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The features of cardiovascular lesions in patients with pulmonary tuberculosis

A rare case of variant angina: Single coronary artery arising from right sinus of Valsalva

Valvular lesions in connective tissue dysplasia: clinical manifestations characteristics, the prognosis of the course

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Contents

Editor's Welcome

Dear colleagues

In the eighth issue of International Heart and Vascular Disease Journal there are leading article, review article, original articles and case report.

The leading article is dedicated to the choice of antihypertensive therapy tactics in patients with coronary heart disease. Author from USA establishes the reasonableness of risk factors' correction, advantages of different drugs and combination therapy in case of stable and unstable angina, concomitant heart failure and diabetes mellitus.

Review article of this issue discusses the use of fixed-dose combination drugs for treatment of patients with arterial hypertensia and high cardiovascular risk. This approach allows to affect several risk factors and to improve adherence to therapy.

In "Original articles" section we published two papers. One of them is dedicated to the results of clinical research investigating cardiovascular involvement in patients with pulmonary tuberculosis and demonstrates some laboratory and ECG evidence of myocardium dystrophy and dysfunction that have been detected. Second work is devoted to connective tissue dysplasia. Results of prospective trial bring light to particular aspects of clinical course and prognosis of this disorder in young patients with valvular lesions.

«Case report» section is presented with two reports that discuss case of a patient with Gitelman syndrome and severe hypokaliemia and rare case of variant angina due to presence of single coronary artery originating from Valsava sinus.

In this issue we published main results of the Great Wall International Congress of Cardiology (GW-ICC), one of the largest cardiology congresses in Asia-Pacific region, which took place in Beijing in autumn 2015.

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

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

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LEADING ARTICLE

Treatment of Hypertension in Patients With Coronary Artery Disease

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Abstract

Patients with coronary artery disease should have their modifiable coronary risk factors intensively treated. Dietary sodium should be reduced. Hypertension should be treated with beta blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Long-acting nitrates are effective antianginal and antiischemic drugs. Calcium channel blockers may be added if angina persists despite beta blockers and long-acting nitrates... The American Heart Association/American Society of Cardiology 2015 guidelines recommend that the target blood pressure should be less than 140/90 mm Hg in patients with coronary artery disease and with an acute coronary syndrome if they are aged 80 years and younger but less than 150 mm Hg if they are older than 80 years of age. Octogenarians should be checked for orthostatic changes with standing, and a a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 65 mm Hg should be avoided . Caution is advised in causing a diastolic blood pressure less than 60 mm Hg in patients with diabetes mellitus or in patients older than 60 years of age. In addition to the beta blockers carvedilol, metoprolol CR/XL, and bisoprolol, patients with hypertension and congestive heart failure should be treated with diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and patients with persistent severe symptoms with aldosterone antagonists if not contraindicated.

Key Words

Myocardial infarction; coronary artery disease; hypertension; beta blockers; angiotensin-converting enzyme inhibitors; aldosterone antagonists; calcium channel blockers; nitrates.

Introduction

Hypertension is a major risk factor for cardiovascular disease [1–9]. These guidelines recommend lowering the blood pressure to less than 140/90 mm Hg in patients younger than age 80 years and to less than 150/90 mm Hg in patients aged 80 years and older if tolerated [1–4, 7–9]. Hypertension is present in approximately 69% of patients with a first myocardial infarction [10], in approximately 77% of patients with a first stroke [10], in approximately 74% of patients with congestive heart failure [10], and in 60% of patients with peripheral arterial disease [11]. Hypertension is

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also a major risk factor for a dissecting aortic aneurysm, sudden cardiac death, angina pectoris, atrial fibrillation, diabetes mellitus, the metabolic syndrome, chronic kidney disease, thoracic and abdominal aortic aneurysms, left ventricular hypertrophy, vascular dementia, Alzheimer's disease, and ophthalmologic disorders [3]. This paper will discuss the management of patients with coronary artery disease recommended by the 2015 American Heart Association/American College of Cardiology/American Society of Hypertension guidelines on treatment of hypertension in patients with coronary artery disease [9].

Coronary Risk Factor Reduction

Modifiable coronary risk factors should be treated. Smokers should be strongly encouraged to stop smoking because it will reduce cardiovascular mortality and all-cause mortality in patients with coronary artery disease. A smoking cessation program should be recommended to smokers [12]. Nicotine replacement therapy [13], bupropion [14], and varenicline [15] are approved pharmacologic treatments for promoting smoking cessation.

Hypertension should be treated with sodium restriction to not exceed 1.5 grams daily, weight reduction if necessary, discontinuation of drugs that increase blood pressure, avoidance of caffeine and tobacco, limiting alcohol intake to no more than two drinks per day in men and one drink per day in women and light weight men, an increase in physical activity, a decrease of dietary saturated fat and cholesterol, and maintenance of adequate dietary potassium, calcium, and magnesium intake [3].

Patients with coronary artery disease should consume a Step II American Heart Association (AHA) diet. Numerous double-blind, randomized, placebo-controlled trials have demonstrated that patients with coronary artery disease treated with statins have a reduction in cardiovascular events and in mortality [16–20]. High-dose statins (rosuvastatin 20–40 mg daily and atorvastatin (40-80 mg daily) lower serum low-density lipoprotein cholesterol 50% or more and should be administered to patients with coronary artery disease [21]. Addition of ezetimibe to high-dose statin therapy has been demonstrated to further reduce serum lipoprotein cholesterol and reduce coronary events in patients after an acute coronary syndrome [22].

