Volume 6, Number 17, March 2018
ISSN: 2309-0901
http://cardioprogress.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Cardiotoxicity of cancer therapy

Use of rosuvastatin in patients with chronic obstructive pulmonary disease

New classification of arterial hypertension according to the ACC/AHA clinical guidelines-2017: opinions of Russian experts

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The publication of articles within the journal is free of charge for authors. Guidelines for authors on submitting manuscripts are available at: www.cardioprogress.ru

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

Printed in Russia

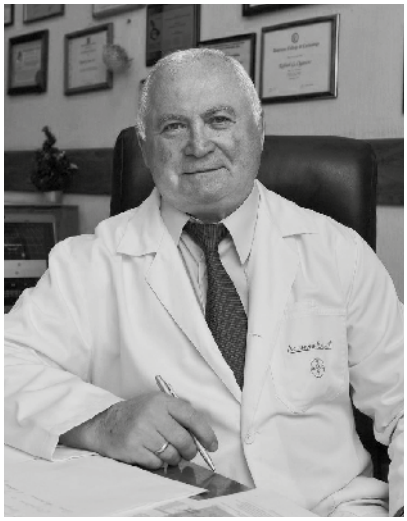
Complete versions of all issues are published: www.elibrary.ru, www.cyberleninka.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Volume 6, Number 17, March 2018

Contents



Editor's Welcome

Dear colleagues!

In the 17th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and experimental articles, experts' opinion and the report on the III Interregional Scientific and Educational Congress of Cardiology and Internal Medicine.

The leading article section includes the work made in collaboration between cardiologists and oncologist. This review article includes epidemiological data on prevalence of cardiologic complications in oncologic diseases and existent comorbidity. Cardiotoxic effects of chemotherapy are observed with great precision. The authors concluded that well-timed detection, monitoring, and treatment of complications that develop during and after cancer therapy are strictly necessary.

Three articles are published in the «Original articles» section. The first article written by the group of clinical practitioners from Moscow is dedicated to investigation of circadian variability of blood pressure in untreated middle-aged patients with grade 1–2 arterial hypertension (AH). The authors found out that untreated patients with 1–2 grade AH aged 45–65 years are different from healthy individuals of comparable age and gender because they have higher variability of systolic and diastolic blood pressure (BP) at night time. 3-month therapy with fixed combination of antihypertensive agents significantly decreased circadian BP variability in this group of patients. The article from Belarus is dedicated to evaluation of functional condition of the vessels and central hemodynamic parameters in healthy young individuals in respect to circulatory type. The author concludes that linear regression of BP parameters widens the possibilities of outpatient diagnostics of clinically latent hemodynamic abnormalities related to functional vascular disturbances. The third original article investigates the influence of rosuvastatin on systemic inflammation, endothelial dysfunction and clinical course in patients with chronic obstructive pulmonary disease (COPD) and high or very high cardiovascular risk without history of cardiovascular events. Statin therapy has anti-inflammatory, endothelium-protective and immunomodulating effects, affects key systemic processes involved in COPD development and is able to modify clinical course of this disease.

The «Experimental articles» section includes an article concentrated on investigation of spectral characteristics of cardiac rhythm variability of rats after treatment with I class antiarrythmics Ethmozin and Ethacizin. Ethmozine increased the role of vegetative nervous system in cardiac rhythm regulation versus humoral factors without changing the interrelation between sympathetic and parasympathetic influences. Ethacizin decreased cardiac rhythm variability in experimental animals, when ethmozine did not change heart rhythm variability.

The «Expert opinion» section is present with opinions of 7 leading experts from different regions of Russia on new revision of AH classification as part of clinical guidelines that have been published in the Journal of the American College of Cardiology and in the AHA Journal of Hypertension. Some experts think that these guidelines are not acceptable for Russia and it is necessary to wait until the decision of the European Society of Cardiology will be published. At the same time, new revision of classification is considered to be a positive phenomenon for AH diagnostics and prevention of its complications.

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

International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation

LEADING ARTICLE

Cardiotoxicity of cancer therapy

Yandieva R.A.[1]*, Saribekyan E.K.[3], Mamedov M.N.[1]

[1] National Research Centre for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia
[2] Hertsen Moscow Oncology Research Center — National Medical Research Radiology Center of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Authors

Rosa A. Yandieva, M.D., research assistant of the department of prevention of comorbid diseases, National Research Centre for Preventive Medicine, Moscow, Russia;
Erik K. Saribekyan, M.D., Ph.D., doctor of sciences, leading researcher of the department of oncology and plastic and reconstructive skin and breast surgery, Hertsen Moscow Oncology Research Center — National Medical Research Radiology Center, Moscow, Russia
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.

Summary

Nowadays cancer is the second leading cause of death in Europe and in Russia. Life expectancy and relapse-free survival in cancer patients have increased significantly due to advanced diagnostics and innovative pharmacological treatment and radiotherapy. In accordance with it, time, the number of patients suffering from various complications including cardiologic ones has increased proportionally. Many chemotherapy agents have cardiotoxic effects that often are refractory to treatment and that are mostly manifested as asymptomatic ECG changes up to myocardial infarction, as various rhythm and conduction disorders, or as toxic cardiomyopathy with signs of severe heart failure. Taking into account all above-mentioned points, well-timed detection, monitoring and treatment of complications arising during and after anticancer therapy become new relevant tasks in clinical practice.

Key words

Cancer, antitumoral drugs, chemotherapy, radiotherapy, cardiotoxicity, prevention.

* Corresponding author. Tel.: 8-977-957-27-00. E-mail: r_yandieva@list.ru

Introduction

Nowadays cancer is the main and one of the most significant healthcare problems in Russia and in the world [1–3]. According to the information collected by Hertsen Moscow Oncology Research Center, cancer morbidity has been increasing constantly during the last few years. 589 341 new cancer cases were diagnosed in 2015, and this number is 4,0 % higher comparing with the previous year (270 046 male cases and 319355 female cases) [4]. Cancer is the cause of each sixth death in the world. 8,8 mln people died due to cancer in 2015. According to the World Health Organization (WHO) prognosis, within the next 20 % this number will increase approximately by 70 % [5].

But cardiovascular diseases (CVD) take the leading position between the causes of lethality in the majority of countries. In particular, more than 4 mln cases of death registered in Europe each year occur due to CVD, and 1 mln of them happen in Russia [6–7]. In terms of percentage, 55.9 % of CVD lethal cases occur in Russia, and 47 % of them occur in Europe [6]. Cardiovascular mortality of men is 4,7 times higher than the one of women, whereas death due to coronary heart disease (CHD), myocardial infarction, and cerebrovascular diseases is 7.2, 9.1, and 3.4 times higher in men than in women, respectively (fig. 1) [8].

When looking at these data, the importance of cancer prevention and treatment becomes obvious. Chemotherapy is the most effective way to fight cancer, but it leads to several complications, and the most frequent ones affect cardiovascular system (CVS). The severity of appearing adverse effects may lead to disability and death between cancer survivors [3, 9]. These adverse effects can result from cardiotoxicity of antitumor therapy especially in case of pre-existent cardiovascular risk factors (RF) [10]. It's important to point out that many features of long-term cardiovascular consequences of radiotherapy or chemotherapy have not been studied enough. The complexity of prediction of antitumor treatment adverse effects leads to hyper-diagnostics of CVD in the majority of cases, and sometimes it may lead even to termination of life-saving cancer treatment.

Creation of national registers of cardiologic problems in cancer allows determination of the impact of single risk factors on complications development in comorbid patients.

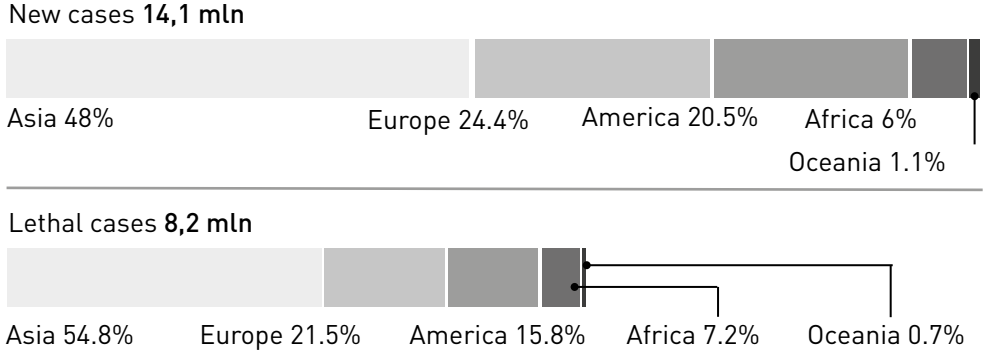
The first official document was published in 2016 by the European Society of Cardiology (2016) and it was dedicated to the cardiotoxicity of radio- and chemotherapy for cancer patients (The Task Force for cancer treatments and cardiovascular toxicity of the ESC) [11].

The risk factors of anticancer treatment include: total dose administered within one day or full course of chemotherapy; total dose of a drug (for example, cumulative dose of doxorubicin is 500–550 mg/m^2); drug order and velocity of administration; patient's history of mediastinal radiation, patient's age (below 15 and above 65 years); female gender; simultaneous administration of other antitumoral agents (cyclophosphamide, bleomycin, etoposide, cisplatin, vincristine, actinomycin, methotrexate); previous therapy with anthracyclin antibiotics; concomitant diseases of cardiovascular system; electrolyte disorders (hypokalemia, hypomagnesemia) [12–18].

Cardiovascular complications of cancer treatment

Nowadays there is no full classification of chemotherapeutic drugs' cardiotoxicity that would take into account the period of its appearance after the start of the therapy.

Time of cardiotoxicity manifestation can vary a lot. Adverse effects of several antitumor agents appear early and it has negative impact on general effective-



Source: Globocan

Figure 1. Prevalence of cancer in different parts of the world

ness of cancer therapy that complicates its management. Negative cardiovascular impact of other agents appears after a relatively long period.

Different chemotherapeutic agents may possess cardiotoxicity, but the anthracyclin antibiotics are particularly important from this point of view since there are numerous evidences of cardiologic complications (CVC) related to their administration.

Cardiotoxicity is subdivided into acute, chronic and subchronic forms [12–14, 19] (Table 1).

CVC caused by anticancer therapy can be divided into 9 main groups: myocardial dysfunction and heart failure (HF), coronary heart disease including myocardial infarction (MI), arrhythmias, arterial hypertension (AH), thromboembolism, peripheral artery disease and stroke, pulmonary arterial hypertension (PH); valvular heart disease (VHD), pericarditis.

It is necessary to highlight that tight interaction between oncologists and cardiologists is necessary to achieve the best possible result without negative effect on antitumor treatment, and to prevent and to control cardiotoxicity [20]. Systolic dysfunction of the left ventricle (LV) is the most threatening CVC of anticancer treatment and it is classified into two main types (Table 2).

It is important to keep in mind that the cardiotoxicity is not an indication for athracycline therapy withdrawal due to their high efficiency for the treatment of solid tumors and blood malignancies and possible negative impact on prognosis in case of treatment discontinuation. At the same time the ability of anthracyclines to cause irreversible myocardial changes and influence patients' lifespan and life quality has been proved. In 5% of cases patients who received doxorubicin had developed congestive HF after reaching cumulative dose of 400 mg/m^2, and the risk of congestive HF increases up to 48% in case of cumulative dose of 700 mg/m^2 [21]. It is necessary to take into account individual sensibility of patients since the standard anthracycline dose may result in no complications in some cases and cause them after the first administration in other patients.

Toxicity caused by administration of cytostatic drugs is related to damage of fast-proliferating cells in the majority of cases. Cells with restricted regenerative potential like cardiomyocytes are also suscep-

Table 1. **Cardiovascular complications of antitumor drug therapy**

	LV dysfunction/HF	AH	Myocardial ischemia	myocardial infarction	Arrhythmias	QT prolongation	Raynaud syndrome	Stroke	Peripheral artery disease	Pulmonary arterial hypertension	Deep vein thrombosis/ pulmonary embolism	Edema	Pericarditis/ pericardial exudation
Anthracyclines	x				x								
Bleomycin			x	x			x	x		x			
5-fluorouracil			x	x	x		x						
Capecitabine			x	x	x		x						
Gemcitabine			x	x			x						
Paclitaxel	x	x	x	x	x	x					x	x	
Cisplatin	x	x	x	x	x		x	x	x		x	x	
Cyclophosphamide	x		x		x					x			x
Vincristine		x	x	x	x		x						
Everolimus		x	x								x		
Temsirolimus		x	x								x		
Trastuzumab	x												
Bevacizumab	x	x	x	x				x			x		
Aflibercept		x		x				x			x		
Sorafenib	x	x	x	x	x	x		x			x	x	
Sunitinib	x	x	x	x	x	x		x			x	x	x
Pazopanib	x	x	x	x				x			x		
Axitinib		x	x	x				x			x		
Regorafenib		x	x	x									
Vandetanib		x						x					
Lapatinib	x		x		x	x							
Imatinib	x	x									x	x	x
Interferon-α	x	x	x	x	x		x	x	x	x	x		
Interleukin 2		x		x									

Table 2. **Comparison of two types of LV dysfunction related to antitumor therapy**

	LV dysfunction	
	Type I	**Type II**
Trigger prototype	Doxorubicin	Trastuzumab
Instrumental diagnostics	Reduction of LV ejection fraction (EF)	Reduction of LV ejection fraction (EF)
Period of manifestation	After the end of chemotherapy, most frequently within the first year	During therapy
Morphological changes of myocardium	Vacuolization Necrosis Abnormal position of cardiac muscle fibers	Absent
Dose-dependence	Yes	No
Risk factors	High cumulative dose of drug (≥250 mg/m^2 of doxorubicin, ≥600 mg/m^2 of epirubicin); Bolus drug administration; Combination with other cardiotoxic antitumor agents (cyclophosphamide, trastuzumab, paclitaxel etc.); Previous/simultaneous radiotherapy of mediastinal area/left part of the chest; CVD (CHD, moderate/significant valvular defects); initial LV dysfunction (LV EF <55 %); CVD RF: • AH • smoking • dyslipidemia • diabetes mellitus • hypodynamia • insufficient or excessive body weight • kidney failure • age <18 and >60–65 years • female gender	previous/simultaneous therapy with anthracyclines and other antitumor agents; CVD (CHD, cardiomyopathy, moderate/significant valvular defects); initial LV dysfunction (LV EF <55 %); CVD RF: • AH • smoking • dyslipidemia • diabetes mellitus • excessive body weight • alcohol consumption • age >60 years
Clinical course after discontinuation of the therapy	Stabilization is possible, but cardiomyocyte damage is irreversible	High probability of full recovery within the next months with good distant prognosis
Restarting therapy after discontinuation	High probability of LV dysfunction progression	Relatively safe if prescribed together with cardioprotective therapy

tible to permanent or transient effect of chemotherapeutic agents. According to Rickard J and colleagues, anthracycline cardomyopathy is the most malignant type of cardiomyopathy that may cause lethality in 50 % of cases within 2 years [22]. Long latent period, progressive course and resistance to cardioprotective treatment aggravate patients' prognosis. Early detection of drug-induced cardiotoxicity allows correcting dosage or velocity of drug administration and changing therapeutic regimens for less toxic drugs of new generation. Considering the importance of this problem, it remains relevant to study various methods of estimation of myocardial function for well-timed detection of cardiotoxicity-related pathologic changes [23]. There are other standard chemotherapeutic agents like cyclophosphamide, iphosphamide, cisplatin, and docetaxel that may cause cardiologic complications. Cyclophosphamide-induced cardiotoxicity is not frequent and it occurs in patients receiving high doses of the drug (>140 mg/kg) before bone marrow transplantation [24]. These patients develop HF within a few days after the treatment. Also alkylating agents similar to cyclophosphamide may cause HF. In case of treatment with platinum-based drugs it is necessary to dilute them in large volumes of appropriate solution for intravenous administration in order to avoid platinum toxicity. This volume overload often leads to HF manifestation or relapse. Docetaxel administration together with trastuzumab or other anthracyclines also increases the probability of congestive HF development. At the same time it is necessary to notice that often it is quite difficult to evaluate the impact of a single drug when they represent a part of a combined treatment.

