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CARDIOVASCULAR DISEASES AND VITAL EXHAUSTION: LONGITUDINAL STUDY IN RUSSIA/SIBERIA (WHO MONICA — PSYCHOSOCIAL PROGRAM)

Gafarov Valery, Voevoda Mikhail, Gromova Elena, Maksimov Vladimir, Gagulin Igor, Yudin Nikolay, Gafarova Almira, Mishakova Tatiana

Aim. To study prevalence rates of vital exhaustion and its effects on 14-year risk of cardiovascular disease (CVD) (arterial hypertension (AH), myocardial infarction (MI), and stroke) development and genetic traits in open population of 25–64-year-old men in Russia/Siberia (West Siberia metropolis, Novosibirsk).

Material and methods. Random representative sample of 25–64-year-old men was studied in a framework of WHO MONICA-Psychosocial Program (MOPSY) in 1994. Maastricht Questionnaire (MQ) was used to assess vital exhaustion. Genotyping for variable number of tandem repeats (VNTR) polymorphisms in DRD4 and DAT genes was performed. All new cases of AH, MI, and stroke were registered among people without CVD for 14 years (from 1994 to 2008). Statistical analysis was done by using software package SPSS 11.5. Cox proportional hazards regression model was used for evaluation of risk coefficient (hazard ratio (HR) taking into account time-adjusted control. X^2 test was used to assess statistical significance of differences between the groups.

Results. In the study population, the vital exhaustion rate was 66,8%. Hazard ration was significantly increased (AH: HR=3,2; MI: HR=2,7; stroke: HR=3,2) in men with vital exhaustion compared with vital exhaustion-free individuals in open population during the first five years of observation. Multifactorial modeling showed that vital exhaustion together with concomitant social gradient determined development of AH, MI, and stroke in open population of 25–64-year-old men. Allele 7 of DRD4 and genotype 9/9 of DAT gene were associated with high level of vital exhaustion.

Conclusion: Open population of 25–64-year-old men (Russia/Siberia, Novosibirsk) showed high level of vital exhaustion, a predictor for risk of developing CVD. Vital exhaustion is significantly associated with certain VNTR polymorphisms of DRD4 and DAT gens.

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Key words: arterial hypertension, myocardial infarction, stroke, vital exhaustion, hazard ratio, DRD4, DAT.

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AH — arterial hypertension, DAT — the dopamine transporter, DRD4 — the dopamine D4 receptor, MI — myocardial infarction, MONICA — Multinational Monitoring of Trends and Determinants in Cardiovascular Disease program, VE — vital exhaustion, VNTR — variable number of tandem repeat.

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СЕРДЕЧНО-СОСУДИСТЫЕ ЗАБОЛЕВАНИЯ И ЖИЗНЕННОЕ ИСТОЩЕНИЕ: ПРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ В РОССИИ/СИБИРИ (ПРОГРАММА ВОЗ МОНИКА — ПСИХОСОЦИАЛЬНАЯ)

Gafarov Valery, Voevoda Mikhail, Gromova Elena, Maksimov Vladimir, Gagulin Igor, Yudin Nikolay, Gafarova Almira, Mishakova Tatiana

Цель. Исследовать распространенность жизненного истощения, его влияния на 14-летний риск развития сердечно-сосудистых заболеваний (ССЗ) (артериальной гипертонии (АГ), инфаркта миокарда (ИМ) и инсульта), а так же генетических особенностей жизненного истощения в открытой популяции среди мужчин 25-64 лет в России/Сибири (г.Новосибирск, мегаполис Западной Сибири).

Материал и методы. Была обследована случайная репрезентативная выборка мужчин 25-64 лет в рамках программы ВОЗ "MONICA-психосоциальная (MOPSY)" в 1994г. Маастрихтский опросник (ОМ) использовался для оценки жизненного истощения. Генотипирование было выполнено для переменного числа тандемных повторов (VNTR) полиморфизмов генов DRD4 и DAT. Все новые случаи АГ, ИМ и инсульта были зарегистрированы у лиц без ССЗ в течение 14 лет (с 1994 по 2008гг). Статистический анализ проводился с помощью пакета программ SPSS 11.5. Кокс-пропорциональная регрессионная модель была использована для оценки риска развития (Hazard ratio — HR) с учетом временного интервала. Тест X2 был использован для оценки статистической значимости различий между группами.

Результаты. В исследованной популяции уровень жизненного истощения составил 66,8%. HR был значительно увеличен (АГ: HR=3,2; ИМ: HR=2,7; инсульт: HR=3,2) у мужчин с жизненным истощением, по сравнению с лицами без жизненного истощения в открытой популяции в течение первых пяти лет наблюдения. Многофакторное моделирование показало, что жизненное истощение вместе с сопутствующим социальным градиентом определяет развитие АГ, ИМ и инсульта в открытой популяции среди мужчин 25-64 лет. 7 аллель DRD4 и генотип 9/9 гена DAT были связаны с высоким уровнем жизненного истощения.

Заключение. В открытой популяции среди мужчин 25-64 лет (Россия/Сибирь, г.Новосибирск) определен высокий уровень жизненного истощения, как предиктор риска развития ССЗ. Жизненное истощение существенно связано с определенными VNTRr-полиморфизмами генов DRD4 и DAT.

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Ключевые слова: артериальная гипертония, инфаркт миокарда, инсульт, жизненное истощение, отношение рисков, DRD4, DAT.

НИИ терапии и профилактической медицины, Новосибирск, Россия.

Over 30 years ago, Appels A. described a syndrome of vital exhaustion (VE) [1]. Several studies have been conducted afterwards showing that VE is associated with coronary events [2, 3, 4], however, the term of VE was not widely recognized. Earlier definition of VE was based on empirical approach aimed at prevention of myocardial infarction (MI) symptoms rather than on the use of existing psychological indicators in ischemic heart disease (IHD) complex [1-6].

Currently, psychosocial factors and, in particular, VE are considered as independent risk factors for developing cardiovascular diseases (CVD) [7-11]. Likelihood of

Table 1

Random representative sample of 25–64-year-old men in the Oktyabrsky District of the city of Novosibirsk: screening study III (1994)

Age groups	n	%
25-34	169	25,7
35-44	136	20,7
45-54	177	27
55-64	175	26,6
25-64	657	100

development of CVD and atherosclerosis is higher in individuals with high level of VE [12-14]. There is still no agreement regarding the effect of VE on stroke development [15, 16]. Some authors believe that the condition of VE develops in population due to long-standing psychosocial problems that are impossible to solve [17, 18]. Dopamine is involved in certain response reactions to surrounding events [19] whereas some dopamine reuptake inhibitors exert antidepressant effect [20]. Therefore, the study of genetic traits in VE is of high demand. It is essential to mention that such studies are absent in Russia.

Taking all the above mentioned arguments into account, the objective of our study was to investigate the prevalence rates of VE, the effects of VE on 14-year risk of developing CVD (AH, MI, and stroke), and the genetic traits in open population of 25–64-year-old men in Russia/Siberia (West Siberia metropolis, Novosibirsk).

Material and method

The random representative sample of 25–64-year-old men (n=657; mean age: 44,3±0,4 years), all residents of the Oktyabrsky district of the city of Novosibirsk, was examined in a framework of the screening III of WHO MONICA Program, MONICA-Psychosocial Subprogram (Multinational Monitoring of Trends and Determinants of Cardiovascular Disease & Optional Study (MOPSY) [21, 22] in 1994 (Table 1). Response rate was 82,1%. Sample was formed according to the requirements of the protocol of WHO MONICA based on electoral lists with the use of random number table. The program of screening examination included:

1) Registration of socio-demographic data. The following socio-demographic indicators were registered according to the requirements of the program protocol: number; place of residence; last name; first name; patronymic name; date of birth; date of registration; gender (male: 1; female: 2); marital status (never married; married; divorced; widowed); education level (university degree; undergraduate/college degree; high-school diploma; elementary school/partially completed high school); professional status (higher manager; middle manager; manager; technical/engineering employee; specialist; heavy-labor worker; moderate-labor worker; light-labor worker; student; retired; disabled worker).

2) The study of VE was carried out based on the short 14-item version of the Maastricht Vital Exhaustion Questionnaire (MQ) adapted to MONICA-MOPSY Program [23-25]. Respondents were requested to answer the questions of MQ test by themselves.

The risk factor levels in the initial examination were analyzed without taking into account temporal dynamics. Methods were strictly standardized and corresponded to the requirements of WHO MONICA program protocols. Processing of data was performed in MONICA Data Center (Helsinki, Finland). Quality control was carried out at MONICA quality control centers (Dundee, Scotland; Prague, Czech Republic; Budapest, Hungary). Presented data were considered satisfactory [26-28].

The formed population sample was used for assessment of the risk of developing CVD. All men with cardiovascular pathologies, documented before or during the screening, were excluded from the study (IHD: n=53; AH: n=328; MI: n=14; stroke: n=17; medical history of diabetes mellitus: n=7; first-time diabetes mellitus diagnosed in the screening: n=20; not found: n=28). Study cohort included 190 men with initial age ranging from 25 to 64 years. Duration of the prospective study was 14 years starting from January 1, 1995 through December 31, 2008. The following end-points were established: first-time cases of AH, MI, and stroke. Registration of all MI cases was based on the program of WHO Acute Myocardial Infarction Register [29]. First-time cases of AH and stroke were registered throughout the period of observation. The following sources for identification of AH and stroke cases were used: reports of annual medical checkups of individuals from the population cohort; clinical charts; hospital discharge reports; district polyclinic reports; death certificates; interrogations with relatives; and autopsy and forensic reports.

As a part of annual medical checkup procedure, standardized measurements of arterial blood pressure (ABP) were performed according to the study protocol. The group of AH included both men with high ABP and those with normal ABP who were taking hypotensive drugs at moment of medical examination or stopped hypotensive therapy less than two weeks prior to the examination [30]. During the period of the study, new cases of AH (n=46), MI (n=30), and stroke (n=22) were documented in the study cohort (Table 2).

Genotyping of variable number of tandem repeats (VNTR) polymorphisms in DRD4 and DAT genes was performed in the Laboratory of Molecular and Genetic Studies at the FSBI "Research Institute of Internal Medicine" SB RAMS (Head of Laboratory: Maksimov V. N.) in accordance with methods described elsewhere [31-34].

Statistical analysis was carried out by using the software package SPSS 11.5. Pearson's chi-squared test (χ^2) was used to determine whether there is a significant difference

Table 2

Vital exhaustion prevalence rates and association with new cases of cardiovascular diseases among 25–64-year-old men

№		Screening III (1994)							
		First-time arterial hypertension		First-time myocardial infarction		First-time stroke		Total	
		n	%	n	%	n	%	n	%
1.VE	25-34	5	14,8	1	5	-	-	27	21,3
	35-44	8	23,5	3	15	-	-	29	22,8
	45-54	8	23,5	3	15	3	23	32	25,2
	55-64	13	38,2	13	65	10	76	39	30,7
	25-64	34	73,9%	20	66,7	13	59	127	66,8
2.NVE	25-34	1	8,3	1	10	1	11,1	8	12,7
	35-44	2	16,7	1	10	1	11,1	10	15,8
	45-54	3	25	4	40	4	44,5	20	31,8
	55-64	6	50	4	40	3	33,3	25	39,7
	25-64	12	26,1	10	33,3	9	41	63	33,2
	Total	46	100	30	100	22	100	190	100

Abbreviations: E — vital exhaustion, NVE — no vital exhaustion.

Table 3

Prevalence rates of vital exhaustion in different age-groups of 25–64-year-old men in open population

Age groups	Screening III (1994)							
	NVE		MVE		HVE		Total	
	n	%	n	%	n	%	n	%
25-34	77	46.7**	80	48.5	8	4.8**	165	100
35-44	64	38.8	78	47.3	23	13.9	165	100
45-54	35	27.1	65	50.4	29	22.5*	129	100
55-64	26	17.3***	95	63.3	29	19.3	150	100
25-64	202	33.2	318	52.2	89	14.6	609	100
	χ^2=46.804 υ=6. p<0.0001							

Annotation: * — p<0,05. ** — p < 0,01, *** — p < 0,001.

Abbreviations: E — vital exhaustion, NVE — no vital exhaustion, MVE — moderate vital exhaustion, HVE — high vital exhaustion.

between the groups [35]. Unifactorial and multifactorial Cox proportional hazards regression models were used for evaluation of risk coefficients (hazard ratio (HR)) taking into account time-adjusted control. [36, 37]. Associations between VE and VNTR polymorphisms of DRD4 and DAT genes were assessed by calculating the odds ratios (OR) and their 95% confidence interval (CI) (min-max). Values were considered statistically significant when P was ≤0,05 for all analyses [38].

Results

In open population of 25–64-year-old men, VE rate was 66,8% (rate of moderate level of VE: 52,2%; rate of high level of VE: 14,6%) (Table 3).

Prevalence rate of VE in cohort of men with first-time AH was 73,9% (rate of moderate level of VE: 58,2%; rate of high level of VE: 15.7%) (χ^2=22,494; ν=2, p<0,0001) (Table 2).

Structure of marital status in men with AH and VE was as follows: never married (3,2%); married (86,7%); divorced (6,9%); widowed (1,6%) (χ^2=6,781; ν=4, p>0,05). Statistically significant results showing higher frequency of AH were found in group of married men with VE compared with those without VE (χ^2=6,771; ν=1, p<0,01).

Pattern of education levels in men with AH and VE was as follows: university degree (29,3%); undergraduate/college degree (25,5%); high-school diploma (18,1%); elementary school/partially completed high school (27,1%) (χ^2=5,31; ν=3, p>0,05).

Statistically significant results showing differences in the frequency of AH development were acquired in group of men with VE who finished elementary school or partially completed high school compared with groups of VE-free men who had university degree, undergraduate degree/college degree, or high-school diploma (χ^2=7,966, ν=1, p<0,01; χ^2=12,166, ν=1, p<0,0001; χ^2=4,292, ν=1, p<0,05; χ^2=4,860, ν=1, p<0,05; χ^2=9,898; ν=1, p<0,01, respectively). Statistically significant results were also found in group of men with VE who had university

diploma compared with group of men with VE who had undergraduate/college degree and VE-free group of men who had high-school diploma (χ^2=9,374; χ^2=6,987, ν=1, p<0,01, respectively).

Professional status of men with VE and AH was as follows: higher managers (5,3%); middle managers (8%); managers (8%); technical/engineering employees (11,2%); heavy-labor workers (15,5%); moderate-labor workers (21.9%); light-labor workers (3,7%); students (0,5%); retired (17,6%) (χ^2=7,75, ν=10, p>0,05).

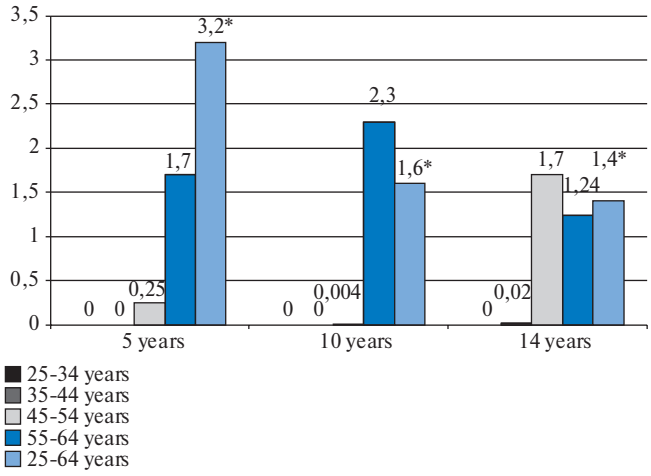

Figure 1. Comparative analysis of relative risk of arterial hypertension development in men with vital exhaustion in different age groups (unifactorial Cox model).
Annotation: * — p<0,05.

Significant differences in frequency of AH were found in VE groups of higher and middle managers, technical/engineering employees; moderate- and light-labor workers, and retired men in comparison with VE-free group of technical/engineering employees (χ^2=6,647, ν=1, p<0,01; χ^2=5,214, ν=1, p<0,05; χ^2=7,462, ν=1, p<0,01; χ^2=4,263, ν=1, p<0,05; χ^2=9,016, ν=1, p<0,01; χ^2=13,523; ν=1, p<0,0001, respectively). Significant differences were also found in VE group of heavy-labor workers compared with groups of technical/engineering employees, light-labor workers, and retired men with VE (χ^2=3,811, ν=1, p<0,05; χ^2=5,370, ν=1, p<0,05; χ^2=10,720; ν=1, p<0,001, respectively). Group of light-labor workers with VE significantly differed from groups of VE-free middle managers and heavy-labor workers (χ^2=4,871; χ^2=5,341, ν=1, p<0,05, respectively).

Unifactorial Cox proportional hazards regression model showed that AH risk among men with VE was 3,2-times higher during the first five years (95% CI 1–7,3; p<0,05) and 1,6-times higher during the first 10 years (95% CI 1–3,4 ; p<0,05) compared to VE-free men. During 14 years, AH risk among men with VE was 1,4-times higher (95% CI 1–3,1; p<0,05) (Figure 1).

Multifactorial Cox proportional hazards regression model included social parameters (educational, professional, and marital statuses) and age. It showed that VE increased AH risk by 2,9 times (95% CI 1–7,9; p<0,05) (Table 4).

Prevalence rate of VE in cohort of 25–64-year-old men with first-time MI was 66,7% (rate of moderate level

Table 4

Risk of cardiovascular diseases in open population of 25–64-year-old men depending on the level of negative vital exhaustion (multifactorial Cox model)

Social factors	Reference group	Group of risk	HR (AH)	HR (MI)	HR (Stroke)
	NVE	HVE	2,9 (1-7,9)*	1,16 (0,6-2)*	2,6 (1-6,8)*
Education	University diploma	Undergraduate/college degree	1,3 (0,2-6)	0,7 (0,3-1,8)	1,8 (0,4-7,6)
		High school	1,8 (0,1-9,7)	1,4 (0,6-3,1)	1,4 (0,3-6,6)
		Elementary school/partially completed high school	2,1 (0,2-41)	2,2 (1,1-4,5)*	4,8 (1,3-17,3)**
Professional status	Higher managers[1]	Middle managers	1,1 (0,5-12)	8,2 (0,9-28)*	-
		Managers	1,6 (0,9-23)	7,3 (0,8-23)*	-
		Technical/engineering employees	0,1-3,09	-	-
		Heavy-labor workers	1,6 (0,6-4,7)	8,3 (1-27)*	5,4 (0,5-57)
		Moderate-labor workers	2,2 (0,9-5,4)	3,2 (0,3-27)	3,1 (0,3-34)
		Light-labor workers	1 (0,04-19)	1,5 (0,1-12)	-
		Retired	7,2 (2,9-17)***	7,2 (0,9-18)	15 (1,6-37)*
Marital status	Married	Never married	2,8 (0,3-23)	3,7 (1,2-11)**	1,9 (0,2-15)
		Divorced	3,3 (1-10,4)*	4,7 (2,3-9,8)***	3,8 (1,2-12,2)**
		Widowed	4,1 (0,8-19)	7 (2,4-20)***	3,6 (0,7-16,7)**
Age groups	25–34 years	35–44 years	0,7 (0,2-2,4)	2,3 (0,6-7,8)	-
		45–54 years	2,8 (1-7,6)	3,8 (1,2-12)*	-
		55-64 years	5,7(2,2-14,5)	5,9 (1,8-19)**	2,4(0,9-6,2)*

Abbreviations: NVE — no vital exhaustion, HVE — high vital exhaustion, HR — hazard ratio, AH — arterial hypertension, MI — myocardial infarction.
Annotations: [1] — Reference group for arterial hypertension: higher managers; reference group for myocardial infarction: technical/engineering employees; reference group for stroke: managers; * — p<0,05. ** — p < 0,01, *** — p < 0,001.

of VE: 44,6%; rate of high level of VE: 22,1% (χ^2=1,597, ν=2, p>0,05) (Table 2).

Marital status of men with VE who suffered from MI was as follows: married (59.1%), never married (75%), divorced (71,4%), and widowed (100%) (χ^2=5,246, ν=6, p>0,05). Statistically significant results showing differences in the frequency of MI development were acquired in group of widowed men with VE compared with groups of never married VE-free men and married men with and without VE (χ^2=4,473, ν=1, p<0,05; χ^2=27,159; χ^2=16,789, ν=1, p<0,0001, respectively). Significant difference was also found in group of divorced men with VE compared with married men with and without VE (χ^2=9,439; χ^2=4,825, ν=1, p<0,05, respectively).

Pattern of education levels in men with MI and VE was as follows: university degree (16%); undergraduate/college degree (16%); high-school diploma (24%); elementary school/partially completed high school (44%) (χ^2=9,271, ν=8, p>0,05).

Significant differences in frequency of MI development were found in VE group of men who completed elementary school or partially completed high school compared with groups of men with and without VE who had university or undergraduate/college degree (χ^2=3,751; χ^2=4,552; χ^2=4,763; χ^2=3,942; ν=1, p<0,05, respectively). Groups of men with VE who had university degree, undergraduate/college degree and high-school diploma significantly differed from group of VE-free men who completed elementary school or partially completed high school (χ^2=12,694, χ^2=14,789, ν=1, p<0,0001; χ^2=8,738, ν=1, p<0,01, respectively).

Professional status of men with VE who suffered from MI was as follows: middle managers (4%); managers (4%); technical/engineering employees (4%); heavy-labor workers (20%); moderate-labor workers (16%); retired (44%) (χ^2=15,795, ν=14, p>0,05).

Statistically significant differences in frequency of MI development were found in group of retired men with VE compared with groups of VE-free middle managers, managers, technical/engineering employees, and moderate-labor workers (χ^2=3,581; χ^2=4,682; χ^2=5,233, ν=1, p<0,05; χ^2=6,174, ν=1, p=0,01; χ^2=5,279, ν=1, p<0,05; χ^2=7,247, ν=1, p<0,01, respectively). Significant differences were found between VE group of moderate-labor workers and VE-free group of light-labor workers (χ^2=3,647, ν=1, p<0,05).

Unifactorial Cox proportional hazards regression model showed that MI risk among men with VE was 2,7-times higher during the first five years (95% CI 1–7; p<0,05) and 2,25-times higher during the first 10 years (95% CI 0,9–5,1; p<0,05) compared to VE-free men. Upon 14 years of the screening study, MI risk among men with VE increased by 2,1 times (95% CI 1,0084–6,472; p<0,05) (Figure 2).

Multifactorial Cox proportional hazards regression model included social parameters (educational, professional, and marital statuses) and age. It showed that effect

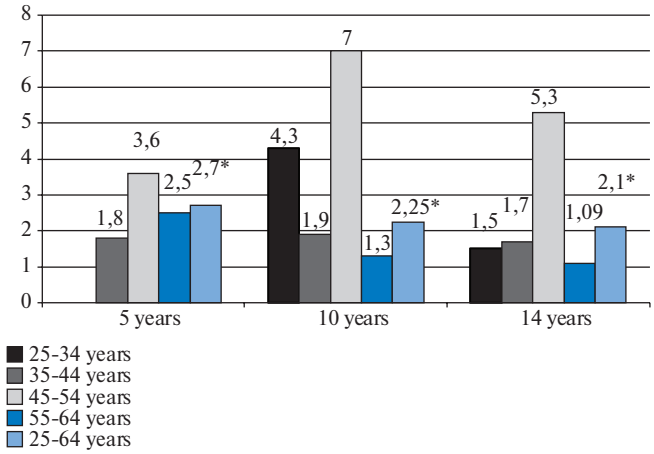

Figure 2. Comparative analysis of relative risk of myocardial infarction development in men with vital exhaustion in different age groups (unifactorial Cox model).
Annotation: * — p<0,05.

of VE on MI risk was less pronounced, but the value was still significant: 1,16 (95% CI 0,6–2; p<0,05) (Table 4).

Prevalence rate of VE in cohort of men with stroke was 59% (rate of moderate level of VE: 41%; rate of high level of VE: 18%) (χ^2=5,219, ν=1, p>0,05) (Table 2).

Marital status of men with VE who suffered from stroke was as follows: never married (5,9%), married (64,7%), divorced (23,5%), and widowed (5,9%) (χ^2=2,579, ν=1, p>0,05).

Statistically significant differences in frequency of stroke were found in group of divorced men with VE compared with groups of married men with and without VE (χ^2=3,696, ν=1, p=0,05; χ^2=6,619, ν=1, p<0,01, respectively). Group of married men with VE significantly differed from group of VE-free widowed men (χ^2=10,825, ν=1, p<0,001).

Pattern of education levels in men with stroke and VE was as follows: university degree (10%); undergraduate/college degree (20%); high-school diploma (10%); elementary school/partially completed high school (60%) (χ^2=1,571, ν=3, p>0,05).

Significant differences in frequency of stroke events were documented in group of men with VE who finished only elementary school or partially completed high school compared with groups of men with VE who had university degree, undergraduate/college degree, and high-school diploma (χ^2=4,272; χ^2=4,334; χ^2=3,590, ν=1, p<0,05, respectively).

Professional status of men with VE who suffered from first-time stroke was as follows: managers (10%); heavy-labor workers (20%); moderate-labor workers (20%); retired (50%) (χ^2=0,918, ν=3, p>0,05).

Statistically significant differences in frequencies of stroke were found between VE groups of retired men and moderate-labor workers (χ^2=3,359; ν=1, p<0,05). Groups of managers and heavy- and moderate-labor workers with VE significantly differed from group of VE-free retired

men (χ^2=7,471, ν=1, p<0,01; χ^2=15,182; χ^2=17,683, ν=1, p<0,0001, respectively).

Unifactorial Cox proportional hazards regression model showed that risk of stroke among men with VE was

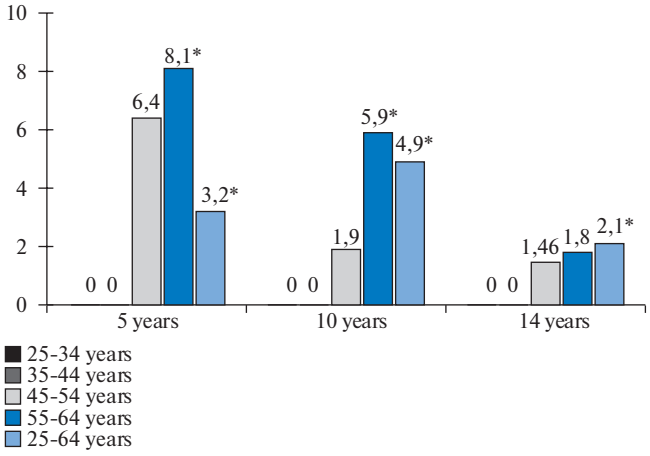

Figure 3. Comparative analysis of relative risk of stroke in men with vital exhaustion in different age groups (unifactorial Cox model).
Annotation: * — p<0,05.

3.2-times higher during the first five years (95% CI 1–9; p<0,05) compared to VE-free men. Presence of VE increased risk of stroke in group of 55–64-year-old men increased by 8,1 times (95% CI 1–63; p<0,046) (Figure 3).

Multifactorial Cox proportional hazards regression model included social gradient and age. It showed that risk of stroke in men with VE was 2,6 (95% CI 1–6,8; p<0,05) (Table 4).

Genotyping data from men with different level of VE showed that carriers of genotype 7/7 were present more often in group of men with high level of VE (2,6%) compared to other groups (χ^2=39,186, ν=36, p>0,05). Carriers of allele 7 were present more often in group with high level of VE (3,3%) compared with VE-free group (1,2%) (Table 5).

Men, carriers of genotype 9/9 in DAT gene, were present significantly more often in high-VE-level group (15,2%) than in moderate-VE-level group (2,3%) with OR=7,4 vs. carriers of other genotypes (95% CI 2,4–22,6) (χ^2=16,238, ν=1, p<0.0001); OR=7,5 vs. carriers of geno-

Table 5

Frequencies of genotypes and alleles of VNTR polymorphisms in DRD4 gene in population and their association with vital exhaustion

Genotypes of DRD4 gene	Population		Vital exhaustion					
			No		Moderate		High	
	n	%	n	%	n	%	n	%
2/2	26	6,1	8	6,3	17	7,7	1	1,3
2/3	1	0,2	0	0	1	0,5	0	0
2/4	53	12,5	20	15,6	23	10,4	10	13,2
2/5	2	0,5	1	0,8	1	0,5	0	0
2/6	10	2,4	4	3,1	6	2,7	0	0
2/7	1	0,2	1	0,8	0	0	0	0
3/3	8	1,9	1	0,8	4	1,8	3	3,9
3/4	24	5,6	8	6,3	9	4,1	7	9,2
3/6	3	0,7	1	0,8	1	0,5	1	1,3
3/7	2	0,5	0	0	2	0,9	0	0
4/4	246	57,9	69	53,9	133	60,2	44	57,9
4/5	4	0,9	1	0,8	1	0,5	2	2,6
4/6	18	4,2	7	5,5	8	3,6	3	3,9
4/7	9	2,1	2	1,6	6	2,7	1	1,3
4/8	1	0,2	0	0	0	0	1	1,3
5/5	3	0,7	1	0,8	2	0,9	0	0
5/6	2	0,5	1	0,8	0	0	1	1,3
6/6	9	2,1	3	2,3	6	2,7	0	0
7/7	3	0,7	0	0	1	0,5	2	2,6
Allele			χ^2=39,186, u=36, p=0,329					
2	26	6,1	42	16,4	65	14,7	12	7,9
3	9	2,1	11	4,3	21	4,8	14	9,2
4	323	76,0	176	68,8	313	70,8	112	73,7
5	9	2,1	5	2	6	1,4	3	2
6	42	9,9	19	7,4	27	6,1	5	3,3
7	15	3,5	3	1,2	10	2,3	5	3,3
8	1	0,2	0	0	0	0	1	0,7
			χ^2=20,495, u=12, p=0,058					

type 9/10 (95% CI 2,3–24,3) (χ^2=13,815, ν=1, p<0,0001), and OR=7,3 vs. carriers of genotype 10/10 (95% CI 2,3–23,11) (χ^2=14,769, ν=1, p=0,0001) (Table 6).

Table 6

Frequencies of genotypes and alleles of VNTR polymorphisms in DAT gene in population and their association with vital exhaustion

Genotype of DAT gene	Population		Vital exhaustion					
			No		Moderate		No	
	n	%	n	%	n	%	n	%
8/8	4	1	2	1,6	2	0,9	0	0
9/9	15	3,7	0	0	5	2,3	10	15,2***
6/10	3	0,7	1	0,8	1	0,5	1	1,5
8/10	1	0,2	1	0,8	0	0	0	0
9/10	149	36,6	49	38,3	79	37,1	21	31,8
10/10	223	54,8	73*	57	118	55,4	32	48,5
10/11	4	1,0	1	0,8	3	1,4	0	0
10/12	1	0,2	1	0,8	0	0	0	0
11/11	7	1,7	0	0	5	2,3	2	3,0
Allele			χ^2=41,076, u=16, p=0,001					
	n	%	n	%	n	%	n	%
6	3	0,4	1	0,4	1	0,2	1	0,8
8	9	1,1	5	2	4	0,9	0	0
9	179	22	49	19,1	89	20,9	41	31,1**
10	604	74,2	199	77,7	319	74,9	86	65,2
11	18	2,2	1	0,4*	13	3,1	4	3
12	1	0,1	1	0,4	0	0	0	0
			χ^2=19,792, u=10, p=0,031					

Annotation: * — p<0,05. ** — p<0,01, *** — p<0,001.

Discussion

In current medicine, there is a generally accepted view that psyche is the most sophisticated and vulnerable apparatus of human adaptation to social and ecological environment. Therefore, this type of adaption may fail the first in cases when the extreme pressure, especially in a situation of chronic stress, has an effect on the organism [39-42]. According to G. Selie's concept of general adaptation syndrome, the long-lasting uncontrollable physical and psychological distress leads to decompensation stage characterized with increased anxiety, depression, feelings of helplessness and despair, which eventually result in the exhaustion stage [43]. In our population, high level of VE occurred more often in the older age groups.

In Russia, similarly to the rest of the world, cardiovascular diseases (AH, MI, and stroke) remain one the most challenging problems of cardiology [44]. Our data showed that vital exhaustion increased the risk of AH development by over three times during the first five years of the study. The strongest effect of VE on the risk of AH development was found in divorced men. The concept of VE is relatively young; this phenomenon was mainly studied as a condition preceding IHD [1-6]. Population-based studies of the effects of VE on AH risk are absent. There are only indirect indications of the pathophysiological mechanisms that occur, for example, via the development of atherosclerosis in young people with VE [13, 14] which perhaps can explain our results [47-49].

Our data showed that the risk of MI development was almost three times higher during the first five years of the study among men with VE compared with those who were VE-free. Vital exhaustion increased the MI risk by over two times during the first 10 and 14 years of observation. Investigation of social gradient demonstrated that the risk of MI development was higher among those men with VE who had elementary level of education and/or belonged to the categories of heavy-labor workers and middle-managers. This heterogeneity of social status of people in whom VE increased the risk of MI development is essential for the phenomenon of VE defined as "mental condition characterized with excessive fatigue, feelings of demoralization or frustration, and increased irritability" whose contributing factors include conflict situations at workplace which explains such a high MI risk in this category of people [1-6, 9]. Influence of marital status is undeniable: the MI risk is higher in men who are divorced, widowed or never married.

Prerequisite for studying the effects of VE on the risk of stroke was the fact that feeling of fatigue is often diagnosed after stroke though many stroke patients reported fatigue before the disease [10, 11]. In our study, VE increased the risk of stroke development by 3,2 times during the first five years of observation. Notably, maximum risk of stroke was documented in the older age group. During 10-year period, risk of stroke increased in main population and decreased in 55–64-year-old age group. Our results agree well with results of prospective cohort study conducted by G. E. Schuitemaker et al. [10] who showed that the risk of stroke in individuals with VE increased by 13% together with an increase in MQ score derived from every single item on the questionnaire scale. This indicator remained statistically significant after standardization based on other risk factors such as systolic blood pressure, diastolic blood pressure, diabetes mellitus, and smoking suggesting that effect of VE on the risk of stroke development was independent of traditional factors. The risk of stroke was higher in men with VE and elementary education level, which perhaps may be explained by the fact that individuals who suffered from stroke mainly belonged to the older age group with predominance of retired men or to the group of heavy- and moderate-labor workers.

Symptoms of VE occurred equally frequently among both married men and men without family (divorced and widowed). Nevertheless, frequency of stroke was higher in divorced and widowed men with VE.

Coordinated work of brain mediators and modulators underlies emotional state and behavior in humans and animals [50]. This provided rationale for our study whose main objective was to analyze association between VE and DRD4 and DAT genes that belong to dopaminergic system of the brain.

Among men with different levels of VE, our data showed that VE increased together with an increase in number of VNTR polymorphisms in DRD4 gene. The high levels of VE were present significantly more often in carriers of allele 7 of DRD4 gene.

According to our current understanding of the dopamine biosynthesis, this mediator is involved in the process of adaptation. Deficit of dopamine leads to exhaustion of the nervous system whereas its increased level results in bipolar disorder [52-57].

It has been shown that affinity of dopamine to the receptor is decreased in individuals with long form of DRD4 gene (number of tandem repeats of six and more). These people are less sensitive to dopamine. Therefore, they require stronger stimulation to achieve the same reaction compared with carriers of short form of the gene [58-60]. This may likely be a cause of the high prevalence rate of genotypes with long alleles of DRD4 gene in men with VE.

As in the case of the DRD4 gene, VNTR polymorphisms in DAT gene can be associated with some pathological conditions where dopamine metabolism is altered [61]. Carriers of VNTR polymorphism of genotype 9/9 of DAT gene were present more often among men with the high level of VE. Similarly, the carrier ship of allele 9 increased chances for pertaining to the above-mentioned group.

Despite available literature is lacking, the reports of studies on associations between VE and VNTR polymorphisms in the dopamine transporter gene, it is nevertheless known that these polymorphisms can be associated with some human pathological conditions where the abnormalities in brain dopaminergic system play the key pathogenetic role. It is known that individuals with short form of DAT gene in genome more often develop posttraumatic stress disorder [53, 63], which can explain the obtained results. It should be noted that the genetic traits found in open male population can be responsible for pathophysiologic alterations in functions and compensation abilities of dopaminergic system, being the predisposing background for development of psychological and social risk factors of cardiovascular diseases (AH, MI, and stroke).

Conclusion

1. The study revealed high prevalence rate (66,8%) of vital exhaustion in open population of 25–64-year-old men, residents of Novosibirsk.

2. Risks of arterial hypertension, myocardial infarction, and stroke were maximal in the presence of vital exhaustion during the first five years of study. Ten- and 14-year risks of arterial hypertension and myocardial infarction decreased compared with corresponding 5-year risks. Ten-year risk of stroke significantly increased in open population of 25–64-year-old men.

3. Vital exhaustion and components of social gradient (education, professional status, marital status, and age) are predictors of development of arterial hypertension, myocardial infarction, and stroke in open population of 25–64-year-old men.

4. The high level of vital exhaustion was significantly associated with allele 7 of DRD4 gene and genotype 9/9 of DAT gene.

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ASSOCIATION OF PSYCHOSOCIAL FACTORS WITH DOPAMINE RECEPTOR D4 (DRD4), DAT GENE POLYMORPHISM AND CARDIOVASCULAR INCIDENCE RISK

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Anxiety is considered as an independent risk factor for cardiovascular diseases (CVD). Relationships between genetic markers of anxiety and risk of developing CVD remain unknown.

Aim. The objectives of the study were to determine trait anxiety prevalence; to find associations between trait anxiety and VNTR polymorphisms in the DRD4 and DAT genes; and to calculate Hazard retio (HR) for developing arterial hypertension (AH), myocardial infarction (MI), and stroke.

Material and methods. Representative sample of 25-64-year-old males (n=2149) was examined in three screening studies in a framework of the WHO MONICA program and MONICA-psychosocial subprogram in Novosibirsk in 1984, 1988, and 1994. All first time MI, AH, and stroke events were registered from 1984 to 2008. Genotyping of VNTR polymorphism was performed for DRD4 and DAT genes. Anxiety levels were evaluated by using the Spielberger's test. Stratified Cox proportional regression model was used for Hazard ratio (HR) estimation.

Results. High level of anxiety (HLA) in an open male population was 50,9%. The DRD4 genotype 4/6 and DAT genotype 9/9 were significantly associated with HLA. HLA increased CVD risk. HR for developing AH and stroke was maximal during the first five years of the study, whereas maximal risk of developing MI was found for 10-year period.

Conclusion. Prevalence of HLA in an open 25-64-year-old male population in Novosibirsk was high. Rates of HLA were significantly associated with certain VNTR polymorphisms in the DRD4 and DAT genes. HLA were associated with increased risk of developing CVD.

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Key words: cardiology; arterial hypertension, myocardial infarction, stroke, trait anxiety, DRD4 gene, DAT gene, risk of developing disease, cardiovascular disease.

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AH — arterial hypertension, DAT — the dopamine transporter, DRD4 — the dopamine D4 receptor, HLA — high level of anxiety, MI — myocardial infarction, MLA — moderate level of anxiety, MONICA — Multinational Monitoring of Trends and Determinants in Cardiovascular Disease program, VNTR — variable number of tandem repeat.

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АССОЦИАЦИЯ ПСИХОСОЦИАЛЬНЫХ ФАКТОРОВ С ПОЛИМОРФИЗМОМ ГЕНОВ РЕЦЕПТОРА ДОПАМИНА D4 (DRD4), ТРАНСПОРТЕРА ДОПАМИНА (DAT) И РИСК РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

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Тревожность рассматривается как независимый фактор риска сердечно-сосудистых заболеваний (ССЗ). Ассоциации между генетическими маркерами тревоги и риском развития ССЗ остаются неизвестными.

Цель. Определить распространенность личностной тревожности в популяции, найти ассоциативные связи между личностной тревожностью и VNTR-полиморфизмом генов DRD4, DAT; рассчитать риск развития (HR) артериальной гипертензии (АГ), инфаркта миокарда (ИМ) и инсульта.

Материал и методы. Репрезентативна выборка мужчин в возрасте 25-64 лет (n=2149) была обследована на трех скринингах в рамках программы ВОЗ "МОНИКА-психосоциальная" в Новосибирске в 1984, 1988, 1994гг. Впервые возникшие случаи ИМ, АГ и инсульта после скрининга в когорте были зарегистрированы с 1984 по 2008гг. Генотипирование VNTR-полиморфизма было выполнено для генов DRD4 и DAT. Уровень тревожности оценивали с помощью теста Спилбергера. Стратифицированная Кокс-пропорциональная регрессионная модель использовалась для оценки риска развития (Hazard ratio — HR).

Результаты. Высокий уровень тревожности (ВУТ) в открытой мужской популяции составил 50,9%. Генотип 4/6 DRD4 и генотип DAT 9/9 были четко связаны с ВУТ. ВУТ достоверно повышал HR ССЗ. Риск развития АГ и инсульта был максимальным в течение первых пяти лет изучения, в то время как максимальный HR ИМ был в течение 10 лет.

Заключение. Распространенность ВУТ в открытой популяции мужчин 25-64-лет в Новосибирске была высокой. Уровни ВУТ имели ассоциации с определенным VNTR — полиморфизмом в генах DRD4 и DAT. ВУТ связан с повышенным риском развития ССЗ.

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Ключевые слова: кардиология, артериальная гипертензия, инфаркт миокарда, инсульт, личностная тревожность, полиморфизм, ген DRD4, ген DAT, риск развития болезни, сердечно-сосудистых заболеваний.

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Solely adverse environmental factors can hardly be fully responsible for the development of elevated levels of trait anxiety [1-6]. The study of 8-16-year-old twins from Great Britain showed genetic correlation between anxiety and depression [7]. The genetic correlation coefficient was as high as 80%, whereas factors of general environment accounted for the rest 20% [7]. Anxiety can be caused by the abnormal dopamine synthesis, [8–10] although the study regarding the relationships between anxiety traits and variable number of tandem repeat (VNTR) polymorphisms in the dopamine D4 receptor (DRD4) and the dopamine transporter (DAT) genes gained controversial results [11-14]. Great interest in studying anxiety is driven also by the fact that anxiety is considered as an independ-

Table 1

Genotype and allele frequencies of variable number of tandem repeat (VNTR) polymorphisms in the dopamine D4 receptor gene in 25–64-year-old male population in Novosibirsk

Genotypes	Population	
	n	%
22	26	6,1
23	1	0,2
24	53	12,5
25	2	0,5
26	10	2,4
27	1	0,2
33	8	1,9
34	24	5,6
36	3	0,7
37	2	0,5
44	246	57,9
45	4	0,9
46	18	4,2
47	9	2,1
48	1	0,2
55	3	0,7
56	2	0,5
66	9	2,1
77	3	0,7
Alleles		
2	119	14
3	46	5,4
4	601	70,7
5	14	1,6
6	51	6,0
7	18	2,1
8	1	0,1

Table 2

Genotype and allele frequencies of variable number of tandem repeat (VNTR) polymorphisms in the DAT gene in 25–64-year-old male population in Novosibirsk

Genotypes	Population	
	n	%
8/8	4	1
9/9	15	3,7
6/10	3	0,7
8/10	1	0,2
9/10	149	36,6
10/10	223	54,8
10/11	4	1,0
10/12	1	0,2
11/11	7	1,7
Alleles		
6	3	0,4
8	9	1,1
9	179	22
10	604	74,2
11	18	2,2
12	1	0,1

ent risk factor for cardiovascular morbidity and mortality [15-18]. To our knowledge, no available prospective population-based study in the literature describes similar data obtained by using the World Health Organization (WHO) programs.

The objectives of our study were to determine trait anxiety levels in an open population of 25–64-year-old males; to carry out an association analysis of trait anxiety and VNTR polymorphisms in the DRD4 and DAT genes; and to calculate Hazard ratio (HR) for developing arterial hypertension (AH), myocardial infarction (MI), and stroke, depending on the anxiety levels over a 24-year period of the study.

Material and methods

Three screening studies were conducted in a framework of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease program (MONICA) [8-10] and MONICA-psychosocial subprogram [21] in 1984, 1988, and 1994, respectively. A total of 2149 males aged 25-64 years, residents of one district of the city of Novosibirsk, were examined. The response rate was 82,1%. Anxiety levels were evaluated by using the Spielberger's test [22]. Spielberger's inventories were filled out by each participant individually. Genotyping of the gene polymorphism was performed in the Molecular Genetics Laboratory of the Research Institute of Internal Medicine by using the methods described in detail elsewhere [23-26]. Frequency distribution of the variable number of tandem repeat (VNTR) polymorphisms in the DRD4 and DAT genes in a population of 25-64-year-old males is shown in Table 1 and Table 2. The cohort for prospective study (n=1423) screened out all male participants diagnosed with ischemic heart disease, cerebrovascular pathology, arterial hypertension (AH), myocardial infarction (MI), and diabetes. During the entire 24 years of the study from 1984 to 2008, all first time MI events (n=104) were registered by using the WHO Acute Myocardial Infarction Register program, whereas the arterial hypertension (n=162) and stroke (n=76) events were documented in the process of the yearly observations on the cohort.

Statistical analysis of data was performed by using the SPSS (Statistical Package for Social Sciences) software package version 11.5. Chi square (χ^2) statistic was used to investigate whether distributions of categorical variables differed from one another in between the groups. The stratified Cox proportional regression model was used for determination of the HR adjusted for different data collection dates. A value of $p<0,05$ was considered statistically significant [27-28].

Table 3

Distribution of genotype and allele frequencies of the dopamine D4 receptor gene and prevalence of trait anxiety

Genotypes	LLA		MLA		HLA	
	n	%	n	%	n	%
22	0	0	18	7	8	4,8
23	0	0	0	0	1	0,6
24	0	0	37	14,5	16	9,6
25	0	0	1	0,4	1	0,6
26	0	0	5	2	5	3
27	0	0	1	0,4	0	0
33	0	0	3	1,2	5	3,0
34	0	0	12	4,7	12	7,2
36	1	33,3	1	0,4	1	0,6
37	0	0	1	0,4	1	0,6
44	2	66,7	153	59,8***	91	54,8
45	0	0	4	1,6	0	0
46	0	0	5	2	13	7,8**
47	0	0	5	2	4	2,4
48	0	0	0	0	1	0,6
55	0	0	0	0	1	0,6
56	0	0	1	0,4	1	0,6
66	0	0	6	2,3	3	1,8
77	0	0	2	0,8	1	0,6
χ^2=69,569, df=36, p=0,001						
Alleles	n	%	n	%	n	%
2	0	0	80	15,6	39	11,7
3	1	16,7	20	3,9	25	7,5
4	4	66,7	369	72,1	228	68,7
5	0	0	8	1,6	6	1,8
6	1	16,7	24	4,7	26	7,8
7	0	0	11	2,1	7	2,1
8	0	0	0	0	1	0,3
χ^2=15,980, df=12, p=0,192						

Annotation: ** — p<0,01; *** — p<0,001.

