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Attitude to cardiovascular disease prevention and treatment in open population: gender differences

Systemic embolism risk factors in kidney transplant recipients during long-term post-operative period

Role of tissue Doppler in the assessment of the effects of obesity on left ventricular structure and systolic myocardial function

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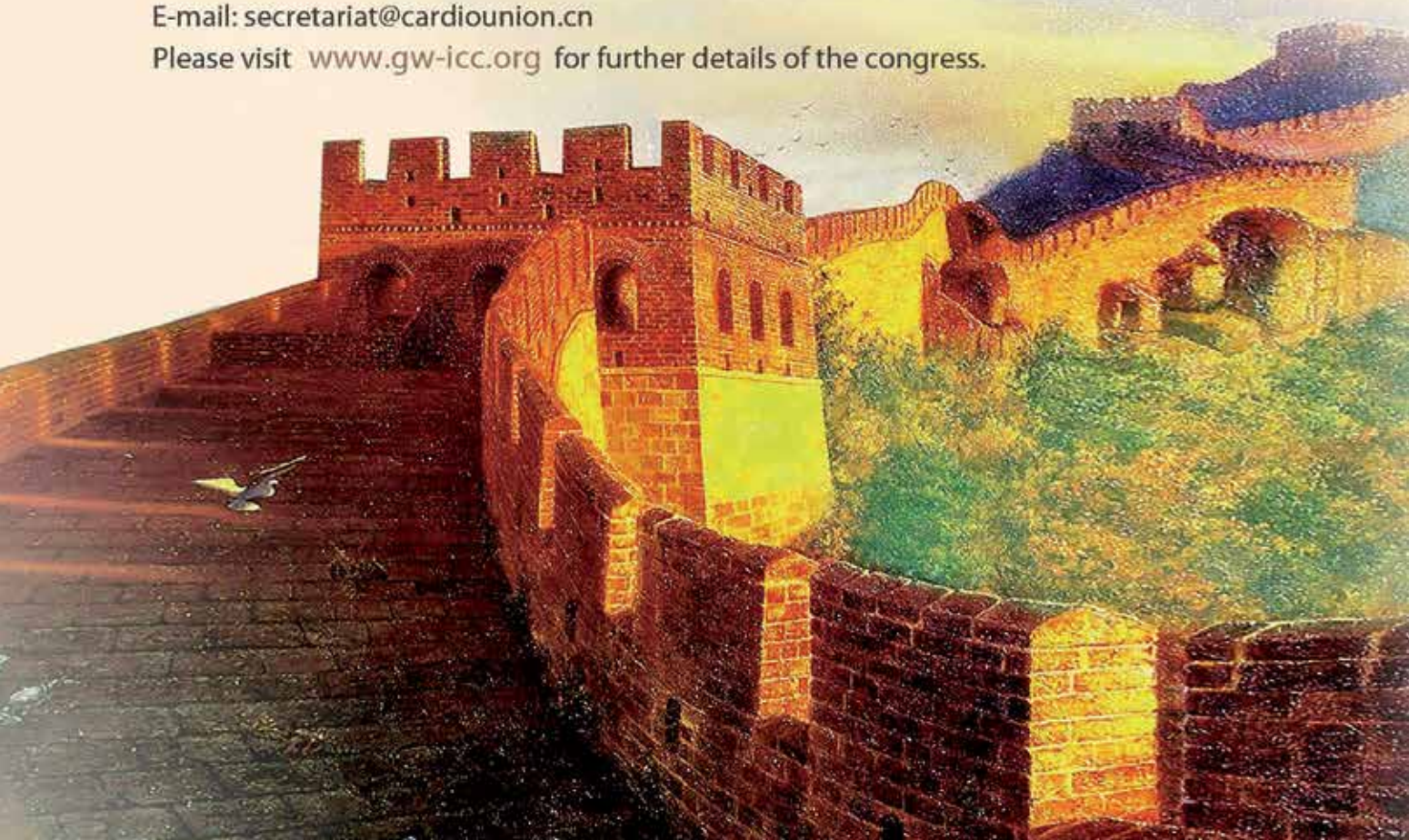

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Contents

Editor's Welcome

Dear colleagues!

Dear colleagues!

In the 13th issue of the International Heart and Vascular Disease Journal, there are leading article, original articles, and a congress report.

The leading article was prepared by the group of leading Russian scientists working in the area of epidemiology of chronic non-infectious diseases. This popular study analyzes gender aspects of cardiovascular diseases' prevention and treatment.

Five articles of authors from Russia, Egypt and Belarus are included into the traditional "Original articles" section.

A group of authors from Saint Petersburg examined 186 patients with AH and identified that the analysis of cognitive evoked potentials is an informative technique in addition to neuropsychological study in the diagnosis of cognitive disorders. The second original article describes the use of results of one major database that allowed forming the concept and classifying nonspecific cardiac morphofunctional syndromes in coronary heart disease. A group of researchers from Ulyanovsk investigated endocrine system pathology associated with acute coronary syndrome in case of mildly changed/intact coronary arteries. The results of this study demonstrated that females aged less than 75 years with thyroid gland disorders have abnormal carbohydrate metabolism, elevated blood pressure and high probability to develop "acute coronary syndrome without ST segment elevation" in case of mildly changed coronary arteries. Belorussian scientists in their study revealed that kidney transplant recipients with atrial fibrillation have high frequency of thromboembolic complications in the long-term postoperative period that requires prescription of indirect anticoagulants in 62,5% of cases in addition to combined immunosuppressive therapy. Egyptian researchers used the tissue Doppler technique to estimate the influence of obesity on left ventricular structure and myocardial function on subclinical level. Definition of deformation and the velocity of deformation measured using this technique may help to predict subclinical changes of myocardial structure and function.

This issue includes also the report about the II Interregional Congress of cardiology and internal medicine that was held in Ulyanovsk on December, 5-6, 2017.

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

Rafael G. Oganov

Editor-in-Chief

President of the "Cardioprogress" Foundation

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LEADING ARTICLE

Attitude to cardiovascular disease prevention and treatment in open population: gender differences

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Summary

Objective
To determine gender differences in the parameters of subjective-objective measure of health in the urban population aged 25-64 years and their attitude to prevention and treatment of cardiovascular diseases (CVD).

Materials and methods
This study was made according with the algorithms of the program of World Health Organization (WHO) «MONICA - psychosocial» on the representative sample of Tyumen population between males and females (2000 people total).

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Results

Obtained results show that the majority of Tyumen population aged 25-64 years, mostly young women and older men, trusts in the possibility of prevention of serious diseases. A major part of this open population objectively estimates the possibilities of modern medicine in the prevention of heart disease, young women have the most critical attitude and old women have the least critical one. More than a half of Tyumen population, particularly men of the old age group, believe in successful treatment of heart disease.

Conclusion

Investigation of people's attitude to CVD prevention and treatment is important for planning and development of prevention strategies, and identification of gender differences in subjective-objective measure of health allows estimating the needs of specific populations in preventive care.

Key words

Open population of Tyumen, gender differences, attitude to prevention, attitude to treatment, cardiovascular diseases.

Introduction

Scientific studies performed as a part of various epidemiologic and prevention programs demonstrated that medical activity of population is a necessary condition for reduction of cardiovascular morbidity and mortality in population [1, 2]. Among the risk factors of cardiovascular diseases (CVD) that characterize condition and features of people's motivation in relation to their health, the parameters of subjective-objective attitude to their health like the attitude to the possibilities of CVD prevention and treatment have particular importance. These parameters have been investigated by one international epidemiological project of the World Health Organization (WHO) called "MONICA psychosocial" (Monitoring trends and determinants in Cardiovascular disease) [3]. The necessity to study this problem is caused by low efficacy of preventive programs, planning and development of which have been performed only as a part of biomedical model of health and healthcare [4, 5]. Attitude to their own health, CVD prevention and treatment have been investigated in numerous national studies, which have related mostly to male's populations [3, 6-10]. At the same time, coronary heart disease is the leading cause of death in males and females, and it is worth to mention that the absolute amount of female death cases due to coronary heart disease is higher than the same number of male ones [11]. There are gender features of CVD formation and course, but gender differences of subjective-objective measure of health in Russian populations are not enough studied; it makes it more difficult to plan, perform and control the efficacy of preventive interventions, realization of which could be more efficient taking into account existing gender differences in population [1, 2, 5, 12, 13].

The aim of this work is to determine gender differences in the parameters of subjective-objective measure of health in the open urban population aged 25-64 years and their attitude to prevention and treatment of CVD.