Diabetics with coronary artery disease should be treated with dietary therapy, weight reduction if necessary, and appropriate drugs if needed to control hyperglycemia. Other coronary risk factors should be controlled.. Metformin should be the initial drug to treat hyperglycemia in most patients [23, 24]. The hemoglobin A1c level should be reduced to <7% in patients with diabetes mellitus [23].

Obese patients with coronary artery disease must undergo weight reduction [12]. Weight reduction is also a first approach to controlling hyperglycemia, mild hypertension, and dyslipidemia. Regular aerobic exercise should be added to diet in treating obesity. The body mass index should be reduced to 18.5 to 24.9 kg/m^2 [12]. Exercise training programs have been found to improve endurance and functional capacity in patients with coronary artery disease [25,26]. The goal to be achieved is at least 30 minutes of exercise daily for 7 days per week with a minimum of 5 days of physical exercise per week [12].

Target Blood Pressure

The American Heart Association/American Society of Cardiology 2015 guidelines recommend that the target blood pressure should be less than 140/90 mm Hg in patients with coronary artery disease and with an acute coronary syndrome if they are aged 80 years and younger but less than 150 mm Hg if they are older than 80 years of age [9]. Consideration can be given to reduce the blood pressure to less than 130/80 mm Hg with a class IIb C indication [9]. Octogenarians should be checked for orthostatic changes with standing, and a a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 65 mm Hg should be avoided [9]. Caution is advised in causing a diastolic blood pressure less than 60 mm Hg in patients with diabetes mellitus or in patients older than 60 years of age [9].

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial included 4,162 patients with an acute coronary syndrome (acute myocardial infarction with or without ST-segment elevation or high-risk unstable angina pectoris) [27]. The lowest cardiovascular events rates occurred with a systolic blood pressure between 130 to 140 mm Hg and a diastolic blood pressure between 80 to 90 mm Hg with a nadir of 136/85 mm [27].

Among 8,354 adults aged 60 years and older with coronary artery disease in the International VErapamil SR Trandolapril (INVEST) study, a baseline systolic blood pressure of 150 mm Hg and higher, and 22,308 patient years of follow-up, 57% had a systolic blood pressure less than 140 mm Hg, 21% had a systolic blood pressure of 140 to 149 mm Hg, and 22% had a

systolic blood pressure of 150 mm Hg and higher [6]. The primary outcome of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke occurred in 9.36% of adults with a systolic blood pressure of less than 140 mm Hg, in 12.71% of adults with a systolic blood pressure of 140–149 mm Hg, and in 21.3% of adults with a systolic blood pressure of 150 mm Hg and higher (p<0.0001) [6]. Using propensity score analyses, compared with a systolic blood pressure of less than 140 mm Hg, a systolic blood pressure of 140 to 149 mm Hg increased cardiovascular mortality by 34% (p =0.04), total stroke by 89% (p = 0.002), and nonfatal stroke by 70% (p = 0.03) [6]. Compared with a systolic blood pressure of less than 140 mm Hg, a systolic blood pressure of 150 mm Hg and higher increased the primary outcome by 82% (p <0.0001), all-cause mortality by 60% (p<0.0001), cardiovascular mortality by 218% (p<0.0001), and total stroke by 283% (p<0.0001) [6].

Antihypertensive Therapy

A meta-analysis of 147 randomized trials of 464,000 adults with hypertension reported that except for the extra protective effect of beta blockers given after myocardial infarction and a minor additional effect of calcium channel blockers in preventing stroke, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers caused a similar decrease in coronary events and stroke for a given reduction in blood pressure [28]. The proportionate reduction in cardiovascular events was the same or similar regardless of pretreatment blood pressure and the presence or absence of cardiovascular events [28]. If beta blockers are used to treat adults with hypertension, atenolol should not be used [29-31].

Coronary Artery Disease

Coronary risk factors should be controlled including smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, and physical inactivity [9]. Dietary sodium should be reduced.

Beta blockers are the initial antihypertensive drugs to use in patients with coronary artery disease who have angina pectoris, who have had a myocardial infarction, and in those who have left ventricular systolic dysfunction unless contraindicated [9]. Patients with prior myocardial infarction and hypertension should be treated with beta blockers and angiotensin-converting enzyme inhibitors.[2-4, 8, 9,28, 32-45]. Atenolol should be avoided [29-31]. If a third drug is needed, aldosterone antagonists may be used based on the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) trial [46]. Patients treated with aldosterone antagonists should not have significant renal dysfunction or hyperkalemia.

In addition to the beta blockers carvedilol, metoprolol CR/XL, and bisoprolol, [9, 47-51], patients with hypertension and congestive heart failure should be treated with diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [9, 47, 52-60], and patients with persistent severe symptoms with aldosterone antagonists [9, 46, 47, 61]. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should also be administered to patients with diabetes mellitus or chronic kidney disease [3, 4, 8, 62, 63].

Hydralazine plus isosorbide dinitrate should be added to African-American patients with New York Heart Association class III or IV heart failure with a reduced left ventricular ejection fraction already receiving diuretics, beta blockers, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [9, 47, 64]. Drugs to avoid in patients with hypertension and heart failure with a reduced left ventricular ejection fraction include verapamil, diltiazem, doxazosin, clonidine, moxonidine, hydralazine without a nitrate, and nonsteroidal anti-inflammatory drugs [9].