Abbreviations: LLA — low level of anxiety, MLA — moderate level of anxiety, HLA — high level of anxiety.

Table 4

Distribution of genotype and allele frequencies of the DAT gene and prevalence of trait anxiety

Genotypes	LLA		MLA		HLA	
	n	%	n	%	n	%
8/8	0	0	2	0,8	2	1,3
9/9	1	25	4	1,6	10	6,3
6/10	1	25	0	0	2	1,3
8/10	0	0	1	0,4	0	0
9/10	2	50	85	35	62	38,8
10/10	0	0	142	58,4	81	50,6
10/11	0	0	3	1,2	1	0,6
10/12	0	0	1	0,4	0	0
11/11	0	0	5	2,1	2	1,3
χ^2=51,105, df=16, p=0,0001						
Alleles	n	%	n	%	n	%
6	1	12,5	0	0	2	0,6
8	0	0	5	1,0	4	1,3
9	4	50	93	19,1	82	25,6
10	3	37,5	374	77	227	70,9
11	0	0	13	2,7	5	1,6
12	0	0	1	0,2	0	0
χ^2=45,402, df=10, p=0,0001						

Abbreviations: LLA — low level of anxiety, MLA — moderate level of anxiety, HLA — high level of anxiety.

Results

Prevalence of trait anxiety in the population of 25–64-year-old males was as high as 97,5%. Moderate level of anxiety (MLA) and high level of anxiety (HLA) were found in 46.6% and 50,9% of participants, respectively. Carriers of the DRD4 genotype 4/4 comprised 59.8% and 54,8% of males in MLA and HLA groups, respectively. Individuals with the DRD4 genotype 2/4 were found significantly more often in MLA group (14,5%) than in HLA group (9,6%). In contrast, carriers of the DRD4 genotype 4/6 were found more often in HLA group (7,8%) than in MLA group (2%) (χ^2=69.569, df=36, p<0,001) (Table 3). Carriers of the alleles 2 and 4 prevailed in MLA group (15,6% and 72,1%, respectively), whereas the occurrence rates for these alleles in HLA group were 11,7% and 68,7%, respectively. The allele 6 was found in 7,8% and 4,7% of HLA group and MLA group, respectively (χ^2=15,980, df=12, p=0,192) (Table 3).

Carriers of the DAT genotype 10/10 comprised 58,4% of MLA group and 50,6% of HLA group. The heterozygote DAT genotype 9/10 was found in 35% of MLA group and in 38,8% of HLA group. The situation among men, carriers of the DAT genotype 9/9, was the opposite, namely: 6,3% of participants had HLA, whereas 1.6% of them had MLA (χ^2=51,105, df=16, p<0,0001) (Table 4). Carriers of the allele 9 prevailed in HLA group (25,6%) in comparison with MLA group (19,1%). In contrast, carriers of the allele 10 were found more often in MLA group (77%) than in HLA group (70,9%) (χ^2=45,402, df=10, p<0,0001) (Table 4).

Over the entire 24-year period of our study, 5,9%, 4,2%, and 16,9% of males suffered from MI, stroke, and newly diagnosed AH, respectively. Prevalence rates of HLA in a cohort of males with newly diagnosed cardiovascular diseases (CVD) were 57,4% (χ^2=8,515, df=1, p<0,001), 58,7% (χ^2=23,185, df=1, p<0,0001), and 68,7% (χ^2=40,355, df=1, p<0,0001) in participants with AH, MI, and stroke, respectively. Within the first five years of observation, HR for developing AH, MI, and stroke in HLA group were 6,8-fold higher (95% CI=3,24–14,18, p<0,05), 2,5-fold higher (95% CI=1,63–4,62, p<0,001), and 6,4-fold higher (95% CI=3,08–13,3, p<0,05) than in MLA group, respectively. A ten-year period of the study showed that HR for developing AH, MI, and stroke in HLA group were 5-fold higher (95%

CI=2,89–11.76), 3,1-fold higher (95% CI=1,48–5,61; p<0,001), and 3,8-fold higher (95% CI=1,67–8,75; p<0,05) than in MLA group, respectively. A twenty-year period of observation revealed that HR for developing AH, MI, and stroke in HLA group were 1,8-fold higher (95% CI=1,087–3,24, p<0,05), 2.7-fold higher (95% CI=1,27–5,71, p<0,05), and 1,6-fold higher (95% CI=1,026–2,965, p<0,05), respectively, in comparison with MLA group. We found a tendency towards an increase in HR for developing CVD in HLA group over the entire 24-year period of the study (Figure 1).

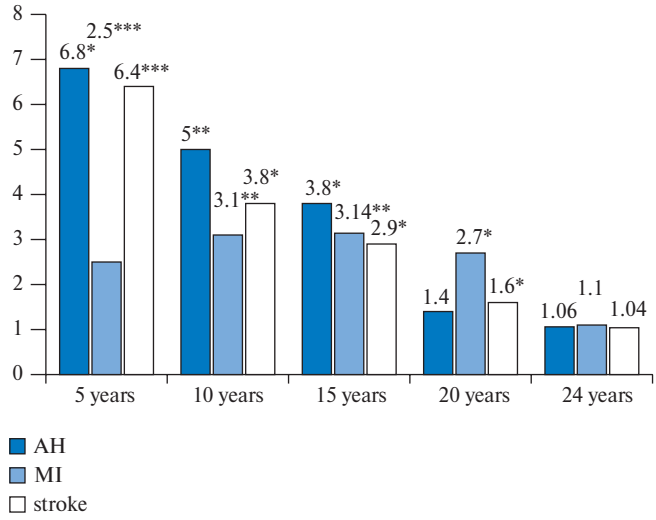

Figure 1. Comparative analysis of relative risk of developing CVD among the study participants with high level of anxiety (HLA) during 24-year period.
Annotation: *– p<0,05, ** — p<0,01, *** — p<0,001.

Discussion

More than half of 25-64-year-old males in the study population had HLA. Carriers of the DRD4 genotypes 4/4 and 2/4 were found more often in MLA group, whereas males with the genotype 4/6 were found more often in HLA group. We observed similar frequency distribution pattern for the DRD4 alleles.

Carriers of the DAT genotype 10/10 were found more often in MLA group than in HLA group. A pattern of frequency distribution among the carriers of the genotypes 9/10 and 9/9 was the opposite, namely: these genotypes were found more often in HLA group than in MLA group. The other genotypes in males with various levels of trait anxiety were found significantly rarer with the prevalence rates ranging from 2% to 5%. The ratios of the alleles 9 and 10 in males with trait anxiety were similar to the ratios of the corresponding genotypes.

Our data provided evidence that trait anxiety significantly increased the risk of developing CVD. Maximal risks for developing AH (HR_{AH}=6,8) and stroke (HR_{S}=6,4) were observed in males with HLA as early as within the first five years of the study compared to MLA group. Relative risks for developing AH and stroke in HLA group decreased with the course of time (for ten-year period: HR_{AH}=5 and HR_{S}=3,8; for 20-year period: HR_{AH}=5 and HR_{S}=3,8). At the same time, HR for developing MI showed a different pattern, namely: maximal risk for developing MI was found within 10 years of the study (HR=3,1); 20-year period revealed some downward trend in MI HR (HR=2,7); both 10-year and 20-year period indices exceeded the HR rates for developing MI within the first five years of the study (HR=2,5).

The differently directed HR trends in developing AH and stroke versus MI can be explained by the fact that HLA, as a cause of AH and stroke, was found more often in the older groups. Further decrease in HR for 10-year and 20-year periods was caused by reduction in a cohort size due to adverse outcomes in these groups. At the same time, HLA, as a cause of MI development, was found more often in the younger age groups, obviously resulting in a different HR trend pattern, namely: maximal HR was registered for 10-year period, whereas minimal HR was found for the first five years [29-31]. The results of our study are consistent with data obtained by other authors [15]. Meta analysis of 20 studies, conducted from 1980 to 2009, showed that anxiety in originally healthy individuals increased risk for developing coronary artery disease (HR=1,26, 95% CI=1,15–1,38, p<0,0001) independently of demographic factors, biological risk factors, and lifestyle.

Conclusion

1. Prevalence of high level of anxiety in 25–64-year-old male population of Western Siberia metropolis (the city of Novosibirsk) was as high as 50,9%.

2. High level of anxiety in 25-64-year-old male population was associated with the DRD4 genotype 4/6 and the DAT genotype 9/9.

3. High level of anxiety in 25-64-year-old male population caused maximal risk of developing arterial hypertension and stroke within the first five years of observation.

4. High level of anxiety in 25-64-year-old male population resulted in maximal risk of developing myocardial infarction within 10-year period, whereas risk of myocardial infarction events during the first five years of observation was minimal.

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WHO PROGRAMS: "REGISTER ACUTE MYOCARDIAL INFARCTION", "MONICA" — DYNAMICS ACUTE CARDIOVASCULAR ACCIDENT AT YEARS 1977-2009 IN GENERAL POPULATION AGED 25-64 YEARS IN RUSSIA

Gafarov Valery, Gafarova Almira

Aim. To study 33-year (1977–2009) dynamics acute cardiovascular accident in general population aged 25-64 years in Russia

Material and methods. Data of WHO studies ("Acute Myocardial Infarction Register" and "MONICA") were analyzed in three districts of Novosibirsk.

Results. Myocardial Infarction (MI) morbidity in 25–64-year-old population in Russia was found one of the highest worldwide. MI morbidity rates remained steady for the entire period of study except for 1988, 1994, 1998 (increase), 2002–2004, and 2006 (decrease). Mortality and lethality resembled morbidity except for 1977–1978 (decrease) and 2002–2005 (increase). Prehospital mortality and lethality significantly exceeded in-hospital deaths. Lethal outcomes after MI exceeded deaths from alcohol abuse by 2-3 times. Mortality and lethality decrease during period of unchanged morbidity suggested improved management of cardiac care; increase in mortality and lethality at a time of decreased morbidity indicated deterioration of medical assistance for cardiac patients. No changes in behavioral and somatic risk factors were found during 1977–2009. Significant increase in levels of psychosocial risk factors was documented.

Conclusion. MI morbidity, mortality, and lethality rates are the markers of increasing social stress in population. Deaths from MI have been the main component of the increase in mortality in Russia.

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Key words: cardiology, dynamics acute cardiovascular accident, epidemiology, risk factors.

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BP — blood pressure, CVD — cardiovascular diseases, f — female, ICC — index of close contacts, IHD — ischemic heart disease, HCE — hypercholesterolemia, m — male, MI — myocardial infarction, MONICA — Multinational Monitoring of Trends and Determinants in Cardiovascular Disease, RR — relative risk, SNI — social network index, WHO — World Health Organization.

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ПРОГРАММЫ ВОЗ: "РЕГИСТР ОСТРОГО ИНФАРКТА МИОКАРДА", "МОНИКА" — ДИНАМИКА ОСТРЫХ СЕРДЕЧНО-СОСУДИСТЫХ КАТАСТРОФ В 1977-2009ГГ В ОБЩЕЙ ПОПУЛЯЦИИ В ВОЗРАСТЕ 25-64 ЛЕТ В РОССИИ

Gafarov Valery, Gafarova Almira

Цель. Изучить динамику острых сердечно-сосудистых катастроф в общей популяции в возрасте 25-64 лет в России в течение 33 лет (1977-2009).

Материал и методы. Программы Всемирной Организации Здравоохранения "Регистр острого инфаркта миокарда", "Моника", проводимые в трех районах г.Новосибирска

Результаты. Заболеваемость инфарктом миокарда (ИМ) оставалась стабильной за весь период изучения, за исключением 1988, 1994, 1998 (увеличение), 2002-2004 и 2006 (уменьшение). Такие же показатели у смертности, за исключением 1977-1978 (уменьшение) и 2002-2005 (увеличение). Уровни смертности и летальности до больницы в 2-3 раза превышают смертность и летальность в больнице. Количество летальных исходов от ИМ превышает смертность от потребления алкоголя в 2-3 раза. Снижение смертности, летальности на фен стабильной заболеваемости ИМ свидетельствует о улучшении организации оказания медицинской помощи заболевшим; увеличение смертности и летальности на фоне снижения заболеваемости ИМ — об ее ухудшении. Не получено динамики поведенческих и соматических факторов риска в течение 1977-2009гг. В то же время отмечено значительное увеличение уровней психосоциальных факторов риска.

Заключение. Показатели заболеваемости, смертности и летальности являются маркерами повышения социального стресса в популяции. Смертность от ИМ была главным компонентом увеличения смертности в России.

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Ключевые слова: кардиология, динамика острой сердечно-сосудистой катастрофы, эпидемиология, факторы риска.

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Russia entered the XXI century with an array of problems affecting both human wellbeing and national security. One of the most severe challenges was the unfavorable demographic situation developed in the 1990s. During those years, the so-called "supermortality" had reached five million people while the life expectancy at birth dropped to extremely low 59 years. It is worthy of note that the medical components of the problem were significant and the cardiovascular diseases (CVD) remained the number one cause of the increased mortality contributing to 55.4% of all deaths. Among 2,200,000 people deceased in Russia in 2000, 1,200,000 died from CVD. The most alarming observation was the fact that morbidity and mortality rates escalated among the people in their most productive years alongside with the increased CVD detection [1-3]. Keeping this in mind, accurate and

comparable data elucidating the long-term CVD trends should be obtained based on the standard, strictly unified programs, which have been in a great demand providing a background for fighting CVD. Such studies enable us to elucidate nature of the undergoing population changes, to outline the ways, and to evaluate potential effect of the preventive measures [4, 5]. Upon reviewing the available literature, we have not found the reports focusing on such studies in Russia.

The goal of the present study was to analyze the 33-year (1977–2009) long-term trends and determinants in morbidity, mortality, and lethality from myocardial infarction (MI) in a high-risk population of the West Siberia metropolis (the city of Novosibirsk) using the unified World Health Organization (WHO) studies: "Register Acute Myocardial Infarction", "Multinational Monitoring of Trends and Determinants in Cardiovascular Disease" (MONICA), and MONICA-psychosocial [6-8].

Material and methods

The WHO "Register Acute Myocardial Infarction"-based study has covered the population aged 25 to 64 years living in three districts of the city of Novosibirsk including the Oktyabrsky district (starting on January 1, 1977) following with the Leninsky and Kirovsky districts (starting on January 1, 1981) [5, 6]. The total population of the three districts included 600,000 people. The WHO MONICA project continued in the same districts since 1983 [7]. No significant differences between data of two programs were found regarding the registered MI events (9). Quality assessment of the diagnostic IM categories was performed by the WHO Quality Control Centre for Event Registration in Dundee (Scotland), and the results were found acceptable [10-14]. 24,835 cases of MI including 8,122 lethal outcomes had been registered in the districts during the long-term monitoring covering the period from January 1, 1977 to December 31, 2009.

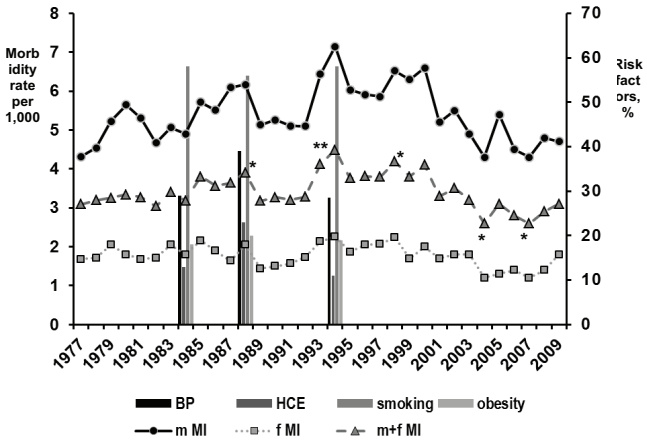

Figure 1. Annual acute myocardial infarction (MI) morbidity rates (per 1,000 population) among 25-64-year-old residents of Novosibirsk and common CVD risk factors (m — male, f — female).
Annotation: * — p<0,05, ** — p<0,01.

Standardization was performed using the standard world population. Representative random samples (a total of 2981 males aged 25 to 64 years) were examined in the Oktyabrsky district accordingly to three standard screening epidemiology programs: the WHO "MONICA", "MONICA-psychosocial", (1984, 1988, and 1994) [7], and the "HEPIEE" (2000). The pilot project was supported by the Welcome Trust grant. The response rates were 71,2%, 71,3%, and 82,1% for the first, second, and third screenings, respectively.

The anxiety was evaluated using the Spielberger's test (anxiety level, subscale of anxiety as personality characteristic) [15]; social support was estimated with the method developed by Berkman & Syme based on calculation of a social network index (SNI) and an index of close contacts (ICC). Encoding of the test consisted in the plotting of the index components and calculating the scores according to the proposed algorithm [16]. All new cases of MI in the cohort were registered among the people who did not have CVD at the moment of examination according to the WHO "Register Acute Myocardial Infarction" data for a period of 20 years (1984–2004). A total of 280 newly diagnosed MI cases were detected.

Statistical analysis of data was performed using the SPSS 11.5 Software. The stratified Cox proportional regression model was used for determination of the Hazard retio (HR); X2 test was used as the most important member of the nonparametric family of statistical tests.

Results

Our results suggested that the MI morbidity in a high-risk population (the city of Novosibirsk) in Russia was one of the highest in the world. Table 1 shows 33-year trends in the MI incidence rates. Dynamics in the MI morbidity was fairly steady except for the years of 1988, 1994, and 1998 that revealed significant morbidity increase (χ^2=5,482, n=1, p<0,05; χ^2=16,31, n=1, p<0,01; χ^2=4,876, n=1, p<0,05, respectively). Statistically proven decrease in the MI incidence rates was found during a period from 2000 to 2004 and in 2006 (χ^2=4,573, χ^2=3,529, n=1, p<0,05, respectively) while, in 2007–2009, we observed an upward trend of the rates. For the entire period of study, a significant age-dependent increase in the MI morbidity was found in both gender groups. The MI incidence rates in males prevailed over those of females by 2–7 times in all age groups (χ^2=12,976, p<0,01; χ^2=19,367, n=1, p<0,001, respectively) (Figure 1). The highest increase in MI morbidity was observed among males (3–5-fold, χ^2=18,826, n=1, p<0,001) and females (5–10-fold, χ^2=21,464, n=1, p<0,001) in the 45–54-year-old age groups in comparison with the preceding age groups. Analysis of the dynamic changes in the MI morbidity in different age groups showed that increase in the MI incidence rates in 1988 was mostly associated with the group of 45–64-year-old males while the increases in 1994 and 1998 were due to MI events among 55–64-year-old

Table 1

Acute myocardial infarction (MI) morbidity, mortality, and lethality in 1977–2009 in Novosibirsk according to the WHO "Acute Myocardial Infarction Register" and "MONICA" Programs.

Years	MI incidence rate per 1,000			MI death rate per 100,000						Lethality, %		
				m			f					
	m	f	m+f	iH	oH	iH+oH	iH	oH	iH+oH	m	f	m+f
1977	4,3	1,6	3,1	70,1	125,4	195,5	32,1	43,7	75,8	45,3	35,6	41,6
1978	4,5	1,7	3,2	25,8	118,0	143,9	20,4	40,8	61,2	31,7	28,8	30,6
1979	5,2	2,0	3,3	32,2	114,5	146,7	13,9	44,4	58,3	28,1	33,9	29,8
1980	5,6	1,7	3,3	23,4	131,8	158,2	14,1	45,2	59,3	28,4	36,8	30,7
1981	5,3	1,6	3,3	39,3	119,6	158,9	3,9	27,6	31,5	29,9	18,9	26,8
1982	4,6	1,7	3,0	37,6	109,5	147,1	13,1	26,5	39,6	27,5	24,8	26,7
1983	5,0	2,0	3,4	26,4	106,3	132,7	5,9	43,7	49,6	26,2	24,2	26,6
1984	4,9	1,7	3,2	36,9	133,6	170,5	15,8	35,5	51,3	32,9	28,0	31,4
1985	5,7	2,1	3,8	48,1	124,5	172,6	21,1	43,9	65,0	31,5	31,8	31,8
1986	5,5	1,8	3,6	39,1	122,7	161,8	7,0	49,7	56,7	30,7	31,2	30,8
1987	6,0	1,6	3,6	59,8	116,7	176,5	5,6	42,9	48,5	29,0	31,5	29,6
1988	6,1	2,0	3,9	80,3	185,6	265,9	13,8	49,8	63,6	43,1	40,7	42,5
1989	5,1	1,4	3,2	23,3	148,8	172,1	7,9	54,9	62,8	34,3	37,1	35,1
1990	5,2	1,5	3,3	39,1	139,3	178,4	16	27,7	43,7	36,6	36,3	36,5
1991	5,1	1,5	3,2	31,5	132,7	166,3	11,8	33,9	45,7	32,8	34,5	33,2
1992	5,0	1,7	3,3	34,2	147,2	181,3	20,3	33,3	53,6	35,6	31,1	34,3
1993	6,4	2,0	4,1	36,1	170,2	206,4	11,3	47,4	58,7	32,1	27,5	30,8
1994	7,1	2,2	4,5	47,3	217	264,2	15,2	66,1	81,3	38,6	36,7	38,0
1995	6,0	1,8	3,7	27,0	147,2	174,1	9,6	43,5	53,1	30,3	28,8	29,9
1996	5,9	2,0	3,8	21,1	148	169,1	7,7	46,3	54,0	29,3	25,7	28,3
1997	5,8	2,0	3,8	26,1	165,4	191,5	11,0	32,0	43,0	33,0	19,8	29,1
1998	6,5	2,2	4,2	42,3	166,6	208,9	14,3	39,7	54,0	32,4	23,1	29,7
1999	6,3	1,7	3,8	29,8	165,0	194,7	6,2	40,6	46,8	30,9	26,8	29,9
2000	6,6	2,0	4,1	19,8	167,5	167,5	12,5	43,7	56,2	25,5	28,6	26,3
2001	5,2	1,7	3,3	29,8	172,7	202,6	11,4	38,4	49,8	38,8	28,6	35,9
2002	5,5	1,8	3,5	29,8	190,2	220,0	12,4	48,8	61,2	40,7	33,5	38,6
2003	4,9	1,8	3,2	16,2	177,7	193,9	11,4	49,8	61,2	39,5	34,3	37,9
2004	4,3	1,2	2,6	35,9	162,7	198,6	15,8	33,6	49,4	46,1	40,3	44,6
2005	5,4	1,3	3,1	27,3	218,8	247,1	9,8	38,2	48,0	32,4	45,2	44,4
2006	4,5	1,4	2,8	26,1	120,0	146,1	2,9	29,4	32,3	32,4	24,1	30,1
2007	4,3	1,2	2,6	19,7	126,5	146,2	7,6	27,7	35,3	33,9	28,5	32,5
2008	4,8	1,4	2,9	14,5	125,0	139,5	10,2	19,4	29,6	29,1	21,2	27,1
2009	4,7	1,8	3,1	15,6	138,4	154,0	6,5	24,9	31,4	32,8	17,4	27,9

Abbreviations: m — male, f — female, m+f — male and female, iH — in-hospital, oH — out-hospital, iH+oH — in-hospital and out-hospital.

males and in the groups of 35–44, 45–54, and 55–64-year-old females. Decrease in the MI incidence rates in 2002–2004 and 2006 was found mostly in males while the upward trend of mortality in 2007–2009 was caused by the MI events in both gender groups with female predominance.

Mortality during the entire 33-year period of study remained fairly steady except the decline in death rates in 1977–1978 (χ^2=9,063, n=1, p<0,05) and in 2006 (χ^2=5,142, n=1, p<0,05) and increased mortality in 1988 (χ^2=11,589, n=1, p<0,001), 1994 (χ^2=13,573, n=1, p<0,001), 1998 (χ^2=8,489, n=1, p<0,05), 2002, and 2005 (χ^2=4,649, χ^2=3,837, n=1, p<0,05, respectively) (Figure 2). Reduction in mortality in 1977–1978 and increase in death rates in 1994 and 1998 were found in both gender groups. On the other hand, the MI mortality significantly increased in 1988, 2002, 2005 and decreased in 2006 only in males.

Dynamics of age-dependent mortality resembled that of morbidity. The MI mortality was increasing from the younger age groups toward the older ones for both sexes through the entire period of study. The mortality rates in males were 2–3 times higher than in females (χ^2=15,841, n=1, p<0,001). The lethality changes resembled dynamics of mortality. During the first two years of study (1977-1978), significant decrease in the lethality was found in both gender groups (χ^2=4.080 n=1 p<0,05). Increase in the lethality of

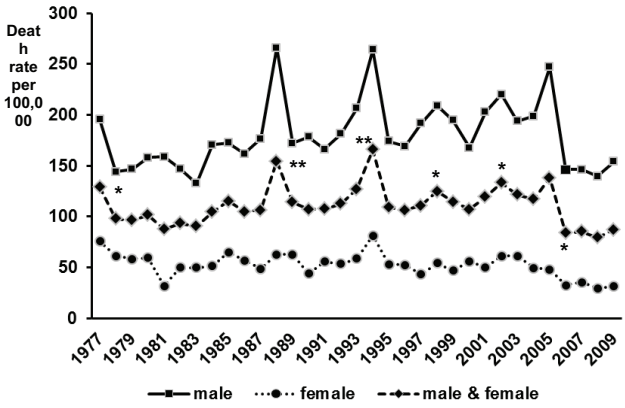

Figure 2. Annual myocardial infarction mortality rates among 25–64-year-old residents of Novosibirsk (deaths per 100,000 population).
Annotation: * — p<0,05, ** — p<0,01.

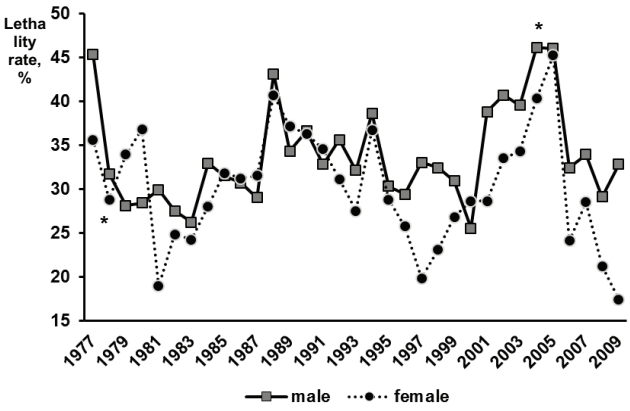

Figure 3. Myocardial infarction (MI) lethality (%) among 25–64-year-old residents of Novosibirsk.
Annotation: *– p<0,05.

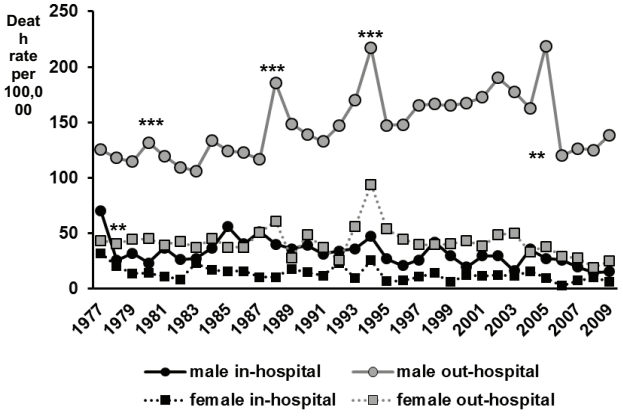

Figure 4. Annual myocardial infarction (MI) mortality rates among 25-64 year-old residents of Novosibirsk in regard to site of death (deaths per 100,000 population).
Annotation: ** — p<0,01, *** — p<0,001.

MI was observed in 1988 (χ^2=5,802, n=1, p<0,05), 1994 (χ^2=6,103, n=1, p<0,05), and in 2001–2005 (χ^2=4,649, χ^2=3,837, n=1, p<0,05) in both sexes and in 1998 (χ^2=5,844, n=1, p<0,05) only in males (Figure 3). During the entire period of the population-based study, the highest rates of lethality in males and females were recorded in the youngest age groups. Unlike the mortality, dynamic changes in lethality during the entire period of study were caused by the MI deaths in both males and females.

In both gender groups, the prehospital mortality and lethality prevailed during all years of study (Figure 4). We found that decline in the mortality and lethality in 1977-1978 was caused by the drop in the in-hospital deaths. At the same time, the decline in mortality in 2006 was caused by a lower number of the prehospital MI events. Increase in the MI mortality and lethality through the entire period of study was associated with the higher rates of the prehospital MI deaths. It should be noted that downward trend in female lethality in 2008-2009 was caused by in-hospital events.

The 18-year study (1977–1998) showed that the MI incidence rates were 2–3-fold higher compared to the death rates caused by alcohol abuse with the exception of the period of the profound social reorganization in 1994 when those rates were equal (χ^2=8,4, n=1, p<0,01; χ^2=14,59, n=1, p<0,002) (Figure 5).

Dynamic changes in the levels of both psychosocial risk factors of ischemic heart disease (IHD) and somatic and behavioral risk factors such as arterial hypertension, smoking, hypercholesterolemia, and obesity were determined based on the results of four screening studies focused on representative random samples of 25-64-year-old population of both sexes in the districts of Novosibirsk in 1994, 1988, and 1994. No significant changes in the levels of the somatic and behavioral risk factors were found (Figure 1).

Significant dynamic changes in the prevalence of anxiety (by Spielberger's test) were observed in the population according to the three screening studies of 1984, 1988, and 1994. Anxiety level increased from 35% to 52%; at the same time; SNI significantly decreased in the period from 1984 to 1994 (χ^2=35,952, n=6, p<0,001) (Figure 5). No statistically proven dynamic changes in the levels of anxiety, ICC, and SNI were found in the fourth screening study.

Males with the high anxiety levels had a significantly higher Hazard retio (HR) of MI development compared to individuals who had the medium levels. During 20-year period from 1984 to 2004, HR was initially increasing from HR =2,5 for five years (95% CI=1,63–4,62, p<0,001) to HR =3,1 for ten years (95% CI=1,48–5.61, p<0,001, respectively), eventually decreasing toward the end of the 20-year period to HR =2,7 (95% CI=1,27–5,71, p<0,05).

Discussion

Our results have demonstrated that the MI morbidity in a high-risk population of the city of Novosibirsk in Russia was among the highest in the world [17-19]. 33-year-long study of the dynamic changes in the MI rates showed steady state stabilization of the MI incidence except for the years of 1988, 1994, and 1998 (significant

increase) and 2002, 2003, 2004 and 2006 (significant decrease). We would like to make a point that the MI events in males of the older age groups contributed to the significant increase in the MI morbidity in 1988. Unlike this, the MI incidence rates in 1994 and 1998 increased mostly due to the higher morbidity among females of almost all age groups (except 25-34-year-olds). Only one group of males (55-64-year-olds) showed the significantly increased MI incidence rates in 1994 and 1998. The MI mortality and lethality rates remained steady during the entire 33-year period of study except for 1977-1978 when they decreased and except for 1988, 1994, 1998, and 2002–2005 when we found an increase in death rates. The age-dependent dynamic changes in mortality resembled those of morbidity. MI death rates in males exceeded mortality of females by 2-3 times. At the same time, MI deaths among both males and females contributed to the dynamic changes in lethality during the entire period of study.

Analysis of mortality and lethality trends in terms of a site of death showed that the prehospital mortality and lethality prevailed during all years of the study. Significant decline in mortality and lethality in males as well as similar tendency in females were found to be associated with an early hospital admission of the MI patients resulting, in turn, in the lower rates of complications and recurrent MI events [20]. It was found that the increase in the MI mortality and lethality in males and females in 1988, 1994, 1998, and 2002-2005 was associated with the higher number of sudden prehospital deaths. An increase in prehospital mortality was found in males in 1988 and 2002-2005 and in both males and females in 1994 and 1998; trend in 2009 was caused by the MI events both in males and females.

Paradoxical absence of the expected reduction in the MI morbidity at a time of the decreased MI mortality and lethality in 1977-1978 as well as a decrease in the morbidity rates at a time of the mortality and lethality increase in 2002-2004 may be explained by improved management of medical assistance for patients in the first instance and some downtrend in cardiac care in the second example.

We could not find associations between the changes in the MI rates and the levels of the main IHD risk factors because their values did not significantly change over time. This was likely due to the fact that the risk factor prevalence in the population was very high anyway. No association between the MI rates and ecological factors was found as well [21]. Strong associations between the MI rates and the psychosocial factors (increase in anxiety level) was determined based on the results of the three screening studies. Amplitude of this parameter reflected the level of social stress in the population. Therefore, the rates of MI morbidity, mortality, and lethality were the markers of growing social and economic instability in the society. This conclusion was confirmed by the observation of the decline in the MI morbidity and mortality in 2006. We cannot rule

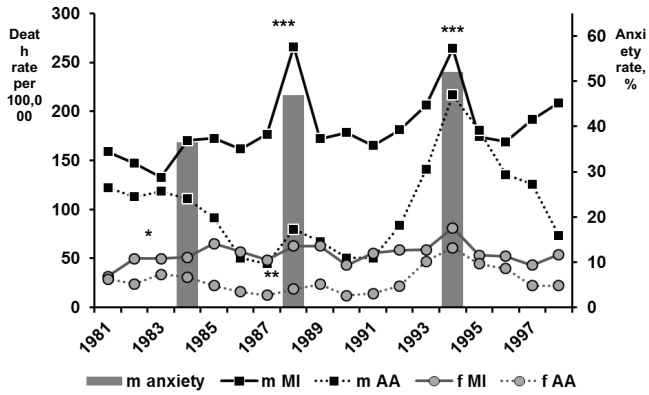

Figure 5. Annual myocardial infarction (MI) and alcohol abuse (AA) mortality (per 100,000 population) rates among 25-64 year-old residents of Novosibirsk and psychosocial factors (anxiety) in male.
Annotation: * — p<0,05, ** — p<0,01, *** — p<0,001.

out that this happened due to alleviation of social tension in the society i.e. decrease in the levels of psychosocial risk factors and augmentation of social support at that time. The period of 2006-2007 and the first half of 2008 were the most favorable years for Russia. During those years, the business revenues significantly grew leading to the higher budget revenues; human wellbeing improved; the government began to support (I) national projects stimulating demographic growth, physical culture and sports, medicine, education, and home mortgage programs; (II) economy development i.e. new job creation; (III) establishment of the stabilization funds. Upon these measures, people started to feel more stable; confidence in the future improved; social tension was alleviated. However, all these implicit indicators were indirectly associated with each other. Direct confirmation of the idea that the MI morbidity, mortality, and lethality can be considered the markers of growing social and economic instability was the fact that high anxiety level was associated with the significantly higher HR for MI development according to the results of 20-year-long study of the CVD-free cohort.

Our study has shown that the MI mortality rates exceeded the death rates caused by alcohol abuse by 2-3 times except the period of profound social reorganization in Russia in 1994 when those rates were equal.

Conclusion

1. We found that the MI morbidity in a 25–64-year-old high-risk population (the city of Novosibirsk) in Russia was among the highest in the world.

2. The MI incidence rates remained fairly steady over the entire period of the 33-year-long population-based study except for the years of 1988, 1994, 1998 (increase) and 2002-2004, 2006 (decrease). Mortality and lethality changes resembled the dynamics of morbidity except for the years of 1977–1978 (decrease) and 2002-2005 (increase). Prehospital mortality and lethality rates significantly exceeded the rates of in-hospital death events. It has been

shown that increase in mortality and lethality in 1988, 1994, 1998, and 2002-2005 was caused by higher number of prehospital deaths while their decrease in 1977-1978 was related mainly to in-hospital mortality and lethality.

3. The mortality and lethality decrease during a period of the steady MI morbidity suggested improved management of cardiac care; increase in the mortality and lethality at a time of the decreased MI morbidity indicated deterioration of medical assistance for cardiac patients.

4. Analysis of the behavioral and somatic IHD risk factors in the population of the city of Novosibirsk during the 33-year period did not reveal significant dynamic changes in these parameters. At the same time, the significant increase in the levels of psychosocial risk factors was detected over the same period.

5. Indirect evidence suggested that the MI morbidity, mortality, and lethality rates were the markers of the growing social stress in the society. Direct confirmation of this thesis was a significant increase of the RR for MI development in the individuals with the high anxiety levels according to the 20-year-long study of the CVD-free cohort.

6. The MI mortality exceeded incidence of deaths caused by alcohol abuse by 2-3 times and was the main determinant of the increase in mortality of urban population in Russia.

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MYOCARDIAL INFARCTION AND STROKE: 16-YEAR RISK AND STRESS AT WORK IN OPEN POPULATION OF 25–64-YEAR-OLD WOMEN IN RUSSIA/SIBERIA (WHO MONICA–PSYCHOSOCIAL PROGRAM)

Gafarov Valery, Panov Dmitry, Gromova Elena, Gagulin Igor, Gafarova Almira

Aim. To determine the effects of stress at workplace on the risks (HR: hazard ratio) of development of myocardial infarction and stroke in open population of 25-64-year-old women in Russia/Siberia (Novosibirsk).

Material and methods. Random representative sample of 25-64-year-old women (n=870) was examined in a framework of WHO MONICA-Psychosocial program in one of Novosibirsk districts. Stress at workplace was studied by using the Karasek scale; attitudes to work and prophylactic exams were studied by using the scale of "Knowledge and attitude towards one's own health" of WHO MONICA-Psychosocial program. During 16 years (1994-2010), all first-time cases of myocardial infarction and stroke were studied in the cohort based on the WHO program of Register of Acute Myocardial Infarction and all available documentation. Cox regression model was used for determination of myocardial infarction and stroke risk over 16 years of follow-up.

Results. Prevalence rate of high level of stress in open population of 25-64-year-old women was 31,6%. High levels of stress at work were associated with high levels of responsibility, inability to get rest at the end of workday, frequent professional dissatisfaction, and decreased working ability. For 16 years, HR was by 3,22 times higher for myocardial infarction ($p<0,05$) and 1,96 times higher for stroke ($p<0,05$) in women with stress at work. Rates of myocardial infarction and stroke were higher in married women who experienced stress at work, belonged to categories of managers and physical labor, and had high and low level of education.

Conclusion. Prevalence of high level of stress at workplace is significant in open population of 25–64-year-old women in Russia/Siberia (Novosibirsk). In the presence of stress at workplace, HR of myocardial infarction and stroke were 2 to 3 times higher than without it. Social gradient affected HR of infarct and stroke.

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Key words: cardiology, myocardial infarction, stroke, stress at workplace, hazard ratio, social gradient.

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CI — confidence interval, CVD — cardiovascular diseases, IHD — ischemic heart disease, HR — hazard ratio, MI — myocardial infarction.

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ИНФАРКТ МИОКАРДА И ИНСУЛЬТ: 16-ЛЕТНИЙ РИСК И СТРЕСС НА РАБОТЕ В ОТКРЫТОЙ ПОПУЛЯЦИИ СРЕДИ ЖЕНЩИН 25-64 ЛЕТ В РОССИИ/СИБИРИ (ПРОГРАММА ВОЗ "МОНИКА-ПСИХОСОЦИАЛЬНАЯ"

Gafarov Valery, Panov Dmitry, Gromova Elena, Gagulin Igor, Gafarova Almira

Цель. Для определения влияния стресса на рабочем месте на риск развития (Hazard ratio — HR) инфаркта миокарда и инсульта в открытой популяции среди женщин 25-64 лет в России/Сибири (г.Новосибирск).

Материал и методы. Случайная репрезентативная выборка женщин 25-64 лет (N=870) была обследована в рамках программы ВОЗ "МОНИКА-психосоциальная" в одном из районов г.Новосибирска. Стресс на рабочем месте был изучен с использованием шкалы Karasek; отношение к труду и профилактическим осмотрам исследованы с помощью шкалы "Знание и отношение к собственному здоровью" программы ВОЗ "МОНИКА-психосоциальная". В течение 16 лет (1994-2010), все первичные случаи инфаркта миокарда и инсульта изучали в когорте на основе программы ВОЗ "Регистр острого инфаркта миокарда" и всей имеющейся медицинской документации. Кокс-регрессионная модель была использована для определения риска инфаркта миокарда и инсульта в течение 16 лет наблюдения.

Результаты. Распространенность высокого уровня стресса на работе в открытой популяции среди женщин в возрасте 25-64 лет составила 31,6%. Высокий уровень стресса на работе был связан с высоким уровнем ответственности, невозможностью отдохнуть в конце рабочего дня, частой профессиональной неудовлетворенностью и снижением трудоспособности. В течение 16 лет, HR был на 3,22 раза выше, для инфаркта миокарда ($p<0,05$) и 1,96 раза выше для инсульта ($p<0,05$) у женщин со стрессом на работе. Частота инфаркта миокарда и инсульта была выше у замужних женщин, которые испытывали стресс на работе, и относились к категории руководителей или физического труда, с высоким и низким уровнем образования.

Заключение. Распространенность высокого уровня стресса на рабочем месте является существенным в открытой популяции среди женщин в возрасте 25-64 лет в России/Сибири (Новосибирск). При наличии стрессовых ситуаций на рабочем месте, HR инфаркта миокарда и инсульта были в 2-3 раза выше, чем без них. Социальный градиент влияет на HR инфаркта и инсульта.

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Ключевые слова: кардиология, инфаркт миокарда, инсульт, стресс на рабочем месте, отношение рисков, социальный градиент.

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Stress associated with work is one of the most important problems of healthcare and safety in developing countries. Changes in the world tendencies imply an increase in requirements for all areas of activity: mass layoffs, outsourcing, high demands for flexibility and necessary skills, and disregard to workplace safety measures, excess workload, psychological pressure, and work-leisure imbalance. All these factors contribute to stress associated with work. Possible relation of stress at work with loss of workforce potential (sick leaves) [1, 2] shows significant negative effect of distress on the economic indicators. At the same time, lack of prospective studies that involve evaluation of

individual characteristics of workers affects understanding of the causal relationships between stress and genesis of somatic disorders especially of cardiovascular diseases (CVD) [3]. The model of stress, focused on the aspects of organization of workplace and work environment [2], identifies the groups subjected to stress at work and stratified by age, gender, professional class, and education level. In perspective, this model contributes to the development of theoretically-based methods of prophylactics at workplace.

In this regard, the aim of the present study was to determine the prevalence rates of stress at work in an open population of 25-64-year-old women and to investigate the effects of stress on hazard ratios (HR) for myocardial infarction and stroke during the long-term period of observation (16 years).

Material and methods

In a framework of the third screening of the WHO MONICA program and MONICA-Psychological subprogram (MOPSY) in 1994 [4], we studied a random representative sample of women (n=870) aged 25–64 years, residents of one of the Novosibirsk districts (Table 1). The sample was formed based on the electoral lists by using the random numbers table. The response rate was 72,5%. The examination was conducted according to the protocol of the MONICA program.

Program of the psychosocial screening study consisted in the registration of social and demographic data including marital status, education level, and psychosocial tests. The levels of stress at workplace were studied by using Karasek scale [5]; attitudes to work and to prophylactic health exams were elucidated by using a scale of "knowledge and attitude towards one's own health" of the WHO MONICA-Psychosocial program.

After the exclusion of all individuals with cardiovascular pathology (arterial hypertension, ischemic heart disease (IHD), stroke, and diabetes mellitus) at the moment of the screening, the cohort was formed (n=560). During the control period (from 1994 to 2010), 35 cases (6,3%) of first-time stroke were found in the cohort based on medical examinations, medical documentation analysis, and death certificates. According to the WHO program "Register of Acute Myocardial Infarction" [6], 15 cases (2,7%) of first-time myocardial infarction (MI) were identified. Statistical analysis was performed by using SPSS 11.5 software package. Cox regression model was used to evaluate Hazard ratio (HR) or MI and stroke in the study cohort. To test statistical significance of differences between groups, chi-square test (χ^2) was used. Values were considered statistically significant when P was <0,05.

Table 1

Age-dependent distribution of 25–64-year-old women examined in the screening study according to the WHO MONICA program (1994)

Age groups	N	%
25–34	214	24,6
35–44	192	22,1
45–54	231	26,6
55–64	233	26,8
25–64	870	100,0

Results

In an open population of 25–64-year-old women, the prevalence rates for high and moderate levels of stress at work were 31,6% and 50,7%, respectively. Proportions of women with high levels of stress at work did not significantly differ between the age groups.

The study of women's attitudes to work showed that 40% of them changed their specialty during the last year and 28% of respondents began to perform extra work. Almost 42% of women were not pleased with their work. Among them, 1,7% disliked their work, 5,3% did not like it, and 34,8% moderately liked their work. Almost half of women (46,5%) had work with high or very high responsibility. Moreover, 42,2% of respondents reported about the changes in work responsibility during the last 12 months. About 40% of women responded that they could not relax or get rest after workday. Women of the older age groups tended to change their specialty less often (Table 2). Respondents from the younger age groups more often performed extra work. Older women reported about a decrease in the workload (34,1% vs. 11,8%; χ^2=46,43; df=6; p<0,001). Workplace responsibility decreased or did not change in the older age groups for the last year; younger age groups reported about an increase in responsibility at workplace. Ability to have rest at home was reported less often in the younger age groups compared with the respondents of the older age groups (12,1% vs. 26,9%; χ^2=45,5; df=12; p<0,001). Aging was associated with an increase in the proportion of persons who reported about a decrease in their working efficiency.

Attitude to own work and prophylactic health exams is an important indicator. Majority of women (64%) reported that they would continue working if they felt unwell at workplace. Only 38% of women said they would stay at home in case of feeling unwell and do their best to return to work.