Materials and methods

Single-stage epidemiological study was performed using representative sample formed from the voting list of the citizens of one of administrative districts of Tyumen city. between 2000 males and females, among them 500 individuals were selected for each one of four decades of life (25-34, 35-44, 45-54, 55-64 years). Inclusion factors for the population sample were: males and females aged 25-64 years registered and living at the territory of the Central administrative district of Tyumen city. Exclusion factors for the population sample were: refugees, militaries, students and prisoners, that was identified according to the respondent's words, these data were not included in the analysis. Each Tyumen dweller included in the population sample received invitation for participation in cardiologic screening. If potential participant didn't answer to the first mail, other three letters were invited to his mailbox with the interval of 7-10 days, otherwise we tried to made an attempt of participants' involvement through phone or personal contact.

Each participant gave informed consent for participation in cardiologic screening in written form. Study's protocol was approved by local Ethic Committee.

The response to cardiologic screening in males was 85% (n=850), and its value in females was 70.4% (n=704). Investigation of patients' attitude to CVD prevention and treatment was performed through compilation of a standard WHO questionnaire "MONICA psychosocial" "Awareness and attitude towards your

health" by the method of house-to house poll. The questions included in this form were accompanied with fixed answers, from which respondents could choose the variant that was the most correct one according with their personal opinion.

Statistical analysis of obtained results was performed using SPSS 11.5, STATISTICA 22.0 and "Microsoft Excel" software according with the rules of variation statistics. Age structure of urban Russian population between 25-64 years was used for the analysis and standardization of obtained data. Pearson's x^2 test was used for statistical assessment of differences between the groups. P-value <0.05 was considered significant.

Results and discussion

The attitude to CVD of males and females aged 25-64 years and belonging to the open population according with their age is presented in the Table 1.

64.3% of male respondents and 67.0% of female respondents of the open population gave a definite answer "yes, definitely yes" on the question "Do you think that healthy person of Your age could avoid several severe diseases if he used some preventive measures in advance?" Statistically significant differences in the answers to these question were obtained in young and elderly age groups: 25-34 years: 58.2% – 71.2% (p<0.05); 55-64 years: 70.7% – 57.0% (p<0.01). 34.8% of male respondents and 32.2% of female respondents had undetermined position for this question (answer "Maybe, yes"), statistically significant differences were observed in the same age groups, on the contrary, more often in males than in females: 25-34 years: 41.8% – 28.2% (p<0.05); 55-64 years: 28.8% – 42.1% (p<0.01). Minimal number of both males and females gave negative answer ("Unlikely") to this question independently on their age (0.9% – 0.8%). At the same time, giving an answer to the question «Do You believe that a healthy person of Your age could get sick with a severe disease within next 5-10 years?", the majority of the open population (62.8% males and 64.9% females) gave uncertain answer ("Probably"), and 36.2% of males and 32.6% of females answered "Very likely". We didn't detect statistically significant gender differences of these parameters in age groups and in population. As in the situation with the first question, minimal number of males and females (.9% – 2.5% (p<0.05), respectively) responded with the answer "Unlikely", significant gender differences in this case were obtained not only for the population in general, but also for the elderly age group of people aged 55-64 years: 0.9% – 2.5% (p<0.05) (Table 1).

Talking about opportunities of modern medicine in CVD prevention, the majority of the open population (44.1% of males and 45.4% of females), independently on their age, had positive opinion, according with which modern medicine may prevent the majority of heart diseases. The majority of females had most categorical opinion ("Yes, all heart diseases") comparing with males in population in general: 10.6% – 5.9% (p<0.001), and in age category of 55-64 years: 17.8% – 5.1% (p<0.001). In general, males and females of the open population had equally realistic attitude to CVD prevention. Answering the question "Do You believe that modern medicine may prevent heart diseases?", 42.4% of males and 37.1% of females gave the answer "It depends on the disease", gender differences were presented in the age group of 25-34 years: 43.4% versus 30.5% (p<0.05). The answer: "Not, just several" was given by the minimal number of males and females (6.9% and 6.1%, respectively) with no significant differences between age groups. Another categorical answer ("Not, neither one of them") was given by 0.7% of males and 0.8% of females (Table 1).

57.5% of males and 51.4% of females, independently on their age, had positive opinion about the possibility of modern medicine to successfully cure the majority of heart diseases. 55.8% of males and 39.3% of females agreed with the answer "Yes, the majority of the diseases" (p<0.001). Women of 55-64 years had the most categorical opinion about it. Comparing with males, the biggest number of females answered "Yes, all heart diseases" and "Not, neither one of them": 13.1%-6.0% (p<0.05) and 1.9%-0% (p<0.05), respectively. 4.3% of males and 0% of females (p<0.01) gave the answer "Not, just several", significant gender differences were present in the age group of 45-54 years: 4.3%-0.1% (p<0.01) (Table 1).

The majority of national studies demonstrated subjective positive attitude of population to preventive health screening, at the same time less than 10% of males and females thought that took enough care about their health [3, 6, 9, 14]. The results of a current study in Novosibirsk population (the same protocol was used for both studies) were comparable in relation to males: 54% of males in Novosibirsk and around 50% of males in Tyumen believed that modern medicine can prevent all or the majority of heart diseases. But gender differences in two urban populations had opposite results: females of Tyumen population had more positive attitude to preventive mea-

Table 1. **Attitude to CVD prevention and treatment in males and females aged 25-64 years in the open population**

Question / Attitude	Age groups										
	25-34		35 -44		45-54		55-64		25–64		SC
	Total (n)	%	Total (n)	%	Total (n)	%	Total (n)	%	Total (n)	%	%
1. Do you think that healthy person of Your age could avoid several severe diseases if he used some preventive measures in advance?											
1.1. Yes, definitely yes	71 / 126	58.2/71.2	150/156	72.1/68.4	93/153	58.5/ 66.2	152/ 122	70.7/57.0**	466/557	66.2/65.5	64.3/67.0
1.2. Maybe, yes	51/50	41.8/28.2	56/71	26.9/31.1	62/75	39/32.5	62/90	28.8/42.1**	231/286	32.8/33.6	34.8/32.2
1.3. Unlikely	0/1	0/0.6	2/1	1/0.4	4/3	2.5/1.3	1/2	0.5/0.9	7/7	1.0/0.8	0.9/0.8
2. Do You believe that modern medicine may prevent heart diseases?											
2.1. Yes, all heart diseases	6/17	4.9/9.6	12/17	5.8/ 7.5	13/24	8.2/10.4	11 /38	5.1/17.8***	42/ 96	6.0/11.3***	5.9/10.6
2.2.Yes, the majority of the diseases	56/96	45.9/54.2	88/107	42.3/46.9	72/92	45.3/ 39.8	91/ 69	42.3/32.2	307/364	43.6/42.8	44.1/45.4
2.3. It depends on the disease	53/54	43.4/30.5*	90/94	43.2/41.2	60/94	37.7/40.7	96/ 85	44.7/39.7	299/327	42.5/38.5	42.4/37.1
2.4. Not, just several	6/9	4.9/ 5.1	17/10	8.2/ 4.4	12/20	7.5/8.7	17/ 16	7.9/7.5	52/ 55	7.4/6.5	6.9/6.1
2.5. Not, neither one of them	1/1	0.8/ 0.6	1/0	0.5/0	2/1	1.3/0.4	0/6*	0/2.8	4/8	0.6/0.9	0.7/0.8
3. Do You believe that nowadays it is possible to treat successfully heart diseases?											
3.1. Yes, all heart diseases	15/16	12.3/9.0	12/20	5.8/8.8	12/19	7.5/8.2	13/ 28	6/13.1*	52/83	7.4/9.8	8.3/9.5
3.2. Yes, the majority of the diseases	73/110	59.8/62.1	116/120	55.8/52.6	92/114	57.9/42.4	120/84	55.8/39.3***	401/428	57.0/50.4**	57.5/51.4
3.3. It depends on the disease	34/49	27.9/27.7	77/83	37.0/36.4	54/86	34.0/37.2	78/87	36.3/40.7	243/305	34.5/35.9	33.3/34.3
3.4. Not, just several	0/2	0/1.1	2/5	1/2.2	0/10	0/4.3**	4/11	1.9/5.1	6/28	0.9/3.3**	1.1/2.8
3.5. Not, neither one of them	0	0	1/0	0.5/0	1/2	0.6/0.9	0/4	0/1.9*	2	0.3/0.7	0.3/0.5

Comments: * - p<0,05; ** - p<0,01; *** - p<0,001; statistically significant differences between males and females are signed with (*); SC – characteristic standardized by age.

sures, whereas in Novosibirsk population males had the same attitude [3].

Conclusion

Therefore, the major part of open urban population believes in the possibility of severe diseases' prevention, the most favorable conditions for preventive programs development were observed in young females of 25-34 years old and in males aged 55-64 years.

The majority of open population estimates realistically the possibilities of modern medicine in the context of heart diseases' prevention; young females aged 25-34 years demonstrate the most critical attitude, and elderly females have the least critical attitude to it.

More than half of Tyumen population believes in successful treatment of heart diseases, males of 55-64 years old have the most positive attitude to it.

