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Pregnancy as the risk factor of arrhythmias

Values of central aortic blood pressure in normotensive students, existing risk factors and possible approaches to create the preventive environment in the University

The probabilistic calculator for prediction of coronary atherosclerosis risk in patients with obesity

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Contents

Editor's Welcome

Dear colleagues!

In the 10th issue of the International Heart and Vascular Disease Journal, there are leading article, review, original articles and the results of V International Forum of Cardiology and Internal Medicine.

The leading article of the issue is dedicated to investigation of arrhythmias and their etiological factors in pregnant women. The results of clinical study demonstrate that complex cardiac rhythm abnormalities can develop both in pregnant women with pre-existing cardiovascular pathology and in patients without organic lesions of internal organs and metabolic disorders.

Review article of this issue presents the work of the group of authors from USA where they discuss the latest technologies and possible use of extracorporal membrane oxygenation in adult patients with respiratory system diseases.

In "Original articles" of the 10th issue section we published four papers. The first work investigates characteristics of central aortic blood pressure in normotensive students considering present risk factors and the authors propose the approaches for development of preventive environment in universities. The article of Bolotova E.V.and coauthors studied the frequency of cardiovascular disease and chronic kidney disease risk factors in 300 patients with chronic obstructive pulmonary disease. The next work is dedicated to investigation of methods of coronary atherosclerosis risk prognosis in patients with obesity. For this reason 85 male patients with I-III grade obesity without clinical manifestations of angina and atherosclerosis of other localizations underwent coronary angiography and multispiral computer tomography of coronary arteries. The article of Kosheleva O.A. and Zhuravleva O.A. represents the results of clinical study dedicated to antihypertensive therapy and metabolic effects of different combined therapy schemes in patients with arterial hypertension and diabetes mellitus.

V International Forum of Cardiology and Internal Medicine, organized by the "Cardioprogress" Foundation, was held in Moscow in March 29-31, 2016. Forum involved more than 1500 participants from the subjects of Russian Federation and from near abroad countries. Scientific program of the Forum included 60 scientific workshops, clinical lectures, round-table discussions, educational seminars for doctors, clinical case presentations and poster sessions. The results of this Forum are present in this issue of the Journal.

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

Rafael G. Oganov

Editor-in-Chief

President of the "Cardioprogress" Foundation

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LEADING ARTICLE

Pregnancy as the risk factor of arrhythmias

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Summary

Objective

To investigate the features of arrhythmias and define possible etiological factors of their development in pregnant women.

Materials and methods

133 patients (average age 27,1±5,7 years) during II-III trimesters of pregnancy were investigated, 113 of them had complex arrhythmias, 20 women had normal sinus rhythm. Depending on presence or absence of arrhythmia and cardiovascular pathology all patients were divided into three groups. Group I (n=62) included women with arrhythmias and organic lesions of cardiovascular system: congenial or acquired heart disease, cardiomyopathies, post-myocarditis cardiosclerosis. Group II (n=51) included patients with idiopathic arrhythmias, control group (n=20) included almost healthy women with normal sinus rhythm.

Results

According with 24hour ECG monitoring, arrhythmias of III-IV classes (classification of Lown B. и Wolff N., 1971) were registered with the same frequency in both groups of patients. At the same time maximal number of ventricular extrasystoles was detected in the group of "idiopathic" heart rhythm lesions and the biggest number of supraventricular extrasystoles was found in the Group I of patients. Pregnant women with mitral valve prolapse had significantly lower frequency of supraventricular extrasystoles, but at the same time the occurrence of ventricular extrasystoles was comparable with main observation groups.

Conclusion

Complex arrhythmias arise both in pregnant women with concomitant cardiovascular pathology and in women without organic lesions of organs and metabolic processes. It requires precise dynamic observation of these patients.

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Key words
Arrythmias, pregnancy, cardiovascular disease, idiopathic arrythmia.

Introduction

Currently there is no official statistical information about arrhythmia frequency in pregnancy, but existing data demonstrate that in 1976-1978 cardiac rhythm and conductivity abnormalities were registered in 5,0% of pregnant women, and in the next decades this number increased up to 11,3% [1], and in 1990 arrhythmias occurred in 7-15,7% of pregnant women [2]. Documented maternal mortality from primary arrhythmias hasn't been registered yet, at the same time experts say that arrhythmias can be letal, and British Confidential Study of cardiac mortality identified 9% of these cases as "sudden adult cardiac death" syndrome [3].

At the same time there are some evidences about arrhythmia development in patients with hemodynamic lesions and significant anatomic changes in cardiovascular system (CVS) [4, 5]. Pregnancy with its hemodynamic, hormonal, vegetative and metabolic changes can become a proarrythmogenic factor especially considering the fact that "female heart" is basically predisposed to arrhythmias. first of all it is related to gender features of electrophysiological processes in heart. In 1920 Bazett H.C. noticed that females have higher heart rate (HR) than males on electrocardiogram (ECG), that they have longer QT interval on electrocardiogram, that remains relatively long after HR correction comparing with males [6]. Villareal R.P. with coauthors demonstrated that 10-20 seconds more long QT interval, and these differences become more significant during menstruation [7]. Apart of these, women have smaller QRS complex duration and voltage, P wave and PR interval duration shortening [8,9]. Non specific changes of repolarization occur more often in women [10]. At first instance, these differences can be explained with initially smaller dimensions of heart in women, but they persist even after correction of heart mass and body weight. These results can be explained with the influence of female sex hormones on potassium and calcium channels. In particular, it was found that estrogens lead to QT duration increase by influencing fast and slow sodium channels current and sodium-calcium exchanges [9]. This exploration was lately proved with other studies that demonstrated how vegetative nervous system takes part in cardiac rhythm regulation [11-12]. Gender features can be related not only to electrophysiological processes, but also to arrhythmia's character. Several epidemiological studies found out that supraventricular tachycardia with narrow QRS complex that develops according with re-entry mechanism in atrioventricular node, is twice more frequent in women than in men [13, 14], and in contrary, supraventricular tachicharia that appears due to re-entry mechanism in atrioventricular node with the presence of additional conductive path is twice more frequent in men [15]. Unfortunately specific studies that would investigate cardiac rhythm abnormalities and define possible etiological factors of their development have not been made still. This problem was chosen as the aim of this work.

Materials and methods

133 women in II and III trimester of pregnancy (average age 27,1±5,7 years) were included in this study after signing the informed consent. All patients were admitted to cardiological department of Moscow City Hospital №63. Apart of routine examination and laboratory diagnostics that included blood tests for electrolytes (sodium, potassium) and thyroid gland hormones (triiodothyronine(T3), thyroxin (T4), thyrotropic hormone (TTH)) patients underwent two-dimensional and Doppler echocardiography (EchoCG) in M-, B-, and continuous wave modes with "Logic-400" machine, 24-hours Holter ECG monitoring, using "Medilog Prima" and "Schiller MT-200".

Statistical analysis was performed using "Biostatistics. Version 4.03" software. We used standard approaches of variation statistics and Student's test for estimation of paired comparisons. Differences were considered significant if p-value was < 0.05.

Results

113 of 133 patients were diagnosed with complex abnormalities of cardiac rhythm (main group) and 20 women had normal cardiac rhythm (control group). According with patients' history, 84 (63,2%) women didn't have bad habits, 49 (36,8%) women used to smoke in past or continued to smoke during pregnancy, and the amount of cigarettes smoked for day varied from 2 to 30, average pack-year number was 5,3±1,8. Almost one half of patients had burdened family history of cardiovascular diseases and metabolic abnormalities: arterial hypertension of one or two parents occurred in 55,6% of cases, myocardial infarction or stroke of one or two parents appeared in

8,2% of cases, obesity – in 33,1% of cases, diabetes mellitus – in 4,5% of cases.

Women didn't complain of palpitations, intermittence before the beginning of current pregnancy. Starting from the middle of the I trimester or initial part of the II trimester patients with arrhythmias started to feel intermittence, "sinking heart", palpitation, sometimes paroxysmal, weakness, increased fatigability, and manifestation of these symptoms led to additional examination. Patients were divided into three groups according with the presence or absence of arrhythmia or other cardiovascular pathology. The group I (n=62) included women with cardiac rhythm abnormalities and organic changes of CVS. The group II included 51 patients with arrhythmias and without observed organic changes of CVS, endocrine system, gastrointestinal tract, thus their arrhythmia was classified as "idiopathic". The third (III) group (n=20) was considered as a control, it included almost healthy women with normal sinus rhythm and the same duration of gestation as the patients of first two groups.

According with the results of clinical and instrumental examination, in the I group such organic changes of CVS were present: hypertrophic cardiomyopathy without left ventricle efferent tract obstruction (n=3), open oval foramen (n=3), dilatation cardiomyopathy without the signs of cardiac insufficiency (n=4), mitral valve insufficiency of rheumatic etiology (n=4), ventricular septal defect that was not treated surgically (n=6), corrected Fallot's tetrad (n=1) and postmyocarditis cardiosclerosis (n=10). Mitral valve prolapse (MVP) was present in many patients (n=30), and I grade mitral regurgitation was found in 9 cases and II grade mitral regurgitation was found in 21 case.

Analysis of the results of 24-hours Holter ECG monitoring included several parameters: main pacemaker, average heart rate (HR) (day/night/24 hours), number of supraventricular extrasystoles (SVES, during hour and during 24 hours), number of ventricular extrasystoles (VES, during hour and during 24 hours), and VES class according with Lown B. and Wolff N. classification in Ryan-McKenn modification. According with these results, the number of extrasystoles during 24 hours varied from 8 thousands to 50 thousands in pregnant women with arrhythmia, couplets (13-80 during 24 hours) and triplets (3-150 during 24 hours) were registered in some women (n=6 and 4 respectively), 5 women had runs of ventricular tachycardia (1-5 during 24 hours) with HR varying from 156 to 229 beats per minute. These cardiac rhythm abnormalities resembled to II-IV class of Lown B.-Wolff N. classification. There were no statistically significant differences in VES gradation between the groups of pregnant women with arrhythmia, but the difference of VES and NVES number was considered statistically significant. The biggest amount of VES was registered in the group of "idiopathic" arrhythmias, and the biggest number of NVES was found in the group of organic cardiac pathology. Group of healthy patients was characterized with normal sinus rhytm and single NVES (Table 1).

Table 1. **Cardiac rhythm abnormalities according with 24-hours Holter ECG monitoring in the groups of patients (M±SD)**

Characteristic	Group I (n=62)	Group II (n=51)	Group III (n=20)
VES class, Lown B. and Wolff N classification	2,9±1,6	2,1±1,8	2,4±1,3
VES number/24 hours.	4300±300	6200±530 [1), 3)]	500±40 [1), 2)]
SVES number/ 24 hours	3800±300	2000±150[1), 3)]	600±50 [1), 2)]

Comment: [1)] — p<0,05 in comparison with Group1; [2)] — p<0,05 in comparison with Group II; [3)] — p<0,05 in comparison with group III.

Taking into account high number of patients with MVP and its high occurrence in population in general, it was particularly interesting to check the character of arrhythmias in this category of pregnant women. We distinguished this group of patients from the group of women with arrhythmias and background cardiovascular pathology (Table 2).

Pregnant women with MVP had SVES significantly less frequently than patients of other groups; practically, there was just one patient who had 1000 SVES during 24 hours. But the number of VES was comparable with the results of the group of "idiopathic" arrhythmias.

Table 2. **SVES/VES ratio in groups of pregnant women with different pathologies (M±SD)**

Extrasystole character	Average number during 24 hours	Organic cardiac pathology (except MVP) (n=32)	MVP (n=30)	«Idiopathic» arrhythmias (n=51)
SVES	1870±290 (max. 17 200)	3900±380 (max. 13 000)	70±11 [1), 2)] (max. 1000)	1800±220 [1)] (max. 17 200)
VES	5160±320 (max. 15 750)	3200±240 (max. 8000)	5300±430 [1)] (max. 15 000)	6200±540 [1)] (max. 15 750)

Comment: [1)] — p<0,05 in comparison with organic cardiac pathology; [2)] — p<0,05 in comparison with «idiopathic» arrhythmias.

Discussion

Rich experience of modern clinical cardiology demonstrates that the reasons of cardiac rhythm abnormalities are very different and still poorly studied. Patients with changed hemodynamics, hormonal status, general and water-salt metabolism and increased load of CVS have high risk of arrhythmia development, and all these predisposing factors are present in pregnant women. Gestation period is characterized with physiologically increased activity of renin-angiotensin-aldosterone system, that raises up circulating blood volume mostly increasing plasma volume up to 40%. The most significant hemodynamic characteristic during pregnancy is increased stroke volume (SV), that increases up to 30-45% in rest state comparing with its values before pregnancy. SV growth increases cardiac output (CO), that reaches maximum during 26-32 week of pregnancy being increased up to 33-50% comparing with initial levels. Physiological tachycardia that develops during pregnancy raises up HR by 15-20 beats per minute by the end of pregnancy comparing with initial levels. 12-34% decrease of peripheral vascular resistance occurs during pregnancy [16]. Our study demonstrated that these hemodynamic factors can lead to arrhythmias in patients with organic lesions of CVS. More than that, important factor of CVS adaptation to pregnancy is systemic vasodilation caused not only by increased nitrogen oxide (NO) and other vasodilating factors secretion, but also by increased levels of estrogens and progesterone, that increase adrenoreceptors' sensitivity to hormones of sympathoadrenal system. Starting from the beginning of pregnancy and up to delivery time reactivity of ß-receptors increases and reactivity of α-receptors decreases, that is necessary to reduce contractive activity of myometrium and provide the carrying of pregnancy [17]. ß-receptor density in myometrium increases due to progesterone action. ß-receptor activation can lead to arrhythmia development, as it was shown in previous studies [18, 19]. Probably so-called "idiopathic arrhythmias" are mostly caused by proarrhythmogenic effect of sympathoadrenal system, functional condition of which increases being influenced by female sexual hormones.