The age-dependent results on attitudes to work and prophylactic health exams in women are presented in Table 3. In the older age groups, we documented an increase in responsibility of women for their own health. For instance, the number of women who would seek medical assistance in case of worsening of their health increased almost three-fold whereas individuals from the younger age groups (25–34 and 35–44 years) reported more often that they would prefer to continue their work despite feeling unwell, however they would make more efforts for the quickest recovery and return to work compared with the older age group (11% vs. 34%; 73,6% vs. 43%; χ^2=55,15;

Table 2

Attitudes to work in an open population of 25–64-year-old women depending on age

Question/attitude	Age groups							
	25–34		35–44		45–54		55–64	
	N	%	N	%	N	%	N	%
14. Have your specialty change during the last 12 years?								
1. Yes	79	43,4	97	46,6	56	30,9	40	30,5
2. No	103	56,6	111	53,4	125	69,1	91	69,5
χ^2=15,49 df=3 p<0,01								
15, Have your work load change during the last 12 months?								
1. I began to do extra work	61	34,1	70	34,8	44	25,0	15	11,8
2. It did not change	109	60,9	113	56,2	104	59,1	80	63,0
3. I have decreased or stopped doing extra work	9	5,0	18	9,0	28	15,9	32	25,2
χ^2=46,43 df=6 p<0,001								
16. Are you pleased with your work?								
1. I do not like it at all	4	2,2	3	1,4	3	1,7	2	1,6
2. I do not like it	15	8,2	7	3,4	7	3,9	8	6,5
3. Moderately	72	39,6	76	36,7	59	32,8	33	26,6
4. O like it	81	44,5	115	55,6	98	54,4	68	54,8
5. I like it very much	10	5,5	6	2,9	13	7,2	13	10,5
χ^2=20,47 df=12 p=0,059								
17. Have your responsibility at work change during the last 12 months?								
1. It did not change	105	58,0	104	50,7	105	58,0	83	67,5
2. It increased	70	38,7	90	43,9	63	34,8	20	16,3
3. It decreased	6	3,3	11	5,4	13	7,2	20	16,3
χ^2=40,00 df=6 p<0,001								
18. How do you estimate responsibility of your work during the last 12 months?								
1. Insignificant	10	5,6	17	8,4	14	7,8	31	25,6
2. Moderate	93	52,2	86	42,4	66	36,7	47	38,8
3. High	66	37,1	88	43,3	91	50,6	38	31,4
4. Very high	9	5,1	12	5,9	9	5,0	5	4,1
χ^2=46,11 df=9 p<0,001								
20. Have you been able to relax and rest after regular workday during the last 12 months?								
1. No, never	12	6,6	9	4,3	11	6,1	9	7,6
2. Rarely	69	38,1	76	36,5	46	25,4	29	24,4
3. It depends	78	43,1	92	44,2	90	49,7	49	41,2
4. Often	16	8,8	26	12,5	17	9,4	10	8,4
5.Yes, always	6	3,3	5	2,4	17	9,4	22	18,5
χ^2=45,5 df=12 p<0,001								

Table 3

Attitudes to work and prophylactic health exams in an open population of 25–64-year-old women depending on age

Question/attitude	Age groups							
	25–34		35–44		45–54		55–64	
	N	%	N	%	N	%	N	%
11. What do you do if you feel unwell at work? (retired and unemployed individuals respond as they were employed)								
1. I continue work	134	73,6**	134	64,4	124	67,8	58	43,0
2. I limit work and rest	27	14,8	54	26,0	34	18,6	31	23,0
3. I go to see a doctor	21	11,5	20	9,6	25	13,7	46	34,1**
χ^2=55,15 df=6 p<0,001								
12. What do you undertake if you have cold and fever?								
1. I work as usual	80	44,0	99	47,1	97	54,5	61	46,6
2. I stay at home and do my best to return to work as soon as possible	70	38,5	88	41,9	63	35,4	45	34,4
3. I remain at home until I feel better	32	17,6	23	11,0	18	10,1	25	19,1
χ^2=11,31 df=6 p=0,079								
13. How do you think? — Is prophylactic health exam useful?								
1. Yes, it is useful	137	74,9	157	75,1	135	73,4	108	79,4
2. Maybe, yes	44	24,0	52	24,9	49	26,6	27	19,9
3. Maybe, no	1	0,5	0	0	0	0	1	0,7
4. It is useless	1	0,5	0	0	0	0	0	0

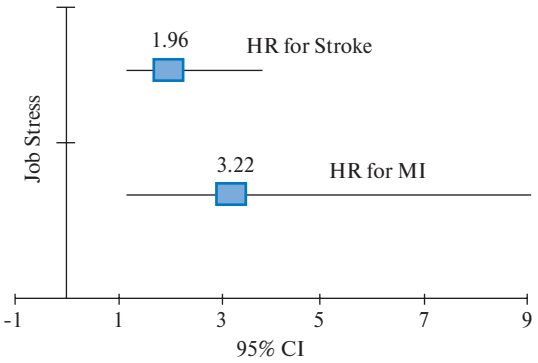

Figure 1. Risk of stroke and myocardial infarction among 25–64-year-old women with high levels of stress at workplace in an open population during 16 years.

df=6; p<0,001). The rates of positive attitude to prophylactic health exams were nearly 100% in all age groups.

We studied the relationships between workplace stress and social characteristics of women who developed MI and stroke.

Pattern of marital status in the cohort of women with stroke who experienced stress at work was as follows: never married (4,5%), married (72,7%), divorced (18,2%), and widowed (4,5%). Pattern of marital status in the cohort of women with MI who experienced stress at work was as follows: married (66,7%), divorced (22,2%), and widowed (11,1%). Increasing trends in the rates of stroke and MI were documented in married women with stress in the family compared with single, divorced, and widowed women.

Education levels in cohort of women with stroke and stress at work were as follows: university education (13,6%); incomplete higher education/secondary specialized college (31,8%); high school diploma (27,3%); and elementary education (27,3%). Women with high school diploma and elementary education who had workplace stress showed higher rate of stroke compared with women who had higher education. Pattern of education in individuals with MI and stress at work revealed prevalence of completely opposite categories: higher education (37,5%), elementary education (37,5%), and secondary education (25%).

Professional status in the groups of women with workplace stress and stroke showed the following structure: middle managers (9,1%); managers (4,5%); technical and engineering employees (18,2%); physically demanding jobs (4,5%); moderately physically demanding jobs (22,7%); easy manual labor (18.2%); and retired (22,7%). Professional status in women with stress and MI was as follows: managers (12,5%); technical and engineering employees (37,5%); easy manual labor (12,5%); and retired (37,5%). Concerning the professional characteristics, data showed tendency toward an increase in the frequency of stroke among women of easy manual labor who had workplace stress; the proportion of women with MI was higher among the stressed pensioners and technical/engineering employees.

For 16 years (1994–2010), women with the high level of stress at workplace had 1,96-fold HR for stroke compared with individuals with the lower levels of stress (95.0% CI 1,01-3,79; p<0,05). In women with the high level of stress at workplace, HR for MI was 3,22 times higher (95.0% CI 1,15-9,04; p<0,05) (Figure 1).

Discussion

Every third woman, residing in West Siberian metropolis, experiences stress at workplace. According to data of the fourth study of the European Working Conditions Survey conducted in the European Union countries in 2005, 20,3% of women report about the presence of stress at workplace and 31% of women believe that work affects their health [7]. The highest levels of stress at workplace were found in the developing countries of East Europe; the lowest levels were found in Great Britain and the Netherlands [7, 8].

High proportion of women (over 40%) reports about an increase in work responsibility and load as well as inability to have rest after work predominantly in younger age groups. In the European countries, individuals who belong to the most active age groups of 25–39 years (23%) and 40–54 years (24%) present with complains of stress; frequency of the reports about fatigue (exhaustion) and stress decreases in the older age categories [9]. In combination with inability to have rest at home after work, these observations explain the higher rates of cardiovascular events in married women experiencing workplace stress which was shown in the present study: about 70% of women with MI/stroke and stress at work were in the category of "married". Modern views support the idea that, apart from the demand for the balance between efforts and rewards at work, the balance between family and work (career) should be improved especially in workers who have small children [10]. Despite the fact that family-career conflict is relevant for both genders, the disbalance is more pronounced in women [11-13].

Obtained data showed that 42% of women were not pleased with their work. In our opinion, this observation is explained by both environmental (such as position held etc.) and personal traits [14, 15]. Women who are unsatisfied with the existing situation at work often report about the inefficacious organization at workplace, poorly defined work tasks, lack of tools to solve professional tasks, and the presence of unresolved conflicts [16].

Almost half of woman in our study estimated their responsibility at work as high. High frequency of terminations of employment and layoffs during that period explains an increase of work load in the rest of personnel, erases the boundaries between the professional categories, and often exposes women to the submissive position both in budgetary and private sectors of economics [17]. As a result, women have fewer supervisory functions and the levels of tension and stress at workplace increase [18, 19]. Such changes hinder the protective effects of education on cardiovascular health in women; frequency of the cardiovascular events becomes independent from the education level in the presence of high level of stress at work. Accord-

ing to our data, the proportion of individuals with MI was similar both for women with higher and elementary education though the rate for stroke showed an upward tendency in the presence of the lower education level.

The large proportion of women (64%) reported that they would prefer to continue work if they felt unwell at workplace. Health-related complains at workplace are often associated with the high levels of stress in women at place of production [1]. At the same time, insufficient care for own health and poor awareness in the presence of hard work are associated with the adverse lifestyle and cardiovascular risk factors [20-23] and can be one of the pathogenetic mechanisms of health deterioration and CVD development. The obtained results showed tendency to increase in the stroke rates among women in the category of "physical labor" emphasizing high level of cardiovascular risk in this class [24].

Therefore, our study demonstrated that stress associated with work significantly increased HR for stroke and MI among women in an open population. Relationships between the professional characteristics and IHD were demonstrated based on other large studies such as British Whitehall II Study and Finnish Helsinki Health Study [25], but only Framingham Offspring Study showed that workplace stress increased risk of IHD in women [26]. The other long-term prospective study showed that the high level of psycho-emotional stress in individuals who lost their job significantly increased risk for stroke and MI [27]. Some investigators have been denying the gender-related effects of professional stress on CVD risk [28], but this merely denotes the need for further studies of gender aspects of psychosocial characteristics at work.

Conclusion

1. Prevalence of pronounced level of stress at workplace in an open population of 25-64-year-old women in Russia/Siberia was high (31,6%).

2. In an open population of 25-64-year-old women, the high levels of stress were associated with the high responsibility at work, inability to have rest at the end of workday, frequent professional dissatisfaction, and decrease in working efficiency.

3. Social gradient ("married" marital status; professional categories of managers and physical labor workers; high and low education levels) affected HR for MI and stroke.

4. In an open population of 25-64-year-old women with high levels of stress associated with work, HRs for MI and stroke were 3,22-fold and 1,96-fold higher over 16 years, respectively.

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METABOLIC AND HEMOSTATIC PARAMETERS IN PRE-DIABETES AND NEWLY DIAGNOSED TYPE 2 DIABETES

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Metabolic changes in diabetes mellitus are associated with hemostatic disorders. However, the sequence of hemostatic events in the early stages of disease remains unclear.

Aim. To assess metabolic and hemostatic parameters and their interaction in pre-diabetes and newly diagnosed type 2 diabetes mellitus (ND T2DM).

Material and methods. The study enrolled volunteers of 40 to 65 years who considered themselves healthy and did not get any medication therapy. Of 170 examined individuals, 46 had impaired carbohydrate exchange (ICE) — 13 with impaired fasting glucose, 17 — impaired glucose tolerance and 16 with ND T2DM. The control group comprised healthy volunteers with normal body mass index and without signs of metabolic abnormalities. The metabolic (carbohydrate, lipid, protein exchange, hepatic transaminase), platelet and plasma hemostatic parameters (mean platelet volume, ADP- &collagen-induced platelet aggregation, coagulation profile, fibrinogen, plasminogen) were investigated. We identified the peculiarities initiating impact of changed parameters on different hemostatic components in patients with pre-diabetes and ND T2DM.

Results. Concentration of insulin, C-peptide, Homa-IR, total cholesterol demonstrated increase in groups with ICE. ADP-induced platelet aggregation, fibrinogen increased in ICE, however these changes were not statistically significant. Mean platelet volume and plasminogen had the tendency to be elevated in pre-diabetes and demonstrated significant increase in ND T2DM.

Conclusion. Metabolic disorders in prediabetic stage initiate changes in platelet hemostasis and fibrinolysis. The increase of MPV and higher concentrations of plasminogen are considered to be significant in ND T2DM.

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Key words: pre-diabetes, newly diagnosed type 2 diabetes mellitus, metabolic disorders, hemostasis — platelets, coagulation, fibrinolysis.

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MPV — mean platelet volume, FPG — fasting plasma glucose, APPT — activated partial thromboplastin time, HDL-CL — high-density lipoprotein-cholesterol, LDL-CL — low-density lipoprotein-cholesterol, TG — triglyceride, HOMA-IR — homeostasis model assessment-estimated insulin resistance, C-p — C-peptides, HbA_{1c} — hemoglobin A1c, BMI — body mass index, WC — waist circumference, C-p — C-peptides, IR — insulin resistance, TC — total cholesterol, AST — aspartate transaminase, ALT — alanine transaminase, ADP — adenosine diphosphate, PLG — plasminogen.

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ПАРАМЕТРЫ МЕТАБОЛИЗМА И ГЕМОСТАЗА ПРИ ПРЕДИАБЕТЕ И ВПЕРВЫЕ ВЫЯВЛЕННОМ САХАРНОМ ДИАБЕТЕ 2 ТИПА

Petrik G. G.[1,2], Kosmacheva E. D.[1,2], Bratchik A. V.[2], Kudryashov R. O.[1], Glushanova V. A.[2]

Метаболические изменения при сахарном диабете (СД) сопряжены с нарушениями гемостаза, последовательность вовлечения компонентов которого на ранних стадиях заболевания не определена.

Цель. Изучение параметров метаболизма, гемостаза и характера их взаимоотношений при предиабете и впервые выявленном СД 2 типа (ВВ СД2).

Материал и методы. Объектом исследования явились добровольцы в возрасте 40-65 лет считающие себя здоровыми и не получающие никакой медикаментозной терапии. У 46 из 170 обследованных выявлены нарушения углеводного обмена (НУО): 13 — нарушение гликемии натощак,17 нарушение толерантности к глюкозе и у 16 ВВ СД2. Контрольную группу составили 13 здоровых добровольцев с нормальной массой тела без признаков метаболически аномального фенотипа. Во всех контингентах исследованы параметры метаболизма (углеводный, липидный, белковый обмен, трансаминазы печени) и тромбоцитарно-плазменного гемостаза (средний объем тромбоцитов, ADP- и коллаген-индуцированная агрегация тромбоцитов, коагулограмма, фибриноген, плазминоген). Определены особенности инициирующих влияний измененных параметров метаболизма на различные компоненты гемостаза при предиабете и ВВ СД2.

Результаты. Концентрация инсулина, С-пептида, HOMA-IR, общее содержание холестерина были повышены в группах с нарушением углеводного обмена. АДФ и коллагеном-вызванной агрегацию тромбоцитов, фибриноген так же были повышены при НУО, однако эти изменения не были статистически значимы. Средний объем тромбоцитов и плазминогена имели склонность к увеличению на стадии предиабета и продемонстрировали статистически значимое увеличение при ВВ СД2.

Заключение. Метаболические нарушения на стадии предиабета инициируют изменения тромбоцитарного гемостаза и фибринолиза. При ВВ СД2 увеличение MPV и повышение концентрации плазминогена принимают значимый характер.

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Ключевые слова: предиабет, впервые выявленный сахарный диабет 2 типа, метаболические нарушения, гемостаз — тромбоцитарный, коагуляционный, фибринолиз.

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Type 2 diabetes mellitus (T2DM) is a significant risk factor for cardiovascular disease [1]. Debuting as a metabolic disease T2DM is accompanied by morphologic changes of the vascular wall, target-organ damaging, developing cardiovascular catastrophes. Atherothrombosis is the leading cause of death in T2DM. People with DM are two times more likely to have a heart disease or stroke than people who do not [2]. It is therefore particularly interesting to

study how the changed metabolic parameters influence on hemostasis. Many investigations and reviews on this issue represent an amazingly deep biochemical analysis of specific triggers of endothelial cell damage, dysfunction of platelets, plasmatic hemostasis [3-5].

However, we didn't find any available reports, describing and identifying connection between separate hemostatic and metabolic parameters of early stages of DM2 on one representative clinical material. Therefore in the present study we investigated metabolic and hemostastic parameters and their relationships in patients with pre-diabetes and with newly diagnosed type 2 diabetes mellitus (ND T2DM).

Material and methods

This study enrolled volunteers aged 40 to 65, who were non-smokers, considered themselves healthy and did not get any medication therapy. Of 170 examined individuals, 46 had impaired carbohydrate exchange (ICE) and met the inclusion criteria: ND T2DM, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). Exclusion criterion was the presence of any other disease, including the previously identified diabetes and the presence of diabetic micro- and macrovascular complications.

DM2 diagnosis is based on fasting plasma glucose level (FPG) ≥7,0 mmol/l (126 mg/dl) or 2–h plasma glucose ≥11,1 mmol/l (200 mg/dl) and HbA_{1c} >6,5%. If level of fasting plasma glucose was 6,1 — 6,9 mmol/L (110 mg/dl to 125 mg/dl) and/or HbA_{1c} 5,7-6,4%, oral glucose tolerance test (OGTT) (75 g oral glucose load) was done. Based on its results, pre-diabetes state was classified as — IFG [(fasting blood glucose 6,1–6,9 mmol/L (110 mg/dl to 125 mg/dl) and 2–h plasma glucose <7,8 mmol/l (140 mg/dl)] or IGT [(fasting plasmaglucose 6,1–6,9 mmol/L (110 mg/dl to 125 mg/dl) and 2-h glucose ≥7,8 and <11,1 mmol/l (140 mg/dl and 200 mg/dl) [6-8].

Systolic and diastolic blood pressure (SBP and DBP, respectively) was measured according to the standard technique [9]. The study included patients with SBD <140 mmHg and DBD <90 mmHg.

The height, weight, waist and hip circumferences were measured in underwear and without shoes. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2).

The control group comprised non-smoking healthy volunteers with normal body mass index (BMI 18,5-24,9 kg/m^2, waist circumference (WC): women <88 cm, men <102 cm, without signs of metabolic abnormalities (BP <130/85 mmHg, fasting glucose <5,5 mmol/l, triglycerides <1,7 mmol/l, HDL cholesterol >1,04 mmol/l in men, and >1,3 mmol/l in women, HOMA IR <2,5).

The Ethical Committee of Kuban State Medical University, Krasnodar, approved the study and all patients and controls gave written informed consent.

Laboratory Research. To estimate the parameters of metabolism and hemostasis venous blood samples was performed after a 12-hour overnight fasting, venous blood samples were drawn in the morning (between 8:00 AM and 9:00 AM).

The hemogram was evaluated using the Automatic Hematology Analyzer ADVIA 120 (Siemens, Germany); the biomedical parameters (including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST)) were determined using enzymatic colorimetric method with the Automatic Biochemistry Analyzer ADVIA 1650, 2400 (Siemens, Healthcare Diagnostics, USA).

Glycated hemoglobin (HbA1c) was measured using reference method (HPLC D-10) (Bio-Rad Laboratories, USA), calibrated to the Diabetes Control and Complications Trial standard. Determination of insulin and C-peptide was performed on an automated immunochemical analyzer Advia Centaur, manufactured by Siemens Healthcare Diagnostics, USA. Homeostasis Model Assessment Model (HOMA) was used to determine the insulin sensitivity index with formula: HOMA-IR=fasting insulin (μU/ml) x fasting glucose (mmol/l)/22,5.

Serum protein fractions were separated by zone electrophoresis on an agarose gel using an automated electrophoresis system Hydrasys (Sebia, France).

All hemostasis-related parameters were determined by turbidimetric and chromogenic methods on the ACL TOP 700 Automated Analyzer (Instrumentation Laboratory Company, USA) using anufacturer`s reagent kit.

Platelet aggregation activity was examined on a turbidimetric platelet aggregation laser-analyzer "Biola 230 LA" (Russia). Sodium adenosintriphosphate (LLC Technology-standard, Russia) and collagen (SPA Renam, Russia) were used as inductors of platelet aggregation in both the cases at the final concentration of 30 μM.

Statistical analysis was performed using the package of program STATISTICA 10 (StatSoft, USA). The results are expressed as Median, upper and lower quartiles (Me (25; 75), where Me — median, 25 and 75 are the 1st and 3d quartiles) comparing the mean ranks for all groups using the Kruskal-Wallis test. Spearman's rank correlation test was used to reveal the correlation between the indexes equal to P-value=0,05 was considered statistically significant.

Results

According to the stated objectives, the patients were grouped into early diabetes (n=16), IGT (n=17) and IFG (n=13) and normal controls (n=13). The group was similar in sex and age (Table 1). However, patients with ICE had excessive BMI exceeding normal index by 50%, 41% and 44% with ND T2DM, IGT and IFG respectively. WC in groups with ICE was also significantly higher than in the normal group.

Analysis of biochemical parameters in patients with ICE showed changes of both carbohydrate and lipid profiles as

Table 1

Clinical characteristics of patients with newly diagnosed type 2 diabetes mellitus, pre-diabetes and control

	1 ND T2DM n=16	2 IGT n=17	3 IFG n=13	4 Control n=13	5 p
Age, year	57,0 (51,0; 61,5)	54,0 (49,0; 57,0)	55,0 (54,0; 56,0)	47,0 (45,0; 53,0)	p_{1-4}=0,06 p_{2-4}=0,95 p_{3-4} =0,62
Sex, M/F	13/3	15/2	10/3	11/13	
BMI, kg/m^2	34,6** (33,2; 39,9)	32,1** (26,5; 34,8)	32·8** (28,7; 33,3)	22,8 (21,2; 23,9)	p_{1-4}=0,000 p_{2-4}=0,000 p_{3-4}=0,001
Waist circumference, cm	109** (106; 113)	99** (94; 106)	102** (93; 111)	76 (72; 78)	p_{1-4}=0,000 p_{2-4}=0,003 p_{3-4}=0,001
Hip circumference, cm	115** (107; 124)	109 (101; 119)	111** (108; 118)	97 (95;103)	p_{1-4}=0,000 p_{2-4}=0,016 p_{3-4}=0,002
SBP, mmHg DBP, mmHg	125* (125;130) 80 (80; 80)	125 (120;125) 80 (80;80)	125* (120; 130) 80 (80;80)	120 (110;120) 80 (75; 80)	p_{1-4}=0,03 p_{2-4}=0,06 p_{3-4}=0,02 p_{1-4}=0,33 p_{2-4}=0,94 p_{3-4}=0,35
Fasting glucose, mmol/l	7,0** (6,5; 8,2)	5,7 (5,4;5,8)	6,0* (5,5; 6,5)	5,2 (4,8; 5,5)	p_{1-4}=0,000 p_{1-2}=0,000 p_{1-3}=0,04 p_{2-3}=1,0 p_{2-4}=0,46 P_{3-4}=0,03
HbA_{1c}, %	6,8** (6,3; 7,6)	6,1* (5,9; 6,2)	5,9 (5,3; 6,7)	5,7 (5,6; 5,9)	p_{1-4}=0,000 p_{1-2}=0,07 p_{1-3}=0,001 p_{2-3}=0,84 p_{2-4}=0,01 p_{3-4}=1,0
Insulin, mU/l	15,6** (12,0; 23,8)	14,0* (12,5;19,0)	14,6* (10,7;17,6)	8,0 (5,6; 5,9)	p_{1-4}=0,000 p_{2-4}=0,002 p_{3-4}=0,005
C-peptide, ng/ml	2,7** (2,3; 3,4)	2,0** (1,8; 2,34)	2,0* (1,5; 2,4)	1,1 (1,0; 1,3)	p_{1-4}=0,000 p_{2-4}=0,003 p_{3-4}=0,02
HOMA-IR	6,6** (3,4; 8,1)	3,5* (2,9; 4,9)	3,6* (3,0; 4,8)	1,8 (1,5; 2,3)	p_{1-4}=0,000 p_{1-2}=0,47 p_{1-3}=0,84 p_{2-4}=0,002 p_{3-4}=0,005
Total cholesterol, mmol/l	5,9* (5,3; 6,8)	5,9* (5,24; 6,7)	5,8 (4,3; 6,7)	4,8 (4,5; 5,1)	p_{1-4}=0,004 p_{2-4}=0,004 p_{3-4}=0,09
LDL cholesterol, mmol/l	3,5 (3,0; 4,2)	3,7 (3,0;4,8)	3,8 (2,5; 4,5)	2,9 (2,6; 3,2)	p_{1-4}=0,25 $p_{2-4=}$0,08 p_{3-4}=0,83
HDL cholesterol, mmol/l	1,5 (1,2; 1,7)	1,54 (1,2; 1,7)	1,5 (1,5; 1,6)	1,6 (1,4; 1,7)	p_{1-4}=1,0 p_{2-4}=1,0 p_{3-4}=1,0
Triglycerids, mmol/l	1,7** (1,3; 2,5)	1,3* (1,1; 1,6)	1,5* (0,8; 2,1)	0,7 (0,6; 0,8)	p_{1-4}=0,000 p_{2-4}=0,004 p_{3-4}=0,006
Albumins, g/l	40,2 (38,8;43,6)	40,6 (39,0;41,9)	38,8 (36,2;41,9)	42,1 (40,4;44,0)	p_{1-4}=0,69 p_{2-4}=1,01 p_{3-4}=1,9

Extension of table 1

alpha-1globulin, g/l	2,2 (1,9; 2,4)	1,9 (1,8; 2,6)	2,1 (2,0; 2,3)	1,9 (1,5; 2,2)	p_{1-4}=1,63 p_{2-4}=0,85 p_{3-4}=1,4
alpha- 2 globulin, g/L	9,6 (8,8; 9,8)	9,6 (9,1; 10,7)	9,8 (9,1; 10,3)	9,0 (8,4; 9,7)	p_{1-4}=0,14 p_{2-4}=1,61 p_{3-4}=1,49
beta-1 globulin, g/l	7,3 (6,4; 8,3)	7,6 (6,2; 8,2)	7,3 (6,5; 8,1)	7,0 (6,7; 7,5)	p_{1-4}=0,64 p_{2-4}=0,77 p_{3-4}=0,17
beta-2 globulin, g/l	3,7 (3,3; 4,7)	4,69 (3,7; 5,02)	4,3 (2,9; 4,4)	3,7 (2,2; 4,4)	p_{1-4}=0,9 p_{2-4}=2,2 p_{3-4}=1,03
γ globulin, g/l	9,7 (8,9; 11,1)	10,3 (8,7; 11,8)	11,3 (8,7; 11,8)	10,8 (8,2; 12,1)	p_{1-4}=0,44 p_{2-4}=0,29 p_{3-4}=0,36
Creatinine, mmol/l	79,4 (74,9;87,6)	81,5 (78,6;92,3)	86 (80; 97,5)	77,0 (71,5;86,6)	p_{1-4}=1,0 p_{2-4}=0,88 p_{3-4}=0,67
Bilirubi, mmol/l	10,7 (8,3; 12,5)	10,4 (8,8; 12,8)	10,1 (8,9; 12,5)	10,2 (6,8; 12,0)	p_{1-4}=1,0 p_{2-4}=1,0 p_{3-4}=1,0
AST	26,0 (20,5;44,5)	22,0 (20,0;27,0)	20,0 (19,0;27,0)	21,0 (19,0;23,0)	p_{1-4}=0,58 p_{2-4}=1,0 p_{3-4}=1,0
ALT	30* (21,0;79,5)	26,0 (18,0;31,0)	23,0 (21,0;29,0)	19,0 (14,0;24,0)	p_{1-4}=0,01 p_{2-4}=0,45 p_{3-4}=0,91

Annotation: * — p< 0,05, ** — p < 0,001.

early as in the pre-diabetes stages. Concentration of insulin, C-peptide and Homa-IR was comparable in IGT and IFG groups and by 1,8 and 2 times higher than in normal. TC in all ICE groups, TG in IGT group and in IFG group were by 22%, 86% and 114% higher than in normal respectively. Maximally expressed changes were observed in ND T2DM, where two-fold increase of insulin content was registered, C-peptide, Homa-IR and TG increased by 2,5, 3,7 and 2,4 times respectively compared to the controls. We didn't identify significant changes of HDL, LDL and protein spectrum in patients with ICE. Parameters of hepatic metabolism demonstrated 1,5 times increased ALT in ND T2DM patients; nevertheless, pre-diabetes stages demonstrated just a tendency to this increase.

Comparison of the groups did not find significant differences between biochemical parameters in patients with ICE, except for Homa-IR which was by 1,8 times higher in patients with ND T2DM, than in patients with pre-diabetes (Figure 1).

The parameters of platelet hemostasis had the tendency to the elevated mean platelet volume (MPV) in patients with pre-diabetes and its significant increase in patients with ND T2DM (Figure 2).

Moreover, we noted the increase of ADP and collagen-induced platelet aggregation. However, these changes were not statistically significant (Figure 3, 4).

The parameters of plasma hemostasis didn't change significantly, however, they tended to increase at the stages

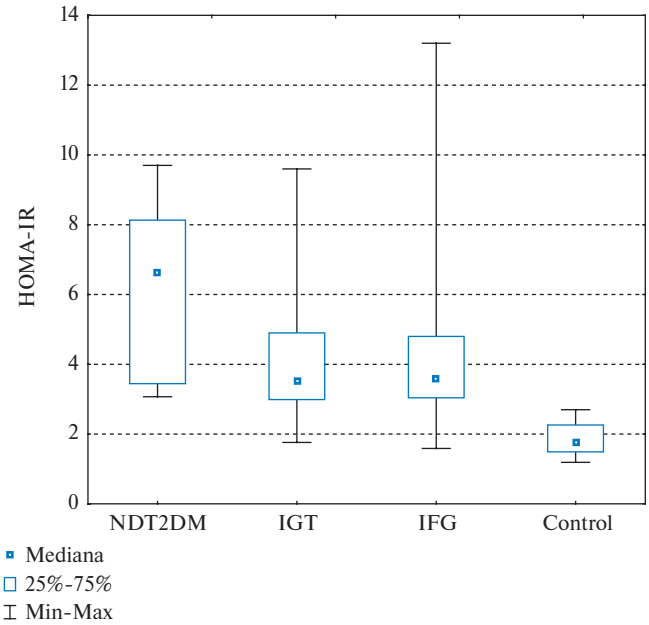

Figure 1. HOMA-IR in patients with ICE and in the control group.

of pre-diabetes and reached statistical significance in patients with ND T2DM (Figure 5).

The identified differences between the groups with regard to insulin-resistance patients with ICE, as well as their role in T2DM formation, we performed the corre-

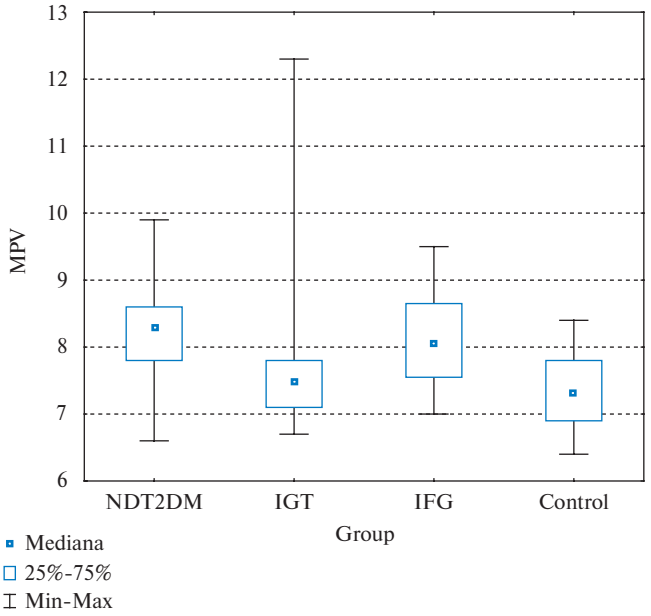

Figure 2. Mean platelet volume in patients with ICE and in the control group.

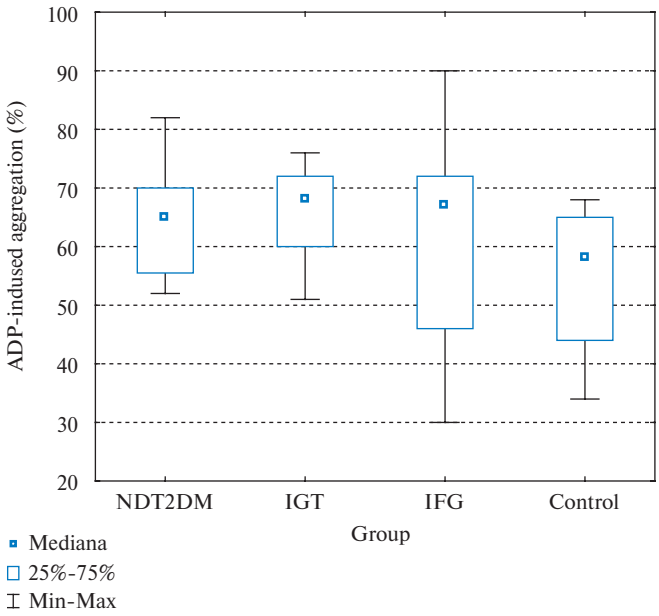

Figure 3. ADP-platelets aggregation in patients with ICE and in the control group.

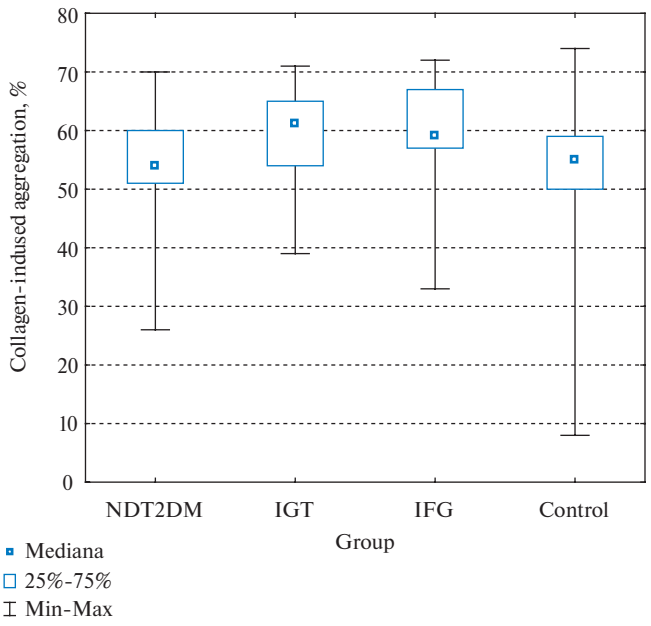

Figure 4. Collagen-indused aggregation in patients with ICE and in the control group.

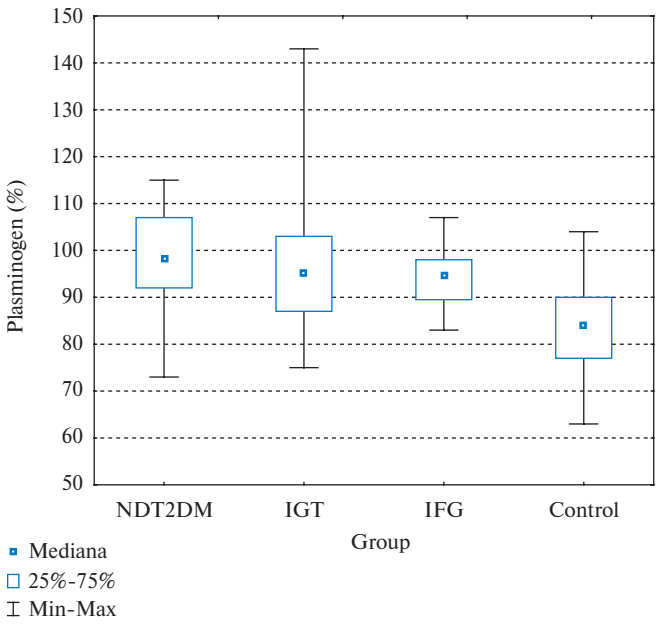

Figure 5. Plasminogen in patients with ICE in the control group.

lation analysis which revealed strong correlation between HOMA-IR and BMI, WC, fasting plasma glucose (FPG), triglycerides (Table 2), mean direct power with HOMA-IR and HbA_{1c}, TC, LDL, AST, ALT, and inverse between HOMA-IR and HDL, number of platelets. Comparing other investigated parameters of metabolism and hemostasis found that insulin had similar in character and expression of HOMA-IR correlation and weak positive connection of insulin concentration with MPV.

FPG demonstrated positive correlation of average strength with WC, HbA_{1c}, TC, LDL, TG, ALT, plasminogen, MPV and it showed inverse mathematical, but direct functional correlation with Activated Partial Thromboplastin Time (APPT). HbA_{1c} level moderately and directly correlated with BMI, WC, C-peptide, HOMA-IR, TC,TG, plasminogen, TC and TG with plasminogen, ADP-induced aggregation demonstrated positive moderate correlation with alpha 1- and beta 2- globulins and inverse correlation with albumins.

Table 2

Spearman's range correlation test

	BMI	WC	FPG	HbA_{1c}	Insulin	C-p	IR	TC	LDL	HDL	TG	AST	ALT	ADP	PLG	Platelet	MPV
FPG	0,50*	0,55*	1,00	0,54*	0,47*	0,66*	0,66*	0,46*	0,30*	-0,08	0,54*	0,17	0,33*	0,01	0,30*	-0,16	0,30*
HbA_{1c}	0,34*	0,34*	0,54*	1,00	0,23	0,39*	0,38*	0,29*	0,15	0,04	0,35*	0,05	0,22	0,15	0,35*	0,13	0,01
Insulin	0,68*	0,68*	0,47*	0,23	1,00	0,87*	0,86*	0,36*	0,30*	-0,37	0,65*	0,28*	0,50*	-0,00	0,19	-0,35*	0,28*
C-peptide	0,73*	0,77*	0,66*	0,39*	0,87*	1,00	0,88	0,43*	0,33*	-0,34	0,75*	0,31*	0,55*	0,03	0,30*	-0,31*	0,23
HOMA-IR	0,63*	0,67*	0,66*	0,38*	0,86*	0,88*	1,00	0,39*	0,31*	-0,27	0,64*	0,34*	0,47*	0,08	0,19	-0,31*	0,21
TC	0,26	0,39*	0,46*	0,29*	0,36*	0,43*	0,39*	1,00	0,91*	0,03	0,45*	0,05	0,21	0,10	0,28*	-0,13	0,06
LDL-CL	0,13	0,30*	0,30*	0,15	0,30*	0,33*	0,31*	0,91*	1,00	-0,16	0,30*	0,01	0,14	0,08	0,23	-0,14	-0,04
HDL-CL	-0,21	-0,36*	-0,08	0,04	-0,37*	-0,34*	-0,27*	0,03	-0,16	1,00	-0,38*	-0,10	-0,14	0,00	-0,06	0,15	0,03
TG	0,62*	0,73*	0,54*	0,35*	0,65*	0,75*	0,64*	0,45*	0,30*	-0,38*	1,00	0,18	0,45*	0,10	0,31*	-0,29*	0,24
Albuming/ L	-0,17	-0,26	0,04	0,01	0,03	-0,01	0,03	-0,13	-0,15	0,18	-0,22	0,22	0,13	-0,32*	-0,01	0,18	-0,19
alpha-1	0,13	0,02	0,15	0,11	-0,13	-0,04	0,05	-0,01	-0,04	0,03	0,03	-0,03	-0,11	0,45*	-0,26	0,02	-0,00
alpha-2	-0,01	-0,01	0,03	0,20	-0,24	-0,14	-0,13	0,27	0,15	0,44*	-0,06	-0,23	-0,25	0,20	0,07	0,23	0,18
beta-1	-0,07	0,15	0,07	0,23	0,10	0,16	0,10	0,35	0,35*	-0,02	0,19	0,07	0,09	0,02	0,28	-0,05	0,05
beta- 2	0,31*	0,14	-0,11	0,07	0,30*	0,22	0,22	0,28	0,35*	-0,06	0,19	-0,03	0,09	0,37*	0,16	-0,12	-0,01
gamma	-0,15	-0,23	-0,02	-0,10	0,06	-0,00	0,10	0,16	0,22	-0,08	-0,09	0,02	-0,03	0,09	-0,11	0,07	-0,04
APPT	-0,14	-0,19	-0,33*	-0,14	-0,02	-0,21	-0,15	0,02	0,13	0,07	-0,25	0,11	0,01	-0,06	-0,23	0,10	-0,12
Plasminogen	0,27*	0,31*	0,30*	0,35*	0,19	0,30*	0,19	0,28*	0,23	-0,06	0,31*	-0,08	0,00	0,05	1,00	-0,05	0,12
Platelet	-0,27*	-0,32*	-0,16	0,13	-0,35*	-0,31*	-0,31*	-0,13	-0,14	0,15	-0,29*	-0,21	-0,30*	-0,04	-0,05	1,00	-0,40
MPV	0,31*	0,31*	0,30*	0,01	0,28*	0,23	0,21	0,06	-0,04	0,03	0,24	-0,02	0,14	0,13	0,12	-0,40*	1,00

Annotation: the noted correlations are marked (*– p<0,05).

The correlation analysis noted the differences in the character and strength of correlation between metabolic and hemostatic parameters in the observed groups. In this way in the control inverse correlations were identified between HOMA-IR and HDL (r=-0,59, p<0,05), FPG et TC (r=-0,56, p<0,05). In addition there is no correlation between the parameters of metabolism and hemostasis in healthy patients, except for positive correlation between APTT and TC, LDL (r=0,55, r=0,76, respectively p<0,05).

In patients who have IFG, correlations lose their significant differences and are characterized by direct relationships between HOMA-IR and fasting plasma glucose (r=0,64, p<0,05), TG (r=0,82, p<0,05), LDL (r=0,81p<0,05), FPG and TG, LDL (r=0,71, r=0,70, respectively, p<0,05) and negative by relationships between FPG and ADP-induced platelet aggregation (r=-0,64, p<0,05), HbA_{1c} level positively correlates with fibrinogen and plasminogen (r=0,65, r=0,85, respectively, p<0,05).

In IGT subjects positive correlations are registered between HbA_{1c} and TG (r=0,52, p<0,05), APTT and TC, LDL (r=0,70, r=0,64, respectively, p<0,05) and negative correlations — between HbA_{1c} and MPV (r=-0,52, p<0,05), and also HOMA-IR and plasminogen (r=-0,67, p<0,05), number of platelets and their mean volume (r=-0,55, p<0,05).

ND T2DM is associated with a strong positive correlation between FPG and HbA1, TC (r=0,62, r=0,54, respectively, p<0,05), number of platelets and ADP, antithrombin III (r=0,57, r=0,69, p<0,05) and negative — between FPG and APTT (r=-0,56, p<0,05), TC and INR (International Normalized Ratio (r=-0,57, p<0,05), plasminogen and CT (r=-0,60, p<0,05).

Discussion

According to the results of our research, pre-diabetes and ND T2DM were diagnosed in the patients having excess body mass and WC. We did not find carbohydrate metabolism disorders among the participants of our research with excess BMI of 18,5-24,9 kg/m^2, women`s WC <88 cm, and men`s WC <102 cm. Hyperinsulinism, insulin resistance, increasing triglyceride concentration were observed in the patients with IFG, IGT and were maximally shown in patients with ND T2DM. TC level was significantly higher than standard indicators in IGT and ND T2DM, while elevated TC level in patients with IFG was not statistically significant.

Metabolic syndrome is characterized by dyslipidemia, high triglycerides in very low density lipoproteins and low HDL cholesterol. Hypertrygliceridemia in T2DM is associated with lower sensitivity of visceral fat tissue to the antilipolytic effect of insulin with boosted lypolises and the transport of free fatty acids into portal blood flow. In patients with hyperinsulinemia, these factors increase hepatic triglyceride synthesis and very low density lipoproteins synthesis of liver [10]. Under hyperglycemia the activity of endothelial lipoproteinlipasa decreases and that of hepatic lipoproteinlipasa increases, these processes being accompanied by suppressing triglycerides and by LDL catabolism by faster decomposing HDL cholesterol.

Therefore, changes of lipid profile are associated with insulin resistance, hyperinsulinemia and impaired carbohydrate exchange. We found close correlations between IMT, WC (reflecting the visceral fat mass) and HOMA-IR, FPG, TC, LDL, HDL, TG, corresponding to the current opinion about the role of metabolic syndrome in the development of T2DM and suggesting the presence of leading risk factors of atherosclerosis development at the earlier stages of overt T2DM [11,12].

Metabolic changes affect hemostasis. The absence of correlation between metabolic and hemostatic parameters in control and their presence in ICE patients show that biochemical changes play a key role in the initiating development hemostasis disorders.

According to "The IDF Consensus worldwide definition of the metabolic syndrome" (2006), the changes in fibrinolytic system (PAI etc) and coagulation (fibrinogen etc) are related to "Platinum standard" of the metabolic syndrome. In our research the tendency towards the increase of plasminogen level was found out in patients with IFG and IGT and was statistically significant in patients with ND T2DM. Strong correlations between HbA1c and plasminogen were observed in patients with IFG. The IGT stage demonstrates inverse mathematical, but direct functional correlation between insulin resistance and plasminogen. These direct correlations between plasminogen and concentration of FGP, TC, C-peptide, TG (Table 2) prove the multifactorial effect of the changed metabolic parameters on fibrinolysis. The obtained data can be explained by the results of the experimental studies, which showed that insulin and glucose participate in the regulation of plasminogen activator inhibitor-1 (PAI 1) gene expression as well as the effect of insulin on the synthesis of PAI-1 by a hepatocellular cell line [13,14]. According to Juhan-Vague and colleagues increased PAI-1 is a constituent of insulin resistance syndrome and adds thrombotic component into the traditional list of risk factors for atheromatosis. Triglycerides, LDL, and lower sensitivity of glycated plasminogen to pro-fibrinolytic enzymes with resistance to degradation are considered to be the other metabolic reasons changing fibrinolytic activity [15-16].

Hyperfibrinogenemia is considered to be an independent prognostic factor of atherosclerotic vascular disease [17]. Most studies on the hemostasis in patients with T2DM noted the mean increase of plasma fibrinogen concentration by 100 mg/dl.18 Although the elevated level of fibrinogen in all ICE-groups was not statistically significant, it showed strong correlations between HbA_{1c} and plasminogen in patients with IFG. Our data agree with the study results of Corrado and colleagues [18] who found a correlation between the duration of disease, concentration of glycated hemoglobin and fibrinogen increase. According to Dunn and colleagues [19], the formation of glycated fibrinogen leads to fibrin clots, which are resistant to plasmin. Therefore suppressing of fibrinolysis in T2DM, underlined by many authors, may be related to both the decrease of fibrinolytic potential and also to the changes in fibrinogen properties.

Platelets are rather vulnerable components of hemostasis in patients with ICE. 20 In addition, hyperinsulinemia, hyperglycemia and changes of lipid profile have a modulating effect on different levels of the platelet hemostasis.

The effect of chronic hyperglycemia on thrombocytopoesis brings about the appearance of large, young thrombocytic forms with high activity [21]. Increased glucose influx into megacariocytes significantly contributes to the increased thrombin-evoked depletion of cyclic nucleotides, and also increased activity of enzymes involved in glycolytic, acetyl-CoA synthesis, and fatty acid–synthesizing pathways [22]. Insulin also stimulates cell cycle and the processes of megakaryocytic cell-line differentiation [23]. The previously reported data about the influence of insulin and hyperglycemia on thrombocytopoiesis make possible to explain the tendency for the appearance in the blood flow of young, high-activity thrombocytic forms in patients with pre-diabetes as well as statistically significant increase of MPV in ND T2DM.