Investigation of people's attitude to CVD prevention and treatment is important for planning and development of prevention strategies, and identification of gender differences in subjective-objective measure of health allows estimating the needs of specific populations in preventive care.

Conflict of interests: None declared

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Assessment of cognitive functions using cognitive evoked potential in patients with arterial hypertension

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Summary

Objective

To assess the possibility of cognitive dysfunction diagnosis using cognitive evoked potential in patients with arterial hypertension.

Material and methods

The study included 186 patients. The average age was 47.9±6.4 years. Cognitive function in all patients was evaluated using neuropsychological testing. Quantitative assessment of cognitive function was determined by the method of cognitive evoked potential (CEP).

Results

Patients were divided into two groups. The first group included 92 healthy individuals. The second group consisted of 94 patients with arterial hypertension (AH). The groups were comparable with respect to age and sex. The group of patients with hypertension was characterized with significant increase in the duration of the CEP (346.17±18.37

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and 335.78±16.57 msec respectively; p<0.01) and reduced amplitude (10.4±4.3 and 16.2±5.7 μV respectively; p<0.01), comparing with group of healthy persons. According to the test results, the hypertension group demonstrated decrease of memory (p<0.01) and cognitive functions in general (p<0.01).

Conclusion

The analysis of cognitive evoked potentials is an accurate method to complement clinical neuropsychological examination in the diagnosis of cognitive disorders in middle age patients with arterial hypertension. The study of cognitive evoked potential can be used for early diagnosis of cognitive impairment in these patients.

Key words

Arterial hypertension, cognitive impairment, cognitive evoked potential

Introduction

Due to increased lifespan number of patients with dementia evidently increases worldwide. Up to 7.7 mln new dementia cases are diagnosed each year. Knowing this, it becomes very relevant to perform diagnostics of predementia states. Light and moderate vascular cognitive disorders are considered to precede dementia in the majority of cases [1, 2]. Neuropsychological methods are traditionally used for the diagnostics of cognitive impairment. The protocol of neuropsychological study can become more complex in order to increase its sensitivity, but it can have some negative consequences. Interpretation of the results of complex neuropsychological techniques can often be ambiguous. During the last years more attention is paid to the techniques that can provide more objective information about cognitive disorders.

Investigation of brain electric reactions to external stimuli has been performed since the moment of the first electroencephalogram registration. In 1875 Russian researcher Vasily Danilevsky and English doctor Richard Caton had independently reported weak electric currents of animal brain registered with galvanometer and had observed their changes under sensory stimulation.

The first distinct registrations of cognitive evoked responses in human were performed by American doctors and audiologists Hallowell and Pauline Davis. British scientist George Dowson had further developed this technique up to its modern form [3]. Evoked potentials (EP) are bioelectric signals that appear at regular time intervals after definite external stimuli. Investigation of brain EP is based on the registration of brain electric response on exogenous stimuli (visual, acoustic, sensory) and endogenous events related to expectation, identification, decision-making and motor response initiation [3]. EP are registered using electrodes placed on patient's head. Brain electric response on visual, acoustic and sensory stimuli is estimated according with the change of main EP parameters like amplitude and latency of different components of the response [4]. The main method of endogenous events' detection that advanced the analysis of cognitive processes is the investigation of cognitive evoked potentials (CEP) or P300. Temporal limbic and brainstem reticular structures participate actively in the realization of this process in human brain [5]. P300 is a part of difficult potential that appears in the model of directed attention while carrying out a cognitive task [6]. The process of significant stimulus selection includes simply sensory part related to physical parameters and mainly reflected in the characteristics of early EP components. The next step is primary identification and classification of stimuli that is the most distinctly reflected in negative deviation 96-250 msec after the start of the stimulus and is called N2 (N200). It's further followed by final identification of the stimulus requiring its comparison with the memory template and decision-making in relation to action associated with it. P300 potential is connected with these events [7].

Distinct correlation between CEP and age has been identified in several studies [8]. These changes of P300 time-amplitude parameters are related to normal aging process accompanied with reduction of dendritic spines' number and synaptic contacts' density at the level of cerebral neurons [8]. Objectivity of obtained data and possibility to detect early cognitive disorders (CD) are significant advantages of this technique. This method can be used not only for cognitive dysfunction diagnostics, but also for differential diagnostics between CD and functional disorders like depression [9, 10].

This method is commonly used in neurology for patients with evident abnormalities [11]. Wide prevalence, high social significance and restricted therapy possibilities make the problem of CD early diagnostics in patients with cardiovascular risk factors very relevant.

The objective of this study was to evaluate the possibility of CEP use for CD diagnostics in patients with AH.

Materials and methods

All patients underwent clinical examination of such anthropometric parameters like waist circumference (WC), thighs circumference (TC) and body mass index (BMI). Blood sampling for plasma glucose levels detection and lipid spectrum characterization was performed using "Abbott" reagents ("Abbott", Germany) and biochemical analyzer (ARCHITECT C8000, Germany). BMI was quantified using Kettle formula: body mass/height^2 (kg/m^2). This study included 186 patients with the average age of 47.9±6.4 years. 94 patients had AH. AH duration was 6.3±1.5 years. To exclude significant anxiety and depression we used the HADS scale (The hospital anxiety and depression scale). Cognitive functions were estimated using neuropsychological scales: short MMSE (Mini-Mental State Examination) scale was used for psychic state estimation, battery of tests for frontal dysfunction, clock drawing test, and Luria's 10 words test. Schulte test was used to estimate the speed of reaction and ability to concentrate attention. WMS (Wechsler Memory Scale) scale was used for memory evaluation.

Quantitative estimation of cognitive functions was performed using CEP method and electromyogram/EP Nicolet Viking Select approach. P300 study technique is based on "odd ball" – paradigm, when series of two stimuli appear randomly, and between them there are "insignificant"(frequent) ones and "significant" (infrequent) ones, and patient should count the number of the latter ones. To register CEP, we used random event stimulation to acoustic stimuli.

We used auditory click stimulus with different tone for a significant one. We used stimuli with duration of 50 ms, significant stimulus' frequency and probability were 2000 Hz and 20-30%, respectively, and for insignificant ones the frequency was 1000 Hz and probability 70-80%. Stimuli's intensity was 80 dB, time period between stimuli was 1 sec. Binaural stimulation was used. Analysis epoch was 750-1000 ms. Number of averaging was 30-70, it was quantified separately for significant and non-significant stimuli. Frequency band was 0.5-30 Hz. After component verification we estimated P300 component's latency and amplitude.

Statistical analysis of obtained data was performed with Statistica 6.0 software using parametric and non-parametric methods depending on data distribution. The results are presented as M±SD. We considered statistically significant the differences with p-value <0.05.

Results

During the study patients were divided into two groups: group I (control, n=92) made of healthy people and group II (n=94) that included patients with AH (table 1). Groups were matched for age and gender of patients. In the group with AH average systolic blood pressure (SBP) measured in the office setting was 144.06±13.05 mm Hg. Average diastolic BP (DBP) was 89.14±7.55 mm Hg. Patients with AH (Group II) had a tendency to slightly higher blood glucose and total cholesterol levels versus control group: 5.46±0.60 and 5.14±0.51 mmol/L (p>0.01) and 5.69±1.04 and 5.31±1.00 mmol/L (p>0.01), respectively.

Table 1. **Clinical examination and laboratory tests results in two groups(M±m)**

Characteristic	Healthy people, n=92 (Group I)	Patients with AH, n=94 (Group II)
Age, years	47.67±6.43	48.07±5.71
Gender, male/female, abs, %	53(57.6%)/ 39(42.4%)	50(53.19%)/ 44(46.81%)
BMI, kg/m^2	22.93±1.85	23.41±2.09
WC, cm	83.67±8.12	85.40±9.97
TC, cm	98.54±4.62	100.15±8.71
SBP, office measurement, mm Hg	117.91±7.40	144.06±13.05 *
DBP, office measurement, mm Hg	77.26±7.19	89.14±7.55 *
Plasma glucose levels, mmol/L	5.14±0.51	5.46±0.60
TG, mmol/L	1.06±0.47	1.40±0.91
TCh, mmol/L	5.31±1.00	5.69±1.04
HDL Ch, mmol/L	1.54±0.40	1.49±0.34
LDL Ch, mmol/L	1.71±0.42	1.79±0.45

Comment: TCh – total cholesterol; HDL Ch – high density lipoprotein cholesterol, LDL Ch – low density lipoprotein cholesterol, TG – triglycerids; *-p<0.01 comparing with the group of healthy patients.

All examined patients underwent estimation of cognitive functions. Patients with AH had significant increase of CEP latent period duration – 346.17±18.37 vs 335.78±16.57 ms, respectively (p<0.01), and P300 amplitude reduction – 10.4±4.3 vs 16.2±5.7 μV, respectively (p<0.01) comparing with the group of healthy people (table 2).