Increased ectopic activity is also related to vegetative dysfunction in patients with MVP, that traditionally is considered as a normal and not requiring therapy especially without hemodynamically significant mitral regurgitation. It is known that MVP is characterized with genetically determined defect of collagen synthesis and lowered levels of intratissular magnesium concentration. In case of magnesium deficiency fibroblasts produce defective collagen of mitral valve cusps. Clinically MVP often manifests with abnormal vegetative regulation of cardiac rhythm that is registered with more than 70% frequency [21]. During pregnancy even almost healthy women can develop the symptoms of such vegetative dysfunction like hypersympathicotonia [22], and patients with MVP can have more prominent symptoms which can lead to lowering the quality of life and, from the point of view of the authors, influence intracardiac hemodynamics, and in case of other risk factors presence they can also provoke resistant ventricular tachiarrythmias.

Thus, the results of the study indicate that complex cardiac rhythm abnormalities in pregnant women develop as the consequence of cardiovascular pathology that includes congenital and acquired valvular disease, postmyocarditis cardiosclerosis, MVP with moderate regurgitation, or they appear in women without organic changes of internal organs and metabolic processes, that requires precise dynamic observation of these patients, and in case of hemodynamic instability or developing life-threatening arrhythmias it is necessary to start well-timed adequate therapy.

Conflict of interest: None declared.

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REVIEW ARTICLE

Extracorporeal Membrane Oxygenation in Respiratory Diseases in Adults

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Abstract

Extracorporeal membrane oxygenation (ECMO) was first used in adults in 1972 in a young patient with post-traumatic acute respiratory distress syndrome (ARDS). The technology is derived from the cardiopulmonary bypass machine used for cardiac surgery, modified for a longer-term support of respiratory and/or cardiac function. There are two major types of support that may be provided with ECMO, veno-venous ECMO (VV-ECMO) and veno- arterial ECMO (VA-ECMO). The former is used in patients with good cardiac function, in an effort to support lung function, while the latter is used in patients with poor cardiac function, in an effort to support the failing heart. Significant advances continue to be made in the field of extracorporeal life support (ECLS) and the modality promises to supplement the management options available for the niche role in management of patients with severe cardiac and respiratory disease. In this review, we discuss the latest developments and usage of ECMO in respiratory diseases in adults.

Key words

Extracorporeal membrane oxygenation, respiratory diseases, adults

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Introduction

Extracorporeal membrane oxygenation was first used in adults in 1972 in a young patient with post-traumatic acute respiratory disease syndrome (ARDS) [1]. The technology arose from cardiopulmonary bypass machine used for cardiac surgery but modified for longer-term support of respiratory and/or cardiac function. Its initial progress was plagued by various complications that ranged from finding the compatible pump mechanisms, to hemolysis, to blood clotting within the tubing, to finding a suitable method of oxygenation of the extracted blood.

Most of the complications were related to the oxygenators. Initially used oxygenators were the simple, less expensive bubble oxygenators where blood is exposed directly to gas. The direct blood-gas interface caused blood trauma and protein degradation, leading to hemolysis, platelet destruction, and microemboli [2, 3]. These systems were eventually replaced with membrane oxygenators, where the blood is separated from gas by a semi-permeable membrane, mimicking human lung and fewer complications [4, 5, 6]. This was a major step in advancement of the technology and with the subsequent improvement in membrane material facilitated safer extracorporeal oxygenation for prolonged period of time

A large randomized controlled trial [7] conducted in 1974 did not show significant difference in mortality between ECMO versus conventionally treated adult ARDS patients and dampened the initial enthusiasm about ECMO. Technology advances and the 2009 H1N1 influenza pandemic spurred the interest on ECMO as a rescue therapy, especially for young patients with ARDS who were failing conventional therapy [8]. This review article is aimed to familiarize readers about ECMO, its indications, its utility, possible complications, and gives a glimpse of possible future directions of care especially in pulmonary disease.

Overview

ECMO refers to the process of long-term extracorporeal support for oxygenation while the failing heart or lung rejuvenates. This is achieved by draining deoxygenated blood via a cannula to an external circuit of primed tubing to a membrane oxygenator which oxygenates the blood and a centrifugal pump which returns the oxygenated blood back into the circulation. Although there are various other components in the circuit, the main ones are the oxygenator and the pump. Typically, the blood flow through the circuit is at the rate of 100ml/kg/minute and requires placement of large bore cannulas, usually 21-24 French for adults. Another significant fact is that CO_2 removal is more efficient than oxygenation because of the solubility and diffusion properties of CO_2 relative to O_2

There are two major types of support that may be provided with ECMO (Table 1), Veno-venous ECMO (VV-ECMO) and veno- arterial ECMO (VA-ECMO).

VV-ECMO

In VV- ECMO, blood is extracted from a large vein into the ECMO circuit where gas exchange takes place. The oxygenated blood is then pumped back into the venous system, which then passes through the right atrium, and the patient's heart pumps the oxygenated blood through the pulmonary and then to the systemic circulation. As it requires the patient's native heart to pump the blood through the circuit, VV-ECMO can be used only in patients with good cardiac function to support the lungs. It does not provide support to maintain cardiac output.

Vessel cannulation may be done in several ways, ranging from a femoral-jugular approach, to a bi-femoral setting, or to a single bicaval double lumen cannula. The oxygenated blood from ECMO mixes with the deoxygenated blood in the right atrium. The systemic oxygen tension will be low and will depend on the cardiac output and the hemoglobin concentration of the patient. One of the major technical problems in VV-ECMO is recirculation. As the oxygenated blood from the circuit is sent back to a vein, some of the oxygenated blood can directly go back to the draining cannula without going to the systemic circulation. A 30% recirculation is generally considered

Table 1. **Types of ECMO**

	VV- ECMO	VA-ECMO
Cannulation type	— Blood drained from vein and returned to vein Vein: jugular-femoral, right atrium -femoral, femoral-femoral, saphenous-saphenous	— Blood drained from vein and returned to artery. Vein: internal jugular, femoral artery: femoral, axillary, subclavian, aorta
Circuit	Connected in series with heart and lung	Connected in parallel to heart and lung
Cardiac Support	yes	No
Cardiac effects	Preload: decreased. Afterload: increased	May reduce right ventricular afterload. No other hemodynamic effects
Arterial PaO2	60–150 mmHg	45–80 mmHg
Indications	Cardiogenic shock	Respiratory failure with preserved cardiac function

acceptable and more commonly seen with single site double lumen cannula where the entry and exit point are close to each other. Factors that can increase the recirculation percentage are position of the cannula (distal to the right atrium), higher pump flow, and low cardiac output.

VA-ECMO

In VA- ECMO, deoxygenated blood is drained into the circuit for oxygenation and ventilation,and returns into the systemic circulation on the arterial side. Thus, VA- ECMO bypasses the heart as well as the lungs, providing both hemodynamic and respiratory support while allowing the native lung and heart to rest and heal. The VA- ECMO mode is similar to the conventional cardiopulmonary bypass used for cardiac surgeries but adopted for a longer period of support. Cannulation can be central or peripheral. In peripheral cannulation, blood is drained from the proximal femoral or jugular vein and returned via the carotid or femoral or axillary artery. The cannulas used are smaller than the central cannulation and can be done emergently at bedside. Central cannulation usually requires sternotomy or thoracotomy and blood is drained from near the right atrium and returned to the proximal ascending aorta. It is a preferred option when used immediately after cardiopulmonary bypass as the same cannulas can be connected to the VA-ECMO circuit.

The cannula position, diameter and length, along with the patient's venous filling, vascular resistance, and pump speed play an important role in the overall blood flow and the hemodynamics. A proportion of the blood flow (~15-20%) can continue to go through the lungs during a VA-ECMO. Therefore, in a patient with poor lung function, the proportion of blood going through the lungs, which are not adequately oxygenated, mix with well-oxygenated blood provided by the ECMO circuit in the aorta. Hence, in the case of peripheral VA ECMO, the coronary arteries, cerebral blood vessels, and proximal branches of the aorta may receive blood with lower oxygen content. Thus, the decision on the location of the cannulas assumes an important role in VA-ECMO [9] in patients with poor lung function.

Indications in Respiratory Diseases ARDS

Extracorporeal life support (ECLS), particularly VV-ECMO, has been used as a rescue therapy in patients with severe ARDS. Though some studies have shown improvement in mortality among ARDS patients over the years, it is still unacceptably high in severe ARDS at 40-52% [10,11]. ECMO started to gain popularity as a rescue therapy in this population since the 2009 H1Ni influenza pandemic. The exact indications for ECMO have varied across institutions. Broadly, it is indicated for refractory hypoxemia on conventional ventilation therapy, severe acidosis, and hypercapnia. The Murray score is a scoring system that includes the chest roentgenogram , PaO_2/FiO_2 ratio, positive end-expiratory pressure (PEEP), and compliance to stratify these patients [12]. According to ELSO (extracorporeal life support organization) guidelines for adult with ARDS [13], ECMO is indicated when despite the optimal care for 6 hours or more, the predicted mortality risk is >80% which is associated with a PaO_2/FiO_2 <150 on FiO_2>90% and/ or a Murray score of 3-4. ECMO should be considered when the mortality risk is >50% which is associated with a PaO_2/FiO_2 <150 on Fio_2>90% and/or a Murray score of 2-3. As of July 2012 [14], the overall survival in adult patients on ECMO for respiratory failure in the past five years ranged from 53% to 61% which is similar to other recent studies [15].

While considering ECMO in patients, one of the most important considerations is the reversibility of the pulmonary disease. Other pre-ECMO characteristics of the patients like advanced age, high ICU severity score, multiorgan dysfunction, immunocompromised status, and poor neurological status negatively impact ECMO outcome [15,16]. Various studies have shown that the earlier the patient placed on ECMO, the better the outcome [17, 18, 19, 20, 21]. Ventilator associated lung injury (VILI) is a significant cause of morbidity and mortality in ventilated patient [22, 23], and reduction in the duration of mechanical ventilation prior to ECMO minimize ventilator associated lung injury and that possibly explains the survival benefit. The ventilator setting while the patient is on ECMO (Table 2) is minimal and lung protective, helps the lung to rest, and reduces VILI.

Table 2. **Ventilator settings while on ECMO**

Peak inspiratory pressure	20–25 cm H2O
Positive end-expiratory pressure	10–15 cm H2O
FIO2	<0.5
Respiratory rate	8–10 breaths/min
Tidal volume	3–4ml/kg

Low volume ventilation prevents VILI in ventilated patients. The problem while on low volume ventilation will be the raising of PCO_2 and acidosis. With the help of extracorporeal CO_2 removal (ECCO2R) technique,

this problem can be overcome. Combining $ECCO_2$ R with low tidal volume ventilation could prove to be the best strategy for management of severe ARDS patients.

Current Evidence

The results of the smaller studies and the first US ECMO multicenter randomized controlled trial conducted by the National Heart and Lung institute in 1974 were discouraging and did not show measurable mortality benefit [24, 25]. In this study, the survival in both conventional and ECMO groups was very poor, only around 10%. These studies were conducted when ECMO technology was primitive. We did not have much understanding in the management of ARDS and was receiving high tidal volume ventilation. However subsequent studies in neonates and children showed a mortality benefit, and it was widely accepted and used in a pediatric population[26, 27].

Some centers continued to work on ECMO in adult populations, and over a period of time, various observational studies demonstrated safe and successful application of ECMO in critically ill adults [28, 29]. The survival rate recorded in the ELSO registery [30] was 41% in 1995, and overall 197 patients had received ECMO for ARDS at that time. This was comparable to European studies published in that time period [31] where around 850 patients received ECMO between 1992-1999. The better outcome with recent studies is attributed to the advanced technology in ECMO as well as the use of low tidal volume lung protective strategies. Morris et al [32] conducted a randomized clinical trial in 1994, which also did not show a mortality benefit as compared with standard therapy. In spite of all the controversies, ECMO gained popularity as a rescue therapy for severe ARDS adult patients during the 2009 H1N1 influenza pandemic [33, 34, 35].

The landmark trial was the CESAR trial [Conventional ventilator support vs Extracorporeal membrane oxygenation for Severe Adult Respiratory failure] [36] concluded in 2006 and published in 2009. It is the major randomized control trial and the first in the literature to show a mortality benefit in patients who were transferred to an ECMO. A total of 180 patients were randomized 1:1 to two groups. A control group continued to receive the conventional ventilation therapy at tertiary care centers, while the intervention group was referred to an ECMO center for consideration of ECMO. Among the 90 patients that were transferred to a center with ECMO capabilities, only 68(75%) patients received ECMO and of which, 63% (57/90) patients survived to six months without disability, compared to 47% (41/87) of those that received conventional therapy (RR 0.69%, 95%CI 0.5-0.97, p=0.03).

There are two major criticisms to the above study. The intervention in the CESAR trial was. referral to a center with ECMO capabilities rather than treatment with ECMO, and actually 25% of the intervention group did not actually receive ECMO. The other major criticism is that the study did not dwell on the management of the patients in the conventional ventilation arm, and it is unclear as to how many patients received low tidal volume lung protective ventilation.

The Australia and New Zealand ECMO Influenza Investigators [33] reported their experience in treating the 2009 outbreak of H1N1 Influenza infection that led to a number of young otherwise healthy patients developing severe ARDS. Among 201 intensive care unit patients in the study, 68 (30%) received ECMO. The mortality in this group was 21% (14 patients), compared with 9% on the non-ECMO group. This accompanies other papers that failed to show a mortality benefit [36, 37]. Meanwhile, other studies showed a mortality benefit [39, 40]. This conflicting evidence necessitated a large multicenter randomized controlled trial that can prove or disprove the benefit of ECMO.

The French group REVA (Research Network on Respiratory Failure and Artificial Ventilation) is conducting the EOLIA study (ECMO to rescue Lung Injury in ARDS), an international multicenter randomized controlled trial in patients with severe ARDS, which is an attempt to provide better evidence. Patients are promptly randomized into ECMO and conventional therapy groups in which the limitations of the CESAR trial are addressed. The results of this study are eagerly awaited.