Chronic hyperglycemia leads to both the modulating effect on thrombocytopoiesis and the direct effect on platelets. Intracellular glucose concentration in a platelet is comparable with its extracellular concentration and associated with excessive formation of superoxide anion, protein kinase activity and decrease of NO [24]. The direct osmotic effect, i.e. exposition of platelets to hypertonic solution of glucose or mannitol solution during one hour is accompanied by activation of platelet glycoprotein IIb/IIIa and by release reaction of α-granules is considered to be another possible direct mechanism [25].

Low antiplatelet effect of insulin caused by its deficit or insulin resistance especially contributes to the development of platelet dysfunction in patients with T2DM. In vitro studies demonstrate that physiological concentrations of insulin have a direct inhibitory effect on platelet activity of healthy people. However, supraphysiological concentrations of the hormone and insulin resistance increase insulin-mediated platelet activity [26].

Platelet activity is also affected by lipid metabolizm disorders. The vast majority of experimental studies acknowledge the increase of platelet sensitivity to the aggregating agents in patients with atherogenic hyperlipidemia [27]. The previous reports show that cholesterol enrichment of membranes modifies platelet activity. Moreover they are associated with a 35-fold increase in sensitivity to epinephrine and 15-fold increase sensitivity to ADP and in higher sensitivity to collagen [28]. Acidity and microviscosity of platelet membrane are closely related to the concentration of plasma triglycerides. Dutu and colleagues [29] demonstrated the correlation between platelet adhesiveness and the level of free fatty acids in patients with hyperlipidemia. However, in the present

study we did not find the significant correlation between platelet activity and TC, TG concentration. Our findings are comparable with the findings of Jovan and colleagues [30] and can be explained by the changes in plasma fatty acid composition. Direct correlations between ADP-aggregation and concentration of beta2-globulines, identified in our study indirectly confirm the effect of changed lipid profile.

Hyperactive platelets initiate coagulation. A lot of data reported in literature confirm the activation of coagulation in patients with T2DM [31, 32]. Our study identified that changes in carbohydrate and lipid metabolism affect the coagulation system. According to the results of correlation analysis, the patients with IGT had close correlations between APPT and TC, and also between APPT and LDL. However, ND T2DM-patients had inverse mathematical but direct functional correlations between APPT and FPG, and between TC and INR. Nevertheless, biochemical analysis of the coagulogramms didn't identify any signs of coagulation. Shortened APPT in patients with ND T2DM and in patients with ICE in our study didn't reach statistical significance. The same results, showing the trend to activation of only some blood coagulation components in pre-diabetes, were reported by Maschrow and colleagues [33].

Thus, metabolic disorders that appear at the early stages of T2DM bring about changes in the hemostasis. Insulin resistance which is developed in people with visceral type of fat deposition in case of IGT and ITG is commonly accompanied by peculiar changes in carbohydrate metabolism and raised TC, TG concentrations. Metabolic disorders initiate non-significant changes in plasma and thrombocytic components of the hemostasis at the early stages of pre-diabetes. ND T2DM is associated with changes of lipid profile similar to pre-diabetes and 2-fold increase of insulin resistance in addition the increase of MPV and concentrations of plasminogen becomes statistically significant.

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INFLUENCE OF OXIDATIVE STRESS AND INFLAMMATION ON THE DEVELOPMENT OF ISCHEMIC HEART DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Aim. Ischemic heart disease (IHD) is the result of endothelial dysfunction, which is associated with inflammation, increased oxidative stress and hyperglycemia. The aim of our study was to examine the aetiology, importance and intensity of inflammation and oxidative stress in IHD development in patients with diabetes mellitus (DM) type 2.

Material and methods. We included 60 male patients with IHD of whom 30 with diabetes type 2. Control group comprised of 12 healthy participants. We analyzed the lipid status, quality of glycemic control (daily glycemia profile — MBG and HbA_{1c}), lipid peroxidation (malondialdehyde-MDA) and inflammation: high sensitivity C reactive protein (hsCRP), intercellular and vascular adhesion molecule-1 (ICAM-1, VCAM-1).

Results. Patients with DM type 2 and IHD were obese with higher levels of HbA_{1c} and MBG compared to other two groups. Systolic and diastolic blood pressure, triglycerides, total and LDL cholesterol were significantly higher and HDL was lower in all patients with IHD compared to the control group. CRP levels, ICAM-1, VCAM-1 and MDA were significantly higher in the groups with IHD compared to the control. MDA and VCAM-1 were higher in patients with IHD and type 2 DM than in patients with IHD. There was a significant positive correlation between hsCRP and LDL cholesterol in patients with IHD, regardless of the presence of DM. Significant positive correlation between VCAM-1 and HbA1c values, and between ICAM-1 and hsCRP were shown only in patients with IHD and DM type 2.

Conclusion. Inflammation, increased oxidative stress, lipid and metabolic disorders showed significant correlation and have an important pathogenic role in the development of IHD, particularly in patients with DM type 2. Increased levels of hsCRP, VCAM-1 and products of lipid peroxidation are characteristic markers of endothelial inflammation and indicators of the presence of atherosclerotic plaque in patients with DM type 2.

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Key words: diabetes mellitus, oxidative stress, inflammation, adhesion molecules.

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BMI — body mass index, CAM — cellular adhesive molecules, DM — diabetes mellitus, HbA1c — glycosylated haemoglobin, HDL — high density lipoprotein, hsCRP — high sensitivity C reactive protein, ICAM-1 — intercellular adhesion molecule-1, IHD — Ischemic heart disease, LDL — low density lipoprotein, MBG — daily glycemia profile, MDA — malondialdehyde, SAP — stable angina pectoris, TC — total cholesterol, UKPDS study — The United Kingdom Prospective Diabetes Study VCAM-1 — vascular adhesion molecule-1.

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САХАРНЫЙ ВЛИЯНИЕ ОКСИДАТИВНОГО СТРЕССА И ВОСПАЛЕНИЯ В РАЗВИТИИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Цель. Ишемическая болезнь сердца (ИБС) является следствием эндотелиальной дисфункции, которая связана с воспалением, повышением окислительного стресса и гипергликемии. Целью нашего исследования явилось изучение этиологии, значения и интенсивности воспаления и оксидативного стресса в развитии ИБС у больных сахарным диабетом (СД) 2 типа.

Материал и методы. Мы включили 60 пациентов мужского пола с ИБС, 30 из которых с СД 2 типа. Группу контроля составили 12 здоровых участников. Мы проанализировали липидный статус, качество гликемического контроля (ежедневный гликемический профиль — MBG и HbA_{1c}), перекисного окисления липидов (малонового диальдегида (MDA)) и воспаления: высокочувствительного С реактивного белка (hsCRP), межклеточные и сосудистые молекулы адгезии-1 (ICAM-1, VCAM-1).

Результаты. Пациенты с СД 2-го типа и ИБС, страдающие ожирением, имели более высокие уровни MBG и HbA_{1c}, по сравнению с двумя другими группами. Систолическое и диастолическое артериальное давление, уровень триглицеридов, общего холестерина и холестерина ЛПНП были достоверно выше, а уровень ЛПВП был ниже у всех больных с ИБС, по сравнению с контрольной группой. Уровни hsCRP, ICAM-1, VCAM-1 и мда были достоверно выше в группах с ИБС по сравнению с контролем. MDA и VCAM-1 были выше у пациентов с ИБС и СД 2-го типа, чем у пациентов с ИБС. Существует значительная положительная корреляция между hsCRP и холестерином ЛПНП у пациентов с ИБС, независимо от наличия СД. Значимая положительная корреляция между VCAM-1 и значениями HbA_{1c}, и между ICAM-1 и hsCRP было показано только у пациентов с ИБС и СД 2-го типа.

Заключение. Воспаление, увеличивается окислительный стресс, липидный и метаболических нарушений показал значимую корреляцию и играют важную патогенетическую роль в развитии ИБС, особенно у пациентов с СД 2-го типа. Повышенный уровень hsCRP, VCAM-1 и продуктов перекисного окисления липидов являются характерными маркерами эндотелиального воспаления и наличия атеросклеротической бляшки у пациентов с СД 2-го типа.

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Ключевые слова: сахарный диабет, окислительный стресс, воспаление, молекулы адгезии.

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The latest studies of atherosclerosis indicate that inflammatory response within the arterial wall is a significant pathogenic factor. The findings show that inflammation contributes to the occurrence of acute cardiovascular disease and it is also the key of initiation and progression of atherosclerosis. However, the characteristics of the inflammatory process in diabetes mellitus (DM) type 2 are still not completely elucidated considering the fact that this disease is characterized by the numerous pro-inflammatory, pro-oxidative and pro-coagulant risk factors. It is considered that hyper-cholesterolemia, hypertension, hyperglycaemia, obesity, hyperinsulinemia, decreasing concentration of estrogens and smoking are the main pro-inflammatory triggers. Initiation of this chronic inflammatory process starts with monocytes adhesion on endothelial surface due to adhesive molecules expressed on the endothelium [1]. Cellular adhesive molecules (CAM), primarily intracellular adhesive molecule-1 (ICAM-1) and vascular cellular adhesive molecule-1 (VCAM-1) are rarely manifested on endothelium in resting phase, and they are activated in the presence of inflammation and could be the indicators of endothelial activation or markers of an early stage of atherosclerosis [2]. This process can be caused by cascade of inflammatory reactions, which include monocytes, macrophages, T lymphocytes and smooth muscular cells. These cells and endothelium produce adhesive molecules, cytokines, growth factors, metalloproteinases which cause accelerated atherogenesis [1, 2].

The increase in CAM in conditions of hyperglycemia leads to accelerated and diffuse atherosclerosis through the increased intensity of oxidative stress, also. It is shown that in diabetes there is a hyper oxidative stress and a reduction of antioxidant protection [3]. The increase of oxidative modification of small and dense LDL particles, which are characteristic of diabetic dyslipidemia, is a key factor in the growth of the lipid core of atheromatous plaque. This process is facilitated not only by increased oxidative stress in the blood vessel wall, but also by reducing antioxidant protection and proinflammatory state. Therefore, in patients with type 2 DM the processes of oxidative modification of proteins and lipids peroxidation are especially enhanced. Oxidative stress affects the expression of many genes in endothelial cells, causing endothelial disfunction [4].

The aim of this study was to examine the connection between inflammation and pathogenic importance and intensity of oxidative stress in the development of ischemic heart disease in patients with diabetes mellitus type 2.

Material and methods

This study was conducted with respect to Good Clinical Practice guidelines and the Declaration of Helsinki. Local Ethic Committee approved the study protocol, and all participants before enrolment in the study signed informed consent.

In a prospective clinical cross-sectional study, 60 male patients with stable ischemic heart disease (IHD), ambulatory treated and 12 healthy male subjects were analyzed. The study did not include patients with acute and chronic inflammatory diseases, liver disease, microalbuminuria and those who had anti-inflammatory medications, vitamins and antioxidants in their treatment. In all patients, a detailed history was taken, complete medical records were obtained, blood pressure measured and body mass index (BMI) was calculated. All subjects were divided into three groups:

- group I — 30 patients with type 2 diabetes mellitus and ischemic heart disease;
- group II — 30 patients with ischemic heart disease without diagnosed diabetes mellitus type 2;
- group III — 12 healthy subjects in whom the examination excluded ischemic heart disease and diabetes mellitus.

Ischemic heart disease implied presence of stable angina pectoris (SAP), which is diagnosed based on the appearance of chest pain with characteristic quality provoked by the physical effort or emotional stress and which stops after rest and/or taking nitroglycerin lingualettes [5]. All patients had a positive stress test performed on ergobicycle with the increasing load on every 3 minutes for 25W until the indication for stopping the test emerged. Patients with angina at rest were excluded from the study.

The diagnosis of diabetes mellitus type 2 has been confirmed from the medical records.

In all groups, blood samples were taken from the cubital vein in the morning, before breakfast and before morning therapy. We performed a biochemical determination by plasma glucose analyzer "AXON" (Bayer Company). Glycaemia were expressed in mmol/L.

We took five capillary blood samples: during the morning, noon, evening (fasting), and postprandial, 2 hours after breakfast and lunch. The mean value of the daily glucose profile (MBG) was obtained by calculating the average value of all five measurements, and expressed in mmol/L.

Glycosylated haemoglobin (HbA1c), high sensitivity C-reactive protein (hsCRP), total serum cholesterol (TC), triglycerides, HDL and LDL cholesterol values were measured on the machine Dimension Xpand using Dade Behring reagents.

Lipid peroxidation was determined by measuring malondialdehyde (MDA) levels, as one of the final products of lipid peroxidation by the method of Andreev et al. MDA at high temperature under acidic conditions with the addition of thiobarbituric acid (TBA) and ferrous ion creates pink coloration. Absorption chromogen was measured at 532 nm. MDA concentrations were expressed in μmol/L.

Adhesion molecules (ICAM-1 and VCAM-1) were measured by ELISA method using commercial test by

Table 1

Clinical and laboratory characteristics of the included groups

Parameters	IHD+DM type 2	IHD	Control
Number	30	30	12
Years	54,5±5	56±6	52±6
sysTA(mmHg)	146±12[(a,b)]	130±16[(a)]	104±5
diaTA(mmHg)	93±7[(a)]	88±12[(a)]	73±6
BMI(kg/m^2)	30,5±3,6[(a,b)]	25,3±2,1	24±1
MBG(mmol/l)	12,1±2,9[(a,b)]	6,4±1	6,1±1
HbA_{1c} (%)	8,9±1[(a,b)]	5,2±1	5±1
Triglycerides (mmol/l)	3,3±1,1[(a)]	2,79±0,7[(a)]	1,73±0,36
Cholesterol (mmol/l)	8,5±1,56[(a,b)]	6,3±1,6[(a)]	5,2±1,1
HDL Cholesterol (mmol/l)	0,95±0,26[(a)]	1,1±0,5[(a)]	1,35±0,37
LDL Cholesterol (mmol/l)	6,1±1,56[(a,b)]	4,2±1,8[(a)]	3,3±1,1
Family history of IHD n(%)	16 (53)[(b)]	26 (86)	3 (25)[(b)]
Smoking n (%)	14 (46)[(b)]	29 (96)	4 (33)[(b)]
Therapy n (%)			
Nitrates	48 (80)	34 (56)	-
Beta blockers	34 (56)	26 (44)	2 (13)
Ca antagonist	10 (16)	22 (36)	1 (7)
ACE inhibitors	26 (44)	24 (40)	3 (27)
Statins	10 (16)	14 (24)	-
Aspirin	43 (72)	26 (44)	-

Annotation: ANOVA test and *post hoc* Tukey HSD analysis or Chi2 test: [a] — p <0,05 vs. healthy subjects, [b] — p <0,05 vs. group with IHD.

Abbreviations: IHD — ischemic heart disease, DM type 2 — diabetes melitus type 2.

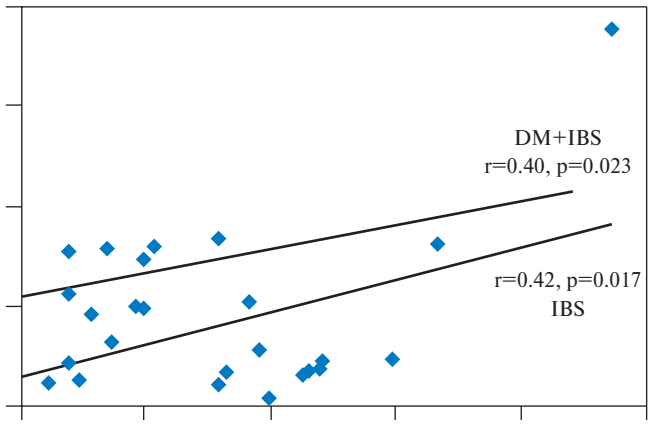

Figure1. Correlation between CRP levels and the protective HDL cholesterol in patients with IHD.

Beckman Coulter Company on Bio-Systems propeller Rider. The results were expressed in ng/mL. For VCAM-1 measurement range was 0-25 ng/mL and sensitivity was 0.74 ng/mL. Accordingly, for ICAM-1 measurement range was 0-16 ng/mL with sensitivity of 0.1 ng/mL.

Statistical analysis were performed in Excel 7.0 and SPSS 11.0 in Windows XP environment using standard descriptive methods (mean, standard deviation, percentage) and appropriate analytical tests depending on the type and size of the sample (Student's t test, chi-square test, ANOVA test and post hoc analysis Tukey HSD test, Pearson's correlation coefficient).

Table 2

The oxidative and inflammatory parameters in groups

Parameters	IHD+DM type 2	IHD	Control
MDA (μmol/l)	16,47±5,84[(a,b)]	13,42±4,01[(a)]	8,24±2,8
hsCRP (mg/l)	4,2±2,5[(a)]	4,1±2,1[(a)]	3,2±1,8
ICAM-1 (ng/ml)	707,4±145,1[(a)]	699,2±125,6[(a)]	543,4±86,6
VCAM-1 (ng/ml)	971±172,2[(a,b)]	823,4±97,6[(a)]	784,9±99,2

Annotation: ANOVA test and *post hoc* Tukey HSD analysis or Chi2 test: [a] — p <0,05 vs. healthy subjects, [b] — p <0,05 vs. group with IHD.

Abbreviations: IHD — ischemic heart disease, DM type 2 — diabetes melitus type 2.

Results

The main characteristics of examined groups are shown in Table 1. Patients with DM type 2 and IHD had significantly higher body mass index (BMI) compared to the patients with IHD without DM and with healthy examinees (p<0,05). HbA_{1c} and MBG levels were significantly higher in patients with DM type 2 and IHD compared to other two groups (p<0,05). Other characteristics of the groups: systolic and diastolic blood pressure, triglyceride and LDL cholesterol values were significantly higher, while HDL was significantly lower in the groups of patients with IHD compared to the control group (p<0,05) (Table 1).

Inflammatory markers (hsCRP, ICAM-1, and VCAM-1) and indicator of the intensity of oxidative stress (MDA) were significantly higher in the groups of patients with IHD, regardless of the presence of DM type 2, compared to the group of healthy examinees (p<0,05). MDA and VCAM-1 values were significantly higher in patients with IHD and DM type 2 compared to the patients with IHD without DM (p<0,05) (Table 2).

Inflammatory and oxidative stress markers, together with lipid and metabolic risk factors, showed positive correlation with hsCRP and LDL cholesterol values, in the groups of patients with IHD regardless of the presence of DM (p<0,05) (Figure 1). Significant positive correlation of VCAM-1 and HbA1c values was found, and the ICAM-1 values correlated with the concentration of hsCRP only in the group of patients with IHD and DM type 2 (p<0,05) (Figure 2 and 3). Similar correlations were not found in the group of healthy examinees.

Discussion

Atherosclerosis is a disease with a great number of risk factors, which accelerate atherogenesis with its cumulative activities. It is considered that in the core of this process, is endothelial dysfunction connected with the inflammation and increased intensity of oxidative stress in the blood vessel wall [1].

Disturbed composition and concentration of lipid in diabetes mellitus type 2 is called diabetic dyslipidemia, and

has all characteristic of dyslipidemia in metabolic syndrome, since both are characterized by insulin resistance. Mentioned disorders are reflected in low values of HDL cholesterol, increase of concentration of total cholesterol due to high LDL cholesterol, presence of postprandial lipemia and hypertriglyceridemia [6]. Our findings in patients with IHD are in accordance with the mentioned study.

Modern understanding of the pathogenesis of atherosclerosis includes inflammatory component in its development. Today, it is considered that this inflammatory process of arterial wall is a consequence of different stimuli. Increased levels of adhesion molecules ICAM-1 and VCAM-1, and hsCRP in patients with IHD are reported by many authors [7]. Accordingly the similar results are obtained in our study. It is known that the concentration of adhesion molecules varies, depending on the stage and the presentation of coronary atherosclerosis. VCAM-1 levels are good markers of activity of the atherosclerotic process, and they are the highest in acute coronary syndromes, while the lowest values are registered in patients with stable angina pectoris. Levels of ICAM-1 molecules are good markers of the presence of developed atherosclerotic lesions and they do not vary significantly compared to the clinical manifestation of coronary atherosclerosis. Usually, both adhesion molecules have significantly higher concentrations in patients with IHD compared to the healthy population [8]. Our findings are in line with those observations (Table 2).

Mechanism of increase in cellular adhesion molecules (CAM) levels can be attributed to hyperglycemia, hyperinsulinemia, oxidative stress, and inflammation and insulin resistance [9]. Therefore, the level of CAM cannot be observed only as a marker of activation of endothelial cells, accelerated adherence and activation of leukocytes, but also as a marker of increased oxidative stress, inflammation and metabolic disorders. This is in accordance with significantly higher VCAM-1 values in patients with IHD and DM type 2, compared to the patients with IHD without DM (Table 2) and we demonstrated positive correlation of VCAM-1 with HbA1c values (Figure 2). All this indicates the importance of metabolic disorders in the development of endothelial dysfunction and accelerated atherogenesis, which is pointed out by other authors [10]. Correlation is found between ICAM-1 and hsCRP concentrations (Figure 3). This connects the presence of developed atherosclerotic lesion with inflammatory disorders in patients with DM type 2 [11].

Lipid peroxidation level measured by the MDA concentration was the highest in patients with DM type 2 and IHD. It was also higher in the group of patients with IHD regardless of the presence of diabetes mellitus compared to the control group (Table 2). Diabetic patients have increased lipid peroxidation which is associated with hyperglycemia and increased risk for IHD. Inflammation,

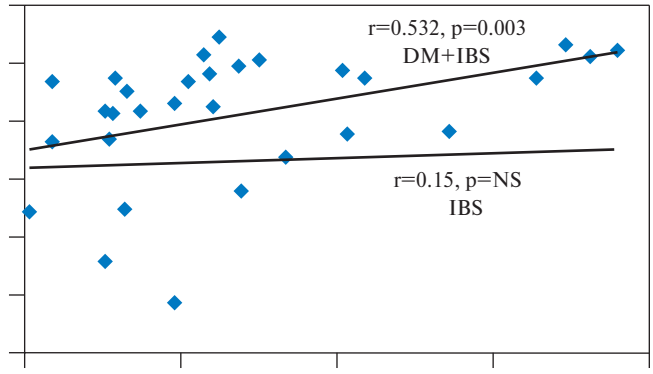

Figure 2. Positive correlation between VCAM-1 and HbA1c in patients with IHD and DM type 2.

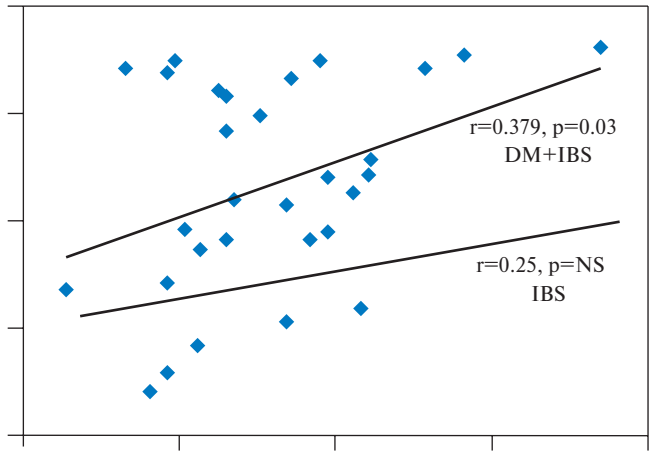

Figure 3. Correlation between ICAM-1 and CRP in the examined groups of patients.

oxidation of LDL particles and increase in CRP are caused by the increase of LDL cholesterol and decrease of HDL with the fall of paraoxonase activity due to the inhibition of paraoxonase 1 by the lipid peroxide [12, 13]. Having in mind the importance of this anti-inflammatory enzyme for the production of CRP it is possible to explain the close connection between diabetes, oxidative stress and inflammation in development of endothelial dysfunction and pathogenesis of atherosclerosis [14]. This was shown in our study by connecting LDL cholesterol and hsCRP concentrations in all patients with IHD.

Direct connection of hyperlipidemia with increased values of hsCRP and CAM is the evidence of noteworthy relation between lipid disorders, endothelial dysfunction and inflammation. The importance of lipid disorders in patients with DM type 2 is exceptionally demonstrated by the fact that decreased HDL and increased LDL have stronger prognostic significance for the occurrence of cardiovascular diseases than the value of hyperglycemia in the UKPDS and other studies [15].

Conclusion

Inflammation, increased level of oxidative stress, lipid and metabolic disorders have significant connection and

have an important pathogenic role in the development of ischemic heart disease, particularly in patients with diabetes mellitus type 2. Increased levels of hsCRP, VCAM-1 and products of lipid peroxidation are markers of endothelial inflammation and indicators of the presence of atherosclerotic plaque in patients with DM type 2. Since these patients have increased risk for cardiovascular diseases, continuous prevention and aggressive treatment of these disorders is required in order to prevent the formation of severe clinical manifestations of atherosclerotic disease.

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THE IMPACT OF INDOOR CYCLING TRAINING ON EXERCISE CAPACITY AND BLOOD LIPID PROFILE OF MEN WITH ISCHAEMIC HEART DISEASE OR AFTER MYOCARDIAL INFARCTION

Dagmara Gloc, Zbigniew Nowak

Aim. In the present study attempts to determine the impact of 1-month Indoor Cycling training on exercise capacity and blood lipid profile were made.
Material and methods. The study group consisted of 50 men under the model A of the 2nd phase of cardiac rehabilitation (20 men of the *Indoor Cycling* group, IC, 20 men rehabilitated accordingly to the recommendations of the Polish Cardiac Society — a standard group, ST and 10 people who did not participate in any cardiac rehabilitation program — a control group, C). The average age of all subjects was 56,60±8,25 years, the average left ventricular ejection fraction was 56%±4,00.
Results. In the IC group there was a significant increase in the test duration (8,47 vs 10,23 min; p<0,001), a significant increase in the MET value (10,86 vs 12,35; p=0,06) and VO_2max (38,43 vs 48,25 ml/kg/min; p<0,001). Parallel changes were observed in the ST group, where the following parameters improved: the test duration (8,51 vs 9,96; p<0,001), MET value (10,57 vs 12,18; p=0,002) and VO_2max (38,42 vs 46,24; p<0,001). No significant changes in rest and maximum heart rate as well as systolic and diastolic blood pressure parameters were found. In C group no significant changes in treadmill exercise test parameters were observed. Alike in the IC, ST as well as in the C group, positive modification of blood lipid profile was observed. The significant increase in the average value of HDL cholesterol in the control group (41,00 vs 49,52 mg/dl; p<0,05) was only found.
Conclusion. *Indoor Cycling* training in the second phase of cardiac rehabilitation is a safe form of therapy and therefore may be an interesting alternative method to the classic bicycle ergometer exercise in the stage of an early cardiac rehabilitation.

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Key words: comprehensive cardiac rehabilitation, coronary heart disease, Indoor Cycling, Percutaneous Coronary Intervention, physical activity, myocardial infarction.

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CABG — coronary artery bypass grafting, CHS — cardiac health status, PCI — percutaneous coronary intervention.

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ВЛИЯНИЕ ВЕЛОСПОРТИВНЫХ ТРЕНИРОВОК НА ТОЛЕРАНТНОСТЬ К ФИЗИЧЕСКОЙ НАГРУЗКЕ И ЛИПИДНЫЙ СПЕКТР КРОВИ У МУЖЧИН С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА ИЛИ ПОСЛЕ ИНФАРКТА МИОКАРДА

Dagmara Gloc, Zbigniew Nowak

Цель. В настоящем исследовании предпринята попытка определения влияния 1-го месяца велоспортивных тренировок на толерантность к физической нагрузке и липидный профиль крови.
Материал и методы. Исследовательская группа состояла из 50 человек проходила испытания по модели А 2-го этапа кардиологической реабилитации (20 человек группа велоспортивных тренировок (IC), 20 мужчин проходили реабилитацию соответственно рекомендациям польского кардиологического общества — стандартная группа (ST), группа 10 человек, которые не принимали участия ни в сердечной программе реабилитации — контрольная группа, C). Средний возраст всех испытуемых был 56,60±8,25 лет, средняя фракция выброса левого желудочка составляла 56%±4,00.
Результаты. В IC группе наблюдалось значительное увеличение продолжительности испытания (8,47 против 10,23 мин; p<0,001), значительное увеличение значения MET (10,86 против 12,35; p=0,06) и VO_2max (38,43 против 48,25 мл/кг/мин; p<0,001). Параллельно наблюдались изменения в ST группе, где показатели улучшились: длительность теста (8,51 против 9,96; p<0,001), значения MET (10,57 против 12,18; p=0,002) и VO_2max (38,42 против 46,24; p<0,001). Не было обнаружено значительных изменений показателей в покое, максимальной частоты сердечных сокращений, а также систолического и диастолического артериального давления. В группе C никаких существенных изменений в на тредмиле не наблюдалось. Как в IC, так и в ST, а также в группе C, положительных изменений липидного профиля крови не наблюдалось. Было отмечено значительное увеличение среднего значения холестерина ЛПВП в группе контроля (41,00 против 49,52 мг/дл; p<0,05).
Заключение. Велоспортивные тренировки на втором этапе кардиологической реабилитации являются безопасной формой терапии и, следовательно, могут быть интересной альтернативой методу классической велоэргометр-велотренажер в стадии ранней кардиологической реабилитации.

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Ключевые слова: комплексная реабилитация сердца, ишемическая болезнь сердца, езда на велосипеде, чрескожное коронарное вмешательство, физическая активность, инфаркт миокарда.

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The most commonly used, yet traditional training forms according to the Cardiac Rehabilitation Standards of Polish Cardiac Society, are aerobic (endurance) training in the form of walking on the treadmill or in the field, bicycle ergometer training, swimming, training on the bicycle, and anaerobic training (anaerobic resistance training) [1, 2]. Physical training, which is introduced in the second stage of cardiac rehabilitation, is well understood and described, but rare publications on the use of modern, innovative forms of exercises for patients with cardiovascular diseases can be found. Younger age of the cardiac patients somehow necessitates the use of modern forms of physical training, which become alternative, interesting and engaging means to provide effective reha-

Table 1

Characteristics of the *Indoor Cycling*, standard and control group

Variable	Indoor Cycling group (n=20)	Standard group (n=20)	Control group (n=10)
Age [years]	57,50±9,51 (39-72)	56,40±9,85 (40-70)	55,40±8,25 (46-67)
Body height [cm]	178±5,46 (168-191)	176,40±5,95 (164-190)	174,90±8,03 (164-190)
Body weight [kg]	84,15±9,35 (70-104)	87,02±14,08 (66,90-117,90)	81,15±16,27 (63,40-117,30)
BMI [kg/m^2]	26,58±2,61 (21,20-32,60)	27,84±3,20 (22,80-34,60)	26,29±3,32 (22,60-32,50)
LVEF [%]	56,05±3,91 (50-60)	56,10±4,19 (50-68)	55,70±4,00 (50-62)

Abbreviations: BMI — body mass index, LVEF — left ventricular ejection fraction, n — the number of patients.

Table 2

The type of diseases in the *Indoor Cycling*, standard and control group

Type of disease	Indoor Cycling group n (%)	Standard group n (%)	Control group n (%)
Ischemic heart disease	20 (100%)	20 (100%)	10 100%)
Type 2 diabetes	4 (20%)	5 (25%)	2 (20%)
Hyperlipidemia	6 (30%)	3 (15%)	0 (0%)
Hypertension	16 (80%)	17(85%)	8 (80%)
Miocardial infarction	16 (80%	16 (80%)	5 (50%)
Total	*20 (100%)*	*20 (100%)*	*10 (100%)*

Abbreviation: n — the number of patients.

Table 3

The method of treatment in the *Indoor Cycling*, standard and control group

Method of treatment	Indoor Cycling group n (%)	Standard group n (%)	Control group n (%)
PCI + STENT	16 (80%)	17 (85%)	8 (80%)
PCI	4 (20%)	3 (15%)	2 (20%)
Total	20 (100%)	20 (100%)	10 (100%)

Abbreviations: n — the number of patients, PCI — percutaneous coronary intervention/

bilitation [3]. One such form is endurance *Indoor Cycling* training. Properly conducted training consists of a warm-up, an appropriate training and an end portion — cool down and stretching, which concerns proper muscle groups and tendons. *Indoor Cycling* training can be carried out in three basic positions of the hands (open, close and forward), in sitting or standing techniques [4]. There are no reports on the possibilities of the use of *Indoor Cycling* as an alternative form to the traditional endurance cycle ergometer training of patients with cardiovascular diseases.

Table 4

The number of stents implanted in the *Indoor Cycling*, standard and control group

Number of stents	Indoor Cycling group n (%)	Standard group n (%)	Control group n (%)
0	4 (20%)	3 (15%)	2 (20%)
1	12 (60%)	10 (50%)	5 (50%)
2	1 (5%)	5 (25%)	3 (30%)
3	1 (5%)	1 (5%)	0 (0%)
4 and more	2 (10%)	1 (5%)	0 (%)
Total	*20 (100%)*	*20 (100%)*	*10 (100%)*

Abbreviation: n — the number of patients.

Table 5

The protocol of the *Indoor Cycling* training unit

Part of the training session	Time (min)	Borg scale	RPM	Position / technique
Warm-up	1-5	9-10	100-110	Position 2 (2½min) Position 1 — SF (2½ min)
Appropriate training	5-10	12-13	110 110 80	Position 1 (2 min) Position 2 (2 min) Position 2 — SC (1min)
	10-17,5	12-14	80 100-110 100 80-100 100	Position 3 — StC (½ min) Position 1 (2½ min) Position 2 (2½ min) Pozycja 2 — StF (½ min) Position 1 (1 min)
	17,5-22,5	13-14	60-80 100 80	Position 2 — SC (1min) Position 2 (3½ min) Position 3 — StC (½ min)
	22,5-27,5	12-13	80 80 100-110	Position 2 (2 min) Position 2 — SC (2 min) Position 2 (1 min)
Cool down	27,5-30	9-10	100	Position 1 — SF
Stretching	30-35	9	-	-

Abbreviations: min — minute, position 1 — close, position 2 — open, position 3 — forward, RPM — Revolutions Per Minute, SC — Seated Climb, SF –Seated Flat, StC — Standing Climb, StF — Standing Fl at.

In the present study attempts to determine the impact of 22 *Indoor Cycling* training units (1-month) on exercise capacity and blood lipid profile were made.

Material and methods

The study group consisted of 50 men under the model A of the second phase of cardiac rehabilitation (results of exercise treadmill test ≥7 MET or 100 W). Groups were comparable in terms of age, body height, body weight and left ventricular ejection fraction. Their characteristics are shown in Table 1. 100% of patients experienced ischemic heart disease, 74% of them had a myocardial infarction (Table 2). The prevailing type of treatment in the study population was percutaneous coronary intervention (PCI) combined with implantation of 1 stent (Table 3 and 4).

Table 6

Methodology of training according to the recommendations of the Section of Cardiac Rehabilitation and Physiology Effort Polish Cardiac Society

The type of training	Methodology	Workload
Endurance training	Training on a bicycle ergometer, 5 times a week 30 minutes	The workload applied on the basis of calculation of heart rate training, starting from 60% of heart rate reserve increased by 10% after 5 units of training, to 80% of heart rate reserve, 14 degrees of subjective scale effort assessment by the Borg scale
Resistance training	Exercises in the form of training station, 5 times a week 30 minutes	
General exercises	Exercises in the gym — elements of aerobic and anaerobic training, stretching, breathing exercises, 5 times a week 30 minutes	

Between November 2014 and January 2015, reducing the number of confounding factors such as age, sex, disease entity, method of treatment, the level of exercise capacity, 50 patients enrolled in the study were allocated according to random selection into the three groups: 20 men, members of the *Indoor Cycling* group, IC, 20 men rehabilitated accordingly to the recommendations of the Section of Cardiac Rehabilitation and Physiology Effort Polish Cardiac Society — a standard group, ST and 10 people who did not participate in any cardiac rehabilitation program — a control group, C). Patients (except from the C group) underwent 22 training units performed 5 times a week. In the ST group the training included: endurance exercise on a bicycle ergometer, resistance training and calisthenics (general exercises). Whereas men in the IC group, instead of the traditional interval training on the ergometer, participated in the *Indoor Cycling* lessons arranged by the same instructor (Table 5). That group also participated in the other two types of trainings (resistance and calisthenics) according to the standards (Table 6). Heart rate frequency was constantly individually monitored during each lesson by the heart rate monitor (Polar FT1), as well as by the instructor.

Inclusion criteria were: formal consent to participate in the study, stable coronary heart disease or uncomplicated course of myocardial infarction, time of last cardiovascular event not less than 2 months and not more than 6 months, an exercise test results ≥7MET / 100W, left ventricular ejection fraction ≥50%. Exclusion criteria were: lack of formal consent to participate in the study, recent myocardial infarction, <2 months of a cardiovascular event, left ventricular ejection fraction <50%, the surgical treatment of coronary artery disease (CABG), unregulated hypertension, unstable ischemic heart disease, arrhythmias, diagnosed cancer, diseases of the central or peripheral nervous system, varicose veins of the lower limbs, degenerative disease of the peripheral joints and spine, past unhealed injuries of the lower limbs, advanced peripheral vascular disease, age ≥75 and incomplete medical documentation.
At the beginning and after 1-month in all groups submaximal exercise treadmill test according to the standard Bruce protocol was performed. The exercise test was terminated in case of a limit heart rate, fatigue, high blood pressure over 230/120 mmHg, ST-segment depression of at least 2 mm, coronary pain and blood pressure drop above 10 mmHg from baseline. Behind a positive exercise test criterion adopted horizontal or diagonal to the bottom depression of ST-segment at least 1 mm measured 80ms after the J point. The following parameters were evaluated: duration of the test exercise [minute], MET value, resting and maximum heart rate [beats/minute], resting and maximum blood pressure [mmHg], resting and maximum double product [mmHg × min], maximal oxygen uptake VO_2max [ml/kg/min] due to the lack of directly measure instruments, the indirect method was appointed by the formula:

$$VO_2max = 13,3 - 0,03(t) + 0,297(t^2) - 0,0077(t^2) + 4,2(CHS)$$

where: t — time [min]

CHS (cardiac health status) — 1: patients with angina pectoris, myocardial infarction, revascularization, 0: patients without symptoms of angina, without a completed myocardial and without revascularization procedures performed) [5].

At the beginning and after 1-month total cholesterol, HDL and LDL fractions and triglycerides [mg/dl] were also analyzed. The assessment of blood lipid profile was made in the analytical laboratory.

The study was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the local Committee of Ethics of the Academy of Physical Education in Katowice — Poland (The Resolution No. 6/2014 of 15.05.2014). Written informed consent was obtained from all participants prior to their inclusion in the study.

For all numerical parameters the arithmetic mean, minimum, maximum and standard deviation were calculated. For the presentation of qualitative data the prevalence of studied traits were used. In order to verify assumptions of tests the Shapiro-Wilk normality test was performed. For the analysis of relationships between variables

Table 7

Results of the treadmill exercise test in three groups of patients before (I) and at the end (II) of cardiac rehabilitation

Variable	Indoor Cycling group (n = 20)	p	Standard group (n = 20)	p	Control group (n = 10)	p
Time I Time II Δ [min]	8,47±1,22 10,23±1,66 1,76***	0,000	8,51±0,89 9,96±1,12 1,45**	0,000	8,76±1,11 8,27±1,40 -0,49	0,815
MET I MET II Δ	10,86±1,20 12,35±1,43 1,50##	0,006	10,57±0,95 12,18±1,42 1,62##	0,002	11,06±2,31 10,00±1,68 -1,06	0,433
HRrest I HRrest II Δ [beats/minute]	65,55±9,06 69,40±10,31 3,85	0,454	72,10±9,15 69,40±9,73 -2,70	0,790	78,60±7,09 76,40±4,99 -2,20	0,975
HRmax I HRmax II Δ [beats/minute]	123,50±14,99 131,15±13,37 7,65	0,169	124,75±14,69 131,65±14,20 6,90	0,264	132,20±15,88 132,80±8,95 0,60	0,999
RRSrest I RRSrest II Δ [mmHg]	127,00±15,59 126,25±13,16 -0,75	0,999	125,00±13,96 126,50±9,88 1,50	0,996	129,00±12,64 138,50±16,50 9,50	0,298
RRDrest I RRDrest II Δ [mmHg]	81,00±8,52 80,00±10,26 -1,00	0,994	78,75±6,66 78,00±5,23 -0,75	0,998	77,50±7,16 79,00±9,66 1,50	0,992
RRSmax I RRSmax II Δ [mmHg]	167,25±18,60 172,00±18,45 4,75	0,762	152,50±19,15 157,00±17,50 4,50	0,800	161,00±15,42 171,50±20,00 10,50	0,309
RRDmax I RRDmax II Δ [mmHg]	85,25±9,38 83,50±9,33 -1,75	0,954	82,75±8,50 81,00±7,18 -1,75	0,954	84,50±7,61 85,00±11,05 0,50	0,999
DPrest I DPrest II Δ	8355,50±1790,45 8734,25±1418,03 378,75	0,917	9055,50±1785,57 8798,00±1532,69 -257,50	0,983	10164,50±1530,31 10626,00±1685,71 461,50	0,954
DPmax I DPmax II Δ	20693,75±3563,36 22577,25±3475,53 1883,50	0,067	19171,00±3909,31 20643,00±2950,12 1472,00	0,247	21204,00±2601,58 22779,00±3139,70 1575,00	0,550
VO_2max I VO_2max II Δ [ml/kg/min]	38,43±6,24 48,25±9,97 9,82&&	0,000	38,42±4,34 46,24±6,54 7,81&&	0,000	39,75±5,55 37,54±6,12 -2,21	0,921

Annotations: all data are presented as means ± standard deviation and the difference (Δ — delta). *** — 0,000 IC vs C, ** — 0,003 ST vs C, ## — 0,007 IC vs C and 0,004 ST vs C, && — 0,001 IC vs C and 0,008 ST vs C.

Abbreviations: p — level of statistical significance (p ≤0,05 for the lowest accepted), DPmax — maximum double product, DPrest — resting double product, HRmax — maximum heart rate, HRrest — resting heart rate, MET — metabolic equivalent, RRDmax — maximum diastolic blood pressure, RRDrest — resting diastolic blood pressure, RRSmax — maximum systolic blood pressure, RRSrest — resting systolic blood pressure, VO_2max — maximal oxygen uptake, n — the number of patients.

ANOVA Kruskall-Wallis analysis was used. Assessing the relevance between arithmetic's the Tukey post hoc test was made. The obtained data was statistically analyzed by Statistica 12 (StatSoft), assuming a statistically significant result with a value of p≤0,05.

Results

The Table 7 shows results of the treadmill exercise test in the three groups of patients before (I) and at the end (II) of cardiac rehabilitation. Compared to the initial result in the field of treadmill exercise test parameters in the IC group there was a significant increase in the test duration (8,47 vs 10,23 min; p<0,001), a significant increase in the MET value (10,86 vs 12,35; p=0,06) and VO_2max (38,43 vs 48,25 ml/kg/min; p<0,001). Parallel changes were observed in the ST group, where the following parameters improved: the test duration (8,51 vs 9,96; p<0,001), MET value (10,57 vs 12,18; p=0,002) and the rate of VO_2max

Table 8

Results of the blood lipid profile in three groups of patients before (I) and at the end (II) of cardiac rehabilitation

Variable	Indoor Cycling group (n=20)	p	Standard group (n=20)	p	Control group (n=10)	p
TC I TC II Δ [mg/dl]	172,12±38,80 160,60±30,13 -11,51	0,339	173,59±36,44 158,77±26,95 -14,82	0,113	184,30±32,59 177,70±13,65 -6,60	0,961
HDL I HDL II Δ [mg/dl]	46,35±13,11 50,11±12,79 3,75	0,312	46,84±11,79 49,09±13,81 2,25	0,808	41,00±12,29 49,52±13,95 8,52	**0,018**
LDL I LDL II Δ [mg/dl]	108,05±29,91 97,02±24,69 -11,03	0,399	97,17±31,79 88,22±24,96 -8,95	0,626	126,60±22,59 110,40±12,60 -16,20	0,357
TG I TG II Δ [mg/dl]	118,05±40,11 111,12±26,02 -6,93	0,931	122,79±50,17 115,78±39,46 -7,01	0,928	138,30±50,53 135,10±36,16 -3,20	0,999

Annotations: all data are presented as means ± standard deviation and the difference (Δ — delta).

Abbreviations: p — level statistically significant (p≤0,05 for the lowest accepted), HDL — high density lipoprotein, LDL — low density lipoprotein, TC — total cholesterol, TG — triglycerides, n — the number of patients.

(38,42 vs 46,24; p<0,001). No significant changes in rest and maximum heart rate as well as systolic and diastolic blood pressure parameters were found. In C group no significant changes in treadmill exercise test parameters were observed.

The analysis also showed significant differences in Δ results between groups (Δ of test duration between IC, S and C group, MET value as well as in VO_2max).

Table 8 presents the results of the blood lipid profile in three groups of patients before (I) and at the end (II) of cardiac rehabilitation. Alike in the IC, ST as well as in the C group, positive modifications of blood lipid profile — a reduction of total cholesterol level and triglycerides were observed. Preferable changes in the total cholesterol fractions — HDL and LDL were also noted. Besides the significant increase in the average value of HDL cholesterol in the control group (41,00 vs 49,52 mg/dl; p<0,05), another changes in the lipid profile of the groups were not statistically significant.

Discussion

Results presented in this study reveals the positive influence of application new, alternative strategy of the *Indoor Cycling* training on men with ischemic heart disease or after myocardial infarction. To our knowledge, this study shows for the first time in the literature the use of this type of physical activity in cardiology patients. Predominantly, in the literature attention is paid to improving exercise tolerance by the influence of standard forms of physical training in patients after myocardial infarction — improvement of the treadmill test time and distance, increase in MET value [6].

Analysis of obtained results before and after the *Indoor Cycling* training shows its positive effect on physical capacity in patients. After training a significant increase in exercise capacity took place. In the final test in both groups of patients underwent cardiac rehabilitation parallel values of test duration, MET value and VO_2max were reported. Similarly, after 1-month of cardiac rehabilitation results were significantly improved in comparison with no rehabilitated group of patients. Maximum and resting heart rate, as well as maximum and resting systolic and diastolic blood pressure not changed significantly. No significantly changes of the treadmill exercise test were reported in control group.

