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Journal of the Cardioprogress Foundation

Diabetes and hypertension: a position statement by the American Diabetes Association: comments of Russian experts

Possibilities of increasing the effectiveness of atrial fibrillation treatment (according to the results of studies presented at the European Society of Cardiology Congress, 2017)

Undernourishment in patients with connective tissue dysplasia: the role of proinflammatory cytokines and adipokines, and genetic factors

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Contact details:
Cardioprogress Foundation and Editorial Office:
Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia
Editorial Office tel.: (+7) 965 236 1600
Official website: www.cardioprogress.ru

Editorial correspondence should be sent to: Mehman Mamedov, Deputy Editor, editor.ihvdj@gmail.com
Articles for publication should be sent to: Anna Arteyeva, Associate Editor, submissions.ihvdj@gmail.com

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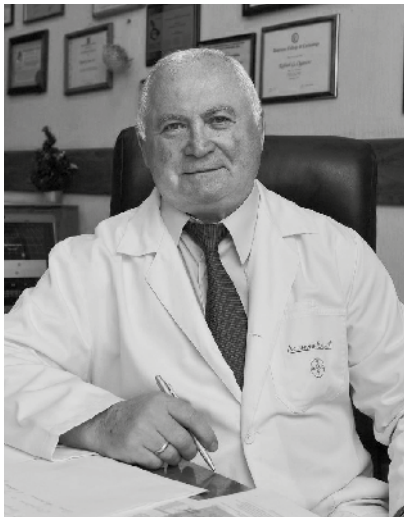
Contents



Editor's Welcome

Dear colleagues!

In the 16th issue of the International Heart and Vascular Disease Journal, there are the leading article, original, review, and experimental articles, and the report on the first Scientifical and Educational Congress of Cardiology and Internal Medicine "Golden ring".

The leading article section includes the opinions of Russian experts on the position statement of the American Diabetes Association about arterial hypertension (AH). New guidelines for AH diagnostics and treatment in patients with diabetes mellitus have been published for the first time within the last 14 years. We invited the researchers from 4 major Russian federal scientific centers to comment these new recommendations. A wide spectrum of problems including definition, screening, and diagnostics of AH, blood pressure target levels, AH treatment including lifestyle modification and pharmacological therapy, management of several groups of patients and treatment of refractory AH have been covered by this document.

Traditional section "Review article" includes the work of professor Sergey Kanorskii. This article discusses the results of clinical studies dedicated to atrial fibrillation treatment that have been presented during "Hot-line" sessions of the European Society of Cardiology Congress 2017.

Three articles were published in the "Original articles" section. The first article written by Egyptian researcher is dedicated to safety and effectiveness of combination of anticoagulant rivaroxaban and antiplatelet drug clopidogrel for atrial fibrillation treatment in patients with acute coronary syndrome. The author concluded that the use of this drug combination for 12 months was safe and effective and resulted in better compliance. Another article of Russian authors is dedicated to estimation of clinical manifestations and patients' history in patients with atherosclerotic lesions of brachiocephalic vessels and neurological symptoms taking into account present comorbid conditions. Significant gender differences, differences of frequencies of thyroid and rheumatologic diseases, purin metabolism abnormalities have been identified. The third study performed by the group of researchers from Omsk evaluated the connection between the levels of specific and non-specific inflammatory mediators, adipokines, and the frequency of soluble leptin receptors mutation in patients with connective tissue dysplasia and undernourishment. Change of adipokines' levels in patients with connective tissue dysplasia could be used not only as diagnostic criteria of undernourishment's severity but also as factors defining different risk of associated diseases.

The experimental issues section is present by a collaboration work performed by Russian and Belorussian researchers. Their study demonstrated that the use of cholecalciferol in hypertensive rats in the dose of 2500 ME/day led to reduction of mean BP, improvement of vascular endothelial function and could be an important addition to hypertensive therapy that requires further detailed investigation.

In this issue we published the results of the first scientific and educational congress of cardiology and internal medicine that involved participants from the cities of the "Golden ring" of Russia. Taking into account the importance of this scientific event, the organization committee decided to hold it each year.

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

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

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LEADING ARTICLE

Diabetes and hypertension a position statement by the American Diabetes Association: comments of Russian experts

Mamedov M.N.[1*], Khalimov Yu.Sh.[2], Agafonov P.V.[2], Bondarenko I.Z.[3], Kalashnikov V.Yu.[3], Dudinskaya E.N.[4], Runikhina N.K.[4], Kotovskaya Yu.V.[4], Tkacheva O.N.[4]

[1] National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia
[2] S.M. Kirov Military Medical Academy, Saint Petersburg, Russia
[3] National Medical Research Center of Endocrinology, Moscow, Russia
[4] Gerontological Clinical Research Center, Pirogov Russian National Research Medical University, Moscow, Russia

Authors

Mekhman N. Mamedov, M.D., Ph.D., doctor of sciences, professor, head of the laboratory of interdisciplinary approach for prevention of chronic non-infectious diseases, National Research Centre for Preventive Medicine, Moscow, Russia.
Yury Sh. Khalimov, M.D., Ph.D., doctor of sciences, professor, head of the department of military-field surgery, deputy chief physician, S.M. Kirov Military Medical Academy, Saint Petersburg, Russia
Pavel V. Agafonov, M.D., Ph.D., lecturer of the department of military-field surgery, S.M. Kirov Military Medical Academy, Saint Petersburg, Russia
Irina Z. Bondarenko, M.D., Ph.D., doctor of sciences, chief scientist of the department of cardiology, endovascular and vascular surgery, National Medical Research Center of Endocrinology, Moscow, Russia
Viktor Yu. Kalashnikov, M.D., Ph.D., doctor of sciences, professor, corresponding member of the Russian Academy of Sciences, head of the department of cardiology, endovascular and vascular surgery, National Medical Research Center of Endocrinology, Moscow, Russia
Ekaterina N. Dudinskaya, M.D., Ph.D., head of the laboratory of age-related, metabolic and endocrine abnormalities, Gerontological Clinical Research Center, Pirogov Russian National Research Medical University, Moscow, Russia

* Corresponding author. Tel. +79262283309. E-mail: mmamedov@mail.ru

Nadezhda K. Runikhina, M.D., Ph.D., doctor of sciences, professor, deputy head of Gerontological Clinical Research Center, Pirogov Russian National Research Medical University, Moscow, Russia
Yulia V. Kotovskaya, M.D., Ph.D., doctor of sciences, head of the laboratory of cardiovascular aging, Gerontological Clinical Research Center, Pirogov Russian National Research Medical University, Moscow, Russia
Olga N. Tkacheva, M.D., Ph.D., doctor of sciences, professor, head of Gerontological Clinical Research Center, Pirogov Russian National Research Medical University, Moscow, Russia

Summary
In September 2017 the experts of the American Diabetes Association (ADA) published a new document dedicated to diagnostics and treatment of arterial hypertension (AH) in patients with diabetes mellitus (DM). AH is one of the main risk factors in people with DM, and its prevalence depends on many circumstances and reaches 80%. It has been proved that BP control with antihypertensive therapy reduces the frequency of cardiovascular diseases related to atherosclerosis, heart failure, and microvascular complications. Published document consists of several parts that include detection, screening and diagnostics of AH, information about target BP levels, AH treatment with lifestyle change and pharmacological therapy, management of several groups of patients and treatment of resistant hypertension. This article contains the comments of leading Russian experts on key points of the new position statement of ADA.

Key words
Arterial hypertension, diabetes mellitus, guidelines.

Introduction
In September 2017 the experts of the American Diabetes Association (ADA) published a new document dedicated to diagnostics and treatment of arterial hypertension (AH) in patients with diabetes mellitus (DM). The previous version of this document was published in 2003.

The importance of this problem is doubtless. AH is one of the main risk factors in people with DM, its occurrence reaches 80% according to major clinical studies, and it depends on type of diabetes and its duration, age, gender, race/ethnic group, history of glycemic control, and presence of kidney disorders. AH is not only the risk factor of atherosclerosis, but also of heart failure and microvascular lesions. It has been proved that BP control with antihypertensive therapy (AHT) reduces the frequency of above-mentioned complications. Nevertheless, these characteristics can be improved with control of several risk factors. The fact that since 1990 significant improvement of BP control has led to reduction of atherosclerosis complications in patients with DM proves this hypothesis.

Recently published document consists of several sections:

- Definitions, screening, and diagnostics of AH with blood pressure targets;
- AH treatment including lifestyle management and pharmacologic therapy;
- Resistant AH;
- Management of pregnant women with AH and DM;
- AH treatment in older adults;
- AHT in the absence of hypertension;

The comments of leading Russian experts on key points of the new ADA statement are published in this review

Definitions, screening, and diagnostics of AH with blood pressure targets
AH is defined as continuing BP elevation ⩾ 140/90 mm Hg. Diagnostics can be complicated in case of masked hypertension and white-coat hypertension. Masked hypertension is defined as normal BP in hospital or in office (<140/90 mm Hg) and BP elevation at home (⩾135/85 mm Hg). White-coat hypertension is a phenomenon when patient exhibits BP above normal range (⩾ 140/90 mm Hg) in a clinical setting and normal BP at home (<135/85 mm Hg) [2]. Traditionally, BP monitoring at home and 24-h BP monitoring are used for diagnostics of these disorders. Orthostatic BP measurement should be performed for initial evaluation of hypertension and sometimes during follow-ups or if patient manifests the symptoms of orthostatic hypotension, and it should be done regularly if patient is diagnosed with orthostatic hypotension. The new ADA statement reports classic rules of BP measurement.

Automated office BP measurement is an alternative method to measure BP. This method was used in two large clinical studies ACCORD [3] and SPRINT [4]. Generally there is some difference between automated office BP measurement and standard office BP measurement. It means that the results of the trials in which this technique was used cannot be directly applied to standard BP measurement. Another important method of BP control is BP self-control at home. Cuff size is very important, since a small cuff would give BP higher than real ones, and a large cuff would give BP values lower than actual BP.

Orthostatic hypotension is an important problem and it correlates with increased risk of death and heart failure [5]. It is known that orthostatic hypotension can be caused by diabetic autonomic neuropathy and that it can be additionally aggravated with antihypertensive drugs [6]. Orthostatic hypotension is defined as reduction of systolic BP by 20 mm Hg or as reduction of diastolic BP by 10 mm Hg within 3 min in comparison measured at sitting or supine position [7]. It is important to evaluate the symptoms of orthostatic hypotension in order to individualize blood pressure goals, choose the most appropriate antihypertensive agents and minimize adverse effects of AHT. More than that, type of antihypertensive drug or timing (switch to nocturnal dosing) may require correction. In particular, α-blockers and diuretics may need to be stopped. People with orthostatic hypotension can use compression stockings or other approaches [8].

AH treatment including lifestyle management and pharmacologic therapy

Epidemiologic and prospective studies show that BP≥115/75 mm Hg is associated with increased rate of atherosclerotic vascular lesions [9], heart failure, retinopathy, kidney disease, and it indicates prognostic value of BP control in patients with DM [10, 11, 12, 13, 14]. Pharmacological treatment of BP ≥140/90 mm Hg is reasonable. According to the UKPDS study, targeting BP <150/85 mm Hg versus BP < 180/105 mm Hg contributes to reduction of macro- and microvascular complications by 24% [15].

In the majority of cases patients with AH and DM should reach systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg during treatment. Lower systolic and diastolic BP values (<130/80 mm Hg) may be appropriate for selected groups of patients with high risk of cardiovascular diseases.

Is there the need of intensive BP control in patients with AH and DM?

The ACCORD BP study examined the effects of intensive BP control (systolic BP <120 mm Hg) comparing with standard BP control (systolic BP <140 mm Hg) in patients with DM 2 type. Intensive BP control did not result in reduction of combination of total major cardiovascular events (myocardial infarction (MI), stroke, or cardiovascular death, hazard ration (HR) 0,88, 95% confidence interval (CI) 0,73 to 1,06), but the risk of stroke was reduced by 41% (HR 0,59, 95% CI from 0,39 to 0,89). Intensive AHT was associated with serious adverse effects in some cases (in 3,3% versus 1,3%) due to increased frequency of hypotension, electrolyte abnormalities and elevated serum creatinine concentration.

Taking into account these analyses, antihypertensive treatment is beneficial when initial average BP is ⩾ 140/90 mm Hg or if target BP values after AHT are ⩾ 130/80 mm Hg [16, 17-19]. In general, between the studies with lower initial or achieved BP AHT reduced the risk of stroke, retinopathy and albuminuria, but its effects on other complications and heart failure were not obvious. Taken together, these meta-analyses consequently demonstrate that treatment of patients with baseline BP ⩾ 140 mm Hg up to reaching target BP levels < 140 mm Hg is beneficial, whereas more intense goals may have additional but lest trustworthy advantages.

Lately the individualization of target BP levels is widely discussed. It is caused by the fact that advantages and risks related to the intensity of therapy may vary in patients depending on the presence of concomitant diseases (for example the risk of progressing kidney disease), glycemic status, age, etc. At the same time it is necessary to take into account the risks associated with treatment (adverse effects), absolute risk of cardiovascular events and expected lifespan.

Patients with higher risk of cardiovascular events (like the risk of stroke) or albuminuria who can reach intensive BP control easily without severe adverse effects may correspond better to intensive BP control. And patients with condition more common in older adults like functional limitations, polypharmacy, and multimorbidity suit better to less intense BP control.

Notably, there are no convincing data available for definition of target BP levels in DM type 1. Association of BP with macro- and microvascular outcomes in DM type 1 are generally similar with the ones of DM type 2 and general population [20]. Although there are no proved results, young people with DM 1 can achieve intense BP control easier and gain some significant long-term benefit from it.

Lifestyle management in patients with DM

For the first time official ADA statement on AH treatment in DM included lifestyle management that has not been defined well for this category of patients in the corresponding section of ADA DM treatment guidelines 2017 ("ADA Standards")

This document reports that lifestyle change is an important aspect of AH treatment in patients with DM 2 type that reduces BP levels, increases the effectiveness of several hypotensive drugs, improves vascular condition and is normally accompanied with lower number of adverse effects of treatment. Nowadays it is well known that all patients with DM and systolic BP > 120 mm Hg or diastolic BP > 80 mm Hg belong to the group of risk to develop AH and its complications [21, 22], and that lifestyle modification helps to prevent or to slow down AH development and the need of pharmacological therapy. To achieve stable change of patient's behavior, his lifestyle should correspond to his needs, and it is also necessary to discuss this aspect together with DM treatment in general. Consulting of moderate and active lifestyle modification in subgroup of patients with risk factors including DM had positive effect on such intermediate outcomes like BP levels, lipids' concentration, fasting blood glucose concentration, body weight especially within 12-24 month period [23]. One recent meta-analysis proved that lifestyle change help to reduce BP in patients with DM 2 type [24].

Diet is the most important lifestyle restriction in this category of patients. Although by now no well-controlled trials dedicated to following diet during the treatment of elevated BP or AH in patients with DM have been conducted, the DASH study (Dietary Approaches to Stop Hypertension) evaluated the influence of different aspects of healthy diet in patients without DM. It has been demonstrated that hypotensive effect of such diet was comparable with the effect of therapy with one pharmacological agent [25]. This diet consists of calories restriction, restriction of sodium intake (<2300 mg/day), increased consumption of fruits and vegetables (up to 8-10 portions per day) and non-fat milk products (2-3 portions per day), and refusal of excessive alcohol consumption [26]. These recommendations are stricter comparing with the ADA standards that includes the Mediterranean diet [27] and various vegetable diets [28] together with the DASH diet. More than that, these standards highlight the negative influence of alcohol on patients with DM receiving insulin and insulin secretion stimulators due to the risk of hypoglycemia. Similarly, the ADA standards recommend refusing smoking and using tobacco products and electronic cigarettes for all patients with DM including the ones with concomitant AH.

Sodium is one of important dietary microelements which concentration correlated directly with BP level. Restriction of sodium intake in patients with DM has not been studied in controlled clinical trials. At the same time, the results of studies performed in patients with primary hypertension demonstrated that moderate restriction of sodium consumption (from 200 mmol [4600 mg] to 100 mmol [2300 mg]) reduced systolic BP by 5 mm Hg and diastolic BP by 2-3 mm [29]. Decreased sodium consumption was characterized with dose-dependent effect. Patients who received hypotensive pharmacological agents and simultaneously restricted sodium consumption demonstrated improved response to these drugs due to reduction of volume-dependent component of hypertension. Notably, comparing with the Russian clinical guidelines for diagnostics and treatment of AH (2013) and with the European ones (ESH (European Society of Hypertension)/ESC (European Society of Cardiology) 2013) allowable daily consumption of sodium is reduced more than twice (from 5-6 g to < 2,3 g) that reflects stricter diet management in patients with DM. Together with this, the ADA standards warn about possible danger of excessive sodium reduction (<1500 mg/day) since several studies demonstrated possible negative effects of such restriction [30, 31].

Physical activity is another important lifestyle aspect in patients with AH and DM. It has been shown that moderate physical activity (30-45 minutes of fast walking for most of the week) decreased BP [32]. The "Standards..." include more detailed recommendations on physical exercise: duration of moderate or intensive physical activity should be 150 min per week or more and it should be distributed for at least 3 days of the week, and duration of any period without physical activity should be not more than 2 days. More than that, in case of long forced staying in sitting position patient should make breaks every 30 minutes to improve the control of glycaemia. Regular physical exercise may reduce BP and require correction of the dose of AHT [33]. Physical activity should be recommended to all patients including older patients with restricted physical abilities. Type and intensity of physical activity should correspond to patient's preferences and functional condition and also patient's pharmacological therapy should be taken into account. For

example, beta-blockers can reduce the tolerability of maximal physical exercise, and diuretics increase the risk of dehydration.