Chronic Obstructive Pulmonary Disease

In chronic obstructive pulmonary disease (COPD), invasive mechanical ventilation is associated with many complications including ventilator associated pneumonia, dynamic hyperinflation of lungs, ventilator dependence, and impaired delivery of aerosolized medications[41, 42]. A modality of ECLS includes extracorporeal carbon- dioxide removal (ECCO2 R) that helps remove carbon dioxide (CO_2) from the circulation. ECCO2R is an intermediate level of ECLS with little technical difference than the complete ECLS provided by ECMO. The blood flow is lower (0.3-0.5litres/min) and able to remove ~25% of CO_2. It has been shown

to reduce the need of invasive mechanical ventilation (IMV) and has also been used to assist removal of CO_2 in patients already on mechanical ventilation, in an effort to reducethe number of days on the ventilator and intensive care unit stay.

A pump-less ECCO2 R A-V circuit has been used to prevent mechanical ventilation in patients in severe exacerbations of COPD [43, 44]. This modality has also been used as a supportive therapy for patients who are already on mechanical ventilation to facilitate early extubation, early mobilization and physiotherapy, even while on ECCO2 R [45, 46, 47]. A feasibility pilot study was done to assess the possibility of early extubation and early ambulation in patients receiving mechanical ventilation using single site ECCO2R, with excellent results. Further studies are required to define the criteria and the patient population that would most benefit from this modality.

ECMO as a Bridge to Lung Transplant

Lung transplant waiting lists are increasing, and there is severe paucity of suitable organ donors. Patients with end- stage lung disease awaiting transplant who are failing medical management need a bridge until a donor becomes available. ECMO helps transitioning of care before, during and after the transplant procedure. The initial concept of bridging originated with left ventricular assist devices (LVADs) for cardiac transplant [48, 49]. Initial studies of patients on ECMO had poor perioperative outcomes [50]. Recently, ECMO has been used safely in patients during transplant and aid their recovery [51-52]. ECMO and ECCO2 R modalities have been used to reduce the need for mechanical ventilation and help participate in rehabilitation and physiotherapy, which has further improved outcomes. It also helped to avoid ventilator-associated complications [53].

Experiences from large academic centers and from international centers have come in throughout the last decade, with many showing improved survival and favorable outcomes. The university of Kentucky and the university of California successfully bridged 31 patients as of 2013 and achieved a 80% 3-year survival [54]. The university of Pittsburgh has used ECMO as a bridge for 31 patients with 25 surviving to transplant. This group demonstrated a 74% survival in the ECMO group [55]. A French group reported their experience with lung transplant with ECMO in 36 patients with 30 making it to transplant. The 2-year survival was reported as 60.5% but outcomes in patients with cystic fibrosis was significantly better than in those with idiopathic pulmonary fibrosis (IPF). This observation suggests that ECMO outcomes may vary depending on the underlying etiology of the lung disease [56].

Extracorporeal Cardiopulmonary Resuscitation

Extracorporeal cardiopulmonary resuscitation (E-CPR) is the term used for institution of ECLS during cardiopulmonary resuscitation to help return of spontaneous circulation (ROSC). A growing body of evidence suggests the utility of ECLS in cardiopulmonary resuscitation in improving outcomes and survival in patients with intra-hospital cardiac arrests (IHCA) and out of hospital cardiac arrests (OHCA)[57, 58, 59, 60]. In prospective observational trials of IHCAs, survival to discharge varied from 20% to 32%, with p values of <0.0001 and 0.002 respectively [57, 58] with a good neurological outcome. Similarly, out of hospital arrests also showed comparable outcomes, with survival of 29.2% at 3 months and a p value of 0.018 [57]. The recently published prospective pilot study, The CHEER trial [61] was carried out for refractory IHCA and OHCA in Australia. These patients had a ROSC of >30 minutes with an initial rhythm of ventricular fibrillation. The reported survival rates were 54% with 13 out of 24 patients surviving to hospital discharge. Further studies are ongoing, so that we can further delineate the patient populations with the most expected survival benefit.

Pulmonary Hypertension and Pulmonary Embolism

ECLS has been used as an emerging therapy in patients with severely decompensated right ventricular (RV) failure and pulmonary hypertension of various etiology. ECMO may be implemented briefly to support the patient while medical management is being optimized during a crisis or as a bridge for lung transplant [62]. Commonly, VA- ECMO is applied, which will decompress the right ventricle, leading to reduction in right ventricular pressures and also preferentially shunts the blood into the ECMO circuit leading to better oxygenation and ventilation [63]. It can provide a bridge to successful lung transplantation in World Health Organization group I pulmonary artery hypertension patients with end-stage cardiopulmonary failure. A retrospective review of use of ECMO for massive pulmonary embolisms in 21 patients demonstrated improvement in survival to 62% when used along with conventional medical management [64].

This improved survival has been supported by other published cases [65].

Future Directions

The most important implication of ECLS is early mobilization, early rehabilitation and early physiotherapy, which has time and again showed to positively impact clinical outcomes [66, 67]. This, along with reduced ventilator requirements and hence less associated complications like VILI will prove to be more beneficial to select groups of patients [68, 69]. As of now, ECLS is being used only in select centers as a rescue therapy for refractory respiratory failure, cardiogenic shock and as a bridge to lung and heart transplant. Advancements in technology in manufacturing of circuitry will lead to compact consoles and ambulatory ECMO machines as a destination therapy for end stage lung disease. The expanding utility of ECLS is rapidly encompassing all forms of respiratory failure from various causes and severe right ventricular failure.

Weaning of ECMO

Weaning from ECMO is a crucial step, and there are no standard protocols as of yet. It is basically provider dependent and usually based on some rough guidelines from scientific societies. Weaning from VA ECMO and VV ECMO are different. However the most basic requisite before weaning is the recovery of the lung and or cardiac function significantly so that the lung and or cardiac rest is no longer needed.

In VV ECMO, weaning is a process where contribution of ECMO to gas exchange (oxygenation and CO_2 removal) is progressively decreased while the native lung takes over its function. The actual circuit blood flow need not be altered to assess the pulmonary function. The clinical parameters that can indicate recovery of pulmonary function [9] are (a) progressive increase in SaO_2 above SvO_2, (b) improvement in $SaO2_{for}$ a given circuit gas flow or a reduced gas flow, (c) improvement in respiratory mechanics - lung compliance, airway resistance, (d) radiological improvement. ELSO guidelines indicates that when the native lung can support 50-80% total gas exchange at a moderate ventilator setting (FiO_2 <0.6-0.5, low PEEP) ECMO discontinuation can be considered. Weaning from VV ECMO (Table 3) is performed by progressively decreasing the gas flow to the oxygenator. At zero flow, if the patient able to maintain stable hemodynamic and ventilator parameters for 4-24hours (varies from center to center) then the patient can be effectively off of ECMO. Extracorporeal support can be then discontinued and decannulated. The goal is to resume mechanical ventilation with ventilator settings that are less injurious and can maintain good oxygenation and ventilation, which would have been impossible prior to initiation of ECMO. Weaning is generally possible in ARDS after 7-10 days on ECMO.

Table 3. **Weaning VV-ECMO in respiratory failure**

• Sweep gas flow set at 0 L/min • FiO_2 set at 0.21 on the membrane • Pump flow not modified	The device may be withdrawn if — PaO2 >60 mmHg, SaO2 >90 % — FiO_2 on the ventilator <60 % — Inspiratory plateau pressure <30 cm H2O For at least 1–2 hours and up to 12 hours

If the patient is on VA-ECMO and the indication of ECMO is for cardiac causes, the myocardial recovery is required before weaning can be initiated. The parameters need to be monitored in these patients are (a) return of pulsatile arterial pressure waveform for 24hrs, hemodynamic stability with baseline mean arterial pressure greater than 60 mmHg in the absence or with low doses of catecholamine (b) decreasing central venous and/or pulmonary pressures (c) improvement of pulmonary function, $PaO2/FiO_2$ <100mmHg. Weaning in VA ECMO is carried out by reducing blood flow through the circuit hourly. Once the blood flow is as low as 1-2 liters/minute and the patient has been hemodynamically stable for few hours, surgical decannulation may be carried out. Doppler echocardiography parameters help in assessing cardiac function while weaning.

Successful weaning from ECMO depends on the underlying cause, it's reversibility, associated comorbidities, and severity of organ dysfunction at the time of ECMO initiation.

Complications on ECMO

Application of ECMO is associated with number of complications. A specialized center with extensively trained personnel and well-experienced staff is required to implement it safely to demonstrate the survival benefit. Improvement in technology and the circuit has decreased complications rate over the past decade. The Extracorporeal Life Support Organization (ELSO) database[14] gives us the rates of complications of patients on ECMO and guidelines to follow for their management. Complications can be broadly classified as physiological and mechanical (Table 4).

The most common complications among them are clot formation and bleeding. As blood passes through

Table 4. **Complications of ECMO**

Physiological complications	Mechanical, related to circuit
Bleeding — cannula site — Intracranial, GI, Pulmonary Thromboembolic Hemolysis Neurologic — seizures, stroke, encephalopathy	Failure of oxygenator Pump failure Cannula problems

the circuit, activation of clotting factors and emboli is a major concern. Anticoagulation is usually done by heparin drip, maintaining activated thromboplastin time of 1.5 times normal values. The reported incidence is 12-17%. Localized bleeding from the cannula insertion site (16%) or from the surgical site (17%) is common and can be managed with simple compression. Major bleedings like intracranial bleeding is reported in 3.9%, pulmonary and gastrointestinal bleeding reported in 8% and 5%, respectively. The hematologic consequences of an ECMO circuit include hemolysis, acquired von Willebrand factor deficiency, and thrombocytopenia contributes to the bleeding and thrombotic risks. After hematological adverse effects, infection remains the significant problem with a reported rate is 21.3%. The other potential complications are encephalopathy, renal dysfunction, and liver injury.

The complications of VA-ECMO are similar to VV-ECMO, with added possible complications (a) pulmonary hemorrhage (b) cardiac thrombosis and (c) limb ischemia from peripheral arterial cannulation. When the left ventricular contractility is poor, the left ventricle continues to dilate from persistent preload and the left ventricular end-diastolic pressure increases. This in turn increases the pulmonary pressure causing pulmonary hemorrhage. With VA- ECMO the pulsatility of the blood flow is lost, and blood stagnates in the aortic root ,increasing the risk of cardiac thrombosis and systemic emboli.

Ethical Considerations

The patients' families must be extensively educated about the process of ECMO and counseled about the possibility of unfavorable outcomes, in spite of the extraordinary measures being taken to maintain life Even after a successful recovery from ECMO, the neurological outcome may still be poor. End of life discussions must be held, either with the patient, or with health care surrogates. The goal of care should be well established as families may wish to continue therapy even if the treating team feels that the patient's condition has progressed to an irreversible state. Daily updates and clear discussion about the prognosis with patients and their families help in avoiding such situations.

Conclusions

Every day, significant advances continue to be made in the field of ECLS. The modality promises to supplement the management options available for severe cardiac and respiratory disease. More widespread data from multiple centers are needed to add to current knowledge and help us understand its role in management of different patient populations and its potential indications.

Conflict of interest: None declared.

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Values of central aortic blood pressure in normotensive students, existing risk factors and possible approaches to create the preventive environment in the University

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Summary

Objective

To investigate the profile of cardiovascular risk factors (CVRF) in young students and to estimate the influence of these factors on central aortic blood pressure (CABP), to discuss possible ways of CVRF correction using university media for spreading information and motivation ideas.

Materials and methods

80 students underwent the estimation of aortic rigidity parameters and presence of CVRF with complex diagnostic software.

Results

Systemic and latent hypertension was diagnosed more frequently in risk factor carriers. Frequency of false hypertension occurrence didn't depend on risk factors (RF) presence. In case of normotension RF presence was associated with higher values of augmentation index. This study also presents data of the Center of Students' health about introduction of real and network forms of mass, group and personalized preventive work among young students using obtained information about possible health hazards.

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Conclusion

Despite the young age and short anamnesis of CVRF presence students demonstrate preclinical but distinct lesions of aortic wall as the one of the most important target organs. It is necessary to introduce more actively the CVRF screening together with CABP estimation into the work of the centers of students' health in order to start in time early preventive interventions.

Key words:

Screening, risk factors, students, premorbid diagnostic, preventive intervention.

Experience of several countries that managed to obtain real reduction of initially high cardiovascular (CV) mortality, demonstrates that CV risk factors (CVRF) correction has more significant impact on achieving such results comparing with coronary heart disease (CHD), arterial hypertension (AH) and their complications treatment [1, 2].

In clinical practice this approach is implemented through creation of mass diagnostics of the system of risk factors (RF) and preclinical lesions in population and particularly in its active part [3, 4]. Examination of young students in the centers of students' health (CSH) or in students' polyclinics [5,6] looks enough promising [7, 8].

Risk groups formation in young persons allows to start early correction of identified hazards with preventive interventions of different levels including the school of students' health [9]. This approach requires elaboration of reasonable screening aiming to estimate effectively the profile of significant RF and asymptomatic changes of target organs [10.11]. It has been identified that for successful screening it is necessary to take into account the age of examined persons [12], their social [8] and psychophysiological status [13, 14]. and also constitutional and anthropometric features [15].

Pathogenetic continuum of main cardiovascular diseases (CVD) in this age corresponds to very early prenosological changes of target organs [16]. Because of this young age gives a good chance to slow down the CVD development and prevent their unfavorable income. This preventive strategy seems to be the most effective one although its prospective results are delayed in time. But the diagnostic step of prophylaxis in young age group as the initial element of mass health examination is undoubtedly not elaborated enough [6]. Technologies of preventive interventions in organized groups of young people are also formed in noticeably low level [7, 8].

The aim of this study is to estimate the influence of CVRF on the central aortic blood pressure (CABP) and its augmentation index (Aix) and to design the approach of these factors correction according with the university informational and motivation resources.