Table 2. **CEP characteristics in patient groups (M±m)**

Characteristic	Healthy people (n=92) (Group I)	Patients with AH (n=94)(Group II)
P300 latent period, ms	335.78±16.57	346.17±18.37 *
P300 amplitude, μV	16.2±5.7	10.4±4.3*

Comment:*-p<0.01 comparing with the group of healthy people

Correlation analysis revealed connection between CEP and BP levels. The correlation between P300 latent period and DBP levels has been found ((r=0.51; p<0.01).

Neuropsychological testing demonstrated that the group of patients with AH had several characteristics significantly different from the control group. MMSE test results were significantly lower in patients with AH comparing with the group of healthy patients – 26.97±2.13 versus 28.9±1.78 points, respectively (p<0.01). The results of the clock drawing test had no significant differences between two groups – 9.34±0.92 vs 9.76±1.44 points, respectively (p>0.01). FAB questionnaire did not reveal significant differences between the groups – 17.2±0.83 vs 17.3±0.89 points, respectively (p>0.01). There was significant reduction of short-term and long-term memory in the group of patients with AH comparing with the control group: 6.24±1.11 vs 8.22±0.44 points (p<0.01) and 110.87±10.63 vs 135.13±12.18 points (p<0.01), respectively. Patients of AH group demonstrated also lowered speed of reaction and ability to concentrate attention comparing with the healthy patients - 197.23±23.78 vs 150.03±21.24 points (p<0.01), respectively. We identified association between SBP (r=–0.34; p<0.001), DBP (r=–0.27; p<0.001) levels and MMSE test results. We also registered statistically significant correlation between SBP levels (r=0.2, p<0.001), AH duration (r=–0.21, p<0.001) and short-term memory characteristics.

Comparison of neuropsychological tests and cognitive functions quantitative estimation results revealed tight connection between them. There was association of CEP latent period and MMSE test results (r=–0.31, p<0.01), clock drawing test (r=–0.24, p<0.01), Wechsler Memory Test (r=0.34, p<0.01), Luria's 10 words test (r=–0.35, p<0.01), FAB-test (r=–0.32, p<0.01), Schulte test (r=0.48, p<0.01).

Discussion

CEP is a complex potential that appears in directed attention paradigm and reflects the process of target stimulus selection [12]. Early CEP components, reflecting its sensory part related to stimulus' physical parameters, are caused by activation of specialized systems of information reception and processing. The stage that corresponds to final stimulus identification requiring its comparison with memory template and decision making in relation to the associated action (ignoring, memorizing, and specified action) has the biggest meaning for clinical use of this technique [13]. P300 potential is related to these events, and processes of directed attention and short-term memory have a particular meaning. But P300 amplitude and temporal parameters aren't connected just with one quality or characteristic of brain or its region. They reflect organization of whole complex of mechanisms responsible for information processing in central nervous system providing various forms of cognitive and perceptive-motor activity of human. P300 generation is realized through complex spatio-temporal interaction of brain cortex, thalamic and hippocampal structures. CEP latent period extension by 20-58 ms strongly correlates with neuropsychological tests results, degree of ventricles dilatation, severity of periventricular leukoaraiosis in computer tomography imaging, but not with the amount of brain infarction loci [14]. Hypothalamus, thalamus, frontal brain cortex are considered by researchers to be a possible area of CEP generation [15]. All mentioned above structures play important role in realization of education and memory processes [16]. This study revealed association of CEP latent period and MMSE test results (r=-0.31, p<0.01), long-term memory and short-term memory parameters (r=–0.34, p<0.01 and r=-0.35, p<0.01, respectively) that proves the results of previous studies.

AH is one of the main pathogenetic factors of vascular dementia development [7, 17, 18]. In the Framingham study 1695 patients with AH aged 55-88 years had been observed for 12-15 years. This observation established significant negative reverse correlation between the BP levels and characteristics of aural and visual memory according with the results of neuropsychological tests [19]. Our work demonstrated similar results. Both SBP and DBP levels were tightly connected with the results of the testing reflecting both the condition of cognitive functions in total and short-term memory parameters. Several authors demonstrated that there was no distinct difference between CEP latent period in aged patients with systolic AH and healthy people [8, 20-22]. In the current study we identified not only the increase of CEP latent period and decrease of its amplitude in patients with AH, but also demonstrated that P300 correlated mostly with DBP levels. We detected significant correlation between neuropsychological tests characteristics and CEP in patients with AH.

Conclusions

CEP characteristics are associated with the results of neuropsychological testing in patients with AH.

P300 investigation can be used for early CD diagnostics in patients with AH

Conflict of interests: None declared.

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Nonspecific cardiac morphofunctional syndromes in patients with coronary artery disease

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Summary

Objective

To state the concept and classification of nonspecific cardiac morphofunctional syndromes in patients with coronary artery disease (CAD) using the analysis of major comparative cross-sectional studies' results.

Material and methods

Data of "Register of coronary angiography procedures" – electronic database including results of of 20.402 consecutive patients' clinical profiles.

Results

Heart ventricles dilatation in CAD patients without myocardial infarction, functional mitral regurgitation and asymmetric left ventricular hypertrophy in stable CAD patients revealed by echocardiography characterize particular types of cardiac remodeling.

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Conclusion

These cardiac morphofunctional syndromes are often conditioned by mixed pathology and they are not always directly related to obstructive coronary atherosclerosis. We suggest calling these changes nonspecific cardiac morphofunctional syndromes.

Key words

Coronary artery disease, echocardiography, nonspecific cardiac morphofunctional syndromes.

Introduction

Coronary artery disease (CAD) remains to be the leading cause of death in population of developed countries and West Siberian region [1]. Due to this one of the most important tasks of modern cardiology is to detect and treat this disease in proper time. Nowadays it is impossible to imagine CAD diagnostics without echocardiography (EchoCG). Traditionally this technique is used for detection of frank and hidden coronary insufficiency, myocardial infarction (MI) and its complications: left ventricle (LV) thrombosis and aneurism, mitral valve chords rupture, LV wall rupture, cardiac tamponade, ischemic cardiomyopathy. At the same time, coronary atherosclerosis is related to several less obvious or non-specific syndromes, the meaning of which is not yet fully understood.

CAD prognosis and survivability are mostly determined by the degree of myocardial remodeling. Post-infarction remodeling is actively studied, though less is known about myocardial remodeling in patients with CAD without the history of MI. Compensatory myocardial remodeling, including the reduction of its contractility can be caused not only by post-infarction changes but also by chronic hypoperfusion of its segments [2]. Taking it into account, it becomes very relevant to search the factors promoting cardiac remodeling in patients with CAD without MI, and to identify its connection with localization, coronary vessels involvement and the type of coronary circulation.

Many studies are dedicated to such form of myocardial remodeling like its compensatory hypertrophy [3-5]. Asymmetrical LV hypertrophy is not enough investigated, its occurrence and clinical significance are not determined yet.

LV remodeling (regional or global) is the cause of mitral regurgitation (MR) development in CAD. Since MR is considered to be the factor, aggravating patients' prognosis, it is relevant to detect connections between ischemic MR and coronary stenosis localization.

The objective of this study was to analyze clinical morphofunctional parameters of patients with CAD and post-infarction cardiosclerosis (PICS) or without history of MI, to identify factors related with cardiac ventricles dilatation, asymmetrical LV hypertrophy, ischemic MR, and to create the conception and classification of non-specific cardiac morphofunctional syndromes in CAD.

Materials and methods

In this study we used the data of "Register of coronary angiography procedures" – electronic database including results of full clinical and instrumental examination of all consecutive patients who underwent coronary angiography in Tyumen Cardiology Research Center starting from 1991 [6]. By the end of the study (July 2015) the Register contained data about 20402 patients. Patients' selection was performed according with the task of each study's part that required its own inclusion criteria. All patients gave written informed consent about the use of their examination data for a scientific study. The protocols of this study were approved by local Ethic Committee. We evaluated demographic, height and weight characteristics, quantified body surface area and body mass index, estimated coronary atherosclerosis risk factors – smoking, arterial hypertension. diabetes mellitus, dyslipidemia, family history. thyroid function, MI history, CAD duration, concomitant diseases. angina pectoris functional class (FC) according with the Canadian Cardiovascular Society grading, and grade of circulation insufficiency according with the NYHA (New York Heart Association) classification. All patients underwent EchoCG in standard views using ultrasound scanners Imagepoint NX, Agilente Technologies – Phillips; Vivid 3, 4, 7, 9 Systems, Vingmed-General Electric – Horten and multi-frequency sensors in the range of 2.5-5.0 MHz. Selective coronary angiography was made according with the technique described by Judkins (1967) using «Diagnost ARC A», «Poly Diagnost C», «Integris Allura» – Phillips angiography equipment. Statistical analysis of the results was performed using STATISTICA (StatSoft, versions 6.1-8.0) и SPSS 17.0 software. We used Kolmogorov-Smirnov test to evaluate normality of data. Statistical significance of results was estimated using Student's t-test or Mann-Whitney U-test, depending on data distribution.