Prognosis and treatment of cardiotoxicity

Cancer therapy is mostly combinative, and it complicates prediction of CVC. Taking into account the use of various combined regimens for cancer treatment and the possibility of early development of CVC, the use of combined therapy significantly complicates CVC prediction [25]. Nowadays liposomal forms of anthracyclines are actively developed. Design of such drugs is based on the idea that an active anthracycline is included in lipid-containing microscopic spheroids or as a part of their covering or inside them and then it is administered intravenously. The described form is less toxic and has the same therapeutic activity. It's possible to correct chemotherapy considering the susceptibility of patient's CVS to anthracyclines. It

Table 3. **Guidelines for treatment of patients with anthracycline-induced LV EF reduction (ESMO guidelines 2012)**

LV EF reduction	Strategy	Cardiac therapy
⩾ 15 % of initial levels if LVEF remains⩾ 50 %	Anthracycline therapy can be continued	Not required
<50 % during anthracycline treatment	Repeated echocardiography (EchoCG) evaluation 3 weeks after, if the same value is detected, anthracycline therapy should be temporally discontinued	Should be performed
<40 % during anthracycline treatment	Chemotherapy with this therapeutic regimen should be terminated	Should be performed, and other alternatives of pharmacological therapy should be discussed

explains the necessity of monitoring and continuous evaluation of myocardial function during all stages of patient's therapy, and correction or discontinuation of it in case of detected heart lesions. Troponin is the marker of anthracycline-induced myocardial damage. In rare cases troponin concentration can remain elevated several weeks after therapy termination. In adult patients high troponin I levels correlate with higher reduction of EF (by 16 %) comparing with patients without troponin elevation (⩽5 %) [26, 27]. Infradiaphragmatic radiotherapy is associated with high risk of CHD development due to atherosclerotic and non-atherosclerotic lesions of CVS complicated with plaque rupture, thrombosis and possible coronary spasm. Coronary ostium lesions are potentially fatal. After radiotherapy on the left breast atherosclerosis develops more frequently in the area of left anterior descending coronary artery and of left coronary, and atherosclerosis of circumflex branch of left coronary artery and right coronary artery are more frequent after Hodgkin's lymphoma treatment [28, 29]. Stress-test based on physical exercise revealed ischemic ECG changes in women who underwent radiotherapy of the left breast cancer comparing with the right breast cancer. CHD associated with cardiotoxicity can have different manifestations: acute coronary syndrome or sudden cardiac death, but more often CHD remains asymptomatic for a long time.

Carditoxicity after lymphoma treatment is more frequent in young patients and it manifests decades after the therapy. CHD development in patients with the history of Hodgkin's lymphoma is 4–7 times higher comparing with the other groups, and total risk of CVD development within the next 40 years after treatment reaches 50 % in this group of patients [30]. These patients have 2–7 times higher risk of myocardial infarction, and their total cardiovascular morbidity rate within the next 30 years is 10 % higher [30]. Taking into account this fact, it becomes reasonable to perform constant screening of patients who received antitumor therapy for detection of pathological changes of CVS during all their life after therapy initiation. Young age, lack of chest surface mould protection, high intensity of radiation, CV risk factors and CHD history are the risk factors of CHD development in patients who underwent radiotherapy together with anthracyclines treatment.

There is no specific treatment of anthracycline-induced cardiotoxicity. Cardiac glycoside have positive temporal effect; beta-blockers (metoprolol, labetalol etc) administration is reasonable for children with systolic dysfunction; angiotensin-converting enzyme (ACE) inhibitors (enalapril, captopril etc) are recommended in patients with increased afterload and asymptomatic LV systolic dysfunction, and diuretics are prescribed for treatment of patients with severe congestive HF. Combined use of bisoprolol and digoxin has positive effect (independently from cardiac rhythm). Bisoprol dose should be adjusted until reaching HR 58–60 beats per minute. Stabilization of patient's condition and optimal blood pressure levels allow addition of ACE inhibitors [31].

In order to prevent LV EF reduction and congestive HF development, it is reasonable to prescribe ACE inhibitors (enalapril) in patients with subclinical I type cardiotoxicity if elevated troponin levels are detected. LV HF requires treatment according to the guidelines of HF treatment (Table 3, Scheme 1).

Conclusion

The success of increased lifespan of cancer patients after introduction of new chemo-radiotherapy regimens is tightly connected with the high risk of cardiologic complications. The presence of various cardiotoxicity manifestations, relatively long period of asymptomatic course and disease progression require early and long dynamic monitoring of the condition of patients who underwent chemotherapy and radiotherapy. Patients' monitoring during all steps of cancer therapy is necessary for well-timed detection of pathological changes in myocardium, for the start of appropriate cardioprotective therapy and also for widening the knowledge of medical specialists about possible consequences of antitumor treatment. Joint work of cardiologists and oncologists is an important condition of patients'

Scheme 1. **Algorithms of diagnostics and treatment of anthracycline-induced cardiotoxicity (ESMO guidelines 2012)**

<table>
<tr><th colspan="4">EchoCG + ECG (QT interval) before the start of anthracycline therapy</th></tr>
<tr><td colspan="2">Anthracycline therapy</td><td colspan="2">Anthracycline therapy is finished and troponin I levels was not evaluated before therapy</td></tr>
<tr><td colspan="2">Troponin I levels evaluation before each chemotherapy cycle</td><td colspan="2">Immediately after the end of anthracycline therapy</td></tr>
<tr><td>Troponin I positive</td><td>Troponin I negative</td><td colspan="2">EchoCG</td></tr>
<tr><td>1) Cardiologist's consultation
2) Enalapril administration during 1 year</td><td>EchoCG should be performed 12 months after the start of anthracycline therapy</td><td></td><td>No LV dysfunction</td></tr>
<tr><td>After it EchoCG should be done after 3,6,9 months</td><td>After it EchoCG should be done once per year</td><td></td><td>EchoCG after 3 months</td></tr>
<tr><td>EchoCG should be performed 12 months after the start of anthracycline therapy</td><td></td><td rowspan="2">LV dysfunction</td><td>No LV dysfunction</td></tr>
<tr><td>After it EchoCG should be done once each 6 months during the next 5 years</td><td></td><td>EchoCG after 6 months</td></tr>
<tr><td colspan="2" rowspan="8"></td><td>1) ACE inhibitors
2) Beta-blockers</td><td>No LV dysfunction</td></tr>
<tr><td>3) Observation</td><td>EchoCG after 6 months</td></tr>
<tr><td></td><td>No LV dysfunction</td></tr>
<tr><td></td><td>EchoCG after 12 months</td></tr>
<tr><td></td><td>No LV dysfunction</td></tr>
<tr><td></td><td>EchoCG every year</td></tr>
</table>

management in the departments of radiotherapy and chemotherapy.

Numerous studies dedicated to the detection of pathological changes in myocardium and to the development of drugs with marked cardioprotective effect have been conducted during the last years.

«Make no harm» is the basic rule in all cases. It is important to explain to patients the importance of regular cardiologic visits and the use of drugs with well-proven efficacy.

Conflict of interest: None declared

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International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation

Circadian variability of blood pressure in untreated middle-aged patients with arterial hypertension

Kochetkov A.I.[1], Borisova E.V.[2], Piksina G. F.[3], Orlov A.V.[3], Ostroumova O.D.[1, 4]*

[1] Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia
[2] City Clinical Hospital named after E.O. Mukhin, Moscow, Russia
[3] National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Moscow, Russia
[4] I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Authors

Alexei I. Kochetkov, M.D., assistant professor of the department of internal medicine and occupational diseases, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.
Ekaterina V. Borisova, M.D., cardiologist of the department of cardiology № 1, City Clinical Hospital named after E.O. Mukhin, Moscow, Russia.
Galina F. Piksina, M.D., Ph.D., cardiologist, head of the department of cardiology № 1, City Clinical Hospital named after E.O. Mukhin, Moscow, Russia.
Artemii V. Orlov, head of students' laboratory of the department № 65, National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Moscow, Russia.
Olga D. Ostroumova, M.D., Ph.D., doctor of sciences, professor of the department of internal medicine and occupational diseases, Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, professor of the department of clinical pharmacology and propedeutics, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.

Summary

Objective

(1) Evaluate the parameters of circadian variability of blood pressure (BP) in untreated patients aged 45–65 years with 1–2 grade, II stage arterial hypertension (AH) comparing with healthy individuals of comparable age and gender; (2) compare the influence of fixed combination (FC) of amlodipine/lisinopril (FC A/L) and FC bisoprolol/hydrochlorothiazide (FC B/H) on circadian variability of BP in these patients.

* Corresponding author. Tel.: +7903-169-68-28; E-mail: ostroumova.olga@mail.ru

Materials and methods

At the first stage of this study we observed 44 healthy individuals (21 males, 23 females, average age 51.5±1.0 years) and 60 untreated patients with AH 1–2 grade, II stage (31 males, 29 females, average age 53.6±0.8 years). At the second stage of this study we randomized the patients with AH into two subgroups. The patients of the first subgroup (average age 52.7±1.1 years) received FC A/L starting from 5mg/10mg per day, and the patients of the second subgroup (average age 54.6±1.0 years) received FC B/H starting from 2.5mg/6.25 mg per day. FC dose was adjusted every 14 days until the target levels of BP below 140/90 mm Hg had been reached, after it patients continued to receive these doses of drugs for 12 weeks.

Results

Patients with AH had significantly higher (p<0.001) variability of systolic BP (SBP) and diastolic BP (DBP) at night (12.1±0.4 and 9.8±0.4 mm Hg, respectively) comparing with the control group (9.3±0.4 и 6.9±0.3 mm Hg, respectively). FC therapy led to significant reduction of office SBP, DBP, pulse BP (PBP), average daytime SBP, DBP, and PBP, average nighttime SBP and DBP. Both drug combinations resulted in significantly (p<0.05) reduced daytime SBP variability, and FC A/L had significantly more evident effects comparing with FC B/H (–2.7±0.7, –0.9±0.3 mm Hg, respectively). FC A/L subgroup was characterized with significant reduction of SBP variability (p<0.05) at night and DBP variability at daytime and night (–1.2±0.5, –0.7±0.3, –1.4±0.6 mm Hg, respectively).

Conclusions

Untreated patients aged 45–65 years with 1–2 grade, II stage AH have higher variability of SBP and DBP at night comparing with healthy individuals of comparable age and gender. 12 week therapy with FC A/L has more evident antihypertensive effects and reduces circadian BP variability better comparing with FC B/H) in these patients.

Key words

Arterial hypertension, circadian variability of blood pressure, 24h blood pressure monitoring, amlodipine, lisinopril, bisoprolol, hydrochorothiazide, fixed combination

Introduction

Arterial hypertension (AH) is the most common and significant risk factor (RF) for cardiovascular disease (CVD) development that significantly increases population mortality and disability and due to it represents one of the most important healthcare problems in all over the world including the Russian Federation [1].

At the same time it has been proved that not only blood pressure (BP) levels but also excessive fluctuations of BP — its increased variability — are associated with target organ lesions (TOL) [2]. Nowadays BP variability has been recognized as a new RF of CVD and brain stroke (BS). Numerous studies [3–10] demonstrated independent impact of short-term (time periods from several minutes to several days) and long-term (during months) BP variability on increase of mortality and on development of TOL not only in patients with AH but also in patients with diabetes mellitus and chronic kidney disease [2]. Several studies [11] demonstrated that BP variability reflects the stiffness of major arteries thus influencing the risk of complications. Some other studies [12, 13] revealed the significance of increased BP variability during daytime and night time for the risk of BS and myocardial infarction development in case of AH. Night systolic BP (SBP) variability was identified to be the RF of BS and myocardial infarction development, whereas night diastolic BP (DBP) variability appeared to be myocardial infarction RF [14].

Consequently, it is necessary to take into consideration the efficacy of antihypertensive agents (AHA) for reduction of BP variability in case of treatment of patients with AH from the point of view of reduction of fatal and not fatal cardiovascular and cerebrovascular complications. It is necessary to highlight that according to the guidelines of the Russian Medical Society on AH [1] and the European guidelines on diagnostics and treatment of AH [15] patients with high and very high risk should receive combined antihypertensive therapy since the start of the treatment, and fixed drug combinations (FC) of AHA should be prescribed in the first instance. According to this, nowadays the problem of AHA FC becomes relevant not only due to their direct antihypertensive effect but also because of effective reduction of BP variability.

It is worth to notice that the influence of selected AHA on BP variability has been evaluated in several studies [16–18], but in available databases there are no comparative studies that would have analyzed the ability of various AHA FC to reduce BP variability.

Investigation of influence of various AHA FC looks very relevant, taking into account all above-mentioned facts. The objectives of our study were: (1) evaluation of parameters of BP variability within 24h in untreated patients aged 45–65 years with arterial hypertension (AH), II stage, 1–2 grade without concomitant CVD comparing with healthy individuals of comparable age and gender; and (2) comparative analysis of FC amlodipine/lisinopril (FC A/L) and FC bisoprolol/hydrochlorthiazide (FC B/H) on these parameters in above-mentioned category of patients with AH.

Materials and methods

At the first stage of this study we observed 44 healthy individuals (control group) (21 males, 23 females, average age 51.5±1.0 years) with normal BP levels and without CVD and 60 untreated patients with AH 1–2 grade, II stage (31 males, 29 females, average age 53.6±0.8 years) who were admitted to the City clinical hospital named after E.O. Mukhin.

Inclusion criteria for patients with AH: patients with AH II stage, males and females aged 45–65 years, office SBP 140–179 mm Hg and/or office DBP 90–109 mm Hg; no history of pharmacological antihypertensive therapy or irregular administration of hypotensive drugs during at least 12 months before involvement in the study.

Inclusion criteria for the control group: almost healthy adult men and women aged 45–65 years; absence of AH.

Exclusion criteria: patient's refusal of participation in the study, III grade obesity [19]; age below 45 or above 65 years; pregnancy, lactation, BP levels ≥ 180/110 mm Hg; clinically significant heart diseases (including cardiogenic shock and acute cardiac failure, history of myocardial infarction, angina, AV block II and III degree without artificial pacemaker, SA block, sick sinus syndrome, hypertrophic cardiomyopathy, aortal and mitral stenosis, chronic heart failure); liver and kidney disorders (severe chronic kidney disease [glomerular filtration rate < 30 ml/min/1.73 m^2 quantified with CKD-EPI], hemodialysis, anuria), respiratory and digestive system disorders, clinically significant immunological disorder including systemic lupus erythematosus, clinically significant endocrinological disorder including diabetes mellitus and secondary AH; gout, mental disorders, dementia, addiction to pharmacological agents, drugs, and alcohol; severe disorders of peripheral circulation including Reynaud syndrome; metabolic acidosis, refractory hypokalemia; clinically significant neurological disorders (including any history of acute cerebral circulatory insufficiency and transient ischemic attack); surgical operation performed up to 3 months before the study (excluding dental and cosmetic surgery); increased sensitivity to lisinopril/amlodipine, bisoprolol/hydrochlorthiazide and other thiazides, sulfonamides and/or other angiotensin-converting enzyme (ACE) inhibitors/dihydropyridine derivatives; increased sensitivity to other components of combined fixed dose medicines; any history of angioedema; history of sultopride administration or of any pharmacological agent (including regular AHA administration) that could have influenced the results of the study within 12 weeks before its initiation, at the moment of inclusion and before the end of this study.

This study was approved by Inter-institutional ethic committee, and all participants of the study signed informed consent.

All patients underwent clinical examination that included measurement of office BP, heart rate (HR), height, weight, waist circumference (WC), body mass index (BMI) quantification, 24h BP monitoring (24hBPM) (MnSDP-2 BPLAB monitor, Limited liability company «Pyotr Telegin», Russia) according to the European Society of Hypertension recommendations on 24hBPM [21, 22]; transthoracic echocardiography (Vivid 7 Dimension GE Vingmed Ultrasound A/S, Horten, Norway equipment) according to the American Society of Echocardiography on quantitative estimation of heart chambers' structure and function (2015) [23]; biochemical blood test (lipid spectrum characteristics, glucose and creatinine levels). Left ventricular mass index (LVMI) was quantified using ASE formula [23]. LVMI values above 115 g/m^2 and above 95 g/m^2 were considered as criteria of left ventricular hypertrophy (LVH) in men and women respectively [23].

At the second stage of this study we randomized the patients with AH into two subgroups each one of which included 30 persons. The patients of the first subgroup (16 males; average age 52.7±1.1 years, 12 smokers (40%), 14 persons with obesity 1–2 grade [46.7%]) received FC A/L starting from 5mg/10mg per day, and the patients of the second subgroup (15 males, average age 54.6±1.0 years, 10 smokers (33.3%), 18 persons with obesity 1–2 grade [60.0%]) received FC B/H starting from 2.5 mg/6.25 mg per day.

If two weeks after the start of the therapy BP was ≥ 140/90 mm Hg [1, 15], FC dose was increased: FC A/L was prescribed as 5/20 mg once per day, and FC B/H was adjusted as 5/6.25 mg once per day in

the morning. If BP levels were ⩾ 140/90 mm Hg even after this change, FC were increased once more: FC A/L was administered as 10/20 mg once per day, and FC B/H was prescribed as 10/6.25 mg once per day in the morning. If two weeks after patient did not manage to achieve BP target levels < 140/90 mm Hg we excluded him from the study. Patients used to buy the medicines on their own. After the target levels of BP below 140/90 mm Hg had been reached, patients continued to receive selected doses of drugs for 12 weeks, and it was followed by repeated 24hBPM.

Statistical analysis of the results was performed using Microsoft Excel 2010 and SPSS Statistics 20 software and PC with Windows 7 operation system. Normality of parameters' distribution was evaluated using Kolmogorov-Smirnov test. Significance of difference was estimated using one-way ANOVA dispersion analysis for quantitative variables and contingency tables (χ^2) for categorical variables. Non-parametric Mann-Whitney U-test and Wilkoxon signed-rank test were used for analysis of not normally distributed data. Correlation analysis was used to evaluate paired connections between two and more continuous variables. 95% confidence interwal was considered for correlation analysis. Qualitative variables are shown as average values (M) ± standard error of the mean (m). Results were considered statistically significant if p-value was < 0.05.