In patients with hypertension and heart failure with a preserved left ventricular ejection fraction, class I theraputic indications include control of systolic and diastolic hypertension, control of the ventricular rate in patients with atrial fibrillation, and reduction of pulmonary congestion and peripheral edema with diuretics [9, 47]. Class IIb therapeutic indications include use of beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or calcium channel blockers [9].

Stable Angina Pectoris

Patients with hypertension and chronic stable angina pectoris should be treated with beta blockers plus nitrates as antianginal agents [9]. The hypertension in these patients should be controlled with beta blockers plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker with addition of a thiazide or thiazide-like diuretic if needed. If either the angina pectoris or the hypertension remains uncontrolled, a long-acting dihydropyridine calcium channel blocker can be added to the therapeutic regimen. Nondihydropyridine calcium channel blockers such

as verapamil and diltiazem cannot be used if there is left ventricular systolic dysfunction. Combining a beta blocker with either verapamil or diltiazem must be used with caution because of the increased risk of bradyarrhythmias and heart failure [9].

Acute Coronary Syndromes

In patients with an acute coronary syndrome, initial therapy of hypertension should include a short-acting beta1 selective beta blocker without intrinsic sympathomimetic activity such as metoprolol tartrate or bisoprolol [9]. Treatment with beta blockers should be started initially within 24 hours of symptoms. In patients with severe hypertension or ongoing ischemia, intravenous esmolol may be considered [9]. In hemodynamically unstable patients or those with decompensated heart failure, treatment with beta blockers should be delayed until the patient is stabilized [9].

In patients with acute coronary syndromes with hypertension, nitrates can be used to reduce blood pressure or to reduce ongoing myocardial ischemia or pulmonary congestion [9]. However, nitrates should not be given to patients with suspected right ventricular infarction or in those with hemodynamic instability. Intravenous or sublingual nitroglycerin is preferred initially [9].

An angiotensin-converting ernzyme inhibitor or angiotensin receptor blocker should be given to patients with an acute coronary syndrome , especially in patients with an anterior myocardial infarction, if hypertension persists, if there is a reduced left ventricular ejection fraction, or if diabetes mellitus is present [9]. If hypertension persists after use of a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a long-acting dihydropyridine calcium channel blocker may be added [9]. Aldosterone antagonists are indicated in patients receiving beta blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after myocardial infarction who have left ventricular systolic dysfunction and either heart failure or diabetes mellitus [9]. However, they should be avoided if the serum potassium is ⩾ 5.0 mEq/L or if the serum creatinine is ⩾ 2.5 mg/dL in men or ⩾2.0 mg/dL in women [9]. Loop diuretics are preferred to thiazide and thiazide-type diuretics in patients with heart failure or in patients with chronic kidney disease and an estimated glomerular filtration rate less than 30 mL/minute [9].

Conflict of interest: None declared.

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Analysis of latest international studies for atrial fibrillation: trends and perspectives

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Summary

The urgency of atrial fibrillation (AF) as the health and social problems, primarily due to the fact that the rhythm of the heart, being a significant cause of heart failure, stroke and other thromboembolic complications, significantly increases the relative risk of total and cardiovascular mortality. In addition, complications of AF are the cause of persistent disability of working age. All this leads to the continuation of a number of randomized studies examining the effectiveness of various methods to control the heart rhythm and heart rate, as well as improving the prognosis of the disease. In this article the provisions concerning drug and non-drug treatment of diseases, subject to revision in the latest national and international guidelines.

Keywords

Atrial fibrillation, recommendations, anticoagulants, antiarrhythmic drugs, ablation

Atrial fibrillation: importance, prevalence, prognosis

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. It is characterized by irregular excitation and contraction of different myocardial parts with heart rate up to 400-700 beats per minute without regular contraction [1]. In Russia both terms, AF and ciliary arrhythmia, the one that has been proposed by G. F. Lang, are equally common to use.

The problem of AF is very important because this arrhythmia, being one of the causes of heart failure, stroke and other thromboembolic complications, significantly increases relative risk of total and cardiovascular mortality. Although AF has high occur-

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rence and relatively benignant course nowadays this arrhythmia is considered to be life-threatening because of big number of consequences that not only reduce quality of life but also increase frequency of severe complications and death. It is known that AF increases five-fold the risk of brain stroke. Frequently ischemic stroke in patients with AF is recurrent and results in the death of patient increasing the costs of treatment [2].

As we mentioned before, AF is one of the most common arrhythmias, occurs in 1–2% of population, and the frequency of AF increases with age. Multicentral trials revealed that the prevalence of this pathology in patients younger than 60 years is ~ 0,5%, in patients over the age of 60 years – 5%, over the age of 75 years – more than 10%. It has been shown that men are more likely to develop AF than women. AF paroxysm is the reason of more than ⅓ of patients' admissions to hospital with arrhythmia [3]. Because of extended lifespan the prevalence of AF has increased by 13% during last 20 years. According with prognosis this number would double during next 50 years. According with AHA (American Heart Association) from 2.7 to 6.1 mln of adult Americans suffer from AF and this number would double during next 25 years. Previously valvular defects (mitral stenosis) were considered to be the most frequent cause of AF. Nowadays arterial hypertension is supposed to be the main etiological agent of AF and the number of patients with idiopathic AF is increasing [4].

Prognosis for patients with AF depends on hemodynamic and thrombogenic complications of this arrhythmia at first, but it is also linked with patient's age, presence and severity of concomitant diseases. AF can be life-threatening because of the risk of thromboembolic complications and myocardial dysfunction that can promote development of heart failure.