Materials and methods

This study demonstrates the results of complex examination of 80 students of Stavropol State Medical University (SSMU) (39 males, 41 females), that was performed on the base of SSMU CSH during second stage of mass health examination of students. The age of students was 19-22 years.

Using questioning and anthropometry we performed screening of such RF like hereditary predisposition of diabetes mellitus (DM), cancer, early CVD, office AH/prehypertension (PH), excessive body weight (EBW), dyslipidemia and hyperglycemia (test-stripes for express-diagnostics), smoking (smoke detector "SmokeCheck"; "Micro Medical Ltd.", Great Britain), the presence of infection nidus, improper feeding according with the questionnaire of National Research Center for Preventive Medicine(NRCPM) [17], hypodynamia according with the World Health Organization (WHO) questionnaire [18] and low stress tolerability according with student questionnaire of U.V.Shcherbatykh [19].

We performed also the comparative analysis of the parameters of central and peripheral blood pressure (PB), that have been obtained with particular programmed diagnostic complex using oscillometric way of BP measurement on the shoulder and consequent modeling of central pulse wave (CPW). BP levels was used as the investigated parameter in two groups of students that were formed according with the presence or absence of other CVRF: 1 group (n=26) – without RF (control group), 2 group (n=54) (main group) – with the presence of CVRF like burdened familiar history, smoking, EBW, improper feeding, hypodynamia and low stress tolerability with the average number of RF =2,7±0,6.

We used special operation system for automatic tubulation of all parameters of CPW measurement.

Apart of traditional brachial artery BP parameters such values like aortic systolic blood pressure (SYSao), aortic diastolic blood pressure (DIAao), aortic pulse BP (PPao), average aortic BP (ABPao), duration of left ventricle ejection period (ED), aortic Aix, pulse pressure amplification (PPA), subendocardial viability ratio (SEVR).

We investigated occurrence of hemodynamic variants of AH/PH based on comparative estimation of aortic and peripheral BP values. We identified the cases of latent hypertension- isolated elevation of aortic BP, false hypertension – isolated elevation of brachial artery BP, systemic AH/PH – elevated BP in aorta and in brachial artery and stable normal BP[20]. Preclinical changes of vascular wall were examined using Aix values of central BP in newly formatted groups (53 student with normal BP in total) taking into account homogeneity of main hemodynamic parameters to exclude the influence of BP levels on mentioned parameter of vascular rigidity. During formation of groups we took into account the age of young patients. For example, in the control group without RF mentioned above brachial artery systolic blood pressure (SBPba) in young females was between 100-120 mm Hg. and 110-130 mm Hg in young males respectively, and brachial artery diastolic blood pressure (DBPba) was around 65-75 mm Hg in both gender groups, because of this we included only persons with corresponding levels of BP into the main group with the presence of RF. According with this the persons with EBW were not included to the main group because in all cases it was associated with higher BP. Thus the study design at the last stage was initially performed taking into account the task of correct investigation of per se vascular rigidity parameters, so by intentional exclusion of possible BP influence on it. According with this, investigated groups were comparable in this last parameter.

The results of students' examination were analyzed with "Statistica 6.0" software ("StatSoft Inc"). Differences with $p<0,05$ were considered statistically significant.

Results and discussion

Analysis of biological and behavioral RF in examined students revealed burdened family history in 37 (46,3%) persons. Profile of modifiable RF was the following: EBW, smoking and elevated BP were registered in 17,5%, 18,5% and 16,3% of students respectively. focal chronic infection was found in one fifth of all examined students. Hypodynamia, improper feeding, low stress-tolerability were registered in 35,0%, 38,7% and 32,5% of students respectively.

Individual comparative analysis of the results of peripheral and central BP measurements in each examined person (Table 1) demonstrated, that in the group of people without RF systemic PH/AH was registered in less than 1% of people, and the same value in students with present RF 10 times bigger ($p<0.01$). In the last group one of ten students had latent PH/AH and this pathology was not present in the group of students without RF. These data prove reasonability of CVRF screening as a simple but diagnostically informative stage of mass health examination of students. The frequency of false PH/AH was almost the same in both groups: every one of twelve students had it. In the end the amount of students with stable normal BP was twice as more in the group without RF comparing with the group of RF carriers.

Table 1. **Occurrence of different types of AH/PH in students according with the results of comparative peripheral and aortal BP estimation**

AH types	All without RF n=26	All with RF n=54
False AH	2 (7,9 %)	4 (7,7 %)
Latent AH	—	5 (9,6 %)
Systemic AH	1 (3,8 %)	19 (36,5 %)**
Normotension	23 (88,3)	24 (46,2)

Comment: ** — $p<0,01$, comparing with the group without RF.

More frequently AH/PH occurred in students with EBW and burdened family history, and they were registered simultaneously in major part of students with elevated BP. It is necessary to mention also the high occurrence of low stress-tolerability in these students, that goes along with previously published works about personal features of young patients that were referred to cardiologist for examination and treatment due to the presence of evident primary AH [14].

In relation to the problem of CV health of young people it is relevant to study properties of vascular wall taking into account all present RF excluding AH/PH, so in all normotensive male and female students. The results of vascular rigidity characteristics in two groups of young males with presence/absence of CVRF and comparable initial levels of BP (Table 2a) demonstrate prominent differences of central pressure Aix.

This characteristic in students with favorable background correlates with its negative values, and it moves to more positive values of the scale in presence of RF. But these differences cannot be considered

Table 2a. **CABP characteristics in young males**

BP characteristics measured on brachial artery and aorta	Юноши без RF n=11				Юноши с RF n=12			
	M	Me	V_{25}	V75	M	Me	V_{25}	V75
SBPba	116	114	112	125	117,3	116,5	115	122
DBPba	68,9	69	66	72	70,6	71	68	74
ABPba	84,8	85	81	88	87,2	87,5	84	92
PPba	46,8	46	44	50	46,6	48	44	50
HR	73,8	73	67	78	75,2	74	68	79
SBPao	101,8	100	98	107	105,1	104	102	111
DBPao	70,2	70	65	73	71,5	71	68	78
ABPao	84,8	85	81	88	87,2	87,5	84	91
PPao	31,3	31	30	32	33,9	34,5	33	38
SBPba-SBPao	14,4	14	13	17	12,2	10,5	10	16
DBPba-DBPao	—1,3	—1	—1	0	—0,9	—1	—1	0
PP-PPao	15,2	16	14	18	13,3	12,5	11	15
Alxao, %	—4,9	—8	—12	2	3,9	0	—5	4
PPA, %	149,9	148	145	158	139	136,5	131	151
ED, mc	280,4	290	255	294	300,9	299,5	269	325
SEVR, %	165,1	160	148	167	165,5	168	135	194

Table 2b. **CABP characteristics in young females**

BP characteristics measured on brachial artery and aorta	Young females without RF n=12				Young females with RF n=18			
	M	Me	V_{25}	V_{75}	M	Me	V_{25}	V_{75}
SBPba	111,9	113,5	105	117	113,1	117,5	104	118
DBPba	69,8	69	66	74	72	71	69	74
ABPba	85,1	84	82	90,5	86,7	87	83	91
PPba	41,5	40	38	46	40,8	40,5	37	46
HR	71,8	72,5	66	78	74,3	75	67	80
SBPao	101,5	100,5	97	106	103,2	106,5	96	108,5
DBPao	71,4	70	66	77	73,4	72,5	71	79
ABPao	85,1	84	82	90,5	86,7	87	83	91
PPao	29,4	30	26	34	29,3	29	25	34
SBPba-SBPao	10,4	9,5	8	13	9,8	10	9	12
DBPba-DBPao	—1,6	—2	—2	—1	—1,38	—2	—2	—1
PPba-PPao	12,2	12,5	10	14	11,4	11,5	10	14
Alxao, %	1,5	1,5	—2	6	7,6*	8	4	12
PPA, %	142,9	140,5	134	153	139,7	139	132	144
ED, mc	305	319,5	282	328	316,6	328	291	341
SEVR, %	134,4	121	116	146	137,8	136,5	122	160

Comment: * — p< 0,05

significant (p=0,08). In young females of both groups (Table 2b) this characteristic has positive values, but at the same time the carriers of mentioned RF had Aix values 5 times bigger than young females without CVRF. The differences between the groups of female students were statistically significant (p=0,04). Thus, the presence of main RF in students promotes the loss of vascular wall elasticity in spite of young age and short history of presence of these factors.

These results indicate evident influence of RF on the characteristics of peripheral and central hemodynamics of young people. The information about association of several AH/PH types with RF supplement significantly the existing data about this problem in young patients [21]. Quite frequently they demonstrate sufficiently frequent diagnostics of isolated CBP abnormalities, and it makes it necessary to detect it during mass health examination together with traditional measurement of peripheral BP on brachial artery. AIx as one of rigidity characteristics increases being influenced with other RF in normal BP conditions. Until recently these aspects of vascular status in young patients estimated using oscillometric method of BP measurement on brachial

artery with consequent CBP modeling appeared only in few studies. And mentioned above studies investigated these CBP characteristics in young normotensive volunteers not considering RF [22]. This affordable approach is particularly relevant for mass health examination of Russian students, because one recent international study [23] demonstrated more high values of cardio-ankle vascular index (CAVI) obtained using volume sphygmograph comparing with Japanese students of the same age. The authors consider that more prominent positive linkage between CAVI and age of students in Russia comparing with Japan can be explained with larger amount of RF influencing vascular wall. Taken altogether, these data prove the necessity of angiologic screening introduction considering main CVRF during mass health examination of students.

It is necessary to develop immediately the system of prophylactic interventions in organized groups of young people. The existing experience indicates that mass health examination of students differs significantly from the one of laboring population [5, 24]. for example, ECG registration is more reasonable to perform in older population comparing with BP monitoring and CBP and Aix measurement. At the same tame lipid and carbohydrate metabolism estimations has the same importance in both populations. It is also necessary to consider that some characteristics have age-related properties. Screening data are the basis for the distribution of students into three health groups that predetermine passing through particular diagnostic, therapeutical and preventive interventions [17, 25]. We organize several motivating and educating events aiming to form stable positive behavioral stereotypes among the students of all health groups in the Health Center of SSMU. To achieve success in this work it is important to reach effective interaction between different departments of the same university. We perform short preventive consulting about the basics of healthy lifestyle with every student of the first year during initial screening. Advanced personal consulting by the interdisciplinary specialists of the Center is provided anonymously and in the real mode on the base of network technologies and hot-line service (phone number is available on the web-page of the Center). Special classes for young people of risk groups that also use network technologies are organized on the base of Health School. Students and specialists of CSH that are involved in the creative process of health-preservation created the platform for mass health examination surveys according with the CMS Lime Survey software (informational system of personalized examination) and with the help of CSH doctors they adapted electronic online-questionnaires that include questions about physical and mental health of respondents. We created a website of young followers of HLS. Students fill the questionnaires about HLS and make a test of their adaptation status before the start of classes at the School and after finishing academic year. This dynamic control of preventive interventions efficacy in the beginning and in the end of academic year proved the increased knowledge of CVRF self-control and improved psychophysiological health resources of the School participants. Positive dynamics was more evident in young females comparing with young males. This complex of interventions, that forms health-oriented environment in university, not only demonstrates good results on the stage of health-oriented consciousness formation but also helps to practice the skill of mass preventive health examination in medical students. This experience is undoubtedly useful for self-protection and future clinical practice of medical students.

Conclusions

Reasonableness of main CVRF screening in young people is proved with instrumental evaluation of CBP and its Aix. If these factors are present, occurrence of systemic AH/PH is 10 times as more. Latent form of isolated aortic BP elevation was registered only in RF carriers. And false AH/PH is registered almost in one out of twelve students independently from RF presence.

CVRF presence in normotensive students is associated with central pressure Aix elevation, and it is particularly evident in young females. Thus, in spite of the young age and short history of damaging factors presence, students have preclinical but enough distinct lesions of aortic wall, that is one of the most prognostically significant target organs.

It is necessary to introduce more actively the technique of CBP evaluation into the work of CSH in office format for early detection of vascular remodeling in mass preventive examination in order to make risk group formation more differentiated, to provide well-timed beginning of preventive interventions and objective control of their efficiency.

From organization point of view students' medical prophylaxis should be performed in close cooperation of CSH, deans, departments, educational and social work professionals, active students, mass media workers and other structures of university. Doctors

of CSH specializing in different clinical disciplines should be initiators and catalysts of such activity.

Conflict of interest: None declared

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The structure of risk factors of cardiovascular disease and chronic kidney disease in patients with chronic obstructive pulmonary disease

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Summary

Objective

To determine the frequency of risk factors of cardiovascular disease (CVD RF) and chronic kidney disease (CKD) among the patients with chronic obstructive pulmonary disease (COPD).

Materials and methods

We examined 300 patients of the Regional clinical hospital №2 with verified diagnosis of COPD I-IV degree of severity according to the GOLD criteria (2011). We studied the frequency of such RF of CVD and CKD: age > 45 years, male gender, arterial hypertension (AH), impaired glucose metabolism, hypercholesterolemia (level greater than 5.0 mmol/L), body mass index (BMI) > 25 kg/m^2, and the frequency and intensity of smoking, glomerular filtration rate (GFR) calculated with CKD-EPI.

Results

We identified the high frequency RF of CVD: 100% of patients had RF of CVD, 92,6% of patients had a combination of 3 or more FR, lowered GFR< 89 mL/min/1,73 m^2 was present in 67,3% patients. 96.4% of patients had age over 45 years, 78,8% of patients were older than 65 years; smoking was detected in 92 % of patients with COPD; hypercho-

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lesterolemia - in 70,3% of cases; AG – in 65,6%; hyperglycemia – in 17,6%; BMI>25 kg/m2 - in 38% of patients with COPD. The inverse correlation between BMI and severity of COPD (r= - 0,324, p<0,05); and the positive correlation of cholesterol levels with age and severity of COPD (r=0,241 r=0,198, p<0,05) have been detected.