In 2001 Belardinelli et al. analyzed the impact 6-month exercise training on functional parameters and quality of life of patients after PTCI or after applying stent. Patients were divided into two groups — practicing exercises (correspond to 2nd stage of cardiac rehabilitation and included training on the ergometer three times a week) and those who prefer sedentary lifestyle, with the recommendation of irregular physical activity. The authors showed insignificant decrease in resting heart rate and a slight increase in peak heart rate in both groups. The mean systolic blood pressure were significantly (p<0,01) decreased in the training group (128 vs 122 mmHg), while in the group without the elements of regular physical activity systolic blood pressure significantly increased (125 vs 131 mmHg; p<0,01). In our analysis, in turn, showed no significant difference in resting and maximum systolic and diastolic blood pressure which can be associated with shorter period of our observation. Moreover, authors highlighted, that only trained patients had significant improvements in

VO_{2peak} (18,6 vs 23,7 ml/kg/min; p<0,001), which is consistent with our test results [7]. After the comprehensive cardiac rehabilitation sessions maximal oxygen uptake increased significantly only in participants, which confirms that only primarily programmed and systematic program of physical activity can contribute to positive changes in capacity. The same conclusion was reached in 2010 Korzeniowska-Kubacka et al. who analyzed the effect of 4,5-month exercise training on diastolic function of the left ventricle in 32 after myocardial infarction (16 men refused to participate — a control group) treated with percutaneous coronary intervention with preserved systolic function and mild diastolic dysfunction of the left ventricle. Authors observed a significant increase in the maximum consumption of oxygen in training group from 26,66 to 28,79 ml/kg/min; p<0,0001 and no significant change in this parameter in the control group (26,23 vs 26,34 ml/kg/min) [8].

In 2013 Paduch also noted the positive impact of 23-days cardiac rehabilitation (an A model of the 2nd stage) on exercise capacity of patients after myocardial infarction. Author assessed, VO_2max which after rehabilitation program differ significantly from the result achieved prior to the initial test (52,50 vs 57,48; p<0,01). Correspondingly, author received a significant improvement in MET value (8,57 vs 8,68; p<0,01). The author received a significant increase in maximal heart rate (128,14 vs 128,85 beats/minute; p<0,05) and time of test duration (670,42 vs 707 s; p<0,001), as well as reduction of maximal diastolic blood pressure (88,57 vs. 85,71 mmHg; p<0,001). No significant changes in resting heart rate, resting systolic and diastolic, maximal systolic blood pressure were revealed [9].

In 2012 Ranković et al. investigated the effects of aerobic exercise training on cardiovascular parameters, lipid profile and endothelial function in seventy patients during second phase of cardiac rehabilitation with stable coronary artery disease. Authors divided patients into the two groups: the group I — 33 patients with coronary artery disease and with regular aerobic training for 3 weeks in the center and 3 weeks after that in their home setting, and the group II (control) — 37 patients with ischaemic disease and sedentary lifestyle. Exercise training consisted of continual aerobic exercise for 45 minutes on a treadmill, bicycle ergometer or walking, three times a week. Authors noted that physical training induced significant reduction of systolic and diastolic blood pressure and heart rate after 6 weeks of cardiovascular rehabilitation (p<0,05). Such positive modifications were not registered in the control group. In patients with moderate aerobic physical training significantly lower heart rate was registered after a 6-week follow-up compared to the group with sedentary lifestyle (p<0,05). Authors highlighted that moderate aerobic physical training reduced systolic and diastolic blood pressure. In our observation we do not find significantly alterations in these parameters [10].

In 2009 Toufan and Afrasiabi evaluated effects of cardiac rehabilitation in 65 patients (50 males and 15 females) on functional capacity, maximum heart rate on exercise treadmill test and serum lipid profile. All of patients practiced aerobic training on bicycle or treadmill 30-40 minutes, 3 times a week for 8-12 weeks. After rehabilitation program 83% of patients improved their functional capacity — MET value increased from 8,7 to 10,8; p<0,001. Also mean time of the tolerance exercise test improved from 7,76 to 9,56 minutes; p<0,001. Average left ventricular ejection fraction was 41% before program and in 72% of patients slightly improved. Alterations obtained by the authors are similar to ours. Maximal heart rate in 72% of patients decreased and in the rest of the population was unchanged or increased [11].

In our study the blood lipid profile was also analyzed. Before analysis, the total cholesterol, triglycerides, as well as the HDL fraction were normal in all of groups. Only in the control group the level of LDL cholesterol significantly different from the reference values.

The mechanism of regular physical activity of the LDL reduction, HDL cholesterol increased and lowering triglycerides most likely associated with an increased sensitivity to insulin, which enhances the expression of lipoprotein lipase in adipose tissue and skeletal muscle of physically active people [12]. Physical exercise may include a decrease in triglycerides and increase HDL level but little specific effect is seen in LDL cholesterol and total cholesterol (TC) [12]. The described changes in the blood lipid profile are important for the prevention and treatment of cardiovascular diseases, including coronary heart disease [13]. High HDL levels acts protectively [12] — an inverse relationship between HDL serum and the risk of coronary artery disease was demonstrated [14]. In this work, except for positive, significantly modification of the HDL fraction in control group, no noteworthy changes of the blood lipid profile were found.

Mentioned before Belardinelli et al. also made the blood lipid profile analysis of cardiac patients. In patients undergoing physical training value of total cholesterol significantly decreased from 235 to 212 mg/dl, as well as the LDL cholesterol 148 vs 131 mg/dl (both changes in the level of p<0,001) and the value of TG (178 vs 155 mg/dl; p=0,02). HDL cholesterol in turn increased but not significantly (34 vs 39,2 mg/dl). In our study results were no significantly different after 1-month of patients practiced the *Indoor Cycling* training, which can be caused by to short time of observation (in opposite to 6-months of Balardinelli et al. However, among patients who did not practice regular physical activity after 6 months a significant increase in total cholesterol in blood serum (225 vs 255 mg/dl; p<0,001), LDL cholesterol (138 vs 148 mg/dl; p<0,001) and TG (181 vs 189 mg/dl) were noted. HDH fraction of cholesterol decreased from 32 to 28 mg/dl. Significant changes between two groups occurred in the total cholesterol and LDL values (p<0,001) [8].

Quoted above Ranković et al. also investigated lipid profile and they noticed that effects of a 6-week cardiovascular rehabilitation on lipid parameters were visible in a significant reduction in triglycerides and significant increase in HDL cholesterol concentration ($p<0,05$). The concentrations of triglycerides were significantly lower and HDL cholesterol significantly higher after in the exercise training group as compared to sedentary patients ($p<0,05$). Conclusions obtained by authors are different from our findings, which can caused by shorter follow-up time and lower population in our study [10].

Toufan and Afrasiabi in their study also received significant improvement in plasma lipid profile. Total cholesterol and LDL reduced in 75% of patients as well as triglycerides in 95% of population during the rehabilitation program. Findings obtained by the authors are consistent with ours. [11].

In 2009 Damijan, in turn, analyzed the possibility of applying vibration training in cardiac rehabilitation. The author studied changes in total cholesterol level in blood serum and HDL cholesterol in 24 students, healthy subjects. The analysis showed that in 76% of population the total cholesterol significantly reduced from 4,53 to 4,30 mmol/l ($p=0,044$), and 76% of study population HDL cholesterol significantly increased from 1,26 to 1,33 mmol/l ($p=0,038$). According to the author insignificant decrease in patients' triglycerides (1,149 vs 0,980 mmol/l) is valuable in terms of prevention of atherosclerosis as an independent risk factor [15].

Our study presents some limitations that are worth to be highlighted. For instance relatively small number of patients. Additionally, we investigated only men patients between 39-72 years which can be the most important factor of disturbing results. In fact, groups were similar to each other in characteristics. Finally, study lasted only 1-month, which is a short period of time to achieve stable changes in the physical performance and blood lipid profile of cardiology treated patients.

Conclusion

This study adds an important piece of evidence to the substantiation for exercise training in patients with coronary artery disease or after myocardial infarction. Study reports, that *Indoor Cycling* training can improve exercise capacity, have a favorable effect on blood lipid profile. *Indoor Cycling* training in the second phase of cardiac rehabilitation in patients with ischemic heart disease or after myocardial infarction is a safe form of therapy and therefore may be an interesting alternative method to the classic bicycle ergometer exercise in the stage of an early cardiac rehabilitation.

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NONLINEAR ANALYSIS OF HEART RATE DYNAMICS DURING RECOVERY FROM FLEXIBLE POLE EXERCISE INTERVENTION

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Aim. Evaluated the acute effects of exercise with flexible pole on complex behavior of heart rate variability (HRV).
Material and methods. We investigated 32 healthy female volunteers aged between 18 and 25 years who executed a session of exercise with flexible pole. HRV was analyzed 10 minutes before and, 10 minutes' post-exercise. We then applied five entropic measures and Poincaré plot directly to the RR-intervals of the electrocardiographic signal.
Results. Sample entropy was significantly decreased during recovery from exercise with flexible pole (0,8329±0,1111 vs. 0,6568±0,1959; p<0,0001). The Poincaré plot indicated reduced dispersion of RR intervals after exercise, indicating reduced HRV.
Conclusion. Exercise with flexible pole was able to acutely reduce chaotic behavior of heart rate dynamics measured by Sample Entropy alone. Care should be practiced when applying this exercise protocol to patients with cardiac diseases and/or abnormalities.

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Key words: cardiovascular system, autonomic nervous system, cardiovascular physiological phenomena, rehabilitation, physical and rehabilitation medicine, exercise therapy.

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HRV — heart rate variability, ANS — autonomic nervous system.

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НЕЛИНЕЙНЫЙ АНАЛИЗ ДИНАМИКИ ЧАСТОТЫ СЕРДЕЧНЫХ СОКРАЩЕНИЙ ВО ВРЕМЯ ВОССТАНОВЛЕНИЯ ПОСЛЕ УПРАЖНЕНИЙ С ГИБКИМ ШЕСТОМ

Ana M. S. Antonio[1], David M. Garner[2], Rodrigo D. Raimundo[3,4], Letícia S. de Oliveira[1], Luiz Carlos de Abreu[3,4], Marcelo T. Navega[5], Vitor E. Valenti[1]

Цель. Оценить непосредственное действие упражнений с гибким шестом на сложное поведение вариабельности сердечного ритма (ВСР).
Материал и методы. Мы исследовали 32 здоровых женщин-добровольцев в возрасте от 18 до 25 лет, которые исполняли сеанс тренировки с гибким шестом. ВСР анализировали за 10 минут до и через 10 минут после тренировки. Затем мы применили пять измерений энтропии и гипотезу Пуанкаре напрямую к РР-интервалам ЭКГ сигнала.
Результаты. Энтропия образца была значительно снижена во время восстановления от физических упражнений с гибким шестом (±0,8329 0,1111 и 0,6568±0,1959; p<0,0001). Гипотеза Пуанкаре указывает на снижение дисперсии интервалов RR после тренировки, указывающих на снижение ВСР.
Заключение. Упражнение с гибким шестом может уменьшить хаотическое поведение в динамике сердечного ритма и измеряется энтропией образца. Использование протокола тренировок для пациентов с заболеваниями сердца и/или иными отклонениями должно получить практическое применение.

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Ключевые слова: сердечно-сосудистая система, вегетативная нервная система, сердечно-сосудистые физиологические феномены, реабилитация, физическая и реабилитационная медицина, ЛФК.

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Autonomic changes during recovery from exercise provides important information that may not be identified at rest [1]. The physiological response of the autonomic nervous system (ANS) to exercise is characterized by initial parasympathetic withdrawal and subsequent increase in sympathetic activity. Following exercise, the parasympathetic reactivation is involved in recovery of heart rate to the basal level [2, 3].

Heart rate variability (HRV) is a simple, inexpensive, non-invasive and reliable measurement of heart rate autonomic regulation. Here we apply the algorithms directly to the RR-intervals derived from the PQRST-waveform of the signal [4].

Exercise with a flexible pole is a useful physiotherapy intervention for upper limb rehabilitation. Hitherto, its acute effects on cardiac autonomic regulation are unclear.

A very recent study revealed that an acute session of flexible pole exercise induced significant changes in heart rate autonomic modulation [5], however, others found no significant change [6, 7]. Investigation of autonomic responses to exercise with flexible pole has relevant information for planning rehabilitation protocols in patients with cardiovascular disorders, since heart rate responses during recovery from exercise provides information regarding risk for cardiovascular events and sudden death [8].

In this sense, non-linear analysis of heart rate dynamics provides qualitative measurement of cardiovascular physiology and the susceptibility to "dynamical disease" [9] states while linear measurement of HRV is limited [4]. Previously, studies which applied geometric measures and linear indices [10] or chaotic global techniques [11] on HRV during recovery from exercise with flexible pole have so far proven inconclusive. Thus, we evaluated the acute effects of exercise with flexible pole on complex behavior of HRV through five entropic measures. These are enforced directly onto the RR-intervals with no power spectral step as is the case with chaotic global methods [12, 13]. The techniques used here were Approximate [14], Sample [15], Shannon [16], Multiscale Renyi [17] and Multiscale Tsallis [18] entropies.

Material and methods

Study Population. To determine the sample size *a priori* knowledge was required, based on Moreno et al. [19], a sample size of 18 participants was stipulated by a test of hypothesis (two-tail), with 5% level of significance and 80% power.

This study consisted of 32 healthy female student subjects, all nonsmokers, aged 19,8±1,6 years old, height 1,62±0,004 m, mass 58,8±10 kg and body mass index (BMI) of 22,2±3,7 kg/m^2. All volunteers were informed about the procedures and objectives of the study and gave written informed consent. All study procedures were approved by the Ethics Committee in Research of the Faculty of Sciences of the UNESP, Campus of Marilia (No. 0554-2012), and were in accordance with Resolution 466/2012 National Health 10/10/1996.

Subjects under the following conditions were excluded: body mass index (BMI) >35 kg/m^2; systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg (at rest); reported cardiovascular, respiratory, endocrine and reported neurological disorders or any condition that did not allow the volunteers to perform the procedures. Subjects under medication that influence the ANS were not included. Volunteers were not evaluated on 10-15 days and 20-25 days after the first day of the menstrual cycle [20]. We also excluded physically active subjects according to the International Physical Activity Questionnaire (IPAQ) [21].

Initial Evaluation. Baseline information included: age, gender, mass, height and body mass index (BMI). Mass was determined using a digital scale (W 200/5, Welmy, Brazil) with a precision of 0,1 kg. Height was established using a stadiometer (ES 2020, Sanny, Brazil) with a precision of 0,1 cm and with 220 cm of extension. BMI was calculated as mass / height^2, with mass in kilograms and height in metres.

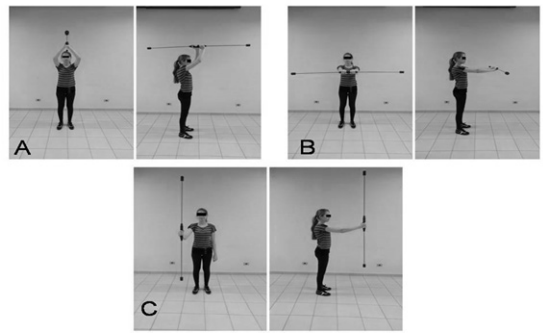

Figure 1. The exercise protocol was composed by the following exercise with both arms on three positions: I) with shoulders at approximately 180° of flexion with the flexible pole on the frontal plane, parallel to the ground (Figure 1A), II) with the shoulders on 90° of flexion with the flexible pole on the transverse plane (Figure 1B), and III) one shoulder at 90° of flexion with the flexible pole on the sagittal plane, perpendicular to the ground (Figure 1C).

Exercise with flexible pole. The flexible pole is an apparatus with a mass of 0,8 kg and of approximately 150 cm length. The flexible pole provides oscillations induced by movements of the upper limbs. Exercise protocols using the flexible pole have been proven to present positive results in shoulder muscle function training [22].

The flexible pole exercises were undertaken (Figure 1) with volunteers at standing position with feet apart (wide base) and shoulder flexion as the proposed position. To maintain the proper shoulder flexion in each upper limb it was used as a target visual feedback with a metronome to oscillate the pole (5 Hz). All exercises were performed for 15 seconds with 50 to 60 seconds of rest between each exercise. Three repetitions were performed for each exercise [11].

HRV analysis. We enforced procedure from Task Force guidelines [23]. Instantaneous RR intervals (RRi) were recorded with a digital telemetry system (Polar® RS800CX; Polar Electro Oy, Kempele, Finland). This system detected ventricular depolarization, corresponding to the R wave on the electrocardiogram, at a sampling rate of 1000 Hz, providing a temporal resolution of 1 millisecond for each RR interval and was previously validated [24]. The Polar heart rate device consisted of' an elastic band and two electrodes worn by the volunteer around the chest, at the level of the xiphoid process just below the pectoralis muscles according to the manufacturer guidelines. To ensure proper signal detection, water was placed on the front two electrodes of the chest strap. RR intervals were then downloaded to the Polar Precision Performance program (v. 3.0, Polar Electro, Finland). The software enabled the visualization of HR and the extraction of a cardiac period (RR interval) file in "txt" format. Following digital filtering complemented with manual filtering for the elimination of artefacts, which were replaced by linear interpolation of adjacent beats, 500 (short-term) stable RR intervals were applied for the data analysis. Only series with more than 95% sinus rhythm were included in the study [23, 25].

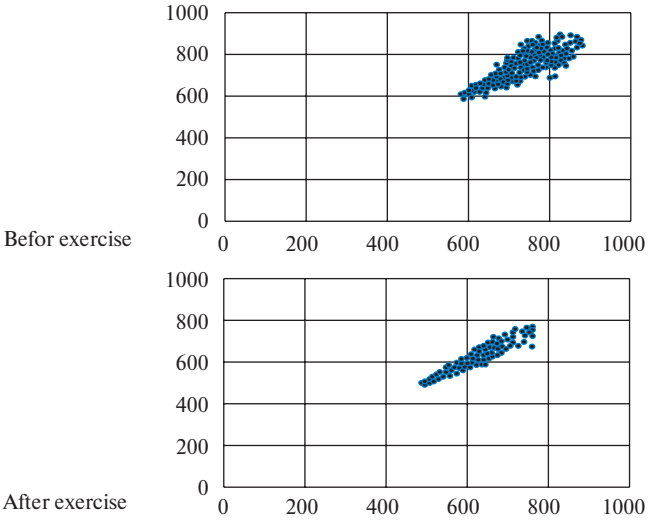

Figure 2. Visual pattern of Poincaré plot observed in one subject before exercise and after exercise.

HRV was analysed in the following periods: control protocol — the 10-minute period before the performance of the exercises and the 10-minute period after the performance with flexible pole — the recovery phase.

Protocol. Data collection was undertaken in the same soundproofed room for all volunteers. The temperature was between 21°C and 25°C and, the relative humidity was between 50% and 60%. Volunteers were instructed not to consume alcohol, caffeine or other ANS stimulants for 24 hours before the evaluation. Data was collected on an individual basis, always between 18:00 and 21:00 to standardize circadian influences. All procedures necessary for the data collection were explained to each subject separately, and the subjects were instructed to remain at rest and avoid talking during the collection.

Poincaré plot. The plot was qualitatively analysed by HRV analysis software based on the figures formed by its attractor. The expected shapes were described by Tulppo et al [26] as:

1) Figures in which an increase in the dispersion of RR intervals is observed with increased intervals, characteristic of a normal plot.

2) Small figures with beat-to-beat global dispersion without increased long-term dispersion of RR intervals.

Shannon Entropy. Entropy is a benchmark of the disorder in dynamical systems, a statistical complexity measurement derived from information theory. Generally, entropy as a measure of lack of knowledge is useful in many situations. For conditions where the connection with physical temperature is unimportant, the Boltzmann's constant can be removed. This normalisation gives us the Shannon entropy [27].

Entropy-based techniques are routinely employed in analysis of medical data especially cardiovascular [29, 30], respiratory [31, 32] and neurological signals [33, 34]. A low entropy dataset is highly predictable — whereas a high entropy dataset is less predictable. Accordingly, high entropy is more disordered. All entropies are numerically expressed between zero and unity with zero being the lowest disorder.

In contrast to Tsallis and Rényi entropies (see below); Shannon entropy is additive. Consequently, if the probabilities can be factorised into independent factors, the entropy of the joint process is the sum of the entropies of the separate processes.

Multiscale Rényi Entropy. The order-q Rényi entropies are a series of entropy like quantities. Here we set the value, entropic order, α to 0.25, 0.35, 0.45, 0.55, 0.65, 0.75. Where α=1 the function is the Shannon entropy and when α=2 it is the squared entropy. When α is varied this provides the multi-scale measure; α=0 is simply the logarithm of *n*. As α is increasing the measures become more sensitive to the values occurring at a higher probability and less to those at a lower probability.

Multiscale Tsallis Entropy. Tsallis entropy is a generalization of the standard Shannon-Boltzmann-Gibbs entropy. It was introduced as a basis for generalizing the standard statistical mechanics. Here we set entropic index, *q* to 0.25, 0.35, 0.45, 0.55, 0.65, 0.75. Where *q*=1 it is the Shannon-Boltzmann-Gibbs entropy.

Approximate Entropy. Approximate entropy is the logarithmic ratio of component wise matching sequences from the signal length, *N*. Other relevant parameters involve *r* which we set to 0.2 of the standard deviation based on factors of the signal that is being analysed and compared to. The factor *m*, is the length of sequences compared which we set to window of 2. It is measured as an integer count of discrete time bins. A minimum value of zero for Approximate entropy would indicate a fully predictable series. Approximate entropy is described algorithmically in Hornero et al [35].

Sample Entropy. It is important to consider Approximate entropy and Sample entropy together as similar mathematical functions. Comparisions with fixed *m, r,* and *N*. *N* is the length of the time series and *m* is the length of the sequences to be compared whereas *r* is the tolerance for accepting matches. As with Approximate entropy in this study we set *r* to 0.2 of the standard deviation. The factor *m*, is the length of sequences compared which we set to window of 2. Again the algorithm for Sample entropy is discussed in Hornero et al [*35*].

Results

The visual analysis through the Poincaré plot illustrated that RR intervals dispersion reduced immediately after exercise with flexible pole (Figure 2).

Normalization of the data is required to decide the necessary statistical test of significance to apply. Here, we applied the Anderson-Darling [36] and Lilliefors tests [37]. The Anderson–Darling test for normality applies an empirical cumulative distribution function. The Lilliefors test is suitable when the number of subjects is low. Here, there are only 32 subjects in each cohort. The results from both tests

Table 1

Mean values, standard deviation and p-value of significance for the five entropic measures

Entropic Parameter	Mean ± SD	Mean ± SD	ANOVA1	Kruskal-Wallis
	Pre (n=32)	Recovery (n=32)	(p-value)	(p-value)
Approximate	0,9091±0,0779	0,8346±0,2294	0,0871	0,2243
Sample	0,8329±0,1111	0,6568±0,1959	<0,0001*	<0,0001*
Shannon	0,7612±0,1089	0,7286±0,1200	0,2595	0,1379
Rényi α=0,25	0,9922±0,0039	0,9910±0,0043	0,2215	0,1452
α=0,35	0,9900±0,0050	0,9884±0,0056	0,2209	0,1415
α=0,45	0,9881±0,0059	0,9861±0,0067	0,2204	0,1415
α=0,55	0,9864±0,0068	0,9842±0,0075	0,2199	0,1415
α=0,65	0,9850±0,0075	0,9825±0,0084	0,2195	0,1415
α=0,75	0,9837±0,0081	0,9810±0,0091	0,2190	0,1379
Tsallis q=0,25	0,7870±0,0980	0,7574±0,1082	0,2551	0,1379
q=0,35	0,7864±0,0983	0,7567±0,1085	0,2551	0,1379
q=0,45	0,7853±0,0987	0,7555±0,1090	0,2552	0,1379
q=0,55	0,7836±0,0995	0,7536±0,1098	0,2553	0,1379
q=0,65	0,7811±0,1006	0,7507±0,1110	0,2557	0,1379
q=0,75	0,7774±0,1021	0,7466±0,1127	0,2563	0,1379

Annotation: the table below shows the mean values, standard deviation and p-value of significance for the five entropic measures for normal subjects and subjects recovering from flexible pole exercises related to RR-intervals. The number of RR-intervals was 500; and after tests of normality ANOVA1 and Kruskal-Wallis tests of significance were applied. For Multiscale Rényi and Multiscale Tsallis entropy the values we calculated were for six values of entropic order and entropic index. For Approximate entropy and Sample entropy (m=2 and r=0,2). Both statistical tests are significant for Sample Entropy at (p<0,0001); where * is highly significant.

were inconclusive. Accordingly, both the parametric one-way analysis of variance; (ANOVA1) and the non-parametric Kruskal-Wallis [38] tests of significance must be applied. Dissimilarities would be considered weakly significant when the probability of a type I error was less than 5% (p<0,05). Further significance is achieved at the level of the probability of a type I error was less than 1% (p<0.01) (Table 1).

Discussion

For cardiovascular and, HRV responses in particular, flexible pole exercise performance has been explored previously in the time and frequency domain indices [10, 11]. Traditional linear analysis of HRV did not find statistically significant responses induced by flexible pole exercise in women, suggesting well-being and safety when performing this exercise [7, 10].

Here, we investigated HRV through entropic analysis and reported the presence of levels chaotic behavior of HRV before and immediately after a 10 minute session of exercise with the flexible pole. Statistical significance was achieved with the Sample entropy algorithm. Since there is only one significant parameter the multivariate techniques [39] applied in similar studies [40] is not required. In this context, our findings do not support the cardiac autonomic safety of flexible pole exercise as previously recommended based on linear HRV indices [8, 10].

This measurement is useful for assessments of the intensity of physiotherapy and rehabilitative treatment required in such patients; and their future susceptibility to cardiovascular irregularities and "dynamical diseases" when undergoing the protocol.

Sample entropy presented in our study is proposed to quantify the entropy rate of short- to mid-length RR intervals, it indicates the complexity of HRV. Small values of Sample entropy are associated to more regular, predictable, processes. Conversely, the greater the complexity, the more physiologically adapted the organism [41].

According to our results, the Sample entropy has decreased when recovering from flexible pole exercises, indicating reduced chaotic behavior during this phase.

This technique which can assess the level of chaotic response to exercise is useful in determining the intensity of the physiotherapy intervention and the risk from cardiovascular pathology and "dynamical diseases" generally in subjects undergoing the protocol.

Contrariwise, Shannon, Multiscale Rényi, Multiscales Tsallis and Approximate entropies measurements were not significantly changed by flexible pole exercise.

Previous investigations also examined HRV responses to the same exercise protocol with flexible pole. De Oliveira et al [7], investigated HRV 30 minutes after exercise with flexible pole. Time and frequency domain and geometric indices of HRV were not significantly changed compared to control rest before exercise.

Dos Santos et al [6], failed to find significant responses of time and frequency domain indices of HRV in women submitted to a single session of exercise with flexible pole. The authors analyzed the initial 60 minutes during recovery from exercise.

However, Ogata et al [5], reported significant heart rate dynamics change induced by flexible pole exercise in healthy men. A decline was reported in parasympathetic heart rate modulation immediately after the exercise protocol, which continued for the initial 10-15 minutes during recovery from exercise.

We may postulate that the difference between studies in men [5] and women [6, 7] is due to increased muscle mass

in men, which may be involved in more intense mechanoreflex responses.

Our data suggests a diminished complex response of heart rate dynamics followed flexible pole exercise, which were not previously detected by linear indices of HRV [6, 7, 10]. In this way, nonlinear HRV evaluated through global chaotic analysis displayed reduction in chaotic behavior immediately after exercise with flexible pole [11], which reinforces our outcomes. Further studies are necessary to investigate the chronic effects of this exercise protocol.

Application of flexible pole exercises has been extensively applied in rehabilitation and physiotherapy clinics. Despite that, there are few scientific studies supporting its effectiveness. Knowledge of the feasibility of its use can provide greater safety in patients with neurological, cardiac and metabolic disorders undergoing the treatment. The application of the protocol in young adults and the lack of research in this area could be a opinion addressed in this study. However, we evaluated only females in order to avoid gender related effects.

Conclusion

An acute session of exercise with a flexible pole reduced the chaotic behavior of heart rate dynamics assessed through the technique Sample Entropy. We suggest that clinicians take care when using this treatment protocol in patients presenting with cardiovascular disorders.

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MULTISLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY IN PATIENTS WITH ANGINA PECTORIS

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Aim. Multislice computed tomography (MSCT) is a non-invasive method for the heart and coronary arteries imaging.
The aim of the research was to establish the diagnostic exactness of MSCT in the revelation of significant coronary artery disease in patients with angina pectoris, using digital subtraction angiography (DSA) of coronary arteries as the gold standard.
Material and methods. In 78 (56 men, 22 women; average age 64,3±11 years), patients with clinical signs of angina pectoris were done examination of the coronary arteries on 64-slice MSCT in order to detect significant stenoses (>50% luminal narrowing). MSCT of coronary arteries was compared with the invasive coronary angiography.
Results. In 78 patients, 864 segments of coronary arteries were available for evaluation. In all segments of coronary arteries, invasive coronary angiography identified 51 lesions. Forty-five lesions were detected by MSCT. The matching sensitivity and specificity were 88% and 97%. Sensitivity, specificity and positive and negative predictive values in a patient-per-patient analysis were 93%, 93%, 90%, and 96%, respectively.
False-negative results — Seventeen segments of coronary arteries with diameter reduction in range 51% to 75% were missed on the MSCT scan. The major of the missed lesions were located in the left anterior descedenting artery and the left circumflex artery (small side branches). Four segments were missed because of severe calcifications and five because of motion artifacts.
False-positive results — Thirty nine segments were incorrectly classified as significantly because of overestimation.
Conclusion. MSCT coronary angiography is an effective, fast, reliable and non-invasive method for the analysis of the coronary arteries. The best results were obtained in patients with healthy coronary arteries (high percentage of negative predictive value), which can significantly reduce the number of invasive coronary angiography. With the improvement of technical characteristics, CT is gaining more importance in the analysis of coronary stenoses and analysis of atherosclerotic plaque.

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Key words: MSCT coronary arteries, DSA coronary arteriography, angina pectoris.

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DSA — digital subtraction angiography, MSCT — multislice computed tomography, VR — volume rendering, DSCT — dual source computed tomography.

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МУЛЬТИСПИРАЛЬНАЯ КОМПЬЮТЕРНАЯ ТОМОГРАФИЯ-КОРОНАРОГРАФИЯ У БОЛЬНЫХ СО СТЕНОКАРДИЕЙ НАПРЯЖЕНИЯ

Ilić S. Dragana, Jankovic Sonja

Цель. Мультиспиральная компьютерная томография (МСКТ) представляет собой неинвазивный метод визуализации сердца и коронарных артерий. Целью исследований было установить диагностическую точность МСКТ в выявлении существенных изменений сердца у больных ишемической болезнью со стенокардией напряжения, с помощью цифровой субтракционной ангиографии (DSA) коронарных артерий, как золотого стандарта.
Материал и методы. У 78 (56 мужчин, 22 женщины; средний возраст 64,3±11 лет), пациентов с клиническими признаками стенокардии были проведены обследования коронарных артерий на 64-срезовой МСКТ с целью выявления значимых стенозов (>50% сужения просвета). МСКТ коронарных артерий было сравнено с инвазивной коронарной ангиографией.
Результаты. У 78 больных, 864 сегментов коронарных артерий были доступны для оценки. Во всех сегментах коронарных артерий, при инвазивной коронарной ангиографии выявлено 51 поражение. Сорок пять поражений были обнаружены МСКТ. Сопоставление чувствительности и специфичности были 88% и 97%. Чувствительность, специфичность, положительная и отрицательная прогностическая ценность анализа пациентов были 93%, 93%, 90% и 96%, соответственно.
Ложно-отрицательные результаты — в семнадцати сегментах коронарных артерий с уменьшением диаметра в диапазоне от 51% до 75% были пропущены при сканировании МСКТ. Основные пропущенные поражения локализовались в левой передней артерии, нисходящей и левой артерии (мелкие боковые ветви). Были пропущены четыре сегмента из-за тяжелой кальцификации и пять из-за артефактов движения.
Ложноположительные результаты — тридцать девять сегментов были ошибочно классифицированы из-за переоценки.
Заключение. МСКТ коронарография — это эффективный, быстрый, надежный и неинвазивный метод анализа коронарных артерий. Наилучшие результаты были получены у пациентов со здоровыми коронарными артериями (высокий процент негативной прогностической ценности), что позволяет значительно снизить количество инвазивной коронарной ангиографии. С улучшением технических характеристик, КТ имеет большое значение при анализе коронарных стенозов и анализе атеросклеротических бляшек.

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Ключевые слова: МСКТ коронарных артерий, коронароангиография ДСА, стенокардия.

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Multislice computed tomography (MSCT) is a non-invasive method for the heart and coronary arteries imaging.

In addition, the results of numerous studies comparing MSCT with digital subtraction angiography (DSA) coronary angiography suggested enhanced sensitivity of the technique as well, with no loss in specificity [1].

The aim of this study is to compare the accuracy of the analysis of the coronary vessels with noninvasive method —

MSCT with invasive coronary angiography as the gold standard.

Material and methods

The study group included 78 patients (56 men, 22 women, mean age 64,3±11 years, range 32–80), patients which had stable angina which is a cardiac examination confirmed. Exclusion criteria were contraindications to iodinated contrast, patients with previous stenting coronary arteries and bypass surgery. We also exclude patients with an acute coronary syndrome. All examinations were done in Department of Radiology University Clinical Center Nis, Serbia.

DSA coronary angiography was carried out according to standard techniques after MSCT. Coronary arteries were divided into segments as stated by the classification of the American Heart Association [2]. All coronary segments visualized upon catheterization were included in the investigation. Reduction of diameter more of 50% in relation to a reference segment were considered to represent important stenoses [3].

MSCT was performed using a Multi-Slice Computed Tomography Toshiba Aquilion 64 system (Toshiba Medical Systems, Tokyo, Japan), with a rotation time of 0,33 seconds and a collimation of 64x0,5 mm.

The tube current was 120 kV and 300 mA. Nonionic contrast material was administered in the cubital vein, with an amount of 80 to 90 ml, depending on the total scan time, and a flow rate of 5.0 ml/s (Iopromide /Ultravist 370, Bayer Health Care Pharmaceutical, Germany). Automated detection of peak enhancement in the descending aorta was used for timing of the bolus on +180 Hounsfield units. Data acquisition was administer during an breath hold of 8 to 10 seconds.

During the MSCT examination, electrocardiography was execute simultaneously for retrospective gating of the data. An initial data set was reconstructed with a slice thickness of 0,5 mm, the ECG was edited manually, when the heart rate was irregular. Post processing were done on the workstation (Vitrea 1, Vital Images, Plymouth, Minnesota).

Conventional diagnostic coronary angiography was performed toward standard techniques on Axiom Artis (Siemens, Germany). Contrast material was the same Iopromide (Ultravist 370).

MSCT angiograms were assessed by two radiologist with some years experience. General information on the standing and courses of the coronary arteries were obtained by volume rendering (VR). Then the primary axial slices were inspected for the presence of significant stenoses (≥50% reduction of diameter), assisted by curved multiplanar reconstructions. Segmentation of the coronary arteries was carried out as established by the American Heart Association/American College of Cardiology guidelines [3]. Conventional angiograms were assessed by an experienced observer without knowledge of the MSCT data who identified the available coronary segments on the basis of the American Heart Association/American College of Cardiology guidelines [3]. Each segment was then evaluated on the basis of the evaluation of 2 orthogonal views.

Sensitivity, specificity and positive and negative predictive values for the detection of stenoses on conventional angiography were determined on segmental bases, vessel and patients. All statistical analyses were performed using SPSS software version 21.0 (SPSS, Inc., Chicago, Illinois).

Table 1

Detection of Significant (>50%) Stenosis With 64 –slice Computed Tomography Coronary Angiography

Coronary segment	N	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV
All segments	864	169	639	39	17	169/186 (90%)	639/678 (94%)	169/208 (81%)	639/656 (97%)
LM	74	4	70	0	0	4/4 (100%)	70/70 (100%)	4/4 (100%)	70/70 (100%)
LAD	285	74	181	21	9	74/83 (89%)	181/202 (89%)	74/95 (77%)	181/190 (95%)
Proximal	74	30	35	5	4	30/34 (88%)	35/40 (87%)	30/35 (85%)	35/39 (89%)
Middle	72	31	35	5	1	31/32 (96%)	35/40 (87%)	31/36 (86%)	35/36 (97%)
Distal	70	6	58	4	2	6/8 (75%)	58/62 (93%)	6/10 (60%)	58/60 (96%)
Side branches	69	7	53	7	2	7/9 (77%)	53/60 (88%)	7/14 (50%)	53/55(96%)
LCX	217	23	180	9	5	23/28 (82%)	180/189 (95%)	23/32 (72%)	180/185 (97%)
Proximal	73	10	60	2	1	10/11 (90%)	60/62 (96%)	10/12 (83%)	60/61 (98%)
Middle	72	7	59	4	2	7/9 (77%)	59/63 (93%)	7/11 (63%)	59/61 (96%)
Side branches	72	6	61	3	2	6/8 (75%)	61/64 (95%)	6/9 (66%)	61/63 (96%)
RCA	288	68	208	9	3	68/71 (95%)	208/215 (96%)	68/77 (88%)	208/211 (98%)
Proximal	76	31	41	4	0	31/31 (100%)	41/45 (91%)	31/35 (88%)	41/41 (100%)
Middle	74	28	41	4	1	28/29 (96%)	41/45 (91%)	28/32 (87%)	41/42 (97%)
Distal	70	6	62	1	1	6/7 (85%)	62/63 (98%)	6/7 (85%)	62/63 (98%)
PDA	68	3	64	0	1	3/4 (75%)	64/64 (100%)	3/3 (100%)	64/65 (98%)

Abbreviations: LM — left main coronary artery, LAD — left anterior descending coronary artery, LCX — left circumflex coronary artery, RCA — right coronary artery, PDA — posterior descending artery, TP — true positive, TF — true negative, FP — false positive, FN — false negative, PPV — positive predictive value, NPV — negative predictive value.

Results

In this study were included 78 successive patients (56 males, 22 females; average age 64,3±11 years). The average time period between MSCT and DSA angiography was 45±65 days.

In 864 segments assessed with conventional coronary angiography. The value of sensitivity was 90,86% (169/186, 95% confidence interval [CI]: 88,77% to 94,58%, the value of specificity was 94,25% (639/678, 95% CI: 92,22% to 95,88%), the positive predictive value was 81,25% (169/208, 95% CI: 75,27% to 86.31%) and the negative predictive value 97.41% (639/656, 95% CI: 95,88% to 98,48%) for the detection of significantly stenotic lesions (Table 1).

Nineteen percent (170 of 864), of all segments were classified as heavily calcified, 30,9% (267 of 864) as moderately calcified and 49,4% (427 of 864) as non-calcified.

Table 2

Diagnostic accuracy of multi-slice computed tomography

Variable	Segment analysis	Vessel analysis	Patient analysis
Sensitivity	90%	88%	93%
specificity	94%	97%	93%
PPV	81%	83%	90%
NPV	97%	98%	96%

Abbreviations: PPV — positive predictive value, NPV — negative predictive value.

The diagnostic performance of MSCT coronary angiography for detection of significant obstructive lesions in non-calcified, moderately calcified and heavily calcified segments (Table 2).

False-negative results — Seventeen segments of coronary arteries with diameter reduction in range 51% to 75% were missed on the MSCT scan. The major of the missed lesions were located in the LAD and LCx (small side branches). Four segments were missed because of severe calcifications and five because of motion artifacts.

False-positive results — Thirty nine segments were incorrectly classified as significantly because of overestimation.

The sensitivity for classification of vessels with or coronary artery disease was 88,24% (95% CI: 76,12% to 95,53%), specificity was 96,48% (95% CI: 93,43% to 98,38%), positive predictive value was 83,33% (95% CI: 70,70% to 92,07%) and negative predictive value was 97,63% (95% CI: 94,91% to 99,12%). In the remaining 308 coronary arteries, 45 were correctly identified in 247 vessels.

Thirty one patients with ≥1 significant lesions were identified by conventional coronary angiography.

Twenty-nine of these patients (94%) were correctly identified on MSCT. Single-vessel disease was in nine patients (11,5%), two-vessel lesions was in ten patients

Table 3

Comparative Study by Autors

		Per segment					Per patients			
Author	N	NS (%)	Sens (%)	Specif. (%)	PPV (%)	NPV (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
16-MSCT										
Mollet [9]	128	7	92	95	79	98	100	86	97	100
Hoffman [10]	103	6	95	98	87	99	97	87	90	95
Achenboch [11]	50	4	94	96	69	99	100	83	100	86
Mollet [12]	51	0	95	98	87	99	97	84	89	95
Garcia [13]	187	29	85	91	36	99	98	55	50	99
Dewey [14]	129	9	83	86	90	95	93	74	93	92
Hausleiter [15]	129	11	93	87	46	99	-	-	-	-
64-MSCT										
Leschka [16]	53	0	94	97	87	99	100	100	100	100
Raff [17]	70	12	86	95	66	98	95	90	93	93
Leber [18]	59	0	88	97	-	99	94	-	-	-
Pugliese [19]	35	0	99	96	78	99	100	90	96	100
Mollet [20]	52	2	99	95	76	99	100	92	97	100
Ropers [21]	82	4	95	93	56	99	96	91	83	98
Nikolaou [22]	72	10	86	95	72	97	97	72	83	95
Hausleiter [23]	114	8	92	92	54	99	99	75	74	99
Achenbach [24]	100	3	86	99	80	99	-	-	-	-
DSCT										
Nikolaou [25]	20	4	95	93	79	98	-	-	-	-
Scheffel [26]	30	1	96	98	86	99	-	-	-	-
Weustink [27]	100	0	95	95	75	99	99	87	96	95
Achenbach [28]	100	3	96	92	90	99	-	-	-	-

Abbreviation: NS — unseen segments.

(12,8%) and twelve patients were classified as having multivessel disease.

Sensitivity for classification of patients with or without CAD was 93,55% (95% CI: 78.54% to 99,02%), specificity was 93,62% (95% CI: 82,44% to 98,59%), positive predictive value was 90,62% (95% CI: 74,95% to 97,91%) and negative predictive value was 95,65% (95% CI: 85,13% to 99,34%).

Discussion

MSCT has the possibilities to detect significant coronary artery stenosis, which is shown by our 64-slice CT data; notwithstanding, this generation of MSCT scanners also has some technical limitations. Recent studies have reported two major limitations in assessing coronary artery disease with MSCT: rigid atherosclerotic calcification and motion artifacts [4, 5].

It is significant that only 17 segments that are labeled as false negative were not exactly diagnosed because of insufficient image quality (Table 1). In addition, the specificity of 90% was observed, with the sensitivity of 94%, on a segmental basis (Table 2). From the clinical point of view, segmental analysis is very important in the further selection of patients for invasive therapeutic treatment. In our study, a sensitivity of 93% was noted, and specificity of 93%, in the detection of patients with coronary arteries disease. Compared to the previous study, no significant deviation values of sensitivity and specificity, from a segmental to a patient analysis [6, 7]. The current observations examinations are in line with the few investigations with 16-slice, 64-slice MSCT and dual source computed tomography (DSCT) that have been published (Table 3) [9-28].

In spite of rapid technologic advancements, some limitations inherent to MSCT persist. First, for high-quality MSCT images a stable and preferably low heart rate remains essential, and there is often need of the administration of β blockers before the examination. Second, another important issue is the current lack of validated quantification algorithms for MSCT.

Conclusion

MSCT coronary angiography is an effective, fast, reliable and non-invasive method for the analysis of the coronary arteries. The best results were obtained in patients with healthy coronary arteries (high percentage of NPV), which can significantly reduce the number of invasive coronary angiography. With the improvement of technical characteristics, CT is gaining more importance in the analysis of coronary stenoses and analysis of atherosclerotic plaque.

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ACUTE EFFECTS OF AUDITORY STIMULATION WITH HEAVY METAL MUSIC ON HEART RATE RESPONSES

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Aim. Investigate the acute effects of heavy metal musical auditory stimulation on cardiac autonomic regulation.
Material and methods. This is a prospective study conducted on 22 healthy women between 18 and 30 years old. All procedures were performed in the same soundproof room. The volunteers remained at rest for 20 minutes and subsequently were exposed to heavy metal (75-84 dB) music for 20 minutes. We analysed the following HRV indices: SDNN, RMSSD, pNN50, LF, HF and LF/HF ratio, RRTri, TINN, SD1, SD2 and SD1/SD2 ratio.
Results. During exposure to heavy metal music auditory stimulation we observed that the LF (ms^2) tended to increase (p=0,06) and reduce HF (nu) (p=0,07) and the LF/HF ratio increased (p=0,05). No significant changes were found for SDNN, pNN50, RMSSD, SDNN/RMSSD ratio, TINN, RRTri, SD1, SD2 and SD1/SD2 ratio.
Conclusion. Auditory stimulation with the selected heavy metal musical style acutely decreased HRV.

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Keywords: cardiovascular system, autonomic nervous system, hearing, music.

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BMI — body mass index, BP — blood pressure, DBP — diastolic blood pressure, HF — high frequency, HR — heart rate, HRV — heart rate variability, LF — low frequency, SBP — systolic blood pressure, SDNN — standard deviation of the average normal RR intervals, RMSSD — square root of the mean squared differences between adjacent normal RR intervals.

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ОСТРОЕ ВОЗДЕЙСТВИЕ НА ЧАСТОТУ СЕРДЕЧНЫХ СОКРАЩЕНИЙ СЛУХОВОЙ СТИМУЛЯЦИИ МУЗЫКОЙ В СТИЛЕ ХЭВИ-МЕТАЛ

Marcela L. Nogueira[1], Anne M. G.G. Fontes[2], Luiz Carlos de Abreu[3], Rodrigo D. Raimundo[3], Vitor E. Valenti[1]

Цель. Изучение острого воздействия на вегетативную регуляцию сердца слуховой стимуляции музыкой в стиле хэви-метал.
Материал и методы. Это проспективное исследование проведено на 22 здоровых женщин в возрасте от 18 до 30 лет. Все процедуры проводились в одной звук-изолированной комнате. Добровольцы оставались в покое в течение 20 минут, а затем их подвергали воздействию музыки в стиле хэви-метал (75-84 дБ) в течение 20 минут. Мы проанализировали следующие показатели вариабельность сердечного ритма: SDNN, RMSSD, pNN50, LF, HF, LF/HF соотношение, RRTri, TINN, SD1, SD2 and SD1/SD2 соотношение.
Результаты. При воздействии слуховой стимуляции музыкой хэви-метал мы наблюдали тенденцию к увеличению LF ($мс^2$) (p=0,06) и снижению HF (nu) (p=0,07) и увеличение соотношения LF/HF в (p=0,05). Не было обнаружено значительных изменений для SDNN, pNN50, RMSSD, сотношения SDNN/RMSSD, TINN, RRTri, SD1, SD2 и SD1/SD2 соотношение.
Заключение. Слуховая стимуляция музыкой в стиле резко снижала HRV.