Results of REACH trial that involved more than 63 000 patients suffering from AF demonstrated significantly higher frequency of cardiovascular death, myocardial infarction (MI), stroke and higher need of hospital admission comparing with patients without AF [5]. It is known that ~ ⅓ of all strokes is associated with AF. Stroke frequency in patients with nonvalvular AF taking anticoagulants is 5% per year, it is 2–7 times higher than stroke frequency in patients without AF. Cerebrovascular complication of AF are particularly frequent in elderly patients. According with Fremingham study for patients with AF (recruiting n=5070 patients during 34 years) the risk of stroke in the age of 50–59 years increases by 4 times, in the age of 60–69 years – by 2.6 times, 70-79 years – by 3.3 times, 80–89 years – 4.5 times. Mitral valvular disease, first of all mitral valve stenosis, is an important risk factor of stroke development. In case of nonvalvular AF such factors like previous episodes of embolism and strokes, arterial hypertension, age >65 years, information about MI, diabetes mellitus in anamnesis, prominent systolic dysfunction and/or congestive heart failure, enlarged left atrium (>50 mm), the presence of thrombus in left atrium can promote developing of stroke [6].

AF can play a role of both initial and aggravating agent for heart failure. Patients with AF have 3-4 times higher risk to develop heart failure. Increased heart rate in AF causes hemodynamic disorders due to reduced filling of ventricles, impaired coronary blood flow and heart contractility, and dilatation of ventricles. If heart rate >130 beats per minute persists for 10-15% of the entire daytime it can lead to developing of tachycardia-induced cardiomyopathy with severe congestive heart failure. But even if heart rate is normal lack of adequate atrial influence on cardiac output and irregular heart rhythm considerably aggravate hemodynamics. In this case stroke volume reduces by 20%, cardiac output – by 0.8–1.0 l/min and pulmonary artery wedge pressure – by 3–4 mm Hg.

Concomitant diseases of cardiovascular diseases has a big impact on prognosis of patients with AF. Patient with arterial hypertension and AF has twofold higher risk of developing complications during 5 tears, five-fold increase in frequency of left ventricle failure developing, three-fold increase in stroke development frequency and three-fold increase of mortality frequency. In case of MI lethality is twice higher and mortality is 1.8 times higher. According with different studies, presence of AF in patients with heart failure gives 2.7–3.4-fold increase in mortality rate and doubles ther risk to develop stroke and thromboembolic complications [7].

Key points of European and Russian guidelines for treatment and prevention of complications

Last Guidelines of European Society of Cardiology (ESC) dedicated to treatment of patients with AF were published in 2012. National Guidelines for diagnostics and treatment of AF proposed by Russian Society of Cardiology (RSC), National Scientific Community of arrhythmologists and Russian cardiovascular sur-

geons association also were revised and published in 2012. It is worth to mention that last National Guideline contains all available information related to this problem including united guidelines of American Heart Association, American College of Cardiology and guidelines of ESC.

Some essential changes in strategies of rhythm and heart rate control and in prevention of stroke and thromboembolic complications have happened after release of previous edition of guideline in 2011. Published results of 3 major studies changed some positions of these guidelines. These trials are: ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF), ROCKET-AF (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF) and PALLAS (The Permanent AF Outcome Study Using Dronedarone on Top of Standard Therapy) [8, 9]. First two clinical trials were dedicated to new anticoagulants: rivaroxaban and apixaban, therapeutic indications for which had been considerably extended.

The PALLAS study recruited 3236 patients but it had been terminated ahead of schedule due to increase of frequency of reaching the first endpoint (stroke) from 1.2% in placebo group to 2.6% in patients taking dronedarone (Hazard ratio (HR) 2.29, p=0.02) and also because of increased MI rate: from 4.1% in placebo group comparing with 7.8% in patients receiving dronedarone (HR 1.97, p=0.001). At the same time statistically significant increase of HR for compromised liver function during dronedarone treatment comparing to placebo had been detected: it occurred in 3.8% and 1.7% of patients consequently (p<0,001) [10].

According with epidemiological characteristic of AF in both guidelines, prevalence of AF in general population is up to 2%. And AH is considered to be the main cause of AF development. ESC highlights the importance of active case finding of AF in stroke prevention. This statement is based on several studies demonstrating that even short episodes and so-called "latent" AF increase the risk of stroke development. Therefore for opportune diagnostics of arrhythmia in patients older than 65 years it is necessary to perform screening including pulse palpation and ECG.

In AF classification apart of categories that have been used for a long time in clinical practice: first detected, paroxysmal, persistent, permanent, it is recommended to define also longstanding persistent AF. This arrhythmia is diagnosed when AF persists for more than one year and the strategy of sinus rhythm restoration has been chosen [2].

For quantitative estimation of AF symptoms it is recommended to use EHRA (European heart rhythm association) score. This score considers 4 classes of symptoms. This scale has been created relatively recently and it allows to estimate the symptoms associated with arrhythmia and their dynamics after sinus rhythm restoration [11].

Strategic attempt to save sinus rhythm has no advantages over "non-intervention" approach to the natural course of arrhythmia provided that the heart rate is under control. This position remains unchanged. At the same time it is proved that excessive heart rate control doesn't improve patients' prognosis. Talking about therapy of AF it is worth to mention that this section of ESC guideline has to be adapted to Russian clinical practice. In ESC guideline ideas about some antiarrhythmic drugs are based on major international clinical trials. At the same time in Russia and some other ex-soviet countries some drugs like allapinin, etacizin, procainamide produced in these countries are successfully used in clinical practice.