Results

The first stage of the study. Characteristics of the study population are present in Twable 1. There were no differences in age, gender, smoking status between the control group and the group of patients with AH (Table 1). Height, weight, BMI, WC were significantly (p<0.001) higher in the group of patients with AH. Also the levels of triglycerides (p<0.001), glucose (p<0.05), and creatinine (p<0.05) were significantly higher in this group (Table 1).

Table 1. **Initial characteristics of the control group and the group of patients with AH**

Characteristic / Group	Control group (n=44)	Patients with AH (n=60)
Age, years	51,5±1,0	53,6±0,8
Smokers, n (%)	8 (18,2)	22 (36)
BMI, kg/m^2	26,5±0,6	31,0±0,5[c]
Waist circumference in men, cm	92,8±2,1	109,4±1,5[c]
Waist circumference in women, cm	87,9±2,3	101,9±2,6[c]
AH, 1 grade, n (%)	-	33 (55)
AH, 2 grade, n (%)	-	27 (45)
Total cholesterol, mmol/L	5,8±0,2	5,9±0,1
HDL cholesterol, mmol/L	1,5±0,1	1,2±0,1[b]
LDL cholesterol, mmol/L	3,6±0,1	3,9±0,1
Triglycerides, mmol/L	1,2±0,1	2,1±0,2[c]
Glucose, mmol/L	5,2±0,1	5,5±0,1[a]
Creatinine, μmol/L	86,6±1,9	91,9±1,8[a]
GFR, quantified with CKD-EPI formula, mL/min/1,73 m^2	84,0±2,4	87,1±1,7

Comment: The results are shown as M±m
[a] — differences are significant (p<0,05) comparing with the control group,
[b] — differences are significant (p<0,01) comparing with the control group,
[c] — differences are significant (p<0,001) comparing with the control group,
BMI — body mass index; HDL — high density lipoproteins, LDL — low density lipoproteins; GFR — glomerular filtration rate; AH — arterial hypertension.

Characteristics of SBP and DBP variability at night time were significantly higher in the group of patients with AH (Figure 1). SBP and DBP variability at day time in the control group (13.7±0.7 and 10.4±0.6 mm Hg, respectively) and in the group of patients with AH ГБ (15.4±0.5 and 11.4±0.4 mm Hg, respectively) did not differ significantly.

Results of the second stage of the study: comparative analysis of FC A/L and FC B/H on circadian BP variability.

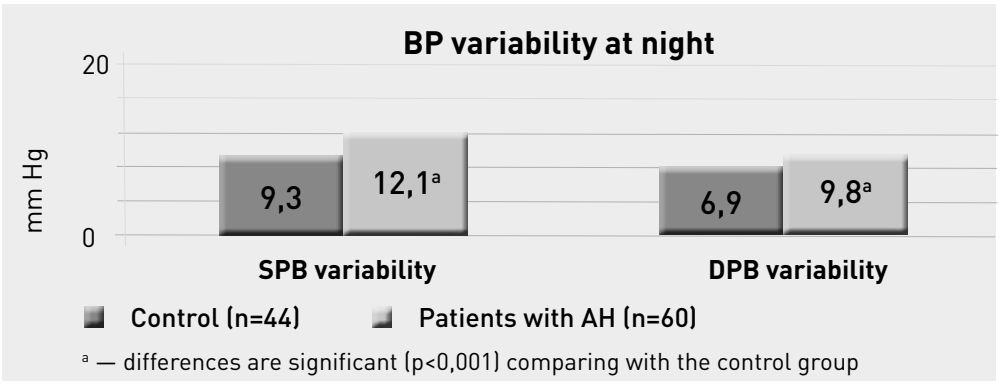

Figure 1. BP variability at nighttime in the group of patients with AH and in the control group during the first stage of the study.
Comment. BP — arterial pressure; SBP — systolic BP; DBP — diastolic blood pressure.

Table 2. **Initial levels and office BP and HR dynamics during the therapy with FC A/L and FC B/H**

Group / Characteristic	FC A/L (n=30)		FC B/H (n=30)	
	Initially	In the end of observation period	Initially	In the end of observation period
SBP, mm Hg	154.4±2.7	130.6±1.2[c]	150.6±2.7	134.0±0.5[c]
DBP, mm Hg	96.5±1.3	83.0±0.6[c]	95.8±1.1	84.6±0.4[b]
PBP, mm Hg	58.0±1.9	47.6±0.9[b]	54.8±2.1	49.4±0.4[a]
HR, beats per minute	72.5±1.6	72.0±1.6	74.5±1.7	66.2±0.8[c]

Comment: The results are shown as M±m.
[a] — p<0.05 comparing with the initial values;
[b] — p<0.01 comparing with the initial values;
[c] — p<0.001 comparing with the initial values.
BP — blood presure; HR — heart rate; FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

Table 3. **Dynamics of average daily, average daytime, and average night SBP, DBP, and PBP during treatment with FC A/L and FC B/H**

Group / Characteristic	FC A/L (n=30)		FC B/H (n=30)	
	Initially	In the end of observation period	Initially	In the end of observation period
Average daily SBP, mm Hg	148.8±2.3	127.5±0.9[b]	150.6±2.6	131.9±1.4[b]
Average daily DBP, mm Hg	93.1±1.2	77.9±0.7[b]	92.9±1.5	77.3±0.9[b]
Average daily PBP, mm Hg	56.3±1.9	49.6±1.0[b]	56.9±1.6	54.7±1.0[a]
Average daytime SBP, mm Hg	153.7±2.4	134.7±0.8[b]	155.0±2.5	137.9±1.3[b]
Average daytime DBP, mm Hg	96.9±1.3	84.4±0.5[b]	96.5±1.5	85.3±0.6[b]
Average daytime PBP, mm Hg	56.8±1.7	50.3±0.8[b]	58.6±1.6	52.6±1.0[b]
Average nighttime SBP, mm Hg	139.3±2.6	119.4±1.2[b]	143.9±3.0	125.7±1.6[b]
Average nighttime DBP, mm Hg	85.1±1.7	70.7±1.1[b]	86.5±1.9	69.1±1.3[b]
Average nighttime PBP, mm Hg	53.9±1.9	48.8±1.5[b]	57.5±2.0	56.5±1.0

Comment: The results are shown as M±m.
[a] — p<0,01 comparing with the initial values;
[b] — p<0,001comparing with the initial values. FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

By the end of the observation period all 60 patients (100%) had reached target levels of office BP (<140/90 mm Hg). In the group of FC A/L10 patients (33.3%) reached it using 5/10 mg dose, and 8 (26.7%) and 12 patients (40%) achieved it using 5/20 mg and 10/20 mg doses, respectively, whereas in the group of FC B/H 13 patients (43.3%) achieved target levels of office BP using 2.5/6.25 mg dose, 11 patients (36.7%) and 6 patients (20%) reached it using 5/6.25 mg dose and 10/6.25 mg dose, respectively. Both drug combinations were well-tolerated. Cough in the FC A/L group was registered in 6.7% of cases; patients of both group episodically reported weakness, vertigo, headache, but these adverse effects were rare, did not influence patients' life quality and did not require drug withdrawal or dose reduction. No swollen ankles and feet, bradycardia or other adverse effects have been registered. Dynamics of office BP characteristics and HR during therapy is present in Table 2.

Office values of SBP, DBP, pulse BP (PBP) were significantly reduced in both groups. The FC B/H group demonstrated also significant reduction of HR (Δ — 8.37±0.99%, p<0.001). Office levels of SBP and PBP got more evident reduction in the group of FC A/L comparing with the group of FC B/H.

BP dynamics registered with 24h BPM are present in Table 3.

Both groups demonstrated significant reduction of average daytime SBP, DBP, PBP and average night SBP and DBP (Table 4). More than that, significant reduction of night BPB values was registered in the group of FC A/L and not in the group of FC B/H (Figure 2).

SBP variability at daytime significantly decreased after treatment with FC A/L and FC B/H, and this reduction was more evident in the group of FC A/L (Table 4). More than that, the group of FC A/L was characterized with significant reduction of SBP variability at night, and DBP variability at daytime and at night.

Discussion

According to known evidences [24], BP variability has prognostic significance for development of cardiovascular and cerebrovascular complications and it is also associated with TOL.

In particular, K. Eguchi et al [25] demonstrated the role of SBP and DBP variability during sleep as the in-

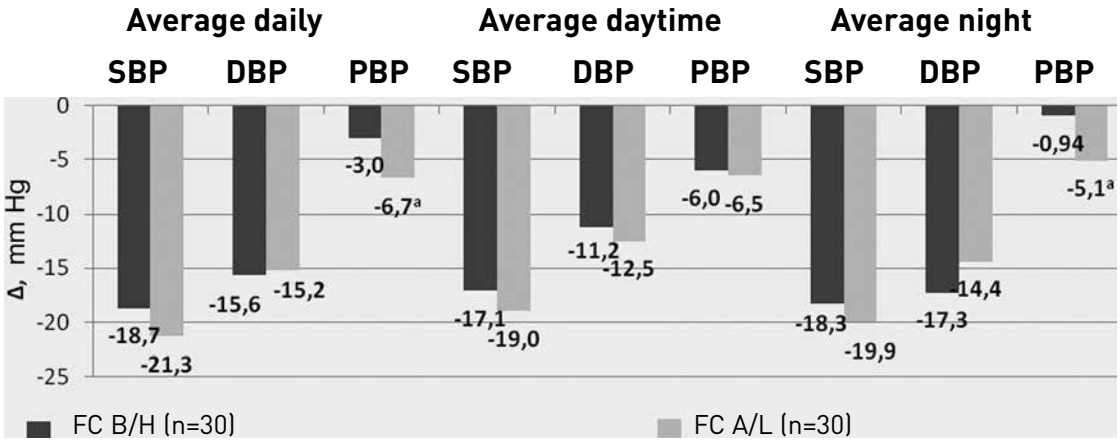

Figure 2. Dynamics of average daily, average daytime, and average night SBP, DBP and PD during treatment with FC A/L and FC B/H.
Comment: [a] — p<0,05 comparing with the initial values; FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

Table 4. **SBP and DBP variability during treatment with FC A/L and FC B/H**

Group / Parameter, mm Hg	FC A/L (n=30)			FC B/H (n=30)		
	Initially	After treatment	Δ	Initially	After treatment	Δ
SBP variability at daytime	15.4±0.9	12.7±0.5[c]	–2.7±0.7	15.2±0.6	14.5±0.5[b]	–0.9±0.3[d]
SBP variability at night	11.8±0.7	10.7±0.5[a]	–1.2±0.5	12.5±0.4	12.3±0.4	–0.1±0.3[e]
DBP variability at daytime	11.0±0.6	10.3±0.5[a]	–0.7±0.3	11.9±0.5	11.9±0.6	0.1±0.4[d]
DBP variability at night	9.4±0.6	8.0±0.4[c]	–1.4±0.6	10.1±0.4	10.3±0.4	0.1±0.3[f]

Comment: The results are shown as M±m.
[a] — p<0.05 comparing with the initial values;
[b] — p<0.01 comparing with the initial values;
[c] — p<0.001 comparing with the initial values;
[d] — p<0.05 between groups;
[e] — p<0.01between groups;
[f] — p<0.001between groups.
FC — fixed combination; A/L — amlodipine/lisinopril; B/H — bisoprolol/hydrochlorothiazide; SBP — systolic blood pressure; DBP — diastolic blood pressure; PBP — pulse blood pressure.

dependent predictor of cardiovascular complications like fatal BS, non-fatal MI, and sudden death. More than that, the number of unfavorable cardiovascular outcomes in the group of patients with increased SBP variability at night time (12.2 mm Hg and more according to study protocol) was significantly higher. Systematic review and meta-analysis performed by S.L. Stevens et al [26] demonstrated that elevated SBP variability at daytime and within 24h correlates with the risk of general and cardiovascular mortality, and increased SBP variability during sleep was related to the risk of unfavorable cardiovascular events development.

Correlation between elevated circadian BP variability and TOL is reported by numerous studies [4, 7, 8, 10, 27–45]. Particularly, it's known that increased circadian BP variability during sleep and awakening correlates with LVH [27–32], and with global longitudinal LV 2D strain (LV GLS) [33–35], parameter characterizing deformational and elastic capacity of LV. It is worth to mention that nowadays LV GLS is recognized as a new RF predicting cardiovascular morbidity and mortality in general population [46]. In addition to this, increased SBP and DBP variability identified with 24hBPM is associated with increased left atrium dimensions and its remodeling [36, 37]. Interrelation between circadian BP variability and kidney (AH target organ) lesions [27, 28, 38, 39] including albuminuria [27, 28] has been identified. The correlation between BP variability and vascular lesions has been established [4, 7, 30, 40–42]. For example, the ELSA study (European Lacidipine Study on Atherosclerosis) [4] demonstrated highly significant correlation (p<0.001) between SBP and PBP circadian variability and number of atherosclerotic plaques in carotid arteries and intima-media thickness. Similar results have been obtained in other studies [7, 40–42]. G. Schillaci et al [8] performed multivariance analysis in their study and established significant correlation between circadian BP variability and carotid-femoral pulse wave velocity (CFPWV) that is the «golden standard» of magistral arteries' stiffness. Another study [30] identified correlation between BP variability measured with 24hBPM and arterial stiffness (CFPWV, cardio-ankle

vascular index (CAVI), ankle-brachial index (ABI), and biological age of arteries). The last study demonstrated the role of elevated BP variability in lesions of the brain as a target organ of AH. Thus, apart from the above-mentioned [12, 13] role of this parameter as the BS predictor, its correlation with the presence of small cerebral vascular lesions in patients with AH I (independently from BP levels and various clinical RF) [43, 44] and its association with cognitive disorders [10, 44, 45] have been demonstrated in several works.

Evaluating parameters of BP variability measured with 24 BPM during the first stage of the study, we identified significantly ($p<0.001$) higher variability of SBP and DBP at nighttime in the group of patients with AH. It is necessary to point out once more that BP variability has been recognized as a new RF for patients with AH, and, as it has been shown by some studies [11], it reflects the stiffness of major arteries thus influencing the risk of complications. It has been shown that average daytime and average night SBP and DBP variability parameters can be independent predictors of development of both cardiac and cerebrovascular events [12, 14]. Taking into account the fact that in our study we detected significantly higher SBP and DBP variability at night time in the group of patients with AH, it is possible to talk about elevated risk of cardiovascular complications (CVC) even at early stages of AH in patients with relatively short duration of the disease.

At the second stage of our study we demonstrated that FC A/L and FC B/H have high antihypertensive activity, since all 60 patients (100 %) who received these drugs had reached target levels of office BP. Our results go along with the other studies [47–53]. Together with this, FC A/L reduced office SBP significantly higher comparing with FC B/H. It is necessary to point out that several works [54–58] demonstrated the prevalence of SBP impact on CVC development.

We also noticed that the group of FC A/L was characterized with significantly higher reduction of office and average night PBP comparing with the group of FC B/H ($p<0.05$). These data correspond to the results of the CAFÉ (Conduit Artery Functional Endpoint, sub-study in the frame of the ASCOT-BPLA study) — the largest trial performed in patients with AH tat evaluated reduction of central (aortal) BP [59]. The CAFÉ study involved 2073 patients from 5 centers, and by the moment of inclusion into sub-study all of them had reached target BP levels. According to the results of the above-mentioned sub-study, SBP and PBP in aorta was significantly lower in the group of patients who received amlodipine and ACE inhibitors [59]. Another study [51] evaluated antihypertensive effects of FC B/H in patients with firstly diagnosed or untreated AH 1–2 grade (13 patients with AH 1 stage, 19 patients with AH 2 stage; average AH duration was 5.1±0.4 years). In the end all 32 patients reached target BP levels < 140/90 mm Hg (routine measurement) and achieved significant reduction of SBP, DBP and HR. According to 24hBPM results, patients who received stable doses of FC B/H for 12 weeks had significantly lower SBP, DBP, and PBP levels at daytime, at night and within 24h. It is important to point out that PBP has high prognostic significance for CVC development. In the SHEP (Systolic Hypertension in the Elderly Program) study BS risk in elderly patients with isolated systolic AH correlated with initially elevated PBP levels independently from average BP values [60]. Correlation between PBP levels and parameters of cardiovascular and coronary mortality was evaluated in one major population study performed in patients aged 40–69 years in France [61]. Results of observation on 12631 persons with normal BP (<140/90 mm Hg) and 6824 patients with AH (SBP>160 mm Hg and/or DBP>95 mm Hg) were analyzed. Characteristics of total and cardiovascular mortality were significantly higher in the subgroups of patients with higher PBP in men (independently from initial BP levels) and women with AH. PBP>50 mm Hg was associated with elevation of cardiovascular mortality by 40 % in men with normal BP and by 48 % in male patients with AH.

In our study we found out that, although both FC reduced significantly SBP and DBP variability at daytime and at night, FC A/L influenced BP variability at daytime and at night significantly better than FC B/H.

It is worth to point out that according to the results of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) [11], BP variability (in particular SBP) is considered to be a strong independent predictor of development of myocardial infarction and BS independently from SBP changes during all study period (around 5 years) and from patients' age and gender. More than that, increased BP variability at daytime and at night turned out to be important for BS development in AH.