Conclusions

Patients with COPD demonstrate the summation of "traditional" RF of CVD, that is determined by COPD on the one hand and on the other – by existing renal dysfunction.

Key words

Chronic obstructive pulmonary disease, risk factors, cardiovascular disease, chronic kidney disease.

Introduction

High occurrence of chronic noninfectious diseases (CNID) during last decades has acquired epidemic sizes and became the leading cause of mortality and disability in population thus defining the priorities of healthcare and preventive medicine [1, 2]. Chronic obstructive pulmonary disease (COPD) has a particular position between these diseases. According with the prognosis of "Global burden of disease" study, COPD will take the third position between mortality causes in population, and nowadays it is the only mortality cause with increasing frequency [3]. It can be explained with the high presence of comorbid pathology in COPD, that is related both to the age of patients and the clinical course of COPD, steadily progressing, chronic disease of respiratory system with proved extrapulmonary effects. Hypoxia, sympathoadrenal system activation, chronic inflammation, oxidative stress and developing endothelial dysfunction, caused by COPD, create the conditions for wide spectrum of comorbid pathologies where cardiovascular diseases (CVD) have their particular position [3, 4].It is proved that CVD mortality risk in COPD is 2-3 times higher and is the cause of death in 50% of mortality cases. At the same time it had been recently established that chronic kidney disease (CKD) is an independent CVD risk factor (RF) and equivalent of coronary heart disease (CHD) [5]. Taking into account common RF of COPD, CKD and CVD and systemic manifestations of COPD, it is possible to consider the presence of kidney dysfunction that increases cardiovascular risk in patients with COPD due to existence of cardiorenal continuum [5, 6]. At the same time, the question of kidney dysfunction occurrence as an independent CVD RF is poorly studied. The aim of this study is to investigate the occurrence of CVD RF, CKD and frequency of kidney dysfunction in patients with COPD.

Materials and methods

This study involved 300 patient with COPD: 70,4% of all patients were males, with average age of 68,51±9,9 years, average duration of disease 20,9±3,2 years, and 29,6% of patients were females with average age of 65,95±10,1 years and average duration of disease 17,2±2,2 years that were admitted to the Regional hospital №2 in Krasnodar for diagnostics and treatment. COPD diagnosis was established according with the GOLD guidelines (2011). Patients were divided into four groups with comparable age according with the COPD degree of severity: 30 patients with I degree COPD (14 females, 16 males), 64 patients with II degree COPD (24 females, 42 males), 135 patients with III degree COPD (25 females, 110 males), 71 patient with IV degree COPD (10 females, 61 males). Average value of forced expiratory volume in 1 second (FEV1, % of predicted value) in the I group was 85,3±4,3%, in the II group – 66,7±6,2 %, in the III group - 46,1±4,5 %, in the IV group – 26,5±3,67 %. We performed comparative analysis of CVD and CBP RF: age > 45 years, male gender, arterial hypertension (AH), carbohydrate metabolism disorders, hypercholesterolemia – total cholesterol levels (TC) > 5,0 mmol/L, excessive body weight, including obesity – body mass index (BMI) > 25 kg/m^2 (WHO, 2004), frequency and intensity of smoking – pack-year index [2]. To identify glomerular filtration rate (GFR) impairment we calculated GFR with CKD-EPI formula (2009, with modifications of 2011) [5, 6, 7].

This study was performed according with the standards of good clinical practice and the Declaration of Helsinki principles. The study's protocol was approved by local ethic committee. All patients gave written informed consent before being included into this study.

Exclusion criteria were the following: decompensation of present chronic diseases and renunciation of participation in the study.

Statistical analysis was performed using variation statistics in statistical software "Statistica 7,0". Kolmogorov-Smirnov test was used to test the normality of characteristic's distribution, distribution was considered normal in case of p>0,05. To study statisti-

cal correlation between different observations we used Spearman's rank correlation coefficient. Student's t-test was used for evaluation of differences between two average values in case of normal distribution, in case of not normal distribution we used Mann-Whitney test. The difference was considered significant if p-value was less than 0,05. Data are present as average value (M)± standard deviation (SD).

Results

According with our results, 100% of COPD patients had CVD RF, and 92,6% of patients had ⩾3 RF (Image 1). Majority of patients was older than 45 years (96,4%, n=289) and 78,8% were considered elderly (> 65 years). Smoking was the second most frequent RF (92% of patients, n=289) (table 1). Average amount of pack-year index was 39,9±6,5 pack-year and it had significant correlation with COPD severity (*r*=0,262, p<0,05). Relative number of patients of male gender as an unalterable CVD and CKD RF was 70,4%. Pack-year index, occurrence and duration of smoking were significantly higher in men (p<0,05).

Hypercholesterolemia was detected in 70,3% of COPD patients when cholesterol levels >5,0 mmol/L was considered liminal. And TC levels higher than target value of 4,5 mmol/L were detected in 89,6% of patients (n=269). Average TC levels was 5,8±1,1 mmol/L. We found direct correlation of TC levels and patients age and COPD severity (r=0,241, r=0,198, p<0,05).

Lowered GFR was found in 67,3% of COPD patients. 37,3% of patients had mild stage of $GFR_{CKD-EPI}$ reduction

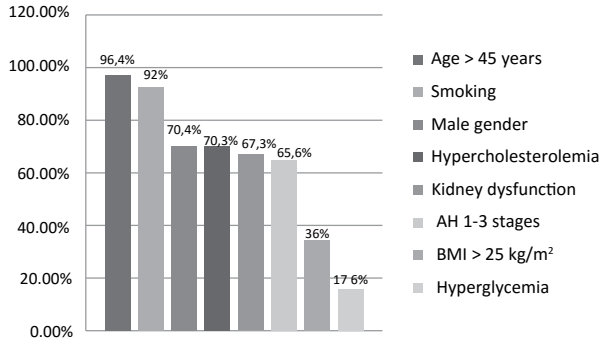

Image 1. CVD RF occurrence in COPD patients

(89-60 mL/min/1,73 m^2), 26,7% of patients had moderate $GFR_{CKD-EPI}$ reduction (59-45 mL/min/1,73 m^2), 3,3% of patients had prominent $GFR_{CKD-EPI}$ reduction (44-30 mL/min/1,73 m^2). Optimal $GFR_{CKD-EPI}$ levels were detected only in 10,7% of COPD patients, hyperfiltration was found in 22% of patients. Together with it, only 28,6% of patients with COPD had hypercreatininemia (creatinine levels > 90 μmol/L), average creatinine levels were around 82,9±22,7 μmol/L.

AH had the six position between RF and it was found in 65,6% of patients. The frequency of concomitant AH was significantly higher in patients with COPD IV severity degree comparing with COPD I severity degree (p<0,05), and it had direct correlation with COPD severity degree (r=0,387, p<0,05) and it had negative correlation with FEV1 values (*r*=-0,362; p<0,05). The frequency of overweight and obesity (BMI > 25 kg/m^2) was 36%. We found negative correlation between BMI and COPD severity (r=–0,324, p<0,05).

Table 1. **Clinical and laboratory characteristics of COPD patients**

Characteristic	COPD I degree n=30	COPD II degree n=64	COPD III degree n=135	COPD IV degree n=71	Total n=300
Gender male/female	16/14	42/22	110/25	61/10	229/71
Age, years	58,2±12,1	65,1±11,9	69,2±9,2	69,2±9,9	66,3±10,3
Smoking, abs. (%)	26 (86%)	57 (89,1%)	125 (92,6%)	68 (95,7%)	276 (92%)
Pack-year index, «pack-year»	15,3±7,2	28,2±12,35	44,3±9,8**	48,5±12,7***	44,8±19,8
FEV_1, % of predicted	85,3±4,3	66,7±6,2	46,1±4,5**	26,5±3,7***	51,5±11,4
BMI, kg/m^2	32,4±7,8	27,9±5,8*	25,1±6,7**	21,2±4,1	26,6±6,1
BMI>25 kg/m^2, abs. (%)	21 (70%)	36 (56,3%)	42 (31,1%)**	15 (21,1%)***	114 (38%)
Creatinine, μmol/L	93,8±21,2	91,2±17,2	82,1±12,5	75,9±16,8	85,7±8,3
TC, mmol/L	5,2±0,9	5,4±0,8	5,5±0,7	5,9±0,9	5,8±1,1
TC>5,0, mmol/L	15 (50%)	39 (60,9%)	95 (70,3%)	62 (87,3%)	211 (70,3%)
GFR, mL/min/1,73 m^2	61,8±18,1	62,9±12,4	69,2±4,3	88,1±6,9	70,2±12,1
DM, IGT, abs, (%)	3 (10%)	8 (12,5%)	22 (16,3%)	22 (26,7%) ***	55 (18,3%)
AH I–III st.	12 (40%)	36 (56,25%)	97 (71,8%)	52 (73,2%)***	197 (65,6%)
CHD+AH, abs. (%)	3 (10%)	35 (54,7%)*	104 (77%)**	52 (81,3%)***	144 (48%)

Comment: * — significance of differences between I and II groups; ** — significance of differences between I and III groups; *** — significance of differences between I and IV groups.

Diabetes mellitus (DM) and impaired glucose tolerance (IGT) had 8th rank position, their frequency was 17,6% in total group. We detected significant differences in blood glucose levels between analyzed groups, maximal overage values (7,5±2,3 mmol/L) were found in IV group.

We analyzed also the frequency of concomitant diseases that have strong influence on COPD patients' prognosis. The AH+CHD combination (64,6% of patients) was more frequently registered in groups of severe and very severe COPD (χ^2=19,5; p<0,05), in males significantly more frequently than in females (χ^2=12,3**;** p<0,05). The evidences of myocardial infarction (MI) were present in 16% of patients (n=48), MI was significantly more frequent in IV group's patients (χ^2=18,5; p<0,05). Cardiac rhythm abnormalities were found in 51 patients (17%) including 25 persons (8,3%) with atrial fibrillation, the frequency of which correlated with the age (r=0,241; p<0,05) and COPD severity (r=0,241; p<0,05). Previous pulmonary embolism was reported in 16 (5,3%) of patients, acute arrest of cerebral circulation was reported in 2 patients with COPD.

Discussion

High occurrence of CVD and CKD RF in COPD patients that reaches 100% is expectable because of systemic COPD manifestations [4, 5, 8]. This study demonstrated the prevalence of people above 45 years (96,4%) among these patients that goes along with modern ideas about COPD as the disease of the second half of life [4, 9]. High percentage of male patients (70.4%) is comparable with existing data about higher occurrence of COPD in men [4, 9]. The frequency of smoking in this study was higher than average frequency in population (92% and 70,5% respectively) of comparable age (>40 years) and the results of GATS (Global Adult Tobacco Survey) (39,1%),(Global Adult Tobacco Survey) (39,1%), that was done in 2009 [10]. At the same time, these results go along with the data about smoking frequency in COPD patients that reaches 89,6% [11]. Extremely high frequency of this RF is explained with the fact that smoking, being one of the most aggressive CVD RF, is the most significant etiological factor of COPD [4,9].

AH occurrence in COPD patients reaches 65,5% and it corresponds results of other studies (34-76%), demonstrating the influence of systemic COPD manifestations on cardiovascular system [4, 9, 12, 13]. High frequency of hypercholesterolemia according with the results of this study (70.3%) can be indirectly indicate the presence of endothelial dysfunction in majority of COPD patients, developing as the consequence of smoking or chronic inflammation [4, 9]. The occurrence of hypercholesterolemia in healthy able-bodied population of Krasnodar was 51,5% that is evidently lower than its occurrence in COPD patients (70.3%) [14]. The frequency of body overweight and obesity in studied group of patients was 36% with expected minimum of BMI in patients with IV COPD degree (21,2±4,1 kg/m^2), that is explained with protein and energetic insufficiency in patients with severe and very severe COPD [15, 16]. The highest number of IGT and DM cases was found in patients with IV grade COPD (26,7%), here we identified also the highest average levels of glycemia (7,5±2,3 mmol/L). These numbers are slightly lower than the ones found in other studies (46-57%) [17]. The frequency of GFR reduction less than 89 mL/min/1,73 m^2 (67,3%) in COPD patients is higher than the same characteristic in able-bodied population of Krasnodar (46,1%). Possibly it can be explained with systemic effects of COPD [14].

Conclusions

High prevalence of main CVD and CKD RF in COPD patients was detected in up to 100% of patients, 92,6% of patients have combination of ≥3 RF.

Typical cardiovascular RF accumulate during COPD progression and it leads to increased frequency and severity of cardiac pathology in patients with severe and very severe COPD.

Considering the majority of CVD and CKD RF as potentially modifiable, their opportune correction in order to improve cardiovascular prognosis is highly relevant.

Conflict of interest: None declared

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The probabilistic calculator for prediction of coronary atherosclerosis risk in patients with obesity

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Summary

Objective

To create a method of coronary atherosclerosis prediction in patients with obesity.

Material and methods

This study involved 85 men, 39-65 years (average age of 47,68±6,65 years) with absence of clinical manifestations of coronary heart disease and atherosclerosis of other localizations. Patients had the obesity of the I-III degree, BMI 36,23±4,31 kg/m² and visceral obesity in case of epicardial fat tissue thickness≥7 mm. 2 groups of comparison were identified according with the performed coronary angiography or multislice spiral computer tomography of coronary arteries. Group I (n=35) included patients with existence of coronary atherosclerosis, Group II (n=50) included patients with absence of coronary atherosclerosis.

Results

As the result of comparison of two groups of an arterial hypertension the existence of carbohydrate violations, triglycerides, leptin, adiponectin and C -reactive protein have been identified as possible predictors of coronary

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atherosclerosis risk. Each predictor received its coefficient of importance after the regression analysis with optimal scaling importance. The size of right classifications as a result of logistic regression was 79,1% that indicates a good predictive ability of this regression model.

Conclusion

The created scale allows to estimate risk of coronary atherosclerosis in the absence of disease clinical manifestations, that is important in terms of well-timed preventive actions and the prevention of the disease progression.

