wall thickness [9].

Although the Working Group «Myocardial Function» of the European Society of Cardiology recommends to use the term «hypertrophy» as the size of heart myocytes, and the term «remodeling» to define rearrangement of cardiac tissue — the process when heart changes its size, geometry and function over time [10], however, these terms are often used interchangeably in clinical practice. Knowledge and understanding of how power load can affect LV geometry and BP in athletes are important, because relative risk of SCD is higher among athletes [11]. The study objective was set based on the analysis of problem relevance, literature sources and the data of requests of sports biologists and doctors.

Materials and methods

The study was conducted at the Department of Sports Medicine of Russian State University of Physical Education, Sport and Tourism from January 2017 to March 2019. We examined 645 heavyweight athletes (weightlifters, powerlifters, bodybuilders) with candidate to master of sports, master of sports and international master of sports qualifications. Average age was 102,7±6,4 kg. Average body weight — 102.7±6.4 kg. All study participants signed informed consent to participate in the study according to the Helsinki Declaration [12]. All athletes underwent general examination, standard resting electrocardiogram, two separate blood pressure measurements, transthoracic echocardiography using Aloka 3500 devices (Japan) with cardiological sector probe with 3.5 Mhz frequency using B- and M-modes, pulse-wave, color and tissue doppler. Left Ventricular mass (LVM) was calculated using modified ASE formula:

$$LVM = 0,8\times[1,04\times((LV\ EDV + IVSTd + LVPWd)\ 3 - LV\ EDV)] + 0,6,$$

where LV EDV — left ventricular end diastolic volume; IVSTd — intraventricular septum thickness during diastole; LVPWTd — left ventricular posterior wall thickness during diastole.

Left ventricular mass index (LVMI) was calculated to body surface area found using Du Bois method. Men with LVMI over 116 g/m^2 had left ventricular hypertrophy (LVH). The type of LVH was estimated according to guidelines of Lung et al. [13] — RLVWTd =2LVPWd/LV EDV, where RLVWTd — relative left ventricular wall thickness during diastole. After the examination athletes were divided into the following cohorts: group-1 (athletes with optimal and normal BP (n=407)); group-2 (athletes with increased BP (n=238)). Athletes with increased or normal increased BP, were additionally interviewed to assess specific arterial hypertension (AH) risk factors. We also used mathematical statistic methods to process obtained data.

Results and discussion

The investigation of 645 heavyweight athletes showed that 238 (37%) had increased BP (SBP — 157,4±5,6, DBP — 91,2±5,3) and heart geometry impairment (table 1, 2). According to the prospective «MONICA / KORA (2018)» study, the prevalence of AH increased from 34% to 63% [14], although there are serious differences on AH prevalence in different countries and age groups. However, the prevalence of AH among young people in Italy (aged from 18 to 35 years) is 11% [15], and in developed countries AH was recorded in 14% and 21% of patients aged from 20 to 29 and from 30 to 39 years, respectively [16]. According to Kazelli et al. study (2,040 athletes aged 25±6 years, 64% — men, Olympic sports), the prevalence of AH among sportsmen was only 3% [17]. Apparently, there are sports with higher rate of AH, for example, Karpinos et al. [18] showed, that the prevalence of AH was higher among American football (19.2%) players compared with other sports (7%). Weiner et al. confirmed these data and showed, that 47% of American football athletes had prehypertension and 14% — stage 1 hypertension. It is also remarkable that football players had significant increase of LV concentric hypertrophy prevalence (31%), and LV mass changes correlated with seasonal SBP changes [19]. The prevalence of increased blood pressure was 21.2% [20] in powersport athletes (excluding weight category), and general prevalence of hypertension among heavyweight athletes (115–120 kg) in China (heavy athletics, judo, wrestling), as well as athletics throwing (javelin, disk throwing and shot put) was 55.4% (49.5% had mild or moderate hypertension, and 5.9% — severe hypertension) [21].

Our comparative analysis of hypertensive athletes showed that LV myocardium wall thickness significantly exceeded normal values (1.2±0.1 mm on average) that may indicate slight hypertrophy. The difference between groups was statistically significant — 0.1 mm ($p<0.01$). Athletes also had proportionally larger size of left atrium and right ventricle diameter (RVD), that reflected balanced process of heart remodeling [22].

The following heart parameters significantly increased in hypertensive athletes compared with normotensive: LVPWT by 0.2 mm ($p<0.01$), RVD by 4.2 mm ($p<0.01$), LVM by 32,2 g ($p<0.01$), LVMI on 17.8 g/m^2 ($p<0.01$), RLVWT by 0.08 mm ($p<0.01$). Hypertensive athletes also had significantly lower EDV — by 0,2 mm ($p<0,05$). We identified 4 types of LV geometry according to RLVWT. The most unfavorable types of heart remodeling are concentric remodeling and concentric hypertrophy, since they are associated with the development of the most severe heart diastolic function disorders, increased diastolic and systolic vascular resistance, left atrium overload, and right ventricle wall hypertrophy [23].

Conflict of interest: None declared.

Table 1. **Comparative analysis of heart geometry in hypertensive and normotensive athletes (N=645)**

Group (N=645)	EDV (mm)	Δ	IVST (mm)	Δ	LVPWT (mm)	Δ
group-1 (n=404)	5,6±0,4	0,2*	1,1±0,1	0,1**	1,0±0,1	0,2**
group-2 (n=238)	5,4±0,3		1,2±0,1		1,2±0,1	

* $p<0,05$; ** $p<0,01$ the differences between groups are statistically significant.

Table 2. **Comparative analysis of heart geometry in hypertensive and normotensive athletes (N=645)**

Group (N=645)	EDV (mm)	Δ	LVM (g)	Δ	LVMI (g/m^2)	Δ	RLVWT (mm)	Δ
group-1 (n=404)	22,8±3,5	4,2**	239,3±40,4	32,2**	107,4±17,5	17,8**	0,38±0,03	0,08**
group-2 (n=238)	27,0±4,3		271,5±32,3		125,2±9,8		0,46±0,02	

* $p<0,05$; ** $p<0,01$ the differences between groups are statistically significant.

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The analysis of office and daily hemodynamics parameters and pharmacological therapy features in patients with chronic kidney disease and arterial hypertension

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Objective. *To study the effect of antihypertensive, lipid-lowering and metabolic therapy on office and daily hemodynamic parameters, central aortic blood pressure, vascular wall stiffness and life quality in patients with or without 1–2 grade of arterial hypertension (AH).*

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Materials and methods. *We examined patients with 1–2 grade of arterial hypertension (AH) and 3 stage of CKD. Hemodynamic parameters were assessed using daily monitor of arterial pressure «BPLab». Life quality was determined using the MOS SF36 questionnaire.*

Results. *Patients with AH and CKD had the most significant changes in central hemodynamics and vascular wall stiffness.*

Conclusion. *The combination of antihypertensive therapy (losartan and diltiazem) with meldonium and rosuvastatin significantly reduced central and peripheral hemodynamics and vascular stiffness parameters. Meldonium, added to standard therapy, significantly improves patient's life quality.*

Key words: *arterial hypertension, chronic kidney disease, central aortic blood pressure, vascular wall stiffness, daily monitoring.*

Conflict of interests: none declared.

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Introduction

BP control reduces cardiovascular risk and include not only blood pressure (BP) level correction, but also all modifiable risk factors, prevents or treats target organ damage and associated clinical conditions.

Kidney damage in patients with arterial hypertension (AH) has been studied by many researchers over the last years [1,2]. It has been proven that chronic kidney disease (CKD) is associated with AH, chronic heart failure (CHF), and diabetes mellitus [3–5]. However, the association between CKD and 1–2 grade AH in young patients as well as the factors affecting the development of CKD have not been studied enough yet.

The effect of various antihypertensive therapy (AHT) on the outcomes was assessed using central aortic pressure (CAP) and wave reflection index (augmentation index — AIx) over the last years [5–10]. Antihypertensive medications affect pulse wave and central hemodynamics parameters differently, despite the same brachial artery BP reduction [9,13].

Objective

To study the effect of antihypertensive, lipid-lowering and metabolic therapy on office and daily hemodynamic parameters, central aortic blood pressure (CAP), vascular wall stiffness and life quality (LQ) in patients with or without 1st or 2d grade AH.

Materials and methods

Our study included patients from the Department of Nephrology and the Department of Cardiology of Kabardino-Balkar State University named after H M Berbekov of Kabardino-Balkar Republic and ambulatory patients from Nalchik city clinics. Group 1 inclusion criteria were: the presence of stage 3 CKD (estimated glomerular filtration rate (eGFR) 30–60 ml/min)) in combination with 1st or 2d grade AH, age from 45 to 72 years, duration of AH less than 10 years lack of regular AHT. Group 2 inclusion criteria were: the presence of 1st or 2d grade AH, age from 45 to 72 years, the duration of AH less than 10 years, lack of regular AHT. Group 3 inclusion criteria were: the presence of stage 3 CKD (eGFR 30–60 ml/min), age from 45 to 72 years. The control group included healthy patients according to examination (general clinical examination, biochemical blood test, special (questioning), statistical, as well as comparative and system analysis methods)).

The first group included 45 patients with stage 3 CKD (eGFR 30–60 ml / min) in combination with 1st or 2d degree AH (average age 60±9 years) — 19 men and 26 women. The second group included 45 patients with 1st or 2d grade AH and without CKD. The third group included 45 patients with stage 3 CKD without AH. The fourth (control) group included 30 clinically healthy participants. All the groups were comparable by age and gender.

Office and daily hemodynamic parameters and daily average CAP parameters were measured using the BPLab daily blood pressure monitor with BPLab Vasotens and BPLab Vasotens-office software from Petr Telegin (Russia) before treatment and 8 weeks after.

LQ was assessed using MOS SF36 questionnaire before and 8 weeks after the treatment. The questionnaire included the following parameters: physical health: physical activity, physical functioning, bodily

pain and general health; mental health: vitality, social activity, emotional functioning, as well as a comparison of patients' well-being.

Statistical analysis of obtained data was performed using Statistica 10.0 software. We calculated the arithmetic mean and standard deviations of the parameters and representativeness errors. Normal distribution of obtained data was presented as M±m, where M is the arithmetic mean of studied parameters, m — representativeness error. The significance of differences between groups was assessed using Student's t-test. A p value less than 0.05 was considered significant.

Table 2. **Pharmacological therapy received by participants**

Group	Received therapy
1 (CKD III+AH), n=45	1. Losartan 100 mg at 8 a. m. 2. Diltiazem 180 mg once a day 3. Rosuvastatin 10 mg at 8 p.m. 4. Meldonium 500 mg 2 times a day at 8 a.m. and 2 p.m.
2 (AH), n=45	1. Losartan 100 mg at 8 a. m. 2. Diltiazem 180 mg once a day 3. Rosuvastatin 10 mg at 8 p.m. 4. Meldonium 500 mg 2 times a day at 8 a.m. and 2 p.m.
3 (CKD III), n=45	1. Rosuvastatin 10 mg at 8 p.m. 2. Meldonium 500 mg 2 times a day at 8 a.m. and 2 p.m.

Results

Clinical characteristics of patients and received therapy are presented in tables 1 and 2, respectively.

The results of the office hemodynamic parameters monitoring before and after the treatment are presented in table 3.

The results of the study show that initial office hemodynamic parameters were higher compared with average daily parameters in all the participants. Office hemodynamic and vascular wall stiffness parameters (arm and ankle SBP, DBP, average daily BP, pulse pressure (PP), heart rate (HR), pulse transit time (PTT), aortic pulse wave velocity (PWVao), augmentation index (AIx), BP rise rate (dPdt), systolic area index (Ssy), cardio-ankle vascular index (CAVIa)) changed significantly in patients with CKD and AH (table 3).