I.R. Ersh et al [53] investigated clinical efficacy of 1 and 2 month therapy with FC A/L in outpatients with AH in observation study. This study included two groups of patients. The first one consisted of 34 patients (16 men and 18 women, average age 47±6.8

years, AH duration 12.6 ± 6.2 years) with AH 1–2 grade who regularly received FC A/L for one year. The control group included 33 patients (15 women and 18 men, average age 48 ± 6.3 years, AH duration 13.4 ± 5.8 years) who took AHA including FC A/L irregularly in case of BP elevation or in case of deterioration of their well-being. This group of patients was used just for the analysis of annual results. Average initial SBP and DBP values in both groups of patients were 171.1 ± 1.8 mm Hg and 98.2 ± 2.3 mm Hg, respectively. The majority of patients had additional CVC RF and/or associated clinical conditions: coronary heart disease, stable angina (I–II functional class), impaired glucose tolerance, dyslipidemia, and smoking. In this study it was found that significant decrease of BP variability measured with 24hBPM occurred after 6 months of regular therapy with FC A/L, and with time these changes became even more evident.

It is worth to highlight the X–CELLENT (The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients) [62], that investigated the influence of candesartan, amlodipine and indapamide on BP reduction and BP circadian variability measured with 24hBPM in 577 patients during 3 months. All 3 drugs effectively reduced BP, but only amlodipine and indapamide significantly lowered circadian BP variability. Several other studies [16, 18] demonstrated the capacity of calcium channel blockers to significantly reduce BP variability.

Conclusion

Taking into account the results of our study, we can conclude that the use of FC A/L comparing with FC B/H contributes to more significant decrease of coronary and cerebrovascular events' risk through the mechanisms modulating BP variability at daytime and at night.

Conflict of interest: None declared

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International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation

Dysfunctional hemodynamic types in healthy young people: functional condition of blood vessels and central hemodynamics

Khursa R.V.*

Belarusian State Medical University, Minsk, Belarus

Author

Raisa V. Khursa, M.D., Ph.D., assistant professor of the department of outpatient therapy, Belarusian State Medical University, Minsk, Belarus.

Summary

Objective

To investigate the functional condition of the blood vessels (endothelium-dependent vasodilatation and pulse wave velocity) and the central hemodynamics (CH) in healthy young people, depending on the type of circulation, defined by linear regression of blood pressure (BP) parameters.

Materials and methods

A total of 120 outpatient healthy young adults and 45 hypertensive patients aged 24.5 ± 0.3 and 29.1 ± 0.7 years respectively were investigated as outpatients before the beginning of treatment. Daily measurements of BP were made several times, the BP set of each patient was used for linear regression, and the hemodynamic types were determined on its coefficients; endothelium-dependent vasodilatation, pulse wave velocity and CH parameters were investigated as well. For statistical processing we used Statistica. 10.0 software.

Results

Regression analysis revealed dysfunctional hemodynamic types in 55.5% of hypertensive patients and in 25.8% of healthy young people, the diastolic dysfunctional type was the most frequent one, and it was found in 20.0% of healthy individuals and in 51.1% of hypertensive patients. Diastolic dysfunctional type in clinically healthy persons represents a latent hemodynamic disorder related to functional vascular disturbances due to increased vascular stiffness. Unlike the harmonic one, this type of dysfunction is characterized with more frequent disturbances of the vasomotor endothelial function (moderate and expressed) and with increased pulse wave velocity (11.4 m/s and 8.1 m/s, respectively, p = 0.00), and there were no differences between normotensive and hypertensive patients (whereas for the harmonic type these differences were significant). Patients with firstly diagnosed AH and different hemodynamic types had similar characteristics of vascular function inside their groups that indicated

* Corresponding author: Tel.: +375 29 318 13 38. E-mail: rvkhursa@tut.by

the existence of different pathogenetic mechanisms responsible for development of these abnormalities. Thus hemodynamic types defined by linear regression of BP parameters and the types of central hemodynamics represent different characteristics of the blood circulation and do not exclude each other.

Conclusion

Linear regression analysis of blood pressure parameters expands the possibilities for diagnosis of clinically latent hemodynamic disorders in normotensive individuals, such as dysfunctional types of the blood circulation, which are associated with functional vascular disorders and to a lesser extent – with disturbances of the central hemodynamics.

Keywords

Blood pressure, linear regression, circulatory types.

Introduction

Wide prevalence, high medical and social significance of arterial hypertension (AH) as the key element of cardiovascular pathology is well-known nowadays. Various aspects of this disease like pathogenesis, endothelial dysfunction and vascular stiffness, inflammation, individual AH phenotypes, blood pressure (BP) measurement techniques, and treatment represent a great interest for researchers [1-5]. At the same time, a period of latent functional cardiovascular abnormalities precedes clinical manifestations of AH, and it explains the necessity of detection of these problems at early stages. BP value as the integral characteristic of cardiovascular system (CVS) function is a promising parameter of early detection of preclinical circulation disorders. Development of modern informational technologies and methods of statistical analysis promotes discovery of new diagnostic possibilities even in this routine technique. In particular, we developed and patented the method of quantitative analysis of BP parameters' connection (QABPC) that represents an elementary regression model of circulation built on random values of patient's BP acquired within some period of time. It is represented as a system of linear equations describing circulation within time interval of observation as interaction between heart and vessels during blood movement:

$$S=Q+a_1W;\ D=Q+a_2W,$$

where S – systolic BP, D –diastolic BP,

W – pulse BP ($W=S-D$).

After simple algebraic modifications a_1 coefficient can be expressed like $a_2=a_1-1$. In this case the regression model of circulation is based on two individual numeric parameters (a and Q) that have distinct physical meaning:

$S=Q+aW$; $D=Q+(a-1)W$, where $a = a_1$.

The coefficient Q reflects the value of BP in the area of descendent pulse wave measured in mm Hg (the characteristic of circulation in distal part of arterioles); the ratio between pressor (a) and depressor (a-1) coefficients defines a QABPC type. We proved the borderline values of a coefficient of the regression model and developed the classification of functional hemodynamic types [6]. It includes the following QABPC types: harmonic one (H), two dysfunctional ones (diastolic – DD and systolic – SD), and borderline harmonic with corresponding dysfunctional trend: borderline diastolic (BD) and borderline systolic (BS) types.

For creation of regression model it is necessary to perform several routine BP measurements within a distinct interval of time (optimal number is 20–25 measurements, if BP variability is low 7 measurements could be enough) and to use PC with appropriate software. Regression parameters characterize CVS function and in particular they describe cardiovascular interaction during blood movement and reflect homeostasis and environmental adaptation of organism. The existence of such hemodynamic types is proven by outpatient BP measurement performed on representative population samples of different gender, age, and health condition. It has been identified that dysfunctional and borderline hemodynamic types are the most frequent in patients with cardiovascular pathology (≥65%), at the same time they can be found in almost healthy individuals with normal BP. In this case it becomes relevant to find out which characteristics of heart and vessels define various circulation types, especially dysfunctional ones, and which is their clinical composition, in particular, in normal individuals?

Correlation between cardio-vascular interaction during blood movement, functional condition of vessels and central hemodynamic parameters are extremely poorly studied.

The objective of this study was to investigate the functional condition of blood vessels (endothelium-

dependent vasodilatation and pulse wave velocity) and the central hemodynamics (CH) in healthy young people, depending on the type of circulation (QABPC type), defined by linear regression of blood pressure (BP) parameters.

Materials and methods

120 healthy young individuals (dispenser groups I and II, 56 males and 64 females) underwent outpatient observation and were included in the Group I (main group), and 45 patients (22 males and 23 females) aged 21–34 years with firstly diagnosed AH (1–2 grade, risk 2–3 before the start of therapy) were included in the Group 2 (comparison group). The average age of patients of the Group I and Group II was 24.5±0.3 and 29.1±0.7 years, respectively.

Patients of both groups underwent daily routine BP measurement during 7–10 days, and obtained BP values were elaborated using the above-described QABPC model that resulted in individual regression models of circulation defining QABPC circulation types and BP values in the area of decreasing pulsation.

Endothelium-dependent vasodilatation (EDV), pulse wave velocity (PWV), and CH parameters were evaluated within the same time interval using rheological techniques and "Impecard-M" equipment.

Brachial artery EDV was defined using reactive hyperemia test after 5 minutes of compression of the arm with a cuff and measurement of rheographic parameters at rest and 1, 2 or 3 minutes after cuff removal (Test 1). After it the second similar test was performed in order to evaluate EDV reserve (Test 2). Relative change of maximal volume flow rate Δ(dz/dt)% was quantified in both cases for each minute of decompression. EDV condition was evaluated in qualitative way on base of Δ(dz/dt)% value: no disturbances, moderate disturbance, evident disturbance, significant disturbance [7]. Time of pulse wave distribution and PWV were quantified according to the technique described at [7], and PWV values below 10.2 m/s were considered normal.

To evaluate CH parameters we performed impedance cardiography with consequent analysis of quantifiable parameters: stroke volume (SV, mL), cardiac output (CO, L/min), cardiac index (CI, L/(min*m^2)), total peripheral resistance (TPR, din*s*cm^{-5}), average BP (ABP, mm Hg), left ventricular filling pressure (LVFP, mm Hg) and evaluated CH type (normokinetic, eukinetic, hypokinetic, hyperkinetic ones) [8].

Statistical analysis was performed using Statistica 10.0 software. All obtained values were checked for normality using Shapiro-Wilk test. Quantitative parameters are present as median values (Me) and inter-quartile interval (25%–75%) in case of not-normal distribution. The significance of differences between relative and absolute values was estimated using χ^2 test and Mann-Whitney U-test, respectively. $p<0.05$ was considered significant.

Results and discussion

The distribution of QABPC types according to BP measurement in observation groups is present in Figure 1. It can be observed that harmonic hemodynamics prevailed in almost healthy young people, whereas dysfunctional types like DD one are more frequent in case of AH (the differences in H, SD, and DD types between groups are statistically significant). These results go along with our previous studies that indicated that DD type prevailed in patients with AH [1]. At the same time 25.8% of healthy individuals of the Group I had dysfunctional hemodynamics with prevalence of DD-type (20.0% of patients of this group), and 35.6% of patients with AH had harmonic type of hemodynamics.

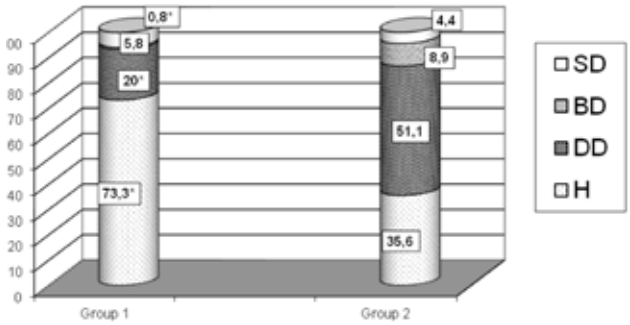

Figure 1. QABPC hemodynamic types in observation groups, % of individuals
Comment - *- statistically significant differences (p<0,05) comparing with the Group 2 (patients with AH).

In this regression model adequately defined relation between BP values D<Q<S corresponds to H type (0<*a*<1). Reduction of pressure coefficient to *a*<0 in SD type reflects the reduction of myocardial contractile function in blood movement that is compensated with increased function of so-called "peripheral heart" made of vessels and muscles (*D<S<Q*). Another inequation D<S<Q is fair, whereas *a*>1 indicates increased role of systolic component in circulation and decreased role of diastolic (vascular) component, in this case *Q<D<S* inequation is feasible (DD type). This interpretation of types and borders between them that can be concluded from the logic of regression is well-compatible with modern conceptions of interaction between the left ventricle (LV) and arterial system

Table 1. **Parameters of regression models (*a, Q*), BP and HR values in observation groups for different QABPC types (Me, 25%–75%)**

Group	Type	n	*A*	*Q*, mm Hg	SBP, mm Hg	DBP, mm Hg	PBP, mm Hg	HR, beats per minute
1	DD	24	1.28*^ 1.17–1.46	64.0^ 53.1–69.1	119.8^ 112.6–128.4	75.2^ 71.4–78.4	42.9^ 39.9–50.0	75.5 66.0–82.0
	BD	1	0.96	79.9	124.0	77.9	46.1	66.0
	SD	7	–0.16* –0.57...–0.07	132.3^ 121.2–154.9	120.8^ 118.0–139.3	74.7^ 71.4–77.7	45.0^ 40.3–49.3	74.0 66.0–82.0
	H	88	0.58^ 0.42–0.74	94.77 85.6–103.7	122.1^ 115.0–128.0	74.9^ 70.9–78.4	46.0^ 41.7–50.3	73.5 63.0–82.0
	Total	120	0.63^ 0.42–0.86	90.1 80.4–102.1	121.0^ 115.0–128.1	75.2^ 71.0–78.3	45.2^ 41.1–50.0	74.0 64.5–82.0
2	DD	23	1.27* 1.20–1.54	75.2 65.0–81.2	138.7 135.0–143.4	89.0 83.0–91.5	49.7 46.7–54.7	72.0 62.0–80.0
	BD	4	1.02* 1.01–1.04	88.3 87.2–90.0	145.2 138.3–149.3	88.8 87.8–91.2	53.9 49.6–59.0	73.0 69.0–83.0
	SD	2	–0.54* –0.7...–0.37	177.9 170.0–185.7	148.4 146.4–150.3	94.0 90.7–97.4	54.4 53.0–55.7	59.0* 50.0–68.0
	H	16	0.62 0.50–0.72	110.5 102.4–117.4	140.91 133.2–144.0	91.3 84.6–93.2	48.90 44.7–54.7	75.5 71.0–91.0
	Total	45	1.06 0.68–1.27	86.36 75.25–107.7	14000 135.0–146.4	89.9 84.80–92.5	50.00 46.8–54.7	73.0 65.0–82.0

Comments:
1 — Differences inside groups with H type (p<0,05); ^— differences with the Group 2 (p<0,05)
2 — Q and a – regression coefficients, SBP, DBP, and PBP – systolic, diastolic, and pulse blood pressure, respectively, HR – heart rate

represented as "pressure-volume" loop, and optimal ratio between arterial elastance and end-systolic LV elastance of healthy individuals stays in the interval of 0.7-1.0 [9, 10].

Measured BP values within the time interval in the Group 1 were significantly different from the ones in the Group 2 that corresponded to diagnosed AH. At the same time these values did not differ between different QABPC types within one group, whereas regression model parameters were significantly different for above-described types (Table 1).

60.8% of almost healthy individuals (n=73) had no disorders of vasomotor endothelial function, and this value was significantly higher than in the Group 2 (7 individuals, 15.5%). EDV disturbances were more frequently detected in the group of patients (84.4%) with AH and varied from moderate to evident and significant ones (p=0.000).

During each minute there were significant differences of relative change of maximal volume flow rate Δdz/dt% between comparison groups as for the first test as for the second one (Figure 2).

The investigation of the frequency of ADV disorders in relation to their QABPC type demonstrated that dysfunctional types and in particular the DD one from the Group 1 were significantly different from the H type being characterized with a higher percentage of people with moderate and evident ADV disorders and, consequently, with a lower proportion of individuals with normal ADV. SD type was enough rare in both groups, but normotensive people belonging to SD type had normal vasomotor function significantly less frequently comparing with the H type. At the same time, there were no significant differences in EDV condition depending on QABPC type in the Group 2 (Table 2). BD type was present just in 1 patient of the

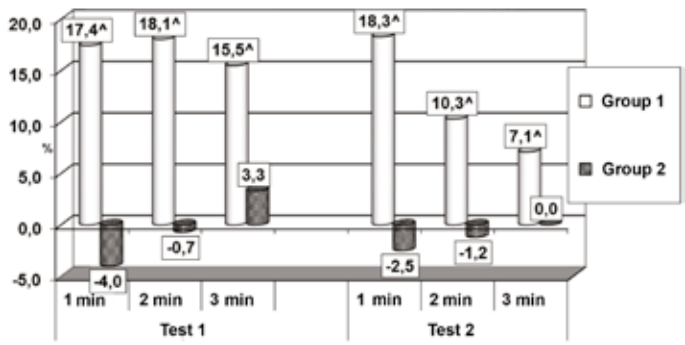

Figure 2. Δdz/dt% values (relative change of maximal volume flow rate, %, Me) in observation groups after reactive hyperemia test.
Comment: ^ - the differences comparing with the Group 2 (p<0.05).

Table 2. **Condition of EDV in different QABPC types in observation group after reactive hyperemia test % (n)**

Test	Type	Healthy individuals (Group 1)					Patients with AH (Group 2)				
		EDV condition					EDV condition				
		n	1	2	3	4	n	1	2	3	4
1	DD	24	37.5*^# (9)	25.0* (6)	37.5* (9)	0^# (0)	24	8.7 (2)	26.1 (6)	43.5 (10)	21.7 (5)
	H	88	69.3^# (61)	5.7^ (5)	15.9^# (14)	9.1^ (8)	16	25.0 (4)	12.5 (2)	43.7 (7)	18.7 (3)
	SD	7	28.6* (2)	28.6 (2)	42.8 (3)		2	50.0 (1)		50.0 (1)	
2	DD	24	45.8* (11)	12.5 (3)	37.5* (9)	4.2# (1)	23	21.7 (5)	21.7 (5)	26.1 (6)	30.4 (7)
	H	88	68.2^# (60)	10.2 (9)	10.2^# (9)	11.4 (10)	16	37.5 (6)	18.8 (3)	37.5 (6)	6.2 (1)
	SD	7	28.6 (2)	28.6 (2)	42.8* (3)		2	50.0 (1)		50.0 (1)	

Comment:
EVD condition: 1 — no disturbance, 2 — moderate disturbance, 3 — evident disturbance, 4 — significant disturbance.
* — difference with H-type of the corresponding group (p<0,05),
^ — difference with the Group 2 in general (p<0,05),
# — difference with the corresponding type of the Group 2 (p<0,05).