Section of antiplatelet therapy of patients with AF makes emphasis on so-called "new oral anticoagulants" (NOAC): direct thrombin inhibitors and direct Xa factor inhibitors. NOAC can be considered as an alternative of vitamine K antagonists. NOAC have some advantages over them like predictable anticoagulant effect with no necessity of constant coagulogram control, less prominent interaction with drugs and food, better efficacy-safety ratio. Key ideas about acetylsalicylic acid (ASA) has been proposed. It is highlighted that preventive efficacy of ASA is not high and the risk of massive bleedings still persists especially in elderly patients. Combined therapy of ASA and clopidgrel should be restricted to small group of patients that refuse to take NOAC.

Naturally risk stratification in patients with AF in relation to thromboembolic complications and stroke in particular remains an important problem. For a long time CHADS2 (Congestive Heart failure, Hypertension, Age, Diabetes mellitus, Stroke (2 ball)) has been used for this purpose.

Last guideline proposes more comprehensive score CHA2DS2-VASc (Congestive Heart failure, Hypertension, Age (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age, Sex category). It gives one point for presence of heart failure, AH, diabetes mellitus, vascular disorders: history of

MI, atherosclerosis of lower extremities vessels and aorta, age of 65–74 years and female sex. This score gives 2 points for age more than 75 years and prior episodes of stroke, transitory ischemic attacks or thromboembolism. CHA2DS2-VASc score for non-valvular AF has wider range of points, includes more risk factors: female xex, age of 64-75 years and vascular disorders. for example women cannot get the score of 0 points according with CHA2DS2-VASc. It is commonly known that CHA2DS2-VASc allows to estimate the risk of stroke development in more detailed and precise way especially in patients with low risk [2].

ESC and RSC guidelines give more importance to radiofrequency ablation (RFA) also as an initial treatment of AF with prominent symptoms and severe clinical course. It is reasonable to perform catheter ablation before prescribing antiarrhytmic drugs in patients with recurrent paroxysmal AF associated with symptoms of hemodynamic disorders after comparing benefits and risks.

New trends in AF treatment: clinical studies results

Majority of AF relapses after pulmonary veins isolation are caused by restoration of conduction between them and left atrium. The UNDER-ATP (UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate) [12] study estimated possibility of reducing relapse risk by additional use of RFA during the first ablation procedure in the areas of conduction induced with ATP (adenosine triphosphate). After randomization 2113 patients with paroxysmal, persistent or longstanding persistent AF underwent pulmonary veins isolation with ATP administration (n=1112) or according with standard protocol (n=1001). Mentioned below conditions have been chosen as a primary endpoint: relapse of atrial tachycardia lasting more than 30 sec or requiring repeated ablation, hospitalization or administration of I and III class of antiarrhythmic drugs during the period since 90 days up to one year after ablation. In the group of patients who underwent pulmonary veins isolation with ATP administration (0.4 mg/kg) conduction between pulmonary veins and left atrium was induced in 307 (27.6%) patients but it was eliminated with additional procedure of RFA in 302 (98.4%) patients. During the first year primary endpoint events haven't been registered with the same frequency in both groups: 68.7% in the group of pulmonary veins isolation with ATP administration and 61.7% in the group of patients who underwent pulmonary isolation according with standard protocol (corrected HR 0.89, for confidence interval (CI) 95% from 0.74 to 1.09 (p=0.25)).

Majority of early AF relapses after ablation are caused by postoperative vulnerability of left atrium. The EAST-AF study (Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for AF trial) [13] investigated capability of antiarrhythmic drugs administered during first 90 days after ablation to reduce the risk of early AF relapse, to decrease left atrium remodeling and to improve long-term clinical outcome. After catheter RFA 2038 patients with paroxysmal, persistent or longstanding persistent AF were randomized for 90 days of I and III class antiarrhytmic drugs administration or for refusal of treatment (n=1022). Primary endpoint events included atrial tachycardia lasting more than 30 sec, necessity of repeated ablation, hospitalization or administration of I and III class of antiarrhythmic drugs during the period since 90 days up to one year after ablation. During first 90 days after ablation absence of relapses have been registered with higher frequency in the group of antyarrhytmic pharmacotherapy: 59.0% versus 52.1% in control group, HR 0.84 for 95% CI from 0.73 to 0.96 (p=0.01) but during the period of further follow-up observation the absence of primary endpoint events in both groups had no significant differences: 69.5% and 67.8% respectively, corrected HR 0.93 for 95% CI from 0.79 to 1.09 (p=0.38). Administration of antiarrhytmic drugs during 90 days after AF ablation decreases the frequency of atrial tachiarrhytmia in this period of treatment but doesn't improve clinical outcome during subsequent follow-up observation.

In case of long-standing persistent AF pulmonary veins isolation is not enough for achievement of successful ablation. In the BELIEF study (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Long-standing Persistent AF Undergoing Catheter Ablation) [14] 173 patients with long-standing persistent AF after randomization underwent standard procedure of pulmonary veins isolation (n=88) or standard procedure together with electric isolation of left atrial auricle with average duration of procedure 77 versus 93 min, respectively.