Reference parameters changed less in patients with CKD without AH. It is also remarkable that patients from this group had increased office hemodynamic and vascular wall stiffness parameters: arm SBP, ankle SBP, DBP, average aortic BP, PP, PTT, PWVao, AIx, dPdt, Ssy, CAVIa, as well as CAP param-

Table 1. **Clinical and demographical characteristics of participants**

Parameter	Group 1 (CKD III+AH) n=45	Group 2 (AH) n=45	Group 3 (CKD III) n=45	Group 4 (healthy) n=30
Average age, years	60±9	62±10	60±9	59±11
Men, n (%)	19 (42)	22 (49)	20 (44)	14 (46)
Women, n (%)	26 (58)	23 (51)	25 (56)	16 (54)
Smokers, n (%)	11 (24)*	11 (24)*	12 (27)*	0 (0)
AH, n (%)	45 (100)*	45 (100)*	0 (0)	0 (0)
1st grade AH, n (%)	20 (44)*	21 (47)*	0 (0)	0 (0)
2d grade AH, n (%)	25 (56)*	24 (53)*	0 (0)	0 (0)
CHF (1–2 FC according to NYHA), n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Potassium, mEq/l	4.8±0.85**	4.8±0.57*	4.9±0.88**	4.2±0.44
Sodium, mEq/l	143±3.29	136±3.35	142±2.84	138±3.12
Uric Acid, μmol/L	444±89	342±85	374±87	272±91
Hemoglobin blood level, g/l	137±23	138±16	136±24	137±15
Hematocrit, %	38.94±5.83	41.83±5.14	39.48±6.60	41.18±4.16
Creatinine blood level, mg/dl	1.47±0.43*	0.88±0.11	1.38±0.37*	0.73±0.17
Serum albumin level, g/l	37±6.4	41±5.1	39±5.5	42±5.4
Albuminuria, mg/day	8.4±3.1*	3.46±0.7	7.3±2.7*	3.08± 0.7
Left ventricular hypertrophy, n (%)	10 (22)*	8 (18)*	0 (0)	0 (0)
GFR according to CKD-EPI, ml/min/1.73 м^2	47.5±11.1**	75.4±7.5	45.9±11.7**	106.8±14.5
CHA2DS2-VASc score	5±1*	3±1	2±1	2±1
Hyperlipidemia, n (%)	45 (100) *	45 (100)*	45 (100)*	0 (0)
Total cholesterol, mmol/l	5.84±0.9*	5.91±0.8*	5.92±1.0*	3.8±0.5
Low-density lipoprotein level, mmol/l	3.323±0.6	3.05±0.7	3.24±0.6	2.1±0.6
High-density lipoprotein level, mmol/l	1.1±0.5	1.2±0.6	1.1±0.5	1.9±0.4
Triglycerides, mmol/l	1.6±0.6	1.7±0.6	1.6±0.5	1.9±1.2

* p<0,05, **p<0,01, *** p<0,001, compared with the control group.

Table 3. **The dynamics of office hemodynamic parameters during combinative treatment**

Parameter		Group 1 (CKD III+AH) n=45	Group 2 (AH) n=45	Group 3 (CKD III) n=45	Group 4 (healthy) n=30
SBP, mmHg (arm)	Initially	152.3±5.72***	148.4±4.24**	132.1±5.47*	113.4±3.52
	After treatment	134.2 ±4.82*#	129.5± 4.25*#	124.2±2.63	
SBP, mmHg, (ankle)	Initially	179.8±4.57***	168.3±3.59***	153.5±4.11*	141.7±3.47
	After treatment	159.5±4.06*##	153.6±3.94*#	148.6±3.73	
DBP, mmHg	Initially	89.2±3.83**	85.8±3.73*	78.4±2.92*	70.2±3.27
	After treatment	78±2.73*#	73±3.04#	71.2±2.74	
Average BP, mm Hg	Initially	139.6±4.91**	136.4±2.53**	124.7±2.22*	110.5±2.82
	After treatment	121.4±2.01*##	116.8±2.81##	121.1±3.02	
PP, mmHg	Initially	72.3±4.74**	68.6±3.53**	48±2.35*	39±3.23
	After treatment	52.5±2.63*##	47.2±2.92##	43.8±2.19	
HR, beats per minute	Initially	82.4±3.13**	76.5±2.89*	71.6±2.32	69±2.04
	After treatment	76.2±2.04*#	74.6±2.15	70.2±1.96	
PTT, ms	Initially	159.3±4.63***	149±4.74***	131.1±3.18**	117.7±2.74
	After treatment	132.8±3.83*##	123.8±3.25###	120.2±2.93#	
PWVao, ms	Initially	19.2±1.92**	17.5±1.77**	12.3±1.41*	7.2±1.82
	After treatment	10.3±1.81##	9.6±1.64#	8.8±1.5	
AIx, %	Initially	44.7±4.73***	38.5±3.26**	28.8±3.69*	18.5±2.83
	After treatment	25.2±3.92##	23.6±3.51##	21.7±3.12	
dPdt, mm Hg/s	Initially	1090.74±92.14***	892.85±69.95***	525.52±45.25**	336.46±22.36
	After treatment	809.75±68.15***#	683.58±55.27**#	425.24±53.41#	
Ssy, mm Hg	Initially	25.3 ± 2.52***	19.7 ± 1.51***	9.21 ± 1.08*	4.9 ± 1.7
	After treatment	9.2 ± 2.25##	7.8 ± 1.14##	5.8 ± 1.13#	
CAVIa	Initially	28.19±2.36***	26.11±2.02**	23.4±2.43*	15.2±1.47
		24.62±1.74*#	22.93±2.61*	18.3±1.62	

* The differences are significant compared with the control group (p<0,05), ** p<0,01, *** p<0,001;
# The differences are significant compared with the initial paraments (p<0,05); ## — p<0,01, ### — p<0,001.

eters (aortic SBP, average aortic BP, aortic PP, aortic AIx (table 4)).

The most significant differences in CAP (aortic SBP, Average aortic BP, aortic PP, aortic AIx) were registered in patients with CKD and AH, when analyzing daily central hemodynamic parameters (table 4).

Patients with CKD without AH initially had significant increase of some central hemodynamic parameters, such as aortic SBP, aortic PP, aortic AIx (table 4).

Central and peripheral hemodynamic parameters significantly decreased in patients from group 1 and 2

Table 4. **The dynamics of daily CAP parameters during combinative treatment**

CAP parameters	Group 1 (CKD III+AH) n=45	Group 2 (AH) n=45	Group 3 (CKD III) n=45	Group 4 (healthy) n=30
Aortic SBP, mmHg — before/after treatment	139.6±5.29*/ 121.5±2.23##	135.9±2.22*/ 117.5±2.64###	125.1±2.23*/ 120.9±3.17	110.4±2.37
Aortic DBP, mmHg — before/after treatment	81.7±3.82*/ 73.4±1.73#	79.3±1.70*/ 72.5±1.12##	76.4±1.78/ 75.8±1.35	73.1±0.78
Aortic average BP, mmHg — before/after treatment	105.8±5.73**/ 88.5±1.69##	100.1±3.45*/ 84.3±2.37##	86.4±2.35/ 85.7±1.89	83.4±1.12
Central arterial pulse pressure (aortic PP), mmHg — before/ after treatment	67.3±4.09***/ 44.7±1.61###	60.7±3.65***/ 41.3±1.92###	45.3±1.68*/ 40.9±1.16#	37.7±1.36
Aortic AIx (AIxao), % before/after treatment	36.6±4.41***/ 20.2±2.13##	27.7±3.52**/ 19.4±1.65#	23.3±2.09*/ 20.3±2.15	16.1±1.22
Aortic AIx (AIxao), % reduced to HR =75 beats per minute before/ after treatment	32.6±4.44**/ 21.2±2.72#	27.4±3.21**/ 20.7±3.62#	23.2±2.06*/ 21.3±2.76	17.6±1.86

* The differences are significant compared with the control group (p<0,05), ** p<0,01, *** p<0,001; # The differences are significant compared with the initial paraments (p<0,05); ## — p<0,01, ### — p<0,001.

during combined antihypertensive, lipid-lowering and metabolic therapy (table 3, 4).

Office hemodynamic and vascular wall stiffness parameters decreased (arm SBP, ankle SBP, DBP, PP, PTT, PWVao, AIx, dPdt, Ssy, CAVIa) and CAP parameters increased (aortic SBP, aortic PP, aortic AIx) (table 3, 4) in patients with CKD without AH (group 3) during antihypertensive and lipid-lowering therapy (meldonium and rosuvastatin, respectively). But the changes were significant only by PTT, dPdt, SsY (table 3) and by aortic PP (table 4) parameters.

LQ parameters between groups were initially comparable. The analysis LQ parameters revealed reliable, statistically significant improvement of the following parameters in patients from groups 1 and 2: physical functioning, vitality, social functioning, emotional functioning, mental health, as well as health psychological component (Figure 1a, 1b).

Physical health parameters significantly improved in patients from group 3, when changes in psychological health parameters were insignificant (Figure 1c).

The best dynamics in LQ parameters were registered in patients from groups 1 and 2 who received AHT and 1000 mg of meldonium per day (Figure 1a and 1b).

Discussion

This study represents features of antihypertensive, lipid-lowering, and metabolic therapy effects on the office and average daily hemodynamic parameters, CAP parameters, vascular wall stiffness and LQ in patients with CKD and AH.

The prognostic significance of CAP and arterial stiffness can be proven by their inclusion into the latest European guidelines on AH (2018) as target organ damage signs [1].

The results of the study showed that the greatest hemodynamics and vascular stiffness parameters increase were observed in patients with CKD and AH.

The smallest changes of reference parameters in patients with CKD without AH, the initial increase in office hemodynamics and vascular stiffness, as well as daily CAP parameters indicate cardiorenal association, which can be presented not only as morphofunctional impairment of renal regulation, but also as hemodynamic and arterial endothelial dysfunction, for example arterial stiffness.

The results of this study reinforce recent studies that have shown an independent inverse correlation between GFR <60 ml/min /1.73 m^2 and the number of cardiovascular events. It is also remarkable that CVD occur in patients with renal dysfunction 64 % more often compared with patients with preserved function, and cardiovascular mortality — by 22–35 % [2, 11, 12].

The results of the Chronic Kidney Disease Prognosis Consortium study, which involved over 1 million patients in general population with high-risk and CKD, showed independent from each other and from main cardiovascular risk factors inverse with GFR and direct with albuminuria correlation with general and cardiovascular mortality and with renal outcomes [2].

Thus, further studies on the correlation between central hemodynamic parameters, arterial stiffness and daily blood pressure monitoring in patients with CKD, AH and dyslipidemia are needed.

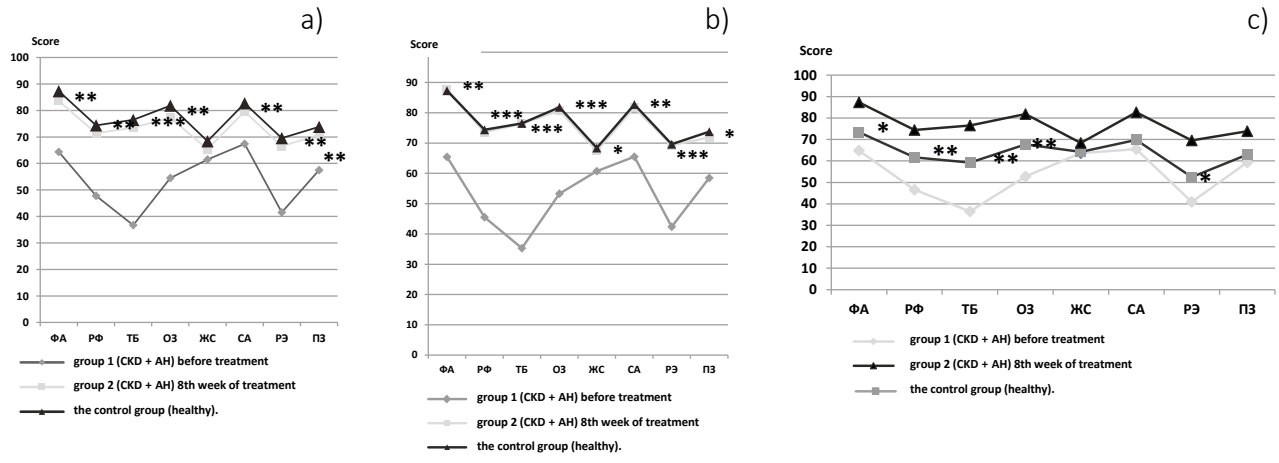

Figure 1. The dynamics of LQ parameters in patients from group 1 (a), group 2 (b) and group 3 (c) during treatment
a) * The differences are significant compared with the control group (p<0,05), ** p<0,01, *** p<0,001; # The differences are significant compared with the initial paraments (p<0,05); ## p<0,01, ### p<0,001.
b) ** The differences are statistically significant compared with the initial paraments p<0,05,** p<0,01, *** p<0,001.

Conclusion

Thus, all the patients had higher initial hemodynamic parameters compared with daily parameters. Patients with stage 3 CKD had increased central and peripheral hemodynamic parameters according to daily BP monitoring. Patients with stage 3 CKD and AH had increased office hemodynamic and CAP parameters, arterial stiffness and decreased arterial elasticity.

The combination of antihypertensive therapy (losartan and diltiazem) with meldonium and rosuvastatin significantly reduced central and peripheral hemodynamics and vascular stiffness parameters in patients with stage 3 CKD and AH. Patients with 1 and 2 grade AH as well as with stage 3 CKD with AH, who received 1000 mg meldonium per day, added to standard therapy, had significant life quality improvement.

Conflict of interest: None declared.