Regular physical activity has another positive effect: it reduces body weight. It is known that the loss of 1 kg of weight correlated with BP reduction approximately by 1 mm Hg [34]. According to the ADA standards, weight loss may be achieved in case of daily energy intake of 1200-1500 kcal for women and 1500-1800 kcal for men. Many patients with DM and obesity have to reduce body weight more than by 5% in order to achieve positive outcomes of glycemic control, and weight loss of 7% and more is considered optimal. Together with this, some drugs promoting weight loss can increased BP and should be taken with caution. Many obese patients have obstructive sleep apnea, and weight loss reduces significantly apnea symptoms, and this, in its turn, leads to additional BP decrease [35]. All above-mentioned strategies of lifestyle modification may influence positively glycemic control and lipid levels, so they should be advised even to patients with light BP increase.

Particular attention of the ADA guidelines 2017 for treatment of AH in DM is paid to regular analysis of pharmacological agents that patient receives, since drugs with possible hypertensive effect can be present between them, including self-administered drugs and plant-derived agents. For example, one of meta-analyses demonstrated that non-steroid anti-inflammatory drugs increase systolic BP by 5 mm Hg [36].

The section dedicated to the lifestyle modification is concluded with the following recommendation of the ADA for patient with systolic BP > 120 mm Hg or diastolic BP > 80 mm Hg: lifestyle change should include weight loss (for patients with excessive body weight or obesity); following the DASH diet that considers reduced sodium consumption, increased potassium intake, increased intake of fruits and vegetables, restriction of alcohol consumption, and increased physical activity (level of evidence – B).

Pharmacological treatment of AH in patients with DM

Lifestyle modification is an important aspect of AH correction, but the choice of the optimal therapy that would have not only hypotensive but also organ-protective effect is not less important. Analysis of previously performed placebo-controlled trials demonstrated that renin-angiotensin-aldosterone system (RAAS) blockers had advantages for cardiovascular and renal events' prevention in patients with DM comparing with other pharmacological agents, independently on their hypotensive effectiveness. According to the ADA guidelines [37], RAAS blockers with nephroprotective effect have a priority for AH treatment in all patients with DM independently on the presence of abnormal kidney function, but these guidelines are based on placebo-controlled trials that had been finished 15-20 years ago [38]. Early prescription of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor type I blockers (sartans, ARB) is reasonable in patients with DM an high cardiovascular risk [39] and/or congestive heart failure [40]. At the same time, other classes of drugs, especially calcium channel blockers and beta-blockers with proved efficacy for treatment and prevention of cardiovascular diseases are frequently used in DM population.

In 2013 ESH/ESC working group for AH treatment proposed to use all groups of hypotensive drugs in patients with DM, but to prescribe RAAS blockers as the first line medications. Also the attitude to BP levels appropriate for starting AHT has changed: it increased from 130/80 mm Hg to 140/90 mm Hg [41]. This change is based on the results of the ACCORD study that demonstrated no additional advantages of target BP levels 130/80 mm Hg for cardiovascular events' prevention.

In the end, the last statement from the Joint National Committee on prevention, detection, evaluation, and treatment of high BP in patients with DM recommended all hypotensive agents' groups, but if there is microalbuminuria or proteinuria the treatment should be started from RAAS blockers [42].

Meta-analysis of 19 randomized controlled trials that included 25414 patients with DM was performed in 2016 due to the absence of single distinct opinion on AHT prescription in patients with DM and AH [43]. It evaluated RAAS blockers efficacy comparing with other classes of hypotensive drugs. This analysis did not include placebo-controlled trials and did not analyze patients with clinically significant chronic heart failure (CHF), for whom the benefit of ACE inhibitors or ARB has been proved.

The results of this analysis demonstrated that RAAS blockers' efficiency had no significant advantages over other antihypertensive agents (calcium channel blockers, beta-blockers, thiazide diuretics) in DM population in the following aspects: total mortality risk (HR 0,99, 95% CI 0,93-1,05), cardiovascular mortality (HR 1.02, 95% CI 0.83-1,24), stable angina, (HR 0.80, 95% CI 0.58-1,11), myocardial infarction (MI)

(HR 0.87, 95% CI 0.64-1,18), stroke (HR 1.04, 95% CI 0.92-1,17), CHF (HR 0.90, 95% CI 0.76-1,07), and the necessity of myocardial revascularization (HR 0,97, 95% CI 0,77-1,22). There was no significant difference in kidney disease progression (HR 0,99, 95% CI 0,78-1,28). RAAS blockers demonstrated significantly lower risk of CHF development just in comparison with calcium channel blockers (HR 0,78, 95% CI 0,70-0,88).

This analysis did not demonstrate the advantage of RAAS blockers over other antihypertensive agents for prevention of poor cardiovascular outcomes in patients with DM. The only exception was fair for patients with DM and CHF. These results prove the recommendations of ESH/ESC guidelines (2013) and the 8th statement of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP (2014) that demonstrated that any class of antihypertensive drugs may e used in patients with DM especially without impaired renal function.

The last ADA guidelines published in summer 2017 maintain the position of hypotensive therapy "concretization" in patients with DM. They take into account the stage of diabetic nephropathy, degree of BP elevation and cardiovascular risks that may influence the choice and intensity of AHT. RAAS blockers have advantage in patients with diabetic nephropathy (urinary albumin-to-creatinine ratio ⩾ 300 mg/g or from 30 to 299 mg/g to blood creatinine level). The possibility to prescribe other classes of hypotensive drugs in case of necessity is preserved. Particular attention is paid to precise monitoring of creatinine and potassium levels for treatment with RAAS blockers. Recommended target BP level is < 140/90 mm Hg, and there are no strict limitations on available therapy.

In general, the last ADA statement widened the possibility of clinical practitioners to rely on their knowledge, intuition and experience and increased their responsibility for AH treatment in patients with DM.

Influence of glucose-lowering agents on BP levels

Hyperinsulinemia and exogenous insulin administration in theory can lead to BP elevation due to vasoconstriction and sodium and liquid retention [44]. Insulin by itself had direct vasodilating action, and basal insulin treatment comparing with the standard one is not connected with BP change in patients with DM type 2 or pre-diabetes (the ORIGIN study [45]).

Taking into account the fact that hyperinsulinemia and insulin resistance are physiological components of BP regulation, activation of sympathetic vegetative system plays the leading role in realization of their effects [42].

In its turn, renal hypersympaticotony being a particular feature of insulin-induced AH, develops as the consequence of hyperinsulinemic stimulation of central mechanisms of sympathetic nervous system and it results in increased noradrenalin secretion in sympathetic synapses of kidney due to activation of renal tissue rennin-angiotensin system during insulin resistance [46].

Sodium/glucose cotransporter 2 inhibitors (iSGLT2) are associated with moderate diuretic effect and BP reduction (systolic BP by 3-6 mm Hg and diastolic BP by 1-2 mm Hg) [47, 48].

This principally new class of glucose-lowering agents has been introduced into clinical practice relatively recently. iSGLT2 reduce glucose reabsorption in kidney and increase glucose excretion with urine up to 60-80 g/day [49].

iSGLT2 potential is not restricted just to glucose homeostasis and partial elimination of glucose from blood.

Additional advantage of this group is BP reduction (systolic BP by 2-4 mm Hg, and diastolic BP by 1-2 mm Hg). More than that, increased glucose excretion and moderate osmotic diuresis induce several systemic effects including the once modeling cardiovascular factors apart from BP reduction: weight loss because of fat tissue, reduction of albuminuria, ureic acid concentration decrease, reduced risk of hypoglycaemia, improved sensitivity of muscular tissue to insulin [50].

Possible mechanisms underlying iSGLT2 hypotensive effect include osmotic diuresis, increased sodium concentration in renal tubuli in macula densa zone that may be considered as a signal for decreased renin secretion by cells of juxtaglomerular apparatus, and possible non-direct effect of NO released in response to reduced oxidative stress in case of improved glycemic control [51].

Glucagone-like peptide-1 agonists (aGLP-1) are also associated with BP decrease [104]. Therapy with aGLP-1 (in particular liraglutide and exenatide) demonstrated moderate reduction of systolic BP [52]. Meta-analysis of observation of 12469 patients, 41% of whom received liraglutide and the rest received exenatide, demonstrated higher hypotensive effect in the group of aGLP-1 comparing with the control group (by 2,22 mm Hg (95% CI: -2,97; -1,47))independently from initial BP levels or degree of HbA1c reduction [53].

August. 25 of 2017 after the results of the LEADER study the U.S. Food and Drug Administration (FDA) approved new indication for aGLP-1 drug liraglutide: reduction of main undesirable cardiovascular events in adult patients with DM 2 type and concomitant cardiovascular diseases. This decision of FDA was partially based on hypotensive effects of this drug [54].

Management of pregnant patients with AH and DM

AH occurs in 8-10% of pregnant women. During the last years there is an obvious increase of frequency of hypertensive complications during pregnancy due to increased age of pregnant women and high prevalence of obesity and DM. AH during pregnancy can manifest for the first time after 20 week (gestational AH) or before (chronic AH), and in both cases it may be complicated with pre-eclampsia development (AH with proteinuria). AH increases the risks of such undesirable maternal and perinatal outcomes like premature birth, surgical delivery, birth of underweight children, and perinatal mortality.

The majority of guidelines on AH management during pregnancy are based on few empiric observations and they vary a lot. The following recommendations on AH treatment in pregnant women with DM have E level of evidence and represent the consensus opinion of experts.

Nowadays the discussion about efficacy of AH treatment during pregnancy is still ongoing due to possible problems with fetal growth. Control of severe AH is recommended for reduction of maternal morbidity and mortality. In case of moderate AH the benefit of AHT for pregnancy outcomes has not been proved in clinical studies. Treatment of moderate AH is capable to prevent development of severe AH. At the same time AHT may cause impaired fetal growth. AHT did not decrease total risk of pre-eclampsia. It is necessary to take into consideration the fact that stricter BP control with target diastolic BP 85 mm Hg comparing with less strict control of BP 105 mm Hg did not improve pregnancy outcomes and did not decrease the risk of birth of underweight children, but together with it decreased the risk of severe AH.. Additional advantages of AHT are focused on reduction of short-term and long-term maternal morbidity, mortality due to stroke and other vascular and organ lesions.

Thus, the guidelines on AH management in pregnant women with DM are formulated in the following way: at first, AHT is not indicated during chronic AH or moderate gestational AH with systolic BP < 160 mm Hg, diastolic BP < 105 mm Hg, and without the symptoms of target organ lesions; at second, target BP levels for chronic AH and previously performed AH may vary in the range of 120-160/80-105 mm Hg.

The American college of obstetricians and gynecologists does not recommend AHT for moderate gestational AH (systolic BP < 160 mm Hg or diastolic BP < 110 mm Hg), since there are no advantages for pregnancy outcomes and potential risks of therapy are enough high. For pregnant women with high risk of pre-eclampsia low-dose aspirin is recommended starting from 12 weeks of gestation. Aspirin improves the deepness of placenta attachment and circulation in spiral arteries. There are evidences that low-dose aspirin reduces the risk of pre-eclampsia in 10-24% of cases, and in general it improves perinatal outcomes, decreases the frequency of delayed fetal development and premature birth. The signs of serious adverse effects from aspirin therapy like increased perinatal death or increased frequency of intracranial hemorrhage of fetus or post-partum hemorrhage for mother have not been identified. Also Russian guidelines indicate the necessity of low-dose aspirin administration starting from 12 weeks of gestation in women with high risk of pre-eclampsia. DM 1 and 2 type are the high risk factors for pre-eclampsia development.

Target BP levels in the range of 120-160 mm Hg for systolic BP and 80-105 mm Hg for diastolic BP are considered safe both for mother and fetus. It is better to avoid lower BP values since BP lower than 120/80 mm Hg may cause impaired fetal growth. It is advised to consider the possibility to reach target BP levels < 140/90 mm Hg in pregnant women with AH and signs of target organ lesions including cardiovascular and kidney diseases in order to prevent progressing of organ lesions during pregnancy.

Recommendations on choice of antihypertensive drug are restricted by warning against ACE inhibitors, ARB, and spironolactone since these agents have teratogenic effects and are contraindicated during pregnancy. Updated ADA guidelines on AH treatment (2017) named antihypertensive drugs effective and safe during pregnancy: metildopa, labetalol, hydralazine, and extended-release nifedipine. In the Russian Federation the following drugs are recommended for administration during pregnancy: metildopa (the first line), extended-release nifedipine (the second line), and beta-blockers (metoprolol, propranolol, sotalol, bisoprolol). Beta-blockers are not advised for treat-

ment of AH in pregnant women with DM due to unfavorable effects on perinatal outcomes, decreased body weight, and increased risk of intrauterine growth retardation. During post-partum period women with gestational AH and pre-eclampsia should be examined for not less than 7-10 days together with precise BP monitoring within first 72 h after delivery due to high risk of complications development. Even normotensive women have a tendency to BP elevation during post-partum period; BP reaches the maximal values by 5th day after the childbirth, and it is the consequence of physiological increase of liquid volume and its mobilization into vascular system. Patients with AH preserve the same trend. The choice of pharmacological agent during post-partum period is mostly determined by lactation, but normally the same drugs that woman received during pregnancy and after delivery are recommended. Long-term observation of these patients is advised since they have higher risks of cardiovascular complications in long-term period.

AH treatment in older adults (≥65 years)

In this section ADA experts concentrate on several key questions related to AH treatment in older patients with DM.

At first, the importance of patient's functional status, comorbidity, and polypharmacy for the choice of AHT strategy and target BP levels is highlighted. The choice of AHT strategy and target BP levels should be made based on estimation of older patient's condition: in fitter patients, a therapeutic strategy similar to that used in younger individuals should be used, whereas in the patients with loss of autonomy and functional limitations (like the need of help for basic daily routines) higher levels of target BP (140-150 mm Hg) and reduced intensity of AHT in the presence of BP <130 mm Hg and orthostatic hypotension should be considered. In this context the ADA statement goes along with the documents prepared by geriatric communities that highlight impossibility of using the same therapeutic regimens tested in multiple randomized clinical trials on fitter patients for older patients with senile asthenia [55].

At second, this document highlights the role of high arterial stiffness as the cause of high systolic BP (that is the goal of AHT) and difficulties related to its achievement. It's recommended to be careful with possible excessive lowering of diastolic BP below 65-70 mm Hg in patients with high arterial stiffness (pulse BP ≥60 mm Hg) , since reaching this levels may increase the risk of coronary complications.

At third, the statement mentions the high risk of iatrogenic complications including hypoglycemia (use of beta-blockers is restricted by their ability to mask hypoglycemia), orthostatic hypotension (should be monitored for any antihypertensive drug prescribed) and reduction of circulating blood volume (may be worsened with diuretics).

Conclusion

AH is a potent modifiable risk factor of diabetic macro- and microvascular complications' development. Numerous clinical studies demonstrated the efficacy of AH correction using several classes of antihypertensive drugs for prevention of cardiovascular and microvascular complications. Meta-analysis of clinical studies demonstrates the benefit of reaching target BP < 140/90 mm Hg in the majority of patient with DM. Lower values of BP may be useful for several patients with high risk of cardiovascular disorders in case of good tolerability of long therapy, and these goals should be evaluated on a case-by-case basis. Apart from lifestyle change, it is necessary to prescribe several classes of antihypertensive agents in order to achieve target BP. It has been shown that ACE inhibitors, sartans, dihydropyridine calcium channel blockers and thiazide-like diuretics improve clinical outcomes and are preferable for BP control in patients with DM. ACE inhibitors or sartans should be included in therapy of patients with albuminuria. Treatment should be individualized for each separate patient based on the presence of concomitant diseases, their expected benefit for cardiovascular diseases related to atherosclerosis, heart failure, progressing nephro- and retinopathy, and the risk of unfavorable events.

Thus, the position statement of ADA systematized the data of AH diagnostics, target BP levels and treatment approaches including lifestyle modification, use of various groups of drugs both in general population of patients with AH and DM and in selected categories of patients.

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REVIEW ARTICLE

Possibilities of increasing the effectiveness of atrial fibrillation treatment (according to the results of studies presented at the European Society of Cardiology Congress, 2017)

Kanorskii S.G.*
Kuban State Medical University, Krasnodar, Russia

Author
Sergey G. Kanorskii, MD, PhD, doctor of sciences, professor, head of the Department of therapy № 2, Faculty of advanced training and professional retraining of specialists, Kuban State Medical University, Krasnodar, Russia

Summary
The review discusses six clinical trials on the diagnosis and treatment of atrial fibrillation, first presented at the scientific sessions of the Hot Line: Late-Breaking Clinical Trials of the Congress of the European Society of Cardiology in 2017. Positive results of these studies demonstrate the possibility of improving the quality of care for patients with atrial fibrillation during the stages of arrhythmia screening, cardioversion, maintaining sinus rhythm, and educational programs.

Keywords
Atrial fibrillation, cardioversion, sinus rhythm maintenance, anticoagulant therapy, catheter ablation, screening.

Atrial fibrillation (AF) is the most common stable cardiac arrhythmia that is currently diagnosed in millions of Europeans. Patients with AF report palpitations, reduced tolerance to physical exercise and life quality and have increased risk of stroke, chronic heart failure (CHF) and death [1]. Importance of AF problem increases together with the aging of population and it starts to attract more attention of modern cardiology [2]. It is enough to mention that 6 (almost one third part) of studies selected for presentation at Hot Line: Late-Breaking Clinical Trials sessions of the European Society of Cardiology (ESC) Congress 2017 (Barcelona, Spain) were dedicated to diagnostics and treatment of AF. It is important to notice that

* Corresponding author. Tel +79172458474. E-mail: kanorskysg@mail.ru

the results of these studies turned out to be positive and could be successfully applicable for routine clinical practice thus increasing the quality of AF patients' management.