Key words

visceral obesity, coronary risk, scale

It has been proved that neurohumoral activity of visceral fat including epicardial fat tissue has an important role in cardiovascular complications (CVC) development in patients with obesity [1, 2]. Due to this the identification of high coronary risk group considering the presence of normal obesity and in particular visceral one would allow to plan and perform prophylaxis interventions in order to prevent CVC with well timing.

At the same time existing scales of coronary risk stratification (Framingham, PROCAM, SCORE) do not take into account main pathogenetic mechanisms that connect obesity and CVC [3-7].

The aim of this study is to create probabilistic calculator for coronary atherosclerosis prognosis in patients with obesity.

Materials and methods

85 males of 38-65 years (average age 47,68±6,65 years) without clinical manifestations of stenocardia and atherosclerosis were included in this study. All patients had I-III grade obesity, body mass index (BMI) around 36,23±4,31 kg/m^2 and visceral obesity according with the epicardial fat tissue thickness (EFTS) >27 mm. Patients with severe concomitant diseases, diabetes mellitus 2 type (DM-2) and bad quality of echocardiography (EchoCG) visualization were excluded from this study.

During enrollment of the study we measured height and weight of patient, quantified BMI according with the formula (weight (kg)*height (m^2). When BMI was ⩾ 30 kg/m^2 patient was diagnosed with normal obesity. Total cholesterol (TC), triglycerides (TG), high density lipids cholesterol (HDLC), low density lipids cholesterols (LDLC) and glucose levels were measured in all patients. Lipoprotein A (LPA), apolipoprotein B (Apo B) and apolipoprotein A1 (apo A1) levels were measured with immune precipitation method. Leptin, adiponectin, resistin levels and interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) concentration in blood serum were identified using enzymoimmunoessay (EIE) kit (BioSource, Belgium). C-reactive protein (CRP) concentration was measured using highly sensitive latex-enhanced immune precipitation kit (Thermo Fisher Scientific, Finland). Epicardial fat tissue thickness was estimated with transthoracic EchoCG and Vivid 5 ultrasound machine (General Electrics, USA) with mechanical sector sensor 3,5 MHz. Three cardiac cycles in long parasternal position were registered. EFTS was measured behind free wall of the left ventricle in the end of systole. on the line that was maximally perpendicular to the fibrous ring of aortic valve used as an anatomic reference point [8, 9]. To estimate subclinical coronary atherosclerosis we performed selective coronaroangiography (CAG) with angiographic machine INNOVA 3100 (USA) or multislice computer tomography (MCT) of coronary arteries (CA) on Aquilion-64 ("Toshiba", Japan) tomography with the proceeding of data at the working station VITREA.

According with CAG and MCT results, we divided the patients with epicardial obesity into two groups: group 1 with the signs of coronary atherosclerosis (n=35) and group 2 (n=50) without signs of coronary atherosclerosis.

STATISTICA 10 and SPSS-21 software were used for statistical analysis. 0,05 was taken as the critical level of statistical significance during checking of the null hypothesis. Normality estimation for quantitative characteristics in compared groups was performed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistical values are present in the text of the article as M ± SD in case of characteristic's normal distribution, where M is an average value, SD – standard deviation, or as Med in case of not normal distribution. To compare central group parameters we used parametric and non-parametric methods: Student's T-test or Mann-Whitney U-test. To create the scale of coronary atherosclerosis prognosis and as a regression model we chose Regression with Optimal Scaling (CATREG) model that was performed with SPSS software.

Results

In order to analyze the relation between coronary atherosclerosis with possible predictors we made preliminary comparative analysis of two comparison groups: group I (n=35) and group II (n=50) in major and additional metabolic, neurohumoral risk factors (RF) and vascular inflammation markers that after were used in current study.

We defined the list of characteristics that had statistical relation with dependent variable – the presence of coronary atherosclerosis, and after formed the list of variables for regression analysis.

Thus, the list of possible predictors included: presence of arterial hypertension (AH), presence of carbohydrate metabolism abnormalities (impaired fasting hyperglycemia or impaired glucose tolerance (IGT)), TG, leptin, adiponectin and CRP. We performed receiving operating characteristic (ROC) analysis to define threshold levels of quantitative predictors and interval variables' reduction.

Optimal level of TG that was taken as a cut-off point was 1,8 mmol/mL(sensitivity 72%, specificity 66,7%), for leptin – 12,8 ng/mL (sensitivity 80%, specificity 64%).

Cut-off point for adiponectin was 10 μmol/mL (sensitivity 84%, specificity 45%), for CPR cut-off point was 5 mg/mL (sensitivity 64%, specificity 76%).

After obtaining cut-off points we made regression analysis with optimal scaling to estimate significance of predictors. These importance coefficients were chosen as weight values for creating the scale. For each one of 6 predictors included in regression model we quantified the points by multiplying absolute value of appropriate importance coefficient and 100 and its rounding to integer (Table 1).

Thus we created preliminary version of this risk scale (Table 1). We tested if the created regression model was adequate by binary logistical regression. The value of true classifications was 79,1%, that is considered high enough and indicates of good prognostic ability of this regression model.

Using this equation, we quantified theoretical values of subclinical coronary atherosclerosis presence probability for each patient. Dispersion diagram that reflects this relation is present at Image 1.

Optimal cut-off value for sum of points according with the results of ROC-analysis that allowed to divide the patients into two groups was 58 points. Thus, if the probability of coronary atherosclerosis is ⩾40%, its risk can be considered as high (Image 1).

To make this risk calculator easier to use we created its version for MS Excel, MS Office 2010 software (Table 2).

Table 1. **Regression analysis results of coronary atherosclerosis predictor significance estimation**

Predictor	Cut-off values	Standardized coefficients		p-value	Partial correlation coefficient	Importance coefficient	Points
		Beta	Standard error				
TG	⩾1.8	0.262	0.105	0.015	0.314	0.234	+23
Leptin	⩾12.8	0.240	0.147	0.107	0.213	0.246	+25
Adiponectin	⩽10.0	0.060	0.087	0.493	0.063	0.043	+4
CRP	⩾5.0	0.233	0.128	0.074	0.251	0.222	+22
AH	Present	0.189	0.089	0.039	0.233	0.126	+13
Carbohydrate metabolism abnormalities	Present	0.236	0.102	0.024	0.278	0.129	+13

Comment: Beta-coefficient reflects summarized impact of predictor on response value, partial correlation coefficient reflects independent impact of predictor on response value.

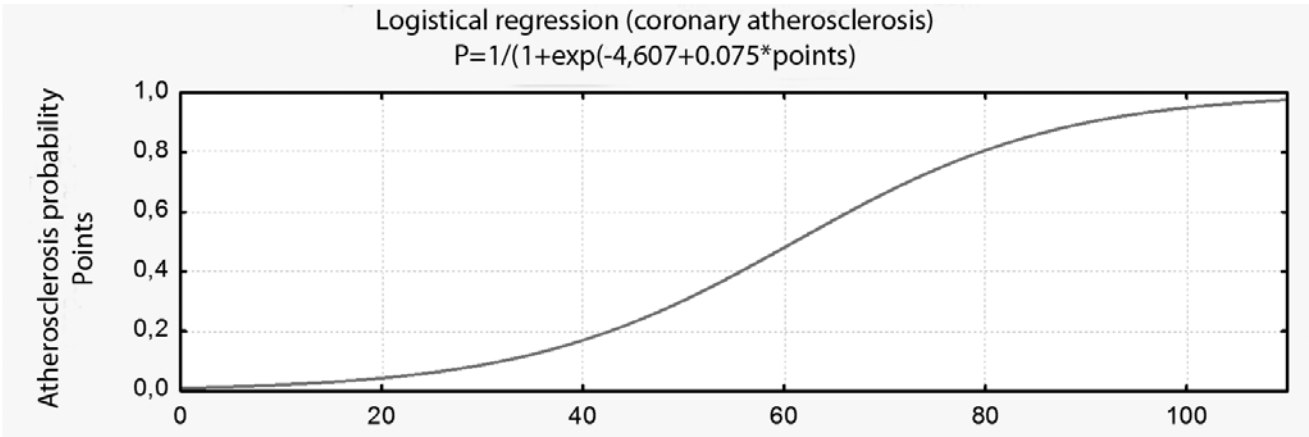

Image 1. Equation and logistic regression function plot that reflects the relation between the sum of points and probability of coronary atherosclerosis presence.

Table 2. **MS Excel interface of the risk calculator for sublinical coronary atherosclerosis prognosis**

A	B	C	D	F	G	H	I	J	K	M
Predictors	TG	Leptin	Adiponectin	CRP	AH	IGT	A0–4.607	B 0.075	Sum of ponts	P (%)
Cut-off values	⩾1.8	⩾12.8	⩽10.0	⩾5	1 (0)	1 (0)				
Weight points	23	25	4	22	13	13				
Patient's characteristic										

Comments: 1. RF information of each patient should be put to the cells of the table. 2. Probability of coronary atherosclerosis presence (%) would appear in «M» cell.

This calculator contains the data of logistical regression. Numerical characteristics of analyzed prognostic criteria for each patient should be put into this calculator and the value of prognostic risk would automatically appear in percentage format in the "M" cell of this table.

Discussion

In this study coronary atherosclerosis in clinically unsuspected patients with visceral obesity was verified in 35 (41%) of patients. In other studies it was identified that 61% of patients of morbid obesity group and BMI ⩾40 kg/m² without coronary heart disease (CHD) clinical manifestations (average age 50,4±10,0 years, BMI 43,8±4,8 kg/m²) had stenosis at least of one CA [10]. Another study that was made in Latin American population, where 88,7% of participants had obesity and 53,2% of participants had metabolic syndrome, identified carotid arteries atherosclerosis signs in 34,8% of cases according with the results of Doppler ultrasound scanning [11]. Patients with metabolic syndrome that was diagnosed according with the ATP III classification and without CHD clinical manifestations had CA calcinosis in 24,7% of cases [12].

In one of Russian studies atherosclerosis plaques were found in 35% of patients of 30-55 years with abdominal obesity [13].

In our study coronary atherosclerosis predictors that are appropriate for risk prognosis were: AH presence, carbohydrate metabolism abnormalities – impaired fasting hyperglycemia or IGT, TG, leptin, adiponectin and CRP.

The correlation between CRP levels and intima-media complex thickness in carotid arteries was found in one study [14]. Previously the connection between CRP and atherosclerotic lesions of CA and other peripheral arteries was demonstrated in another study [15]. It was also proved that CRP and oxidized LDLC have direct relation to inflammatory lesions of arteries in CHD [16]. Another study identified the association of proinflammatory marker IL-6 and CA calcinosis [17]. Leptin levels were associated with CA calcinosis independently from weight and other RF that proves proatherogenic role of leptin [18]. It is known that CRP is one of the main chronic inflammation markers and it participates directly in CA atherosclerosis progression [19]. One study demonstrated that visceral fat tissue stimulates CRP synthesis [20].

Patients with CHD and low adiponectin levels have more prominent atherosclerotic CA lesions according with CAG results comparing with the patients with higher concentrations of this protein [21]. Low adiponectin concentrations in combination with high IL-6 levels in patients with obesity and metabolic syndrome were associated with the risk of cardiovascular disease development, and the highest risk of DM-2 and CHD development was found in patients with the combination of low adiponectin and HDLC levels [22]. Low adiponectin concentration had positive correlation with the degree of CA calcinosis and asymptomatic stenosis that was identified with angiography technique in patients with DM-2 or without it [23].

Conclusions

Investigation of neurohumoral and proinflammatory activity of visceral fat tissue proved the connection of these factors and coronary atherosclerosis. At the same time visceral obesity degree, adipokines and proinflammatory markers still haven't been used in any scale of coronary risk estimation that reduces significantly the precision of cardiovascular risk evaluation in patients with obesity.

Probabilistic calculator of coronary atherosclerosis risk prognosis in patients with visceral obesity that have been created by the authors of this study allows to take into account main pathogenetic mechanisms that link obesity and coronary atherosclerosis. Evaluation of TG, leptin, adiponectin, CRP, presence of AH and carbohydrate metabolism disorders in every single patient with visceral obesity allows to predict the presence or absence of subclinical coronary artery atherosclerosis with the probability of 79,1%,

that is particularly important for early prophylaxis and prevention of disease progression.

Conflict of interest: None declared

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Combined therapy's antihypertensive efficacy and influence on metabolic parameters in patients with arterial hypertension and diabetes mellitus

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Summary

Objective

To compare three regimen of long-term combined antihypertensive therapy in order to reach target levels of blood pressure (BP), dynamics of daily BP profile and metabolic parameters in patients with arterial hypertension (AH) associated with diabetes mellitus, type 2 (DM-2).

Materials and methods

69 patients with the combination of AH and DM-2 completed the treatment course (male/female 22/47; average age 57,1±6,5 years). Target BP <130/80 mm Hg. in the group №1 (n=22) was achieved using the combination of perindopril arginine, indapamide retard and amlodipine, in the group №2 (n=25) it was reached with the combination of valsartan, indapamide retard and amlodipine, and in the group №3 (n=22)– using the combination of amlodipine, indapamide retard and metoprolol succinate. Body weight and the levels of office BP, 24 hour ambulatory BP monitoring, parameters of lipid and carbohydrate metabolism were measured before prescription of drugs and 30-32 weeks after and HOMA index was quantified.

Results

The degree of office BP levels reduction didn't differ in all three groups of patients. Values of systolic BP (SBP) and diastolic BP (DBP) "load" for 24 were higher in the patients of the group №3 comparing with the group №1, and achieved levels of night SBP were higher than in the group №1 and the group №2. The treatment based on

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perindopril arginine and amlodipine and not the combination of valsartan and amlodipine led to decrease of body weight and HbA1c serum levels. Patients of groups №1 and 2 were united into one common group of therapy based on renin-angiotensin-aldosterone system (RAAS) blockers, and after the treatment increased levels of high density lipids cholesterol (HDL cholesterol) levels (from 1,29±0,2 to 1,45±0,3 mmol/L, p=0,006) and improved glycemic control (expressed as HbA1c levels reduction from 8,1±2,2% to 7,0±2,3% (p=0,01)) were detected, and it was present in case of unchanged glucose-lowering therapy and was realized in case of three-component regimen (after addition of amlodipine). Combination of metoprolol succinate, indapamide retard and amlodipine was considered as metabolically neutral in patients with DM-2.