Group 1 and in 4 patients of the Group 2, so it is not present in the Table 2.

Probably, in case of already developed AH not only vascular but also other pathogenetic mechanisms contribute in formation of hemodynamic types, whereas clinically latent hemodynamic shifts that manifest as dysfunctional hemodynamic types in normotensive people are related to functional vascular disturbances as impaired EDV. At the same time the majority of normotensive people with dysfunctional hemodynamic types have initial and expressed stages of EDV disorders, similar with the ones observed in patients with AH. The absence of significant differences in the frequency of moderate and evident EDV between dysfunctional types of normotensive people (Group 1) and patients with AH (in general and for corresponding types) is notable, it allows considering normotensive individuals with dysfunctional hemodynamics as the group of high risk of AH development.

Evaluation of endothelial reserve (Test 2) revealed similar percentage of individuals with different EDV condition in groups in general and depending on their type (Table 2).

Δdz/dt% values did not differ significantly within each group, apart from DD and H types in test1: healthy individuals had significantly lower Δdz/dt values measured after 3 minute comparing with the H type (10.8% and 20.7%, respectively, p<0.05); and the same differences were detected in the group of patients with AH after 2 minutes (-1.4% and 13.6%, respectively, p<0.05). Probably, dysfunctional hemodynamic types like the DD one are characterized with delayed and less evident vascular reaction on stress test and reserve capacity of endothelium, in particular in case of AH, is reduced. At the same time healthy individuals with H-type were significantly different from patients with AH for every minute of the study, and healthy individuals with dysfunctional types DD and SD had no such differences. These results indicate pathological origin of these types due to their hemodynamic similarity with AH.

Endothelial disbalance leads to increased stiffness of vascular wall and impaired damping capacity that shortens the time of pulse wave distribution (PWT) and increases PWV. High frequency of EDV in dysfunctional hemodynamic types affects these characteristics. In particular, PWT of DD type was significantly shorter and PWV was significantly higher than the ones of H type (11.4 m/s and 8.1 m/s, respectively, p=0.001) and did not differ from PWV of patients with AH (p<0.05), whereas the differences of this parameter between H type of normotensive individuals and patients with AH were statistically significant (Table 3). Patients with AH had no significant differences of PWT and PWV for different QABPC types that goes along with the above-mentioned absence of differences in frequency and expression of endothelial vasomotor function disturbances between different types.

Increase of PWV and the frequency of EDV abnormalities registered in DD-type of healthy individuals has been previously demonstrated by our group in the study where we performed QABPC analysis of BP values after 24h BP monitoring. It perfectly corresponds to the results of this study [8].

Thus, dysfunctional QABPC types reflect clinically latent hemodynamic disturbances in normotensive people, and impaired vasomotor function of the vessels (EDV) and increased PVW belong to them. In its

Table 3. **Time and PWV in different QABPC types in observation groups (Me, Q 25%–Q 75%)**

Group	Type	n	PWT, c			PWV, m/c		
			Me	Q 25%	Q 75%	Me	Q 25%	Q 75%
1	DD	24	50.0*	40.0	65.0	11.4*	8.1	13.7
	BD	1	160.0	160.0	160.0	3.3	3.3	3.3
	SD	7	60.0	50.0	70.0	9.0	7.7	9.6
	H	88	70.0^	60.0	80.0	8.1#	7.0	9.5
	Total	120	60.0^	50.0	80.0	8.5#	7.1	9.6
2	DD	23	50.0	40.0	70.0	11.4	8.0	13.5
	BD	4	45.0	30.0	140.0	12.6	6.7	21.4
	SD	2	50.0	40.0	60.0	12.6	10.8	14.3
	H	16	75.0	40.0	130.0	7.5	4.1	14.6
	Total	45	50.0	40.0	80.0	11.0	7.0	14.3

Comment:
* — difference with H-type of the corresponding group, p<0,05;
# — comparison with the Group 2 in general, p<0,05

Table 4. **Characteristics and types of CH in observation groups, Me/25%–75%**

Parameters, CH types		Group 1, n=120	Group 2, n=45
CH parameters	Initial SV, mL	68.0 / 55.5–80.5 *	56.1 / 36.9–66.2
	Initial CO, L/min	5.0 / 4.0–6.0 *	4.0 / 3.1–5.2
	Initial CI, L/min×m^2	2.8 / 2.2–3.4 *	2.0 / 1.6–2.7
	Initial TPR, din×s×cm^{-5}	1537.6 /1237.0–1892.8 *	2158.1 / 1567.2–2902.2
	Initial ABP, mm Hg.	92.5/85.0–99.3*	105.3/ 93.0–114.0
	Initial LVFP, mm Hg	16.9 / 15.9–18.0	17.6 / 16.4–18.3
CH types	Normokinetic, % (n)	50.0% (60)*	28.9% (13)
	Eukinetic, % (n)	6.7% (8)	4.4% (2)
	Hyperkinetic, % (n)	20.0% (24)*	6.7% (3)
	Hypokinetic, % (n)	23.3% (28)*	60.0% (27)

Comment:
*— p<0,05 comparing with the Group 2.

turn, it can become the background for future AH development. There were no significant differences of LVFP in both groups that may be explained by relatively young age of the participants and early stages of AH in the majority of patients of the Group 2. The percentage of patients with pathological hypokinetic type of CH was significantly higher in case of AH, whereas normokinetic and hyperkinetic types prevailed in normotensive patients. SV, CO, CI, and LVFP after stress test (ergometric stress testing) and at rest differed significantly between groups. The same differences were observed for all initial values of these parameters apart from LVFP.

Figure 3 demonstrates the distribution of CH types in different QABPC types in observation groups.

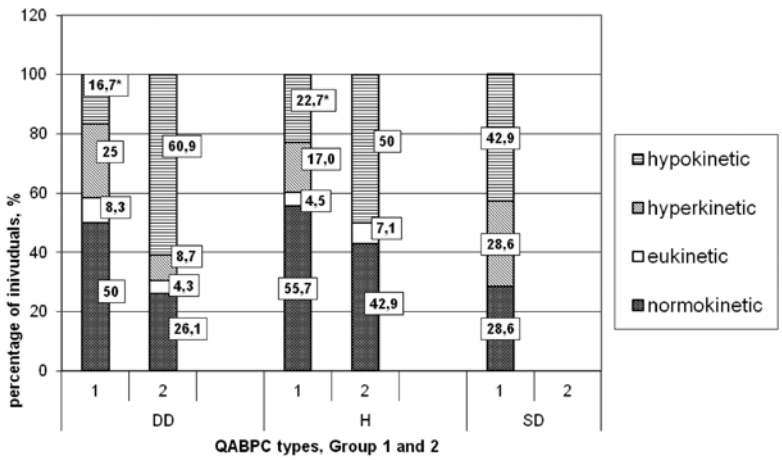

Figure 3. CH types distribution for different QABPC types, %
Comment. * — difference with the corresponding type of the Group 2, p<0.05.

Statistically significant differences of CH parameters and types between different QABPC types within each group have not been found. It may indicate that hemodynamic types identified according to regression analysis (QABPC-types) and CH types defined after rheographic assays represent different characteristics of circulation and do not substitute but complete each other for diagnostic purposes. In particular, it is possible to hypothesize that QABPC mostly reflects the circulation in distal parts of circulatory system (terminal parts of arterioles). At the same time, the lack of differences between different QABPC types within each of observation groups may be explained by small number of patients with DD and SD types, in particular with the SD one (7 persons from the Group 1, 1 person from the Group 2), that makes it favorable to perform other studies in this direction.

CH parameters (apart from initial LVfP and LVfP at rest) of healthy young individuals with H-type were significantly different from the ones of hypertensive patients, but SW and CI of SD type did not differ significantly from the values of these parameters in normotensive patients, and these values were lower than the corresponding ones for H-type of each group ($p>0.05$). More than that, there was the tendency for TPR increase ($p>0.05$) in particular after stress test (Table 5).

These results allow considering the reduction of heart's pumping function observed in SD-type and go along with the explanation of this type using the regression model that gives the leading role in heart pumping to the "peripheral heart". At the same time, taking into account small number of patients with this QABPC type as in the current study as in population in general [1], it is necessary to increase the number of patients to obtain more confident results.

Regression analysis of BP parameters (QABPC) demonstrated dysfunctional hemodynamic types in 55.5% of young patients with AH before the start of the treatment and in 25.8% of healthy young individuals with normal BP. DD type prevailed between dysfunctional types in both groups: it was present in 20.0% of healthy individuals and in 51.1% of patients with AH. This type is characterized with increased pressor parameter of regression (coefficient a(a>1)) that indicates the increased role of systolic component (cardiac output) for blood movement and decreased role of the diastolic (vascular) component. In this case the pressure of pulseless blood flow becomes less than diastolic one, whereas the H type keeps this value equal to diastolic BP. Thus, this regression doesn't correspond to normal physiological parameters characterizing the interplay between "cardiac" and "vascular" components of the blood flow. This hemodynamic type is pathological, and its presence in healthy individuals indicates the presence of latent hemodynamic disturbances.

Our study demonstrated that normotensive young people with DD-type had functional vascular abnormalities. In particular, this type is associated with abnormal endothelial vasomotor function (moderate and evident), increased PWV (that indicates increased vascular stiffness). Parameters of vascular function

Table 5. **Several parameters of CH in studied groups depending on individuals' QABPC type, Me/25%-75%**

Parameters	Group 1, QABPC type				Group 2, QABPC type			
	DD	BD	H	SD	DD	BD	H	SD
Initial SV, mL	67.2*/ 55.4–77.6	34.2	68.0*/ 56.2–80.6	73.7* / 54.2–102.1	54.9/ 29.0–68.7	59.2/ 54.8–69.7	55.4/ 47.2–60.4	54.2/ 32.1–76.3
Stress SV, mL	63.2/ 52.4–76.0	26.1	62.6*/ 52.4–81.4	76.1/ 55.5–77.2	51.9/ 36.9–65.3	59.0/ 53.6–65.8	55.2/ 47.1–78.0	47.5/ 33.2–61.7
SV at rest, mL	63.4*/ 56.2–78.1	24.2	68.4*/ 59.6–84.1	69.6*/ 55.2–87.6	55.4/ 32.8–65.1	64.8/ 51.6–71.8	50.6/ 45.2–63.0	56.2/ 34.8–77.5
Initial CO, L/min	5.1 */ 4.2–6.6	2.6	5.0*/ 4.1–5.9	4.4/ 4.0–6.9	3.9/ 2.3–5.2	4.8/ 3.8–5.8	4.1/ 3.3–5.4	3.1/ 2.2–4.0
Stress CO, L/min	5.3/ 4.1–7.2	2.2	5.7*/ 4.4–7.0	5.0/ 4.5–6.6	4.4/ 3.1–6.1	6.7/ 5.5–8.3	4.1/ 3.6–7.1	5.0/ 4.4–5.5
CO at rest, L/min	5.0 */ 4.2–6.4	1.8	5.2*/ 4.1–6.2	4.7/ 4.3–6.0	3.7/ 2.5–5.7	5.1/ 3.8–5.9	3.7/ 3.2–5.5	3.2/ 2.3–4.0
Initial CI, L/min*m^2	3.2/ 2.4–3.9*	1.2	2.8*/ 2.2–3.4	2.6/ 2.1–4.0	2.1/ 1.2–2.7	2.4/ 1.8–3.2	2.0/ 1.6–3.0	1.4/ 1.0–1.9
Stress CI, L/min*m^2	3.4*/ 2.4–4.0	1.1	3.3*/ 2.5–4.2	2.7/ 2.3–3.8	2.4/ 1.5–3.1	3.7/ 2.9–4.2	2.3/ 1.7–3.6	2.2/ 2.1–2.4
CI at rest, L/min*m^2	3.0*/ 2.4–3.8	0.9	2.9*/ 2.3–3.4	2.5/ 2.2–3.5	2.0/ 1.5–2.9	2.7/ 1.8–3.2	2.0/ 1.5–3.0	1.4/ 1.0–1.9

Comment.
* — $p<0,05$ comparing with the Group 2

measured in healthy individuals with DD type had no statistical differences comparing with patients with firstly diagnosed AH, whereas the differences with H-type healthy individuals were significant. These functional vascular disorders in DD-type prove the accuracy of the above-mentioned interpretation of this regression model characterizing this type as a functional disturbance of vascular (diastolic) circulation component.

Patients with firstly diagnosed AH had worsened parameters of vascular function (EDV, PWV, PWT) comparing with healthy individuals of comparable age. At the same time these parameters did not differ significantly between different QABPC types within one group, as it was described for the group of healthy individuals. It may indicate the involvement of other mechanisms into formation of dynamic QABPC types in AH.

QABPC types identified with linear regression of BP parameters and CH types (assessed with rheographic examination) represent different characteristics of hemodynamics and do not substitute but complete each other for diagnostic purposes.

Conclusion

Regression model of circulation built on BP parameters (QABPC) widens diagnostic resources for such clinically latent hemodynamic disorders as dysfunctional circulation types related to functional disturbances of vessels and CH. Additional examination and dynamic observation are required in almost healthy patients with dysfunctional circulation.

Conflict of interest: None declared

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International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation

Use of rosuvastatin in patients with chronic obstructive pulmonary disease

Samorukova E.I.*, Adasheva T.V., Zadionchenko V.S., Bagatyrova K.M., Li V.V.

Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia

Authors

Elena I. Samorukova, M.D., Ph.D., senior researcher at the department of outpatient therapy, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.
Tatiana V. Adasheva, M.D., Ph.D., doctor of sciences, professor of the department of outpatient therapy, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.
Vladimir S. Zadionchenko, M.D., Ph.D., doctor of sciences, professor, professor of the department of outpatient therapy, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.
Kalimat M. Bagatyrova, M.D., Ph.D., associate professor at the department of outpatient therapy, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.
Vera V. Li, M.D., Ph.D., doctor of sciences, professor of the department of outpatient therapy, Moscow State University of Medicine and Dentistry named after A. I. Evdokimov, Moscow, Russia.

Summary

Objective

To investigate the effects of rosuvastatin on systemic inflammation, endothelial dysfunction, and clinical course of chronic obstructive pulmonary disease (COPD).

Materials and methods

This study included 110 patients with COPD and without history of cardiovascular events. These patients had high or very high cardiovascular (CV) risk (10.0 [8.0; 18.0]) according with the SCORE (Systematic Coronary Risk Estimation) scale. In order to correct CV risk, 90 patients with COPD were prescribed with rosuvastatin (10 mg) and dose titration up to reaching target levels of low density lipoprotein cholesterol according to CV risk calculated within 1 year. Control group consisted of 20 patients with COPD. We estimated the levels of high sensitive C-reactive protein (hs-CRP), inflammatory (Tumor Necrosis Factor α (TNF-α), interleukin-8 (IL-8)) and anti-inflammatory cytokines (IL-4, IL-10) in blood serum, and Vascular Cell Adhesion Molecule type 1 (VCAM-1).
Clinical course of COPD was estimated according to the number of COPD exacerbations and St.George's Respiratory questionnaire. Tolerance to physical exercise was determined using 6 minute walk test.

* Corresponding author. Tel.: +79851359172. E-mail: wlrad@bk.ru

Results

Therapy of rosuvastatin led to significant reduction of hs-CRP levels (21.5%, p=0.001), TNF-α (26.7%; p=0.001), IL-8 (32.6%; p=0.001), IL-4 (15.4%; p=0.001), IL-10 (16.5%; p=0.001), VCAM-1 (28.9%, p=0.003); number of COPD exacerbations (25%, p<0.001), severity of COPD symptoms according to St.George's Respiratory questionnaire (19.9%, p<0.001). The tolerance to physical exercise increased (13.2%, p<0.001). The main group demonstrated increased tolerance to physical exercise (13.2%, p<0.001). Plasma levels of TNF-α (19.3%; p=0.001) and IL-4 (30%; p=0.001) were increased in the control group together with 5% reduction of distance in 6 minute walk test (19 meters; p=0.001).

Conclusion

Rosuvastatin has anti-inflammatory, endothelium-protective, and immune-modulatory effects, influences the key systemic processes of COPD and CV diseases formation, and it can also modify the clinical course of COPD (reducing the number of exacerbations and severity of symptoms, improving tolerance to physical exercise), in patients with COPD. It is recommended to calculate CV risk and perform its correction according with the common guidelines in all patients with COPD.

Key words

Rosuvastatin, statins, chronic obstructive pulmonary disease (COPD), systemic inflammation, COPD exacerbation, COPD symptoms.

Introduction

Chronic obstructive pulmonary disease (COPD) is a global problem of modern medicine [1]. Nowadays the number of patients suffering from this disease is increasing [2]. Also the mortality caused by COPD is increasing. COPD became the 3rd leading cause of death in the world after cardiovascular diseases (CVD) [3].