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The association between chronic kidney disease and cardiovascular risk factors in patients with type 2 diabetes mellitus

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Objective. *To study the association between chronic kidney disease (CKD) and cardiovascular risk factors in patients with type 2 diabetes mellitus (T2DM).*

Materials and methods. *This clinical epidemiological study included 528 patients with T2DM aged 30–69 years. Social, demographic, behavioral risk factors and life quality were determined using «ARIC» questionnaire. We also assessed the level of glycemia, glycohemoglobin, creatinine, microalbuminuria (MA) and glomerular filtration rate (GFR).*

Results. *Increased creatinine level (p<0,001), high stress level (p=0,006), decreased GFR (p<0,001) were accompanied by 300 mg/gl MA. Patients with albuminuria more often had movement disorders (p=0,015), self-care (p<0,001) or everyday activity (p<0,001) impairment, pain or discomfort (p=0,001). Employment reduced the incidence of albuminuria (p=0.043), low and medium alcohol consumption had antiproteinuric effect (p=0.003), low physical activity was MA predictor (p=0.011). GFR decreased with age (p <0.001), patients with family history of angina pectoris more often had decreased renal function (p=0.031). Most patients with decreased GFR had increased body mass and obesity (p<0,001), most of them had medium or high stress level (p=0,003). Patients with GFR<60 ml/min had high creatininemia and MA (p<0,001); decreased GFR contributed to self-care impairment (p=0,020).*

Conclusion. *7,9 % of patients with T2DM had GFR<60 ml/min, 35,7 % — MA. We assessed general and individual MA and decreased GFR risk factors. Systematic screening will prevent CKD development.*

Key words: *Type 2 diabetes mellitus, chronic kidney disease, microalbuminuria, risk factors.*

Conflict of interests: none declared.

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Introduction

Type 2 diabetes mellitus (T2DM) contributes to the development of chronic kidney disease (CKD) [1]. Despite that fact, CKD is rarely timely diagnosed. After 4 years of type 1 diabetes mellitus diagnosis (T1DM) it is recommended to assess microalbuminuria (MA) every year, and, in case of T2DM, regardless of its duration, it is necessary to determine MA immediately, because T2DM is often detected when there are clinical and subclinical complications.

Albuminuria and decreased glomerular filtration rate (GFR) (<60 ml/min) are diagnostic criteria of CKD [2, 3], and MA — initial CKD manifestation [4]. Both these parameters can manifest together and separately [5].

Pathogenesis of CKD include general and specific pathophysiological mechanisms [2, 6, 7]. It is known that endothelial dysfunction and increased kidney vascular permeability lead to MA, and vascular occlusion — to GFR decrease [8]. Various risk factors also contribute to the development of CKD and can act together and separately [4].

Decreased GFR and albuminuria are not only the factors of diabetic nephropathy, but also independent risk factors of cardiovascular events and mortality [9]. Therefore, patients with T2DM and impaired kidney function, including its initial stage, need to underwent risk factors screening [7]. Only in this case it is possible to prevent the development of the disease and its complications, including disability and death, since GFR ⩽30 ml/min indicate the presence of stage 2 diabetic nephropathy.

Patients with T2DM have specific CKD prevalence and risk factors in every region.

Objective

To study the risk factors of CKD, life quality features and laboratory parameters in patients with T2DM among Azerbaijani cohort.

Material and methods

This clinical and epidemiological study included 528 patients (30,5 % — men and 69.5 % — women) with T2DM aged 30–69 years (54,1 ± 0,3 years). All the respondents answered the questions of ARIC questionnaire prepared by World Health Organization experts for clinical and epidemiological studies, that assessed socio-demographic, behavioral risk factors and life quality aspects.

Patients who smoked at least one cigarette per day were considered smokers. Patients who consumed over 7 bottles of beer, and / or over 700 grams of strong wine, and / or over 1 liter of wine, and / or over 300 grams of vodka or other strong drink over 5 times a week were considered alcohol abusers. Patients were considered low- and medium-alcohol drinkers if the number of alcoholic beverages was less than mentioned above values.

If patient didn't move less than for 5 hours per day, walked for at least 30 minutes per day and / or exercised for at least 2 hours per week, physical activity was considered normal. In case of lower activity, we determined physical passivity.

The disturbance of one type of metabolism — carbohydrate, lipid or salt, was considered as mild (1–1.9 points), the presence of two types metabolism disturbances — as moderate (2–2,9 points) and the presence of all three types — as severe (⩾3 points) malnutrition; 0–0,9 points were considered as healthy nutrition.

Symptoms of stress were calculated using hospital scale: 1–1.9 points — severe, 2–2.9 points — moderate, 3–3.9 points — mild stress level, and 0–0.9 points — the absence of stress.

Body mass index (BMI) <25 kg/m^2 was considered normal, ⩾25 kg/m^2 — overweight and obese. According to the report of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) experts, abdominal obesity (AO) was considered as ⩾102 cm waist circumference in men and ⩾88 cm in women.

Life quality was assessed using the EQ-5D (European Quality of Life İnstrument) questionnaire, that assessed problems with movement, self-care, daily activity, pain, discomfort, anxiety, depression and the dynamics of life quality parameters.

Blood glucose ⩾7 mmol / L measured in ulnar vein on an empty stomach after 9–12 hours of fasting were considered as hyperglycemia, and glycohemoglobin (HbA1c) ⩾7 % was a sign of inadequate diabetes control. Creatinine level was determined by photometric method using STAR FAX apparatus: 53–115 μmol/l in men and 44–90 μmol/l in women were considered normal.

GFR was calculated using the Cockcroft-Gault formula: ⩾90 ml/min/1.73 m^2 was considered as normal or stage 1 CKD, 60–89 — stage 2, 30–59 — stage 3, 15–29 — stage 4, and <15 ml / min / 1.73 m^2 — as the 5th or terminal stage of renal failure.

The level of MA was determined using test strips (Hungary), 30–300 mg / dl was considered pathological. In clinical and epidemiological studies this

method of albuminuria assessment was superior to albumin / creatinine ratio since its simpler to perform [10, 11].

The statistical analysis was carried out using MS EXCEL-2013 and SPSS-20 software and variational (Kruskal-Wallis test), dispersion (Fisher's F-test) and discriminant (Pearson's tetrachoric and polychoric criteria) methods.

Results

The results of the study showed that the frequency of MA was higher in women compared with men, despite the fact that the frequency of 30 and 100 mg/dl MA was 2 times higher and 300 mg/dl — 3 times higher, this difference was statistically insignificant (Table 1). Similar changes were registered in patients with decreased GFR and the highest parameter was registered in patients with 2nd stage CKD.

Average age of patients was over 50 years in both groups despite MA severity and did not differ significantly, patients with GFR <60 ml/min were significantly older.

The level of education did not affect MA and GFR parameters significantly in patients with T2DM. Patients with secondary education had decreased GFR and the highest MA parameters, respondents with secondary professional education most often had 300 mg/dl MA.

Table 1. **The determinants and features of MA and GFR reduction depending on social and demographic factors**

Parameters	Gradation	MA (mg/dl)				P* (Kruskal-Wallis test)	GFR (ml/min/1.73 м²)			P* (Kruskal-Wallis test)
		0	30	100	300		≥90	89–60	<60	
Sex, n (%)	Men	86 (27.7)	49 (34.3)	9 (33.3)	4 (25.0)	0.508	64 (31.4)	61 (26.9)	12 (32.4)	0.543
	Women	224 (72.3)	94 (65.7)	18 (66.7)	12 (75.0)		140 (68.6)	166 (73.1)	25 (67.6)	
Age, years	n M±м (95 % CI)	310 54.3±0.4 (53.6–55.0)	143 53.9±0.6 (52.7–55.0)	27 55.1±1.4 (52.2–57.9)	16 54.7±1.8 (50.8–58.5)	0.821 p (Fisher's F-test)	204 51.6±0.5 (50.7–52.5)	227 56.0±0.4 (55.2–56.8)	37 58.8±1.0 (56.7–60.8)	<0.001 p (Fisher's F-test)
The level of education, n (%)	No education	4 (1.3)	0	0	0	0.172	2 (1.0)	2 (0.9)	0	0.435
	Higher education	106 (34.2)	34 (23.8)	7 (25.9)	4 (25.0)		54 (26.5)	80 (35.2)	13 (35.1)	
	Professional education	58 (18.7)	35 (24.5)	4 (14.8)	6 (37.5)		50 (24.5)	40 (17.6)	9 (24.3)	
	Secondary education	123 (39.7)	64 (44.8)	13 (48.1)	4 (25.0)		91 (44.6)	83 (36.6)	14 (37.8)	
	Incomplete secindary education	19 (6.1)	10 (7.0)	3 (11.1)	2 (12.5)		7 (3.4)	22 (9.7)	1 (2.2)	
Employment status, n (%)	Employed	190 (61.3)	104 (72.7)	21 (77.8)	12 (75.0)	0.043	136 (66.7)	148 (65.2)	28 (75.7)	0.939
	Unemployed	120 (38.7)	39 (27.3)	6 (22.2)	4 (25.0)		68 (33.3)	79 (34.8)	9 (24.3)	
Family status, n (%)	Not married	7 (2.3)	4 (2.8)	0	2 (12.5)	0.478	5 (2.5)	7 (3.1)	1 (2.7)	0.347
	Married	253 (81.6)	109 (76.2)	21 (77.8)	11 (68.8)		162 (79.4)	181 (79.7)	28 (75.7)	
	Divorsed	7 (2.3)	4 (2.8)	0	1 (6.2)		5 (2.5)	5 (2.2)	1 (2.7)	
	Widow/ widower	43 (13.9)	26 (18.2)	6 (22.2)	2 (12.5)		32 (15.7)	34 (15.0)	7 (18.9)	
Family history of DM, n (%)	No	176 (56.8)	86 (60.1)	12 (44.4)	8 (50.0)	0.453	109 (53.4)	131 (58.1)	27 (73.0)	0.869
	Yes	134 (43.2)	57 (39.9)	15 (55.6)	8 (50.0)		95 (46.6)	95 (41.9)	10 (27.0)	
Family history of CAD, n (%)	No	276 (89.0)	130 (90.9)	25 (92.6)	16 (100.0)	0.485	174 (85.3)	211 (93.0)	33 (89.2)	0.013
	Yes	34 (11.0)	13 (9.1)	2 (7.4)	0		30 (14.7)	16 (7.0)	4 (10.8)	
Family history of MI, n (%)	No	276 (89.0)	132 (92.3)	24 (88.9)	16 (100.0)	0.391	174 (85.3)	213 (93.8)	32 (86.5)	0.031
	Yes	34 (11.0)	11 (7.7)	3 (11.1)	0		30 (14.7)	14 (6.2)	5 (13.5)	

* $p < 0.05$ — the difference between studied parameters.

The severity of MA and CKD in employed patients were 2–3 times lower, however the differences between CKD parameters were not statistically significant.

MA and CKD were registered mostly in married patients; widowers were on the second place.

Patients with family history of DM had higher frequency of 100 mg/dl MA and 1st stage of CKD. The MA severity did not differ significantly in patients with family history of myocardial infarction (MI) and coronary artery disease (CAD), 1/10 of patients had <60 ml/min GFR.

Non-smokers predominated in the studied cohort and the frequency of 100 mg/dl MA as well as the most severe stage of kidney disfunction was higher in smokers (Table 2).

The prevalence of MA and CKD was higher in patients with low and moderate alcohol consumption as well as the frequency of 100 mg/dl MA and 2nd stage of CKD. The only statistically significant difference was the association between MA and alcohol consumption.

Average BMI corresponded stage 1 of obesity in patients with MA, excessive body mass and mild obesity in patients with decreased GFR. Most patients with MA had ≥25 kg/m² BMI, and GFR decrease resulted in statistically significant decrease of this indicator. Respondents with both signs of CKD revealed AO, moreover, this indicator directly correlated with GFR, and AO played significant role in reducing GFR values.

Patients involved in the study had mostly low physical activity. These patients had higher frequency of 100 mg/dl MA and ≥90 ml/min GFR, moreover, only MA changes statistically depended on the level of physical activity.