AF is caused by arterial hypertension, CHF, obesity requiring correction in the majority of patients [3-5], but the link between affecting these factors and arrhythmia's clinical course are not enough studied. Available pharmacological and interventional methods of AF treatment often fail to prevent its progression and complicate long-term maintenance of sinus rhythm. Structural remodeling of left atrium underlies the progression of AF from paroxysmal to constant form [6]. These ideas tested in the RACE 3 study helped to prove the hypothesis of improvement of AF treatment by modification of risk factors.

Open prospective study RACE 3 included patients with symptoms of recently persistent AF and/or CHF. Patients with left atrium diameter > 50 mm in parasternal axis were not included in this study. After randomization patients underwent conventional treatment (n=126) or aggressive correction of risk factors (n=119) that consisted of cardiologic rehabilitation (physical activity, restricted sodium consumption or calorie restriction in case of body mass index ≥27 kg/m^2, or reduction of liquid consumption depending on CHF severity, regular follow-ups checking the adherence to treatment), administration of antimineralocorticoids, statins, angiotensin-converting enzyme antagonists and/or blockers of angiotensin type II receptors in maximal tolerated dose (target systolic blood pressure levels < 120 mm Hg). After at least 3 weeks of treatment electric cardioversion was performed, after it the therapy was continued for 12 months. The registration of sinus rhythm for at least 6/7 parts of time during 24-h electrocardiogram (ECG) monitoring within 7 days was considered as the primary endpoint and it was detected in 63% of patients in the group of conventional treatment and in 75% of patients who underwent aggressive correction of risk factors (p=0,021).

The hypothesis of RACE 3 study has been proved in general, meaning that precise correction of lifestyle and cardiovascular risk factors is effective, safe and possible to use, that it helps to maintain sinus rhythm in patients with recent persistent AF and not severe CHF. At the same time the advantages that have been achieved in the group of aggressive intervention have failed to be explained by positive influence of therapy on atrial remodeling, since after 1 year of treatment their dimensions remained unchanged. The authors of this study proposed that heart remodeling appeared before AF manifestation, consequently even aggressive treatment resulted to be too late to influence heart dimensions. Two decades ago we saw significant reduction of left atrium in patients with paroxysmal AF after combination of effective hypotensive therapy (calcium channel blockers, angiotensin-converting enzyme inhibitors) and antiarrhythmic therapy (allapinin, ethacizine, propafenol, amiodarone and their combinations) [7]. It's possible that regression of left atrium remodeling in patients with AF is possible in case of use of antiarrhythmic agents providing stabilization of sinus rhythm.

The advantages that have been achieved by the group of aggressive intervention in the RACE 3 study were quite modest. Possibly, it was caused by refusal of any strong agent influencing AF like antiarrhythmic drugs or catheter ablation.

Optimal treatment of patients with combination of AF and CHF/left ventricular dysfunction remains a topic of discussion because up to date there are no clinical studies that could have demonstrated evident advantages of one therapeutic approach.

Patients with symptomatic paroxysmal or persistent AF with left ventricular ejection fraction (LVEF) ≤35%. All patients had implanted cardioverter defibrillator that allowed constant ECG monitoring. After randomization patients underwent radiofrequency catheter ablation of AF (isolation of pulmonary veins with additional linear ablation according to operator's indications) (n=153) or received conventional therapy (n=184) with consequent follow up for 3-60 months. The median of observation period was 37,8 months, and the frequency of the primary endpoint (death of any cause or admission to hospital due to CHF progression) was significantly lower in the group of ablation (28,5%) comparing with the control group (44,6%, relative risk (RR) 0,62, 95% confidence interval (CI) from 0,43 to 0,87 p=0,007). Mortality of any cause was registered in 13,4% of cases after catheter ablation versus 25% in the group of conventional therapy (RR 0,53, 95% CI 0,32-0,86, p=0,011). The frequency of admission to hospital due to CHF was 20,7% in the group of catheter ablation and 35,9% in the group of conventional therapy (RR 0,56, 95% CI 0,37-0,83; p=0,004). Mortality and frequency of admission to hospital due to cardiovascular causes in patients who underwent ablation was lower by 51% (0=0,008) and by 28% (p=0,05), respectively. Up to this study it has not been proved that ablation or antiarrhythmic agents could reduce mortality and frequency of admission to

hospital in patients with AF. The results of CASTLE AF study explain the feasibility of sinus rhythm maintenance in patients with AF and early stages of CHF. It is also possible that treatment costs may be reduced due to less frequent admission to hospital.

It is necessary to admit that antiarrhythmic drugs are used in the majority of AF cases for maintaining sinus rhythm. But is it possible to improve the prognosis of these patients in this case? 10 years ago we reported the results of our study that involved 223 patients aged up to 65 years with non-valvular persistent AF and CHF, II/III New York Heart Association (NYHA) functional class. These patients received the treatment maintaining sinus rhythm (n=113) or reducing the heart rate with persisting AF (n=110) during 2 years. The first therapeutic strategy resulted in significant reduction of general and cardiovascular mortality and reduced frequency of ischemic stroke. Sinus rhythm control was accompanied with increased tolerability of physical exercise, reduced clinical manifestations of CHF, increased LVEF and improved patients' life quality [8].

Cardioversion is as much important for AF treatment as anticoagulants are important for stroke prevention. Patients who have been prepared for AF cardioversion normally received heparin and/or warfarin for stroke risk reduction. Previous randomized prospective studies of Af cardioversion compared rivaroxaban (X-VeRT) [9] and edoxaban (ENSURE-Af) [10] with heparin/warfarin and demonstrated comparable efficiency and safety of various anticoagulants together with low frequency of complications.

The EMANATE [11] study included 1500 patients with firstly diagnosed non-valvular Af that were supposed to undergo cardioversion. After randomization these patients received apixaban (5 mg twice per day or 2,5 mg twice per day if one of these two conditions was present: age ⩾80 years, body weight ⩽60 kg or plasma creatinine levels ⩾1,5 mg/dL, n==753) or heparin and warfarin (n=747). Researchers could choose to set up the initial dose of apixaban as 10 mg (or 5 mg, respectively) if cardioversion was immediate. Within 30 days (90 days, if cardioversion was not performed) the number of strokes was 0 versus 6 (p=0,0164), the number of major bleeding was 3 versus 6, and of clinically significant ones was 11 versus 13 in the groups of apixaban and standard anticoagulation, respectively. There were no cases of systemic embolism in any of anticoagulant therapy regimens. Thrombi in left atrial appendage were visualized in 61 patients, and all of them received anticoagulants. Follow-up examination was performed after 37±11 days and revealed resolution of thrombi in the groups of apixaban and heparin/warfarin in 52% and 56% of cases, respectively.

As many other similar studies, EMANATE had no enough statistic power to make final conclusions about the advantages of one anticoagulant therapy regimen over another for AF cardioversion. Taking into account predictably low number of complications of modern antithrombotic prevention, selection of the best anticoagulant would have required a randomized study with around 50000 participants that would be almost impossible to perform. Nevertheless, nowadays new oral anticoagulants are considered to be effective, safe, and convenient alternative to vitamin K antagonists for AF cardioversion.

AF is the cause of one out of five ischaemic strokes and these strokes result to be more dangerous comparing with the ones in patients without AF, they lead to severe disability and death in 60% and 20%of cases, respectively [12]. At least 2/3 of all strokes that occur in patients with AF can be prevented with administration of oral anticoagulants [13]. Only one half of patients with AF who are supposed to take anticoagulants receive them for real, and 80% of patients with ischemic stroke had inadequate anticoagulant therapy before its manifestation [14]. Underestimation of the role of oral anticoagulants in AF management is typical for countries with low economical development and it may be connected with insufficient education level of medical staff and patients [15].

The project IMPACT-AF involved 2281 patients with indications for anticoagulant therapy (the risk of stroke according to CHA_2DS_2-VASc score ⩾2, rheumatic valvular lesions) from Argentina, Brazil, China, India and Romania [16]. After randomization the first group of patients (n=1184) participated in educational program (education, receiving information in printed form, webinars, phone calls, adherence control, clinical visits) apart from being prescribed with conventional treatment, whereas the control group (n=1092) underwent just standard treatment procedure. After approximately 12 months the percentage of patients of the first group who took oral anticoagulants increased from 68% to 80%, and in the control group it changed from 64% to 67%. During all observation period 11 and 21 strokes were registered in the group of intervention and in the control group, respectively. Multidirectional educational intervention aiming to improve the use of oral anticoagulants has led to significant increase of patients' compliance that

may improve stroke prevention in patients with AF. Approaches that had been used in this study were simple enough to be used in routine clinical practice at least in countries with moderate level of economical development.

Previous randomized studies reported that catheter isolation of pulmonary veins prevents AF more effectively than antiarrhythmic drugs [17]. But continuous cardiac rhythm monitoring was not used in these studies that did not allow precise estimation of AF duration. Neither one of the studies that evaluated ablation for AF treatment did not use life quality as the primary endpoint, although relieving of symptoms is the main result of AF ablation. Instead of it AF recurrence that lasted 30 seconds was taken as the primary endpoint, and it hardly corresponded to successful therapy. The main objective of the CAPTAF study was comparison of AF treatment using catheter ablation or antiarrhythmic drugs, and life quality of patients was taken as primary endpoint.

The CAPTAF included 155 patients with AF who failed to maintain sinus rhythm with antiarrhythmic drugs treatment and had at least one symptomatic episode of paroxysmal AF that required cardioversion during previous 12 months. All patients had implantable cardiac rhythm monitor. After randomization 79 patients underwent catheter isolation of pulmonary veins or received antiarrhythmic drug therapy according to the current guidelines (n=76). Positive change of general health condition according to the Short Form 36 estimated during the following 12 months (primary endpoint) was significantly higher in the group of ablation: 11,0 points versus 3,1 in the group of pharmacological treatment (p=0,0084). Severity of AF symptoms estimated using the classification of the European Heart Rhythm Association 12 months after was reduced to higher extinct in the group of ablation (from 3,0±0,7 to 1,6±0,8) comparing with the group where patients received antiarrhythmic drugs (from 2,9±0,7 to 2,1±1,1; p=0,0079). At the same time there was no statistically significant difference of reduction of AF burden in studied groups. Lack of statistically significant differences of AF burden reduction between the groups indicates that other mechanisms could explain better the improvement of life quality and symptoms that was reached by pulmonary veins' isolation. The authors of this work hypothesized that improved life quality in the group of ablation could be related to the absence of antiarrhythmic drugs' adverse effects. The researchers supposed that the life quality and not the number of AF episodes longer than 30 s should be the primary endpoint of future studies of therapy for sinus rhythm maintenance.

Asymptomatic AF is associated with higher risk of thromboembolism comparing with AF manifesting with common symptoms due to lower awareness of doctors and patients [18]. AF that appears from time to time (paroxysmal AF) can disappear spontaneously but it is accompanied with increased risk of stroke and requires prescription of antithrombotic therapy identical to the one used for permanent AF [19]. Current ESC guidelines on Af management suggest performing primary screening of this arrhythmia in population of people older than 65 years checking their pulse and registering ECG [1]. Several clinical studies aim to estimate the possibilities of various portable monitors to detect asymptomatic/manifesting with few symptoms AF.

REHEARSE-AF [20] project consisted of AF screening in people without AF, having CHA_2DS_2-VASc score ≥2, and aged ≥65 years that used cardiomonitor AliveCor Kardia (n=501) or conventional management (n=500). Cardiomonitor registered ECG after person touched it with two fingers of right and left hands and transferred it to iPOD supporting WiFi technology. This diagnostic procedure was performed twice per week during 12 months and ECG registration with automatic description, consultation of physiologist or/and cardiologist was supplied in case of symptoms' manifestation. Af detection was considered as the primary endpoint and it was registered in 19 patients in the group that used cardiomonitor and in 5 patients from the group of conventional treatment (RR 3,9 95% CI 1,4-10,4; p=0,007. The number of registered strokes/transitory ischemic attacks/systemic embolism cases was 6 versus 10 in cardiomonitor and control groups, respectively (RR 0,61 95% CI 0,22-1,69, p=0,34). This gadget for easy distant ECG interpretation allows detection of AF in elderly people with increased stroke risk in outpatient conditions more frequently.

Patients demonstrated high compliance to ECG control since more than 2/3 of them made it twice per week at least during 75% of time of the study. Elderly people reported their confidence in cardiomonitor registrations and satisfaction with its presence. According to the researchers, if the use of tested observation program was reasonable from clinical and economical point of view, it would be used in target population.

These studies demonstrate significant progress of arrhythmology in diagnostics and treatment of AF.

After 15 years of refusal of aggressive interventions for sinus rhythm maintenance for reducing heart rate in persisting AF the first strategy starts to demonstrate some optimistic trends. The approaches of AF detection, cardioversion, prevention of AF relapses, educational programs are further developing. Improvement of AF eradication using catheter ablation and, possibly, creating more safe and effective antiarrhythmic agents would allow improving life quality and prognosis of the population of people with AF that is growing fast.

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Safety and efficacy of rivaroxaban plus clopidogrel in atrial fibrillation patients after acute coronary syndrome

Mohamed Abdelshafy Tabl
Benha University, Benha, Egypt.

Author
Mohamed Abdel Shafy Mohammady Tabl, Faculty of Medicine, University of Benha, province of Al-Kahlubiya, Benha, Egypt.

Summary

Background

Proper antithrombotic management of patients with AF and ACS is challenging. The current ESC guidelines in 2014 recommend 'triple therapy' with OAC plus aspirin and clopidogrel for 1 or 6 months titrated to double therapy for 6 or 11 months. The effectiveness and safety of double therapy with rivaroxaban plus clopidogrel for 12 months are uncertain in such scenario.

Methods

Single-center non randomized prospective trial enrolled 100 participants with AF who had UA/NSTEMI treated either medically or underwent PCI. Fifty patients received rivaroxaban 20mg once daily plus clopidogrel (75mg) for 12 months (group:1). Another 50 patients received triple then double therapy of dose-adjusted vitamin K antagonist plus (clopidogrel and aspirin) according to ESC guidelines up to 12 months (group:2). The primary outcome was the combination of minor and major non CABG TIMI bleeding up to 12 months. The secondary outcomes were major adverse cardiovascular events (cardiac mortality, non fatal MI, stent thrombosis or stroke).

Results

Rates of both minor and major bleeding were lower in Group:1 (Rivaroxaban plus clopidogrel) but with no significant differences (OR=0.73 [95% CI=0.73to1.4]; NNT=12.5; P=0.58). RRR of bleeding rates in the rivaroxaban group was (25 to 27%). The composite rates of MACCE showed no significant differences in both groups (36% vs 30%, OR=1.14 [95% CI=0.6to2.0]; P=0.652). In subgroup analysis, patients in group:1 who treated with PCI had lower rates of non fatal MI and definite stent thrombosis in comparison to group:2 (RRR=16%; P=0.63).

* Corresponding author. Tel.: +2001223723050. E-mail: mshafytabl@yahoo.com

Conclusion

Rivaroxaban (20 mg OD) plus clopidogrel (75 mg) for 12 months was safe and effective in participants with AF and UA who treated medically or PCI. We recommend this regimen over standard triple therapy with a dose-adjusted vitamin K antagonist. This regimen provide better adherence and advantage that patients do not need to switch from triple to dual therapy.

Keywords

Atrial fibrillation; Unstable angina; Rivaroxaban.

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia; about 25% of AF patients have coronary artery disease (CAD). Among patients undergoing percutanous coronary intervention (PCI), approximately 5% to 21% of patients have concomitant AF [1]. For decades, oral anticoagulants (OAC) have been effectively used to decrease complications associated with medical conditions such as AF, mechanical heart valves or deep venous thrombosis. Aspirin and P2Y12 inhibitors (DAPT) discovered to be inferior to OAC for preventing stroke. Similarly, OAC are not effective as DAPT after stent implantation [2].

Combination therapy between OAC and DAPT (Triple therapy) seems like an attractive option for preventing both stroke and in-stent thrombosis but must be balanced against a suspected higher bleeding risks [3]. Generally, bleeding events with triple therapy have been found to be 3.7 times higher than that with warfarin alone and 4 times than with aspirin as a monotherapy [4]. The yearly incidence of bleeding with triple anti thrombotic therapy have been found to reach 12% compared to only 3.7% for DAPT [5].

Lack of large randomized control trials in assessing the optimal anti thrombotic regimens for high-risk patients with concurrent AF and unstable angina (UA) has resulted in divergence in medical society recommendations [6]. In clinical practice, physicians' strategies broadly vary according to self experience. The decision is usually influenced by the anticipated bleeding risk of combined pharmacotherapy. For safety purpose, it is very important to decide how many anti-thrombotic agents and at what intensity we should be treating patients [7].

Patients and methods

Study population

This single-center, prospective, non randomized trial performed from March 2016 to May 2017. Inclusion criteria was AF (prior, persistent, or >6 hrs duration); physician decision that OAC is indicated; UA-NSTEMI and/or PCI with planned DAPT. Exclusion criteria was previous ACS, PCI or CABG; absolute contraindications for OAC; patients with prosthetic valves or rheumatic mitral stenosis; discontinue of OAC during follow up or shifted in between vitamin K or non vitamin K oral anticoagulants (NOACs); any cardiac or non cardiac surgery/procedure which required OAC withhold during follow up.

Study protocol

Designed as a safety and non inferiority trial to estimate TIMI non-CABG bleeding risks of rivaroxaban 20mg once daily (OD) plus clopidogrel 75mg compared to a dose-adjusted vitamin K antagonist plus DAPT (triple therapy). Sample size of 100 AF patients none randomly divided after having recent diagnosed attack of UA/NSTEMI into two groups.

Group 1 (50 patients): received rivaroxaban 20 mg OD combined to clopidogrel 75mg for 12 months.