Patients who underwent electric isolation of left atrial auricle had no AF relapses during one year of observation: 56% versus 28% in control group, HR 1.92 (p=0.001). Both groups of patients then underwent repeated ablation with isolation of left atrial auricle. During 2 years of observation AF haven't been

registered in 76% of initially performed left atrial auricle isolation and in 56% of patients who underwent it during the second procedure (p=0.003). Left atrial auricle isolation seems to be reasonable and requires pathophysiological investigation.

Comparing with vitamin K antagonists NOAC have short half-life time that requires high patients' compliance. Randomized trial AEGEAN (Assessment of an Education and Guidance program for Eliquis Adherence in Non-valvular AF) [15] involved patients with AF taking apixaban either being involved into educational program: information leaflet, special key holder, mobile phone notification, access to virtual coagulologic clinic(n=579) or receiving information about the disease and its treatment in standard way. Adherence to apixaban treatment regimen (twice for a day) was controlled using electronic gadget inside the box of the medicine. During 24 weeks patients took anticoagulant daily and on regular basis in 88,3% and 88,5% of cases (p=0.89), didn't interrupt the treatment on the 30th day of treatment in 91.1% and 90.5% of cases (p=0.76) in the groups of educational program and control, respectively. This study didn't find out additional benefit of educational program in patients with AF during treatment with apixaban.

During standard electric cardiostimulation such problems like electrode displacement and failure, infection, heart perforation, vein occlusion, tricuspid regurgitation, can occur. In the LEADLESS II study [16] totally leadless autonomous cardiac stimulators (42 mm long, 6mm diameter) were implanted in non-surgical way (catheter, via femoral artery) into the right ventricle of 300 patients who needed constant one-chamber stimulation Acceptable threshold ≤ 2,0 V with duration 0.4 mc and stimulation amplitude after 6 month was chosen as a primary efficacy endpoint and absence of serious adverse effects related to stimulator after 6 months was taken as a primary safety endpoint. Primary efficacy and safety endpoints were achieved in 90% and 93.3% of patients, respectively. During 6 month electrode displacement occurred in 1.7% of patients, heart perforation – in 1.3% of cases and ineffective stimulation – in 1.3% of cases. Later cardiostimulator was implanted to 226 patients and complications rate had a tendency to decrease. Working period of battery is estimated as 15 years. The question about tactics in case of cardiostimulator failure (remove or implant another one) hasn't beens solved yet.

Conclusion

Increasing prevalence of AF and its complications requires further investigation of efficiency of different approaches for heart rhythm control and rate of ventricular contractions and also antiplatelet drugs efficiency in this category of patients. Results of clinical studies presented at the last meeting of ESC that took place in London in autumn of 2015 certainly will be used in new guidelines for treatment of patients with AF.

Conflict of interest: None declared.

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New opportunities for cardiovascular risk reduction

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Summary
Combined antihypertensive therapies, especially fixed-dosed, have become a major approach in the management of arterial hypertension. angiotensin-converting enzyme (ACE) inhibitor/calcium antagonist combination is among the most effective ones. Statin group drugs involvement into this combination is advisable since almost 70 % of patients have increased serum cholesterol levels . Creation of polypill, fixed combination of 3 and more drugs impacting various risk factors of cardiovascular pathology, is widely discussed last years. fixed combination of Lisinopril (ACE inhibitor), Amlodipin (calcium antagonist) and Rosuvastatin (a hypolipidemic drug from statin group) can be considered as a polypill. It is expected that application of such polypill should increase patient compliance and accordingly improve therapy efficiency in patients with high cardiovascular risk.

Keywords
Arterial hypertension, angiotensin-converting enzyme inhibitors

Risk factors (RF) of cardiovascular disease (CVD) have been well investigated for a long time: first of all it is worth to mention arterial hypertension (AH), dislipidemia and smoking. It has been proved that reducing cardiovascular risk (CVR) factors leads to decrease of cardiovascular disease rate and mortality, unfortunately frequency of drug administration, therapy efficacy and patients' compliance in groups of high and very high CVD remains low. In Russia approximately 40% of adult males suffer from AH, half of them have dislipidemia, more than 60% of males are smokers [1].

At the same time poor patient compliance remains a major health problem [2]. What should be done? In 2003 the strategy of fixed-dose combination drug (Polypill) consisted of antiplatelet drug, statin and an-

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tihypertensive drug had been proposed by N.J. Wald and M.R. Low [3]. Since then the problem of polypill development, ingredients and administration is discussed at international meetings including important ones like annual congress of European Society of Cardiology.

Initially one of polypill's ingredients was folic acid (0.8mg) aimed to reduce such RF as increased homocysteine levels but later folic acid was excluded because of lack of evidence of effective reduction of myocardial infarction and stroke risks [4]. Creators of polypill performed meta-analysis of 15 major clinical trials and found out that polypill administration in all patients older than 55 years allows 80% reduction of CVD frequency. After this meta-analysis the strategy of polypill use for primary prevention of cardiovascular disorders started to develop. According with N.J. Wald and M.R. Low administration of polypill to all patients of the age of 55–64 (independently of RF presence) would protect them from coronary heart disease (CHD) and stroke development during next 10–12 years [3]. Simultaneous reduction of LDL cholesterol levels of 1.8 mM and diastolic BP of 11 mmHg would result in 88% reduction of CHD risk and 80% reduction of stroke risk. These authors consider that the frequency of adverse effects would not exceed 8–15% with necessity of drug withdrawal in 1–2% of cases.