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The relationship between music and medicine is a fast growing area that in the past has been largely focused on the use of music as an alternative and complementary therapy [1]. Relaxant music has been reported to present positive influence on stress reduction, relaxation, pain management, neural cognition and cardiac function [2, 3]. Auditory stimulation with music is known to induce several psychological responses, leading to changes in the autonomic nervous system [4, 5].

In this context, the heart rate variability (HRV) is a non-invasive method that evaluates the cardiac autonomic control in humans, it is a conventionally accepted term to describe the fluctuations in the intervals between consecutive heart beats (RR intervals), which are related to the influences of the ANS on the sinus node [6].

Great part of studies has observed the relaxing effect of classical music. On the other hand, genres such as heavy metal, hip hop and techno music are commonly associated with physiologic excitement [7].

Although two recent studies showed reduced HRV during exposure to heavy metal musical auditory stimulation in healthy women [8, 9], others found absence of cardiac

autonomic responses induced by heavy metal music in healthy men [10, 11]. In addition, the aforementioned studies used different protocols that combined heavy metal with classical baroque music styles.

Elucidating the physiological responses involved in acute musical auditory stimulation is important for the development of future therapies to help cardiovascular disorders treatment. Therefore, this study was undertaken to evaluate the acute effects of auditory stimulation with a selected heavy metal music style on cardiac autonomic regulation.

Material and methods

Study Population. We analysed 22 apparently healthy student women aged between 18 and 30 years old. All volunteers were informed about the procedures and objectives of the study and, after agreeing, signed a consent form. All study procedures were approved by the Research Ethics Committee (REC) of the institution (case number. 2011/382) and followed the Resolution 196/96 of the National Health Council.

Non-inclusion criteria. We did not include women under the following conditions: body mass index (BMI) >35 kg/m^2; systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg (at rest), endocrine, cardiovascular, respiratory and neurological related disorders or any condition that avoided the subject to perform the study. In order to avoid effects related to sexual hormones we did not include women on the 11^{th} to 15^{th} and 21^{th} to 25^{th} days after the first day of the menstrual cycle [12].

Initial assessment. The volunteers were identified by collecting the following information: age, weight, height and BMI. Anthropometric measurements were obtained according to the recommendations described in the literature. Weight was measured using a digital scale (W 200/5, Welmy, Brazil) with a precision of 0,1 kg. Height was determined using a stadiometer (ES 2020 Sanny, Brazil) with a precision of 0,1 cm and 2.20 m long. The body mass index (BMI) was calculated using the following formula: weight (kg)/height (m^2). We measured heart rate (HR) and blood pressure (BP). HR was measured with the Polar RS800CX heart rate monitor (Polar Electro, Finland). BP was indirectly measured by auscultation through calibrated aneroid sphygmomanometer (Welch Alyn — Tycos, New York, USA), and stethoscope (Littmann, Saint Paul, USA) with subjects seated.

Measurement of auditory stimulation. The measurements of equivalent sound levels were performed in a soundproof room, using an audio dosimeter SV 102 (Svantek, Finland). It was programmed measuring circuit 7 in "A" weighting, slow response [9].

The measurements were made during the session, which lasted a total of five minutes and 15 seconds for the exciting heavy metal music. We used the type of microphone insert (MIRE — microphone in real ear), which was placed inside the ear canal of the subject, just below the microphone, connected to the personal stereo.

Before each measurement, the microphones were calibrated with the acoustic calibrator CR: Model 514 (Cirrus Research plc). This tool was used to analyse the Leq (A), which is defined as the equivalent sound pressure level and the sound level corresponds to the same constant time interval. It contains the same total sound energy, which also analysed the spectrum of sound stimulation (eighth track) frequency [8] (Figure 1).

Experimental Protocol. Data collection was performed at a room temperature between 21° C and 25° C and with humidity between 50 and 60%. The volunteers were instructed not to ingest alcohol and caffeine for 24 hours prior to evaluation. The collection was made individually between 6 and 10 PM, and the volunteers were instructed to remain at rest, avoiding talking during the experiment.

After the initial evaluation the heart monitor belt was then placed over the thorax, aligned with the distal third of the sternum and the Polar RS800CX heart rate receiver (Polar Electro, Finland) was placed on the wrist. Subsequently, the volunteers remained at seated rest for 20 minutes with the headset off.

Then the volunteers were exposed to musical auditory stimulation with heavy metal (Gamma Ray: "Heavy Metal Universe") style for a period of 20 minutes.

Analysis of HRV. The RR intervals recorded by the Polar RS800CX heart rate monitor (with a sampling rate of 1000 Hz) were transferred to the Polar Precision Performance software (v. 3.0, Polar Electro, Finland). The software allowed the visualization of the HR and the extraction of a file relating to a cardiac period (RR interval) in a "txt" file. After digital filtering supplemented with manual filtering to eliminate artefacts and premature ectopic beats, a number of 1000 RR intervals were used for data analysis. Only series with more than 95% of sinus beats were included in the study [13].

To analyse the linear indices in the time and frequency we used HRV analysis software (HRV Kubios v.1.1 for Windows, Biomedical Signal Analysis Group, University of Kuopio, Finland) [14,15].

Analysis of linear indices of HRV. The analysis in the time domain was performed by means of SDNN (standard deviation of the average normal RR intervals), RMSSD (square root of the mean squared differences between adjacent normal RR intervals), SDNN/RMSSD ratio and pNN50 (percentage of adjacent RR intervals with a difference of duration greater than 50ms).

For HRV analysis in the frequency domain we used spectral components of low frequency (LF: 0,04 to 0,15 Hz) and high frequency (HF: 0,15-0,40 Hz), inabsolute (ms^2) and normalized units and the ratio between components of low and high frequency (LF/HF). Spectral analysis was calculated using the algorithm of fast Fourier transform [6].

Geometric indices of heart rate variability. HRV analysis was performed by means of geometrical methods:

RRtri, TINN and Poincaré plot (SD1, SD2 and SD1/SD2 ratio). The RRtri was calculated from the construction of a density histogram of RR intervals, which contains the horizontal axis of all possible values of RR intervals measured on a discrete scale with 7,8125 ms boxes (1/128 seconds) and on the vertical axis, the frequency with which each occurred. The union of points of the histogram columns forms a shape like a triangle. The RRtri was obtained by dividing the total number of RR intervals used to construct the histogram by their modal frequency (RR interval value that most frequently appeared on RR) [6].

The TINN consists of the measure of the base of a triangle. The method of least squares is used to determine the triangle. The RRtri and the TINN express the overall variability of RR intervals [16].

The Poincaré plot is a map of points in Cartesian coordinates, constructed from the values of RR intervals obtained, where each point is represented on axis x (horizontal/abscissa) by the previous normal RR interval, and on axis y (vertical/coordinate), by the following RR interval.

For quantitative analysis of the plot, an ellipse was fitted to the points of the chart, with the center determined by the average RR intervals, and the SD1 indexes were calculated to measure the standard deviation of the distances of the points to the diagonal y=x, and SD2 measures the standard deviation of the distances of points to the line y = — x + RRm, where RRm is the average of RR intervals. The SD1 is an index of instantaneous recording of the variability of beat-to-beat and represents parasympathetic activity, while the index SD2 represents HRV in long-term records, and reflects the overall variability. Their ratio (SD1/SD2) shows the ratio between short and long variations of RR intervals [16].

The qualitative analysis of the plot was made through the analysis of the figures formed by its attractor, which were described by Tulppo et al [16] in:

Figure in which an increase in the dispersion of RR intervals is observed with increased intervals, characteristic of a normal plot.

Small figure with beat-to-beat global dispersion without increased dispersion of RR intervals in the long term is related to cardiac disorders or autonomic dysfunction [15].

Statistical analysis. Standard statistical methods were used to calculate the means and standard deviations. The normal Gaussian distribution of the data was verified by the Shapiro-Wilk goodness-of-fit test (z value of >1.0). For parametric distributions we applied the paired Student T test. For non-parametric distributions we used the paired Wilcoxon test. Differences were considered significant when the probability of a Type I error was less than 5% (p≤0,05). We used the Software Biostat 2009 Professional® 5.8.4.

Results

Table 1 shows the values for DBP and SBP, HR, mean RR intervals, weight, height and BMI of the volunteers.

Table 1

Baseline DAP and SAP, Mean RR, weight, height and BMI of the volunteers

Variable	Value
Age (years)	20,8±2,7
Height (m)	1,63±0,07
Weight (kg)	59,9±10,1
BMI (kg/m^2)	22,51±2,9
HR (bpm)	83,2±19,4
Mean RR (ms)	708,6±81,3
SAP (mmHg)	105,4±8,4
DAP (mmHg)	69,5±8,4

Abbreviations: DAP — diastolic arterial pressure, SAP — systolic arterial pressure, HR — heart rate, Mean RR — mean RR interval, BMI — body mass index, m — meters, kg — kilograms, bpm — beats per minute, ms — milliseconds, mmHg — millimeters of mercury.

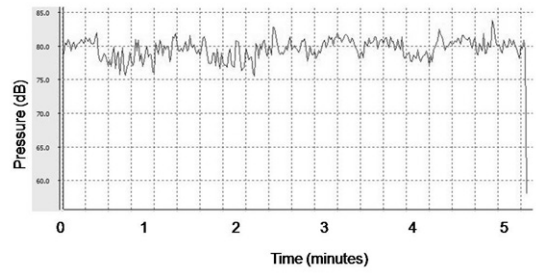

Figure 1. Equivalent sound level of auditory musical stimulation.

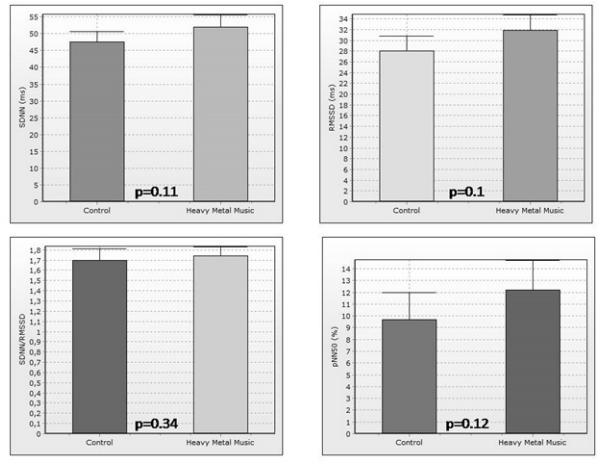

Figure 2. Time domain indices of HRV before and after exposure to auditory stimulation with music.
Abbreviations: SDNN — standard deviation of normal-to-normal R-R intervals, RMSSD — root-mean square of differences between adjacent normal RR intervals in a time interval, pNN50 — percentage of adjacent RR intervals with a difference of duration greater than 50ms, ms — milliseconds.

The time domain indices of HRV during exposure to heavy metal musical auditory stimulation are presented in Figure 2. We noted no significant difference between before (control) and during exposure to the selected music regarding SDNN, RMSSD, SDNN/RMSSD ratio and pNN50 indices.

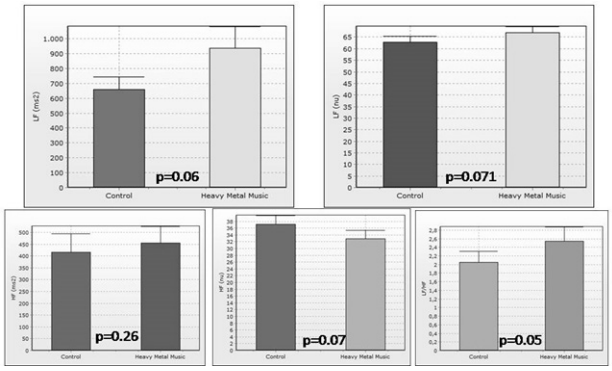

Figure 3. Frequency domain indices of HRV before and after exposure to auditory stimulation with music.
Abbreviations: LF– low frequency, HF — high frequency, LF/HF — low frequency/high frequency ratio, ms — milliseconds, nu — normalized units.

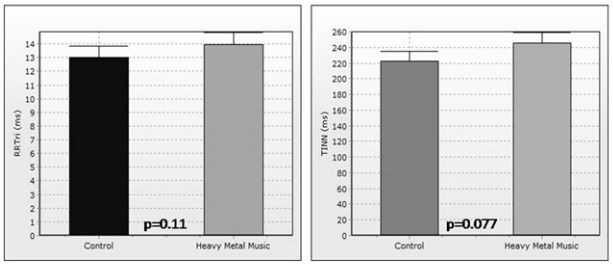

Figure 4. Linear geometric indices of HRV before and after exposure to auditory stimulation with music.
Abbreviations: RRtri — Triangular index, TINN — triangular interpolation of RR intervals, ms — milliseconds.

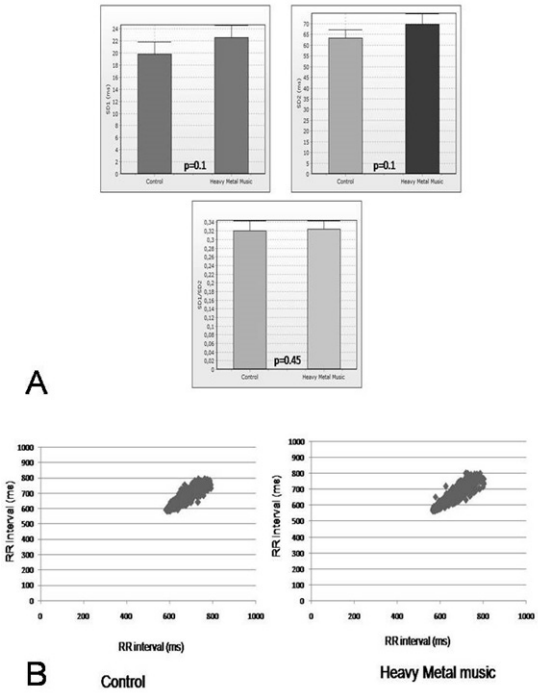

Figure 5. (A) Poincaré plot indices before and after exposure to auditory stimulation with music. (B) Visual pattern of the Poincaré plot observed in one subject before (Control) and during musical auditory stimulation with heavy metal style (heavy metal music).
Abbreviations: SD1 — standard deviation of the instantaneous variability of the beat-to beat heart rate, SD2 — standard deviation of long-term continuous RR interval variability, SD1/SD2 ratio — ratio between the short — and long — term variations of RR intervals, ms — milliseconds.

In relation to the frequency domain indices of HRV, we observed that the LF in absolute and normalized units as well as the LF/HF ratio tended to increase whereas the HF in normalized units tended to reduce during musical auditory stimulation with heavy metal style, however, it did not reach statistical significance. On the other hand, the HF index in absolute units did not change during auditory stimulus (Figure 3).

Figure 4 displays data for the geometric indices of HRV. The both TINN and RRTri did not significantly change during heavy metal musical auditory stimulation.

In Figure 5A we note that the Poincaré plot indices SD1, SD2 and SD1/SD2 ratio were not different between before (control) and during exposure to heavy metal song style.

Figure 5B shows an example of the Poincaré plot patterns from one subject during no music and excitatory heavy metal musical auditory stimulation.

Discussion

Our study aimed to investigate the acute effects of auditory stimulation with a selected heavy metal music style on cardiac autonomic regulation in healthy women. We observed that it tended (p=0.05) to change the time domain indices of HRV increasing the LF/HF ratio. The qualitative analysis through Poincaré plot indicated that during exposure to music there was higher dispersion of RR intervals, indicating increased HRV.

We reported absence of significant changes for the time domain indices of HRV (pNN50, SDNN, RMSSD and SDNN/RMSSD ratio). There are two recent studies that support our findings. Roque et al [8] found no significant change of the time domain indices of HRV during exposure to the same heavy metal music. The same authors reported absence of significant changes in the time domain indices of HRV during exposure to Heavy Metal Universe from Gamma Ray in another study [9]. In this sense, we hypothesize that the statistical method applied on RR interval during this selected musical auditory stimulation is not able to detect significant changes.

According to our data, the selected heavy metal music slightly increased the LF index in absolute units. The same music was shown to reduce that index [8]. However, in the mentioned investigation the authors used a different protocol that was based on consecutive exposure to heavy metal and classical baroque music styles. The volunteers were randomly exposed to the both music styles in the same day. In this line, a recent study [10] that used the

same experimental protocol of Roque et al [8], reported reduction of global HRV in men during exposure to Heavy Metal Universe from Gamma Ray. Taken together, we hypothesize that the mix of the music styles have influenced on their data.

The visual analysis through the Poincaré plot showed that during exposure to heavy metal musical auditory stimulation there was a decrease in the dispersion of RR intervals compared to the moment with no auditory stimulation, indicating higher HRV during music exposure. This result is supported by the increased LF/HF ratio during exposure to music. The Poincaré plot analysis is a simple method used as a qualitative tool [17] and also as a geometrical analysis by fitting an ellipse to the shape of the Poincaré plot in order to calculate HRV indices [18]. This analysis is considered nonlinear, because it performs a description of the nonlinear dynamics of a mechanism that can identify the hidden correlation patterns of a time series signal. It is suggested that nonlinear analysis is more sensitive to detect changes not recognized through linear analysis of HRV [19].

In our study the selected heavy metal music ranged between 75 and 84 dB. The intensity of musical auditory stimulation is an important issue to be raised. Lee et al [20] observed that white noise exposure above 50 dB enhanced sympathetic cardiac component of HRV. It was noted cardiac accelerative reaction that habituated over trials in subjects exposed to repeated 60 dB and 110 dB white-noise stimuli. The authors found a strong correlation between the noise intensity and LF/HF ratio, indicating the higher the noise intensity the higher the cardiac sympathetic tone. Nevertheless, there are differences between musical auditory stimulation and white noise. White noise is characterized by a small range of intensity [21], while the intensity of music fluctuates. Musical auditory stimulation influences the limbic system [22], but it has not yet been established whether white noise induces a positive or negative response in the cognitive system. In this context, it may be postulated that the effects of auditory stimulation on the cardiac autonomic regulation depend on the type of auditory stimulation.

The acute effects of music on cardiac autonomic regulation may be explained by proposed physiological mechanisms. Evidences from neurochemical studies revealed that emotional responses induced by music are related to reward circuitry, depending on dopamine release in the nucleus accubens [23]. Musical auditory stimulation in rats was shown to increase calcium/calmodulin-dependent dopamine synthesis in the brain, inducing a blood pressure decrease [24]. The suprachiasmatic nucleus of the hypothalamus was also reported to be involved in sympathetic and pressoric responses in anesthetized rats induced by music ("Träumerei" from Kinderszenen Op.15-7) [25].

An important highlight was the use of women for investigation of cardiac autonomic responses induced by music in order to avoid sex-dependent effects. Investigations regarding differences between men and women in relation to emotional manifestation and involvement showed conflicting results [26, 27]. Recently, it was reported that the same selected heavy metal music style reduced the global indices of HRV in men [10]. A previous study indicated that sex-based differences in psychophysiological responses to auditory stimulation with music are intensely influenced by sexual hormones [27]. Nonetheless, a different study showed women to be more stress reactive compared with men in reaction to musical auditory stimulation [26].

Another relevant point to be raised is the exclusion of volunteers during specific phases of the menstrual cycle, because the menstrual cycle was also indicated to affect baseline nonlinear properties of HRV [12]. In order to exclude the interference of the follicular and luteal phases of the menstrual cycle on cardiac autonomic regulation we did not evaluate volunteers on 10-15 days and 20-25 days after the first day of the menstrual cycle. In this context, a previous study from da Silva et al [28] reported no significant effect of Heavy Metal Universe from Gamma Ray on HRV indices in the time and frequency domain. However, the authors did not exclude women in the luteal and follicular phases of the menstrual cycle.

Conclusion

Acute auditory stimulation with a selected heavy metal music style slightly decreased HRV.

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RENAL FUNCTION AFTER CORONARY BYPASS SURGERY IN PATIENTS WITH PRE-DIABETES

Kremneva L. V., Suplotov S. N.

Aim. To reveal the predictors of renal dysfunction due to surgical revascularization of myocardium in stable angina patients with prediabetes.

Material and methods. Totally, 48 patients with prediabetes studied, having indications for coronary bypass grafting (CBG) at the age 60±7,4 years with coronary heart disease (CHD) anamnesis 6±5,4 years. Multivessel disease of coronary vessels had 68,8% of patients, LCA stem stenosis >50 % had 10,9% of patients. On-pump CBG was done in 87,5% of patients, off-pump — 12,5%. Duration of on-pump period was 95±23 min., number of distal anastomoses for one patient — 2,8±0,8. Baseline, on the first and second days post-CBG, and if needed later, the creatinin concentration was measured in the blood, as glomerular filtration rate (GFR) by CKD-EPI equation. Of the development of renal dysfunction in CBG we decided if GFR decreased below 60 mL/min/1,73 m^2. In statistics we took continuous variables as M±SD and as Me (25%–75%) depending on the type of distribution. Renal dysfunction predictors were defined with the method of staged regression.

Results. In patients with stable angina and prediabetes we found moderate transient decrease of GFR after CBG comparing to the baseline level with Me 89,4 (78-105) to Me 77,8 (59-96) mL/min/1,73 m^2 (p<0,01). Significant decrease of GFR after CBG had the patients with in-hospital complications (introperational myocardial infarction, acute heart failure, atrial fibrillation paroxysm) — Me 92 (82-107) and Me 72,4 (56-89) mL/min/1,73 m^2, p=0,000 differ from the patients groups not having complications, p=0,797. The part of persons developing CBG related renal dysfunction was 21,7%. Decrease of GFR <60 mL/min/1,73 m^2 after CBG is associated with older age, lower baseline GFR and longer on-pump period.

Conclusion. Among patients with stable angina and pre-diabetes the part of those developing CBG related renal dysfunction was 21,7%. The increase of on-pump time more than Me 105 (86-136) minutes significantly increased the relative risk of renal dysfunction development after CBG.

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Key words: prediabetes, renal dysfunction, coronary bypass graft.

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CHD — coronary heart disease, CP — cardiopulmonary bypass, MI — myocardial infarction, CABG — coronary artery bypass grafting, CMD — carbohydrate metabolism disorders, DM — diabetes mellitus, GFR — glomerular filtration rate, GTT — glucose tolerance test, FC — functional class, CKD — chronic kidney disease, CHF — chronic heart failure, ECG — electrocardiography, EchoCG — echocardiography, TnT — troponin T.

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ФУНКЦИЯ ПОЧЕК ПОСЛЕ КОРОНАРНОГО ШУНТИРОВАНИЯ У ПАЦИЕНТОВ С ПРЕДИАБЕТОМ

Kremneva L. V., Suplotov S. N.

Цель. Выявить предикторы развития дисфункции почек после хирургической реваскуляризации миокарда у больных стабильной стенокардией с предиабетом.

Материал и методы. Обследовано 48 больных с предиабетом, имеющих показания к коронарному шунтирования (КШ) в возрасте 60±7,4 лет с длительностью ишемической болезни сердца 6±5,4 года. Многососудистое поражение коронарных сосудов имелось у 68,8 %, стеноз ствола левой коронарной артерии >50% — у 10,9% лиц. Операция КШ в условиях искусственного кровообращения (ИК) выполнена у 87,5 %, на работающем сердце — у 12,5% больных. Длительность ИК составила 95±23 мин., количество дистальных анастомозов на одного пациента — 2,8±0,8. Исходно, в первые и вторые сутки после КШ, при необходимости в более поздние сроки, измеряли концентрацию креатинина в крови, рассчитывали скорость клубочковой фильтрации (СКФ) по формуле CKD-EPI. О развитии дисфункции почек в связи с КШ судили по снижению СКФ ниже 60 мл/мин/1,73 м^2. При статистической обработке материалов непрерывные переменные представлены как M±SD или как Me (25 %–75 %) в зависимости от типа распределения. Предикторы развития почечной дисфункции определяли методом пошагового регрессионного анализа.

Результаты. У больных стабильной стенокардией с предиабетом выявлено умеренное транзиторное снижение СКФ после КШ в сравнении с исходным уровнем с Me 89,4 (78-105) до Me 77,8 (59-96) мл/мин/1,73 м^2 (p<0,01). Значимое снижение СКФ после КШ имелось у лиц с госпитальными осложнениями (интраоперационный инфаркт миокарда, острая сердечная недостаточность, пароксизм фибрилляции предсердий) — Me 92 (82-107) и Me 72,4 (56-89) мл/мин/1,73 м^2, p=0,000 в отличие от группы пациентов, не имевших осложнений, p=0,797. Доля лиц с развившейся в связи с КШ почечной дисфункцией составила 21,7%. Снижение СКФ <60 мл/мин/1,73 м^2 после КШ ассоциировано с более старшим возрастом, более низкой исходной СКФ и более продолжительным периодом ИК.

Заключение. Среди больных стабильной стенокардией с предиабетом доля лиц с развившейся в связи с КШ почечной дисфункцией составила 21,7%. Увеличение продолжительности ИК более Me 105 (86-136) минут значимо повышало относительный риск развития дисфункции почек после КШ.

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Ключевые слова: предиабет, почечная дисфункция, коронарное шунтирование.

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Coronary artery bypass grafting (CABG) is one of the most effective treatments for coronary artery disease (CHD) patients with multivessel coronary artery disease. However, CABG, as any invasive procedure, has a certain risk of complications, among which renal dysfunction is quite frequent. According to different authors, the incidence of renal dysfunction after CABG is between 8 and 30% and is associated with an increased risk of hospital complications and mortality [1-3].

Factors, predisposing for the renal dysfunction process after CABG, include age, diabetes mellitus (DM), chronic heart failure (CHF), increased baseline blood creatinine level, a long period of cardiopulmonary bypass (CP), aorta occlusion, etc. [2, 4].

Among patients undergoing surgical myocardial revascularization, about 30-40% are people with carbohydrate metabolism disorders (CMD) [5]. However, the incidence and risk factors for renal dysfunction after CABG among these patients are not studied.

The aim of the study was to identify predictors of renal dysfunction in connection with surgical myocardial revascularization in patients with stable angina with early carbohydrate metabolism disorders.

Materials and methods

The study included patients with chronic CHD with early CMD admitted to the hospital for CABG surgery. Indications for CABG were determined in accordance with the recommendations on myocardial revascularization (ESC/EACTS, 2010) [6]. Exclusion criteria from the study included age over 75 years, DM, myocardial infarction (MI) and cerebral crisis not older than two months, significant stenoses of the brachiocephalic arteries, valvular heart disease and left ventricular aneurysm, which required surgical treatment, erosive gastritis and exacerbation of peptic ulcer, acute inflammatory diseases and exacerbation of chronic inflammatory diseases, severe diseases of kidneys, liver and lungs, terminal CHF, cancer pathology.

Before surgical myocardial revascularization, all patients underwent an examination including blood tests, urine tests, biochemical blood test, in particular creatinine level measurement, an oral glucose tolerance test (GTT), electrocardiography (ECG), echocardiography (EchoCG), ultrasound examination of brachiocephalic arteries, arteries and veins of the lower extremities, fibrogastroscopy, coronary angiography by M. R. Judkins technique (1967) using a Philips Polidiagnost C (Netherlands) angiographic complex.

Blood creatinine was measured by Jaffe method using Synchron CX Systems (Beckman Coulter, USA). Kidney function was assessed by glomerular filtration rate (GFR) in accordance with the classification of chronic kidney disease (CKD) NKF/KDOQI (2002) [7]. GFR was calculated by the CKD-EPI formula [8]. All patients, except patients with known DM, underwent an oral GTT using standard methods. The criteria for diagnosis of early CMD (pre-diabetes), which included fasting hyperglycemia (study twofold of fasting glucose >5,5<6,1 mmol/l) and impaired glucose tolerance test (IGTT) (blood glucose 2 hours after a glucose load ≥7,8<11,1 mmol/l), were conventional (WHO, 1999; WHO and ADA, 2003) [9]. Blood glucose was measured by an electrochemical method with chip sensors using BIOSEN C_line clinic equipment (Germany). On days 1 and 2 after CABG or later, if necessary, blood creatinine was re-measured and GFR was calculated by the above mentioned formula. The renal dysfunction process due to CABG was judged by the decrease in GFR less than 60 mL/min/1,73 m^2. One day after CABG, and later as necessary, blood troponin T level (TnT) was measured in all patients using the Cardiac reader semiquantitative immune chromatographic assay device (Roche Diagnostics, Switzerland).

The following hospital complications were evaluated before discharge: cases of intraoperative MI, acute heart failure, which required the use of inotropic agents; paroxysmal atrial fibrillation, cardiac death. Intraoperative MI was diagnosed based on the recommendations (2007).

The ethics committee approved the study protocol. All participants provided written informed consent prior to inclusion.

Among 200 patients with chronic CHD admitted to hospital for CABG, early CMD was detected in 64 (32%) individuals. 10 patients were not included in further analysis by exclusion criteria. GFR was determined at least three times after CABG in 48 of 54 patients with early CMD. The average age of 48 patients with CHD with pre-diabetes was 60±7,4 years; CHD duration was 6,2±5,4 years. There were 37 (77,1 %) men and 11 women (22,9%). With reference to the classification by the Canadian Cardiovascular Society, FC II angina was diagnosed in 6 (12,5%), FC III in 37 (77,1%) and FC IV in 5 (10,4%) patients. 39 (81,3%) patients had a history of MI. According to the NYHA classification, symptoms of CHF I FC were found in 1 (2,1%), II FC in 19 (39,6%), and III FC in 28 (58,3 %) patients. 15 (31,3%) patients smoked; 46 (95,8%) patients had arterial hypertension, 27 (56,3%) patients had obesity. GFR of under 60 mL/min/1,73 m^2 before CABG was found in 1 (2,1%) patient. Coronary angiography suggested single-vessel coronary disease in 5 (10,4%) patients, two-vessel coronary disease in 10 (20,8%) patients, multivessel coronary disease in 35 (68,8%) patients, left main coronary artery stenosis greater than 50% in 5 (10,9%) patients. Prior to CABG surgery, 23 (47,9%) patients received angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, 13 (27,1%) patients received calcium antagonists, 46 (95,8%) patients received beta-blockers, 24 (50%) patients received statins, and 42 (87,5%) patients received long-acting nitrates.

CABG under CP conditions was performed in 42 (87,5%) patients and on a beating heart in 6 (12,5%) patients. The duration of CP was 94,8±23 minutes and of aorta occlusion 45,5±15 minutes. The number of distal anastomoses per patient was 2,8±0,8.

During the period of hospitalization 7 (14,6%) cases of intraoperative MI, 13 (27,1%) cases of acute heart failure, which required the use of inotropic agents, were registered; 10 (20,8%) patients had paroxysmal atrial fibrillation. There were no deaths. TnT level in the whole sample of patients was 0,4±0,52 ng/mL and 1,3±0,74 ng/mL in patients with MI. Complications during the hospital period (cases of intraoperative MI, acute heart failure, paroxysmal atrial fibrillation) occurred in 23 (47,9%) patients; none of these complications was recorded in 25 (52,5%) patients.

Statistical processing of the study materials was performed using the SPSS software package. Results are presented as M±SD, where M is an arithmetic mean and SD is a standard deviation, or as Me (25%–75%), which is a median (interquartile range of percentile 25-percentile 75), depending on the distribution type. To assess the significance of differences between groups Student's t-test, Mann-Whitney U-test and the method of percent comparing were used. The reliability of the dynamics of indicators was determined using the paired Student's t-test or Wilcoxon test, depending on the distribution

type. To identify characteristics of prognostic value, the stepwise logistic regression analysis method was used. Characteristics differences with a significance level of P<0,05 were judged to be significant.

Results

In our study, we obtained data that the rate of early CMD in patients with CHD, who were hospitalized for CABG, was 32%.

In patients with chronic CHD with early CMD a decrease in GFR after surgical myocardial revascularization compared with the baseline Me from 89,4 (77,6-104,8) to Me 77,8 (58,7-95,6) mL/min/1,73 m^2 (P<0,010) was registered. The number of patients, who had GFR<60 mL/min/1,73 m^2 after CABG, increased from 2,1% (1 patient) to 22,9% (11 patients) (P<0,064). The proportion of people with renal dysfunction due to CABG was 21,7% (10 patients). None of the patients had a reduction in GFR less than 30 mL/min/1,73 m^2 after the intervention. The maximum decrease in GFR occurred on the day one or two after CABG and was transient; by the time of hospital discharge, GFR reached baseline in most patients.

Dynamics of GFR in patients with renal dysfunction due to CABG was the following: Me 81,5 (71,7-106,9) and Me 47,4 (39,1-56,3) mL/min/1,73 m^2 before and after operation, respectively, P=0,003. In the group of patients who did not have renal dysfunction after CABG (n=37), the change in GFR was not significant (P=0,252) and was the following: Me 91,2 (81,6-104,6) and Me 85,6 (70,2-99,6) mL/min/1,73 m^2 before and after the intervention, respectively.

We have analyzed GFR dynamics in some groups of the patients: patients who had CABG under CP conditions or on a beating heart without CP use; as well as in groups of patients with complications during the hospital period or in patients who did not have complications (cases of intraoperative MI, acute heart failure, which required use of inotropes, paroxysmal atrial fibrillation).

In the group of patients who had CABG under CP conditions, we observed a decrease in GFR with Me from 89,1 (76,3-103,7) to 77,6 (57,8-98,4) mL/min/1,73 m^2, P=0,036. In the group of patients who had an operation without CP use, GFR also decreased from Me 96,4 (81,9-107,9) to Me 82,9 (63,4-91,8) mL/min/1,73 m^2, P=0,046. Consequently, GFR significantly decreased in both groups, both when performing CABG under CP conditions and without CP use. However, significant differences in the level of GFR decrease due to CABG between the analyzed groups of patients have not been identified: in the group of patients who had an operation with the use of CP, GFR decrease was 29,4±3,1%, and in the group of patients who had an operation without CP use, it was 19,5±4,6%, P=0,392.

In the group of patients with complications during hospital period after CABG (n=23), a decrease in GFR in relation to the baseline was observed from Me 92 (81,8-106,9) to Me 74,2 (56,3-89,2) mL/min/1,73 m^2, P=0,000. In the group of patients who did not have the above mentioned complications, no significant GFR dynamics was registered: Me 85,1 (76,2-100,2) and Me 79,5 (61,1-102) mL/min/1,73 m^2 before and after the intervention, respectively, P=0,797.

Consequently, our study found that moderate transient decrease in GFR due to CABG in patients with CHD with pre-diabetes was observed in the whole sample of patients; in patients who have surgery performed under CP conditions, and on a beating heart without the use of CP; a more pronounced decrease in GFR after the intervention was registered in the group of patients, who had complications during the hospital period.

To identify predictors of renal dysfunction due to CABG, the patients with chronic CHD with early CMD were divided into 2 groups: patients who after CABG had GFR less than 60 mL/min/1,73 m^2 (n=11); and patients who after CABG had GFR higher than 60 mL/min/1,73 m^2 (n=37). In patients of the two groups the following parameters were analyzed: clinical and biochemical characteristics, EchoCG results, angiographic parameters, number of cardiovascular risk factors, blood glucose levels during OGTT, surgery indicators, average and peak values of glycaemia on day one after the intervention, need for short-acting insulin use for hyperglycemia correction on day one after the surgery and conducted therapy. The analysis included 68 characteristics. Indicators, for which there were differences (P<0,05) between these groups of patients, are presented in the *Table*.

It follows from the Table that a decrease in GFR after CABG less than 60 mL/min/1,73 m^2 was associated with older age, lower baseline GFR and a prolonged period of CP.

Figures, presented in the Table, are included in a stepwise logistic regression analysis. A predictor of decrease of GFR less than 60 mL/min/1,73 m^2 due to CABG in patients with chronic CHD with pre-diabetes was an indicator of CP duration (β=0,034, χ^2=4,232, P=0,040, the relative risk is 1,035, 95% confidence interval is 1,002-1,069). Thus, the increase of the CP duration over Me 105 (86-136) minutes significantly increased a relative risk of the renal dysfunction process (GFR decrease after the intervention to less than 60 mL/min/1,73 m^2) due to CABG.

Discussion

Due to the steady increase in the number of patients with CMD or with renal dysfunction in a general population of the world population, the percentage of people with pre-diabetes,

Table

Indicators associated with a reduction in GFR to <60 mL/min/1,73 m^2 due to CABG in patients with chronic CHD with pre-diabetes

Indicators	GFR* after CABG (mL/min/1,73 m^2)		P
	> 60 (n=37)	< 60 (n=11)	
Age (years)	59±7,2 58 (53-62)	63±7,2 66 (59-69)	0,039
Baseline GFR* (mL/min/1,73 m^2)	93±17,6 91 (82-105)	82±21.2 81,5(71.7-106.9)	0,010
CP† duration (min)	90±21 85 (74-100)	108±25 105 (86-136)	0,030

Annotation: the top row of the Table presents data of M±SD, the bottom row presents median and interquartile range.

Abbreviations: GFR* — glomerular filtration rate, CP† — cardiopulmonary bypass.

as well as with CKD, referred to surgical myocardial revascularization, are also increasing.

According to the analysis conducted in previous studies, the percentage of people with early CMD among patients with CHD is 37% [10]. Similar results were obtained in our study: the percentage of patients with pre-diabetes among patients hospitalized for CABG was 32%. According to I.Z. Kiladze et al. (2013) and J. Chalmers et al. (2012) [11, 12], the occurrence of III stage CKD among patients referred to CABG was 3,1%–5,4%.

In our study, as well as in the works of Y.A. Morozov et al. (2008), A.N. Shonbin et al. (2013) and I.Z. Kiladze et al. (2013) [2, 4, 11], there was a moderate decrease in GFR after surgical myocardial revascularization compared with baseline. The frequency of re-developed renal dysfunction due to CABG in patients with CHD with pre-diabetes was 21,7%, which is also consistent with the results found in the literature on patients with stable angina: from 8% to 30% [3, 13]. Therefore, when analyzing the results of our restudy and data found in the literature, we did not receive confirmation of the fact that in patients with stable angina with pre-diabetes the incidence of renal dysfunction due to CABG is higher than in patients without CMD.

GFR decrease due to CABG was registered in interventions performed under CP conditions as well as in interventions on a beating heart without CP use. No significant differences in the severity of GFR decrease between groups of patients of CABG performed under CP conditions and on a beating heart without CP use were found, although the literature provides evidence that in interventions under CP conditions the incidence and severity of the following renal dysfunction is lower compared with interventions on the beating heart without CP use [11]. The discrepancy of our results and the data found in the literature is probably due to the fact that in our study the group of patients who had CABG on a beating heart without CP use was small (n=6).

We have also found that in patients who had complications during the hospital period following CABG, GFR decrease was more pronounced than in patients who did not have the complications.

The study shows that in patients with CHD with pre-diabetes, kidney dysfunction (GFR less than 60 mL/min/1,73 m^2) after CABG was not associated with any of the indicators of glycemic control (fasting glucose and 2 hours after glucose load in GTT; peak and average blood glucose levels on day one after CABG). At the same time, we received confirmation of some of the facts cited by other authors, in particular, that older age, reduced baseline GFR and a prolonged CP period correlate with the renal dysfunction process after surgical myocardial revascularization [4, 11, 14].

A prolonged CP period was a predictor of renal dysfunction process due to CABG in patients with CHD and pre-diabetes, thus the increase of CP duration over Me 105 (86-136) minutes significantly increased a relative risk of the renal dysfunction process after the intervention (GFR decrease after the intervention to less than 60 mL/min/1,73 m^2). The obtain results are in close agreement with literature data, testifying that a prolonged CP period is one of the leading risk factors for renal dysfunction process after surgical myocardial revascularization [4, 11, 14].

Conclusion

Thus, the following facts were the main result of our study. Almost every third patient, referred to CABG, has pre-diabetes. Patients with stable angina with pre-diabetes have a moderate transient GFR decrease after the intervention compared with baseline. In most patients, GFR reaches baseline by the time of discharge from the hospital. A more pronounced GFR decrease after the surgery is observed in the group of patients, who had complications during hospital period. The proportion of patients with renal dysfunction due to CABG (GFR decrease to less than 60 mL/min/1,73 m^2) is 21,7 %. In view of our own results and literature data, the incidence of renal dysfunction due to CABG is not significantly different among patients with pre-diabetes and without CMD. The factor associated with the process of postoperative renal dysfunction in patients with chronic CHD with pre-diabetes is a prolonged CP period. The increase in the CP duration to over Me 105 (86-136) minutes significantly increases the risk of postoperative renal dysfunction.

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ALTERNATIVE TO Q WAVE DIAGNOSIS USING CARDIAC ACTION POTENTIAL PROPAGATION TIME MEASUREMENT

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The diagnosis of myocardial infarction is done by ECG through the observation of Q waves in one or more leads. The paper describes the relationship between Q waves and the propagation time of the Cardiac Action potential and a technique by which this time of propagation itself can be measured. Rather than observing the Q wave pathology in its very small peak of the total QRS complex, a more refined method is thus made available for continuous patient observation. This propagation time rises from 15 ms to 35 ms or more in progressive pathological conditions. A simulation has been done which illustrates how the Q wave is generated from the travelling action potential wave in the ventricle. The authors have utilized the easy to use novel EPIC Microelectrodes from Plessey Electronics, which are jelly free and provide easy attachment by simple skin contact. Multiple sensors were placed on the chest and the propagation time was measured by differential voltages between them. An embedded controller was used to pick these signals in digitized form and calculate the time intervals. The measurement procedure is simple and highly non invasive. Records from outpatients with cardiac pathology were taken and it was verified that this AP time increases with the Q wave width. This AP propagation time is a more refined method of observing pathological changes than the Q wave, since progressive changes in cardiac condition can be indicated by changes in the millisecond values. It has been verified that the values match with to the usual Q wave width timings.

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Key words: electrocardiogram, action potential, Q-wave, action potential propagation time, EPIC sensor.

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AP — action potential, APP — action potential propagation, MI — myocardial infarction, ECG –electrocardiogram, STEMI — ST elevation with myocardial infarction, EPIC — electric potential integrated circuit, ADC — analog to digital converter, DSO — digital storage oscilloscope.

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АЛЬТЕРНАТИВА ДИАГНОСТИКЕ Q-ВОЛНЫ С ИСПОЛЬЗОВАНИЕМ ИЗМЕРЕНИЯ ВРЕМЕНИ РАСПРОСТРАНЕНИЯ СЕРДЕЧНОГО ПОТЕНЦИАЛА

Ananthi S., Vignesh V., Padmanabhan K.

Диагностика инфаркта миокарда проводится с помощью ЭКГ через наблюдения Q-волны в одном или более отведениях. Рассмотрена взаимосвязь между Q-волнами и временем распространения сердечного потенциала и метод, с помощью которого это распространение может быть измерено. Вместо того чтобы наблюдать патологию Q-волны в ее самой маленькой точке возвышения во всем комплексе QRS, становится доступным более современный метод для непрерывного наблюдения за пациентом. Это время распространения поднимается от 15 мс до 35 мс или более при развивающихся патологических состояниях. Совершенное моделирование показано, как Q-волна генерируется из блуждающего потенциала действия волны в желудочке. Авторы использовали простой в использовании современный EPIC микроэлектрод производства Plessey Electronics, который не требует лубрикатора и обеспечивает легкое крепление путем простого контакта с кожей. Многочисленные датчики были размещены на груди и время прохождения измерялось с помощью дифференциального напряжения между ними. Встроенный контроллер использовался, чтобы фиксировать эти сигналы в цифровом виде и вычислять интервалы времени. Процедура измерения проста и весьма неинвазивная. Были использованы записи амбулаторных больных с кардиальной патологией и выяснилось, что этот потенциал действия возрастает с шириной Q-волны. Этот метод распространения потенциала действия является наиболее усовершенствованным методом наблюдения патологических изменений Q-волны, поскольку прогрессивные изменения в состоянии кардиологического больного могут быть отмечены путем изменения значения миллисекунд. Было проверено, что полученные значения совпадают с обычной шириной Q-волны.

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Ключевые слова: ЭКГ, потенциал действия, Q-волна, время распространения потенциала действия, датчик EPIC.

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The recording of ECG in cardiac care uses the externally placed electrode differential potentials. The heart's ventricular contraction is due to the conducting nerve impulse from the Atrio Ventricular node to the entire ventricular volume. This internal potential is known as the "Action Potential" (AP) [1] and this propagates through the ventricle in each heart beat. It has a sharp rise (<20ms), a plateau period (0,4-0,6s) and a droop time (0,2-0,4 s) back to the resting potential and is about 100 mV is amplitude.

Time measurements on a full ECG of a heartbeat have been made in several ways and even automatic analysis of variations attempted [2]. However, what we deal with in this paper is the time of AP propagation, which is initiating the compression of the ventricle.

The effect of a traveling wave of this action potential is seen as the familiar ECG waveform. In it, the QRS complex is a representation of the rising AP. Several models for QRS complex estimation have also been reported as signal processing exercises [3].

The propagation of the action potential impulse through the ventricle is via nexus or gap junctions [1, 4] and the specific subcellular distribution of the gap junctions packed by rod shaped cardio myocytes causes continuous conduction [5]. In a pathological condition, the substrate associated with Myocardial infarction (MI) contains islands of surviving myocardium interconnected by narrowed strands with reduced coupling through nexus junctions. In diseased heart, structural non homogeneities are present [6] which cause delay in the AP Propagation. Assessment of myocardial injury is indicated by the external ECG waveforms through Q wave changes (Figure 1), T wave abnormality, ST deviation present long after a MI and so on. Myocardial infarction recognized through just ST elevation (STEMI) is not very decisive in assessing MI and methods of vector cardiography alone could detect delays in AP propagation [7].

Q waves with amplitude more than one fourth of the R wave in Einthoven and Wilson leads are taken as pathological. It is stated [8] that patients with Q wave MI had worse prognosis compared to those without Q wave MI and hence warrant a closer follow up. The presently observed Q wave diagnosis relies on the small segment within 1 to 2 squares in the ECG record (Figure 1). Time measurements based on the width and half height of the Q wave vary from 15 to 35 or even 40 ms in MI. It is stated that a mere presence or absence of a Q wave greater than 30 ms in duration may lead to "correct" diagnosis of infarction or not in 79% of trials.

The genesis of the Q wave has been simulated as due to the propagation delay of the cardiac action potential wave. Any interim delay in the ventricular fibers will cause a Q wave to appear on the externally recorded ECG electrodes.

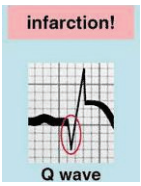

Figure 1. Q waves in a ECG record is significant in myocardial pathology.