Group 2 (50 patients): received triple therapy for 6 months (warfarin plus DAPT) if treated with PCI with at least one stent followed by double therapy (warfarin plus aspirin 75mg or clopidogrel 75mg) for another 6 months. Patients underwent PCI and were in high risk of bleeding (HAS-BLED score ≥ 3) received triple therapy for only one month followed by 11 months of double therapy. Patients who treated medically during follow up period received double therapy for 12 months [8] (Figure 1).

Methods

For all patients full history, clinical examination, 12 leads electrocardiogram , transthoracic echocardiography, laboratory investigations in form of cardiac troponins, serum creatinine, liver function test, complete CBC, HbA1C, coagulation profile including INR ratio were done to confirm diagnosis of chronic AF, assess both bleeding and stroke risks.

CHA2DS2-VASc risk score was used for stroke risk assessment at baseline, males with score ≥2 and fe-

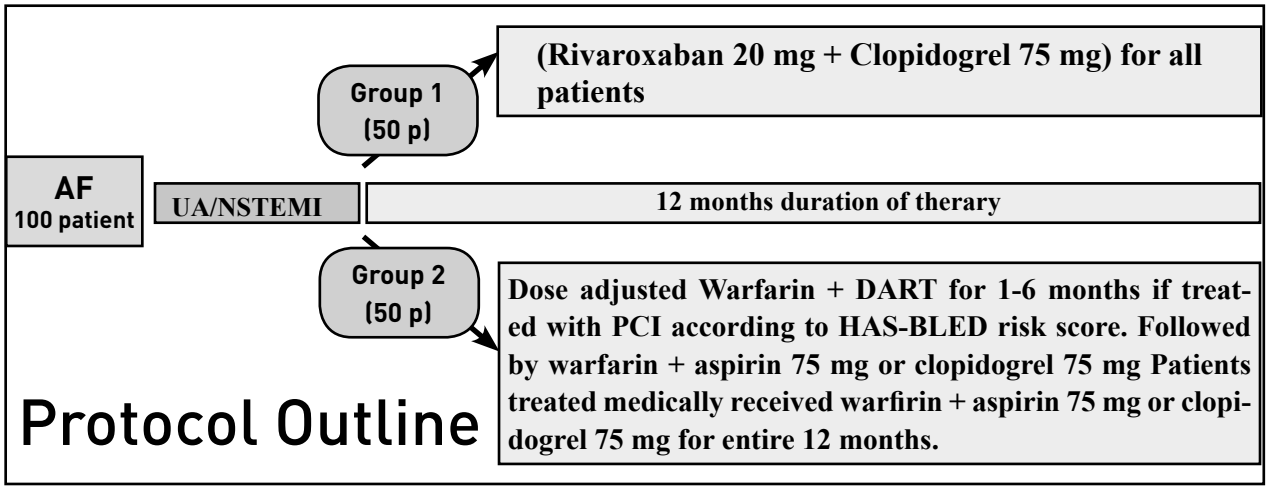

Figure 1. Protocol outline of the study.

males with score ≥3 considered high risk. Males with score ≥1 and females with score ≥2 considered low to moderate risk [9].

HAS-BLED risk score was used for bleeding risk assessment at baseline , patients in both groups had been classified into low risk of bleeding if have score ≤2 and classified into high risk of bleeding if have score ≥3 [10].

Study endpoints and definitions

- The Primary end points were composite of major or minor TIMI non-CABG clinically significant bleeding:

1. Major defined as any intracranial bleeding, any clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit, any fatal bleeding (bleeding that directly results in death within 7 days).

2. Minor defined as any clinically overt bleeding, resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit [11].

- The secondary end points were composite of MACCE (cardiac mortality, non fatal MI, stroke/TIA or definite stent thrombosis according to ARC definition) [12].

Statistical analysis

The association between variables and treatment groups was investigated by chi-square or Fisher exact tests. Parametric unpaired Z score test was applied to evaluate differences for continuous variables between both groups. The association between type of treatment and clinical endpoints was expressed as the odds ratio (OR), and the 95% confidence interval (CI) also was reported. Relative risk reduction (RRR) analysis was applied to detect the valuable reduction of bleeding outcomes between two groups. A p value less than 0.05 were considered significant (2-sided). All analyses were carried out using Stata 12 software (StataCorp LP, College Station, Texas).

Results

Study population

Demographic, clinical, risk stratification, angiographic and coronary intervention variables are presented in (Table 1). There were no significant differences between the two groups regarding age, gender, diabetes mellitus (DM), hypertension, previous bleeding or stroke/TIA. High risk patients for CHA2DS2-VASc score or HAS-BLED score were equivalent in both groups (P= 0.7&0.63) (Table 1).

Table 1. **Baseline demographic, clinical, risk stratifications, angiographic, and coronary intervention characteristics by treatment Group**

	Group 1 (N=50)	Group 2 (N=50)	Z score	P value
Age, median(yrs)	66.3	66.9	0.1	0.8
Male, no. (%)	27 (54%)	27 (54%)	0	1
DM, no. (%)	20 (40%)	21 (42%)	0.1	0.89
HTN, no. (%)	29 (58%)	30 (60%)	0.1	0.91
Previous bleeding	9 (18%)	5 (10%)	0.98	0.32
Previous stroke	14 (28%)	15 (30%)	0.16	0.87
HAS-BLED score ≥3	17 (34%)	14 (28%)	0.47	0.63
CHA2DS2-VASc ≥ 2 (m), ≥3 (f)	31 (62%)	37 (74%)	0.38	0.7
Medically treated patients	18 (36%)	16 (32%)	0.29	0.7
PCI undergoing patients	32 (64%)	34 (68%)	0.19	0.8
Patients received ≥1 new generation DES	24 (48%)	24 (48%)	0	1

TIMI non CABG major or minor bleeding rates

The primary endpoint of composite major and minor TIMI non CABG bleeding occurred in 11 patients (22%) in the rivaroxaban group (Group 1) and 15 (30 %) in the Group 2, with odd ratio (OR) of 0.73 [95% CI=0.73 to 1.4]; NNT=12.5; P=0.58. (Table2 & Figure2) After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ⩾3), Bleeding rates remained lower with rivaroxaban group (OR=0.66; [95% CI=0.56 to 0.76]; NNT=7.6; P=0.28). The relative risk reduction (RRR) of bleeding rates in the rivaroxaban group ranged from (25 to 27%) (Table 2).

Secondary endpoints

The secondary endpoint of composite non fatal MI, definite stent thrombosis, stroke/TIA and CV mortality occurred in 18 patients (36%) in the rivaroxaban group (Group 1) and 15 (30%) in the Group 2, with (OR of 1.14 [95% CI=0.6 to 2.0]; P=0.652) (Table 3). This non significant differences remained among subgroup of AF patients with high risk for stroke at baseline (CHA2DS2-VASc ⩾2 for males and ⩾3 for females) [14/31 (36%) vs 12/37 (30%); OR=1.2; [95% CI= 0.65-2.44]; P=0.28) (Table 4). In subgroup of patients who received stenting after UA/NSTEMI, composite rates of definite stent thrombosis and non fatal MI were lower in rivaroxaban group [6/32 (18.75%) vs 8/34 (23.5%); RRR=16%; p = 0.63] (Table 4).

Discussion

For decades, antithrombotic therapies have been effectively used to decrease complications associated with medical conditions such as AF, mechanical heart valves or deep venous thrombosis. Aspirin and clopidogrel (DAPT) is considered the standard of care to prevent stent thrombosis. For preventing stroke in AF patients with high-risk, DAPT discovered to be inferior to OAC. Similarly, oral anticoagulants are not effective as a monotherapy after stent implantation [2]. So, combined therapy of OAC and DAPT (triple therapy) seems like an attractive option for preventing both stroke and in-stent thrombosis in high-risk

Table 2. **Rates of TIMI non CABG bleeding in study groups and in subgroups with high risk of bleeding at baseline**

Primary end points	Group 1 (N=50)	Group 2 (N=50)	Odd ratio (95% CI)	RRR	NNT	Z score	P value
Composite of bleeding	11 (22%)	15 (30%)	0.73 (0.73–1.4)	-0.26	12.5	-0.911	0.5840
TIMI major bleeding	3 (6%)	4 (8%)	0.75 (0.76–3.18)	-0.25	50	-0.3919	0.696
TIMI minor bleeding	8 (16%)	11 (22%)	0.7 (0.32–1.6)	-0.27	16.6	-0.764	0.447
	HAS-BLED score ≥3 in Group 1 (N=17)	HAS-BLED score ≥3 in Group 2 (N=14)	Odd ratio (95% CI)	RRR	NNT	Z score	P value
Composite of bleeding	6(22%)	9(30%)	0.66 (0.28–1.55)	-0.26	7.66	-1.03	0.35
TIMI major bleeding	1(6%)	3(8%)	0.33 (0.03–2.7)	-0.25	8.2	-1.06	0.29
TIMI minor bleeding	5(16%)	6(22%)	0.75 (0.27–2.1)	-0.27	13.7	-0.36	0.7

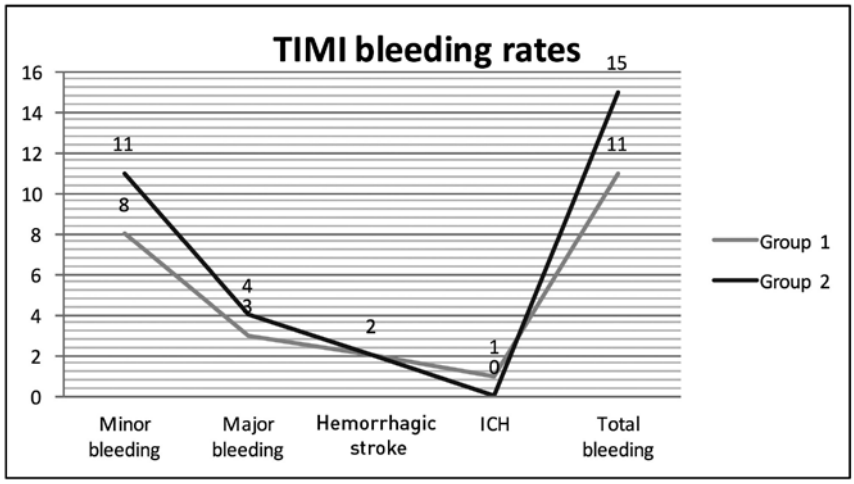

Figure 2. TIMI bleeding rates in both groups

Table 3. **Secondary endpoints in study groups**

Secondary endpoints	Group 1 (N=50)	Group 2 (N=50)	Odd ratio (95% CI)	Z score	P Value
Composite of MACCE	18(36%)	15 (30%)	1.14 (0.62–2.0)	0.45	0.652
CV mortality	4 (8%)	3 (6%)	1.3 (0.3–5.5)	0.361	0.696
Non fatal MI	3 (6%)	2 (4%)	1.43 (0.2–8.4)	0.458	0.65
Stroke/TIA	5 (10%)	5 (10%)	1 (0.9–1.1)	0	1
Definite stent thrombosis	4 (8%)	3(6%)	1.3 (0.3–5.5)	0.39	0.696

Table 4. **MACCE in subgroups of high risk of stroke and composite of coronary events in subgroups treated with PCI in both groups**

	CHA2DS2-VASc score ≥2 for males and≥3 for Females in Group 1 (N=31/50)	CHA2DS2-VASc score ≥2for males and≥3 for females inGroup2 (N=37/50)	OR (95% CI)	Z score	P Value
Composite of MACCE	14/31(36%)	12/37 (30%)	1.2 (0.65–2.44)	1.07	0.28
CV death	4/31 (8%)	3/37 (6%)	1.3 (1.4–1.2)	0.64	0.51
MI	3/31 (9.7%)	2/37 (4%)	1.5 (1.6–1.4)	0.67	0.5
Stroke/TIA	3/31(9.7%)	3/37 (8%)	1 (0.9–1.1)	0.22	0.88
Definite stent Thrombosis	4/31 (8%)	4/37 (10%)	1.3 (1.41.2)	0.26	0.78
	Patients in Group1 PCI treated (N=32/50)	Patients in Group2 PCI treated (N=34/50)	RRR	Z score	P value
Composite of coronary events	6/32 (18.75%)	8/34 (23.5%)	16%	-0.47	0.638
Non fatal MI	2/32 (6.25%)	2/34 (5.8%)	17%	0.062	0.952
Definite stent thrombosis	4/32 (12.5%)	6/34 (17.6%)	16%	-0.526	0.56

patients with concurrent AF and unstable angina but must be balanced against a suspected higher bleeding risks [3]. Generally, bleeding events with triple therapy have been found to be 3.7 times higher than that with warfarin alone and 4 times than with aspirin as a monotherapy [4]. Similarly, adding warfarin to DAPT increases the relative risk for bleeding up to 2.2, and the yearly incidence of bleeding up to 12% compared to 3.7% for DAPT [5].

Lack of large randomized control trials in this area has resulted in divergence in medical society recommendations. ESC guidelines in 2014 recommended that high-risk patients with concurrent AF and unstable angina treated with PCI should receive triple therapy for one month up to 6 months depending on their bleeding risk. Patients treated medically should receive double therapy of warfarin and clopidogrel or aspirin for 12 months [13, 14]. Different scenarios could be noticed in ACC/AHA and other international guidelines! In clinical practice, physicians' strategies broadly vary according to self experience! The decision is usually influenced by the anticipated bleeding risk of combined pharmacotherapy [15].

In Meta analysis of large randomized trials (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF) included 42411 patients, NOACs significantly reduced stroke or systemic embolic events by 19% compared with VKA with lower rates of ICH and hemorrhagic strokes. However, there are few randomized studies in which triple therapy including rivaroxaban with DAPT in patients with ACS [16].

Single P2Y12inhibitor or DAPT in AF patients after ACS and/or PCI

Aiming to reduce bleeding risks in combined anti thrombotic regimens, The Option to omit aspirin from the regimen and treat only with an (N)OACs and a single P2Y12 inhibitor was first studied in WOEST trial, which showed that warfarin plus clopidogrel reduced bleeding risk and improved efficacy versus triple therapy. In the most recent study PIONEER AF PCI, Rivaroxaban with reduced doses 15 mg once-daily plus one P2Y12 inhibitor (clopidogrel) reduced the rates of TIMI minor and major bleeding (16.8%; HR) versus triple therapy included warfarin plus DAPT [17].

In correlation with WOEST & PIONEER AF PCI results , this study showed lower rates of composite major and minor TIMI non CABG bleeding in the group received rivaroxiban 20mg once daily plus clopidogrel (OR=0.73; NNT = 12.5; p value = 0.58). These rates remained lower with rivaroxiban group even in subgroup of patients with high bleeding risk (OR=0.66; NNT= 7.6; p = 0.28) with RRR of bleeding rates ranged from (25 to 27%) (Tables 2).

The reduced versus full dose of NOACs

The efficacy and safety of optimal reduced doses of NOACs in Patients with AF and ACS or PCI was only

powered in few trials [18]. In the PIONEER AF PCI trial, Rivaroxaban with reduced doses included in two arms (15 mg once-daily plus clopidogrel) or (2.5 mg twice-daily plus DAPT). The rates of TIMI minor and major bleeding were lower in first arm (16.8%; HR) and second arm (18.0%; HR) versus 26.7% in the warfarin arm. Risk of MACCE included stroke did not differ between the three arms [17]. Rivaroxaban 2.5 mg BID is approved in Europe for the prevention of atherothrombotic events in adult patients after ACS but it has not been tested for stroke prevention in patients with AF. Rivaroxaban 15 mg OD is approved for stroke prevention in patients with AF [19]. According to stroke risk reduction in AF, our study showed non inferiority of rivaroxiban with standard full dose 20mg OD plus clopidogrel in comparison to triple therapy with dose adjusted VKA (10% in both groups). (Table 3) This non inferiority remained among subgroup of AF patients with high risk for stroke at baseline (CHA2DS2-VASc ≥2 for males and ≥3 for females) [36% versus 30%; OR=1.2; P=0.28] (Table 4).

The novelty of current study

The novelty of current study that rivaroxiban with full dose (20mg) plus clopidogrel was effective in reduction of both stroke and stent thrombosis risks and also was completely safe in reduction of major and minor bleeding in comparison to triple therapy including warfarin with RRR = 25-27%. (Tables 2&3)

The ongoing trials on NOACs versus warfarin in patients with AF and ACS or PCI

The ongoing RE-DUAL PCI phase 3b randomized trial will evaluate dual therapy with dabigatran 150 mg or 110 mg twice daily vs. triple therapy with warfarin in AF patients undergoing PCI with stenting (elective or due to an ACS) [20].

The ongoing AUGUSTUS phase 4 randomized trial will evaluate dual therapy with Apixaban Versus Warfarin in patients with AF and ACS and/or PCI [21].

Study limitation

The statistic analysis of study results could be affected with the relative small sample size.

Conclusion

Rivaroxaban OD plus single P2Y12 inhibitor regimen was associated with improved safety compared with a standard VKA-based triple therapy strategy in patients with AF and UA and/or PCI. Furthermore, the simple dosing regimen of the rivaroxaban 20 mg OD strategy may be associated with better adherence and also provides the practical advantage that patients do not need to switch from triple to dual therapy. Considering both safety and practical use, the single full dose of rivaroxaban 20 mg plus single antiplatelet therapy (clopidogrel) could become the approach of choice once approved.

Conflict of interest: None declared

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The effects of age, gender and concomitant diseases on patients with atherosclerotic lesions of brachiocephalic vessels

Luzina T.V.*, Urvantseva I.A., Efimova L.P., Almazova E.G.

Regional cardiological hospital "Center of diagnostics and cardiovascular surgery", Surgut, Khanty-Mansi autonomous okrug-Ugra, Russia

Authors

Tatyana V. Luzina, M.D., Ph.D. student, Regional cardiological hospital "Center of diagnostics and cardiovascular surgery", Surgut, Russia

Irina A. Urvantseva, M.D., head of the Department of cardiology, School of medicine, Surgut State University, head of the regional cardiological hospital "Center of diagnostics and cardiovascular surgery", Surgut, Russia

Larisa P. Efimova, M.D., Ph.D., associate professor of the Department of cardiology, School of medicine, Surgut State University, Surgut, Russia

Elena G. Almazova, senior lecturer of the Department of informatics and computational technologies, Surgut State University, Surgut, Russia

Summary

Objective

To estimate clinical manifestations and history of patients with atherosclerotic lesions of brachiocephalic vessels, neurological symptoms, and concomitant diseases.