Polypill efficacy depends on initial CVR level. In patients with high level of CVR polypill containing 4 drugs (antiplatelet drug, statin, hydrochlorothiazide, ACE inhibitor) would reduce CHD and stroke development risk by 62% and 60% respectively. At the same time polypill administration in patients with low CVR would result in 44% and 21% reduction of CHD and stroke development risk respectively.

Later in USA it has been demonstrated that wide application of polypills would allow to prevent CHD development in 2 mln people and stroke occurance in 1 mln people for 10 years. According with the authors of meta-analysis polypills usage has distinct economical advantages. It is known that long-term therapy with fixed-dose combinations of antihypertensive drugs increases patient adherence up to 21% comparing with free drug combinations.

Opponents of polypill strategy believe that polypill containing fixed doses of drugs would not allow to reach target levels of LDL, HDL and blood pressure. But it is worth to mention that even 1 mM reduction of LDL cholesterol levels can help to reduce CHD and stroke risk by 40% and 10% respectively, and 10 mmHg reduction of diastolic blood pressure would decrease risk of CHD and stroke by 40% and 60% respectively.

Later clinical researchers started to investigate the use of polypill not only for primary prevention (in patients with various cardiovascular risk) but also for secondary prevention (after myocardial infarction). Polypill components varied in different groups of patients. For example it has been proposed to use polypills containing not only statin and antiplatelet drug but also beta blockers and ACE inhibitors in patients with myocardial infarction because use of three or four drugs significantly increased survival rate comparing with the group of patients after MI who used to receive one or two drugs [5].

According with evaluations made by Word Health Organization combined administration of aspirin, two antihypertensive drugs and one statin to patients with CVR would allow twofold reduction of mortality rate and it would increase the expected lifespan by 2 years. Program of Polypill estimation as a strategy for secondary prevention has been already developed in European Union. Realization of FOCUS project (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) has started in five countries including Argentina, France, Italy, Spain and Switzerland. First stage of this study (FOCUS-1) aimed to investigate adherence of patients receiving standard free drug combinations (separately given drugs). Second stage of this study (FOCUS -2) estimated patient adherence and drug safety in approximately 1500 patients who received polypill containing fixed drug combination of aspirin, ramipril (ACE inhibitor) and simvastatin. As it was expected patient adherence to fixed drug combination was significantly higher comparing with free drug combinations (68% versus 58% respectively, $p<0.049$) [6].

According with TIPS (The Indian Polycap Study) trial polypill costs in developing countries can be reduced up to 20 cents/day (for comparison, in developed countries polypill value is estimated as 1 USD/day) [7]. This value can be achieved with the use of generic drugs, cheap packing, distributor and marketing costs and also with reducing the number of medical appointments and laboratory tests [8–10].

During last decades administration of fixed drug combinations (for example renin-angiotensin system blockers together with thiazide diuretic or calcium channel blockers) for treatment of arterial hypertensia has become common. What is the difference between polypill and usual fixed drug combination

for AH treatment? Majority of antihypertensive drugs contain two active components, whereas polypill should be made from 3 or more drugs. Combination of reserpine, hydralazine, hydrochlorthiazide, metil-ergocristine and potassium chloride can be considered as polypill and it has been used in clinical practice. Nowadays this medication is supposed to be outmoded although in past it has played a certain role in AH treatment.

It is worth to mention that the high occurrence of comorbidity requires creation and usage of polypills, that can contain statins, antiplatelet drugs in addition to effective AH medications. And instead of receiving 3–4 drugs with complicated dosage schedule patient could take one pill for a day. It is expected that polypill usage would allow to solve the problem of patient compliance to therapy.

It is also important to use generic drugs instead of original substances in polypill composition since it would reduce polypill cost and would make it affordable for all segments of society. It is possible to create polypills for coronary heart disease treatment (consisting of aspirin, statin, beta bloker and amlodipine), chronic kidney disease (renin-angiotensin system blockers, statin and antianemic drug), type 2 diabetes mellitus (renin-angiotensin system blockers, indapamide, statin, aspirin and metformin).

Existing connection between AH and dyslipidemia requires simultaneous targeting of both these risk factors. Unfortunately it is not always possible to reduce these risk factors just with the change of lifestyle and it makes the use of medications with proved efficacy in CVD prevention necessary especially knowing that for a lot of patients it can be tough to drastically change diet, to increase physical activity and to refuse smoking. [11].

Fixed drug has been used for secondary prevention of CVD in patients with arterial hypertension and associated hyperlipidemia in Russia and other countries. This drug was created as the realization of an idea of multifactorial prevention - simultaneous targeting several risk factors as the most effective prevention strategy. Efficacy of simultaneous blood pressure (BP) and dyslipidemia targeting has been proved in ASSCOT-LL trial (Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering): administration of 10 mg of atorvastatin together with antihypertensive therapy resulted in additional reducing of total risk of non-fatal myocardial infarction and death from coronary heart disease by 36% and reducing of risk of all cardiovascular complications by 29% [12]. It has been also proved that addition of statin to antihypertensive therapy increases its efficacy [13]. So amlodipine addition to combination of amlodipine and atorvastatin was a good decision, because amlodipine is one of the most effective and well-studied from evidence-based medicine point of view dihydropyridine calcium channel blockers. Amlodipine belongs to III generation of calcium channel blockers, it has the biggest half-life period between all other calcium antagonists (CA) (35-52 h), gradual increase and decrease of plasma concentraton, high antihypertensive efficacy, proved antiischemic and antiatherogenic effect [14, 15]. Both AH and coronary heart disease are indications for amlodipine administration. Amlodipine is one of few CA that are allowed to use in chronic heart failure as antihypertensive or antiischemic drug because it has no negative inotropic effect. Some clinical trials like ASCOT, ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) that investigated efficacy of ACE inhibitors and CA combinations typically used amlodipine. Both trials proved not only efficacy of this combination in BP lowering, but also its influence on frequency of cardiovascular complications in patients with AH. Majority of them had such associated pathologies like coronary heart disease, diabetes mellitus, obesity, so these patients belonged to the group of high cardiovascular risk, In ACCOMPLISH trial patients with the same control level of BP receiving ACE inhibitors and CA amlodipine had 20% lower risk of cardiovascular complications comparing with the group receiving ACE inhibitors and diuretic. Figuratively speaking, it was a competition between amlodipine and thiazide diuretic in which amlodipine has won.