Table 2. **The features of the association between CKD indicators and behavioral risk factors**

Parameters	Gradation	MA (mg/dl)				p* (Kruskal-Wallis test)	GFR (ml/min/l/1.73 m²)			p* (Kruskal-Wallis test)
		0	30	100	300		≥90	89–60	<60	
Smoking, n (%)	Non-smoker	276 (89.0)	123 (86.0)	21 (77.8)	15 (93.8)	0.274	184 (90.2)	200 (88.1)	32 (86.5)	0.889
	Smoker	34 (11.0)	20 (14.0)	6 (22.2)	1 (6.2)		20 (9.8)	27 (11.9)	5 (13.5)	
Alcohol, n (%)	No alcohol consumotion	47 (15.2)	47 (32.9)	8 (29.6)	8 (50.0)	0.003	53 (26.0)	43 (18.9)	9 (24.3)	0.478
	Low and moderate alcohol consumption	225 (72.6)	74 (51.7)	16 (59.3)	7 (43.8)		122 (59.8)	157 (69.2)	25 (67.6)	
	Alcohol abuser	38 (12.3)	22 (15.4)	3 (11.1)	1 (6.3)		29 (14.2)	27 (11.9)	3 (8.1)	
BMI, kg/m²	n M±m (95% CI)	310 32.9±0.3 (32.3–33.6)	143 32.1±0.5 (31.2–33.0)	27 32.2±0.9 (30.3–34.1)	16 30.8±1.5 (27.6–34.0)	0.298 p (Fisher's F-test)	204 34.3±0.4 (33.6–35.0)	227 31.5±0.4 (30.8–32.2)	37 29.6±0.8 (28.1–31.2)	<0.001 p (Fisher's F-test)
BMI, n (%)	<25 kg/m²	18 (5.8)	10 (7.0)	1 (3.7)	3 (18.8)	0.298	5 (2.5)	19 (8.4)	5 (13.5)	<0.001 p (Fisher's F-test))
	≥25 kg/m²	292 (94.2)	133 (93.0)	26 (96.3)	13 (81.3)		199 (97.5)	208 (91.6)	32 (86.5)	
Waist circumflex (ATP III), sm	n M±m (95% CI)	310 106.0±0.7 (104.7–107.4)	143 105.7±1.0 (103.6–107.8)	27 107.2±2.0 (103.0–111.4)	16 103.7±4.3 (94.5–112.9)	0.821 p (Fisher's F-test)	204 109.4±0.7 (107.9–110.9)	227 103.9±0.8 (102.2–105.5)	37 99.9±2.0 (95.9–103.9)	<0.001 p (Fisher's F-test)
Low physical activity, n (%)	No	156 (50.3)	65 (45.5)	6 (22.2)	4 (25.0)	0.011	87 (42.6)	122 (53.7)	16 (43.2)	0.235
	Yes	154 (49.7)	78 (54.5)	21 (77.8)	12 (75.0)		117 (57.4)	105 (46.3)	21 (56.8)	
Malnutrition, n (%)	No	84 (27.1)	33 (23.1)	9 (33.3)	3 (18.8)	0.639	38 (18.6)	70 (30.8)	13 (35.1)	0.204
	Mild	116 (37.4)	59 (41.3)	11 (40.7)	7 (43.8)		79 (38.7)	95 (41.9)	10 (27.0)	
	Moderate	93 (30.0)	44 (30.8)	6 (22.2)	5 (31.2)		71 (34.8)	54 (23.8)	11 (29.7)	
	Severe	17 (5.5)	7 (4.9)	1 (3.7)	1 (6.2)		16 (7.8)	8 (3.5)	3 (8.1)	
Stress, points	n M±m (95% CI)	310 2.03±0.03 (2.0–2.1)	143 1.86±0.04 (1.8–1.9)	27 1.87±0.11 (1.6–2.1)	16 1.83±0.11 (1.6–2.1)	0.006 p (Fisher's F-test)	204 1.88±0.03 (1.8–1.9)	227 2.04±0.04 (2.0–2.1)	37 2.07±0.11 (1.9–2.3)	0.003 p (Fisher's F-test)

* p < 0,05 — the difference between studied parameters.

Our study revealed inverse correlation between malnutrition and the severity of GFR and MA. Thus, the frequency of albuminuria and CKD was higher in patients with mild malnitrition, mostly with 300 mg/dl MA and 89–60 ml/min GFR.

Patients with 300 mg/dl MA had high average stress level, patients with <60 ml/min GFR — moderate level. It is also remarkable that stress indicator played important role in the developement of both CKD parameters.

Most patients involved in the study noted certain movement problems (Table 3). The severy of MA correlated with movement impairment.

Patients with MA had more problems with self-care compared with patients with decreased GFR, ⅓ of patients with 300 mg/dl MA and 1/12 patients with GFR < 60 ml/min were unable to wash and put on their cloth on their own.

Almost half of patients with MA, mostly with 100 mg/dl MA, and decreased GFR had some problems with everyday activity. Everyday activity impairment correlated with MA severity in patients with <60 ml/min GFR, ⅓ of them had 300 mg/dl MA.

Questioning revealed that patients with decreased GFR had more frequent pain and discomfort compared with patients with MA. The MA severy correlated with pain and discomfort frequency and ⅗ of patients with the most severe stage of MA had these symptoms.

Patients with both signs of CKD had relatively high frequency of anxiety and depression. We noted the direct correlation between the prevalence of unsignificant and serious anxiety and depression with MA severity. Over half of patients with 300 mg/dl MA underwent some anxiety or depression and only 1/10 of patients had severe clinical manifestations of these

Table 3. **Life quality indicators in patients with MA and decreased GFR**

Parameters	Gradation	MA (mg/dl)				p* (Kruskal-Wallis test)	GFR (ml/min/l/1.73 m²)			p* (Kruskal-Wallis test)
		0	30	100	300		≥90	89–60	<60	
Movement, n (%)	No problems	85 (27.4)	26 (18.2)	4 (14.8)	1 (6.2)	0.015	44 (21.6)	61 (26.9)	9 (24.3)	0.143
	Some problems	224 (72.3)	115 (80.4)	23 (85.2)	14 (87.5)		158 (77.5)	166 (73.1)	26 (70.3)	
	Bed-patient	1 (0.3)	2 (1.4)	0	1 (6.2)		2 (1.0)	0	2 (5.4)	
Self-care, n (%)	No problems	219 (70.6)	65 (45.5)	10 (37.0)	3 (18.8)	<0.001	85 (41.7)	152 (67.0)	19 (51.4)	0.020
	Some problems	89 (28.7)	69 (48.3)	17 (63.0)	8 (50.0)		103 (50.5)	69 (30.4)	15 (40.5)	
	Disable to wash and put on cloth on their own	2 (0.6)	9 (6.3)	0	5 (31.2)		16 (7.8)	6 (2.6)	3 (8.1)	
Daily activity, n (%)	No problems	162 (52.3)	50 (35.0)	6 (22.2)	2 (12.5)	<0.001	85 (41.7)	114 (50.2)	16 (43.2)	0.177
	Some problems	135 (43.5)	78 (54.5)	18 (66.7)	8 (50.0)		103 (50.5)	101 (44.5)	16 (43.2)	
	Disable to perform daily activity	13 (4.2)	15 (10.5)	3 (11.1)	6 (37.5)		16 (7.8)	12 (5.3)	5 (13.5)	
Pain, discomfort, n (%)	Absent	52 (16.8)	18 (12.6)	2 (7.4)	1 (6.2)	0.004	34 (16.7)	33 (14.5)	3 (8.1)	0.282
	Some pain and discomfort	173 (55.8)	75 (52.4)	12 (44.4)	5 (31.2)		99 (48.5)	127 (55.9)	23 (62.2)	
	Severe pain and discomfort	85 (27.4)	50 (35.0)	13 (48.1)	10 (62.5)		71 (34.8)	67 (29.5)	11 (29.7)	
Anxiety, depression n (%)	Absent	174 (56.1)	77 (53.8)	9 (33.3)	5 (31.2)	0.059	105 (51.5)	125 (55.1)	22 (59.5)	0.733
	Some anxiety and depression	109 (35.2)	53 (37.1)	15 (55.6)	9 (56.2)		78 (38.2)	82 (36.1)	11 (29.7)	
	Severe anxiety and depression	27 (8.7)	13 (9.1)	3 (11.1)	2 (12.5)		21 (10.3)	20 (8.8)	4 (10.8)	
Life quality, n (%)	Improved	40 (12.9)	18 (12.6)	3 (11.1)	2 (12.5)	0.547	23 (11.3)	35 (15.4)	5 (13.5)	0.571
	Did not change	61 (19.7)	25 (17.5)	2 (7.4)	2 (12.5)		36 (17.6)	42 (18.5)	8 (21.6)	
	Worsened	209 (67.4)	100 (69.9)	22 (81.5)	12 (75.0)		143 (71.1)	150 (66.1)	24 (64.9)	

* p < 0,05 — the difference between studied parameters.

Table 4. **Features of laboratory parameters in patients with various CKD stages**

Parameters	Gradation	MA (mg/dl)				p* (Fisher's F-test)	GFR (ml/min/1.73 m²)			p* (Fisher's F-test)
		0	30	100	300		≥90	89–60	<60	
Glucose, mmol/l	n M±m (95% CI)	293 11.8±0.3 (11.3–12.3)	130 10.8±0.4 (10.1–11.5)	26 11.4±1.0 (9.4–13.3)	14 11.4±1.7 (7.8–15.0)	0.220	204 11.3±0.3 (10.7–11.9)	226 11.6±0.3 (11.1–12.2)	37 11.1±1.0 (9.1–13.1)	0.691
HbA1c, %	n M±m (95% CI)	96 8.9±0.2 (8.5–9.4)	35 8.5±0.4 (7.7–9.2)	4 7.9±0.6 (6.0–9.8)	3 8.4±0.8 (5.1–11.6)	0.564	47 9.09±0.31 (8.47–9.7)	81 8.73±0.24 (8.26–9.2)	9 8.1±0.82 (6.21–9.99)	0.393
Creatinine, μmol / l	n M±m (95% CI)	293 83.2±1.1 (81.0–85.5)	131 81.8±1.7 (78.4–85.2)	26 92.0±6.7 (78.3–105.8)	14 165.9±32.9 (94.8–236.9)	<0.001	204 70.9±0.7 (69.5–72.4)	227 87.9±0.9 (86.1–89.7)	37 153.4±12.4 (128.3–178.4)	<0.001
MA, mg/dl	n M±m (95% CI)	—	—	—	—		198 22.3±4.6 (13.2–31.3)	225 17.4±3.4 (10.7–24.2)	37 138.9±34.5 (69.0–208.8)	<0.001
GFR (ml/min/1.73 m²)	n M±m (95% CI)	291 87.9±1.2 (85.5–90.2)	129 88.8±1.8 (85.1–92.4)	26 83.7±4.9 (73.6–93.7)	14 56.4±7.4 (40.5–72.4)	<0.001	—	—	—	

* p < 0,05 — the difference between studied parameters.

disorders. ⅓ of patients with <60 ml/min GFR had some anxiety and depression, 1/10 — serious anxiety and depression disorders.

11,1–15,4 % of patients with MA and decreased GFR had impovenet and 7.4–21.6 % — no changes and 66.1–81.5 % — worsening of clinical condition. Patients with 100 mg/dl MA and ≥90 ml/min GFR mostly had worse clinical condition compared with last year.

Table 4 shows that both groups had high average glycemia level, blood glucose was lower in other groups compared with patients without albuminuria, patients with <60 ml/min GFR had the lowest glycemia level.

The average level of HbA1c was high in all gradations and, moreover, it directly correlated with GFR.

Albuminuria increase and GFR decrease were accompanied by statistically significant increase of blood creatinine. Average MA values inversely correlated with GFR; thus, we estimated the lowest GFR value in patients with 300 mg/dl MA and the highest albuminuria in patients with <60 ml/dl GFR.

Results and discussion

Total MA prevalence in the population was 35.7 %, that almost corresponded to the value obtained by other researchers (36 %) [12]. In both studies, one of the most important reasons for the high incidence of MA was inadequate glycemic control.

56.4 % of patients had <90 ml/min GFR, 48.5 % had 2nd stage, 7.5 % — 3d stage, 0.2 % — 4th, and 0.2 % — terminal stage of CKD (7.9 % of patients had <60 ml/min GFR). The ONTARGET study showed that 31 % of patients had <60 ml / min GFR [13] that was 3 times higher compared with our data.

According to Fink H.A. et al. there are gender differences in the prevalence of CKD — the incidence of CKD among women was higher (12.6 %) compared with men (9.7 %) [14]. Similar results were obtained in our study — 32.2 % of men had <90 ml/min GFR, and in women this indicator was two times higher.

It was proved that the rate of CKD development increases with age, and GFR decreases by 1–> 10 ml/min/year with age in patients with DM [15]. We also showed that CKD progression was associated with age, at the same time, average age of patients with 100 and 300 mg/dl MA was higher compared with patients without or with mild albuminuria.

The level of education did not affect GFR and MA. The presence of MA and GFR decrease were noted mostly in patients with secondary professional and higher education. The ONTARGET study showed that increased level of education inversely correlated with CKD development [13]. These results can be explained by the fact that patient adherence to treatment increases with education level that contributes to the decrease of renal dysfunction progression. It can be concluded that it is necessary to improve measures on treatment and prevention of T2DM, especially in educated patients.

In our study the frequency of MA was significantly higher in unemployed patients compared with employed patients in contrast with Dunkler D. et al. [13] results. There results can be explained by the nephroprotective effect of physical activity in working patients that slowed MA progression.