Materials and methods

We registered all cases of atherosclerosis of brachiocephalic arteries in patient with neurological manifestations followed up in the outpatient diagnostic center of the regional hospital. We selected 100 cases of brachiocephalic arteries' atherosclerosis combined with neurological symptoms and comorbid pathologies from the patients undergoing neurological follow-up. Patients were divided into age groups according with the WHO and ILO classifications.

Results

It has been shown that 50% of males and 100% of females in the middle age group have arterial hypertension (AH), in this age group there were no female cases of diabetes mellitus (DM) and all male patients had DM. Only 33%

* Corresponding author. Tel. +79824178409. E-mail: Luzvladimir@yandex.ru

of middle-aged women had thyroid diseases. 62% of men and 31% of women of the advanced middle age group had coronary heart disease (CHD). DM was present in 24% of advanced middle age males and 14% of advanced middle age females. In this age group 41% of women and 8% of men had thyroid diseases. 77% of elderly women and 43% of elderly men had CHD. DM was present in 46% of elderly women and 21% of elderly man, whereas thyroid diseases were found in 23% of women and 7% of men of elderly age. Rheumatic diseases were found in 31% of women and 7% of men. Multifocal atherosclerosis takes the leading position between observed concomitant diseases, and it is followed by AH and CHD at the second and third positions, respectively. CHD is more frequent in men.

Conclusion

Results of this study revealed significant gender differences and different prevalence of thyroid diseases, rheumatic diseases, and purinee metabolism abnormalities. Analysis of comorbid structure in atherosclerosis of brachiocephalic arteries revealed prevalence of concomitant cardiovascular diseases in all age groups.

Key words

Brachiocephalic arteries, atherosclerotic lesions, comorbidity

Introduction

Problems of modern time like aging of population, urbanization, global change of lifestyle and social tension increase the burden of chronic non-infectious diseases [1].

Efficiency of treatment of acute conditions has increased significantly, at the same time there is a noticeable growth of number of patients with chronic diseases in particular combining two and more somatic pathologies. At the same time clinical medicine is developing in the direction of further specialization that creates additional difficulties for treatment of comorbid diseases. Nowadays more attention is paid to teamwork, but members of the same team should understand each other well enough and know general strategies of treatment of patients with comorbid diseases.

The frequency of cardiovascular diseases (CVD) in the structure of general mortality in the Russian Federation reaches 56% and 85% of cases are related to coronary heart disease (CHD) and cerebrovascular diseases [2]. During the last decades CVD mortality has decreased by 23% in Russia, and expected life span is increasing, reaching 64 years in men and 75,6 years in women. It leads to the aging of population and consequently increases the frequency of combined pathology for one single person [3]. The problem of comorbidity of diseases related to atherosclerosis acquires particular importance for modern medicine. According to nowadays concepts, atherosclerosis is a systemic disease, and it can be localized in different vascular areas including the vessels of heart, brain, neck, kidney and peripheral arteries [4]. The CAPRIE study that analyzed the results of more than 19 thousands of patients registered multivascular lesions in more than 26,3% of patients, as much often as the lesions of one single vessel [5]. It is particularly important that atherosclerosis is the cause of one third part of all strokes. Atherosclerosis of aortic arc vessels, particularly common carotid artery bifurcation, is the main cause of ischemic strokes that represent 20% of all strokes [6].

According to results of other studies, comorbidity is based on the presence of the same risk factors for different chronic non-infectious diseases within one patient. Arterial hypertension, impaired lipid metabolism, cardiometabolic disorders, smoking, and chronic stress [7-10].

Improvement of comorbidity diagnostics in atherosclerosis of brachiocephalic arteries (BCA) may help to increase the effectiveness of treatment and prevention, and it makes our study relevant.

The objective of this study is to estimate clinical manifestations and history of patients with atherosclerotic lesions of brachiocephalic vessels, neurological symptoms, and concomitant diseases

Materials and methods

We registered all cases of atherosclerosis of brachiocephalic arteries in patient with neurological manifestations followed up in the outpatient diagnostic center of the regional hospital during the period from January of 2010 to December of 2012. We selected 100 cases of brachiocephalic arteries' atherosclerosis combined with neurological symptoms and comorbid pathologies from the patients undergoing neurological follow-up. Patients were divided into age groups according with the WHO and ILO classifications [11]. The I group included 5 patients aged 36-45 years (2 men, 3 women), the II group included 66 patients aged 46-60 years (37 men, 29 women), the III

group consisted of 27 patients aged 61-74 years (14 men, 13 women).

Inclusion criteria:

1. Age 18-75 years;
2. Presence of BCA atherosclerosis;
3. Presence of somatic comorbidity;
4. Signed informed consent;

Exclusion criteria:

1. Acute decompensation of chronic diseases;
2. Acute vascular manifestations;
3. Absence of signed informed consent;

Apart from obtaining patients' history and performing physical examination, we obtained results of total blood count and biochemical blood test from the patients. Blood for blood tests was taken during fasting period in the morning. After 15 min of exposure 10 ml of each blood sample was centrifuged with 3000 rpm in order to separate serum and perform the assay using biochemical automatic analyzer SysmexXT 4000, Japan. Urea, creatinine, C-reactive protein (CRP), lipid spectrum characteristics were determined (Cobas 501 apparatus). Levels of glycated hemoglobin (HbA1C) were measured using immune-turbidmety end-point technique.

For estimation of BCA atherosclerotic lesions all patients underwent ultrasound examination using ultrasound equipment Logis C6 CE, USA.

Data are present as mean values (M) and standard deviation (SD). Significance of differences was determined using non-parametric Student's t-test in case of normal distribution, and in case of not normal distribution Mann-Whitney test was used. Differences were considered significant if p-value was < 0,05. Significance of differences of qualitative characteristics was evaluated using χ^2 criterion and exact Fisher's test.

Results and discussion

Average age of general group of males and females was 57±7 years. The majority of patients belonged to the age interval from 50 to 64 years. There were no significant differences in gender distribution between groups (Table 1).

100% of patients of the middle aged subgroup had multifocal atherosclerosis, 80% of them had arterial

Table 1. **Characteristic of patients with atherosclerotic lesions of BCA and comorbid diseases**

Age groups (subgroups)	Disease	Total, n=100		Males, n=55		Females, n=45		Significance of differences (m/f), p
		Abs	%	Abs	%	Abs	%	
n=5 middle adult age 36-45 years	Arrhythmias	3	60	1	50	2	67	0,81
	AH	4	80	1	50	3	100	0,54
	CHD	1	20	0	0	1	33	0,41
	Multifocal atherosclerosis	5	100	2	100	3	100	1
	AVD	0	0	0	0	0	0	
	Diabetes mellitus, 2 type	2	40	2	100	0	0	0,083
	Thyroid diseases	1	20	0	0	1	33	0,35
	Rheumatologic diseases	0	0	0	0	0	0	
	Purine metabolism abnormalities	0	0	0	0	0	0	
	Systemic diseases	0	0	0	0	0	0	
n=66 late adult age 46-60 years	Arrhythmias	14	21	6	16	8	28	0,31
	AH	59	89	33	89	26	90	0,99
	CHD	32	48	23	62	9	31	0,07
	Multifocal atherosclerosis	62	94	35	95	27	93	0,95
	AVD	2	3	1	3	1	3	0,86
	Diabetes mellitus, 2 type	13	20	9	24	4	14	0,33
	Thyroid diseases	15	23	3	8	12	41	0,005
	Rheumatologic diseases	10	15	3	8	7	24	0,09
	Purine metabolism abnormalities	3	5	0	0	3	10	0,050
	Systemic diseases	1	2	0	0	1	3	0,25
n=21 elderly age 61-74 years	Arrhythmias	8	30	5	36	3	23	0,54
	AH	26	96	13	93	13	100	0,85
	CHD	16	5	6	43	10	77	0,25
	Multifocal atherosclerosis	25	93	13	93	12	92	0,99
	AVD	2	7	1	7	1	8	0,95
	Diabetes mellitus, 2 type	9	33	3	21	6	46	0,26
	Thyroid diseases	4	15	1	7	3	23	0,28
	Rheumatologic diseases	5	19	1	7	4	31	0,15
	Purine metabolism abnormalities	0	0	0	0	0	0	
	Systemic diseases	0	0	0	0	0	0	

hypertension (AH), and 60% of them had various arrhythmias, diabetes mellitus was found in 40% of cases in this group, and CHD and thyroid diseases were present in 20% of cases, respectively. There were no acquired valvular defects (AVD), systemic diseases or purine metabolism abnormalities in this group.

In the subgroup of late adult age 94% of patients had history of multifocal atherosclerosis, 89% of patients had AH, 48% of them had CHD, thyroid diseases and diabetes mellitus were found in 23% and 21% of cases, respectively.

In the subgroup of elderly age 96% of patients had AH, 93% of patients had multifocal atherosclerosis, diabetes mellitus and arrhythmias were found in 33% and 30% of cases, respectively. Rheumatologic diseases were found in 19% of cases, thyroid diseases were detected in 15% of patients, AVD were found in 7% of patients, CHD was present in 5% of patients, and purine metabolism abnormalities and systemic diseases were not registered. There were no significant differences of age distribution between groups.

50% of patients of the middle adult age group had 50% of men and 100% of women, diabetes mellitus was not found in women of this subgroup, but it was detected in 100% of men. Thyroid diseases were found in 33% of women of this subgroup and were absent in men (Figure 1).

62% of men and 31% of women had history of CHD. Diabetes mellitus was found in 24% of men and 14% of women. Thyroid diseases were found in 41% of women and 8% of men. Rheumatologic diseases were registered in 24% of women and 8% of men (Figure 2).

In the group of elderly age 77% of women and 43% of men had CHD, diabetes mellitus was found in 46% of women and 21% of men, thyroid diseases were observed in 23% of women and 7% of men. Rheumatologic diseases were registered in 31% of women and 7% of men (Figure 3).

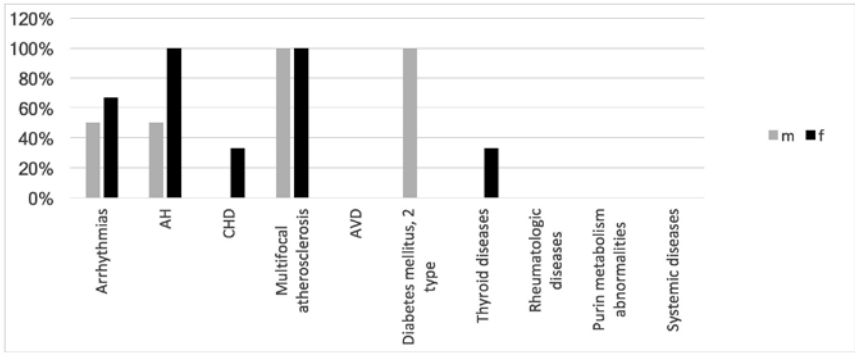

Figure 1. Gender differences in comorbid diseases distribution in group "Middle adult age"

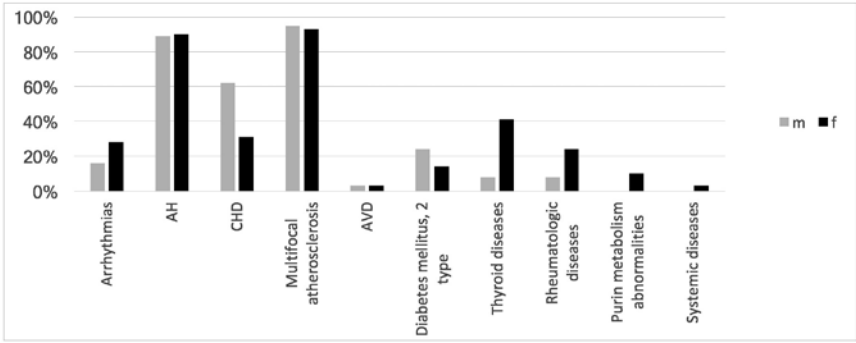

Figure 2. Gender differences in comorbid diseases distribution in group "Late adult age"

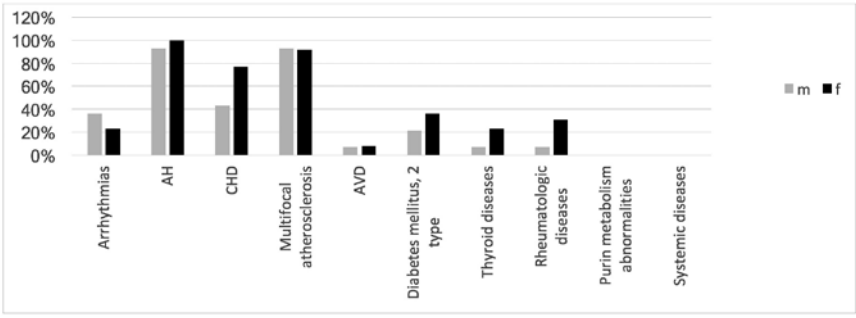

Figure 3. Gender differences in comorbid diseases distribution in group "Elderly age"

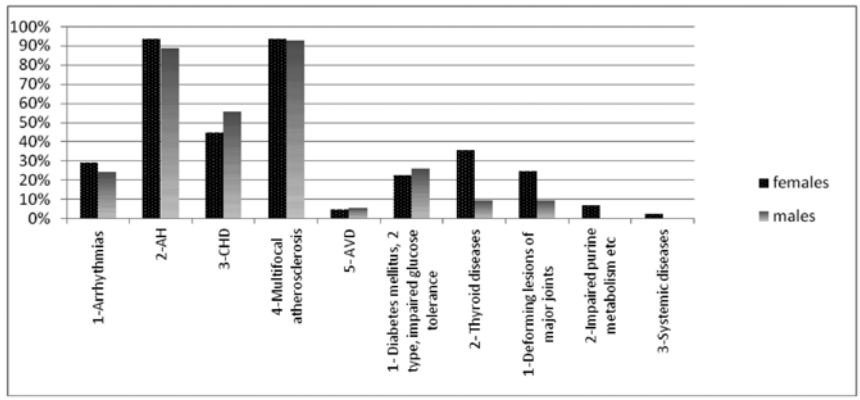

Figure 4. Gender structure of comorbidity in general group

Analysis of the structure of comorbid diseases demonstrated that multifocal atherosclerosis of BCA prevailed between them (Figure 4). AH took the second position. The third most frequent concomitant disease was CHD, and this disease was more frequent in men than in women. The fourth position was taken by thyroid diseases in women and diabetes mellitus in men. The fifth frequent comorbidity was arrhythmia. Deforming lesions of major joints followed it in women, and in men the sixth position was taken by deforming lesions of major joints and thyroid diseases. The seventh position in women was present by diabetes, and the eighth position in women was associated with purine metabolism and other metabolic abnormalities, and in men the eights position was taken by AVD.

According to the results of other studies, the prevalence of comorbidity reaches 21-98%. We identified correlation between the frequency of comorbid pathologies and age. The frequency of comorbidity in young patients (18-44 years) was 69%, and it increased up to 93% in middle-aged patients (45-64 years) and reached 98% in elderly patients (above 65 years) [12]. Studies conducted during the last years demonstrated that elderly and old patients started to prevail between all cases of acute myocardial infarction that aggravates severe clinical condition of these patients. Population study of Yu. Shamurova and colleagues registered polypathies in 68,8% of men and 80,3% of women. The prevalence of comorbid pathology in women is more frequent then in men reaching 82% and 72%, respectively [13]. The STERKH study demonstrated that more than 70% of patients who visited cardiologist had a combination of two CVD and more. Combination of CHD and AH was registered in 35,3% of patients, and combination of CHD, AH and any other CVD was found in 23,3% of patients. The most frequent concomitant diseases for CVD were diabetes mellitus (19,1% of cases) and chronic obstructive pulmonary disease (10,4%) [14].

It is known that the number of patients with several chronic diseases increases together with the growth of lifespan. Elderly age is associated not only with more severe clinical course of acute period of a disease but also with poorer post-hospitalization prognosis [15].

Conclusion

Results of this study revealed significant gender differences between patients with thyroid diseases, rheumatic diseases, and purine metabolism abnormalities. Analysis of comorbid structure in atherosclerosis of brachiocephalic arteries revealed prevalence of concomitant cardiovascular diseases in all studied groups. Multifactorial prevention that aims to correct general causes of vascular comorbidity can reduce the risk of cardiovascular catastrophes in general.

Conflict of interest: None declared

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Undernourishment in patients with connective tissue dysplasia: the role of proinflammatory cytokines and adipokines, and genetic factors

Nechaeva G.I., Nadei E.V., Lyalyukova E.A.*, Tsikunova Yu.S.
Omsk State Medical University, Omsk, Russia

Authors

Galina I. Nechaeva, M.D., Ph.D., doctor of sciences, professor, head of the department of internal medicine and family medicine, Omsk State Medical University, Omsk, Russia
Elena V. Nadei, M.D., assistant professor of the department of internal medicine and family medicine, Omsk State Medical University, Omsk, Russia
Elena A. Lyalyukova, M.D., Ph.D., doctor of sciences, professor of the department of internal medicine and family medicine, Omsk State Medical University, Omsk, Russia
Yuliya S. Tsikunova, M.D., Ph.D. student of the department of internal medicine and family medicine, Omsk State Medical University, Omsk, Russia

Summary

Objective

Evaluate the levels of specific and non-specific mediators of inflammation (interleukins 1 and 6 (IL1 and IL6, respectively), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), adipokines (leptin, soluble leptin receptor, adiponectin, resistin) and the frequency of mutations of soluble leptin receptors (Arg223Gln) in undernourished patients with connective tissue dysplasia

Materials and methods

A cross-section study involved 94 patients (50% males, 50% females). Average age of patients was 30,5±0,8 years. The I group included 34 patients with connective tissue dysplasia and signs of undernourishment, the II group consisted of 30 patients with connective tissue dysplasia and no signs of undernourishment, the control group included 30 patients without connective tissue dysplasia. The groups were similar with respect to age and gender. We estimated the levels of IL1, IL6, TNF-α, CRP, leptin, soluble leptin receptors, adiponectin, resistin, and the frequency of mutations of soluble leptin receptors (Arg223Gln).