"Probabilistic" calculator of "Statistica" software was used for comparison of two relative frequencies inside one group or two unconnected groups. x^2 test and two-sided Fisher's test were used for comparison of discrete variables. Pearson's correlation coefficient (parametric) and Spearman's correlation coefficient (non-parametric) were used for investigation of correlation between variables. P-value <0.05 was considered statistically significant for all tests. Logistic regression with estimation of relative risk and 95% confidence interval (CI) was used for evaluation of variables' role in formation of outcome.

Results and discussion

Analysis of several comparative single-stage studies allowed formulating the concept of cardiac morphofunctional syndromes in CAD. According to this concept, typical CAD syndromes, having well-known diagnostic value, characterizing common forms of myocardial remodeling and directly related to coronary lesions localization and extension, are supposed to be considered specific. Syndromes, characterizing particular, atypical cardiac remodeling forms in CAD, frequently caused by mixed pathology and not always directly related to the factor of coronary stenosis are suggested to be called non-specific.

Identification of factors related to LV dilatation in patients with CAD without MI

2443 patients with CAD without MI have been selected from the Register, 50 patients had LV dilatation (LV end diastolic diameter >60 mm) and 1992 without LV dilatiation. Patients with intermediate values of LV diameter were not included in the study in order to achieve more precise group separation. LV dilatation was detected in 2.5% of patients. Patients with dilated LV had lower LV ejection fraction comparing with the patients with normal LV dimensions: 41.9±10.3% vs 60.7±4.9% (p=0.001), they had higher frequency of LV impaired function: 77.8% vs 2.2% (p<0.001), and higher class (III) of heart failure: 3 4.1 vs 20.5% (p<0.001), whereas high values of angina pectoris FC and multivascular coronary lesions were less frequent: 39.5% vs 55.8% (p=0.033); 24.5% vs 37.7% (p=0.050), respectively. Multivariate analysis demonstrated that the presence of one coronary artery lesions reduced LV dilatation risk in patients with CAD without MI by 57% [7]. Therefore, coronary stenosis was not the leading factor of LV dilatation pathogenesis in these patients, and it allowed us considering this morphofunctional syndrome as non-specific one.

Identification of factors associated with right ventricle (RV) dilatation

1362 patients with Q-wave MI, including 99 patients with RV dilatation and 1263 without it, and 1209 patients with CAD without MI and history of MI, 75 of them with RV dilatation and 1134 without RV dilatation, were selected from the Register. Transversal diastolic diameter ⩽ 26 mm measured in parasternal position was considered normal [8]. In order to achieve more precise division into groups, we included patients with RV diameter ⩾ 30 mm into the group of patients with enlarged RV. Patients with slightly enlarged RV (>26 mm and <30 mm) were excluded from the study. RV dilatation frequency in patients with CAD and PICS and in patients with CAD without MI was 7.3% and 6.2%, respectively. In both groups of patients RV dilatation was not related to localization and extension of coronary lesions, but correlated with parameters characterizing morphofunctional condition of LV [9, 10]. Lack of correlation between RV dilatation and coronary arteries' lesions and its negative correlation with angina pectoris severity indicate possible non-ischemic nature of RV dilatation in patients with CAD without MI, therefore, allowing considering this morphofunctional syndrome as a non-specific one.

Identification of factors related to LV asymmetric hypertrophy

2469 patients with chronic CAD and LV hypertrophy (myocardial mass index > 115g/m^2 for males and >95 g/m^2 for females), 297 of them had asymmetric LV hypertrophy and 2172 had symmetric LV hypertrophy. Ratio between interventricular septum thickness and LV posterior wall thickness ⩾ 1.3 was considered as the criterion of asymmetric hypertrophy. LV asymmetric hypertrophy was detected in 5.8% of patients with chronic CAD. It was related to EchoCG signs of PICS (odds ratio (OR)=2.29; 95% CI 1.64-3.20), LV systolic dysfunction (OR=2.26; 95% CI 1.54-3.30), and cardiac rhythm abnormalities (OR=1.43; 95% CI 1.01-2.00), increased end-diastolic LV and RV dimensions (OR=0.88; 95% CI 0.84-0.91 and OR=1.08; 95 % CI 1.03–1.13,respectively), enlarged aortic root diameter (OR=1.07; 95% CI 1.02-1.11), and increased LV myocardial mass (OR=1.01; 95% CI 1.009-1.014). Therefore, asymmetric LV hypertrophy is related to more evident CAD clinical manifestations that allowed estimating this cardiac syndrome as a non-specific one. Independent correlation with right coronary artery stenosis (OR=1.08; 95% CI 1.02-2.15) demonstrates possible positive

effect of myocardial revascularization in these patients [11].

Identification of factors related to significant functional MR

We selected 1570 patients with CAD and PICS, 403 of them had MR grade ⩾2 and 1167 patients had no MR,between them 765 males (139 with MR grade ⩾2 and 626 without MR) and 137 females (53 with MR grade ⩾2 and 84 without MR). We also selected 1238 patients with CD without MI history: 76 patients with MR grade ⩾2, and 1162 without MR, between them 1067 males (66 with MR grade ⩾2 and 1001 without MR) and 203 females (20 with MR grade ⩾2 and 183 without MR). Since MR severity has direct correlation with CAD patient prognosis, in this study we included patients with hemodynamically significant MR (MR grade ⩾2, regurgitant volume ⩾ 30 ml) [12]. We did not include patients with heart valvular disease, mild MR, since it is often considered to be physiological, and patients with acute CAD, because MR in these patients is often reversible [13].

There are two mechanisms of MR development in CAD: the first one is related to global pathological remodeling of LV (LV dilatation with dilatation of annulus fibrosus of mitral valve); the second one is explained by myocardium regional lesions and displacement of one of papillary muscles. In both cases MR is caused by insufficient closure of mitral valve cusps. Male patients with PICS typically had MR development mechanism based on regional myocardial lesions with right coronary artery involvement (OR 2.14; 95% CI 1.18-3.87), and global myocardium remodeling with LV dilatation and heart failure FC as the causes of MR were more frequent in female patients (OR 1.64; 95% CI 1.24-2.17 and OR 4.426; CI 1.40-12.88, respectively) [14].

In patients with CAD without MI and PICS MR was related to cardiac rhythm and conduction abnormalities, higher left atrial size index and lower LV ejection fraction [15, 16]. Lack of correlation with coronary angiography parameters demonstrated low significance of coronary stenosis in MR development in this group of patients. MR features in patients with CAD mentioned above allow considering this morphofunctional syndrome as a non-specific one.

Conclusion

One of the main conclusions following cardiac remodeling study in patients with CAD without MI is the possibility of non-ischemic factor influence on the development of ventricular dilatation and ischemic MR. It is necessary to take into account the possibility of such influence and detect etiological factor associated with ischemia in proper time, correcting, if necessary, treatment strategy.

Mentioned above results allowed to develop the classification of specific and non-specific cardiac morphofunctional syndromes associated with CAD (Table 1).

Table 1. **Cardiac morphofunctional syndromes in patients with CAD**

Specific	Non-specific
I. Ischemic cascade markers: 1) LV diastolic dysfunction 2) LV systolic dysfunction - regional (asynergy types: hypokinesis, akinesis, dyskinesis) - global II. MI and its complications: - papillary muscle or tendinous chords rupture - pericarditis - LV aneurism - LV thrombosis - free myocardial wall rupture with pseudoaneurism formation or cardiac tamponade - interventricular septum rupture	I. LV dilatation in the absence of MI II. RV dilatation in patients with and without MI III. LV asymmetric hypertrophy IV. Ischemic MR

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Endocrine system pathology as the risk factor of acute coronary syndrome without ST segment elevation in intact coronary arteries

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Summary

Objective

Investigate endocrinological pathologies associated with acute coronary syndrome (ACS) in case of intact coronary arteries.

Materials and methods

We examined 168 patients with the diagnosis of acute coronary syndrome and analyzed the results of routine laboratory tests including carbohydrate metabolism and thyroid function parameters.

Results

In case of suspected ACS females have intact coronary arteries more often than males. More than 90% of this group of patients have arterial hypertension, often they have dyslipidemia, arrhythmias, history of old myocardial infarction. Myocardial infarction's possibility appears more often when there is concomitant diabetes mellitus.

Conclusion

Females under 75 years old with thyroid gland pathology, impaired carbohydrate metabolism and elevated blood pressure have higher possibility to develop ACS without ST segment elevation in intact coronary arteries. It is reasonable to include thyroid hormone blood levels estimation into standard ACS diagnostic algorithm and intact coronary arteries detection.

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Key words
Acute coronary syndrome, intact coronary arteries, arterial hypertension, hypothyroidism, diabetes mellitus, females under 75 years old.