Conclusion

Although all three antihypertensive therapy regimens allow to reach target BP levels in the majority of patients with AH+DM-2, the value of night AH correction and metabolic effects of this therapy re not equal.

Key words

Arterial hypertension, diabetes mellitus, combined therapy, circadian rhythm, metabolic effects.

Introduction

The number of Russian patients suffering from diabetes mellitus type 2 (DM-2) is drastically increasing, and it goes along with worldwide tendency [1]. Strict control of blood pressure (BP) is a necessary condition to improve cardiovascular and renal prognosis of patients with diabetes, and for the majority of DM-2 patients combined antihypertensive therapy (AHT) is recommended since the beginning of treatment because arterial hypertension pathogenesis involves many components in case of associated pathology [2]. Although according with modern guidelines, it is possible to choose any drug that allows achieving target BP levels, and rennin-angiotensin-aldosterone system (RAAS) blockers are considered preferable only in case of present albuminuria/proteinuria [2, 3], it is not possible to exclude that they can have advantages over other antihypertensive drugs (AHD) in patients with DM-2 due to their high organoprotective potential and favorable metabolic effects. ß-blockers administration (ß-B) in patients with diabetes is reasonable due to hyperactivation of sympathetic nervous system, but they are known to cause unfavorable metabolic shifts, due to it their combination with dihydropyridine calcium receptor blockers (CB) seem to be more promising. Up to nowadays it is still unclear if the dynamics of 24-hours BP profile characteristics differs after achievement of target levels in different therapeutic schemes of combined AHT, and possible advantages of RAAS blockers and metabolic effects of different AGD combinations in patients with DM-2 require further investigation.

The **objective** of this study – is to perform comparative estimation of three regimen of long combined AHT based on two variants of RAAS blockers and other AGD in relation to reaching target BP levels, dynamics of daily BP profile and metabolic parameters in patients with AH+DM-2.

Materials and methods

Open, randomized, comparative in parallel groups trial included patients with AH associated with DM-2. Patients with symptomatic AH, acute vascular complications that occurred less than one year before inclusion into study, unstable angina, arrhythmias requiring special treatment, chronic heart failure > than 2 functional class (NYHA), evident peripheral atherosclerosis, DM type 1, clinically apparent diabetic nephropathy, severe concomitant diseases, absolute contraindications to investigated drugs. Target BP level at the moment of the beginning of this study was defined as BP < 130/80 mm Hg. according with the previous issue of guideline dedicated to AH diagnostics and treatment [4]. After patients signed informed consent about participation in this study, all their previous AHT except of "emergency" drugs was cancelled for the period of 2-3 weeks, and after it patients underwent examination Then patients were randomized into three groups, in which AHT started from perindopril, valsartan or amlodipine respectively. AHT intensity increased in stepwise way: in the beginning of treatment patients were administered with 5 mg of perindopril arginine (n=23), 80 mg of valsartan (n=25) and 5 mg of amlodipine (n=23). After three weeks of treatment if the target levels of PB had not been achieved, indapamide retard (IR) in the dose of 1.5 mg (in the morning, on an empty stomach) was added to the therapy. After every three weeks if the target levels still had not been achieved therapy was augmented with: increased daily dose of perindorpil up to 10 mg, valsartan - up to 160 mg, amlodipine - up to 10 mg; addition of amlodipine 5mg/day to the therapy with RAAS inhibitors and then increase of

Table 1. **Clinical characterization of patients completed the therapy (n=69)**

Characteristic	Group 1 (n=22)	Group 2 (n=25)	Group 3 (n=22)
Gender (male, female)	5 (22.7%)/ 17 (77.3%)	11 (44%)/ 14 (66%)	6 (27.3%)/ 16 (72.7%)
Average age, (years)	57.1±6.1	58.04±6.9	56.1±6.8
AH duration, years	10 (5–15)	16 (9–30)#	9 (5–15)
DM duration, years	4 (3–8)	9 (3–12)	4 (2–10)
Body mass index, kg/m^2	33.3±4.3	32.4±4.4	33.4±4.6
Fasting glucose levels, mmol/L	7.4±2.0	7.7±2.0	7.6±2.1
HbA_1c, %	7.8±2.0	8.3±1.8	8.2±1.8
Office SBP, mm Hg	148.3±8.4	150.3±14.3	149.6±12.3
Office DBP, mm Hg	90.5±7.1	89.0±8.6	89.9±8.9
SBP 24h, mm Hg	136.9±9.9	132.3±10.8	138.1±14.7
DBP 24h, mm Hg	82.4±7.5	78.0±6.9#	81.7±11.8
Smoking	3 (13.6)	4 (16%)	4 (18.2%)

Comment: — p<0.05: — for comparison of group 1 and 2

its ose up to 10 mg per day; addition of metoprolol succinate to amlodipine, starting from 50 mg per day and, if necessary, increasing its dose up to 100 mg. Thus, patients of the first group received perindopril arginine in combination with IR and amlodipine, patients of the second group – valsartan, IR and amlodipine, patients of the third group – amlodipine, IR and metoprolol succinate. This study included 71 patients, and 69 patients (male/female – 22/47, average age 57,1±6,5 years) – their clinical characterization is present in Table 1. Therapy of one female patient was cancelled due to development of dry cough, one adverse effects of perindopril monotherapy. Therapy of another female patient was terminated because of shin edema, adverse effect of amlodipine monotherapy. Body weight, office BP values, results of 24-hours outpatient BP monitoring, lipid, carbohydrate and insulin metabolism characteristics and HOMA index value were obtained before drug prescription and 30-32 weeks after the beginning of therapy.

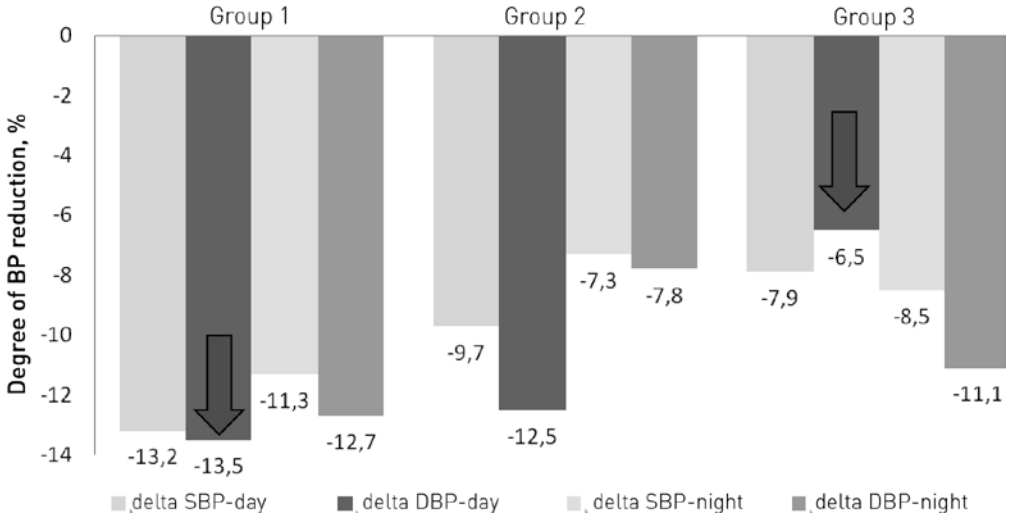
Statistical analysis was performed using Statistica 6.0 software (StatSoft Inc, USA). Kolmogorov-Smirnov test was used to check the normality of selection. Results are present as M±m where M is mean value, m – error of mean, or median (Me) or interquantile range (Q25-Q75), where Q25 is the 25th quartile, Q75 is the 75th quartile. Significance of differences was controlled with Mann-Whitney test. p=0,05 was taken as the critical significance level for hypothesis testing

Results

Degree of office BP reduction and reached levels did not differ in all three groups, BP levels after treatment were 124,5±6,5/76,5±4,9**,** 125,0±9,2/77,0±4,8 and 126,5±6,2/76,2±5,7 in groups 1, 2 and 3, respectively). Percentage of patients who reached target BP levels was: for therapy based on perindopril arginine -95,5%, for therapy based on valsartan – 80%, for therapy based on amlodipine – 86,4% (differences are not significant).

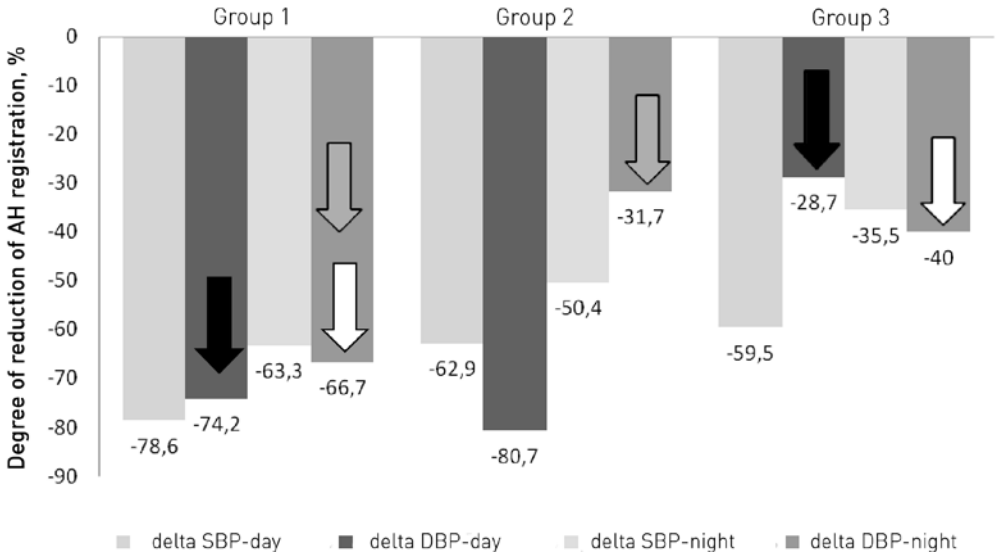
If RAAS blockers were not present in therapy scheme, 24 hours systolic BP (SBP) reduction was not enough, especially at night time: patients of the 3rd group had higher levels of night SBP comparing with its levels after therapy based on RAAS inhibitors; the degree of day SBP reduction was more evident in the 1st group (-11,6 (-16,2; -7,9)%) comparing with the 3rd group (8,3 (-10,3; -4,2)%, p=0,05). It is worth to mention that reached levels of night SAD in case of therapy based on amlodipine, IR and metoprolol succinate combination were higher than its target levels (<120 mm Hg). So, night SAD levels in the 3rd group were 120,2±10,9 mm Hg., whereas its levels in groups 1 and 2 were 113,9±8,9 и 112,8±13,8 mm Hg, respectively. Images 1 and 2 demonstrate the degree of day diastolic BP (DBP) reduction (p=0,03) and reduction of DBP loads during all studied periods in this group were less evident than in the 1st group. More than that, comparing groups 1 and 3, we found that the frequency of "double" AHT administration in the group 1 was higher (59,1% vs 27,3%, p<0,05), and the frequency of "triple" therapy in the group 1 was lower (39,1% vs 63,6%, p=0,07). So, in case of two drugs combination reaching of target BP levels was more likely for RAAS blocker and IR combination comparing with IR and CB combination that required addition of the third drug for adequate BP control.

At the same time, therapeutic regimen based on perindopril and amlodipine combination had advantages over the combination of valsartan and amlodip-



Comment: arrows indicate the differences between the degree of delta-DBP-day reduction in groups 1 and 3 (p<0,05).

Image 1. Comparison of BP reduction degree (%) in different therapeutic schemes of combined AHT in patients with AH+DM-2.



Comment: black and white arrows indicate the differences between the degree of reduction of diastolic AH duration at daytime and night in groups 1 and 3 (p<0,05), blue arrows indicate the differences between the degree of reduction of night diastolic AH duration in groups 1 and 2 (p<0,05)

Image 2. Comparison of the degree of AH duration reduction (%) with different schemes of combined AHT in patients with AH+DM-2

ine, because it caused better night diastolic AH correction: duration of diastolic AH at night time was significantly more reduced in the group 1 comparing with the group 2 (p=0,02). The percentage of patients who received amlodipine and its average dose didn't differ significantly between two groups: 39,1% in group 1 vs 48% in group2 and 6,3±3,5 mg/day. vs 6,5±3,3 mg/day, respectively. It was also documented that antihypertensive effect of the therapy based on angiotensin receptor type II antagonists (ARAII) and CB was associated with higher heart rate (HR) at night time, comparing to the combination of angiotensin-converting enzyme (ACE) inhibitors and CB. Individual analysis demonstrated that the highest level of HR during sleep after treatment was between the patients with less prominent degree of 24 hours SBP reduction: –6,9 (–10,8; –2,7)% vs –15,9 (–21,5; –8,6)% (p<0,05).

During estimation of impact of different schemes of compined AHT on metabolic characteristics we identified that only patients of group1 demonstrated significant weight loss from 87,8±11,9 to 85,8±11,4 kg (p<0,05) and glycated hemoglobin levels (HbA1c) from 7,8±2,0% to 7,2±1,9% (p<0,05) in absence of any changes of glucose-lowering therapy, whereas there was no such dynamics in other two groups. There was only the tendency to HOMA index of insulin resistance reduction in the 2nd group from 5,44 (3,4-6,8) to 3,8 (2,3-5,2) (p=0,07).

To perform sub-analysis that aimed to estimate metabolic effects of combined therapy based on RAAS blockers, we united the patients who received ACE inhibitor and ARAII into one common group (n=47) and analyzed the dynamics of lipid and carbohydrate metabolism characteristics in this group of patients.