CVD are the most frequent and severe comorbid diseases influencing the life quality and lifespan of patients with COPD [4–6]. Different authors indicate COPD as the cause of death in 25.0–48.8% of all death cases, 23.3% and 20.9% of them are caused by respiratory insufficiency and lung cancer, respectively [6, 7].

CVD prevalence in COPD patients is 50.0–56.5%, whereas CVD frequency in patients without COPD is 25.6% [8].

It has been found that COPD progression, increase of respiratory insufficiency worsens the prognosis of patients with COPD. Scientists agree that decrease of forced expiratory volume expired in the first second (FEV1) is one of the factors of cardiovascular lethality [9–12].

COPD patients have high cardiovascular risk, and COPD by itself is an independent factor of cardiovascular complications and mortality [13].

According with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2017), COPD is a common disease that can be prevented and treated and that is characterized with persisting respiratory symptoms and restricted airflow related to bronchial and/or alveolar abnormalities normally caused by severe impact of damaging particles or gases [1].

At the same time, COPD is a systemic disease with extrapulmonary (systemic) manifestations that include cardiovascular system lesions, cachexia, skeletal muscle dysfunction, and osteoporosis [4, 14, 15]. Numerous observation, epidemiologic, and retrospective studies demonstrated that high levels of the markers of systemic inflammation correlated with higher frequency of admission to hospital, rapid COPD progression, and higher general and cardiovascular lethality in patients with COPD [10, 16–19].

Lungs are the epicenter of inflammation in COPD patients, and the distribution of inflammatory cytokines and oxidants into systemic circulation (so-called «spill over» effect) starts from there and leads to development of systemic inflammatory reaction [16, 20, 21].

Pulmonary inflammation in COPD patients is a pathologically enhanced inflammatory response of the airways on long-term exposure to various irritants, and cigarette smoke is the most important one of them. Inflammation plays the key role in bronchopulmonary and cardiovascular systems remodeling in COPD patients.

Modern inhalation therapy of COPD considers using M-cholinolytics, β2-agonists, glucocorticoids and reduces the severity of COPD symptoms, frequency and severity of COPD exacerbations, improves physical exercise tolerability and life quality in COPD patients, but unfortunately it fails to influence the mor-

tality of these patients and prevent progression of pulmonary function loss [1].

The active search of anti-inflammatory medications for COPD patients is going on. Potential role of various drugs like N-acetylcysteine, phosphodiesterase-4 inhibitors, cytokine antagonists, macrolides, statins, rennin-angiotensin-aldosterone system blockers has been already investigated [22, 23, 24]. At the same time, neither one of compounds with anti-inflammatory and antioxidant mechanism of action has not been included into COPD treatment guidelines by now.

Several observation retrospective studies demonstrating the following clinical effects of statin administration in COPD patients have been published, and these studies reported the reduction of total mortality, mortality caused by COPD exacerbation, decreased need of intubation during COPD exacerbation, COPD-related mortality, and reduced number of COPD exacerbations, decreased risk of admission to hospital and lung function impairment, improved tolerance to physical exercise and smaller risk of lung cancer [20, 21, 25–29].

Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) reductase that inhibit cholesterol synthesis in liver thus mediating their lipid-lowering effect.

Pleiotropic effects of statins are caused by the fact that they abrupt formation of cholesterol synthesis pathway products like farnesyl pyrophosphate and geranyl-geranyl pyrophosphate which in their turn activate intracellular signaling regulatory molecules from the family of GTP-binding proteins (Ras, Rho, Roc) via isoprenylation. Statins reduce activation of these molecules, inhibit nuclear factor NF-kB, and activate peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ) that decreases expression of adhesion molecules and chemokines (CCL2 and CXCL8), reduces synthesis of cytokines, proteinases, and down-modulates inflammation (Figure 1) [16, 17, 21, 30].

The objective of this study was to investigate the effects of rosuvastatin on systemic inflammation, endothelial dysfunction, and clinical course of COPD.

Materials and methods

This study included 110 patients with COPD (males) with 2–3 stages of the disease estimated with airflow restriction, of stable course or at least one month after successful management of COPD exacerbation who did not receive systemic glucocorticoids during at least the last 6 months. The average age of patients was 63.0 [61.0; 70.6] years. The smoking index was 49.0 [40.0; 70.0] pack-years. All patients signed informed consent for participation in this study.

Exclusion criteria were the following: history of bronchial asthma, cardiovascular events, diabetes mellitus, chronic decompensated pulmonary heart, refractory arterial hypertension (BP>140/90 mm Hg) and other diseases that could have interfered with results estimation.

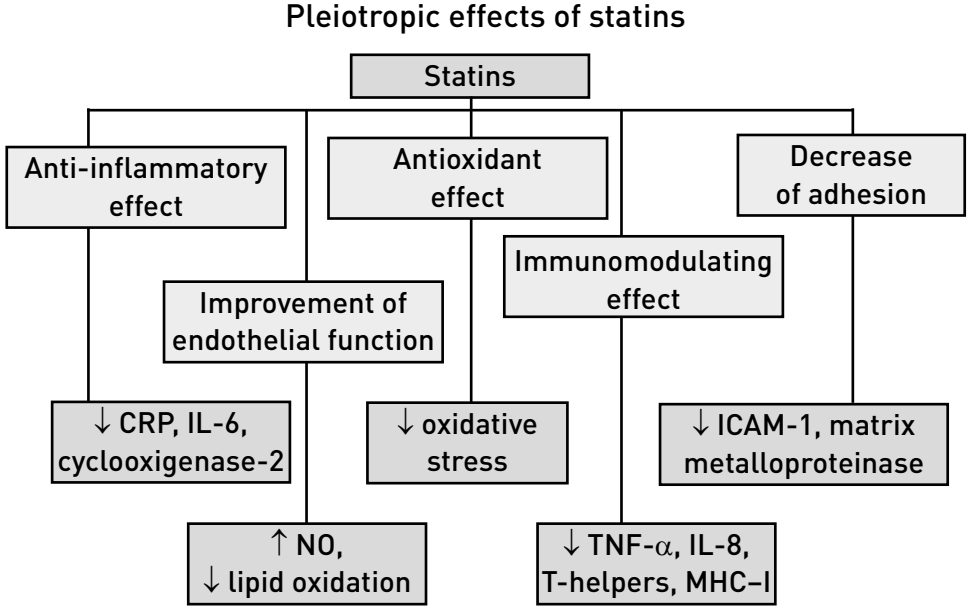

Figure 1. Pleiotropic effects of statins
CRP — C-reactive protein, IL-6 — interleukin– 6, IL-8 — interleukin 8, NO — nitric oxide, TNF-α — tumor necrosis factor — α, ICAM—Inter-Cellular Adhesion Molecule 1, MHC II — major histocompatibility complex

Table 1. **Lipid profile dynamics in COPD patients during therapy with rosuvastatin**

	Rosuvastatin group n=90				Control group n=20		
Parameters	Before treatment	After treatment	Δ (%)	p_1	Initially	After 12 months of observation	p_2
Total cholesterol (mmol/L)	5.7 [4.9; 7.1]	3.3 [2.9; 4.4]	–31.0 [–42.1; –27.6]	<0.001	5.6 [4.9; 6.9]	5.7 [4.9; 7.0]	Ns
Triglycerides (mmol/L)	1.0 [0.8; 2.1]	0.8 [0.7; 1.4]	–25.0 [–31.3; –12.5]	<0.001	1.1 [0.8; 2.0]	1.2 [0.8; 2.1]	Ns
HDL cholesterol (mmol/L)	1.5 [1.3; 1.8]	1.6 [1.4; 1.7]	6.7 [–5.6; 7.7]	Ns	1.5 [1.2; 1.7]	1.5 [1.2; 1.6]	ns
LDL cholesterol (mmol/L)	3.3 [2.9; 3.8]	1.6 [1.2; 1.8]	–50.2 [–63.2; –39.5]	<0.001	3.2 [2.7; 3.9]	3.4 [2.6; 4.0]	ns

Comment: data are present as median, the first and the third quartile (Me [Q25%, Q75%].
Δ (%) — the difference between «before» and «after» values measured in % and present as Me [Q25%, Q75%]. We used two-sided Wilkoxon t-test for estimation of differences before and after therapy with rosuvastatin. Ns — non-significant.
p_1 –significance of differences before and after therapy with rosuvastatin
p_2 — significance of differences in the control group before the study and after one year of observation

All patients underwent cardiovascular risk (CVR) estimation according with the SCORE (Systematic Coronary Risk Estimation) score that was either high or very high 10.0 [8.0; 18.0]. Patients were divided into two groups.

Rosuvastatin group included patients with COPD and it consisted of 90 individuals who received rosuvastatin for CVR correction (10 mg per day for 1 year with dose titration until reaching target levels of low density lipoprotein (LDL) cholesterol according with quantified SCORE risk: very high SCORE risk — LDL cholesterol ⩽1.8 mmol/L, high SCORE risk — LDLD cholesterol ⩽2.5 mmol/L).

20 patients with COPD were included in the control group. Members of both groups had comparable age, smoking history, COPD duration and severity, number of exacerbations, and COPD inhalation therapy. Basis COPD therapy remained unchanged during all study duration. Patients received inhalation anticholinergic drugs (ipratropium bromide, tiotropium bromide), β2-adrenomimetics (fenoterol), inhalation glucocorticoids according with the GOLD guidelines.

Concentration of cholesterol, triglycerides, LDL cholesterol, high density lipoproteins (HDL) cholesterol was performed before therapy initiation and 1, 3, 6, and 12 months after the start of treatment with rosuvastatin.

We estimated the levels of high sensitive C-reactive protein (hs-CRP), inflammatory (Tumor Necrosis Factor α (TNF-α), interleukin-8 (IL-8)) and anti-inflammatory cytokines (IL-4, IL-10) in blood serum, and Vascular Cell Adhesion Molecule type 1 (VCAM-1) in order to evaluate endothelial dysfunction using enzyme-linked immunosorbent assay.

Clinical course of COPD was estimated according to the number of COPD exacerbations and St.George's Respiratory questionnaire. Respiratory function was controlled in the beginning of the study, 6 months after the start of the treatment and one year after it. Tolerance to physical exercise was determined using 6 minute walk test.

Statistical analysis was performed using the SPSS version 22 software. Since the data were not distributed normally, data are present as median value, the first and the third quartile. Two independent samples were compared using Mann-Whitney test, whereas two-sided Wilkoxon t-test was used for comparison of two dependent samples. Comparison of dichotomous variables was performed using two-sided Fisher's exact test (for independent samples), whereas for paired nominal data we used McNemar's test. Differences were considered significant in case of $p<0.05$.

Results and discussion

All patients have reached target LDL-cholesterol levels after dose titration. There was no statistically significant dynamics of HDL cholesterol concentration (Table 1). The control group demonstrated no statistically significant dynamics of blood lipid concentration.

There were no significant changes of concentration of liver transaminases, blood glucose, and glomerular filtration rate.

Hs-CRP levels were decreased by 21.5% (p=0.001) during therapy with rosuvastatin, whereas no statistically significant dynamics was observed in the control group (Table 2).

Patients receiving rosuvastatin demonstrated significant decrease of VCAM-1 concentration by 28.9% (p=0.003), and control group patients had no significant dynamics of this parameter (Table 2).

Rosuvastatin group was characterized with statistically significant decrease of serum levels of inflammatory markers (TNF-α, IL-8) and anti-inflammatory cytokines (IL-4, IL-10) that indicated reduction

Table 2. ***Dynamics of markers of systemic inflammation and endothelial dysfunction in COPD patients during therapy with rosuvastatin***

	Rosuvastatin group n=90				Control group n=20			
Parameters	Before treatment	After treatment	Parameters	Before treatment	After treatment	Parameters	Before treatment	After treatment
Hs-CRP,mg/L	3.3 [2.2; 4.7]	2.8 [1.7; 3.8]	–21.5 [–23.5; –19.1]	0.001	3.4 [2.3; 4.6]	3.6 [2.5; 4.4]	Ns	ns
VCAM-1, ng/mL	1176 [846; 1380]	795 [740; 875]	– 28.9 [–35.3; – 4.8]	0.003	1160 [850; 1390]	1190 [960, 1400]	Ns	Ns
Blood TNF-α, pg/mL	7.02 [5.68; 7.8]	5.2 [3.8; 6.3]	– 26.7 [–32.5; –18.6]	0.001	7.3 [5.50; 7.9]	8.76 [6.27; 8.37]	19.33 [13.6; 6.18]	0.001
Blood IL-8, pg/mL	2.71 [1.5; 3.48]	1.8 [0.93; 2.85]	– 32.6 [–38.1; –17.3]	0.001	2.61 [1.71; 3.60]	3.9 [1.93; 3.66]	Ns	Ns
Blood IL-4, pg/mL	1.4 [0.8; 2.21]	1.18 [0.64; 1.99]	–15.4 [–20.4; –10.6]	0.001	1.40 [0.9; 2.22]	1.82 [1.2; 2.93]	30.0 [23.2; 63.54]	0.001
Blood IL-10, pg/mL	26.4 [15.2; 39.45]	22.0 [7.6; 39.1]	–16.5 [–50.5; –0.33]	0.001	25.2 [17.5; 39.4]	26.6 [18.0; 39.3]	Ns	Ns

Comment: see Table 1.

of systemic inflammation (Table 2). Lower levels of anti-inflammatory cytokines could be explained with smaller necessity of their involvement into systemic inflammatory reaction and suppression of macrophage activity. Control group patients demonstrated increased concentrations of TNF-α (19.33 %, p=0.001) and corresponding increase of IL-4 levels (30 %, p=0.001) that may be caused by progression of systemic inflammation (Table 2).

Decreased levels of markers of systemic inflammation and endothelial dysfunction during rosuvastatin therapy indicate their anti-inflammatory, immunomodulating, and endothelium-correcting action in patients with COPD.

Evaluation of COPD clinical course during therapy with rosuvastatin

Rosuvastatin therapy resulted in significant 25 % decrease of the number of COPD exacerbations during one year (Table 3).

The frequency of COPD respiratory symptoms (the «Symptoms» scale), physical exercise restriction (the «Activity» scale), the number of psychological and social problems related to COPD (the «Impact» scale) determined using Saint George's Questionnaire significantly decreased that demonstrated the positive impact of rosuvastatin on COPD clinical course. There was no statistically significant dynamics in the control group (Table 3).

According to the results of 6-minute walk test, patients with COPD who received rosuvastatin demonstrated statistically significant increase of physical exercise tolerance as the distance passed in this test increased by 50m (13.2 %) (p<0.001). Control group patients were characterized with decrease (p=0.001) of this test results by 19 m (5 %) and may be explained by COPD progression (Table 3).

There was no statistically significant dynamics of spirometry results during rosuvastatin therapy,

Table 3. **Dynamics of COPD clinical course during therapy with rosuvastatin**

	Rosuvastatin group n=90				Control group n=20		
Parameters	Before treatment	After treatment	Parameters	Before treatment	After treatment	Parameters	Before treatment
Number of COPD exacerbations	2.0 [1.0; 4.0]	1.5 [0.5; 3.5]	–25.0 [–50.0; –12.5]	<0.001	2.0 [1.0; 3.9]	2.0 [1.2; 3.8]	ns
Number of meters passed at 6-minute walk test	378.0 [270.0; 450.0]	428.0 [280.0; 531.0]	13.2 [3.7; 18.0]	<0.001	379.0 [271.0; 448.3]	360 [260.0; 420.0]	0.001
St.George's Respiratory questionnaire							
Symptoms, points	70.2 [56.0; 85.6]	56.2 [37.7; 74.9]	–19.9 [–32.7; –12.5]	<0.001	70.2 [56.0; 85.6]	76.9 [62.1;86.5]	ns
Activity, points	45.5 [36.6; 51.2]	38.0 [29.6; 47.2]	–16.4 [–19.1; –7.8]	<0.001	46.3 [33.6; 50.2]	45.4 [34.1; 88.2]	ns
Impact, points	36.0 [32.7; 38.1]	35.6 [33.9; 38.0]	–1.1 [–0.26; +3.7]	Ns	36.2 [32.5; 37.1]	35.6 [33.1; 38.4]	ns
Total score, points	47.8 [41.0; 54.4]	39.3 [31.4; 46.6]	–17.8 [–23.4; –14.33]	<0.001	48.1 [40.5; 55.9]	49.2 [42.8; 56.8]	ns
Comment: see Table 1							

whereas the control group demonstrated statistically significant reduction of FEV_1 ($p<0.001$).

Thus, rosuvastatin has anti-inflammatory, endothelium-protective, and immunomodulating effects in COPD patients, influences the key systemic processes of COPD and CVD development, and is able to modify the clinical course of COPD (reducing the frequency of exacerbations and severity of symptoms and improving physical exercise tolerability).

Our results correspond to previous studies that have been conducted in different countries and assessed statin use in COPD patients [20, 21, 25, 27–29].

In order to perform optimal CVD prevention in COPD patients, it is necessary to include COPD in cardiovascular risk stratification scales.

It is also necessary to conduct major randomized studies on statin use in COPD patients with/without CVD.

It is also reasonable to compare effects of various statin therapeutic regimens in COPD patients (drugs, dose, and duration of treatment) in order to reduce the risk of cardiovascular complications and to slow down COPD progression.

The problem of individual LDL-cholesterol target levels for slowing down the disease progression in COPD patients remains unsolved, and additional criteria of statin efficacy in COPD patients have not been elaborated yet.