* Corresponding author: Tel. +7 950 788 60 92. E-mail: lyalykova@ rambler.ru

Results

Undernourishment was associated with changes of immune status in patients with connective tissue dysplasia. These changes consisted of leucopenia, lymphocytopenia, decreased CRP concentration, higher levels of proinflammatory IL1 and IL6. IL6 changes correlated with the severity of undernourishment in connective tissue dysplasia (moderate negative correlation), the severity of leucopenia correlated with the degree of TNF-α levels decrease (significant direct correlation). We registered the change of adipokines' concentrations that was expressed as low leptin and resistin levels, higher concentration of adiponectin and soluble leptin receptors. In 73,44% of patients these changes were associated with soluble leptin receptor gene polymorphisms: Arg223Gln A/G was present in 50,0% of patients, and Arg223Gln G/G was found in 23,44% of patients.

Conclusion

Change of the levels of adipokines in patients with connective tissue dysplasia may be used not only as diagnostic criteria of severity of undernourishment, but also as factors determining different risks of associated pathologies. Increased IL-6 levels combined with low CRP concentration can be a sign of latent inflammatory process, autoimmune and allergic diseases, and decreased concentration of TNF-α associated with leucopenia can be an evidence of the risk of infectious or oncologic diseases.

Key words

Connective tissue dysplasia, leptin, adiponectin, resistin, c-reactive protein, tumor necrosis factor-α

Introduction

Malnutrition is an important phenomenon for internal medicine due to bad prognosis associated with this syndrome, high risk of chronic diseases development and high letality.

It is known that a part of metabolic disorders are genetically determined and that mutations of receptors of adipokines, hormones produced by adipose tissue, can lead to metabolic abnormalities [1].Although the frequency and the intensity of impaired trophologic status in patients with connective tissue dysplasia (CTD), malnutrition remains poorly studied [2, 3].

The objective of this study was to evaluate the levels of specific and non-specific mediators of inflammation (interleukins 1 and 6 (IL1 and IL6, respectively), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), adipokines (leptin, soluble leptin receptor, adiponectin, resistin) and the frequency of mutations of soluble leptin receptors (Arg223Gln) in undernourished patients with connective tissue dysplasia

Materials and methods

A cross-section study involved 94 patients (50% males, 50% females). Average age of patients was 30,5±0,8 years. The I group included 34 patients with connective tissue dysplasia and signs of undernourishment, the II group consisted of 30 patients with connective tissue dysplasia and no signs of undernourishment, the control group included 30 patients without connective tissue dysplasia. The groups were similar with respect to age and gender. Diagnosis of genetically determined (non-syndromic) CTD was defined according to the National guidelines [4]. Estimation of trophological status was performed according to the Russian guidelines (2012) [5]. Hormone levels were evaluated using enzyme-linked immune sorbent assay (ELISA) and the following kits:l Leptin- ELISA «DBC», Canada; human leptin receptor - ELISA«BioVendor», Czech Republic; resistin- ELISA «Mediagnost», Germany; adiponectin - ELISA «Mediagnost», Germany. Genetic mutations were estimated using polymerase chain reaction and electrophoretic detection of reaction products with amplificator of scientific production company "Liatech". Evaluation of proinflammatory cytokines levels was done using appropriate test-systems for ELISA (ELISA-BEST) and multiwall spectrophotometer iMark (BIORAD). Statistical analysis of the results was performed using Statistica 6.0 software.

Results

Clinical characteristic of patients is present in the Table 1. Patients with CTD and undernourishment had lower body weight, body mass index (BMI), brachial muscles circumference (BMC), triceps skin-fold thickness (TSFT), and number of lymphocytes. These parameters are standard for diagnostics of undernourishment and they are included in the "scale of organism's nutritional status" [5].

Apart from the change of "standard parameters", patients with CTD and undernourishment had statistically significant reduction of leukocyte levels in

Table 1. **Clinical characteristic of patients**

Parameter	I group (n=34)	II group (n=30)	Control group (n=30)	p
	M±m	M±m	M±m	
Height, cm	169,5± 0,96	172,0±0,70	166,5±1,97	>0,05
Body weight, kg	48,5±0,74	65,0±1,04	59,0±2,08	<0,016
BMI, kg/m^2	17,76±0,16	22,5±0,21	22,85±0,28	<0,017
BMC, cm	23,0±0,31	24,0±0,50	24,5±0,35	>0,053
TSFT, cm	7,8±0,06	10,6±0,04	10,65±0,12	<0,012
Total protein, g/L	58,0±0,49	60,5±0,57	65,0±0,47	>0,052
Albumin, g/L	34,0±0,23	33,5±0,49	33,5±0,49	>0,056
Lymphocytes, %	14,0±0,88	27,0± 0,77	25,5±0,69	<0,005
Leukocytes	5,75±0,21	6,75±0,12	6,8±0,10	<0,036

Comment: BMI – body mass index, BSA – body surface area, BMC – brachial muscles circumference, TSFT – triceps skin-fold thickness.

Table 2. **Proinflammatory cytokines' levels in studied groups**

Characteristic	I group (n=34)	II group(n=30)	Control group (n=30)	P
CRP	1,86±1,19	3,52±0,69	4,21±1,92	<0,01
IL -1	8,01±0,83	7,28±0,40	6,79±0,67	<0,02
IL -6	1,59±0,18	1,368±0,15	1,16±0,37	<0,01
TNF- α	11,76±1,41	13,03±1,79	9,71±1,25	<0,01

Comment: C-reactive protein, IL-1 – interleukin 11, IL-6 – interleukin-6, tumor necrosis factor α – TNF-α

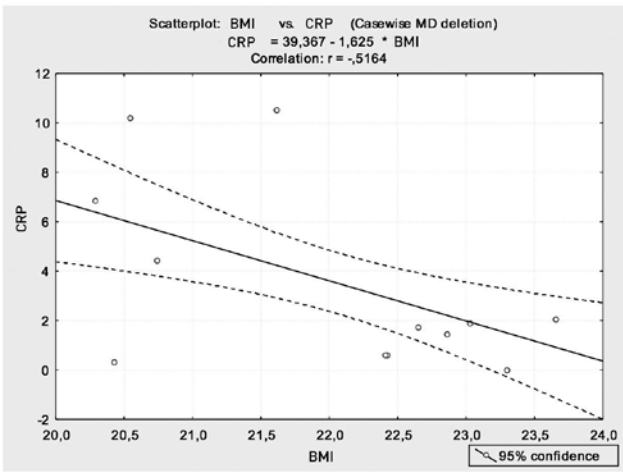
peripheral blood (5,75±0,21 × 10^9/L, comparing with the II group - 6,75±0,12 × 10^9/L and the control group - 6,8±0,11 × 10^9/L, (p=0,036; p= 0,043 respectively).

Complex evaluation of immunological status demonstrated that patients with CTD and undernourishment had higher levels of interleukin-1 (IL-1) and interleukin-6 (IL-6), whereas the concentrations of C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) were lower than in patients of the II group and the control group (Table 2).

Correlation analysis revealed significant reverse correlation of moderate power between BMI dynamics and CRP concentration in patients with CTD and undernourishment (r=-0,35, p=0,438, Figure 1A) or normal body weight (r=-0,52, p=0,0327, Figure 2A), at the same time there were no significant correlations in the control group (Figure 3A). Undernourished patients with CTD demonstrated significant reverse correlation of BMI and IL-6 concentration (r=-0.39, p=0,0041, Figure 1B), and this correlation was not observed in the II group and in the control group (Figures 2B and 3B, respectively).

Patients with CTD and undernourishment demonstrated significant direct correlation between TNF-α levels and leukocyte concentration in peripheral blood (r=0,41 p=0,0381) (Figure 4A), at the same time there was no correlation between this parameter and lymphocyte concentration (one of standard parameters characterizing undernourishment) (Figure 4B).

ELISA essay with the use of allele-specific polymerase chain reaction revealed significant differences in serum concentration of several fat tissue me-



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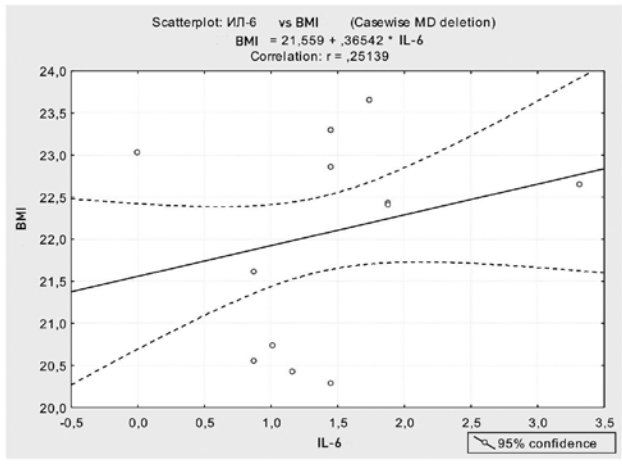
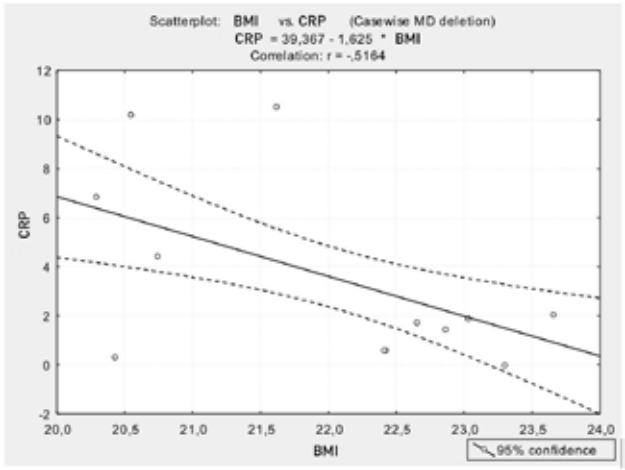


B

Figure 1

A. Correlation between BMI and CRP in patients with CTD and undernourishment

B. Correlation between BMI and IL-6 in patients with CTD and undernourishment



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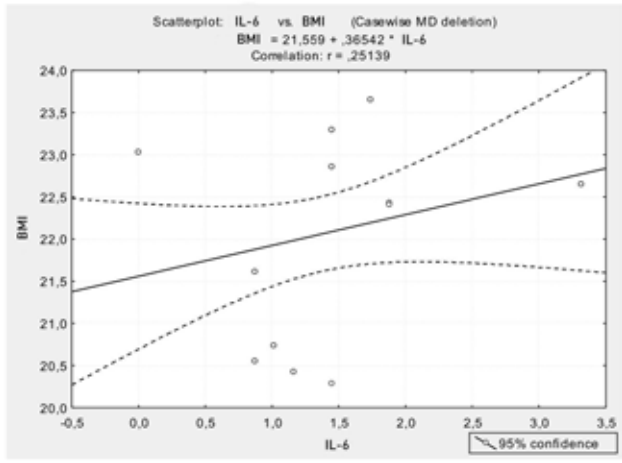
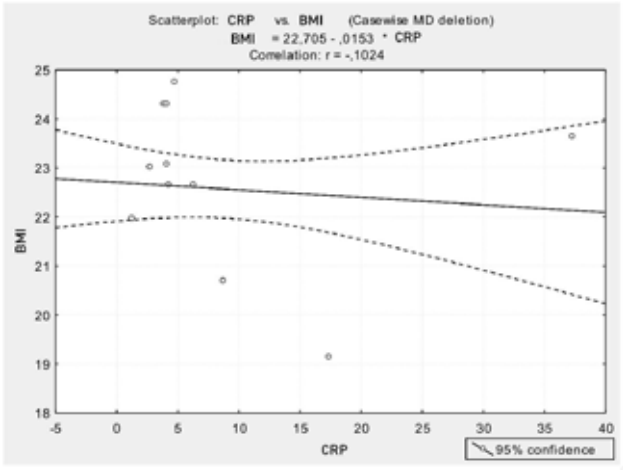


B

Figure 2

A. Correlation between BMI and CRP in patients with CTD and normal body weight

B. Correlation between BMI and CRP in patients with CTD and normal body weight



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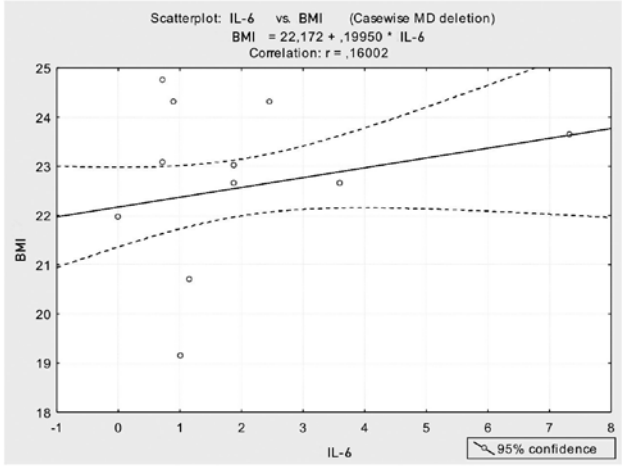
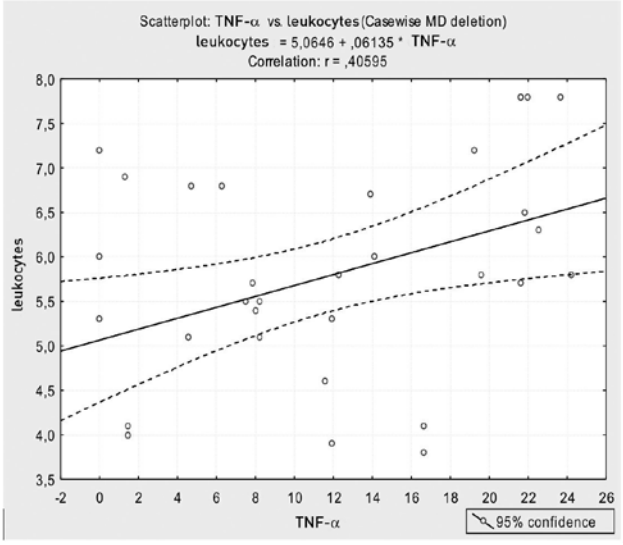


B

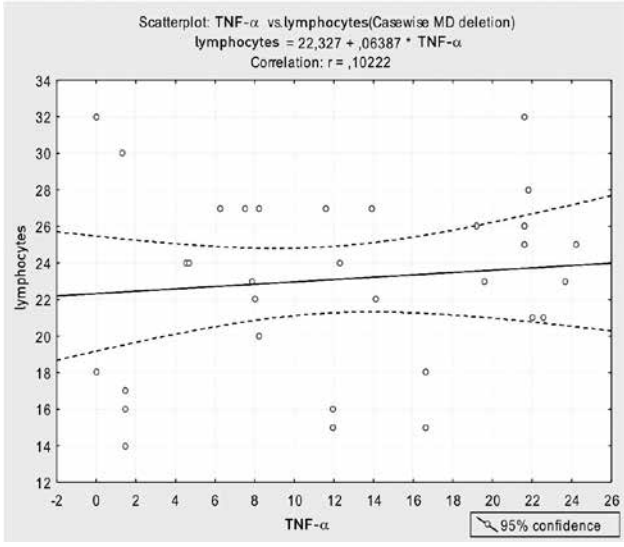
Figure 3

A. Correlation between BMI and CRP in the control group

B. Correlation between BMI and CRP in patients with CTD in the control group



A



B

Figure 4

A. Correlation of leukocyte count and TNF-α in patients with CTD and undernourishment

B. Correlation of lymphocyte count and TNF-α in patients with CTD and undernourishment

Table 3. **Characteristics of adipokines in studied groups**

Characteristics	Patients with CTD and signs of undernourishment	Patients with CTD without signs of undernourishment	Control group	P
Leptin 0,51±0,17		0,88±0,15	2,25±0,20	<0,01
Leptin receptors	7,35±0,45	6,24±0,56	5,91±0,35	<0,02
Resistin	4,58±0,24	7,64±0,60	5,50±0,34	<0,01
Adiponectin	13,38±0,45	9,54±0,46	10,59±0,53	<0,01

Table 4. **The frequency of LEPR mutations in studied groups**

Parameters	I group, n (%)	II group, n (%)	Patients with CTD, n (%)	Control group,n (%)
LEPR mutations (Arg223Gln) A/A	14 (41,18 %)**	3(10,0 %)	17(26,56%)	12(40,0%)
LEPR mutations (Arg223Gln) A/G	12(35,29 %)**	20(66,67 %)	32(%50,0)*	18(60,0%)
LEPR mutations (Arg223Gln) G/G	8(23,5 3%)	7(23,33 %)	15(23,44%)**	0

Comment:
* statistically significant differences comparing with the control group,
** statistically significant differences comparing with the II group.

diators. Adiponectin, soluble leptin receptor (LEPR) levels in patients with CTD and low body weight were significantly higher than in patients with CTD without undernourishment and in the control group, and the concentrations of resistin and leptin were consequently lower in patients with CTD and undernourishment comparing with patients with CTD without signs of undernourishment and the control group (Table 3).

Investigation of the frequency of LEPR (Arg223Gln) mutations in patients of studied groups revealed that 73,44% of abnormalities of leptin metabolism in CTD are genetically determined.