It is known that genetic predisposition and family history of cardiovascular diseases (CVD), which are independent risk factors for kidney damage develop-

ment, contribute to the development of diabetic nephropathy [16]. Our data are similar to the results of Abdelhafiz A.H. et al. — 1/10 of patients with DM and family history of MI had < 60 ml / min GFR.

It was found that moderate alcohol consumption significantly reduced the risk of CKD development [13]. Our study obtained similar results — the majority of patients without albuminuria (about 3/4) and low rate of 300 mg / dl MA had low or moderate alcohol consumption. Patients who did not consume alcohol had higher incidence of MA. Thus, low and moderate amounts of alcohol had anti-albuminuric effect, but alcoholic beverages did not affect GFR significantly.

Obesity is also a serious CVD and kidney damage risk factor [5,8]. In our study most patients were overweight and had obesity. Despite the fact that this parameter did significantly contribute to the development of MA, patients with <60 ml / min GFR had excessed body mass and obesity significantly less common compared with patients with stages 1 and 2 of CKD. CKD decompensation led to body mass decrease, which was an indicator of uremic intoxication and unfavorable prognostic marker.

A significant CKD risk reduction was associated with regular physical activity in several studies [13]. Similarly, in our study patients with low physical activity had higher incidence of MA, but this risk factor did not reduce GFR significantly.

According to the results of the ONTARGET study [13], stress did not significantly affect the development of CKD; on the contrary, in our study, moderate and high stress levels prevailed in patients with severe MA and <60 ml/min GFR.

It is well known that adequate glycemic control plays an important role in preventing kidney damage [7]. As a result of inadequate diabetes management, albuminuria develops after 4 years [17], and the annual rate of MA to macroalbuminuria transition ranges from 2.8 to 9 % [18]. Chronic hyperglycemia leads to glomerular hyperfiltration, that is considered as the main diabetic nephropathy sign and, therefore, GFR gradually reduces [19]. Our patients did not have adequate glycemic status control. Patients with MA had high HbA1c level, and low glycemia in patients with <60 ml / min GFR may be associated with Zabrodi phenomenon, that is an unfavorable prognostic marker. Average values of HbA1c decreased with kidney filtration rate. This fact may be associated with discomfort and worsening of life quality in patients with CKD progression, that may lead to glycemic status control improvement.

Giordano Imbroll M. et al. determined that the increase of creatinine blood level was associated with albuminuria progression and GFR decrease [20]. In our study, this indicator also directly correlated with MA and inversely — with GFR.

At the same time, albuminuria was the most significant predictor of GFR decrease during the following year [21]. Similar results were obtained in our study, for example, increased severity of MA was associated with decreased GFR, and vice versa.

Thus, in the Azerbaijani cohort of patients with T2DM, it is necessary to perform monitoring of CKD prevalence, socio-demographic, and behavioral risk factors, as well as correct glycemic status adequately. Only in this case is it possible to slow down the development and progression of serious renal dysfunction and protect patients from life-threatening cardiovascular complications.

Conclusion

7,9 % of patients with T2DM had GFR < 60 ml/min, 35,7 % — MA. We assessed general and individual MA and decreased GFR risk factors.

Increased creatinine level, high stress level, and GFR decrease were associated increased level of MA. MA was often accompanied by movement restriction, self-care and daily activity impairment, as well as pain and discomfort. Employment reduced the incidence of albuminuria, low and moderate alcohol consumption had an antiproteinuric effect, and low physical activity was albuminuria predictor.

Patients with CKD had mainly moderate and high stress levels, family history of CAD was associated with GFR decrease, glycemia directly correlated with GFR and inversely — with age, creatinine blood level and MA. The incidence of renal dysfunction was higher in overweight patients with obesity and limited self-care.

Conflict of interest: None declared.

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The assessment of inflammatory diseases of periodontium as cardiovascular disease risk factor

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Objective. *To study the association between inflammatory diseases of periodontium and cardiovascular diseases (CVD) in patients with different cardiovascular risk.*

Materials and methods. *Patients were divided into four groups: patients with light (n=25), moderate (n=34), severe (n=30) periodontitis and control group without inflammatory diseases of periodontium (n=20).*

Results. *Systemic inflammatory response syndrome with increased high-sensitive C-reactive protein (hs-CRP) and IL-6 are additional pathogenic factors that connects inflammatory diseases of periodontium and cardiovas-*

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cular diseases. The association between the course of somatic and dental pathology requires a joint effort from dentists and cardiologists to identify common risk factors modification.

Conclusion. *Specialists of related disciplines need to evaluate the prognostic significance of risk factors when assessing subclinical atherosclerosis and periodontium condition in order to perform preventive measures.*

Key words*: periodontitis, cardiovascular diseases, cardiovascular risk, hs-CPR, inflammation, atherosclerosis.*

Conflict of interests: none declared.

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Introduction

One of the main global medicine goals are to increase life expectancy and improve its quality. It is also important to improve the property of life itself, especially among progressively increasing number of elderly people. Since functional and morphological impairment of vascular system progress with age, the main mortality cause are cardiovascular diseases. That is why cardiovascular disease (CVD) prevention is essential. Cardiological specialists study closely, all, mainly chronic, processes in the body that affect the state of vascular wall. They mainly include local inflammation, that with the increase of its duration may significantly aggravate or cause chronic inflammatory process. In our country the association between these processes has been studied since 1920s, and has also been investigated by foreign experts [1–4].

Myocardial infarction (MI) — is the main manifestation of coronary artery wall inflammation. MI is one of the leading causes of death in the Western world. Can periodontitis or other inflammatory diseases of oral cavity cause CVD, is there a systemic relationship and association with atherosclerosis and diabetes mellitus (DM) – are the main issues of modern dentistry. Dentist's practice is associated with treatment of significant number of patients (> 30 %) with a history of somatic diseases [5]. The aging of population and the presence of risk factors contribute to the number of concomitant diseases and organism capabilities decompensation [6].

The association between chronic generalized periodontitis (CGP) and CVD is complicated. Negative impact of CVD on the development and the course of periodontal diseases has been proven in a number of studies [5, 7, 8], but the inverse effect of existing chronic periodontitis on CVD risk and their complications has not been studied enough yet. Currently, the pathogenesis of many somatic diseases is being associated with systemic inflammatory response (SIR) with both infection and aseptic inflammation [1, 2]. With severe local inflammation or failure of the mechanisms that limit its course, hs-CRP rises, cytokines enter the circulatory system and lead to the development of SIR [9].

The aim of our study was to establish the association between inflammatory periodontal diseases and the development of CVDs in patients with various cardiovascular risk (CVR).

Objective

To study the association between inflammatory diseases of periodontitis and CVDs in patients with different cardiovascular risk.

Materials and methods

We divided all the patients into four groups — with mild (n=25), moderate (n=34) and severe CGP (n=30) and the control group — without CGP (n=20).

Patients with mild CGP were aged 45.5±1.85 years, with moderate and severe CGP — 48.6±2.08 and 49.3±1.8 years, respectively. The age of patients from the control group was 45.7±2.91 years. Subgroups did not differ by age. Patients with mild CGP included 8 (32 %) men and 17 (68 %) women. Patients with moderate CGP — 10 men (29 %) and 24 women (71 %). Patients with severe CGP — 6 men (20 %) and 24 women (80 %).

The level of hs-CRP was determined by a high-sensitive immunoturbidimetric method with carboxylated polystyrene particles using Sapphire 400 biochemical analyzer, Japan, and the level of pro-inflammatory IL-6 using PW40 Microplate Washer analyzer, BIO-RAD LABORATORIES SAS, France.

CVD risk was assessed using the SCORE (Systematic Coronary Risk Evaluation) scale that determines 10-year risk of fatal cardiovascular events. Over 5 % is considered to be the high risk and 1–4 % — low risk.

Statistical analysis of obtained data was performed with descriptive statistics methods and ROC curves using STATISTICA 10 software.

Results and discussion

Patients with mild, moderate, and severe CGP, had SCORE risk 0.3±0.11, 1.4±0.41, and 1.6±0.37, respectively. Patients from the control group had 0.8±0.37 SCORE. High SCORE risk in the control group occurred in 5% of patients from the control group and in 0%, 8.8%, and 13.3% of patients with mild, moderate, and severe CGP, respectively. The significance of differences between groups was assessed using Fisher analysis of variance. Multiple comparison showed significant differences between groups: the severity of CGP directly correlated with CVD risk.

Sensitive markers that characterize SIR include hs-CRP, IL-6 and fibrinogen. The upper limit of hs-CRP blood level is 5 mg/l, of IL — 6–10 pg/ml, fibrinogen — 4 g/l. The paraments of these markers in patients included in our study are presented in table 1.

The level of blood hs-CRP increased with the severity of periodontitis. Compared with the control group, the level of hs-CRP increased by 66.7% (p <0.05), 95.2% (p <0.01) and 2.8 times (p <0.001) in patients with mild, moderate and severe periodontitis, respectively. IL-6 parameters had similar pattern. The upper limit of IL-6 increased even in patients with mild chronic periodontitis (11.0±3.38 pg/ml). During comparison with the control group, blood IL-6 level significantly increased in patients with mild (2.4 times), moderate (2.8 times) and severe (3.2 times) CGP (p <0.05). Fibrinogen significantly increased in patients with severe chronic periodontitis compared with the control group by 30.3% (p <0.05). Patients with mild and moderate periodontitis had only a tendency to fibrinogen increase. Thus, in patients with CGP, SIR markers increased with the severity of periodontitis.

Considering that CGP is an inflammatory disease, and the connection between inflammation and atherosclerosis had been studied closely recently, hs-CRP can serve as mediator [3, 4, 5]. The results of two independent researches, published in 2005, showed that hs-CRP is involved in the process of atherosclerosis and, consequently, in the occurrence of stroke and acute MI. Authors emphasize that the level of hs-CRP directly correlates with cardiovascular complications [3, 4]. According to American Heart Association (AHA), hs-CRP is recommended to be included into screening recommendations for patients with a moderate cardiovascular risk [3].

We used ROC curves in order to clarify the diagnostic significance hs-CRP blood level during CVD risk assessment. We selected patients with severe CGP and high SCORE risk. The condition of these patients was considered as «1», and we also assessed their hs-CRP blood level. The rank of patients with mild and moderate CGP and low SCORE risk was considered as 0. Obtained results are described further. The differential separation point of hs-CRP or the cut-off point was 3.4 mg/L. When this level was exceeded, patients with CGP had increased risk of severe periodontal lesion and CVD complications development with 94.4% diagnostic sensitivity and 47.8% specificity. The area under the ROC curve (AUC, Area Under Curve) was high (AUC=0.690±0.064) with p=0.0029 (z=2.98) that confirmed the prognostic significance of the risk assessment test (Figure 1).

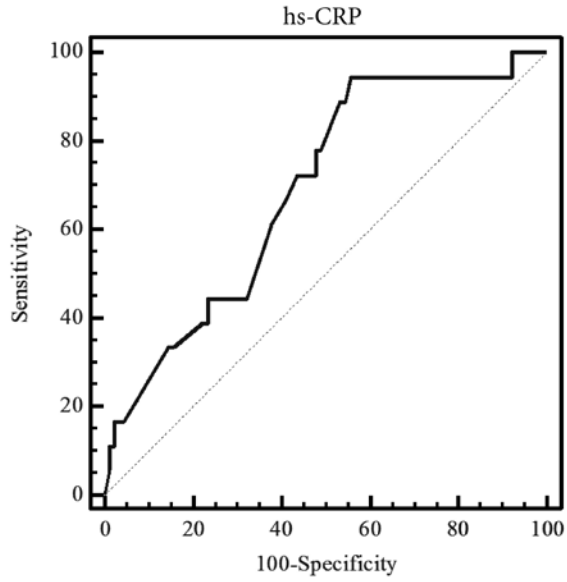

Figure 1. ROC-curve of hs-CRP level as CVD risk marker in patients with CGP

Table 1. **Sensitive SIR markers in patients with different CGP severity and the control group**

Parameters	CGP severity			Control group n=20	P*
	mild n=25	moderate n=34	severe n=30		
hs-CRP, mg/l	3.5±0.28	4.1±0.44	5.8±0.27	2.1±0.30	0.039
IL-6, pg/ml	11.0±3.38	12.8±2.62	14.5±1.40	4.6±1.96	0.016
Fibrinogen, g/l	3.2±0.1	3.4±0.12	4.3±0.08	3.3±0.13	0.64

***** significance of differences between groups was assessed using Fisher analysis of variance.

Thus, it is necessary to control hs-CRP and IL-6 blood levels in patients with CGP, in order to prevent the progression of periodontitis and the development of CVD.