Introduction

According with the World Health Organization (WHO), 17.5 million people died from cardiovascular diseases in 2012, of these deaths, an estimated 7.4 million (42.3%) were due to coronary heart disease (CHD). According with the Federal State Statistics Service (Rosstat), mortality due to cardiovascular system diseases was 49.6% of total number of death cases. CHD is the cause of death in more than half of all cases, and it corresponds to 26.7% of all number of deaths [1]. Therefore, cardiovascular diseases and CHD in particular remain one of the main causes of mortality in the Russian Federation.

The term "acute coronary syndrome" (ACS) as a working diagnosis was introduced by the specialists of Russian Society of Cardiology (RSC) to indicate exacerbation of CHD. Coronary artery (CA) thrombosis occurring at the place of atherosclerotic plaque rupture with consequent development of ischemia is considered to be a typical pathogenetic mechanism of ACS. Formation of occluding (sub-occluding) thrombus at the place of atherosclerotic plaque erosion is possible in some cases [2]. But the phenomenon of unstable angina occurring within mildly changed and unchanged CA had been described in the sixties of XX century [3]. According with the results of national and international studies, the frequency of mildly changed and unchanged CA varies between 10 and 30% [4, 5].

The GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes) trial (n=12142) detected non-significant CA changes in 30.5% and 14.9% of female and male patients, respectively. The results of this study have been further proved by the TIMI IIIb trial (Thrombolysis in Myorardial Infarction, Phase IIIb) (n=1473) that identified mildly changed CA in 14-19% of patients with ACS.

According with the results of one Russian study of 2015 (n=711), the frequency of unchanged or mildly changed CA during examination of patients with suspected ACS was 37.9% [6].

Therefore, ACS pathogenesis is a complex phenomenon that cannot always be explained by "typical" pathological mechanism. Because of this, several etiological and pathogenetic theories of ACS development in mildly changed CA have been proposed: vasospastic, metabolic [7], related to CA tortuosity [8], coronary microcirculation impairment [9], endothelial dysfunction, decreased local NO production, pathologic susceptibility to heartache, and others [10, 11].

Consequently, detection of unchanged and mildly changed CA in ACS becomes a complex diagnostic and therapeutic problem [12-14].

Materials and methods

1292 patients aged up to 75 years with diagnosis "ACS without ST segment elevation" and discharge diagnosis "Unstable angina" had been admitted to Ulyanovsk Regional hospital for in-patient treatment or for diagnostic coronary angiography (CAG) during the period of 2011-2015. 168 individuals with intact/mildly changed CA were selected from all admitted patients (1019 males and 273 females). Average age of patients was 56.34±8.79 years (varying from 27 to 75 years).

All patients underwent CAG (Siemens Axiom Artis, Germany angiography equipment with a pixel size of 184 μm); not less than 5 views of left CA and not less than 2 views of left CA have been analyzed.

Standard laboratory tests were performed using Olympus AU-400 (Japan) equipment and software and included obligatory analysis of carbohydrate metabolism characteristics. Thyroid gland (TG) function was assessed by estimation of thyrotropic hormone (TTH), thyroxin (T4), triiodothyronine (T3), thyroid peroxidase (TPO) antibodies levels measured in 84 patients.

Exclusion criteria for this study were the following: patients' renunciation of CAG intervention, age above 75 years, extracardiac causes of chest pain – acute attacks of peptic ulcer disease, reflux esophagitis, exacerbation of cervical and thoracic osteochondrosis, congenital and acquired valvular heart disease.

We estimated the significance of differences between studied characteristics using x2 criteria and Spearman's correlation analysis. Statistical analysis of results was performed using Statistica 10 software. The differences were considered statistically significant, if the p-value was less than 0.05.

Results and discussion

Statistical analysis revealed that up to 30% of females admitted to hospital with the diagnosis of ACS with-

out ST elevation have mildly changed or intact CA significantly more frequently than males (Table 1)

Table 1. **Gender differences of mildly changed CA occurrence in ACS without ST elevation**

Mildly changed/intact CA	Females	Males
yes	82	86
not (stenosing atherosclerosis)	191	933

Comorbidity estimation revealed that 157 (93%) patients have arterial hypertension (AH), 137 (82%) have dyslipidemia, 61(36%) have different arrhythmias (mostly extrasystoles). 25 (15%) individuals have history of myocardial infarction (MI). TG pathology was observed in 35 (42%) patients, 28 (17%) patients have obesity and impaired carbohydrate metabolism, including 18(10.7%) individuals with diabetes mellitus (DM), 17 (10%) patients have osteochondrosis of the spine, 8 (9%) males have prostate adenoma, 12 (7%) patients have lower extremity varicous veins, 5 (6%) female patients have uterine myoma, 5 (3%) patients have chronic pyelonephritis and bronchial asthma, 3(2%) have chronic bronchitis, urolithiasis and cholelithiasis (Figure 1).

Initially 11% of patients had the history of TG disorders. Hypothyroidism in elderly people has non-specific clinical manifestations and is often asymptomatic that complicates diagnosis verification. According with the results of Colorado study, finished in 2000 and involved 25862 patients, 25% of patients had apparent hypothyroidism without any symptoms, and 35% of patients had subclinical hypothyroidism [15]. Laboratory tests for TG function revealed pathological changes in 41.6% of patients, and hypothyroidism was the dominant pathology presented in 71.4% of cases. It is known that the number of hypothyroidism cases increases with age, especially in females. Average hypothyroidism occurrence in elderly women is 10 times higher than in elderly men [16]. The results of the Whickham study (n=2779) revealed that total prevalence of hypothyroidism was 14 cases per 1000 females (or 19 cases per 1000 females, taking into account possibly omitted cases) and 1 case per 1000 males [17].

It was demonstrated that hypothyroidism leads to coronary circulation impairment [18]. According with the results of meta-analysis of 11 prospective studies (n=55287), the presence of hypothyroidism (TTH levels elevation > 10 μU/L) increases the risk of CHD development and death from it [19].

Glucose metabolism impairment was detected in 29 patients (17.2%), and 18 patients (10.7%) had DM. 33.3% of them (n=6) have the history of MI. Prevalence of MI history in individuals without DM is significantly lower (12.6%). Some studies demonstrate the existence of interrelation between hypothyroidism and DM. One of possible mechanisms underlying it may be explained by gluconeogenesis suppression that leads to decreased glucose synthesis with further compensation of this insufficiency by decreased glucose utilization by muscles and other peripheral tissues [20]. There are evidences about increased glucose-induced insulin secretion in hypothyroidism that is decreased during therapy with L-thyroxine. [21]. Combination of hypothyroidism and DM increases

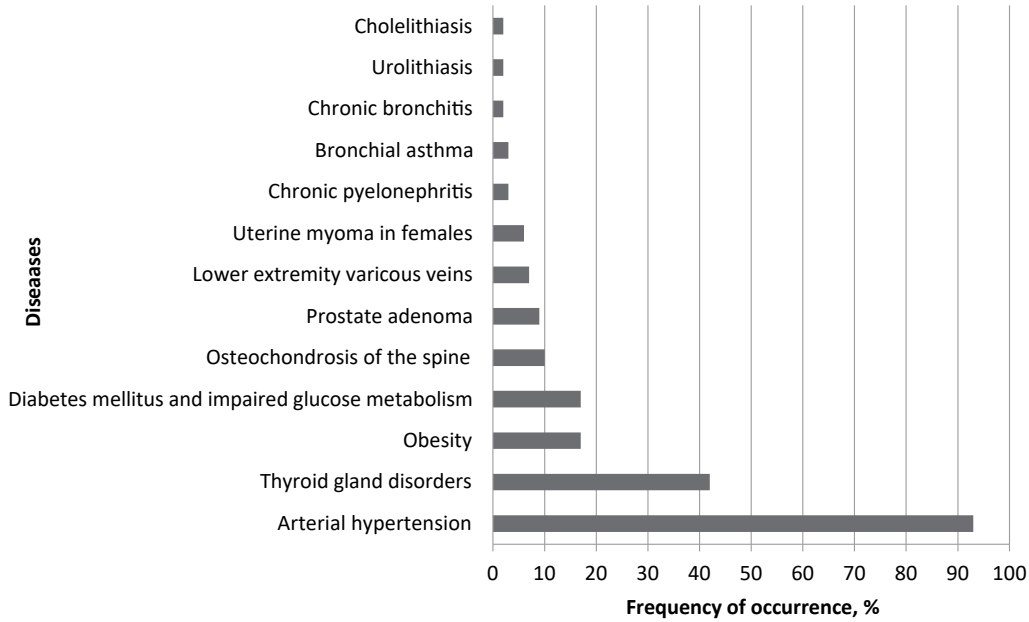

Figure 1. The frequency of different diseases occurrence in ACS without ST segment elevation with mildly changed CA.

the risk of cardiovascular diseases, and TG pathology is more significant. Patient with DM and subclinical hypothyroidism have higher cardiovascular risk comparing with patients with DM and compensated TG pathology [22].