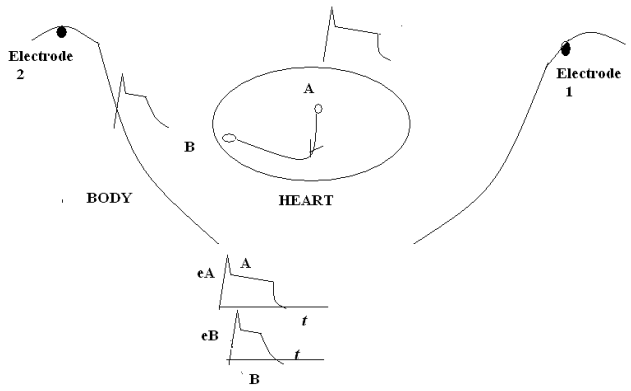

Figure 2. Showing the waveforms in the Ventricular fibers reaching the electrodes on the body surface.

This fact has been verified by simulating a propagating action potential wave and its effect on the voltages picked from the chest electrodes.

In Q wave patients, the presence of MI certainly causes local delay in the AP propagation and hence the time course of its propagation is a vital diagnostic aid in cardiac care.

At higher heart rates, the AP propagation time was not found by our measurements to decrease. Since it depends only on the anatomy of the ventricular fibers, MI causes AP delay which is almost the same even at higher heart rates. But, because of conduction contraction coupling, [9] fibrillation will set in with MI and high rates. A slow conducting segment will contract incongruously with the rest of the myofibers, leading to fibrillation. The AP propagation time measurement and its continuous trend observation will help a long way to avert events.

The paper is arranged as follows. The second section describes about our novel synchronous multiple lead recording. The third section describes the measurement circuitry using a PIC microcontroller on an LCD display. The fourth section provides some verification results. The conclusion states the points of importance and the usefulness of the technique for cardiology work.

Material and methods

A. Simulating Q waves from Action Potential waves

In order to correlate the AP Time of propagation with the Q wave, an useful analysis was made in MATLAB. Figure 2 shows the torso and the typical electrode points from where the signal waves are picked up.

The action potential waveform has the following parameters:

1. Initial rise time t_r (Mainly membrane dependent — Capacitance)
2. Resting potential p_r (Depends on external Sodium Concentration)
3. Peak potential p_1 (Depends on Potassium concentration inside to outside ratio)
4. Peak time $t_{p\ (ms)}$ (Depends on membrane recovery time for K^+ efflux)
5. Exponent decay of repolarization t_{c1} (Calcium membrane recovery rate)
6. Calcium conducting time t_{CA} (Amount of Ca ions in external fluid).

For instance, the data [40 -30 85 20 350 0.25] indicates t_r=40ms, p_r=-30mV, p1=80mV and so on for a typical action potential waveform.

The two waveforms at locations A and B are slightly different because:

I) The action potentials are locally generated signals in the cardiac fibers. There might be slight differences in the ionic concentrations locally. Therefore, the potentials differ.

II) The plateau period of the A.P. is dependent on Calcium concentration and also on the rate of contraction of that fiber. The distal fibers have shorter plateau period

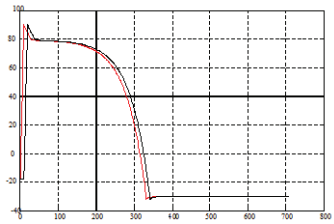

Figure 3. The action potentials waves at the two points A and B.

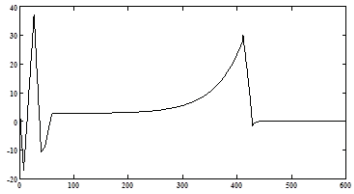

Figure 5. A Q wave is seen when the first parameter is changed forAP2.

and so the wave of A.P. at B restores to resting potential quicker.

III) The action potential wave is electro-tonically conducted from A to B. The rise of the A.P. at A is triggering the immediate fiber; this raises the threshold of membrane conductance change and at this immediately next fiber. That elicits an A.P. in that next fiber. In this manner, the entire path of fibrous tissue from point A to point B is triggered one after another. A time is taken for this and hence the start of the A.P. at B is delayed by the time taken for the electro-tonic conduction. There is a delay between the two waveforms shown at A and B.

Now let us assume that the voltage externally picked at electrode point 1 on the far away body surface is proportional to the voltage to the point A inside and that the voltage picked at body surface electrode point 2 is proportional to the voltage at point B inside.

It is true that the signal at 1 is not only due to that at A but also to that at B. However, because 1 is near to A, we get a better contribution from A than from B.

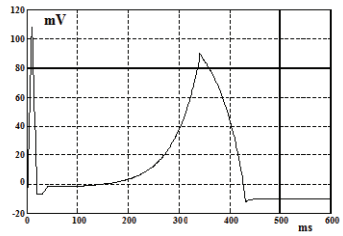

Figure 4. This is a typical ECG wave as usually seen in Lead I for normal heart.

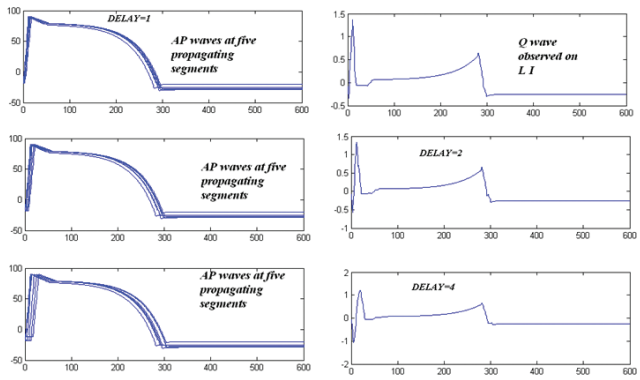

Figure 6 and b. The left figures shows the AP waves at the sequential segments on the path A-B. The right figures deduce the ECG from the electrode voltages 1,2. Three delay values are assumed.

Thus, we can write

$e_2 - e_1 = G_2 e_B - G_1 e_A$ (2.1)

The G's are the conductance's of tissue in between the body surface and points A, B. Points 1 and 2 are going to the amplifier inputs, which is a differential amplifier (Figure 3).

The subtracted waveform will be of the shape of the usual ECG between lead terminals 1, 2 (Figure 4).

There is no significant Q wave in the above Figure 4.

Rise time change en-route causes Q wave

A look at the simulated wave in figure below (Figure 5) is a clear example ECG (though sketchy) having a Q wave.

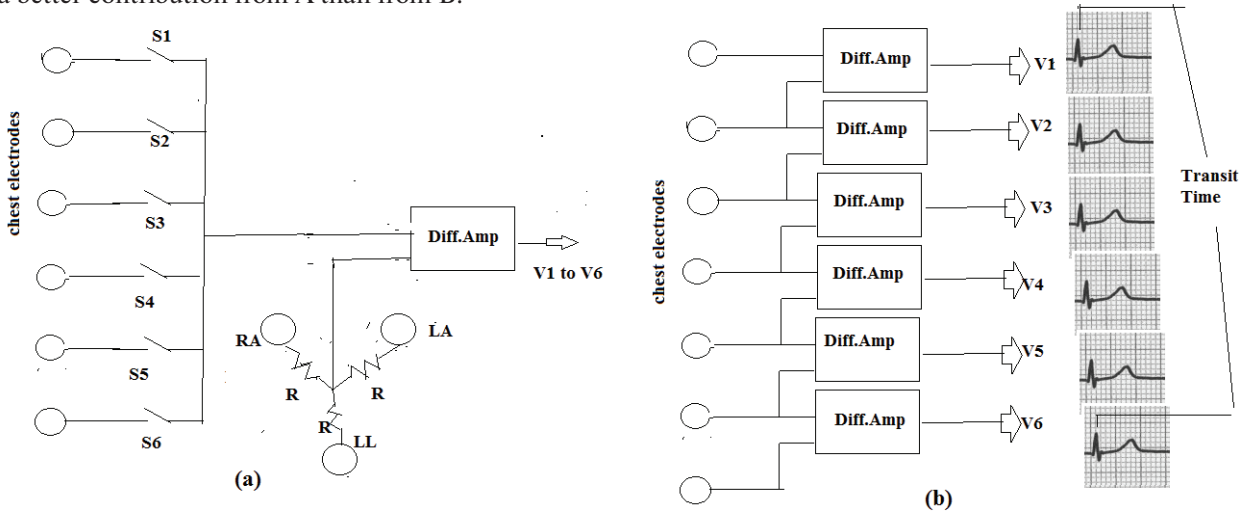

Figure 7. The use of multiple differential amplifiers along with EPIC electrodes 1 to 6 for transit time measurement.

Its peak value is 40-45% of the R wave and hence is a pathology simulation. Let us now put down the simulation parameters, which gave rise to this figure.

Parameter for AP1 = ([40 -30 85 20 350 0.25]);

Parameter for AP2 = ([20 -30 85 20 380 0.21]);

Delay = 7 ms for AP2

Suppose we are to record ECG from a set of five electrodes placed on the chest from right to left, somewhat at equal distances. The five Action potential waves are assumed to have delays at the five segments on the path along the ventricular tissue as shown in Figure 6a. Conductance values are assumed from the segment sites to the electrode positions. The Figure 6b shows this waveform, with the Q wave in it. As the delay increases, the Q wave width and depth both increase. This indicates how the AP propagation time is a more realistic measurement than the very small looking Q wave in the usual ECG records.

B. Simultaneous multiple electrode recording

So, if we have to measure the delay in propagation time over the entire ventricle, multiple electrodes must be placed on the chest wall and the difference voltages between them will show the time of propagation by the positions of the R wave peaks. For this purpose, all waveforms must be obtained from the same heartbeat, i.e., simultaneously. If we have to find out the said propagation time in one single beat, it will require multiple differential amplifiers (Figure 7). The outputs of these may then be compared by the time instants of the QRS peaks to recognize how the wave is propagating and initiating the action potentials through the ventricle.

We now describe the Synchronous Recording technique for measuring the time of propagation of the AP. To cite a previous reference, single action potential records from *in vitro* cardiac Purkinje fibers from sheep have been displayed with digital electronic circuitry [10] and the maximum rate of rise of the AP has been measured by McGillvray et al [11], but so far, non invasively, AP propagation time has not been measured with any instrument. This AP propagation time in a heartbeat in only between 15 to 20 milliseconds in the normal heart, while significant increase is related to conduction disturbances in the heart chamber due to infarction.

The electrode system for the purpose is also very simple, with six electrodes spread on the chest similar to the V leads and the 5 differential voltages are used to determine this time. The pathological Q waves in the ECG are the most often looked at patterns by the cardiologist. The increase in amplitude and width of this Q wave is associated with infarct tissue. The Q wave, as is being observed in standard ECG records, occupies just 1-2 mm of space horizontally and about 15mm vertically. When it is required to check for improving heart conditions after a pathological Q wave, the same has to be carefully observed for very small changes in the width of it, which is after all, only 1 to 2mm in the record. Thus, any improvement in the heart with drugs for blood thinning etc., cannot be noticed easily. Since the Q wave is dependent only on the propagation time of the AP, it is much more useful if one could read the beat to beat propagation time. Changes from 30 ms little by little, down to 25 ms, as the heart recovers, could be observed. This is useful to understand the efficacy of drugs administered in the care unit. An instrument of this kind has not been described or manufactured for cardiac care so far.

Usually, ECG waveforms for the Leads 1-3, the Auxiliary leads and the precordial leads are taken independently. Though these waveforms do not pertain to one and the same heart beat, the recorded waves indicate the pathology because there are not such fast changes in the beat to beat waveforms. The current ECG technique of recording with ECG Recording apparatus does not use simultaneous recording.

When we arrange all the V lead electrodes all at once on the chest and record the waveforms differentially from the sets of leads, we are able to do a synchronous recording. Such a recording from several leads is able to indicate the propagation of the R wave from one set of electrodes to another. Since the sharp rising R wave on the external skin electrode coincides with the first rise of the intracellular action potential, we could follow the propagation of the AP through the ventricle. By measuring the time difference between the R waves in the first and the last electrode, the propagation time is found. The value of this time is displayed directly in milliseconds, once in every two beats.

If the propagation of the AP is smooth and uniform throughout the ventricle with the same speed, then the time of propagation is not more than 15ms. In pathological cases, where there are conductance disturbances brought about by tissue damage, there is a local slowing down of the rise time of the AP in the damaged fibers and hence the overall time increases. In the case of patients with Right Bundle Branch Block (RBB), the time increases to more than 30 ms.

Q waves with amplitude more than $1/4^{th}$ of the QR amplitude and wider than 15ms appear when there is such delay in the AP propagation. Diagnosis presently relies more on the Q wave, as seen in its small graph. The AP transit time is a more realistic approach to such diagnosis.

The AP waveform is not exactly the same in all the fibers throughout the ventricle. The inner fibers from where the wave propagates have a longer plateau period. As the wave progresses into the ventricular tissue, the main variations in the AP are in the plateau period and the depolarization time. These variations affect the ST segment slope and the T wave. Simultaneous recording from all electrodes can elicit information about the place of such conditions which cause a drooping T wave and hence an ST elevation.

If the propagation does not meet with infarct tissue, then the time between the electrodes is uniformly increasing; otherwise, a sudden increase of time between R waves

of two adjacent electrodes indicates pathological problem local to these electrodes. Thus, where the time exceeds nominal 20 ms values, it is necessary to note the timings between all the electrode pairs, 1-2, 2-3, 3-4, 4-5, 5-6.

Then the differential voltages from these electrodes in the order 1-2, 2-3, 3-4, etc., were taken and observed on a multiple channel Agilent make digital storage oscilloscope. It was by taking the recorded digital values form it through its USB to the computer laptop and through Matlab programs, that we could get the displays and enumerate the time between the several wave peaks of QRS as well as the time course of propagation of the action potential from right side to the left side of the heart.

It was very soon realized that it would be more useful if an on-line continuous indication of the time course of action potential through the heart in several sections from right to left could be provided as an adjunct to the actual ECG wave records.

In a heart with a RBB, the time is slow initially but further to the bundle branches, the AP propagation is very fast. In other words, by looking at these intermediate timings, it is possible to assess where the pathological problem of ischemic tissue or infarct area is likely to be and what could be the artery on the heart that might have led to this condition.

C. Electrode set up for the Measurement

Electrodes and pre-amplifiers for ECG have long been under development to provide patient comfortable signal acquisition. For instance, a ground-free multichannel amplifier with a simple 2 electrode bio-amplifier is described in [12].

Plessey Microelectronics has brought out sensor electrodes for use as ECG electrodes recently [13]. These electrodes do not need the presently employed contact resistance reducing jelly. Such a jelly is usually applied to ECG electrodes on the skin. This sensor (Figure 8) couples the signal capacitively and hence a mere placement on the skin surface firmly is sufficient without any applied jelly. Jelly pastes applied to skin lower the contact resistance very much and lead to the possibility of electric shock in case of faults in monitoring apparatus connected to the care patient. Because the Plessey electrodes use capacitive coupling, they are high impedance contacts and are free from such electric shock. Further, the Plessey electrode is not just a contacting metal plate like the present ECG electrodes. This is actually an integrated circuit chip directly held on the skin and includes the pre-amplifier with its high input impedance and high common mode rejection ratio built into it. Thus, with these Plessey electrodes, it is much easier to pick the ECG signal and amplify it further with a simple differential amplifier. Instead of special FET input balanced circuits at the input end, an ordinary OPAMP suffices because the output impedance of the EPIC sensor is low.

Yet another usefulness of these electrodes is that several chips can be closely kept on the skin, as is done for taking

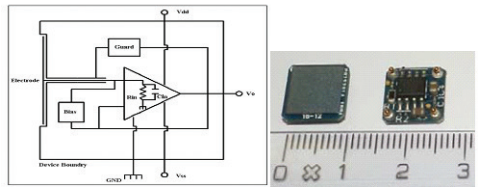

Figure 8. Plessey "EPIC" Capacitive ECG Micro Electrode and its internal schematic diagram.

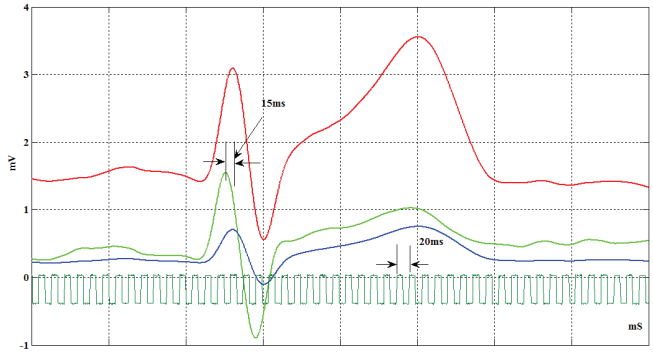

Figure 9. Showing a patient Action potential propagation by means of three differential electrode voltages from right to left. This is a case of slight ST elevation with a time of 15 ms.

V-lead signals. With jelly contact, there will be jelly spreading, causing a short circuit if electrodes are closely spaced on the chest skin. Further, as no jelly at all is required here, we need not prepare the surface of the skin before placing the electrodes.

We could place several electrodes all at the same time and the simultaneous ECG records from all of them could be taken.

By using several electrodes spread on the chest from right to left, similar to the V leads though not exactly at the specific locations for V leads, we were able to record the ECG signals differentially. At first we employed a multi channel Digital Storage Scope for the purpose which was adjusted to take 5 Kilosamples of data on all channels per second so that the fine tips of the R wave could be collected. The DSO data was collected through its USB support and transferred to a laptop computer running Matlab 2012.

From Q wave observations, small changes in pathology cannot be inferred; but with this time measurement, which will change slowly in a progressively deteriorating or convalescing heart, the same can be measured with an accuracy of 0,1 ms.

For illustration, two such graphs are shown below. The first one is that of a patient with mild ST elevation and the time of APP is indicated as 15ms (Figure 9).

As another illustration, the Figure 10 gives a 35 ms delay for the patient who has noted Q wave. The three graphs shown pertain to the three leads from right to left of the chest. It may be noted that the half width of the Q wave is also of the same time as the Time of Action potential Propagation.

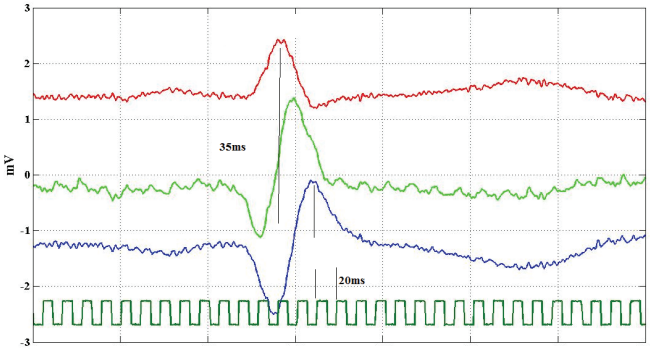

Figure 10. This figure is that of a heart with Q wave pathology (NSTEMI) and shows 35 ms delay.

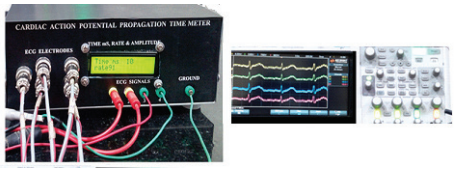

Figure 11. The instrument shows the time of APP. Electrodes to chest are taken from connectors on the left and the amplified signals can be taken for observation from the sockets "ECG Signals". The Digital Storage scope shows the waveforms.

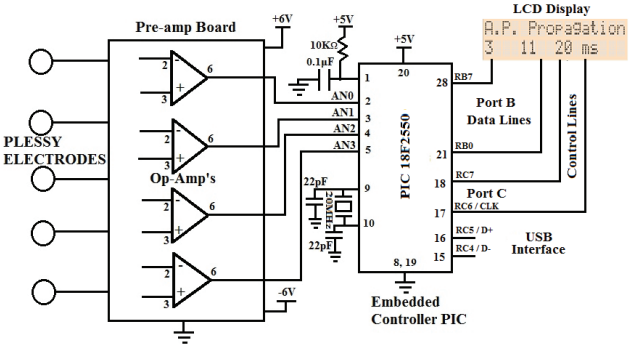

Figure 12. The use of an embedded controller could display the propagation timings.

Table 1

The flow chart of the program with the embedded microcontroller

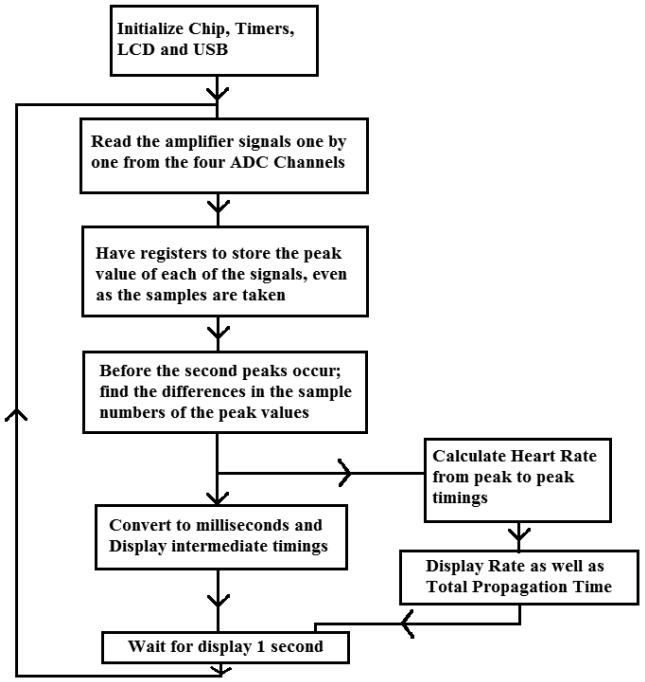

Table 2

Some clinical tests on cardiac patients

Pathology as per ECG of patients	No. of patients examined	APP TIME
T- inversion	4	10-15 ms
RBB with Mild Q	7	30-40 ms
RBB without Q	15	20-25 ms
STEMI	7	25-30 ms
NSTEMI	5	30-45ms

D. Measurment and on line continuous display of action potential propagation time

Figure 11 shows the instrument as such. The signals from five such sensor pads are connected to four operational amplifiers for differential amplification (Figure 12). Thus, we obtain four signals, with an amplification of 500 for each. These signals are connected to a four channel digital scope. Further, these signals are also connected to the analog to-digital converters on the PIC18F2550 microcontroller. The ADCs in it can be operated at 50 microsecond per sample. The values of the four channels are processed by the embedded controller to determine the QRS peak of each of the signals. To eliminate the effect of base line drift, in addition to finding the peak of the signal, the first derivative of the signal is also found between successive samples and the maximum point of the derivative is also found for all the four signals. If the two timings, viz., the time of the recognized peak and the time of the maximum rate of change coincide, then the readings are assessed to be correct and the time differences between the signals are calculated based on the sampling rate. These are the three time values which are displayed on line in the LCD alphanumeric display connected to the embedded controller circuit. The display is updated every five seconds and hence changes in the timings, if found to be progressively increasing or improving, can be used for diagnosis of the condition of the heart.

The program for the PIC18F2550 to perform this task and provide an on line display of the propagation was developed using the the powerful OSHON simulator for PIC18 Series [15]. The flow chart of the program is shown in table I.

It is normally thought that at an increased heart rate, say from 72 to 100, the timings will decrease proportion-

ately. But it was found that the rate does not relate to the timing of the propagation of the action potential. The timing is very small compared to the sinus rhythm which causes the heart beat to vary and hence there is not much change even at a higher rate of heart beat.

The following description is given for the electronic enthusiasts about the circuit. The PIC18F2550 series is a Microchip Inc. make embedded controller with 20 MHz clock and built in peripherals like PWM,ADC UART and USB interface. The chip has an excellent reset circuit and operates with power on reset action, for which a resistor of 10k and a 0.01uF capacitor are connected to pin no.1. Pins of port A, from 2 to 6 are configured by a command code to operate as analog to digital converter input pins. The reference voltage pin can be given a voltage different from the 5V supply of the chip and by giving 2 V as a reference, the range of digital values will be 0 to 255 for 0-2 V. The operational amplifiers used with the Plessey electrodes are simple 741 devices. The power supplies for the OPAmp are obtained from two 6V batteries, rather than mains derived supplies, so as to eliminate hum completely. From these same 6V batteries, through a resistor pair, the + and −5V supplies for the Sensor electrodes are derived and limited by 5V zener diodes. The PIC chip being connected through USB to a lap top computer, gets its supply of 5V from the latter. The laptop is kept pre-charged and unplugged from mains for safety while connecting electrodes to the chest. Apart from the analog input signal connections, the PIC chip is connected to an alphanumeric two row LCD display. This needs 8 data lines and four control lines, which are available as shown in the Figure 13 from the chip ports B and C. Additionally one bit of port C is programmed and taken to an output pin. It provides a pulse at each and every data acquisition sample period. This serves to calibrate the timing of the QRS peak displacements while setting up. After noting this time period, the actual timings are evaluated in milliseconds and displayed on the two rows of the LCD.

Results

Cardiac Care outpatients at the nearby Hospital were tested with their consent by placing the EPIC electrode strip on the chest and the time of Action Potential Propagation (APP) measured. Their ECG records and previous medical reports were also noted. From the set of tests, the following table verifies that concept.

Patients with long standing myocardial infarction were those who had the T_{APP} prolonged to as much as 40ms. They are classified as non ST elevation myocardial infarction candidates (NSTEMI) as per diagnostic parlance. Those who had recent MI with ST elevation (STEMI) had also long T_{APP} upto 30ms.

As far as patients with known conductance disturbance with or without Q wave of significance, the time delay due to Bundle Branch Block pathology gives readings in the 20-25 ms for those without Q waves and 30-40 ms with

Figure 13. The Mode I display shows the four QRS peak values and the corresponding timings in ms. In mode II of display, it shows the total AP Propagation time and the heart rate.

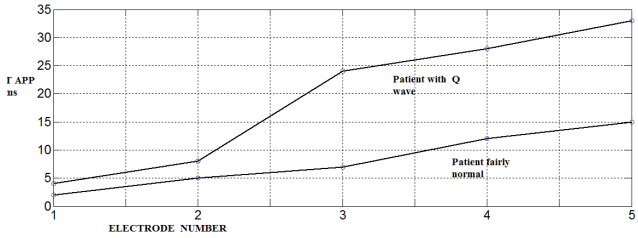

Figure 14. Showing the delays between Electrodes 1 to 5 as they are placed in the precordial lead positions for fairly normal heart and one with MI.

those who have an associated infarction at the time of their heart attack. Patients with T wave inversion are not gullible at all because T wave inversion due to Ischemia does not very much increase the T_{APP}. Thus from a group of patients, thus far it is learnt that the T_{APP} will increase in the case of infarction and RBB and is a more decisive parameter for pathological classification than Q waves.

By plotting the intermediate timings as shown in the insert figure (LCD Display) of Figure 14, a plot could be made to show how the AP propagates. Because it is impossible to position the electrodes with a uniform mapping of the heart by external placement, the line joining the intermediate delay is somewhat skewed and not a straight line. But, the location where the time delay is present is indicated in the above figure for a patient with Q wave, as between the mapping positions of electrodes 2 and 3.

Conclusion

We have realized a method for synchronous recording of ECG waveforms and used the same to evaluate the time of propagation of the Action potential in the ventricles. The EPIC microelectrodes are a boon because of their no-jelly contacts makes it instantly possible to fix the electrodes and observe the reading of time of APP with the least patient discomfort. It also eliminates the complex differential amplifiers normally used for high CMRR and input impedance. The time of action potential is measured on our simple embedded controller. Cardiac monitor makers could include this in their own hardware and display this AP propagation time for good. The usefulness of this time in cardiac diagnosis has been stressed in the paper.

Acknowledgment. The experimental data shown were collected from the Vadapalani Multi-Speciality Hospital, Chennai with individual permissions from the patients.

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ANGIOTENSIN II RECEPTOR TYPE 1 EXPRESSION IN PATIENTS WITH MULTIFOCAL ATHEROSCLEROSIS

Mykhailichenko I. S.

Local expression of rennin-angiotensin system (RAS) components significantly increases in patients with arterial hypertension and atherosclerosis with or without elevation of RAS activity in the blood. Our objectives was to assessment and compare the expression level of angiotensin II type 1 receptor in the smooth muscle cells in arteries of patients with multifocal atherosclerosis and the role of local angiotensin II receptor type 1 (AT1R) expression in the disease progression. The study results suggest that the tissue RAS activity increases inhomogeneously among patients. It was interestly that AT1R expression levels in intact arteries does not differ of those in atherosclerotic arteries. Most of patients had expression of angiotensin II type 1 receptor in smooth muscle of arteries; strong elevation had 43,8% — 50,0%. Our study suggest of role of local RAS activity, but we proposed existence of another than only angiotensin II type 1 receptor mechanisms of low or high susceptibility of arteries to atherosclerosis in patient with multifocal atherosclerosis.

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Key words: renin-angiotensin system, angiotensin II receptor type 1, multifocal atherosclerosis.

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RAS — rennin-angiotensin system, AT1R — angiotensin II receptor type 1, CVD — cardiovascular disease, Ang II — angiotensin II, BP — blood pressure, SMC — smooth muscle cell, AH — arterial hypertension, IHC — immunohistochemical.

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ЭКСПРЕССИЯ РЕЦЕПТОРОВ АНГИОТЕНЗИНА II 1-ГО ТИПА У ПАЦИЕНТОВ С МУЛЬТИФОКАЛЬНЫМ АТЕРОСКЛЕРОЗОМ

Михайличенко Е. С.

В патогенезе кардиоваскулярной патологии одну из ведущих ролей играет ренин-ангиотензиновая система (РАС). При этом в развитии атеросклероза и ремоделирования сосудов особо важное значение имеют компоненты тканевых, локальных РАС. В данном исследовании мы изучали плотность рецепторов ангиотензина II 1-го типа (AT1R), как маркера активности РАС, в гладкомышечных клетках сосудов (ГМКС) у пациентов с мультифокальным атеросклерозом и артериальной гипертензией. Оказалось, что только у 50% пациентов наблюдалась высокая плотность AT1R в ГМКС, при этом в маммарных артериях, наименее подверженных атеросклерозу, плотность AT1R не отличалась от таковой в сосудах, пораженных атеросклерозом. Механизмы, определяющие неоднородность активности тканевых компонентов РАС у пациентов с атеросклерозом, требуют дальнейшего изучения.

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Ключевые слова: ренин-ангиотензиновая система, рецептор ангиотензина II 1-го типа, мультифокальный атеросклероз.

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Renin-angiotensin system (RAS) plays a central role in pathogenesis of cardiovascular diseases (CVDs) [1]. Its primary biologically active component angiotensin II (Ang II) mediates both direct physiological effects of RAS as vasoconstriction and blood pressure (BP) regulation and pathophysiological ones affecting the function of practically all organs including heart, kidneys, blood vessels, and brain. So, Ang II plays an important role in development of hyperplasia and hypertrophy of smooth muscle cells (SMC) of vessels, hypertrophy and remodelling of myocardium, arterial hypertension (AH), myocardial infarction, atherosclerosis, in-stent restenosis, and renal fibrosis [2, 3]. Here, most of AngII pathological effects occur via its interaction with angiotensine II type 1 receptors (AT1R). Traditionally, RAS is considered as circulating hormonal system, however, according to current data, except the circulatory RAS, majority of organs and tissues do also have local, tissue RAS that possess local paracrine and autocrine functions where the tissue RAS components express and function independently of circulatory RAS [4]. In this connection, study of local RAS activity and their contribution into development of CVDs is a research area of current interest. As the expression level of AT1R determines the biological efficiency of Ang II and RAS in whole, study of AT1R density and mechanisms of its regulation poses an especial interest.

Objective: assessment and comparing the activity of tissue RAS based on the assessment of level of AT1R expression in SMC of intact and atherosclerotic arteries of patients with multifocal atherosclerosis.

Material and methods

We investigated 30 resected medium caliber arteries. 16 arteries of patients with low extremity atherosclerosis collected during vascular reconstructive operations made the first study group. The second group consisted of 14 intact mammary arteries collected during coronary bypass

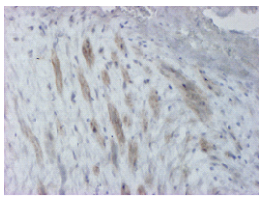

Figure 1. Focal IGH expression of AT1R in human atherosclerotic artery. Visualization system DAKO Envision Flex+ x150.

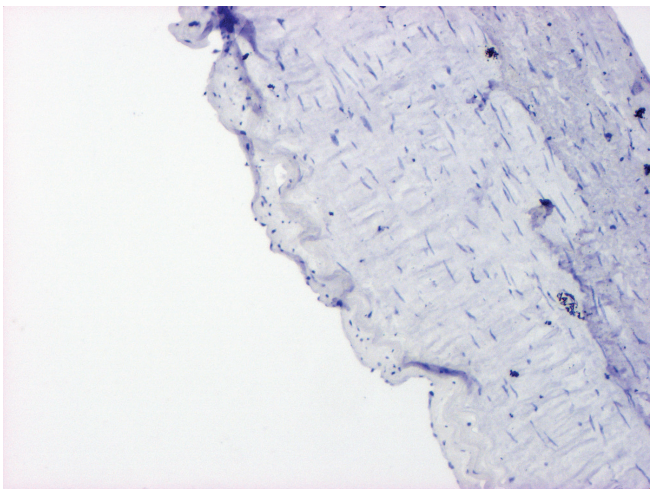

Figure 2. Lack of IGH expression of AT1R in human atherosclerotic artery. Visualization system DAKO Envision Flex+ x75.

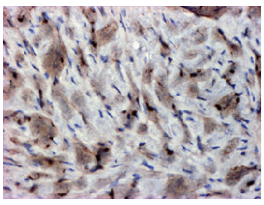

Figure 3. Strong IGH expression of AT1R in human atherosclerotic artery. Visualization system DAKO Envision Flex+ x75.

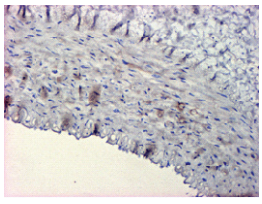

Figure 4. Focal IGH expression of AT1R in human mammarian artery. Visualization system DAKO Envision Flex+ x75.

in subjects with multi-vessel coronary disease. The groups did not differ significantly by age, gender, arterial hypertension severity, concomitant disorders (diabetes mellitus, obesity etc.). Multifocal atherosclerosis was detected at all patients according to the data of arteries ultrasound examination and angiography.

Collected material was put into neutral buffered formalin solution 10% (pH 7,4) and fixed during 24 hours. After dehydration, the pieces were poured into paraffin according to standard techniques. On rotation microtome Shandon Finesse 325 (Thermo Scientific, USA) serial histological sections 4 mcm thick that were further stained with hematoxylin and eosin according to standard techniques. Degree of expression of 1 type receptor to angiotensine II in muscular layer of vessels was studies with immunohistochemical (IHC) techniques. For IHC research, sections were placed onto adhesive — coated slides Super Frost Plus (Menzel, Germany). To retrieve the antigens, rehydrated sections underwent thermal treatment in solution Target Retrieval Solution (DAKO, Denmark) with use of microwave oven Samsung CE118KFR. After blocking of non-specific binding of proteins with protein block (DAKO) and of endogenous peroxidase activity with peroxidase block (DAKO) primary antibodies were applied. The polyclonal antibodies to Anti-AGTR1 (SIGMA, Sweden) were used. Visualization of primary antibodies was performed with the aid of high-sensitivity polymer detection system EnVision FLEX+ (DAKO). As a substrate for horseradish peroxidase DAB+ (DAKO) was used. Specimens were additionally stained with Mayer's hematoxylin. Next, the stained sections were mounted into semi-synthetic medium Eukit (Kaltek, Italy).

Microscopic examination of specimens and morphometric studies were performed with microscope Olympus AX70 Provis (Olympus, Japan) with the support of image analysis software application Analysis 3.2 Pro (Soft Imaging, Germany) according to recommendations of the software developer. In each case of IHC research the expression of Anti-AGTR1 marker as brown cytoplasmic or membrane staining was studied in 30 fields of view with magnification x200. Staining intensity of angiotensin II receptors in muscular layer of arteries was assessed semiquantitatively by percentage of positive cells according to 3-level scale: «-», negative (lack of positively stained cells); «+», focal or weak expression (<50% of positive cells); «++», diffuse or strong positive reaction (>50% of positive cells) [5].

Results

Similar results were achieves in both groups. In 8 arteries of the first group (50,0%) the low or focal expression (+) of AT1R was found (Figure 1), in other 7 arteries the AT1R expression (43,75%) was strong. There was no AT1R expression (-) in 1 case (6,25%) (Figure 2). In the 2nd group in 50% (n=7) of arteries the strong AT1R expression was found (Figure 3), in other 50% of cases (n=7) the AT1R expression was focal (Figure 4) or weak (Figure 5). Thus, significant AT1R expression was observed not depend on the studied vascular bed (p>0,05) (Table 1).

Conclusion

The study results suggest that the tissue RAS activity increases inhomogeneously among patients with multifocal atherosclerosis. AT1R expression levels in intact arteries does not differ of those in atherosclerotic arteries. AT1R

Table 1

Comparison of 2 groups. Chi-square test. Chi-square=0,94

Index		Frequency of occurrence, abs. (%±m%)		Significance level of difference, p
		1st group (n=16)	2nd group (n=14)	
AT1R expression	-	1 (6,3±6,1)	–	0,626
	+	8 (50,0±12,5)	7 (50,0±13,4)	
	++	7 (43,8±12,4)	7 (50,0±13,4)	

expression in SMCs is negative in patients with severe atherosclerosis that puts under the doubt the key role of RAS in pathogenesis of vascular remodelling in some cases. Further researches of mechanisms that influence the level of RAS tissue components expression are needed. The studies of low susceptibility cause of mammary arteries to atherosclerosis in high RAS activity in the presence of severe lesions of arteries at other sites are required. Probably the study of efficacy of RAS inhibitors in patients with various AT1R tissue expressions will allow to develop the prognostic methods of therapy efficiency and to individualize the treatment. Most of patients had expression of angiotensin II type 1 receptor in smooth muscle of arteries; strong elevation had 43,8% — 50,0%. Our study suggest of role of local RAS activity, but we proposed existence of another than only angiotensin II type 1 receptor mechanisms of low or high susceptibility of arteries to atherosclerosis in patient with multifocal atherosclerosis.

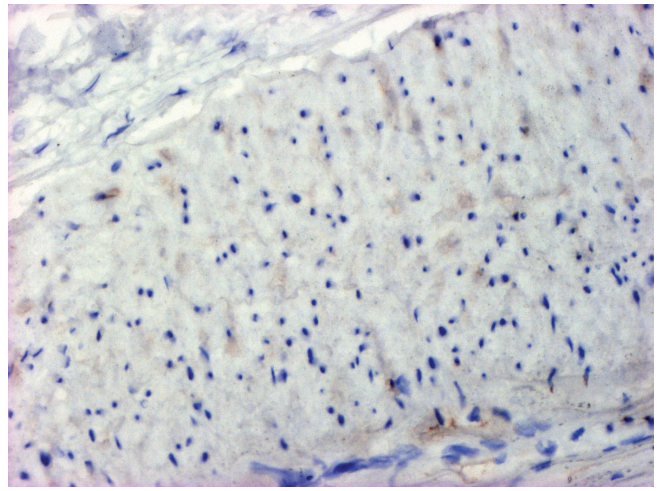

Figure 5. Weak IGH expression of AT1R in human atherosclerotic artery. Visualization system DAKO Envision Flex+ x75.

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HEART RATE TURBULENCE AS A MORTALITY PREDICTOR IN LONG-TERM STUDY IN PATIENTS WITH CORONARY HEART DISEASE

Gareeva D.[1], Zagidullin N.[1], Lakman I.[2], Islamova R.[2], Zagidullin Sh.[1]

Pathological heart rate turbulence (HRT) after premature ventricular complexes (PVCs) in patients with coronary heart disease (CHD) and myocardial infarction (MI) may predict higher mortality rate.

Aim. To estimate the predictive power HRT in 5 year observational study in patients with CHD.

Material and methods. 173 patients with CHD and in whom HRT was possible to record, were analyzed from 2010-2011 until 2015 with survival rate and turbulence slope (TS) and turbulence onset (TO) estimation.

Results. Pathological TO showed no correlation with survival rate (p>0,05) but pathological TS in 5 years period (p=0,00026) correlated with survival rate with post-MI patients. Moreover, it had a predictive power also with non-MI patients (p=0,0032). The survival (Kaplan-Mayer) curves between normal and pathological TS started to divide from the 36 months of observation. Presence of nTS in post MI patients increased mortality rate in 5,14 times (p=0,00002) and in non-MI — in 4,99 times (p=0,00002).

Conclusions. HRT slope parameter showed to be highly effective in mortality risk prediction in patients with CHD.

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Key words: heart turbulence rate, total mortality, myocardial infarction.

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CHD — coronary heart disease, ECG — electrocardiography, HRT — heart rate turbulence, MI — myocardial infarction, PVCs — premature ventricular complexes, TO — turbulence onset, TS — turbulence slope.

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ТУРБУЛЕНТНОСТЬ СЕРДЕЧНОГО РИТМА КАК ПРЕДИКТОР СМЕРТНОСТИ В ДОЛГОСРОЧНОМ ИССЛЕДОВАНИИ У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

Gareeva D.[1], Zagidullin N.[1], Lakman I.[2], Islamova R.[2], Zagidullin Sh.[1]

Патологическая турбулентность сердечного ритма (HRT) после преждевременных желудочковых комплексов (PVCs) у больных ишемической болезнью сердца (ИБС) и инфарктом миокарда (ИМ) может прогнозировать более высокую смертность.

Цель. Для оценки предсказательной силы HRT у 5-летнего обсервационного исследования у пациентов с ИБС.

Материал и методы. 173 пациентов с ИБС, у которых HRT удалось записать, были проанализированы с 2010-2011 до 2015 года на выживаемость и наклон турбулентности (TS) и начало турбулентности (TO).

Результаты. Патологические TO не показали никакой корреляции с коэффициентом выживаемости (p>0,05), но патологические TS в течение 5 лет (p=0,00026) коррелируют с частотой выживания у пост-ИМ пациентов. Кроме того, они имеют предсказательную силу также у не-ИМ пациентов (p=0,0032). Кривые выживаемости (Каплан-Майер) между нормальной и патологической TS начали делить от 36 месяцев наблюдения. nTS у больных ИМ увеличилось смертность в 5,14 раза (p=0,00002), а у не-ИМ — в 4,99 раза (p=0,00002).

Заключение. Параметр HRT показал высокую эффективность в прогнозировании риска смертности у пациентов с ИБС.

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Ключевые слова: турбулентность сердечного ритма, общая смертность, инфаркт миокарда.

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In the last decades, cardiovascular morbidity and mortality from diseases are on the leading positions in the Russian Federation. According to the World Health Organization, more than 16.5 million people a year die from cardiovascular diseases, including CHD — more than 7 million, accounting for 29.3 and 12.6% of the total mortality accordingly. Mortality from myocardial infarction (MI) in the post-MI period remains also high so is the incidence of sudden cardiac death [1], which determines the need of diagnostic and preventive measures. New parameter "heart rate turbulence" (HRT) which reflects the short-term regression of the heart rhythm with subsequent acceleration after premature ventricular construction (PVCs) was scientifically proved in 1999 [2]. It was shown that in patients with postMI period the pathological is observed, which reflects high cardiovascular risk in the patients. [3, 4]. However, it is still not clear whether the HRT reflects the high cardiovascular risk in patients without MI in the past.

The aim of the study was to improve the diagnostics of coronary heart disease in patients with HRT as a cardiovascular risk factor.

Material and methods

More than 3.000 24h electrocardiographic (ECG) record in patients with CHD were analyzed, that were treated in the department of cardiology in 2010-2011 in clinical hospital №21 Ufa, and 205 patients meeting the criteria for inclusion

Table 1

Inclusion and exclusion criteria in the study

Inclusion criteria	Exclusion criteria
Established diagnosis of coronary artery disease in accordance with the European Society of Cardiology criteria (2008); Presence of ventricular premature construction (PVCs) according 24h ECG meet the following criteria [5]: • RR intervals <2000 and> 300 ms, • PVCs with difference between the preceding sinus intervals <200 ms • PVCs with difference <20% of the average of 5 consecutive sinus intervals • PVCs prematurity index >20% and postectopic interval longer than the average RR on 20% or more; Patients should receive permanent anti-anginal therapy at the time of the study; Absence of exclusion criteria; Age <75 years [5]	Pacemaker installed; Chronic heart failure NYHA II-IV; Permanent / persistent form of atrial fibrillation and flutter; Atria-ventricular block of 2-3 degree; Sick sinus syndrome; The complete bundle-branch block; Heart rate >80 beats/min; Severe valvular heart disease, cardiomyopathy; Renal and hepatic failure; Alcohol abuse, drug addiction, the pathology of the central nervous system (cancer, metabolic, infectious, mental and others disease, brain injury, depression, epilepsy, dementia, transient ischemic attack, cerebrovascular accident in the acute stage)

were selected for the experimental group. Inclusion and exclusion criteria are presented in Table 1.

The primary endpoint in the study was overall mortality during the 4-5 year follow-up after the initial determination of HRT.

Heart rate turbulence can be determined by standard 24-hour ECG monitoring (Figure 1) [3, 6]. Two phases of HRT, the early sinus rate acceleration and late deceleration, are quantified by 2 parameters termed as turbulence onset (TO) and turbulence slope (TS). TO is calculated as: $TO = (RR_1+RR_2) - (RR_{-2}+RR_{-1}) (RR_{-2}+RR_{-1})\times100$, where RR_{-2} and RR_{-1} are the 2 R-R intervals immediately preceding the PVCs coupling interval, and RR1 and RR2 are 2 R-R intervals immediately following the compensatory pause. TS is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm R-R intervals within the first 15 sinus rhythm R-R intervals after the PVCs. Normally, there is an acceleration of sinus rhythm after PVCs, which is reflected in the negative TO value with a subsequent slowdown with positive TS.

Patients with HRT are usually stratified into three categories: 1) HRT category 0 means TO *and* TS are normal (nTO and nTS accordingly); 2) HRT category 1 means 1 of TO *or* TS is abnormal (pTO and aTS accordingly); and 3) HRT category 2 means both TO *and* TS are abnormal.

24-hour ECG monitoring was performed by"Kardiotekhnika-04-8 (M)" ("INKART", St. Petersburg) 24h monitoring with hardware, allows to record and analyze forms of ventricular complexes in accordance with HRT analysis. HRT analysis was performed in 2010-2011 in time of patients` hospitalization, and later in 2011-2015 the follow up telephone contacts was performed annually to monitor the primary endpoint.

Group analysis is presented in mean values (M) and standard deviation (m). Statistical analysis was performed using survival tables and Kaplan-Meier survival regression models, particularly the proportional hazards model (Cox model). Model coefficients estimation was obtained by maximum likelihood. Statistical analysis was performed using "Statistica 10.0"program (module "Survival analysis").