Performed ROC analysis revealed that the differential separation point of apolipoprotein A1 (APO-A1) blood level or the cut-off point was 170 mg/dl. Patients with CGP and decreased APO-A1 blood level (below 170 mg/dL) had higher risk of severe periodontal lesions and CVD complications development with 74.6% diagnostic sensitivity and 72.7% specificity. The area under the ROC curve (AUC) was high (AUC=0.794±0.04) with p <0.0001 (z=6.67) that confirms the prognostic significance of the risk assessment test.

We performed multiple regression analysis in order to establish the association between systemic inflammatory markers, blood lipid spectrum and the severity of the disease in patients with CGP. Based on the results of multiple regression analysis, we obtained the following mathematical expression:

$$Z = 0{,}068 – 0{,}0004 * x + 0{,}36 * y,$$

where:

Z — disease rank: 1 — mild; 2 — moderate; 3 — severe CGP, 0 — absence of the disease;

x — APO-A1 (mg/dl), y — hs-CRP (mg/l).

β-regression coefficient that reflects the effect of APO-A1 on the disease severity, was 0.012 (p=0.028), and 0.76 (p <0.001) for hs-CRP.

The three-dimensional relationship between the severity of chronic periodontitis, the level of hs-CRP and APO-A1 blood level is the following: the blood level of hs-CRP increase and APO-A1 decrease aggravate the severity of periodontal pathology (Figure 2).

In order to reduce the systemic inflammatory response, the dentist needs to carry out effective periodontal treatment. Patients with high CVD risk are the priority group for specific preventive measures. According to modern pathogenesis of atherosclerosis theory, CVD risk factors lead to endothelial dysfunction and initiate inflammation. Subclinical inflammation is caused by sequential cascade of mutually regulated factors, including cellular, humoral immunity, as well as inflammatory mediators, including interferon, interleukins, proteins of inflammation acute phase.

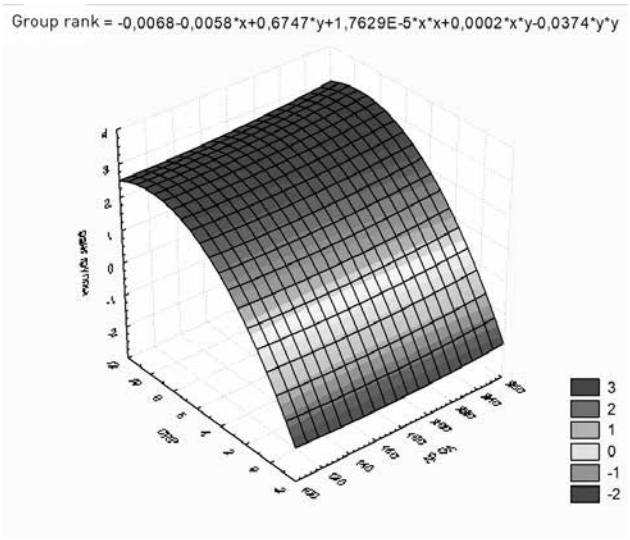

Figure 2. Three-dimensional relationship between the severity of chronic periodontitis, the level of hs-CRP and APO-A1 blood level decrease. The X axis shows the APO- A1 blood level in mg/dl, the y axis shows the hs-CRP blood level in mg/l, the Z axis shows the disease rank.

Conclusion

1. According to the results obtained in this study, we can consider inflammatory periodontal diseases as one of the additional risk factors of CVD development. This conclusion is based on the fact that cardiovascular risk (CVR) increases with the severity of chronic generalized inflammatory process, by 8.8% in patients with moderate CGP and 13.3% — with severe (p=0.04).

2. Specialists of related disciplines need to evaluate the prognostic significance of risk factors when assessing subclinical atherosclerosis and periodontium condition in order to perform preventive measures.

Thus, the presence of CGP can be considered as the aggravating factor of CVD course, and, possibly, CVD predictor. Effective preventive measures, diagnosis and treatment of inflammatory periodontal diseases can reduce CVR.

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The efficacy and cardiovascular safety of phosphodiesterase type 5 inhibitor in men with stable coronary artery disease and erectile dysfunction

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Objective. *To study the efficacy and cardiovascular safety of sildenafil in men with stable coronary artery (CAD) disease and erectile dysfunction (ED).*

Materials and methods. *The prospective study included 50 men aged 40–69 years with stable CAD, low and medium cardiovascular risk of complications according to Princeton Consensus and ED. Men with CAD and ED were randomized into two comparable groups. The first group (n=27) received 25 mg of sildenafil 3 times a week additionally to standard therapy. In case of ineffectiveness, the dose reached 50 mg after 1 month of therapy. The control group (n=23) received only standard therapy. The duration of follow-up was 3 months. Before and after the therapy we assessed: the dynamics of erectile function, symptoms of urination, the severity of chronic stress, hemodynamic, anthropometric parameters and electrocardiographic (ECG) parameters.*

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Results. *The erectile function twice increased according to international index of ED by the end of the study that was statistically significant compared with the initial parameter and control group. The symptoms of urination decreased by 30 % according to international scale during sildenafil treatment compared with the control group without dynamics of total parameter according to MIEF-5 questionnaire. The level of chronic stress decreased by ⅓ according to questioning. The dynamics of stress severity did not differ significantly in control group. The analysis of ECG at rest did not reveal any negative dynamics in the frequency of heart rhythm disturbances and coronary circulation parameters during sildenafil treatment.*

Conclusion. *Course therapy with low doses of sildenafil as part of complex therapy can be used for ED treatment in patients with CAD with low and moderate risk according to Princeton Consensus.*

Key words: *Princeton Consensus, erectile dysfunction, sildenafil, coronary artery disease.*

Conflict of interests: none declared.

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Introduction

Erectile dysfunction (ED) is male sexual dysfunction characterized by the inability to develop or maintain an erection during sexual activity that has always been one of the main issues of male health. Nowadays it remains complex and still significantly affects life quality of male population. Its prevalence among men from various age groups reaches 33 % and correlates with age and related diseases [1].

It is known that men of working age with coronary artery disease (CAD) have decreased exercise tolerance and life quality that also negatively affects men sexual activity. On the other hand, it is known that cardiovascular disease (CVD) risk factors are the main causes of ED development in men of working age. Many prospective studies noted that ED can serve as CAD and other CVDs predictor [2].

For a long time, there was an opinion that the risk of sudden cardiac death is higher in patients with CVD during sexual intercourse. However, further studies have shown that these ideas were exaggerated. New highly effective methods of ED treatment gave men the opportunity to resume their sex lives, including patients with CVDs. Princeton Consensus has been developed in order to standardize the problem of sexual activity and cardiovascular risk and divided patients with sexual dysfunction into three groups. Those at low risk could initiate or resume sexual activity and be treated for sexual dysfunction, at moderate risk — further investigations are needed. For those at high risk, sexual activity should deferred until stabilized cardiac condition [3].

Over the last years, many researched showed successful treatment of ED and other somatic diseases with low doses of phosphodiesterase type 5 (PDE5) inhibitors [4]. There are many studies on the effect of PDE 5 inhibitors on CVDs and its interaction with standard cardiac therapy. It is necessary to study the dynamics of main cardiovascular parameters during low doses of PDE5 inhibitors therapy in order to assess the possibilities of pharmacological treatment in patients with ED and CAD.

Objective

To study the efficacy and cardiovascular safety of sildenafil treatment in men with CAD and ED in patients with low and moderate risk according to Princeton Consensus.

Materials and methods

The study included 50 men aged 55.4±2.8 years with stable CAD and ED, who came to City Clinic No. 212 of the Moscow Health Department from September 2018 to February 2019.

Inclusion criteria: sexual dysfunction in men over 35 years in combination with one or more of the following diseases (chronic prostatitis, CAD, type 2 diabetes mellitus (T2DM), arterial hypertension (AH), International Index of Erectile Function (IIEF) below 21, controlled 1–2 grade of AH, stable CAD (I —II functional class of angina, postinfarction cardiosclerosis)), I —II FC of chronic heart failure (CHF).

Exclusion criteria: patients with high cardiovascular risk according to Princeton Consensus, grade 3 AH, uncontrolled AH, III –IV FC of CHF, unstable angina, myocardial infarction and acute cerebrovascular accident over the last 6 months, nitrate therapy, individual sildenafil intolerance, acute stage of chronic diseases, malignant neoplasms, T2DM, severe course or decompensation of the disease, participation in other studies.

Socio-demographic characteristics of men with CAD and ED included in the study are presented in table 1.

Table 1. **Socio-demographic characteristics of men with CAD and ED**

Parameters	Main group, n=27	Control group, n=23	p*
Age, years	55.9 ± 3.4	55.3 ± 1.8	insignificant
Education, n (%) Higher Secondary	8 (29.6 %) 19 (70.4 %)	8 (35 %) 16 (65 %)	insignificant insignificant
Family status, n (%) Married Single	24 (89 %) 3 (11 %)	19 (82 %) 4 (18 %)	insignificant insignificant
Employment, n (%) Employed Unemployed	17 (63 %) 10 (37 %)	15 (65 %) 8 (35 %)	insignificant insignificant
Alcohol consumption, n (%) Alcohol abuser Not an alcohol abuser	8 (29.6 %) 19 (70.4 %)	6 (26 %) 17 (74 %)	insignificant insignificant
Smoking, n (%) Smoker Non-smoker	19 (70 %) 8 (30 %)	16 (69.6 %) 7 (30.4 %)	insignificant insignificant

***** Insignificant — insignificant difference between groups.

Methods

The standard questioning was performed using specially developed for this study questionnaire (based on the ARIC, World Health Organization (WHO) and National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation questionnaires).

Chronic stress was assessed using the Reeder questionnaire that included 10 questions and five possible answers to each question. The questionnaire identifies three levels of stress: low (score 3.01–4), medium (score 2.01–3) and severe (score 1–2).

Studied anthropometric parameters included height, body mass, waist circumference (WC) and body mass index (BMI). According to WHO recommendations, WC was measured between the edge of the lower rib and ileum. BMI (Quetelet index) was calculated as the ratio of body mass in kilograms to the square of height in meters (BMI=/h2, where m — body mass of the patient (kg), h — height (m)).

Office blood pressure (BP) measurement was performed using tonometry on the patient's right hand while sitting after 5-minute rest. Systolic blood pressure (SBP) was recorded when 1 Korotkov sound appeared (phase I), diastolic blood pressure (DBP) — with the sounds disappeared (phase V). The level of BP was evaluated twice with 2–3 minutes interval, the average result was included into the study. The level of BP > 140/90 mm Hg was considered as AH and / or when the patient received antihypertensive therapy; awareness — the patient knows about the presence of AH; treatment — the patient receives antihypertensive therapy; treatment effectiveness — the patient receives antihypertensive therapy, and BP reaches target level. We also noted patient's heart rate (HR).

12-lead electrocardiogram (ECG) was registered at rest. ECG interpretation was performed according to scheme specially developed for this study (based on the Minnesota code standards, Rose G., Blackburn H., 1968).

ED was assessed using IIEF questionnaire (Rosen RC et al., 1997) that allows to estimate 5 components of sexual function: erection, orgasm, sexual attraction, sexual and general satisfaction. This study assessed erectile function [5]. 22–25 points was considered as normal erectile function, 17–21 points — mild impairment; 12–16 points moderate to mild impairment, 8–11 — moderate impairment, 5–7 points — severe impairment.

The severity of urination disorders was assessed using the IPSS questionnaire (The International Prostate Symptom Score, WHO, 1992). Patients answered each of 7 questions by noting the best answer. Interpretation of the results: from 0 to 7 points — mild; from 8 to 16 points — moderate; over 20 points — severe impairment.

Study protocol

Men with CAD and ED were randomized into 2 comparable groups:

The main group (27 patients) received standard CAD therapy and 25 mg of sildenafil 3 times a day. In case of ineffectiveness, the dose reached 50 mg after 1 month of therapy. The duration of follow-up was 3 months.

The control group (23 patients) received only standard CAD therapy. Characteristics of received medications is presented in table 2. The differences between groups by received therapy were insignificant.

Before and after the study we assessed risk factors (RF) dynamics, clinical condition and life quality in mild and moderate risk groups according to Princeton Consensus using instrumental cardiac and laboratory investigations and questionnaires [6].

During short control visit at the middle of the study (after 1 month) we performed short questioning, BP and HR measurement and ECG registration at rest.