Investigation of correlation between TTH levels and lipid spectrum characteristics revealed unidirectional changes. There was a moderate direct correlation between TTH and low density lipoprotein (LDL) levels ($p<0.05$, $r=0.53$)and high density lipoprotein (HDL) levels ($p<0.05$, $r=0.4$), and cholesterol (Ch) levels ($p<0.05$, $r=0.4$).

Hypothyroidism can be the cause of unidirectional changes of blood lipid spectrum [23]. Hepatic lipase and cholesterylester transfer protein regulate lipoprotein levels [24]. These enzymes remodel lipoproteins, exchange Ch and triglycerides' esters between lipoproteins. Enzymes' activity changes considerably in case of hypothyroidism, and it results in increased blood lipoprotein levels [25].

TG hormones deficiency decreases the amount of LDL receptors in liver and consequently diminishes LDL excretion and increases their levels. TG hormones' effects are mediated by nuclear receptors of thyroid hormones having the ligand-binding site and the site interaction with deoxyribonucleic acid (DNA). Thyroid hormones interact with ligand-binding domain of the receptor, after it DNA-binding domain interacts with DNA-hormone-sensitive fragment, responsible for LDL receptor gene transcription [26].

More than that, unlike other organic compounds consumed with food or synthesized in organism, structural base of cholesterol cannot be decomposed into CO2 and H2O. That's why the major part of Ch is excreted with bile acids. Thyroid hormones regulate the activity of cholesterol-7-α-hydroxyilase, enzyme participating in bile acids synthesis from Ch [27]. The activity of this enzyme reduces in case of hypothyroidism, and it, in its turn, increases Ch levels [28].

Therefore, all discussed above mechanisms in some extent lead to unidirectional changes of blood lipid spectrum in hypothyroidism.

Conclusion

We identified that around 30% of females under the age of 75 years, admitted to the hospital with provisional diagnosis of "ACS without ST elevation", have intact CA, this phenomenon is observed significantly more often in female patients comparing with males.

AH is the most frequent pathology in patients with ACS and mildly changed CA, being present in around 93% of all cases. The risk of MI development in this group of patients increases significantly in case of concomitant DM-2 type.

Changes of lipid metabolism characteristics in case of unchanged CA majorly evidence TG pathology. Endocrine system diseases (impaired carbohydrate metabolism and TG pathology) aggravate CAD treatment and can be considered as predictors of coronary artery insufficiency even in mildly changed and intact CA.

Conflict of interests: None declared

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Systemic embolism risk factors in kidney transplant recipients during long-term post-operative period

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Summary

Objective

To assess systemic embolism risk factors in kidney transplant recipients, who manifested atrial fibrillation in long-term post-operative period.

Materials and methods

A prospective cohort study of 175 kidney transplant recipients was carried out in the Republican Scientific and Practical Center of Organ and Tissue Transplantation of the healthcare institution «9th municipal clinical hospital». The risk stratification of ischemic stroke and systemic embolism development was performed using the $CHA_2DS_2VAS_c$ score.

Results

It was found out that the occurrence of risk factors of thromboembolic complications was high in kidney transplant recipients who had atrial fibrillation in long-term post-operative period; it required indirect anticoagulants prescription in addition to a combined immunosuppressive therapy in 62% of cases.

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Conclusion

Warfarin prescription in this category of patients was not accompanied with increased frequency of severe hemorrhagic complications in comparison with general population during 3 years of observation.

Key words

Organ transplant recipients, systemic embolism, atrial fibrillation, anticoagulant therapy.

Introduction

The frequency of thromboembolic complications (TEC) in general population is 1-2 cases for 1000 individuals per year. Risk of thromboembolism development mostly depends on genetic and exogenous factors; the degree of risk varies depending on performed surgical interventions [1]. TEC development risk for abdominal surgery is 0.6-3.1%. Appendectomy, cholecystectomy and hernia repair belong to the group of surgical interventions with low risk (0.6%). Gastrointestinal tract operations are characterized with moderate risk (1.8%) and splenectomy corresponds to high risk (3.1%). 50% of patients who underwent orthopedic operations without preoperative preventive interventions develop venous thromboembolism, and anticoagulants' administration reduces thromboembolism risk up to 18 cases for 1000 individuals per year. According with published data, organ transplantation increases the risks of venous thromboembolism for surgical intervention and immunosupressive therapy [1, 2].

From the moment of the start of calcineurine use the number of TEC after kidney transplantation has decreased, varying from 2 to 14%. The results of retrospective study that involved 480 donor kidney recipients were published in 1987, and it demonstrated that 8.3% of patients had pulmonary artery embolism with the peak of morbidity during first 4 months after transplantation. The study that had been performed during the period from 1985 to 1995 and involved 1833 patients revealed lower frequency of TEC complications (4.2%) with the peak of morbidity between third and fifth months after transplantation. The risk of development of late TEC occurring 1.5-3 years after the transplantation estimated using Medical Care database, which included 28924 kidney transplant recipients, was 1.5%. Published data demonstrate high frequency of TEC development after kidney transplantation [3-6].

Risk factors of venous and systemic TEC in general population include surgical interventions, history of deep veins' thrombosis, elderly age, cancer, obesity, renal failure, long immobilization, presence of central venous catheters, pregnancy and postpartum period, oral contraceptives administration, presence of inherited and acquired thrombophilia, abnormal cardiac rhythm and conductivity, chronic heart failure, diabetes mellitus, arterial hypertension (AH). Organ transplants' recipients belong to the group of risk not only due to the presence of traditional risk factors of venous and systemic thromboembolism, but also due to the causes directly related to transplantation [7, 11]. Procoagulative effect of immunosuppressive drugs has been reproduced in in vitro conditions, but it is impossible to assert that these changes in organism occur just because of administered therapy, not taking into account other risk factors acquired in the post-operative period.

Abnormal blood coagulation increases the risk of transplant loss due to transplant vessels' thrombosis and thrombotic complications after organ transplantation. Transplant thrombosis' prevention in the early post-operative period after donor organ transplantation is provided by early post-transplantation anticoagulant therapy. Therefore, it is recommended to concentrate on TEC risk factors' and blood clotting abnormalities' detection in advance, in particular, in patients with recurring thrombosis of vascular bypass or present history of TEC. It is strictly required to perform well-timed and detailed examination before transplantation in this category of patients. In particular, it is necessary to evaluate such characteristic like antithrombin III and protein C activity, activated protein C (Factor V Leiden) and protein S resistance and antiphospholipid antibodies' concentration. Kidney transplantation may be performed in patients receiving antithrombotic therapy: warfarin, aspirin, clopidogrel. It is necessary to take into account characteristics of blood clotting process and perform coagulation tests in these patients in case of surgical intervention.

The most frequent causes of TEC in the early post-operative period are blood stasis in vessels downstream the iliac vein due to its cross-clamping during anastomosis formation, intima lesions, aggressive dissection in the area of vessels, post-operative immobilization and insufficient hydratation. Lower extremity deep vein thrombosis can extend on renal

vein or become a cause of life-threatening pulmonary embolism.

According with the clinical guideline for kidney transplantation, established by order of the Ministry of Health of the Republic of Belarus №6 from 05.01.2010 and clinical guidelines of the European Association of Urology, patients with lower extremity deep veins thrombosis should receive anticoagulant therapy for not less than 3 months. Heparin therapy should be substituted with warfarin as much early as possible. Since heparin is inactivated by kidney, patients with inadequately functioning transplant have high risk of postoperative bleeding caused by direct anticoagulants overdose.

Patients with high risk of thrombosis should receive 5000 MU of unfractionated heparin subcutaneously before operation, but it is necessary to bear in mind the risk of hemorrhagic complications in renal failure, therefore it is not recommended to administer more than 10000 MU of unfractionated heparin per day taking into account the possibility of additional intraoperative drug introduction for several indications. Kidney transplant recipients should wear compression stockings for several days after operation in order to prevent lower extremity deep vein thrombosis. Anticoagulant therapy with low molecular weight heparin is inadmissible for outpatient conditions, because the extent of anticoagulation may be unpredictable and coagulation control may be complicated. Aspirin administration for thrombosis prevention is more favorable for outpatients in the early post-operative period [8].

In the long-term post-operative period the occurrence of atrial fibrillation (AF), influencing the development of systemic TEC and leading to patients' incapacity, high mortality and higher treatment's costs, increases due to several reasons like improved survivability of kidney transplant recipients, cumulation of such risk factors like AH, heart failure, valvular heart disease, diabetes mellitus, coronary heart disease, thyroid gland disorders in the cohort of patients. Indirect anticoagulants have gained a stable position in TEC prevention, but the risk of bleeding complications during their administration in patients with various comorbid conditions and AF forms makes it relevant to search for additional criteria of optimal antithrombotic therapy selection in organ transplant recipients.