Conclusion

In all COPD patients cardiovascular risk should be estimated according with common methods and indications for statin administration as well as individual target LDL-cholesterol levels should be identified. It is reasonable to include rosuvastatin to therapeutic regimens of COPD patients, since rosuvastatin affects the key systemic mechanisms of COPD progressing and cardiovascular damage and it also has anti-inflammatory, antioxidant, and endothelium-protective effects being able to modify COPD course and to improve the prognosis of COPD patients.

Conflict of interest: None declared

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International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation

EXPERIMENTAL STUDY

Comparison of the effects of I class antiarrythmics Ethmozine, Ethacizin on spectral characteristics of cardiac rhythm variability in rats

Popova E.P.*

I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Author

Ekaterina A. Popova, Ph.D., assistant professor at the department of pharmacology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.

Summary

Objective

To investigate the change of spectral characteristics of heart rate variability of outbreed male rats under the influence of Class I antiarrhythmic drugs Ethmozine and Ethacizin.

Materials and methods

Heart rate variability was estimated using the method of spectral analysis assessed with the «Astrocard» equipment (Russia).

Results

We demonstrated that Ethmozine administration decreased the percentage of very low frequency (VLF) and increased the proportion of low (LF) and high (HF) frequency waves by 33% and 37%, respectively. Ethacizin decreased the total spectral power by 81% and consequently led to reduction of all spectral parts' amplitude: VLF, LF, HF oscillations were reduced by 83%, 73% and 87%, respectively. Analysis of spectral structure revealed the decrease of HF oscillations number by 37% and the increase of LF oscillations number by 17%.

Conclusions

Ethmozine increased the role of vegetative nervous system in cardiac rhythm regulation versus humoral factors without changing the interrelation between sympathetic and parasympathetic influences. Ethacizin decreased cardiac rhythm variability in our animal model, when ethmozine did not change heart rhythm variability. Ethacizin increased the influence of sympathetic nervous system on myocardium.

* Corresponding author: Tel. +7 (903) 208-58-35. E-mail: kispo-pharm@mail.ru

Key words
Variability of heart rate, class I ahtiarrhythmics, drug of class I, Ethmozine, Ethacizin.

Introduction

Lately the spectral analysis of cardiac rhythm variability (CRV) allowing estimation of humoral and vegetative factors' impact on chronotropic cardiac function attracts more and more attention of researchers due to its high informativity and relative simplicity [1, 2, 3, 4]. Studies dedicated to effective choice of medication based on such modern techniques like CRV analysis and electrocardiogram (ECG) [4, 5, 6] dispersion marking are of high interest. The use of spectral parameters for the choice of treatment of arterial hypertension, arrhythmias, myocardial infarction (MI), and other cardiovascular diseases (CVD) has been reported [6, 7, 8]. This method is being actively developed nowadays [1].

It is well-known that ischemia, MI, and stable ventricular tachycardia are associated with increased impact of sympathetic nervous system on the heart [9]. At the same time, it has been found that action of several antiarrhythmic agents could be weakened in presence of increased sympathetic influence on heart function. Experimental and clinical evidences demonstrated that antiarrhythmic action of I class antiarrhythmic agents [10, 11, 12] could be reduced or modified after isoproterenol infusion. It is known that CRV analysis may have an important role for the prognosis of CVD. Antiarrhythmic drugs are normally included into combined therapy of ischemia and MI and are used independently for treatment of various arrhythmias.

Antiarrhythmic agents Ethmozine and Ethacizin belong to Class I antiarrhythmics according to the Vaughan-Williams classification and represent ω-aminoacyl-derivatives of phenothiazine. Ethmozine has characteristics of Class IA and IB drugs, it does not influence myocardial contractivity and conductivity, does not decrease blood pressure [13, 14], and has moderate coronary-dilating effects, spasmolytic and M-cholinolytic action. Ethmozine is effective for treatment of extrasystoles, paroxysmal tachycardia, and atrial fibrillation [15]. Ethmozine has kinetic parameters of affinity to sodium channels similar with the Class IC drugs [16]. At the same thime Ethmozine blocks sodium channels in inactive condition like the drugs of IB class [13, 17]. Ethacizin reduces maximal reproducible frequency of atrial and ventricular contractions and is effective in aconitine model of arrhythmia [18]. It also reduces effectively the number of ectopic contractions in experimental model of MI in dogs [19], decreases the dimensions of ischemic area and improves coronary circulation [17, 18]. Electrophysiological studies demonstrated that Ethacizin blocks effectively not only fast entrance of sodium, but also slow entrance of calcium [17, 19]. Ethacizin is being effectively used for treatment of supraventricular and ventricular arrhythmias in clinic.

The objective of this study was to investigate the change of spectral characteristics of heart rate variability of outbreed male rats under the influence of Class I antiarrhythmic drugs Ethmozine and Ethacizin.

Materials and methods

Experiments were performed on wild-type male rats (weight 170–200 g). Animals were kept in cages (10 animals per cage) in vivarium at 12h light/dark cycle, 22–24 °C temperature, 60% humidity, and standard diet.

Animals underwent ECG registration using electrodes fixed on their chest with cuff. The «Poly-Spectrum-Rhythm» equipment (Russia) was used for ECG registration. ECG was registered during 5 minutes. Ethmozine and Ethacizin were administered intraperitoneally in dose 2 mg/kg and 1 mg/kg, respectively, in 0.2 mL volume 30 minutes before ECG registration. Control group animals were injected with 0.2 mL of physiological saline solution. CRV spectral analysis was performed after ECG registration. The above-mentioned equipment is used for measurement of major part of spectral analysis system [20]. We quantified the following parameters [20, 21]:

- RRNN, ms — average duration of RR interval;
- TP, ms^2 — total spectral power of RR interval oscillations;
- VLF, ms^2 — spectral power of RR intervals in very low frequency area;
- LF, ms^2 — spectral power of RR intervals in low frequency area;
- HF, ms^2 — spectral power of RR intervals in high frequency area;
- LFnorm, relative units (r.u.) — spectral power of RR interval in low frequency area expressed in r.u.;
- HFnorm, r.u. — spectral power of RR interval in high frequency area expressed in r.u. (relative values of each spectral component/(TP — VLF component));
- %VLF — % of VLF oscillations in TP;

- %LF — % of LF oscillations in TP;
- %HF — % of HF oscillations in TP.

We studied CRV characteristics in rats of control group (injected with physiological solution) and after Ethmozine or Ethacizin administration. Statistical analysis was done using one-factor dispersion analysis. Newman-Keuls test was used for estimation of differences between groups.

Results and discussion

1. Ethmozine effects on CRV spectral parameters in rats

Ethmozine did not cause significant change of TP (Table 1).

Ethmozine administration decreased VLf spectral power by 22 % and increased Lf spectral power by 64 % (Figure 1).

There was the trend of increased absolute values of HF spectral power. Analysis of spectral structure demonstrated the decrease of VLF proportion and the increase of LF and HF percentage by 33 % and 37 %, respectively. Thus, ethmozine decreased the role of humoral factors and increased the role of vegetative factors without changing TP characterizing CRV. The interplay between sympathetic and parasympathetic influences did not change significantly. Ethmozine administration did not result in significant change of the heart rate (HR).

2. Ethacizin effects on CRV spectral parameters in rats

Ethacizin decreased TP by 81 % and consequently reduced the power of VLF, LF, and HF spectral components by 83 %, 73 %, and 87 %, respectively (Figure 1). Spectral structure analysis demonstrated the decrease of HF percentage by 39 % and the increase of LF percentage by 17 %. Similar changes were registered with analysis of normalized spectral powers. Characteristics expressed in r.u. demonstrated the

Table 1. **Change of statistical parameters and spectral characteristics of CRV in rats after Ethmozine (2 mg/kg, intraperitoneally) and Ethacizin (1 mg/kg, intraperitoneally) (n=10).**

Parameters	Control group	Ethmozine	Ethacizin
Statistical parameters			
1. RRmin, ms	118.3±1.75	118.5±4.7	117.7±3.84
p*		>0.05	>0.05
2. RRmax, ms	156.8±9.3	162.3±11.7	149.9±12.9
p*		>0.05	>0.05
3. RRNN, ms	133.8±5.8	131.8±4.4	130.4±4.87
p*		>0.05	>0.05
4. CV, %	4.3±1.8	5.3±1.33	3.9±1.05
p*		>0.05	>0.05
Spectral characteristics			
5. TP, ms2	277±15.5	277.4±79.3	53.19±10.9*
p*		>0.05	0.0001
6. VLF, ms2	205.5±16.3	160.9±53*	35.1±8.07*
p*		0.02	0.0001
7. LF, ms2	59.8±9.25	97.9±35.7*	16.4±4.3*
p*		0.004	0.0001
8. HF, ms2	12.5±4.25	18.7±8.6	1.6±0.56*
p*		>0.05	0.0001
9. LF norm, r.u.	82.8±1.8	83.9±4.8	89.9±4.9*
p*		>0.05	0.0001
10. HF norm,r.u.	17.2±1.8	16.1±4.8	9.8±4.37*
P*		>0.05	0.0001
11. LF/HF	4.96±0.7	5.6±1.7	10.6±3.8*
p*		>0.05	0.0001
12. %VLF	68.1±5.1	57.9±7.9*	65.9±5.9
p*		0.003	>0.05
13. %LF	26.4±4.1	35.1±7.3*	30.98±5.7
p*		0.004	>0.05
14. %HF	5.12±1.27	7±2.1*	3.1±0.98*
p*		0.026	0.0001

RRmin, ms — minimal duration of RR interval;
RRmax, ms — maximal duration of RR interval;
RRNN, ms –average duration of RR interval;
* significance of differences between Ethmozine and Ethacizin groups and control group.

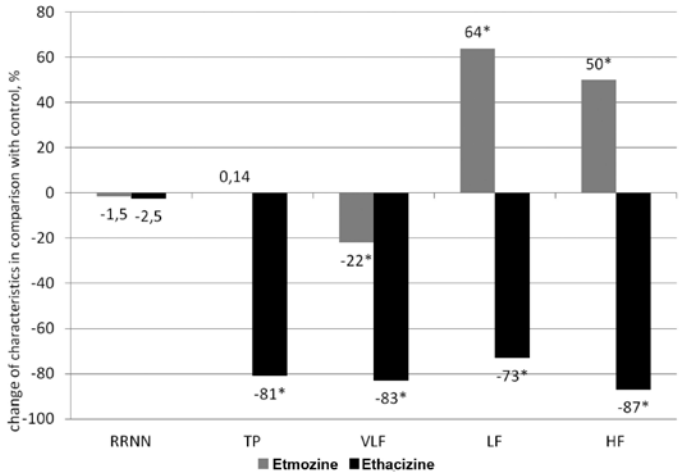

Figure 1. Ethmozine (2 mg/kg, intraperitoneally) and ethacizin (1 mg/kg, intraperitoneally) effects on CRV spectral characteristics in rats (n=10).
* — p<0.05

change of LF and HF spectral powers and did not consider changes of VLF component thus reflecting the interplay between sympathetic and parasympathetic vegetative nervous system. Ethacizin increased Lf spectral power by 8.6 % and decreased Hf spectral power by 43 %. Ethacizin caused evident decrease of CRV, increased sympathetic influence on myocardium and decreased the role of vagus nerve on cardiac rhythm regulation. Ethacizin did not change HR.

Ethacizin significantly reduced CRV in rats, whereas Ethmozine had no effect on this parameter. Significant decrease of CRV after Ethacizin administration comparing with Ethmozine is probably related to its ability to block calcium channels. There are evidences of strong negative modulation of CRV by calcium channel blockers [6]. It is worth to point out that Ethacizin decreases vagus nerve effects on animal heart and incrases sympathetic activity. Ethacizin does not change the influence of humoral factors on cardiac rhythm. Ethmozine increases the role of vegetative nervous system on chronotropic cardiac function if the role of humoral factors is lowered. At the same time the interrelation between sympathetic and parasympathetic influences remains unchanged.

Conclusion

Ethacizin decreases CRV in rats, whereas Ethmozine does not change this parameter.

Ethacizin administration leads to increased sympathetic activity of myocardium in experimental animals without significant change of humoral factors role in cardiac rhythm regulation.

Ethmozine administration decreased the influence of humoral regulation of cardiac rhythm. The role of vegetative nervous system increases, but the interrelation between sympathetic and parasympathetic effects remains unchanged.

Conflict of interest: None declared

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International Heart and Vascular Disease Journal
Volume 5, Number 15, September 2017

Journal of the Cardioprogress Foundation

New classification of arterial hypertension according to the ACC/AHA clinical guidelines-2017: opinions of Russian experts

Summary

This article includes 7 opinions of the leading experts of different regions of Russia related to new revision of arterial hypertension (AH) classification as part of clinical guidelines that have been published in the Journal of the American College of Cardiology and in the AHA Journal of Hypertension. These changes are related to the levels of systolic blood pressure (BP) 130–139 mm Hg and/or diastolic BP 80–89 mm Hg that are classified now as the Grade 1 AH. Updated guideline also contains new target values for patients undergoing AH treatment. Opinions of Russian experts differ. Some of them think that these guidelines are inappropriate for Russia, and that it is necessary to wait for the guidelines of the European Society of Cardiology. At the same time, this change of classification can be considered as a positive phenomenon for AH detection and prevention.

Key words

Arterial hypertension, new classi*fication, clinical guidelines*

New revision of arterial hypertension (AH) classification was one of the most important events of the American Heart Association (AHA) Congress that was held in Anaheim (USA) on November, 11–15, 2017. In particular, changes in the new document are related to the levels of systolic blood pressure (SBP) 130–139 mm Hg and/or diastolic blood pressure (DBP) 80–89 mm Hg that are classified now as Grade 1 AH. The updated guideline contains also new target values of blood pressure (BP) for patients undergoing AH treatment: 130/80 mm Hg.

Revised classification became the subject of wide discussion. Russian experts also shared their opinions. The comments of academician R.G. Oganov (Moscow), professor G.G. Arabidze (Moscow) and professors O.A. Koshelskaya (Tomsk), G.A. Baryshnikova (Moscow), S.G.Kanorskii (Krasnodar), V.S Zhuk (Saint

Clinical guidelines of ACC/AHA Hypertension Guidelines (2017)	SBP and DBP, mm Hg
Normal BP	<120 and < 80
Elevated normal BP	120-129 and < 80
AH 1 grade	130-139 or 80-89
AH 2 grade	≥140 or ≥90

* Clinical guidelines were published in the Journal of the American College of Cardiology and in the AHA Journal of Hypertension.
* 2 grade AH with higher BP values should be classified as a higher AH category.

Corresponding author: Tel. +7 926-228-33-09. E-mail: mmamedov@mail.ru

Petersburg), and Yu.A.Bunin (Moscow) are listed here below.

Rafael G. Oganov, academician of the Russian Academy of Sciences (Moscow)

Appearance of new AH classification developed by the AHA should be considered as a positive phenomenon.

Once more it will attract attention to AH problem and will become the base for new studies. At the same time one should not hurry to introduce these guidelines in routine clinical practice. According to existent AH guidelines, AH is prevalent in all countries, effectiveness of its diagnostics and treatment is low, and adverse effects of therapy are enough frequent.

It is necessary to wait for analysis and reaction of European cardiologist, the World Health Organization (WHO) and other international organizations on these American guidelines, and it's particularly important to obtain convincing arguments of efficacy and safety of antihypertensive therapy according to the criteria mentioned in new guidelines, especially in elderly and comorbid patients.

Grigory G. Arabidze, professor (Moscow)

According to the new AHA criteria of AH, pre-hypertension is included into the system of AH, and it considers cardiologic observation at more early stages of the disease. Nevertheless, we should accept that this measure has led to almost 15% increase in the number of patients with AH in the USA. According to the AHA and JNC7 guidelines (2017), total prevalence of AH in US adults is 45,6% (95% confidence interval (CI) 43,6%-47,6%) and 31,9% (95% CI 30,1%-33,7%), respectively. At the same time, performed analysis (Paul Muntner, Robert M. Carey, Samuel Gidding, Daniel W. Jones, Sandra J. Taler, Jackson T. Wright Jr. and Paul K. Whelton. Potential U.S. Population Impact of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline) indicated that the number of patients to whom initial pharmacological therapy should be recommended would not increase significantly reaching 36,2% (95% CI 34,2%-38,2%) and 34,3% (95% CI 32,5%-36,2%) of adult American population, respectively, so by 1,9%. In my opinion, the same situation will be observed in Russia, because at the early stages of AH treatment strategy is focused on secondary prevention that includes risk factors correction and lifestyle modification. In Russia patients undergoing medical observation since the early stages of AH will become more compliant to pharmacological treatment only after unsuccessful long-term use of preventive and non-pharmacological measures. At the same time, I hope that treatment, aiming more aggressively to reach target levels of blood pressure, will reduce the frequency of complications and admissions to hospital. It has been proved by the results of observation in the Swedish Register [1].