LEPR (Arg223Gln) G/G mutations were found in 23,44% of patients with CTD (p<0,05) and undernourishment, Arg223Gln A/G mutation were present in 50,0% of patients (p<0,05), and they were absent in the groups of comparison and control (Table 4).

Patients with LEPR G/G genotype had body weight 16,5±0,3 kg lower (p<0,0001) comparing with A/G genotype (II group), and their body weight was 10,5±1,3 kg lower comparing with the patients having AA genotype (p<0,0001).

This study demonstrated that the presence of undernourishment in patients with CTD is accompanied with evident immunological changes like leucopenia, lymphocytopenia, lower CRP levels, and high concentration of proinflammatory cytokines (IL-1, IL-6). IL-6 changes in patients with CTD and low body weight correlate with the degree of BMI reduction (negative correlation of moderate power), and the severity of leucopenia correlates with TNF-α concentration (significant direct correlation). These changes have been registered together with imbalanced levels of key mediators regulating energetic homeostasis (leptin, leptin receptors, resistin, adiponectin) and in 73,44% of cases they were associated with polymorphism of soluble leptin receptor gene (Arg223Gln)G/G.

Discussion

It is known that fat tissue is not only the largest energy storage in the organism, but it also possesses para-, auto-, and endocrine activity secreting big number of hormones called adipokines, between which there are leptin, adiponectin, resistin, grelin, insulin-like growth factor-1 etc.

Apart from it, adipocytes, like T-lymphocytes and macrophages, produce many cytokines and trigger the chain of inflammatory processes, and inflammation processes become stable, systemic and highly intensive.

IL-6 is one of proinflammatory cytokines produced by adipocytes that reveals its action not only in fat tissue, but also at systemic level [6]. IL-6 acts as a potent activator of hypothalamic-pituitary-adrenal axis and consequently lead to cachexia. Changes of leptin and IL-6 concentrations correlate with decrease of CD8+ T-lymphocytes count and increase of CD4= lymphocytes number that can participate in pathogenesis of autoimmune diseases.

It is known that TNF-α also reflects the severity of muscle and fat tissue depletion and that it is produced by activated neutrophils and mononuclear phagocytes. Apart from it, TNF-α is the key mediator of antitumoral immunity, and TNF-α reduction can reflect not only activation of antimicrobial immunity, but also indicate a certain degree of oncological risk [7].

Thus, increased levels of proinflammatory cytokines like IL-6 together with low concentration of C-reactive protein may indicate the presence of slowly developing latent inflammatory process or the

risk of autoimmune or allergic diseases, and reduced concentration of TNF-α together with leucopenia may be a sign of infectious diseases or cancer.

Conclusion

The presence of undernourishment in patients with CTD is accompanied with evident abnormalities of key adipokines' levels like reduced concentration of leptin and resistin in peripheral blood, increased concentration of soluble leptin receptors and adiponektin levels.

Apart from it, imbalanced immunological parameters like leucopenia and lymphocytopenia, lowered CRP levels and higher concentrations of proinflammatory cytokines like IL-1 and IL-6 have been registered.

Detected immunological changes in patients with CTD may be used not only as diagnostic criteria of severity of undernourishment, but also as factors determining different risks of associated pathologies. Increased IL-6 levels combined with low CRP concentration can be a sign of latent inflammatory process, autoimmune and allergic diseases, and decreased concentration of TNF-α associated with leucopenia can be an evidence of the risk of infectious or oncologic diseases.

Conflict of interest: None declared.

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EXPERIMENTAL STUDY

Role of vitamin D in the development and correction of stress-induced arterial hypertension in rats

Yankovskaya L.V.[1]*, Semyachkina-Glushkovskaya O.V.[2], Iskra T.D.[2], Sharif-Ali E.Sh.[2], Al Kassab Valid M.M[2], Agranovich I.M.[2], Shorina L.N.[2]

[1] Grodno State Medical University, Grodno, Belarus
[2] Saratov Chernyshevsky State University, Saratov, Russia

Authors

Lyudmila V. Yankovskaya, M.D., PhD, head of the Department of outpatient therapy, Grodno State Medical University, Grodno, Belarus
Oksana V. Semyachkina-Glushkovskaya, Ph.D., doctor of sciences, professor, head of the department of human and animal physiology, biological faculty, Saratov Chernyshevsky State University, Saratov, Russia
Tatiana D. Iskra, Ph.D., associate professor of the department of human and animal physiology, biological faculty, Saratov Chernyshevsky State University, Saratov, Russia
Esmat Sharif Sharif Ali, Ph.D student of the department of human and animal physiology, biological faculty, Saratov Chernyshevsky State University, Saratov, Russia
Al Kassab Valid Makhdi Muslim, graduate student of the department of human and animal physiology, biological faculty, Saratov Chernyshevsky State University, Saratov, Russia
Ilana M. Agranovich, Ph.D student of the department of human and animal physiology, biological faculty, Saratov Chernyshevsky State University, Saratov, Russia
Lidia N. Shorina, Ph.D., associate professor of the department of human and animal physiology, biological faculty, Saratov Chernyshevsky State University, Saratov, Russia

Summary

Objective

To investigate the levels of 25-hydroxyvitamin D (25(OH)D) and effects of additional cholecalciferol intake on endothelial function and blood pressure (BP) in case of chronic stress-induced arterial hypertension (AH) in rats.

* Corresponding author. Tel. +375 29 7890 891. E-mail: yankovliuda@yandex.by

Materials and methods

This study was performed on 136 adult wild type male rats with body weight ranged between 200-250g. Rats were placed in the condition of overpopulation for 4 months that led to development of stress-induced AH in the majority of rats by the end of this period. In order to investigate the role of vitamin D on the mechanisms underlying AH development, rats were administered with cholecalciferol (2500 MU/day) during all the period of overpopulation experiment. We estimated therapeutic effects of cholecalciferol on BP levels and endothelial function that was evaluated using blood levels of nitric oxide and acetylcholine-dependent vasodilatation. As the control we used hypertensive rats who did not consume cholecalciferol and healthy animals.

Results

Development of stress-associated AH was accompanied with suppressed endothelial vascular function that was expressed as reduction of NO concentration in blood and endothelium-dependent vasodilatation after acetylcholine administration. Use of cholecalciferol (2500 MU/day) in hypertensive rats led to reduction of average BP levels, and improved the characteristics of endothelial function and increased NO production.

Conclusion

Long-term administration of cholecalciferol (2500 MU/day) to hypertensive rats leads to normalization of hemodynamic parameters and improves the characteristics of endothelial function. The results of our study demonstrate that cholecalciferol can become an important additional component of antihypertensive therapy, but it requires further detailed studies.

Key words

Arterial hypertension, cholecalciferol, nitric oxide, endothelium-dependent vasodilatation, vitamin D.

Introduction

Numerous studies have demonstrated the link between low concentrations of vitamin D and increased risk of development of arterial hypertension (AH), atherosclerosis, myocardial infarction, metabolic syndrome, diabetes mellitus, several autoimmune and other diseases [1, 2, 3, 4]. Nowadays vitamin D deficiency is considered to be a new risk factor for development of cardiovascular diseases (CVD) that becomes particularly relevant due to their high prevalence of vitamin D hypovitaminosis in the population, up to 60-96% in different age groups [5, 6, 7]. Direct involvement of vitamin D in regulation of vascular homeostasis has been hypothesized because of exploration of the presence of vitamin D receptors (VDR) in the cells of all cardiovascular system (CVS). More than that, many types of cells including vascular smooth muscle myocytes, endothelial cells and cardiomyocytes are capable to produce 1-α hydroxylase enzyme that catalyzes the conversion of 25-hydroxy-vitamin D (25(OH)D) into its more active form 1,25 dihydroxy-vitamin D (1,25(OH)2D), natural ligand of VDR. Thus, the cells of CVS are able to provide vitamin D metabolism and to produce vitamin D active form for their own regulatory mechanisms.

Many studies demonstrated that D (1,25(OH)2D) directly regulates rennin-angiotensin system and endothelial function, inhibits proliferation of vascular smooth muscle cells, reduces the intensity of coagulation [8, 9, 10, 11]. More than that, vitamin D effects can be mediated through its involvement of calcium and phosphate homeostasis, immune/inflammatory response, carbohydrate balance etc. Several animal models of AH development caused by acute vitamin D deficiency have been created [8, 20]. In vitro experiments demonstrated that VDR activation induces NO production in vascular endothelial cells and increases their functional capacity. Apart from it, vitamin D participates in regulation of proliferation, migration and mineralization of vascular smooth muscle cells [1, 7]. At the same time, review articles demonstrate contradictory data on the role of vitamin D in stabilization of hypertensive state [12]. The questions of mechanisms underlying vitamin-D-dependent changes of BP levels and AH development remain open. It's possible that the main explanation of contradictory results of performed studies is that up to now we have no full distinct understanding of mechanisms mediating vitamin D regulation of BP and CVS. Up to nowadays this lack of knowledge prevents us from using vitamin D-containing drugs for CVD prevention and treatment.

The objective of this study was to investigate the levels of 25-hydroxyvitamin D (25(OH)D) and effects of additional cholecalciferol intake on endothelial function and BP in case of chronic stress-induced AH in rats.

Materials and methods

This study was performed on 136 adult wild type male rats with body weight ranged between 200-250 g. Animals were kept in vivarium conditions and received standard meal. All experiments were performed according to the principles of Helsinki agreement on ethical animal experimentation. Hemodynamic parameters (mean blood pressure – mBP, and heart rate (HR)) were registered in awake rats using the equipment for direct BP registration in small animals (PowerLab/400 ML 401, ID Instruments, 2002, Australia) and Chart 4 software with BP sensors (MLT0699, PowerLab, ID Instruments). For this experiment polyethylene catheter was implanted into aorta of rats through the left branch of carotid artery under general nembuthal anesthesia (0,40 mg/kg) [13, 14].

Stress-induced AH in experimental animals has been modeled in the condition of long-term overpopulation [15]. BP and HR measurements were performed according to standard procedure of direct BP registration. Blood of animals was taken in the morning during fasting period. BP levels, 25(OH)D and NO concentrations were evaluated monthly following the development of hypertension in rats.

25(OH)D concentration in blood (ng/mL) was estimated using immunofluorescence analysis and RAT 25OH VITAMIN D TOTAL ELISA kits (Cat. No.: RIS022R).

NO concentration (μg/mL) was evaluated using Griess test and "SF-2000 Bio" spectrophotometer at 583 nm wavelength [16, 17].

Endothelium-dependent vasorelaxation in normotensive and hypertensive rats was investigated under intravenous administration of acetylcholine (0,3 μg/kg, Pharma, Czech Republic) together with estimation of maximal mBP change within the first minute after bolus injection of the drug.

All experimental animals were divided into 4 groups: normotensive rats (NR) who had normal BP, hypertensive rats (HypR) with elevated values of mBP and HR; NR+D3 and HypR+D3 that consisted of normotensive and hypertensive rats who received pharmacological treatment with vitamin D (Colecalciferol, 2500 ME in form of water solution) daily during 4 months. Each group consisted of 8-12 rats.

Statistical analysis of results was done using "Statistica 7.0" software. Data are shown as mean value ± standard error (M±m). Comparative comparison between two groups was assessed using Student's t-test. Pearson's correlation test (r) was used for evaluation of correlation between variables. Characteristic of dynamics (Δ) was quantified as difference between repeated and initial measurements. The null hypothesis was rejected if $p < 0,05$.

Results

Table 1 demonstrates the values of mBP, HR and 25(OH)D concentration in blood of rats after 1, 2, 3 and 4 months of experimental model of stress-induced AH. As it can be seen from the results shown in Table 1, experimental rats started to develop AH after 4 months of chronic stress that was proved by significant increase of mBP and HR comparing with the control group. HypR demonstrated significant decrease of vitamin D concentration by 46% (Δ46±1%; $p<0,05$) (Table 1). NO production has changed by 56% in the same way (Δ56±1%; $p<0,05$) comparing with the control group. So, average NO concentration in blood was 0,17±0,01 μg/mL, that was lower($p=0,04$) than in intact animals who had NO blood concentration in the range of 0,38±0,02 μg/mL (Table 1).

mBP values after acetylcholine administration are present in Figure 1 that demonstrates decrease of mBP by 58±5% in NR after acetylcholine administration and proves intact endothelium-dependent vasodilatation in these animals. There were no statistically significant mBP changes after acetylcholine administration; the dynamics was Δ8±1% that demonstrates the development of endothelial dysfunction during chronic BP elevation (Figure 1).

The results reflecting the influence of pharmacological substitution of vitamin D on studied parameters in the groups NR+D3 and HypR+D3 are pres-

Table 1. **mBP, HR and 25(OH)D values in blood of rats during AH development**

Parameters	Control n=10	Stress-induced AH model			
		1 month n=10	2 months n=10	3 months n=10	4 months n=10
mBP, mm Hg	109±3	115±4	112±5	117±3	149±3*
HR, beats per minute	382±14	397±12	394±11	401±12	444±14*
25(OH)D, ng/mL	19,9±1,1	18,2±0,6	19,0±0,6	18,1±0,5	10,8±0,5ra*
NO, μg/mL	0,38±0,02	0,34±0,01	0,36±0,05	0,29±0,08	0,17±0,01 *

* $p<0,05$ comparing with the control.

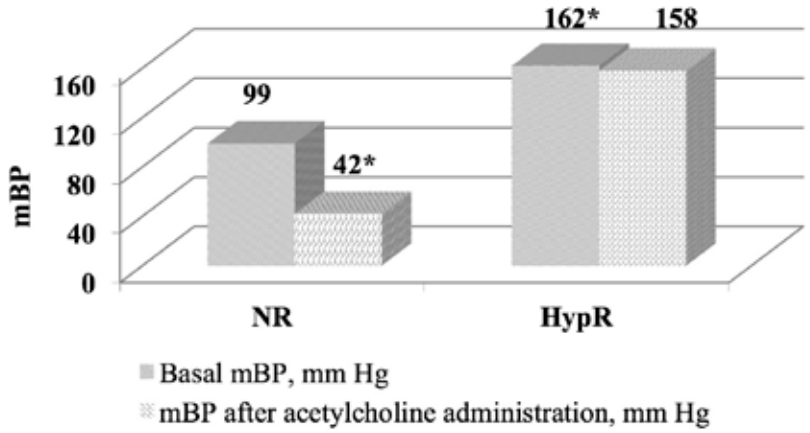

Figure 1. mBP values after acetylcholine administration in NR and HypR groups.
* - p< 0,05 comparing with the control; † - p< 0,05 comparing with basal mBP.

Table 2. **mBP and 25(OH)D and NO blood concentrations in rats receiving cholecalciferol**

Parameters	NR, before drug administration n=10	NR+D3 n=10	HypR before drug administration n=10	HypR+D3 n=8
mBP, mm Hg	109±3	106±3	149±3*	127±3†*
NO, μg/mL	0,38±0,02	0,36±0,03	0,17±0,01*	0,29±0,02†*
25(OH)D, ng/mL	19,9±1,1	20,3±0,7	10,8±0,5*	13,9±0,3†*

* p<0,05 comparing with NR,
† p<0,05 comparing with initial values.

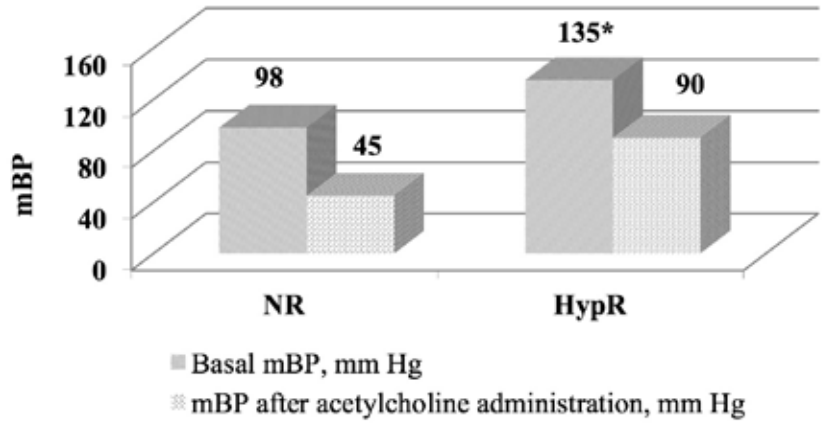

Figure 2. mBP values after acetylcholine administration in NR and HypR groups who received cholecalciferol for 4 months.
* - p< 0,05 comparing with the control; † - p<0,05 comparing with the basal mBP levels.

ent in Table 2, and they demonstrate that long-term (during all period of AH development in rats) daily administration of cholecalciferol 2500 ME had therapeutic effect on mBP, NO and 25(OH)D blood concentrations. Thus, mBP was significantly reduced by 15% in HypR+D3 group (p<0,05), and 25(OH)D and NO blood concentrations were increased by 29% (p<0,05) and 70% (p<0,05), respectively. At the same time, although these parameters have significantly improved, they didn't reach normal values. It is worth to mention that cholecalciferol administration in NR had no effect neither on mBP levels nor on 25(OH)D and NO blood concentrations (Table 2).

Investigation of the effects of long-term administration of cholecalciferol on endothelium-dependent vasodilatation revealed similar results, thus vitamin D pharmacological administration had therapeutic action on hypertensive and not on normotensive rats (Figure 2). As it can be seen on the Figures 1 and 2, vascular sensitivity to acetylcholine did not change in NR, but it significantly improved by 34% (p<0,05) in HypR, and the intensity of this reaction was 4,3 times higher comparing with the group that did not receive cholecalciferol (Figure 2).