The objective of this study was to assess systemic embolism risk factors in kidney transplant recipients, who manifested AF in long-term post-operative period.

Materials and methods

This prospective cohort study that included 175 kidney transplant recipients was performed on the base of the Republican Scientific and Practical Center of Organ and Tissue Transplantation and the Healthcare Institution «9th municipal clinical hospital of Minsk. 90 (51.4%) of patients were males, 85 (48.5%) of patients were females, average age was 44.7±6.18 years. 78 (44.6%) patients who underwent kidney transplantation were diagnosed with AH, in the long-term postoperative period (>12 months after transplantation), 64 patients (36.5%) had family history of early onset of cardiovascular diseases, 45 patients (25.7%) had burdened family history of diabetes mellitus 2 type, the occurrence of smoking was 13.1% (n=23).

Paroxysmal and/or persistent form of AF was diagnosed in 27 recipients. AH II-III stage that was presented in 48.1% of patients (13 kidney transplant recipients) prevailed in the etiological structure of AF, combination of AH and coronary heart diseases was diagnosed in 9 individuals (33.4% of patients involved in the study), 5 patients (18.5%) were diagnosed with idiopathic form of AF due to lack of known AF causes. Ischemic stroke and systemic embolism development risk stratification was performed using CHA_2DS_2VAS**c** score (Congestive Heart failure, Hypertension, Age (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age, Sex category).

Selected category of patients underwent screening testing of platelets, hemostasis and in-deep examination of several hemostatic complications development markers (D-dimer, von Willebrand factor, antithrombin III, protein C).

Results and discussion

Kidney transplant recipients had lowered protein C concentration (58.24±6.18%), increased D-dimer levels (507.24±19.32 ng/mL) and von Willebrand factor (176.14±21.14%) levels comparing with the reference values during the long-term postoperative period (12 months±1 week). Obtained results allow supposing the presence of reverse cause-and-effect relation in hemostatic abnormalities development in kidney transplant recipients: prothrombotic condition and endothelial lesions may be caused by immunosuppressive therapy, presence of AH or coronary heart disease. It was slightly unexpected to detect lack of correlation between observed hemostasis system changes, underlying disease that had led to renal failure and transplantation type. The percentage of residual factor dispersion (δ^2) was 64%, that does not

allow considering obtained analytic data statistically significant and requires further analysis dedicated to identification of significant cause-and-effect relation between hemostasis' abnormalities and factors leading to their development in the long-term postoperative period. Revealed protein C reduction and endothelial damage markers (increased von Willebrand factor's levels) contributes to a single system of the risk factors of the hemostasis abnormalities development. Protein C concentration in the group of donor kidney recipients can influence the impaired synthesis of natural anticoagulants, because it is difficult to explain the changes with increased intake of anticoagulant proteins due to the lack of the signs of blood clotting activation leading to excessive amount of thrombin [9-10]. At the same time, AF presence aggravated observed hemostasis' abnormalities increasing the risk of TEC development in the long-term postoperative period in spite of successfully performed kidney transplantation.

Ischemic stroke and systemic embolism development risk stratification was performed using CHA_2DS_2VAS**c** score (Figure 1).

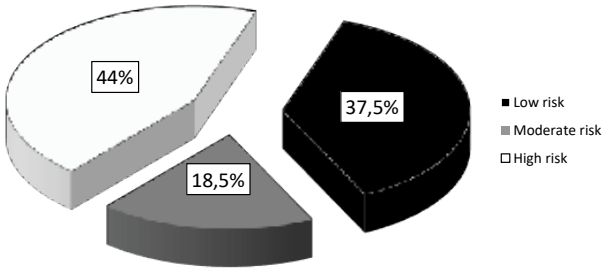

Figure 1. Stratification of ischemic stroke and systemic embolism development risk according with the CHA_2DS_2VAS**c** score.

37.5% of kidney transplant recipients with AF had low risk of systemic embolism development (0 points according with CHA_2DS_2VAS**c**), 18.5% had moderate risk of systemic embolism (1 point of CHA_2DS_2VAS**c** score), 44% of participants had high risk of systemic embolism (>1 points of CHA_2DS_2VAS**c** score). Main risk factors of systemic embolism in kidney transplant recipients with AF were: AH (81.5% of patients), female gender (10 patients (37%)), diabetes mellitus (7 patients (25.9%), vascular diseases (19 (70.4%) individuals). Kidney transplant recipients with A– 19 (70.4%) who had high risk of systemic embolism development received warfarin therapy under international normalized ration (INR) control for the prevention of embolism starting from the moment of arrhythmia detection. During 3 years of observation three patients having >1 points according with the CHA_2DS_2VASc score and receiving therapy with warfarin had been registered with bleeding complications that required admission to hospital and warfarin withdrawal: macrohematuria (1 case), recurrent epistaxis (2 cases).

Conclusion

Kidney transplant recipients with AF have high frequency of TEC requiring indirect anticoagulant prescription in 62.5% of cases in addition to combined immunosuppressive therapy in long-term postoperative period. Three-year therapy with warfarin was not associated with increased number of major bleeding complications in kidney transplant recipients having high risk of systemic embolism development comparing with the general population.

Taking into account the presence of additional hemostasis risk factors (reduced protein C concentration, increased D-dimer's and von Willebrand factor's concentrations), antithrombotic therapy prescription in long-term post-operative period should be considered in all stages of these patients' dynamic observation.

Conflict of interests: None declared

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Report on the results of II Interregional conference of cardiology and internal medicine (December 5-6, 2016, Ulyanovsk)

II Interregional Conference of cardiology and internal medicine was held in Ulyanovsk on December, 5-6, 2017. The congress was supervised by the Ministry of Healthcare of the Russian Federation, Russia President Plenipotentiary Representative Office in the Privolzhsky Federal district and the Government of Ulyanovsk region. The Ministry of Healthcare of family and social welfare of Ulyanovsk region, State scientific center of preventive medicine, Ulyanovsk State University and the foundation for advancement of cardiology "Cardioprogress" were responsible for organization of the Congress.

Scientific and educational conference was held on the base of Ulyanovsk State University. P. S. Degtyar', the minister of healthcare and social welfare of Ulyanovsk region, V. I. Midlenko, the head of the Institute of medicine, ecology and physical culture, and R. M. Linchyak, assistant director for scientific and outpatient work of State scientific center of preventive medicine, made a welcoming speech for participants during the opening ceremony.

838 medical doctors and delegates from 20 cities of the Privolzhsky Federal district and other regions of Russia took part in the conference.

Two-day scientific program included 23 scientific meetings, clinical lectures, round table discussions, master-classes and practicing doctors' schools with 86 participants from 14 cities of the Russian Federation and one lector from Spain. Conference's topics included different aspects, starting from prevention of chronic non-infectious diseases and somatic diseases' comorbidity and finishing with surgical approach to the treatment of cardiovascular diseases and cardiorehabilitation. It is worth to mention that scientific meetings of 8 national medical schools were organized during the conference as part of its scientific program. State scientific center of preventive medicine (headed by a corresponding member of the Russian Academy of Science S.A.Boytsov) was presented by 25 leading scientists and professors. Internal medicine department of Ulyanovsk State University medical faculty (dead professor V. V. Gnoyevykh) actively participated in the congress. The Ministry of healthcare, family and social welfare of Ulyanovsk region held a meeting dedicated to prophylactic medical examination and organization of screening of socially significant diseases. Traditionally, the conference program included two scientific meetings for young researchers with 10 participants. Winners received certificates and guaranteed possibility to publish articles in leading national scientific journals.

Coordination board of the Ministry of Healthcare of the Russian Federation issued certificates for the participants about continuous medical education with 12 credit hours after pre-examination; for the first

time it approximates the significance of a regional scientific event to the level of national meetings and congresses.

Collection of scientific works (220 abstracts from 34 cities of Russia and CIS countries) was published in supplementary materials of December issue of "Cardiovascular therapy and prevention" journal. Collection of scientific works is available at the website of the "Cardioprogress" foundation (www.cardioprgress.ru).

The conference was widely covered by federal (the "Russia 1" channel) and regional (regional TV channel, newspapers, government website) mass-media, reportages and necessary information were published in profile medical journals and on the website of the Ministry of the Healthcare of the Russian Federation.

At the closing ceremony conference's chairmen pointed out high level of organization and applied significance of scientific program. Charman's assistant M. N. Mamedov presented the resolution with the results of two-year work.

Preparation and organization of scientific and educational event has been provided by 84 research workers of State scientific center of preventive medicine, medical faculty of Ulyanovsk State University, and the Ministry of healthcare, family and social welfare of Ulyanovsk region.

The next III Interregional Conference of cardiology and internal medicine will be held in November 2017 in Saransk.

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Guidelines for authors

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

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Sources in Russian with transliteration:

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