Olga A. Koshelskaya, professor (Tomsk)

Decrease of diagnostic BP levels associated with 1 stage AH (SBP 130–139 mm Hg or DBP 80–89 mm Hg) and elimination of "pre-hypertension" term leads to significant and doubtfully reasonable increase of prevalence of patients with AH in population not less than by 1/3, and description of BP levels in range of 120–29 mm Hg and <80 mm Hg as "elevated BP" (instead of previously used term "pre-hypertension") brings a lot of confusion with terms in use and is hardly motivated. Use of this approach for BP evaluation will go hand in hand with 2–3 fold increase of AH prevalence in individuals younger than 45 years and in the age group above 55 years AH will be diagnosed in at least 75% of men.

Since the authors of these guidelines indicate that pharmacological therapy for reaching target BP levels <130 mm Hg is still reasonable just for patients with increased and high cardiovascular risk (CVR), suggested decrease of BP values diagnostic for its "elevated level" and 1 stage AH at least for primary prevention may, from one side, motivate patients to follow healthy lifestyle, from another side it doesn't exclude negative influence of this idea on their psychological status. Due to this it is particularly important to evaluate correctly the degree of CVR. To note, in the USA this estimation is performed with another calculator that is not used in the Russian Federation (RF).

Another reason for confusion is the single universal recommendation for reaching target BP levels <130/80 mm Hg even in elderly patients without making any difference for the presence of other cardiovascular disorders and comorbid conditions. Although the experts responsible for preparation of these guidelines highlight that these guidelines are based on vigorous evidences including the SPRINT study results [2], especially the last argument is quite controversial since in this study BP levels were checked just with ambulatory methods, and this approach decreases significantly detectable BP levels comparing with office BP measurement. More than that, claimed principles of single criteria for achieving BP are contradictory with the results of several

modern meta-analyses including the most recent one that demonstrated differences in association of BP levels reached during antihypertensive therapy with decreased risk of cardiovascular morbidity and mortality for primary and secondary prevention depending on initial BP values [3]. There are evidences indicating that antihypertensive therapy aiming to reach SBP < 130 mm Hg (comparing with target levels < 140 mm Hg) has no survival or cardiovascular prognostic benefit for patients with diabetes mellitus or if pharmacological treatment is prescribed for initial BP levels below 140 mm Hg (comparing with initial BP levels >140 mm Hg), and more than that it is associated with increased risk of death due to coronary complications [3].

Intensification of pharmacological therapy suggested with recommended criteria of BP evaluation and decreased target BP levels will be applicable to many patients (approximately to 1/3 of them) that may lead to unmotivated expenses and potential growth of adverse effects frequency related to more aggressive antihypertensive therapy.

Taking into account all above-mentioned facts, I consider the use of suggested criteria of BP evaluation in the RF unmotivated and unreasonable.

Increased precision of BP measurement, necessity of ambulatory BP control and importance of non-pharmacological treatment look satisfactory and promising.

Galina A. Baryshnikova, professor (Moscow)

Revision of AH classification was not unexpected since it was pre-determined by the results of the SPRINT study [2]. This approach has its followers and enemies. Previously in 2007 it was recommended to reach target BP levels <130/80 mm Hg in the groups of high and very high risk, but soon after this recommendation was refused. The European Society of Cardiology (ESC) highlighted that just non-pharmacological treatment should be used in case of elevated normal BP. Using the old criteria, we managed to reach target BP levels just in 22–24% of patients with AH, and it's very likely that use of more strict criteria will make it impossible to reach target BP levels in the majority of patients. Nowadays it may be difficult to persuade them to accept treatment if their BP values exceed 160 mm Hg, and this task starts to look almost impossible for BP values around 130 mm Hg. It explains the motivation to use just non-pharmacological methods for treatment of pre-hypertension.

In my opinion, wide use of fixed drug combinations should be encouraged in several groups of patients including patients with low and medium CVR in order to provide higher compliance, and it is necessary to lower BP gradually taking into account individual tolerability especially in elderly patients.

Another point is that the SPRINT study demonstrated that clinical practitioners should not be afraid to lower down BP values below 125–130 mm Hg and that they should not hurry to reduce doses and number of fixed drug combination components in case of good tolerability of this BP levels by patients.

I prefer well-analyzed approaches, and it would be also interesting to know the opinion of the ESC and the European Society of Hypertension.

Sergei G. Kanorskii, professor (Krasnodar)

It is well known since a while that the risk of cardiovascular complications grows linearly with elevation of BP levels starting from 115/75 mm Hg, according to the results of several population studies (Lewington S. et al., 2002). These data contradicted with results of numerous randomized trials of antihypertensive therapy that reported J-shaped phenomenon: increased risk of cardiovascular complications in case of SBP < 130 mm Hg. At the same time it was possible to avoid the development of J-shaped phenomenon in the SPRINT study [2]. According to the opinion of several experts, it has happened due to the use of innovative method of BP registration (automatic oscillometric monitor) that tended to lower down measured BP values comparing with traditional office approach. New American AH classification (2017) eliminates contradiction between population observations and the tasks of modern antihypertensive therapy. At the same time it is important for clinical practitioner to take into account individual tolerability of lower BP levels by patients.

Vadim S. Zhuk, professor (Saint Petersburg)

The thing that we witness now is reasonable evolution of guidelines that resonated strongly in 2014. I am talking about the American document JNC8 that eliminated Grade 3 AH and established BP level of 160/90 as the final one in AH classification.

New guidelines established on November 11–15 in Anaheim make our emotive perception shift from rational acceptation to completely surrealistic feeling. Nobody knows the real aim behind the actions of American experts that has turned one third part of

healthy individuals into patients with AH! I would like to avoid thinking that the cause of it is the reformation of healthcare system or investing or financing in pharmacological industry. I would like to believe that the real goal was beneficial, but the motivation behind it remains unclear. If this decision is based on results of the SPRINT study [2] and similar ones it is worth to remember that BP was measured using ambulatory techniques different from common clinical practice. Apart from it, could more than 9000 patients reflect the real population situation with all its diversity?

Will it be easy to inform patient that BP 130/80 mm Hg is considered a disease and should be treated? Calm revision of this document helps to understand that from several points of view it is not so radical. For example, it separates target and threshold BP levels. What does it give? Although target BP values are defined as <130/80 mm Hg for everybody, old threshold BP values (140/90 mm Hg) should be used for individuals without the risk of atherosclerotic cardiovascular diseases and in patients with history of lacunar stroke for its secondary prevention.

The scale of risk evaluation recommended in this document has not been validated yet in European and Russian populations.

Another aspect that should be taken carefully is the definition of threshold and target BP levels in elderly patients (age >75 years, or 80 and 85 years) and in healthy young individuals that may have BP values around 130/80 mm Hg and more in several different conditions.

Yury A. Bunin, professor (Moscow)

According to this guideline, it is recommended to use antihypertensive drugs for lowering down BP starting from SBP ⩾130 mm Hg or DBP ⩾ 80 mm Hg if patients have other cardiovascular diseases (secondary prevention) or 10-year risk of atherosclerotic cardiovascular disease development (mortality due to coronary heart disease (CHD), non-fatal myocardial infarction, fatal and non-fatal stroke) estimated with the ASCVD scale. If all above-mentioned characteristics are absent pharmacological treatment should start for SBP⩾140 mm Hg or DBP⩾90 mm Hg. So it becomes clear that the category of patients requiring pharmacological treatment of AH widens significantly.

The first line antihypertensive drugs include thiazide diuretics, dihydropiridine and non-dihydropiridine calcium channel blockers, angiotensin-converting enzyme inhibitors, and sartans. Other antihypertensive drugs including beta-blockers are advised to be used as the second line drugs. Patients with Grade 1 AH should start pharmacological treatment from one first line drug, whereas Grade 1 AH requires using two first line drugs.

These guidelines are concluded with detailed algorithm of using various antihypertensive drugs for various comorbid conditions (CHD, chronic heart failure, atrial fibrillation, dementia, diabetes mellitus, stroke, etc).

Conflict of interest: None declared.

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Results of the III Interregional Scientific and Educational Congress of Cardiology and Internal Medicine (Saransk)

The III Interregional Scientific and Educational Congress of Cardiology and Internal Medicine was held in Saransk on November 28–29, 2017. The congress was supervised by the Ministry of Healthcare of the Russian Federation, Russia President Plenipotentiary Representative Office in the Privolzhsky Federal district, the Ministry of Healthcare of the Republic of Mordovia, the State scientific center of preventive medicine, N.P. Ogarev Mordovia State University, and Mordovian Republican Society of Internal Medicne, and the foundation for advancement of cardiology «Cardioprogress». The congress coincided with the 50-year anniversary of the Medical Institute of Mordovia State University.

The academician of the Russian Academy of Sciences (RAS) R.G. Oganov, the vice-rector in scientific work of Mordovia State University P.V. Senin, and the head of the Medical Insitute and RAS corresponding member L.A. Balykova welcomed participants during the opening ceremony.

The head of treatment and preventive care department of the Ministry of Healthcare of the Republic of Mordovia N.P. Kulkova welcomed congress' participants about principal goals that medical community of the republic and medical universities face and about efficacy of the republican measures aiming to reduce mortality from cardiovascular diseases and other socially significant disorders.

The main conference topics were concentrated on medical support of athletes and on prevention of non-infectious diseases. The questions of modernization of diagnostics and treatment of patients in the field of cardiology and internal medicine together with highlighted role of comorbid pathology and prevention of risk factors were discussed during numerous lectures, interdisciplinary meetings and clinical presentations focused on healthcare needs and prepared with integration of medical science and clinical practice.

More than 500 doctors from the Republic of Mordovia and other regions of Russia (Moscow, Saint Petersburg, Nizhnii Novgorod, Ulyanovsk, Kazan, Penza, Ryazan) and from Kazakhstan (Aktobe).

Two-day scientific program included more than 30 scientific presentations and lectures from the leading experts of the Russian Federation. Scientific program included problems of sports medicine, gastroenterology, hepatology, nephrology, pulmonology, prevention of chronic non-infectious diseases, comorbidity of somatic pathology and cardiorehabilitation. Clinical lectures of the leading professors (R.G. Oganov, L.A. Balykova, G.A. Baryshnikova, E.V. Kolpakov, A.M. Shutov, D.I. Sadykova, S.V.Dudarenko, A.N. Maksudova, O.N. Sisina, and others) dedicated to important topic of modern cardiology aroused a high interest.

Traditionally, the conference included a scientific meeting for young researchers from different countries. Their presentations were dedicated to the problems of cardiology, gastroenterology, endocrinology and immunopathology of cancer. Conference chairmen highlighted high level of all presentations. Winners received certificates. For the first time the scientific program included the «Nursing in internal medicine» section that gathered interesting participants from Saransk, Saint Petersburg, Nizhnii Novgorod, Astrakhan and Penza.

Collection of scientific works was published in supplementary materials of «Cardiovascular therapy and prevention» journal. Collection of scientific works is available at the website of the «Cardioprogress» foundation (www.cardioprgress.ru)

The conference was widely covered by regional mass-media, reportages and necessary information were published in profile medical journals and on the website of the Ministry of the Healthcare of the Russian Federation.

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Anniversary of Rafael Oganov, president of the «Cardioprogress» Foundation

A famous Russian cardiologist, scientist, clinical practitioner, doctor of medical sciences, professor, academician of the Russian Academy of Sciences (RAS), honoured worker of science of the Russian Federation, winner of the State Prize of the RSFSR, winner of the Russian Government Prize, honoured president of the Russian Society of Cardiology, editor-in-chief of the «Cardioprogress» journal, Rafael G. Oganov celebrated his 80-year anniversary on 9th of December, 2017.

Rafael Oganov was born in a working class family in Moscow. He passed a great life and creative path from a clinical resident to an academician of the Russian Academy of Medical Sciences (RAMS), a scientist, a doctor and a teacher widely known in Russia and abroad.

In 1966, after graduating with honors from the medical faculty of the 2nd Moscow Medical Institute, he started his clinical residency and postgraduate study at the Department of Hospital Therapy, headed by Academician P.E. Lukomsky. Later, as the department's assistant, he acquired good clinical and pedagogical experience. During these years, the scientific interests of Rafael Oganov were devoted to the study of the sympathoadrenal system and violations of carbohydrate metabolism in myocardial infarction and other forms of coronary heart disease. Obtained results became the basis of his Ph.D. and doctoral dissertations. From 1988 to 2011 he participated in the creation of the State Research Center for Preventive Medicine and headed it.

This research center was founded in the Soviet Union thanks to the efforts of Rafael Oganov, and the main tasks of this institution were to study and analyze the epidemiological situation in the country and on this basis, the development and implementation of preventive programs to reduce morbidity and mortality from cardiovascular and other chronic non-infectious diseases have been added.

In 1997 he was elected a corresponding member of the RAMS, and in 2000 he became a full member of it (nowadays this medical department is represented as part of the RAS), and he also was the member of the Higher Attestation Commission of the Ministry of Education and Science of Russia from 2012 to 2017.

The range of scientific interests of Academician Oganov is very wide and varied. The scientific research carried out under his guidance allowed the USSR and then the Russian Federation to obtain data on the prevalence of major cardiovascular diseases and their risk factors.

For the first time, the programs allowing prediction of the risk of cardiovascular death for the next 5–10 years and estimation of preventive interventions have been developed. Numerous successful studies that investigated the prevalence of cardiovascular risk factors in children, adolescents and students have been conducted, and after long observation it allowed developing and testing prevention programs of healthy lifestyle in children and adolescents.

Epidemiological studies carried out under the guidance of Academician Oganov in Russia pushed

the development of large cooperative programs implemented not only for the prevention of cardiovascular diseases, but also for the integrated prevention of non-infectious diseases based on common risk factors, such as MONICA (coordinator 1983–2001), Russia-US intergovernmental cooperative program on «Epidemiology and prevention of cardiovascular and pulmonary diseases» (coordinator, 1988–1998), the SINDI program (coordinator, 1991–2006), widely known in our country and recognized abroad. Nowadays the results of these studies are actively used for scientific research and in practical public health for organization of national and regional prevention programs.

Having high scientific professionalism and experience, deep sense of duty and responsibility, Rafael Oganov rightfully enjoys influence and respect of scientific and medical community and worthily represents the national medical science at the international level. The sign of recognition of the international reputation of Rafael Oganov for his large-scale, epidemiological work of the Center is the fact that he is a part of the Coordinating Committee for the development of a New European Model for Risk Assessment of Cardiovascular Disease, SCORE, which has now been further developed, and widely used in Russia and Europe. Academician R. Oganov is a member of the European Society of Cardiology since 1991 and he is a member of the American College of Cardiology since 2010.

Academician Oganov created the scientific school of epidemiology of non-infectious diseases and preventive medicine that works fruitfully even in the field of practical public health organization. He is the author and co-author of more than 680 scientific works published in the leading medical journals in Russia and abroad, the author and co-author of 8 patents, 16 books and monographs, the most significant of which are «Preventive Cardiology» (1985), «Cardiology» (2004), «Heart diseases» (2006), «Cardiology: national guideline» (2007), «Guideline on medical prevention» (2007), «Preventive Cardiology (Guideline for medical doctors)» (2007), «School on diagnostics and treatment of metabolic syndrome» (2007), and «Evidence-based medicine. Handbook for postgraduate and additional professional medical education» (2010), «Postprandial hyperglycemia as the target of prevention of cardiovascular diseases and diabetes mellitus (Handbook for medical doctors)» (2010), «The school of health. Coronary heart disease: guideline for medical doctors» (2011), «The school of health. Coronary heart disease: materials for patients» (2011), «High-quality clinical practice with elements of evidence-based medicine (Handbook for postgraduate and additional professional medical education)» (2011).

He supervised 16 doctorate and 30 Ph.D. dissertations. Academician Rafael Oganov has the highest indices of scientific citation in Russian and international databases: RSCI, WoS, Scopus.

A high sense of duty and responsibility, honesty, exactingness, rich scientific erudition together with great clinical experience are the main characteristics of Rafael Oganov, and thanks to them he is deeply respected by his students, colleagues, and Russian and international medical community.

The experience of Academician Oganov as the scientist, clinical practitioner and leader together with good organizational skills were on demand not only in the State Research Center for Preventive Medicine. Thanks to his energy, high scientific erudition, and human qualities, a great success has been reached by the creative community of Russian cardiologists. Not by chance he had been staying at the position of the Russian Society of Cardiology for 3 terms (12 years). He is the Editor-in-chief of several scientific journals: «Cardiovascular therapy and prevention», «International Heart and Vascular Disease Journal», the deputy Editor-in-chief of the «Rational pharmacotherapy in cardiology» journal, and he is also a member of the editorial board of the following journals: «Preventive medicine» and «Cardiology».

Rafael Oganov was awarded the Order of the Badge of Honor and medals of the Exhibition of Economic Achievements.

Possessing high inner culture, personal charm, benevolence, active life position, a sence of justice and responsibility for the destinies of people, he continues successfully the best traditions of Russian medicine. He faces his anniversary being full of energy, creative ideas and plans. Nowadays Rafael Oganov is the chief researcher and the head of the department of comorbid conditions of the State Research Center for Preventive Medicine, the chairman of the international group of experts on non-infectious diseases of the Northern Light Partnership in Healthcare and Social Well-being.

The «Cardioprogress» foundation and the editorial board of the «International Heart and Vascular Disease Journal» congratulate dear Rafael Oganov on his anniversary and heartedly wish him many years of healthy and creative life.

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Journal of the Cardioprogress Foundation

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(version 2017)

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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.

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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.

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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/.

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