Table 2. **Received therapy characteristics**

Medication	Main group, n (%)	Control group, n (%)	Significance of differences*
Sildenafil 25 мг	3 (11%)	-	-
Sildenafil 50 мг	24 (89%)	-	-
Calcium channel blockers	6 (22%)	5 (21.7%)	insignificant
Beta-blockers	8 (29.6%)	7 (30%)	insignificant
ACE inhibitors/ sartans	10 (37%)	9 (39%)	insignificant
Statinis	12 (44%)	10 (43%)	insignificant
Mineralocorticoid receptors antagonists	7 (30%)	5 (21.7%)	insignificant

***** Insignificant — insignificant difference between groups.

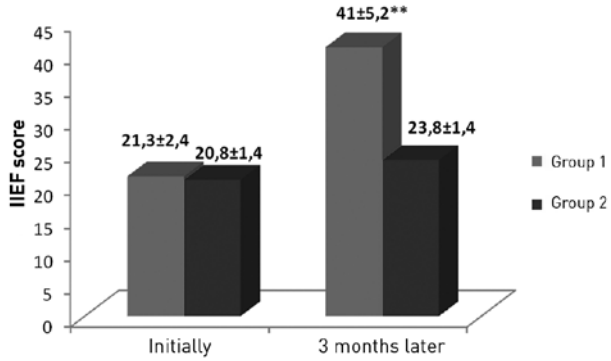

Figure 1. Erectile function dynamics in patients after the therapy

Statistical analysis of obtained data was performed using Statistica 6,0. Software. Quantitative variables are presented as mean (M) and standard error of mean (m). The significance of differences was assessed using Student and Wilcoxon paired t-test. A p value less than 0.05 was considered significant.

Results and discussion

Our study is dedicated to the investigation of the efficacy and cardiovascular safety of course therapy with PDE5 inhibitor sildenafil in patients with CAD. Previous studies have shown that course PDE5 inhibitor therapy was superior to its single use in patients with ED. But there are not so many studies on the course PDE5 inhibitor therapy in patients with CAD and ED. Before therapy it is necessary to asses its effectiveness, interaction with other medications, tolerance and safety.

The analysis of participants comorbidities was performed by assessing its frequency (Table 3).

Table 3. **Participant's comorbidities characteristics**

Clinical diagnosis	Main group, %	Control group, %
2nd stage AH	13 (48%)	10 (43%)
3rd stage AH	6 (22%)	5 (21.7%)
CAD	14 (52%)	13 (56%)
CHF	8 (29.6%)	7 (30%)
DM	6 (22%)	5 (21.7%)
Obesity	6 (22%)	6 (26%)
ED	27 (100%)	23 (100%)
Chronic prostatitis, remission	23 (85%)	20 (87%)

According to the protocol, patients were divided into two groups: the main group, which received sildenafil and the control group — without PDE type 5 inhibitors. Therapy received by patients before the investigation did not change. The dose of sildenafil reached 50 mg after 1 month of therapy in 89% of patients. By the end of the course erectile function improved twice that was statistically significant ($p<0,01$) compared with initial value and the control group (Figure 1).

According to previous studies PDE5 inhibitors therapy positively affects urinary function that is commonly associated with hyperplasia or other prostate disorders [8]. According to IPSS questionnaire (The International Prostate Symptom Score, WHO, 1992) most patients had ED and moderate urinary function impairment [9]. During sildenafil treatment, symptoms of urinary dysfunction decreased by 30% compared with the control group where there were no dynamics of IPSS score. The differences between groups were statistically significant (Figure 2).

It is known that ED is associated with life quality and psychosomatic status of men of reproductive age [1,5]. We assessed chronic stress level in patients before and after the study. The chronic stress indicator improved by 1/3 (from 2.8± 0.2 points to 4.1±0.2 points, $p<0.01$) in patients from the main group according to the questioning. The dynamics of chronic stress was insignificant in patients from the control group (2.9±0.1 versus 3.4±0.2 points, $p>0.05$). The differences between groups were statistically significant ($p<0.05$).

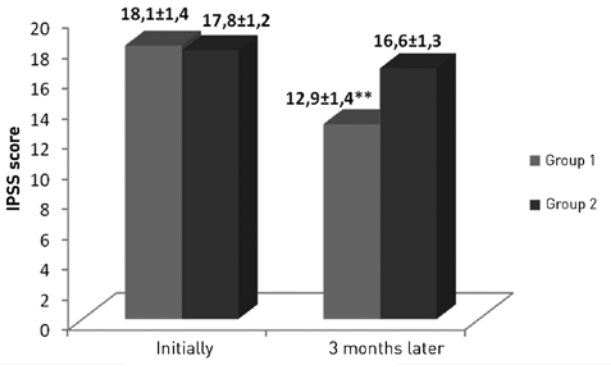

Figure 2. The dynamics of International Prostate Symptom Score

Table 4. **Hemodynamics and anthropometric parameters during sildenafil course therapy**

Parameter	Main group		Control group	
	Before therapy, n=27	After therapy, n=27	Before therapy, n=23	After therapy, n=23
SBP	141.1 ± 9.45	134.9 ± 6.2	138.6 ± 3.8	132.7 ± 2.6
DBP	83.2±6.4	78.7 ± 3.6	79.6±2.5	75.1 ± 1.7
HR	74 ± 4.8	77 ± 4.3	74.8 ± 3.2	72.4 ± 2.8
WC, cm	96.8 ± 1.5	93 ± 1.4*	95.9 ± 1.8	94.8 ± 1.2
Body mass, kg	84.4 ± 1.7	79.4 ± 1.6*	83.6 ± 1.4	82.4 ± 1.7
BMI	28.6±1.27	25.2±1.3*	28.9±0.9	27.8 ±1.3

* $p < 0,05$.

One of the main objectives of our research was the assessment of the dynamics of the main RF in study participants (table 4).

There are two features that we need to consider while prescribing PDE5 inhibitors in patients with cardiovascular pathology. Firstly, these medications reduce BP by 8 mmHg on average. But PDE type 5 inhibitors are not contraindicated in patients with AH. Secondly, PDE type 5 inhibitors interact with nitrates [10].

Thus, patients from both groups received antihypertensive therapy from four groups, and this therapy did not change during the investigation. Hemodynamic parameters (SBP and DBP) slightly decreased in both groups and did not differ between groups. HR was normal during the study.

We also assessed the dynamics of anthropometric parameters. Initially, about 60 % of men with CAD and ED had abdominal obesity. During the course of sildenafil therapy waist circumflex significantly decreased in the main group that may be associated with increased sexual and physical activity. But these changes were not statistically significant compared with the control group. The dynamics of body mass and BMI had similar pattern.

We assessed not only the effectiveness, but also the safety of sildenafil course therapy in patients with CAD. Our study included patients with low and moderate cardiovascular risk of sexual activity according to Princeton Consensus. Thus, the results of our study show that FC of CAD and the frequency of its episodes did not change in patients with angina pectoris. Thadani et al. also showed that during the therapy with 10 mg of vardenafil per day, symptoms of angina pectoris and myocardial circulation did not change in patients with CAD and ED [11]. According to ECG analysis, there were no negative dynamics of vascularization and conduction during 50 mg of sildenafil treatment (Table 5). The main group data were comparable with the control group.

All the patients before the study were supplied with self-control diary of adverse effects. The most common adverse effect was transient flushing that was registered almost in every forth patient (table 6). Every fifth patient had dizziness. These results were comparable with previous data and did not lead to therapy interruption or canceling [8].

Table 6. **Adverse effects of course sildenafil treatment**

Adverse affect	N (%)
Flushing	7 (26 %)
Priapism	2 (7 %)
AP increase	4 (15 %)
Dizziness	5 (18 %)
Chest discomfort, abdominal pain	3 (11 %)

Conclusion

This study shows that ED is common in patients with CAD risk factors. Performed course of sildenafil therapy significantly improved erectile function, decreased urinary dysfunction symptoms and the severity of chronic stress. Course therapy with low doses of sildenafil affected hemodynamic and anthropometric parameters as well as ECG pattern. Thus, PDE type 5 inhibitors as part of complex therapy can be used for ED treatment in patients with CAD with low and moderate risk according to Princeton Consensus.

Conflicts of interest: None declared.

Table 5. **ECG features during sildenafil treatment**

Parameter	Main group		Control group	
	Before therapy, n=27	After therapy, n=27	Before therapy, n=23	After therapy, n=23
Atrial fibrillation (AF), n (%)	2 (7 %)	2 (7 %)	1 (4 %)	1 (4 %)
QRS ⩾ 120 ms, n (%)	3 (11 %)	3 (11 %)	2 (9 %)	2 (9 %)
Left ventricular hypertrophy (LVH) signs, n (%)	17 (63 %)	17 (63 %)	15 (65 %)	15 (65 %)
Negative T wave in chest leads, n (%)	10 (37 %)	8 (29 %)	7 (30 %)	6 (26 %)
Pathologic Q wave, n (%)	2 (7 %)	2 (7 %)	2 (9 %)	2 (9 %)
Vesicular extrasystole, n (%)	6 (22 %)	5 (18 %)	5 (21,7 %)	4 (17 %)
Supraventricular extrasystole	7 (26 %)	8 (29 %)	6 (26 %)	5 (21,7 %)
AV block, 1st stage	3 (11 %)	3 (11 %)	1 (4,3 %)	1 (4,3 %)

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REVIEW ARTICLE

Anticoagulative therapy after stroke in patients with atrial fibrillation

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Atrial fibrillation (AF) is one of the most serious complications in stroke patients. Meta-analysis of several studies showed that the risk of recurrent stroke is 2,5 higher in patients with AF and stroke/transient ischemic attack (TIA). According to current guidelines (ESC 2016) secondary stroke prevention in patients with AF include effective new oral anticoagulant (NOAC) and medication adherence measures. NOAC decreased cardiovascular mortality and the risk of major and intracranial bleeding compared with vitamin K antagonists in stroke/ TIA patients. The review article presents NOAC indications, dosing and administration recommendations.

Key words: *atrial fibrillation, stroke, anticoagulants, effectiveness, safety.*

Conflict of interests: none declared.

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Atrial fibrillation (AF) is one of the most common cardiovascular disease (CVD) risk factors. The prevalence is 1,5–2,0 % among adults according to epidemiological studies. The prevalence of AF increases with age [1,2]. AF comorbidity with other diseases also has prognostic value. According to EORP AF data, among 3049 patients with AF and average age of 68,8 years, 71 % had arterial hypertension (AH), 47,5 % had chronic heart failure (CHF), 36,4 % — coronary artery disease (CAD), every third patient had cardiomyopathy and every fifth –type 2 diabetes mellitus (T2DM) (Table 1) [3].

There is an opinion, that clinically manifested strokes are the tip of an iceberg of vascular brain diseases. The number of investigations showed that 40 % of patients with 1–2 grade AH have organic vascular pathologies according to MRI data. In general, the frequency of intractable intracranial strokes is

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5–23 % according to imaging methods and biomarkers.

Table 1. **Comorbidities in patients with AF (according to EORP AF data)**

Average age, years	68,8
CAD, %	36,4 %
Congestive heart failure, %	47,5 %
AH, %	70,9 %
DM, %	20,6 %
Hypercholesterinemia, %	48,6 %
Cardiomyopathy, %	35,3 %
Other cardiovascular diseases, %	8,1 %
Chronic kidney disease, %	13,2 %

Atrial fibrillation and the risk of complications in stroke patients

AF is one of the most serious complications in patients after stroke. The meta-analysis of several studies showed that the risk of stroke increases by 2,5 times in patients with AF and stroke/ transient ischemic attack (TIA). The risk of ischemic stroke/ TIA is 7,6 % and the risk of symptomatic intracranial hemorrhage — 3,6 % during the first 90 days in stroke patients with AF. Mortality during the first year after stroke in patients with AF is 50 %. It is also remarkable that the frequency of AF is relatively high in stroke patients — 30 % [4].

In general, the history of thromboembolic complications is the risk factor of coronary events in patients with AF. However, CHF in patients with left ventricular ejection fraction (LVEF) ⩽40 %, age ⩾75 years and metabolic syndrome can also cause cardiovascular events [5].

According to current guidelines (ESC 2016), secondary prevention of stroke in patients with AF include effective new oral anticoagulant (NOAC) and medication adherence measures. NOACs are superior to vitamin K antagonists (VKA) or aspirin in patients with AF and history of stroke. Patients with TIA and stroke during anticoagulant therapy should underwent adherence estimation and optimize it if needed [1].

The effectiveness of new oral anticoagulants in stroke or transient ischemic attack patients with atrial fibrillation

The results of new studies on the effectiveness of NOAC compared with standard therapy — warfarin, have been published. The REAFFIRM study included the retrospective analysis of the US Truven MarketScan database from January 2012 to June 2015 in order to compare the effectiveness and safety of rivaroxaban, apixaban, dabigatran with warfarin for secondary stroke prevention and systemic embolism in patients with AF in clinical practice. The primary endpoint of the investigation was the general frequency of ischemic stroke and intracranial haemorrhage. NOAC was superior to other medications according to the results [6].

Three large studies (ROCKET AF — rivaroxaban, RE-LY — dabigatran, ARISTOTLE — apixaban) studied the effectiveness and safety of oral anticoagulants (OA) in patients with AF after stroke, the prevalence of which was from 19 % to 52 %. The results of these studies showed that recurrent strokes frequency reduced by 21 % (apixaban) and 26 % (dabigatran) compared with warfarin, and mortality reduced by 11 % and 14 %, respectively. NOACs reduce the risk of intracranial bleeding and large bleedings compared with warfarin [7–10].