Combined AHT that included RAAS blockers caused improvement of glycemic control that was reflected in HbA1c levels reduction from 7,9±2,0 to 7,2±2,0% (p=0,01), although there were no changes of glucose-lowering therapy, and there was also a tendency to reduction of initially high median values of HOMA insulin resistance index from 4,1 (2,7-5,9) to 3,8 (2,3-5,2) (p=0,08). More than that, we identified positive changes of lipid-transporting blood components that was expressed as a tendency to increase of high density lipids (HDL) cholesterol concentration in serum from 1,26±0,2 to 1,32±0,3 mmol/L (p=0,08). These favorable metabolic changes were realized through the group of patients who received "triple" therapy with addition of amlodipine. Table 2 demonstrates that there were no statistically significant changes of carbohydrate and lipid metabolism characteristics in patients receiving RAAS blockers combined with IR, whereas patients who received RAAS blocker together with IR and amlodipine demonstrated such evident positive metabolic changes like reduction of HbA1c serum levels from 8,1±2,2% to 7,0±2,3% (p=0,01), change of ratio of low density lipids (LDL) cholesterol/HDL cholesterol from 2,4±0,9 to 2,3±1,0 (p=0,05) and increase of HDL cholesterol concentration from 1,29±0,2 to 1,45±0,3 mmol/L (p=0,006).

Discussion

Diabetes mellitus is an important predictor of bad clinical prognosis. Its association with AH goes along with early atherosclerosis development, coronary heart disease, high frequency of vascular catastrophes, cardiac failure and impaired kidney function, and because of it the problem of rational AHT and organoprotective therapy in this category of patients is very important [1, 2]. It is known that modern guildelines allow prescription of any AHD for reaching target BP levels in patients with DM, and RAAS blockers are considered preferable only in case of present albuminuria/proteinuria [3]. At the same time there are many evidences that RAAS blockers have potential advantages particularly in patients with diabetes due to the presence of high potential of organ protection and favorable metabolic effects [2-4]. Nowadays RAAS blockers and their combination have the biggest amount of evidences proving the presence of organoprotective properties that do not depend on their antihypertensive action and ability to improve cardiovascular prognosis in general population of patients with AH and diabetes [2-13]. The most promising approaches to improve the prognosis of patients with AH+DM-2 are combinations of RAAS blockers with dihydropyridine CB or thiazide-like diuretic IR, that have synergic antihypertensive, organoprotective and metabolic effects and good base of evidences of their efficacy in reduction of cardiovascular morbidity and mortality [5-10]. It is known that indapamide drug form with prolonged release demonstrated metabolic neutrality in patients with DM [14]. Combination of dihydropyridine CB and ß-B in patients with DM is more reasonable from pathogenetic point of view but at the same time much less studied.

Table 2. **Biochemical characteristic dynamics in different schemes of AHT**

Characteristic	RAAS blockers+IR (n=26) (n=26)		RAAS blockers+IR+amlodipine (n=20)	
	Before treatment	After treatment	Before treatment	After treatment
Fasting glycemia, mmol/L	7,6±2,0	7,2±1,9	7,3±2,1	7,5±1,9
Postprandial glycemia, mmol/L	9,5±3,5	9,1±3,0	8,6±3,2	8,3±3,1
Insulin, basal, μU/mL	11,6 (11,0–16,3)	10,9 (9,2–15,2)	13,7 (9,7–19,1)	13,7 (7,9–19,1)
Insulin, posprandial, μU/mL	37,8 (21,8–52,3)	32,6 (19,8–55,2)	29,5 (23,4–43,7)	32,4 (18,1–39,8)
C-peptide, basal, μU/mL	2,8 (2,5–3,4)	2,9 (2,3–3,4)	2,9 (2,3–3,8)	3,9 (2,6–4,3)
C-pepdide, postprandial, μU/mL	7,0 (4,5–8,9)	6,1 (4,3–9,4)	7,7 (5,3–8,9)	6,8 (5,6–7,9)
HbA1c, %	7,9±1,9	7,6±1,8	8,1±2,2	7,0±2,3*
Total cholesterol, mmol/L	4,9±0,9	4,8±0,9	5,2±1,2	5,5±1,5
Triglycerides, mmol/L	1,8±0,7	1,8±0,7	2,0±0,7	1,9±0,7
LDL cholesterol, mmol/L	2,8±0,8	2,7±0,7	3,0±1,1	3,2±1,3
HDL cholesterol, mmol/L	1,24±0,3	1,21±0,3	1,29±0,2	1,45±0,3**
LDL cholesterol/HDL cholesterol, standard units	2,4±0,8	2,4±0,8	2,4±0,9	2,3±1,0*

Comment: * — p<0,05: significance of differences between characteristic values achieved with treatment and their initial levels показателями; ** -p<0,05: significance of differences between characteristic values achieved with treatment in 2 subgroups.

This study aimed to perform comparative estimation of efficacy of three therapeutic regimens of long AHT based on two RAAS block variants or dihydropyridine CB in relation to reaching target BP levels, dynamics of night AH and metabolic characteristics in patients with DM-2. It was demonstrated that, although there was no significant difference between the frequency of reaching office BP target levels in three groups of patients, the percentage of patients who received combination of two AHD was significantly higher in the group which received combined therapy based on ACE inhibitor, comparing with the group where patients did not receive RAAS blockers. We identified that adequate correction of night AH was impossible in absence of RAAS inhibitors. Activity of intrarenal RAAS under dihydropyridine CB [15] and less prominent antihypertensive action of ß-blockers at night hours due to naturally impared adrenergic activity during sleep can be considered as possible reasons of this BP reduction [16]. More evident decrease of the frequency of night diastolic AH in patients of the 1st group comparing with the 2nd group can be explained with additional impact of ACE inhibitors on kallicrein-kinin system that allows the drugs of this class to have more prominent and more stable during daytime and night time influence on neurohumoral systems and BP regulation [17]. Antihypertensive effect of therapy based on combination of ARAII and CB was accompanied with increased HR at night time, especially in patients with less evident reduction of 24-hours SBP, that can reflect some activation of sympathoadrenal system under amlodipine influence that was not compensated with valsartan action.

These results indicate of metabolic neutrality of CB, IR and ß-B combination in patients with diabetes, since no negative changes of carbohydrate, insulin or lipid metabolism were detected. At the same time, combined administration of ACE inhibitor, IR and amlodipine caused favorable metabolic shifts: statistically significant improvement of glycemic control and weight loss. Results of meta-analysis performed by Sharma A., et al. (2001) go along with our data, it has been reported that patients who received ACE inhibitors lost 0,3-5,3 kg of weight during therapy [18]. More evident influence of the therapy based on ACE inhibitor and CB combination on HbA1c comparing with combined use of ARAII and CB can be explained with this possible mechanism: ACE inhibitors potentiate endogenous kinins' effects and cause secondary stimulation of prostaglandins in different organs including pancreas [19], that increases transmembrane transport of glucose into cells.

It is necessary to understand which exactly AHD combination was responsible for detected improvement of glycemic control and weight loss in patients who received ACE inhibitor, IR and amlodipine, and to identify if RAAS blockers by themselves have benignant influence on metabolic characteristics in patients with DM-2. To answer this question we analyzed metabolic effects of two-component (without amlodipine addition) and three-component (with addition of amlodipine) therapy in united group of patients who received perindopril and valsartan. We found out significant improvement of glycemic control, tendency to increase of antiatherogenic part of blood cholesterol and reduced insulin resistance index in the common group of RAAS blockers that was realized because of patients who received combination of amlodipine with RAAS blockers and IR, whereas in absence of amlodipine no significant change of lipid and carbohydrate metabolism was detected. Observations of synergic positive metabolic effects of RAAS blockers and amlodipine go along with existing ideas of clinical benefits of this combination.

Rubio A.F., et al. found out that normotensive patients with DM who received combination of ACE inhibitor and CB for nephroprotection achieved better glycemic control than the same patients who received monotherapy with ACE inhibitors [20]. The study of Fogari R., et al. (2010) demonstrated that valsartan and amlodipine combination improves insulin sensitivity of tissues better than separate therapy with each drug [21], and after this it was proposed that combined administration of RAAS blocker and CB can play an important role in metabolic control of DM patients due to antihypertensive action of these drugs.

Conclusion

Our results demonstrate that although all three therapeutic regimen of long AHT allow to reach target BP levels in majority of patients with AH+DM-2, their degree of night AH correction and metabolic effects are not equivalent. Therapeutic scheme based on amlodipine, IR and metoprolol succinate combination is less effective in correction of night systolic AH than combination of RAAS blocker, IR and amlodipine. Combined administration of ACE inhibitor, IR and amlodipine has advantages over combined therapy with ARAII, IR and amlodipine in majority of patients with DM-2, it promotes weight loss and reduction of HbA1c levels. Increased levels of HDL cholesterol and favor-

able dynamics of glycemic control in case of combined therapy with RAAS blocker, IR and amlodipine can be explained with their synergic metabolic effects and they can be realized after addition of amlodipine to the therapy.

Study's limitations

This study has several limitations. First of all, target levels of glycated hemoglopin at the moment of inclusion into the study have not been achieved in patients of all three groups. At second, only half of patients did not receive lipid-lowering therapy with statins at the moment of inclusion into the study and did not take it constantly during the study that can have an impact on estimation of AHT influence on metabolic characteristics.

Conflict of interest: None declared

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Journal of the Cardioprogress Foundation

Results of V International Forum of Cardiology and Internal Medicine

V International Forum of Cardiology and Internal Medicine was successfully held in Moscow, Russian, in the New building of Russian Academy of Sciences Presidium on March 29-31, 2016 . The work of Forum has been supported by the Ministry of Healthcare of the Russian Federation, the World Heart Federation, Moscow City Department of Healthcare, Federal State Institution National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Russian society of Cardiology and Foundation for the Advancement of Cardiology "Cardioprogress".

Rafael G Oganov was the chairman of the Forum, Mehman N Mamedov was the chairman of organizing committee and Jurii A Vas'uk was the chairman of scientific committee.

Specialized journals and newspapers were responsible for informational support of V International Forum of Cardiology and Internal Medicine.

- Cardiovascular therapy and prevention
- Cardiology
- Russian Cardiologic Journal
- International Heart and Vascular Disease Journal
- Rational Pharmacotherapy in Cardiology
- Polyclinic
- Preventive Medicine
- Pharmateca
- Newspaper "Medical herald"

Forum involved more than 1500 participants from 58 subjects of Russian Federation and from near abroad countries (Azerbaijan, Belarus, Kazakhstan, Kirgizia, Latvia, Moldova, Uzbekistan). Informational letter of the Ministry of Healthcare of the Russian Federation and instruction for Moscow region were issued for official specialists' participation in the work of the Forum. All Forum participants and delegates registered themselves and received informational materials for free. According with the system of continuous medical education credits Forum participants received certificates with 15 credits (points).

Leading specialists from various fields of internal medicine: cardiology, neurology, gastroenterology, pulmonology, endocrinology, nephrology, rheumatology and also general practitioners participated in the Forum.

Scientific program of the Forum included two plenary meetings with participation of leading experts from Russia and abroad, 54 scientific workshops, clinical lectures, round-table discussions, educational seminars for doctors, clinical case presentations and 4 poster sessions involving 80 poster papers. Forum recruited participants from 58 cities and regions of the Russian Federation and other countries. Presentations were dedicated to all areas of cardiology including healthcare organization in cardiology, mass health examination, emergency cardiology, cardiac surgery, interventional arrhythmology, pediatric and adolescent cardiology, risk factors, metabolic disorders and closely related topics: endocrinology, gastroenterology, nephrology, neurology, family medicine, rehabilitology, It is worth to mention that

the Forum didn't raise any conflict of interests and it respected ethic aspects of drugs and medical devices information presentation. 95% of posters and workshops were declared to be independent.

The Forum conducted a workshop of young scientists that involved 7 speakers younger than 35 years from various parts of Russia and CIS countries.

10 scientific sessions including plenary meetings have been recorded for future use in distant learning of doctors who were unable to participate in the Forum. These materials will be published soon on the website of the "Cardioprogress" foundation.

Conference book included 450 abstracts from 58 cities of the Russian Federation and CIS countries. These works were dedicated to studying different aspects of somatic disorders: arterial hypertension, dyslipidemia, obesity, metabolic syndrome, diabetes mellitus, arrhythmias, ischaemic heart disease, chronic heart failure, kidney and gastrointestinal tract disorders and chronic obstructive pulmonary disease. Special issue of "Cardiovascular therapy and prevention" (15 March, 2016) will be dedicated to the materials of this meeting, and this information also will be published on the official website of the "Cardioprogress" foundation (www.cardioprogress.ru).

Organizing committee of V International Forum of Cardiology and Internal Medicine rewarded 9 scientists and doctors with 6 nominations:

- For contribution to the development of distant learning
- For contribution to the development of Russian science
- For contribution to primary cardiologic service
- For contribution to international collaboration with the "Cardioprogress" foundation
- For assistance in the realization of the "Cardioprogress" foundation regional projects
- For assistance in the realization of the "Cardioprogress" foundation regional projects

14 pharmaceutical companies, manufacturers of medical devices and medical publishers took part in Forum exhibition.

"Cardioprogress" foundation released special official newsletter dedicated to the Forum and organized its delivery to 3000 mail and 6000 email addresses in Russia and CIS countries

Leading federal mass communication media and TV channels including Vesti.ru, TASS, Evening Moscow, Moscow24, Medportal.ru, Medical newspaper and Medical news covered works and results of the Forum.

The next VI International Forum of Cardiology and Internal Medicine will be held in March 2017.

We would be glad to receive your opinion and suggestions on our e-mail address inf.cardio@gmail.com. It would allow us to improve the quality of the Forum organization.

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Journal of the Cardioprogress Foundation

Guidelines for authors

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Sources in Russian with transliteration:

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