Discussion

Results of this study demonstrated that the development of stress-induced AH is accompanied with suppressed endothelial function of vessels that results in reduced NO blood concentrations and impaired endo-

thelium-dependent vasodilatation after acetylcholine administration. These results go along with the existing conception of impairment of endothelial vasodilatation during AH development [17, 18]. Previous clinical and experimental studies demonstrated reduced activity of NO-ergic system and vascular sensitivity to acetylcholine in AH [10, 16, 19, 20-22].

In order to investigate the role of vitamin D in AH development we performed several experiments divided into two stages. During the first step we estimated concentrations and changes of vitamin D levels in blood of adult rats during hypertensive status formation. The results demonstrated that high BP levels corresponding to AH correlate with the development of vitamin D deficiency (Table 1). These data go along with the results of several authors that reported reduction of vitamin D levels in hypertensive animals [1-3, 11, 23-27]. Other AH models like rats spontaneously acquiring AH showed that together with AH development these animals form the deficiency of the main active metabolite of vitamin D production and that it goes along with suppressed endothelium-dependent contraction of aorta due to decreased concentration of free calcium in the cytoplasm of endothelial cells [11].

The second part of experiments aimed to find an answer to the question: Is it possible to substitute pharmacologically vitamin D and to correct its deficiency and associated vascular disorders? To solve this problem, we evaluated such characteristics like mBP, 25(OH)D and NO concentrations in blood of rats during long-term daily administration of cholecalciferol 2500 ME that is supposed to be its most effective dose for additional AH correction according to several studies [1, 2, 3, 20]. Cholecalciferol was additionally administered to rats during 4 months of hypertension formation in these animals. It has been shown that cholecalciferol had no effects on these parameters in NR, whereas HypR demonstrated reduction of mBP and improvement of endothelium-dependent vasorelaxation and increased NO production (Figures 1 and 2).

It goes along with the existent experimental results demonstrating that antihypertensive effects of vitamin D are mediated through improvement of endothelial function (increasing the activity of endothelial NO-synthase, decreasing expression of endothelial adhesion molecules, through anti-inflammatory effects) and suppression of renin-angiotensin-aldosterone system activity, reducing oxidative stress and involvement of several genomic mechanisms. [8, 9, 11, 24, 26, 27].

It is worth to mention that pharmacological replacement of vitamin D deficiency in HypR was not sufficient for efficient AH treatment. Although its therapeutic effects on mBP and characteristics of endothelial vascular function were significant.

Conclusion

Long-term administration of cholecalciferol (2500 MU/day) to hypertensive rats leads to normalization of hemodynamic parameters and improves the characteristics of endothelial function. The results of our study demonstrate that cholecalciferol can become an important additional component of antihypertensive therapy, but it requires further detailed studies.

Conflict of interest: None declared

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Results of the First Scientific and Educational Congress of Cardiology and Internal Medicine «Golden ring»

The First Scientific and Educational Congress of Cardiology and Internal Medicine «Golden ring» was held in Vladimir on October 3–4, 2017. This congress was organized by the National Research Centre for Preventive Medicine, by the Healthcare department of Vladimir region and by Vladimir State University named after A.G.Stoletov and N.G. Stoletov.

This scientific and educational conference was organized on the territory of Vladimir State University. The management of the university took the organization of the conference with great responsibility, and more than 60 staff members and students took part in organization of this conference. All meetings were streamed online on official website of Vladimir State University.

Honored chairmen (M.Yu.Kolkov, R.G. Oganov) and co-chairmen (A.M. Saralidze, A.V. Kiryukhin) welcomed participants during the opening ceremony. The rector of Vladimir State University thanked conference organizers and highlighted the contribution of the director of the National Research Centre for Preventive Medicine O.M. Drapkina, the chairman of regional department of the Russian Society of Cardiology in Vladimir Region E.V.Kulibayev, and deputy chairman of the conference, professor M.N.Mamedov.

According to the tradition, several healthcare professionals received certificates for their contribution into development of internal medicine service from R.G. Oganov.

288 medical doctors, scientists and delegates from 12 cities of Vladimir and other regions and Moscow participated in the conference. The Healthcare department of Vladimir region issued an order providing participation of medical doctors in the conference.

Two-day scientific program included 13 scientific symposiums, clinical lectures, round table lectures, master classes and clinical practitioners' classes. The topics of the conference included the wide spectrum of problems starting from prevention of chronic non-infectious diseases and somatic comorbidity to surgical treatment of cardiovascular diseases and cardiorehabilitation. It is worth to mention that several joint symposiums were organized during the conference, and they involved National Research Centre for Preventive Medicine, Tyumen Cardiologic Center, and Vladimir State University. Physiologists, biophysicists, and medical devices' developers participated in scientific educational conference for the first time.

10 leading scientists and professors from the National Research Centre for Preventive Medicine participated in the conference, including the director, corresponding member of the Russian Academy of Sciences O.M. Drapkina.

The Coordination Council of the Ministry of healthcare of the Russian Federation gave the certificates of continuous postgraduate education of 12 credit hours that for the first time increased the significance of

a regional scientific event up to the size of national meetings and congresses.

Federal («Russia 1/Vladimir» channel) and regional media (regional TV channels, newspapers) provided informational support of the conference, and reports and additional information was published on the websites of the Healthcare department of Vladimir region and Vladimir State University.

During the closing ceremony conference's chairmen pointed out high organization level and high applicable value of the scientific program. The conference was appreciated and it received positive opinions of medical professionals and other participants.

Taking into account the importance of this scientific event, the organization committee decided to hold it each year.

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Journal of the Cardioprogress Foundation

Guidelines for authors

International Heart and Vascular Disease Journal
Requirements for Submission and Publication

(version 2017)

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

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

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

This is an open access journal, which means that all content is freely available without charge to the user or his/her institution. Users are allowed to read, download, copy, distribute, print, search, or link to the full texts of the articles in this journal without asking prior permission from the publisher or the author. This is in accordance with the *Budapest Open Access Initiative* (BOAI) definition of open access.

1. Submission requirements and publishing policy

1.1. A manuscript should be submitted to the following e-mail address: submissions@inbox.ru

Editorial Office tel.: +7(965) 236-16-00

1.2. A manuscript is accepted for further consideration only if the manuscript, or any substantively similar version, has not been submitted to and published in any other journal, or disseminated via any other media, such as the Internet.

1.3. The Author, submitting the manuscript to the Editor, assigns the Editor to publish it. The Editors have the right to incorporate within the manuscript any illustrated or text material, including advertisements. The Editors may allow third parties to put such content into the manuscript.

1.4. Submission of the manuscript to the Editors implies that the Author agrees to transfer the exclusive property rights for the manuscript and other objects of the copyright, like photos, drawings, graphics, tables, etc., to the Editors. The Editors obtain the right to reproduce (partly or fully) all the content submitted, including objects of the copyright, in press and on the Internet; to distribute; to translate the manuscript and other provided content into any language; to export and import copies of the issue where the article of the Author was published; and to revise the manuscript.

1.5. The Author transfers the rights specified in clauses 1.3 and 1.4 to the Editors without any time limitations or territory restrictions, including the territories of the Russian Federation.

1.6. The Editors have the right to transfer the rights received from the author to a third party or to prohibit any use of materials published in the journal by a third party.

1.7. The Author guarantees that he or she holds the copyright to all materials submitted to the **International Heart and Vascular Disease Journal**. In case of violation of this guarantee by the Author and consequent claims to the Editors, the Author is obliged to settle all the claims at his/her own expense. The Editors are not responsible for copyright violation by the Author.

1.8. The Author retains the right to use the published material or its parts for personal use, includ-

ing scientific and educational purposes. The Author retains the right to publish extracts from the published material or its parts in other journals, on the condition that reference is made to the original publication in the **International Heart and Vascular Disease Journal**.

1.9. The copyright is considered transferred to the Editors once confirmation has been sent to the author confirming the manuscript has been accepted for publication.

1.10. Reprinting of an article published in the **International Heart and Vascular Disease Journal** by third parties is only permitted with written permission from the Editors. If permission is granted, reference to the issue of the **International Heart and Vascular Disease Journal** in which the article was published and to the year of publication is obligatory.

1.11. The Editors are obliged to provide the Author with one copy of the issue in which the article is published. The Author(s) should provide his/her full postal address(es) including post code(s) at the end of the manuscript.

1.12. Manuscripts may be reviewed by independent experts. Manuscripts which are reviewed will be reviewed on a double blind basis: Authors will not know the identity of reviewers and reviewers will not know the identity of Authors. The name of the institution where an Author works or conducts research also remains confidential. The reviewer(s) comments and opinions will be sent to the Author and the Author invited to make any changes and/or corrections. In the case of an Author not returning changes and/or corrections to the Editors by an agreed date, the Editors have the right to make their own changes and/or corrections, or permit changes and/or corrections suggested by the reviewers, or to refuse to publish the manuscript. Editing, shortening and correction of the manuscript, and changes to a graph, picture or table design are made in order they comply the format and standards of the **International Heart and Vascular Disease Journal**.

1.13. The Editors are not responsible for the accuracy of information presented in the manuscripts.

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

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

2. General recommendations for submission of original scientific works

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

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

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

2.4. If the manuscript contains pictures, tables, graphics, or photocopies that have been published previously, reference to the author(s) and publication is necessary. It is the Author's responsibility for determining whether permission is required for the duplication of material, and for obtaining relevant permission.

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

3. Publication of uncontrolled trials results

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

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

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of «good clinical practice". Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The

«Material and methods» section must contain details of the process of obtaining participants informed consent, and notification that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

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

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

5. Authorship

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

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

6. Conflict of interests/financing

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

7. Manuscript content

7.1. Title page

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

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

7.1.3. Information about the authors, including full names (last name, first name, patronymic name, if applicable; scientific degrees and titles, positions at main and secondary jobs, including corporate posts).

7.1.4. Full name, full postal address, e-mail address, and telephone number of the "Corresponding author" who will be responsible for any contact with the Editors.

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

7.1.6. It is desirable to provide information about grants, contracts and other forms of financial support, and a statement about any conflict of interests.

7.2. Summary

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

7.2.2. Original studies summary should contain the following sections: Aim, Material and methods, Results, and Conclusion. The summary of a review should provide the main themes only. A manuscript must contain all data presented in the summary.

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

7.3. List of abbreviations and their definitions

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

7.4. Text

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

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

7.4.3. Please, use international names of drugs in the title. Exceptions are possible when use of trade names is well-founded (for example, in studies of bio- or therapeutic equivalence of drugs). It is possible to use a trade name in the text, but not more than once per standard page (1800 symbols including spaces).

7.4.4. You must provide titles and subtitles in the sections: Methods, Results and Discussion. Each reference, image or table should be numbered and specified in order of appearance in the text.

7.4.5. All units of measurement should be provided according to the International System of Units (SI) system. No abbreviations, except standard abbreviations of chemical and mathematical terms, are acceptable.

7.4.6. Each image, chart, table, photo, and reference must be indicated in order of appearance in the text.

7.4.7. References in the text must be numbered in Arabic figures, and provided in square brackets.

7.5. Statistics

7.5.1. All submitted materials may be revised to ensure relevance and accuracy of statistical methods and statistical interpretation of results. The Methods section should contain a subsection with detailed description of statistical methods, including those used for generalization of data; and of methods used for testing hypotheses (if those are available). Significance value for testing hypotheses must be provided. Please indicate which statistical software was used to process results and its version if you use more complex statistical methods (besides a t-test, a chi-square, simple linear regression, etc.).

7.6. Acknowledgements

7.6.1. The Acknowledgements section or Appendix should not exceed 100 words.

7.7. References

7.7.1. Please use separate sheets and double spacing for the list of references. Give each source a consecutive number starting on a new line. The list of references should be structured in order of citation. Use Index Medicus to search for abbreviations of the names of journals.

7.7.2. All documents referred to in the text, should be included in the list of references.

7.7.3. The list of references should not include any dissertations, theses published more than two years ago, or information that is impossible to check (local conference materials, etc.). If material is taken from a thesis, please, mention that in brackets — (thesis).

7.7.4. It is desirable to refer to periodicals with a high impact factor, if possible.

7.7.5. In order to increase the citing of authors, transliteration of sources in Russian are made in the International Heart and Vascular Disease Journal using official coding. Names of authors and journals are transliterated by means of coding, and semantic transliteration (translation) is used for the titles of articles. If a source has an original transliteration, the latter is used. The Editors will be grateful if authors provide the transliterated

variant of the list of references. You can use online services: http://translit.ru for making transliteration.

7.7.6. Authors are responsible for the accuracy of information provided in the list of references.

7.7.7. The list of references should conform to the format recommended by the American National Information Standards Organization (NISO), accepted by the National Library of Medicine (NLM) for its databases (Library's MEDLINE/Pub Med database) and updated in 2009. Authors should use the official site of the NLM: http://www.nlm.nih.gov/citingmedicine to find recommended formats for the various types of references. Examples of references provided in accordance with the NLM recommendations are given below:

Periodicals

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

Sources in Russian with transliteration:

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

Please provide initials after the last names of authors. Last names of foreign authors are given in the original transcription. Names of periodicals can be abbreviated. Usually such abbreviations are accepted by the Editors of those periodicals. These can be found on the Publisher's site or in the list of abbreviations of Index Medicus.

Punctuation in the list of references should be considered. A comma should not be put between the name of the journal and the year of its release. After the year of release a semicolon is put without a space, then a colon follows the volume number, and finally page numbers are given. There are no indications like "volume", "№", «pages». Russian periodicals often have no indication of volume or numbering of pages within a year. In this case the number of an issue should be specified in brackets.

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

Chapters in a book

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

Sources in Russian with transliteration:

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

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

Books

Sources in Russian with transliteration:

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

Websites

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

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

7.8. Diagrams, charts, and drawings

7.8.1. Diagrams, charts, and drawings should be submitted electronically in the following formats: «MS Excel», «Adobe Illustrator», «Corel Draw» or «MS PowerPoint». Diagrams, charts, and drawings must be allocated on separate pages, numbered in order of citation, and have names and notes if necessary. They must not repeat the content of tables. Please indicate the names and units of measurement for graph axes. Provide the legend for each graph (denote lines and filling). If

you compare diagrams, provide significance of differences. Do not use 3-D models for histograms. If appropriate, please identify places in the text where you wish graphics, drawings and graphs to be inserted.

7.8.2. Photographs must be submitted electronically with a minimum resolution of 300 dots per inch (dpi). Microphotos must be cropped so that only main content is left. Arrows should be used to show main features. All symbols, arrows and legends on gray-scale illustrations should be in contrast with the background.

7.8.3. Size of legends on images and photos should be big enough to be legible after compression for publication. The optimal size is 12 points.

7.8.4. All abbreviations should be defined either after the first citation in a legend, or in alphabetic order at the end of each legend. All symbols (arrows, circles, etc.) must be explained.

7.8.5. If data was published earlier, it is desirable to provide written permission from the publisher for the use of this data.

7.9. Tables

7.9.1. Tables should be typed with double spacing, have numbers in order of citation in the text, and names. Tables should be compact and demonstrative. Names of columns and rows must reflect the content. Data presented in tables should not be repeated in the text or images. Please clearly specify units of measurement of variables and form of data presentation (M±m; M±SD; Me; Mo; percentiles etc.). All figures, sums and percentages must be thoroughly checked and correspond to those in the text. Explanatory footnotes should be provided below the table if necessary.

7.9.2. Abbreviations should be listed in a footnote under the table in alphabetic order. Symbols of footnotes should be given in the following order: *, †, ‡, §, | |, ¶, #, **, † † etc.

7.9.3. If a table(s) was published earlier, it is desirable to provide written permission from the publisher for use of this table(s).

8. Rules for the Review of Manuscripts

8.1. Reviewing of articles is carried out by members of the editorial board as well as invited reviewers - leading experts in the relevant field of medicine in Russia and other countries. The decision on the choice of a reviewer for the examination of the article is made by the editor-in-chief, deputy editor-in-chief, scientific editor, editorial director. The review period is 4 weeks, but at the request of the reviewer it can be extended.

8.2. Each reviewer has the right to refuse to review if there is a clear conflict of interest, reflecting on the perception and interpretation of the manuscript materials. Based on the results of the review of the manuscript, the reviewer gives recommendations on the future of the article (each decision of the reviewer is justified):

- The article is recommended for publication in this form;
- The article is recommended for publication after correcting the deficiencies noted by the reviewer;
- The article needs additional review by another specialist;
- The article can not be published in the journal.

8.3. If the review contains recommendations for correcting and finalizing the article, the editorial board of the journal sends the author a text of the review with a proposal to take them into account when preparing a new version of the article, or to argue them (partially or completely) with arguments. The finalization of the article should not take more than 2 months from the moment of sending an electronic message to the authors about the need to make changes. The article refined by the author is sent again for review.

8.4. In the event of the authors' refusal to modify the materials, they must, in writing or verbally, notify the editorial office of their refusal to publish the article. If the authors do not return the revised version after 3 months from the date of sending the review, even if there is no information from the authors refusing to modify the article, the editorial board removes it from the register. In such situations, the authors are notified of the removal of the manuscript from the registration in connection with the expiration of the time allotted for revision.

8.5. If the author and reviewers have unresolved contradictions regarding the manuscript, the editorial board is entitled to send the manuscript for additional review. In conflict situations, the decision is made by the editor-in-chief at a meeting of the editorial board.

8.6. The decision to refuse publication of the manuscript is taken at a meeting of the editorial board in accordance with the recommendations of reviewers. An article not recommended by a decision of the editorial board for publication is not accepted for reconsideration. The notice of refusal of publication is sent to the author by e-mail.

8.7. After the editorial board accepts the decision to admit the article for publication, the editorial office informs the author about it and specifies the terms of publication.

8.8. The presence of a positive review is not a sufficient basis for the publication of the article. The final decision on publication is made by the editorial board. In conflict situations, the decision is made by the editor-in-chief.

8.9. The original of the reviews is kept in the editorial office of the journal for 3 years.

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Tel: 007 965 236 1600

Email: inf.cardio@gmail.com

Moscow, Russia