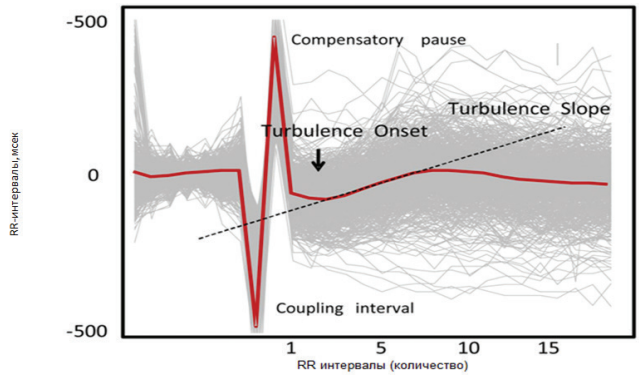

Figure 1. Estimation of HRT by 24-hour ECG:HRT smoothed curve (red curve) after averaging the signal from single tachograms (gray lines). The arrow indicates the start of turbulence (turbulence onset) and turbulence slope (turbulence slope)

Table 2

Characteristics of the investigated contingent

Parameters	Values, n=173
Age, years	67,06±0,79
Gender (m/f),	106/67
Height, cm	169,6±1,8
Weight, kg	84,6±3,0
BMI, kg/m^2	29,4±0,89
Coronary / coronary artery bypass grafting/ stenting, n	23
History of myocardial infarction, n	137
Arterial hypertension, n	130
Stroke, n	10
Diabetes mellitus, n	21
Cholesterol, mmol/l	4,78±0,08
Ejection fraction, %	54,0±1,06

Results

The main part of patients with HRT was defined by ECG 24h records analysis in 2010-2011. The survival status was estimated by follow up telephone contact and by medical events registration in state medical statistical program "Promed" providing survival data during next 5 years. 32 patients retired from the study because of contact

Table 3

Characteristics of heart rate turbulence

Parameters	HRT (n=173)
PVCs number/day	176,9±18,8
Heart rate, beats/min	68,1±0,57
TO, %	–0,96±0,25
TS, ms/RR	6,14±0,38

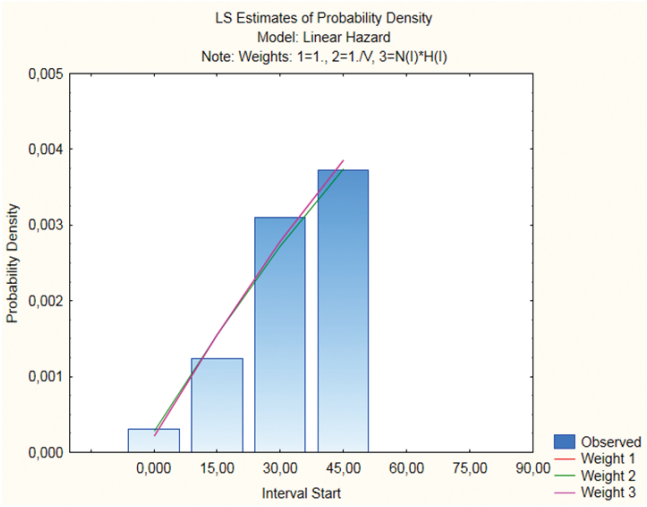

Figure 2. Mortality risk over 5 years period in patients with aTS (X axis — months, and Y–mortality risk).

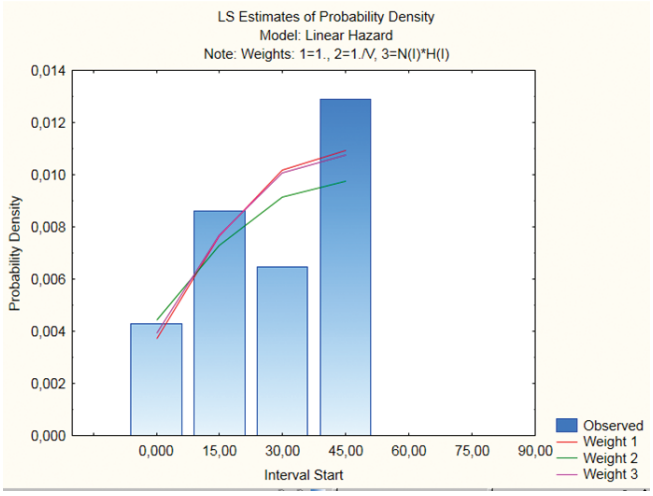

Figure 3. Mortality risk in 5 years in patients with aTS (x axis — months, y axis mortality risk).

lost and 173 patients remained available for analysis and long-term results. Table 2 shows the characteristics of patients in the study. The average age of the patients was 67.06±0.79 years, 67 women, and 106 men. Patient's height was 169,9±1,8 cm, weight — 84,6±3,0 kg, body mass index (BMI) — 29,4±0,89 kg/m^2. The number of post-MI patients was 137, patients with coronary angiography / coronary stenting / or coronary artery bypass grafting — 23, after stroke — 10, with arterial hypertension — 130, diabetes mellitus — 21. Some other cardiovascular parameters: blood cholesterol — 4,78±0,08 mmol/l, and left ventricular ejection fraction — 54,0±1,06% were also identified.

In Table 3 the electrophysiological characteristics of VPC and HRT are presented.

The number of PVCs was 176,9±18,8/day, and average heart rate — 68,1±0,57 beats/min. HRT parameter TO was 0,96±0,25%, and TS — 6,14±0,38 ms/RR.

As described above, we investigated 2 HRT parameters, which have predictive power for patients prognosis: TS and TO [3, 6]. TO was not significant for survival models, and we analyzed relationship of mortality and HRT in survival analysis with TS parameter only. Abnormal TS (aTS) is ≤2,5 ms/RR, and normal (nTS) — >2,5 [3,6]. Table 4 shows the mortality in the group based on TS.

Survival in the 5-year interval depending on heart rate turbulence

In first phase, the overall mortality over the 5-year period was evaluated. For calculation of mortality and survival graphs for the 5-year period the 2 groups of patients: with nTS and aTS were compared with each other.

The mortality risk in patients with HRT. Figure 2 presents mortality risk assessment within 5 years in patients with CHD and nTS. The graph was constructed by subtracting of given interval from the value of the survival function values of the next interval and then dividing by the "width" of the corresponding interval.

Mortality risk was minimal for the first 20 months after the initial HRT, it gradually increased later and the achieved the maximal probability in 30-45 months range.

Mortality risk in patients with aTS. In patients with CHD and aTS The following mathematical model of mortality during the observed period was used:

Table 4

Mortality in long-term period in patients with HRT

Parameters	n	12 months	24 months	36 months	48 months	60 months
nTS	135	2	6	8	5	3
aTS	38	8	5	1	6	1
All	173	10	11	9	11	4

$$\lambda_i(t|x_i)=\lambda_0(t) * e^{1.61*TS\_D.},$$
$$\text{where } TS\_D=\begin{cases}1, \text{ if } ts \le 2.4\\ 0, \text{ if } ts > 2.4)\end{cases}$$

Testing of the model showed its significance: an estimated value of χ ^ 2- statistics 16,8, which exceeded the tabular value of 5,992, determined in 2 degrees of freedom and a significance level of $p<0,05$. Cox model parameters was statistically significant: presence of aTS influenced mortality risk over five year period — the presence of aTS in CHD patients compared to nTS enhanced mortality likelihood in 4,99 times. Considering the confidence level of 95% the mortality risk in the five-year period in compare with nTS increased into 2,37-10,51 times.

Figure 3 shows graph of mortality in 5-year time interval for patients with aTS. The function was constructed similarly as for patients with nTS (see above). In patients with aTS the mortality risk was minimal during the first 15 months after the start of monitoring, upraised from 20 to 30 months, and achieved maximum between 45 and 60 months.

Figure 4 shows both nTS and aTS mortality curves. The divergence of the curves starts from 24 months, and intensifies with years.

Analysis of mortality depending on TS and myocardial infarction

According to most of published data, pathological HRT has predictive power only in post-IM patients [7-9], so we compared Kaplan-Meier survival curves based on MI in the past and on nTS/aTS (Table 5).

While analyzing the data for five years 2 survival models depending on TS parameters and presence of MI in the past were created. In the first model, we compared survival curves in post-MI patients and nTS/aTS, and the second — in non-MI.

Survival curves in post-MI patients and nTS/aTS. For a more detailed analysis of difference in survival rates post-MI patients with nTS (n=106) and aTS (n=30) are investigated. Based on Kaplan-Meier survival graph (Figure 5), according to Gehan's-Wilcoxon criteria, the survival rate in post-MI patients with nTS was considerably higher than with aTS (p=0,00026).

The survival rate in non MI patients with nTS/aTS. In this model, the compare of survival rates in non-MI patients with nTS (n = 30) and aTS (n=7) was performed. In Kaplan-Meier survival graphs (Figure 6) the survival rate of patients without MI and with nTS were significantly higher than with aTS (p=0.00318).

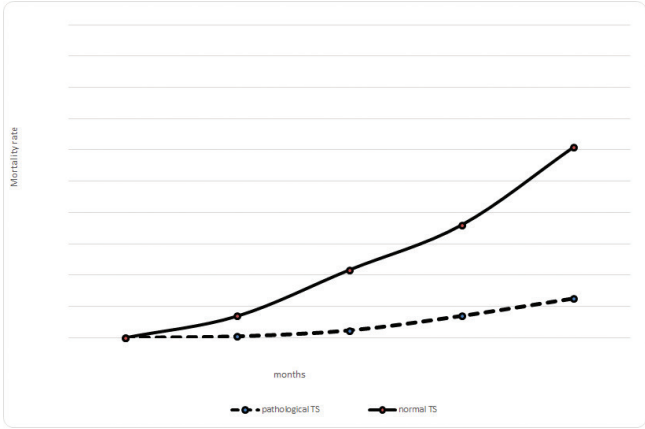

Figure 4. Mortality within 5 years in patients with CHD with nTS/aTS.

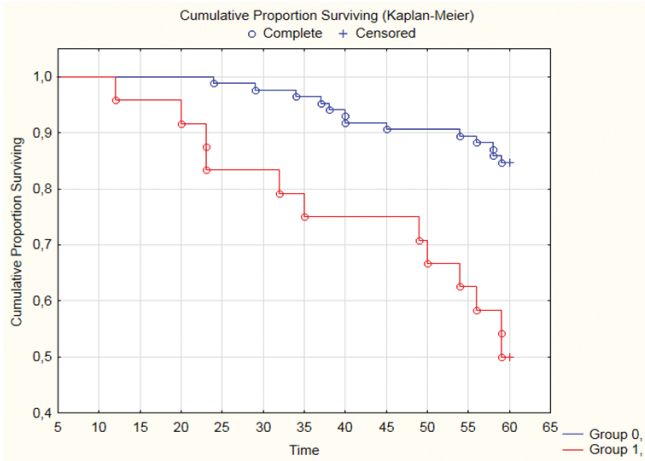

Figure 5. 5-year survival Kaplan-Mayer curves in post-MI patients with nTS (blue) and aTS (red).

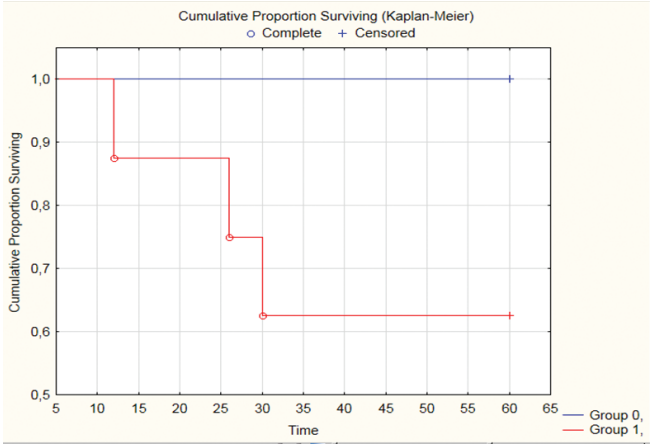

Figure 6. Survival graphs in non-MI patients with nTS (blue) and aTS (red).

Table 5

Mortality rate in patients with CHD and HRT

Models	n	12 month	24 month	36 month	48 month	60 month
IM+nTS	106	0	6	5	5	4
IM+aTS	30	8	5	0	5	1
noIM+nTS	30	2	0	2	0	0
noIM+aTS	7	0	0	1	2	0

Discussion

Populational cardiology based mostly on the success of evidence-based medicine. One of the modern achievements are cardiovascular risk scales, for example in patients with PVC in whom it is possible to estimate HRT [3]. We analyzed 173 patients with CHD, in whom was possible to estimate HRT. The 5-year observation was done to determine the primary end point — general mortality. Two HRT parameters were previously shown to have predictive power: TS and TO [3]. In our study TO didn`t show impact on long-term survival of patients, only TS was analyzed. In the first step, we analyzed the 5-year survival rate depending on normal and abnormal TS (nTS/aTS). Presence of aTS in patients with CHD increased the death likelihood for 5.1 times in compare with nTS. The maximal mortality risk after HRT record was in 45-60 weeks range, and the divergence of survival curves started from the second year. On the second step, we compared the survival curves of patients with previous MI and with nTS and aTS. Existence of aTS significantly increased mortality in compare with nTS (p=0,00026). The role of HRT, a significant risk factor in patients with CHD with previous MI, has been proved in several large-scale retrospective and prospective studies [3, 8, 9]. All HRT studies, except of CAST (Cardiac Arrhythmia Suppression Trial), used the same reference values of TO and TS parameters, that is, 0%, and 2.5 ms/RR intervals, accordingly. In patients with HRT category 2 (i.e. with aTO and aTS) mortality risk increased by 4,4-11,3 times within 2 years compared to patients with normal HRT (0 category).

Then, we compared survival curves with nTS and aTS in patients without MI. Parameter aTS also raised the mortality (p=0.00318) but surely less then in post-MI patients. Prognostic role of HRT in CHD patients without a history of MI was not properly studied [11, 12] and, based on presented data, aTS may predict mortality risk in patients without MI in the past [12, 13].

Conclusion

It was proved that in patients with CHD and PVCs, abnormal TS parameter of HRT is highly predictive in determining the general mortality over a 5-year period, where the divergence of the survival curves starts from the second year of monitoring. Unlike other observations, the differences between survival graphs was shown not only for patients with previous MI but also without it.

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QUALITATIVE RESEARCH IN CARDIOLOGY: TO BE VIRTUOUS OR FAIL

Taratukhin E. O.

Qualitative research is an aristocracy among research methods. Being capable to reach the understanding of events so deep and individual that unattainable for quantification, it requires the same level of capacities from an investigator. In cardiology, biomedical in her origins, novel patient-centered paradigm demands new understanding of the relevance: the relation of scientific findings with clinical application, which, from this point of view, involves the person's biopsychocultural wholeness. Essential controversy originates from the positivistic impossibility of generalization of qualitative findings, and their broadly assumed fallibility. The results of a study depend on the personality of researcher: the interpreter. If such personality, being invited to another person's realm, is not enough virtuous, the results of research will be vain. This article focuses on the need and possibility of implementation qualitative research to cardiovascular science on the way to patient-centered paradigm of healthcare. Some argumentation provided, as some literary review of recent qualitative trials in cardiovascular field.

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Key words: personalized medicine, patient-centered care, empathy, interview, psychological assessment, psychosomatics, biopsychosocial, philosophy of medicine.

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КАЧЕСТВЕННЫЕ ИССЛЕДОВАНИЯ В КАРДИОЛОГИИ: ВИРТУОЗНО ИЛИ НИКАК

Таратухин Е. О.

Качественные исследования — аристократия среди методов исследования. Будучи способными достичь понимания событий так глубоко и индивидуально, как недостижимо для количественной оценки, методы требуют того же уровня способностей от исследователя. В кардиологии, медико-биологической в своих истоках, пациент-центрированная парадигма требует нового понимания ответственности: связи научных открытий и клинического применения, которые, с этой точки зрения, включают в себя биопсихокультуральную целостность человека. Существенные противоречия исходят из позитивистской невозможности обобщения качественных данных и из представления об их погрешности. Результаты исследования зависят от личности исследователя, их интерпретатора. Если такая личность, приглашенная в мир другого человека, не будет в высшей степени целостна, исследование окажется тщетно. Данная статья посвящена вопросам необходимости и возможности осуществления качественных исследований в кардиоваскулярных разработках на пути к пациент-центрированной парадигме здравоохранения. Представлена аргументация и литературный обзор последних качественных исследований в кардиологии.

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Ключевые слова: персонализированная медицина, пациент-центрированная помощь, эмпатия, интервью, психологическая оценка, психосоматика, биопсихосоциальный, философия медицины.

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We are living in the age of revolution. Among the multiplicity of changes occurring each very day in our understanding of the nature, revolution in understanding of ourselves is obviously not the least dramatic. Medicine, in this sense, acquires the strength she never had before: ability to change human body on every level, originating from genes — the core of our incarnation. The so-called personalized medicine is a modern tool for precise and direct influences on human bodies to cause wanted change without broader unexpected and adverse reactions. Personalized medicine, high-technologic and futuristic, is becoming a novel discourse with its symbolic interactions, mythologies, even simulacres. This is so for physicians who understand that not only body constitutes human beings, but their soul and personality: the psyche which is studied by psychologists, and social interaction which is under the humanities responsibility.

Biomedical point of view takes the body as sophisticated biochemical laboratory, hosts of molecular interactions that, originating from DNA, consequently present as ourselves. However, such complexity is even not sufficient, as there is plenty of feedback interactions. Epigenetics, psychoimmunology and other modern interdisciplinary fields show us that interaction happens in opposite directions together: genes determine phenotype, and living world of the phenotype influences the genes to be expressed and even transferred to descendants.

Such point of view makes modern medicine a medicine of human wholeness that shall include everything from the very genes to personality in its psychosocial complexity. And cardiology — one of the key players among non-communicable diseases managers — is to change on the way towards becoming a real cure for her patients.

European Society of Cardiology in their Position Paper have put it, that not only modern technologies will drive personalized medicine, but patients must be taken in all their cultural background, including thoughts and wishes, cultural aspects (as e.g. sex vs gender), relationships, experiences, — i.e. personality. Published in 2014, this paper was issued consequently after the papers of WHO related to Peoples Centered Care paradigm. Tokyo conference (2007) on the Reorientation of Healthcare systems in 21st Century, was concluded with the issuance of Technical Papers for People-Centered Care [1, 2]. Key points of this paradigm are the ways in which individuals, families and communities play roles in promoting health. Among these ways are understanding of the disease and factors influencing health, selection of the most appropriate treatments, monitoring symptoms and treatment effects, adopting healthy behaviors, etc. Such conditions are definitely not biomedical, but psychological and psychosocial. Hence the question raises how to make non-physicians to be able to fulfill these, and how to involve them — their selves — fully, not formally, into the processes of healthcare.

Every physician working with a patient as with human, not moving body, will not refuse that the personality is a term that is intuitively clear, however almost impossible to define. Personality is based on embodied part, with psychological traits and cultural relationships. The latter two are not studied by medical science, and are the subjects of either psychological range of approaches, or the humanities. Yet there is an opposite flow of cultural influences towards the body, that are mediated by psychological phenomena. Personality, having been constituted by biology that blossoms in culture, is being continuously changed by culture influencing biology.

To study, to assess biology, scientists have experimental and observational methods. They collect cases; sameness of the studied trait provides information about the law of nature and grounds consequent influences on biology to change it in the way personality wants to.

However, neither culture, nor pure psychology, can be studied experimentally and quantitatively. There is always a gap for symbolization, interpretation. Such specifics require another sort of insight.

Qualitative methods are the methods of social sciences. Even there such approaches are a kind of marginal, being condemned for lack of evidence, for impossibility to provide universal, generalizable data. This is so if to take paradigm of total interchangeability of investigators. That is, if for quantitative approaches there is no need for selection of an exact doer, when the tool is well-prepared and complete (i.e., questionnaires), qualitative require specific skills and capacities, even virtues, to merge deeper into the covert details of another human world of experience. Moreover, data from purely qualitative methods cannot be statistically proved. Only operationalization of concepts might be a mechanism for more or less quantification. But the latter is out of the essence of qualitative research.

In cardiology, a biomedical field in its gist, application of qualitative methods is challenging, and the path to introduce data obtained with these methods into clinical practice, is thorny.

Nevertheless, qualitative research enters cardiology. And it is up to researches, whether to fulfill demands of clinical practice or to fail.

One of the points that can be applicable for this sort of data acquisition, is a study of perspectives. Thus, Pals et al. (2015) report on the study of patient and physician perspectives on new technologies in clinical practice. The investigators were interested whether the new technologies (e.g., technology to detect cardiovascular autonomic neuropathy in diabetes) in cardiovascular practice are accepted by patients, and physicians as well. Study relied on the data from observations of medical consultations, on interviews with patients and with physicians. Findings showed quite serious misunderstandings in application of the new technology by patients, as by physicians. Conclusions the authors made in the study, were that more information should be provided to patients and dialogue based approach is needed when communicating test results [3].

Another study was done by Lambert-Kerzner et al. (2015) concerning the perspectives of patients on factors of adherence to medical regimens following acute coronary syndrome. They start from the issue of poor adherence of patients that leads to an increased risk of re-hospitalization and higher mortality. In-depth interviews were conducted with patients after acute coronary syndrome. In these interviews patients pointed that some factor might improve their adherence, such as frequent interactions with providers, reminder calls, social support, adherence routines, and last but not least the positive attitudes toward acute coronary event. It was important for patients to be active participants in health care decision making. The concepts that emerge according to the data obtained, were, as concluded by the authors: respectful collaborative communication, training of healthcare providers to elicit and acknowledge patients' views [4].

Patients perspectives on pharmacists' prescribing were the object of McCann et al. (2015) study. Researchers used case studies approach with focus groups for three contexts of prescription: hypertension, diabetes, anticoagulation. Analysis revealed one overarching theme: team approach to patient care; there was also lack of awareness despite general positive attitude towards pharmacist prescribing [5]. Virdee et al. (2015) studied patients' views on polypill for cardiovascular risk. The method was semi-structured interviews with following qualitative description. The results showed the concepts of concern about appropriateness of polypill despite benefits, skepticism about polypill as "blanket" approach. Authors conclude that in population-wide offering of polypill there is need for patients education [6].

These studies demonstrate some crucial properties of qualitative research. On the one hand, the data obtained in

these studies could be gathered with properly designed questionnaires. On the other, some shades of the senses are acquirable only from deeper interpersonal exchange, such as in-depth interview. The difference here rests upon the aim: either to find out a kind of pattern or to define the way of experiencing.

However, there is still a lot of further issues. Sticking childish question "What is?.." one could ask "What is a positive attitude?", "What is a real participation in decision making, as patients are not physicians?", "What is it practically to elicit and acknowledge the views?", "What do the concerns and doubts consist of?". These are the matter of deep understanding and interpretation. Even more, as Susan Sontag stated in her famous "Against interpretation", we need an "erotics of art" in place of hermeneutics. Can one draw from this statement, that neither re-symbolization nor explanation are needed to reach perfect understanding of a cultural event, but experiencing?

What are, if not experiencing, patient's issues on their condition, health, life quality, understanding of their disease and decision making? To evidence personal experiences for clinical practice or policy making, qualitative data, lacking statistical proof, must fulfill some other criteria of trustworthiness. In the Oxford Handbook of Qualitative Research (ed. by Patricia Leavy), one can find such criteria. These include the eight (by Tracy, 2010): worthy topic, rich rigor, sincerity, credibility, resonance, significant contribution, ethics, meaningful coherence (cited from Cho&Trent, 2014), [7]. Are these criteria applicable for cardiology-related qualitative research?

The answer is yet to be given. However, if to look closer, one might say that the role the results of research would play in clinical practice, does determine value. Definition of "the role", as I see it, depends upon the worth of biopsychocultural nature of the ill person for managing process. And if physician works with personality, but not just somatic disorder, the answer is definitely "yes".

Astin et al. (2014) report on the synthesis of qualitative research for lifestyle change to reduce coronary risk. They point that few people fully succeed in daily activities improving lifestyle. After comprehensive review of 27 studies with over five hundred participants the authors found common elements as transformation of self-identity; reassessment of "past, present and future"; urge to get back to "normal"; defining lifestyle change as part of wider "life" change; experiencing life as "worth living". Conclusion remarks include an important concept of a person-centered model of the explanation how lifestyle change is situated within "wider" life changes. Authors synthetize a scheme of Lifestyle Change Process. They also remark that there is need for health professionals who are able to provide support for people experiencing grief and that recognition of lifestyle necessity by physicians is not obviously shared by patients and their families. The latter can be a source of tension, and it is worthy to have skills or even aptitudes for person-centered care that aligns with both closely linked physical and psychological dimensions [8].

This study, a meta-analysis, shows important issues on the position and applicability of qualitative research in the field of cardiovascular science and practice. As soon as we expect some transformations of lifestyle, we have to remember that "life style" includes the word "style" from the humanities and the word "life" that is totally interdisciplinary. To achieve such aim as behavior (a term from psychology; part of the "life style") shift, we need to utilize instruments of scientific fields that deal with the style, i.e. symbolic, interpretative, cultural matters. Such matters are unreachable for quantification and to study and apply this, researcher must deal with the methods from the studies of culture, but implemented to living people. This is a challenge for both psychological and social sciences. However, medicine oughts to include them, because it is in her essence.

To be relevant for modification of treatment approaches in cardiology, with the specific aims for global personal life changes (not simply describe and analyze), qualitative research must be extremely virtuous, thorough, ethic and have intrinsic capacities enough to become an instrument for clinical utilization. Requirements for research in this sense are the requirements to researchers, who must be really extraordinary skillful to correctly obtain and process information from human for humanity. Metaphorically, these are the properties of the noble.

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ATRIAL FIBRILLATION AND RENAL DYSFUNCTION: CURRENT STATE OF THE PROBLEM AND THE PROSPECTS OF FURTHER STUDY

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The review of literature is devoted to interrelations between atrial fibrillation (AF) and kidney function. The focus is on the most probable mechanisms of renal dysfunction in patients with atrial fibrillation such as fibrosis, inflammation, neurohormonal activation. The impact of central and renal hemodynamics disorders on chronic kidney disease development in atrial fibrillation patients is under consideration. The problem of atrial fibrillation in end-stage renal disease patients also gets the authors' attention. We identified unresolved issues and the prospects for their further research.

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AF — atrial fibrillation, ATII — angiotensin II, CAD — coronary artery disease, CHF — congestive heart failure, CKD — chronic kidney disease, CRP — C-reactive protein, CVD — cardiovascular disease, DM — diabetes mellitus, GFR — glomerular filtration rate, HTN — arterial hypertension, MMPs — matrix metalloproteinases, PIIINP — N-terminal propeptide of type III collagen, RAAS — renin angiotensin aldosterone system, SNS — sympathetic nervous system, TGF-β1 — tissue growth factor β1, TIMPs — tissue inhibitors of metalloproteinases, TNF-α — tumor necrosis factor-α.

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ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ И ФУНКЦИЯ ПОЧЕК: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ ДАЛЬНЕЙШЕГО ИЗУЧЕНИЯ

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Обзор литературы посвящен анализу взаимосвязей фибрилляции предсердий и функции почек. Рассмотрены наиболее вероятные механизмы формирования почечной дисфункции при фибрилляции предсердий: фиброз, воспаление, нейрогуморальная активация. Обсуждается роль нарушений центральной и почечной гемодинамики в развитии хронической болезни почек у больных мерцательной аритмией. Освещена проблема фибрилляции предсердий у пациентов с терминальной почечной недостаточностью. Определены нерешенные вопросы и перспективы дальнейших исследований по данной проблеме.

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Ключевые слова: фибрилляция предсердий, почки, хроническая болезнь почек.

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Atrial fibrillation (AF) is revealed in 1-2% of total population [1]. Severe complications and adverse outcome make AF lead among all arrhythmias, which is responsible for stroke, embolism, heart failure and a two-fold mortality increase [2].

Cardiovascular and renal diseases are known for their close and multifaceted relationship. Cardiovascular disease (CVD) is the most frequent cause of death for patients with chronic kidney disease (CKD). The latter at the same time is an independent risk factor for adverse outcome of coronary artery disease (CAD), arterial hypertension (HTN), congestive heart failure (CHF) [3].

Considerably less investigation is devoted to renal function in AF patients. The most evident reason for such relationship might be the commonness of pathologic processes underlying both AF and CKD, namely, HTN, atherosclerosis and diabetes mellitus (DM) [4]. Yet, the analysis of major prospective researches has shown that such association persists in patients without CVD and DM [5]. Molecular mechanisms have not conclusively been revealed to give insight into the reason behind the relationship between AF and CKD including the concomitant CAD and HTN.

Renal function assessment is gaining a particular urgency on the background of wide introduction into clinical practice of new oral anticoagulants for stroke prevention in AF, as their safe administration is closely related to renal function due to a high renal clearance. The present literature review is devoted to the current state of the art.

Renal function at AF

In patients with AF, the occurrence of CKD is 18–21% [6, 7] while in total population it is 10–13% [5]. A number of researches have uncovered a direct relationship between AF frequency and severity of kidney dysfunction. Thus, as the glomerular filtration rate (GFR) decreased, the probability of AF development increased. To the contrary, AF presence suggested the most probable occurrence of CKD [5].

In patients with AF coupled with CHF a noticeable GFR decrease was associated with a high mortality risk [8]. AF presence was related to the increased level of serum

cystatin C [9], a more precise marker of renal function than creatinine [10]. In CAD patients the decrease of GFR calculated by cystatin C up to 30 ml/min/1.73 m^2 and less was followed by a threefold increase in the likelihood of AF development [4].

The direct dependence of albuminuria/ proteinuria degree on AF presence was revealed. Specifically, in patients with AF on the background of CAD and CHF, AF was linked to proteinuria development [4-6, 11]. In NIIGATA study (2009) proteinuria development risk in AF patients increased 2,2 times [5]. G. E. Gendlin at al. (2010) showed that in patients with permanent AF on the background of CHF albumin excretion with urine was almost two times higher than at sinus rhythm of 31,4 and 16,7 mg/l, respectively [8]. Injury of kidney parenchyma is likely to enlarge as AF is progressing: in paroxysmal AF proteinuria was found in 8.5% of cases, whereas in persistent AF — in 13,7% [11]. At the same time, some investigations do not give evidence in favour of AF and GFR association [7].

What are the plausible mechanisms of relationship between AF and renal function? Today there is no a single justified theory providing an explanation for the interdependence of these pathological processes. The analysis of the carried out investigations has made it possible to distinguish three closely interrelated pathophysiological processes that can be responsible for both AF and CKD pathway. These are tissue fibrosis, inflammation and neurohormonal activation. Besides, AF might be the cause of kidney injury due to changes in central and renal hemodynamics. Conversely, severe uremic poisoning instigates AF development.

Atrial and kidney fibrosis in AF and CKD

Atrial and kidney fibrosis is a morphological basis for both AF and CKD. Atrial fibrosis changes the cardiomyocyte electrophysiological properties and therefore becomes a substrate for AF emergence and maintenance [12]. Degradation of extracellular matrix proteins is generally caused by matrix metalloproteinases (MMPs). Thus, MMPs regulate the exchange of matrix, catalysing the breakdown of its components and changing the activity of growth factors and signalling molecules [13]. MMPs activity varies with recurrent rhythm disturbance including AF. In paroxysmal and persistent AF patients, MMP-9 level was twice as high while in permanent AF patients it was more than threefold in comparison to the healthy [14].

The tissue inhibitors of metalloproteinases (TIMPs) suppress MMP activity that allows treating them as fibrosis indicators. Reduced TIMP-4 and TIMP-1 levels are found to be associated with AF presence [15]. Obviously, a high MMP-9 activity and/or a drop in TIMP-1 regulation account for the excessive stimulation of collagen synthesis in the myocardium, which facilitates the atrial fibrosis formation and instigates AF development. Yet, the lack of tissue specificity of the markers in question does not permit to assert conclusively that their levels are related to atrial fibrosis rather than to fibrosis on the whole [16].

In kidneys over the whole nephron length, MMPs encoded by MMP-2, MMP-3, MMP-9 genes are revealed [17]. A number of researches have noted the link of MMP-2, MMP-9 activity variations and their TIMP-1, TIMP-2 tissue inhibitors with kidney fibrosis [18]. The increase in MMP-9 activity associated with microalbuminuria has been ascertained as well [17, 18].

Transforming tissue growth factor β1 (TGF-β1) is proinflammatory cytokine. Its excess expression stimulates the fibroblasts growth, extracellular matrix synthesis and fibrosis progressing. The level of TGF-β1 in AF patients is known to be higher than in patients with sinus rhythm [19]. This, however, is inconsistent with the data of Cardiovascular Health Study (CHS, 2014) according to which the growth of TGF-β1 was not associated with the new AF cases in the elderly [20]. On the other hand, it boosts glomerulosclerosis and interstitial fibrosis [21]. An only study on animals concerning the AF and kidney fibrosis interrelation showed that induced AF paroxysm raised TGF-β1 level in renal tissue [22].

N-terminal propeptide of type III collagen (PIIINP) accounts for the collagen III content and is considered lately as a fibrosis marker [23]. The level of PIIINP in AF patients was higher than in patients with sinus rhythm. The increase of PIIINP in blood was suggested as a predictor of arrhythmia recurrence after cardioversion [24]. At the same time, a high concentration of PIIINP in urine was observed in the tubulointerstitional fibrosis cases. A double gain in PIIINP in urine regardless of GFR and albuminuria severity was followed by acceleration rate of CKD progressing in 1.2 times [25].

The data presented allow some fibrosis indicators (MMP, TIMP, TGF-β1 и PIIINP) to be considered as common kidney injure and AF markers though no special investigations were conducted earlier to substantiate this hypothesis.

Atrial inflammation and CKD

A convincing body of evidence has been amassed for inflammation in the atrial myocardium of the AF patients. The extent of structural changes in atria was found to depend on the level of inflammation markers [26]. AF presence as well as the risk of its recurrence after cardioversion were linked to the rise in high-sensitive C-reactive protein (CRP) [27]. In paroxysmal AF patients the level of tumor necrosis factor-α (TNF-α) in blood was 3.8 times higher than in the ones with sinus rhythm [28]. The interleukin-15 level directly correlated to the number of AF episodes [29]. Regaining the sinus rhythm resulted in the statistically significant decrease of elevated levels of inflammation markers [26].

However, cause-effect relationship between inflammation and AF has not been ultimately ascertained. The inflammatory cell infiltration and calcium overload are considered to contribute to atrial oxidative stress and fostering the atrial fibrosis development [12]. This may upset the mechanical and electrophysiological functions of atrium. Yet, the first

paroxysm of arrhythmia is believed to occur independently while inflammation supports arrhythmia recurrence [26]. Finally, there is evidence for inflammation being a consequence of AF, whereas the rise in the inflammatory markers is due to the disease underlying AF development [30]. Inflammation does not seem to be the sole reason for atrial arrhythmogenic but is most likely to play a part in building up "readiness" for AF paroxysm development [26].

At the same time, the rise in the inflammatory markers is also observed in CKD patients [31]. CRP level has been found to correlate directly with the severity of albuminuria in hypertensive patients [32]. The increase in TNF-α and interleukin 1 and 6 content was associated with both the drop in GFR and the rise in albuminuria [33].

Therefore, there are grounds to believe that subclinical inflammation is one of the reasons for AF and CKD association. Whether it manifests itself as a single systemic process or these are separate unrelated inflammatory changes still remains unclear.

Neurohormonal activation at AF and CKD

Activation of the renin angiotensin aldosterone system (RAAS) is known to be typical for AF patients. Several mechanisms of structural and electrophysiological atria remodelling under the action of RAAS mediators aldosterone and angiotensin II (ATII) have been described. These are the increase of atrial tissue fibrosis, stretching and dilation of the atria, a direct impact on the ion channel function and cardiomyocyte intercellular interaction [34]. Besides, aldosterone induces local inflammation in coronary artery endothelium and myocardial perivascular spaces [2]. AF patients showed the increase of type 1 receptors to AT II density and a growing level of angiotensin converting enzyme in the left atrial tissue [35].

RAAS activation has been proved for CKD patients. In CKD patients, the plasma aldosterone level was found to grow with the disease worsening [36]. AT II is responsible for the glomerular arterioles spasm, predominantly of the efferent one, bringing about hyperfiltration, glomerular hypertrophy and, as a consequence, focal glomerulosclerosis [37].

It is reasonable to suggest, that the rise in RAAS activity, e.g. in high-renin form of HTN or CHF, stimulating AF development results in kidney fibrosis. Furthermore, ATII and aldosterone activate NAD(P)H oxidase to promote endothelial dysfunction as well as heart remodelling and kidney damage [38].

An elevated activity of sympathetic nervous system (SNS) can also provoke AF. Excessive catecholamines affecting myocardium and ion transport induce persistent tachycardia, heart rate variability violation and QT dispersion increase. This lowers the threshold of arrhythmias [39].

The role of SNS hyperactivity is also considered for CKD pathogenesis. It is common knowledge that 30% of norepinephrine excreted in urine and up to 70% of epinephrine come from blood to kidney. The remaining amount is released directly into the kidney from renal nerve endings. Sympathetic hyperactivity and RAAS activation underlie the glomerular efferent arteriola spasm and hyperfiltration development [40, 41]. Furthermore, catecholamines of high concentration are apt to exert a direct damage on renal interstitium. Parenchymal sclerosis and renal ischemia, in their turn, are primarily responsible for afferent signals to integrating brain nuclei in response to which the synthesis of catecholamines takes place by feedback mechanism [42].

Disorders of intrarenal and systemic hemodynamics in AF as the reason for renal dysfunction

Kidney embolism is another mechanism of AF negative effect on kidneys with a distinct cause-effect relationship. In population, renal artery embolism is encountered seldom enough. The incidence of peripheral embolism is 0.4% [43] and that of visceral embolism is 15% [43]. In AF patients, kidney embolism is registered in 3% of cases [44]. The most common reason for renal artery embolism is atrial flutter [43]. As a rule, acute renal failure is progressing in the case of large-sized emboli. Microembolization results in gradual decline in renal function due to ischemia, inflammation around emboli and hypertension [45]. However, this phenomenon is quite difficult to verify for lack of marked clinical manifestations, which does not allow us to judge reliably its prevalence.

In AF cardiac output decreases by 5 to 15% with further decline in the minute volume of the heart and blood pressure [46] which leads to renal hypoperfusion [47] with the development of ischemia and kidney damage.

AF in patients with end-stage renal disease

Of special consideration is the AF, which develops on the background of end-stage renal disease. 11–27% of patients on chronic haemodialysis are revealed to have a developing AF, which is 10–20 times more frequent than in general population [48]. Other evidence is reported for AF to be diagnosed in each sixth dialysis patient. The frequency of arrhythmias in dialysis patients amounts up to 40–76% [49]. In its turn, mortality of the patients in this category is twice as high as that of the patients without AF [50].

For the most part the researchers are agreed here that namely severe uremia and associated with it oxidative stress are the reasons for AF development [51]. Besides, during haemodialysis AF can be provoked by intradialytic hypotension, haemorrhage, electrolyte shifts as well as iatrogenic factors: receiving of psychotropic, anticonvulsive drugs and certain antibiotics. In the intradialytic interval, arrhythmias can occur because of hyperkalemia. AF is also developing at ineffective dialysis syndrome [52].

Conclusion

The literature analysis suggests pathogenic relationships to be found between AF and kidney disease. The core of a single pathophysiological mechanism can be attributed to systemic inflammation and neurohormonal activation, primarily RAAS and SNS, being responsible for excessive collagen deposition in the myocardium and electric atrial remodelling on the one hand, and kidney

fibrosis, intraglomerular hypertension and endothelial dysfunction of glomerular capillaries, on the other. Most often, this mechanism is at work in atherosclerosis, HTN and CHF. AF may result immediately in renal damage due to renal artery embolism. Conversely, severe renal failure may initiate AF. Cause-effect relationship between AF and CKD still remain obscure. The idiopathic AF impact on renal function is not conclusively established, which calls for further specially designed epidemiological and experimental studies.

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PERSISTENT LEFT SUPERIOR VENA CAVA IN PATIENT WITH PAROXYSMAL ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

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Persistent left superior vena cava (PLSVC) is a rarely occurring congenital anomaly with the incidence of 0.3% in general population. This anomaly results from the persistence of the left anterior cardinal vein. In 90% of cases blood from PLSVC flows into the coronary sinus and then to the right atrium. It may complicate the placement of central vein catheters in the jugular and subclavian veins and, as such, cardiologists should be aware of the existence of this anatomic variant. Here we describe an adult patient with persistence of the left superior vena cava identified during made echocardiography test in a 57-year-old male patient with paroxysmal atrioventricular nodal reentrant tachycardia (AVNRT) who was admitted to a cardiac ward on a regular basis for ablation procedure.

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PLSVC — persistent left superior vena cava, AVNRT — atrioventricular nodal reentrant tachycardia.

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СТОЙКАЯ ЛЕВАЯ ВЕРХНЯЯ ПОЛАЯ ВЕНА У ПАЦИЕНТА С ПАРОКСИЗМАЛЬНОЙ АТРИОВЕНТРИКУЛЯРНОЙ УЗЛОВОЙ РЕЕНТЕРАБЕЛЬНОЙ ТАХИКАРДИЕЙ

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Стойкая левая верхняя полая вена (PLSVC) является редко встречающейся врожденной аномалией с частотой 0,3% в общей популяции. Это приводит к аномалии с сохранением левой передней кардинальной вены. В 90% случаев кровь из PLSVC впадает в коронарный синус и затем в правое предсердие. Это может осложнить размещения центральных венозных катетеров в яремной и подключичной венах и, об этом анатомическом варианте кардиологи должны быть осведомлены. Здесь мы опишем взрослого пациента с сохранной левой верхней полой веной, выявленной в ходе эхокардиографии, сделанной 57-летнему пациенту мужского пола с пароксизмальной атриовентрикулярной узловой возвратной тахикардией (AVNRT), который был госпитализирован в кардиологическое отделение на регулярной основе для проведения исследования.

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Ключевые слова: стойкая левая верхняя полая вена, пароксизмальная атриовентрикулярная узловая реентерабельная тахикардия.

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A 57-year-old male patient with paroxysmal atrioventricular nodal reentrant tachycardia (AVNRT) was admitted to a cardiac ward on a regular basis for ablation procedure. The patient's history revealed fast heart rate episodes for several years, arterial hypertension treated for five years, hyperlipidemia and peptic ulcer disease. Physical examination showed a regular heart rate of 70bpm, quiet systolic murmur over the mitral valve and normal breath sounds. Resting ECG showed no abnormalities. A routine transthoracic echocardiography revealed concentric left ventricular wall thickening and moderate mitral valve regurgitation. Special attention was paid to an untypical accessory structure detected in the left atrium area (Figure 1). Transthoracic echocardiography was performed in order to expand the diagnostic process. The investigation showed the vessel directly adjacent to the left atrium. The doppler examination showed flow inside the structure, yet without a visible connection with the left atrial cavity (Figure 2). A congenital venous anomaly was suspected in the form of persistent left superior vena cava. X-ray fluoroscopy was done to confirm the type of the anomaly. Administration of contrast into the peripheral vein of the left superior limb resulted in visualization of the investigated structure followed by visualization of the coronary sinus. Electrophysiological examination was done due to AVNRT previously documented in ambulatory ECG investigations. Programmed atrial stimulation repetitively induced nodal reentrant tachycardia with a ventricular rate of 140bpm. Radiofrequency ablation of slow pathway modified the conduction and caused a lack of inducibility of the tachycardia in control programmed stimulation.

Persistent left superior vena cava (PLSVC) is a rarely occurring congenital anomaly with the incidence of 0.3% in general population [1]. In the majority of cases the anomaly is asymptomatic, but it is frequently (12%) accompanied by other malformations such as atrial septal

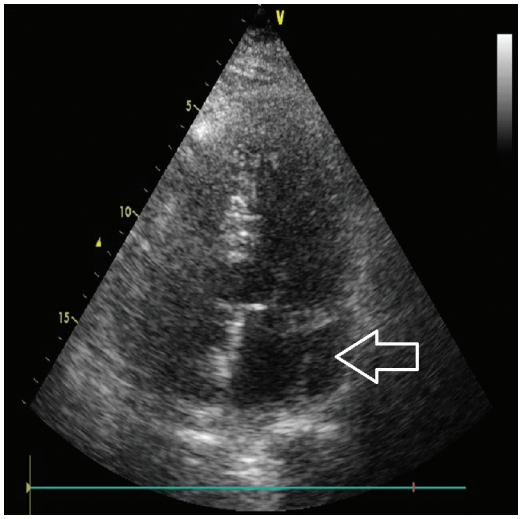

Figure 1. Transthoracic examination, four-chamber view. Persistent left superior vena cava (PLSVC) visible as an untypical accessory structure in the left atrium area.

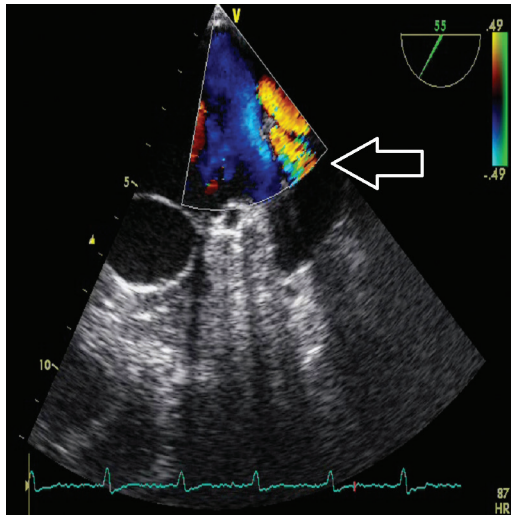

Figure 2. Transesophageal echocardiography, mid esophageal view 55º. Accessory structure between left atrial appendage and left upper pulmonary vein.

defect, ventricular septal defect, aortic coarctation, transposition of the great vessels, tetralogy of Fallot, anomalous connections of the pulmonary veins or single atrium [1, 2, 3]. In 90% of cases blood from PLSVC flows into the coronary sinus and then to the right atrium. In the remaining 10% of cases, the PLSVC is directly connected to the left atrium. Superior vena cava mostly occurs in the hypoplastic form (82-90%) [1]. In the presented case, PLSVC coexisted with the anomaly in the heart conduction system — an accessory pathway in atrioventricular node causing AVNRT.

Summarizing, attention should be paid to this rare developmental anomaly due to a possible difficulty in superior vena cava access in the case of medical procedures and a possibility of the coexistence of other cardiac pathologies. In the presented case, PLSVC was accompanied by an accessory pathway in atrioventricular node.

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