Anticoagulative therapy guidelines

Patients with TIA or stroke during anticoagulative therapy should underwent anticoagulative therapy adherence estimation and optimize it (Figure 1).

The resumption of anticoagulant therapy in patients with AF after stroke / TIA depends on stroke severity and the presence of bleeding risk factors [11].

NOAC therapy can be resumed not only after a stroke, but also after intracranial bleeding.

The combination of NOAC and antiplatelet therapy in patients after TIA or stroke, is not recommended.

Patients after NOAC therapy had lower risk of ischemic events without differences in hemorrhagic complications compared with patients without OACs [12].

National Institutes of Health Stroke Scale [13] (NIHSS) is used for the estimation of stroke severity, neurological deficits, and consists of 11 items:

- Each item scores a specific ability between 0 and 4 — higher score indicative higher level of impairment.
- The maximum possible score is 42.

There are 5 gradations depending on the score:

- no stroke symptoms;
- minor stroke;
- moderate stroke;
- moderate to severe stroke;
- severe stroke.

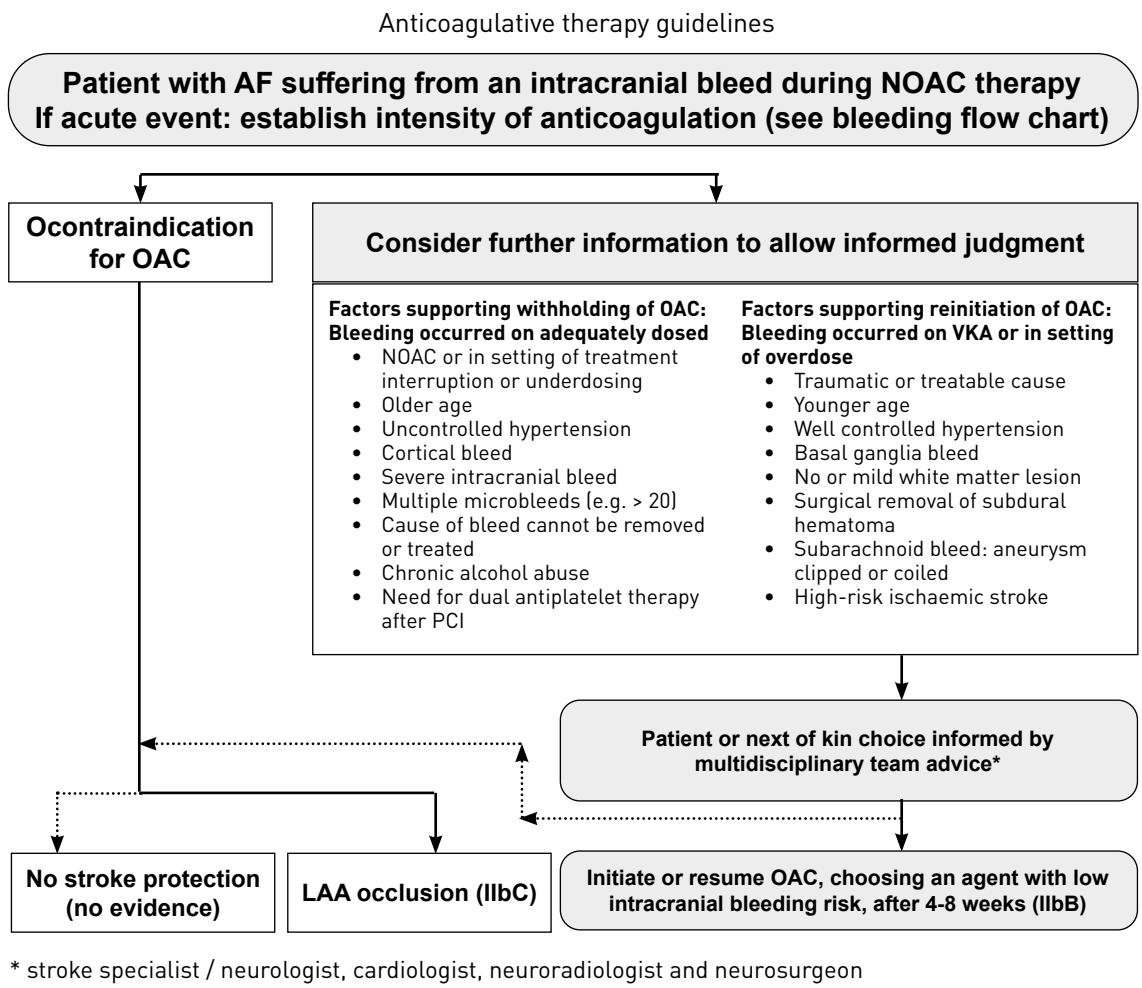

Figure 1. Anticoagulative NOAC therapy guidelines in patients with AF and intracranial bleeding

The estimation of additional risk factors, affecting earlier or later beginning of treatment with new oral anticoagulants

When initiating NOAC therapy in patients with AF after ischemic stroke / TIA we have to consider the following factors:

- bleeding occurred on VKA or in setting of overdose;
- traumatic or treatable cause;
- younger age;
- well controlled hypertension;
- basal ganglia bleed;
- no or mild white matter lesions;
- surgical removal of subdural hematoma;
- subarachnoid bleed: aneurysm clipped or coiled;
- high-risk of ischemic stroke.

The beginning/reinitiating of NOAC after ischemic stroke/ TIA depends on the severity of stroke. The 1–3–6–12 day rule is advocated. Patients with TIA can start OAC therapy in 1 week. Patients with NIHSS <8 or minor stroke — in 3 weeks. Patients with moderate stroke and NIHSS 8–15 — in 6 weeks. Patients with severe stroke and NIHSS >16 — have the longest interval when prescribing NOACs [1,12].

Anticoagulative therapy in patients with AF after intracranial bleeding can be reinitiated 4–8 weeks after.

Clinical situations supporting withholding of oral anticoagulants

In some cases, we have to reduce or withhold the NOAC in order to prevent possible complications. These cases are listed below:

- bleeding occurred on adequate or reduced dose;
- NOAC or in setting of treatment interruption;
- older age;
- uncontrolled hypertension;
- cortical bleed;
- severe intracranial bleed;
- multiple microbleeds (e.g. > 20);
- cause of bleed cannot be removed or treated;
- chronic alcohol abuse;
- need for dual antiplatelet therapy after PCI.

Conclusion

Patients with AF and the history of stroke/TIA have higher risk of stroke recurrence. These group of patients also have higher risk of intracranial bleeding. NOAC reduced cardiovascular mortality and the risk of major bleeding or intracranial bleeding in patients with the history of stroke/TIA compared with vitamin K antagonists therapy.

Conflicts of interest: None declared.

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International Heart and Vascular Disease
Journal • Volume 7, № 23, September 2019

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[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

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VII. Copyright and publishing policy.

This section regulates the relationship between the editorial Office (Publisher) of *International heart and vascular disease journal* (the «editorial Office») and the author or group of authors who submitted their manuscript for publication in the *International heart and vascular disease journal* (the «Author»).

The author, by sending the article to the Editor, agrees that the editorial Board of the journal shall be transferred to the exclusive property rights to use the manuscript (transferred to the Editorial Board of the journal material, including such protected objects of copyright as photos of the author, drawings, diagrams, tables, etc.), including the reproduction in print and on the Internet; distribution; translation into any languages of the peoples of the world; export and import of copies of the journal with the article of the Author for distribution, to bring to the public.

The editorial Board reserves the right to reduce and edit the materials of the manuscript, to carry out scientific editing, to reduce and correct articles, to change the design of graphs, drawings and tables to bring into line with the design of the journal, without changing the meaning of the information provided.

When using the article, the editors have the right to supply it with any illustrated material, advertising and allow third parties to do so.

The editorial Board has the right to assign the rights received from the Author to third parties and has the right to prohibit third parties from any use of materials published in the journal for commercial purposes.

The author guarantees that he has exclusive rights to use the submitted material. In case of violation of this guarantee and the presentation of claims to the editorial Board, the Author independently and at his own expense undertakes to settle all claims. The editorial Board is not responsible to third parties for violation of the Author's guarantees.

The Author retains the right to use the published material, its fragments and parts for personal, including scientific and teaching purposes.

The Author transfers the above rights to the Editors without limitation of their validity period, in the territory of all countries of the world without limitation, including the territory of the Russian Federation.

The rights to the manuscript are considered to be transferred By the author of the editorial Office from

the moment of sending an information letter about the acceptance of the manuscript to the press.

Reprinting of materials published in the journal by other individuals and legal entities is possible only with the written permission of the editorial Board, with the obligatory indication of the journal name, number and year of publication.

The editors are not responsible for the accuracy of the information provided by the Author.

The author, sending the manuscript to the Editor, gives permission to use and process personal data.

The editorial Board reserves the right to reduce and correct the articles, to change the design of graphs, figures and tables to comply with the standard of the journal, without changing the meaning of the information provided. In case of untimely response of the author (s) to the request of the editorial Board, the editorial Board may at its discretion make changes to the article or refuse to publish.

Sending to the editor of works that have already been sent to other publications or printed in them is absolutely not allowed. The editors are not responsible for the accuracy of the information provided by the authors. Articles sent in violation of the rules of registration are not accepted by the editorial Board for consideration.

VIII. The procedure for rewiewing manuscripts

1. The manuscript should be sent in electronic form to the Editor through the website — http://www.heart-vdj.com. The manuscript should be drawn up in accordance with these requirements for scientific articles submitted for publication in the journal.

2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the «Antiplagiat» system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

4. All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

5. The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the article or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

9. If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

10. All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication.

After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

11. The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

12. Original reviews are kept in the Editorial office for 5 years from the date of publication.

13. In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

1. According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

2. Each issue of the journal is formed by a separate Executive editor appointed by the editor-in-Chief and/or editorial Board. It is the responsibility of the editor-in-charge to select high-quality articles for publication, and he can be guided by both thematic principles and a separate scientific direction.

3. All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

4. The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

1. Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

2. Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

3. We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

XI. Revocation or correction of articles

The full text of the journal's policy on Revocation and correction of articles is available in the information section on the website. The editors follow COPE Recommendations issued by the Committee on publishing ethics (COPE) — http://www.publicationethics.org.uk. in cases:

Editors of journals should consider the opinion of the publication, if:

they have clear evidence of the unreliability of the information published, either as a result of conscious actions (for example, falsification of data), or due to good faith errors (for example, errors in calculations or experiments); the findings have been previously published in another publication and there is no proper reference, authorization and justification for re-publication (i.e. duplicate publication).); it is plagiarism; describes unethical research.

Editors of journals should consider the concerns, if:

they received information about the authors ' inappropriate actions, but there is no clear evidence of such behavior; there are arguments that the results of the work are unreliable, and the institution in which the authors work is not going to find out the truth; they believe that the investigation into the alleged violations committed by the authors in connection with the publication has either not been or will not be fair, impartial and convincing; the authors ' violations are being investigated, but the results are not expected soon enough.

Journal editors should consider making amendments if:

a small part of the rest of the high-quality publication is unreliable (especially because of conscientious errors); the list of authors / sponsors contains errors (i.e., it does not contain someone who is worthy to be an author, or a person who does not meet the authorship criteria).

In most cases, a review is not appropriate if:

authorship needs to be changed, but there is no reason to doubt the validity of the findings.

XII. Position E-log backup (if journal is no longer published)

The purpose of backup is to prevent loss of information in case of hardware, software, critical and crisis situations, etc.

Information of the following main categories is subject to backup: — personal information of authors (personal directories on file servers); — pdf of published articles; — information about literary links to the article in the DOI system.

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

XIII. Journal subscription

Information on subscriptions is available on the journal website in the section «Subscription»:

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

Editorial office:

Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia

e-mail: editor.ihvdj@gmail.com

Submission Preparation Checklist

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1. The manuscripts are accepted if has not been published or submitted for publication elsewhere.

2. The file of the submitted article is in the format of a Microsoft Word document. It does not contain the names of the authors and institutions.

Files with a letter of transmittal and General information have been prepared for upload to the site.

3.The cited literature is presented in full, framed by the Rules for the authors and does not contain duplicates. All references are indicated in the text of the article.

4. Text should be typed with an interval of one line spacing, font Times New Roman, 12 pt; to highlight the accents it is recommended to use italics rather than underlining (except Internet links). All images, graphics and tables are placed within the text according to the meaning of the particular part of text (and not at the end of the document).

5. Text should follow the stylistic and bibliography requirements as stated in Regulations located in the Part «About Us.»

6. Please, remove the authors' names from the title of the article and other parts of the document to ensure the anonymity of reviewing.

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