ASCOT and ACCOPLISH trial allowed to conclude that ACE inhibitors and dihydropyridine CA combination is highly effective. After it pharmaceutic companies started to create fixed drug combinations of ACE inhibitors and CA, most frequently with amlodipine. One of these highly effective drug combinations. contains combination of amlodipine and ACE inhibitor lisinopril. This substance has its own unique features. This is the only hydrophilic ACE inhibitor that is administered in active drug form unlike other ACE inhibitors (prodrugs) for which the active form is metabolized one. Because of this reason lisinopril activity doesn't depend on lifer function, and it allows lisinopril to be used as drug of choice in patients with fatty hepatosis, liver cirrhosis etc. In other words, lisinopril effect in case of concomitant liver pathol-

ogies is more predictable, this drug doesn't compete with other drugs for microsomal enzymes of liver and pharmacokinetics interaction with other drugs. doesn't occur. Efficacy of lisinopril doesn't change in smoking patients even if it is well known that nicotine is a potent microsomal enzyme inducing agent and it can accelerate biotransformation of some antihypertensive drugs.

Well-known ALLHAT study (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) involved 42 thousands of patients with AH demonstrated that lisinopril not only reduced BP but also reduced the risk of severe complications development, such as death, stroke, MI, new cases of diabetes mellitus and turned out to be more effective to prevent chronic heart failure than amlodipine [18].

During the last years use of combined antihypertensive therapy especially in the form of fixed drug combination has become common, because of its distinct advantages such as increased efficiency and accordingly the possibility to reach target BP levels in majority of patients, reducing of possible adverse effects and generally good tolerance because of lower doses of medicines in fixed drug combination, increase of adherence to therapy because of maximally simplified drug regimen (in ideal situation, one pill for a day). Patients with high and very high additional risk of complications are recommended to use polypills since the beginning of treatment [19, 20]. In general monotherapy is effective not more than in 30% of patients.

Registration of drug containing amlodipine and lisinopril together with rosuvastatin, one of the safest and the most potent statin drug currently, is expected in the close future. Rosuvastatin not only slows down progression of atherosclerosis. Rosuvastatin not only slows down the progression of atherosclerosis (REVERSAL study (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study)) but also causes regression of atherosclerosis (ASTEROID study (A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound - Derived coronary atheroma burden) [21, 22]. It is important to notice that rosuvastatin not only reduces levels of LDL cholesterol to target levels but also increases HDL cholesterol levels by 8–10% [23]. JUPITER (Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin). is one of the most known studies dedicated to rosuvastatin in primary prevention. In this study patients without apparent dyslipidemia but having high level of C-reactive protein (it is included into the list of cardiovascular complications) received rosuvastatin in the dose of 10mg. Five years after the risk of cardiovascular complications, stroke, need of revascularization and, the most important were significantly lower and general mortality reduced by 20%. More than that, reduction of highly sensitive C-reactive protein levels was achieved [24].

Statins are mainly prescribed to patients with dyslipidemia, but it is worth to mention that it is necessary to administer statins to patients without dyslipidemia in case if they have SCORE risk more than 5%. as it is necessary to administer them to patients with CHD. Therefore it would be possible to administer combination of amlodipine, lisinopril and rosuvastatin to the patients with AH and high additional risk of cardiovascular complications independently from basal level of LDL cholesterol. It is important to remember that statins not only drugs eliminating dyslipidemia but mainly drugs used to increase patients' survivability.

Efficacy and safety of lisinopril, amlodipine and rosuvastatin combination have been investigated in ROZALIA study [25]. Lisinopril and amlodipine were administered as a fixed drug combination (dosage 50mg/5mg, 20mg/5mg, 20mg/10mg) and rosuvastatin (10/20mg) was added to this combination. This trial involved 2452 patients with AH stage 1-2, hypercholesterolemia and high (93.2%) or very high (6.8%) cardiovascular risk that was defined according with presence of diabetes mellitus, metabolic syndrome, peripheral artery disease (Figure 1). After 6 months frequency of reaching target BP and LDL cholersterol levels were estimated (Figure 2 and 3 respectively) , including patients for whom it was impossible to perform before. By the end of the study 91% of patients achieved target levels of BP less than 140/90 mm Hg. and 57% of patients had BP less than 130/80 mm Hg. 94% of patients older than 80 years reached target levels of BP (<150/90 mm Hg.) by the end of the study. There were no differences in the efficacy of antihypertensive therapy in groups of patients with diabetes mellitus, metabolic syndrome and peripheral artery disease and the efficacy didn't depend on preceding therapy.

In one month evident dynamics of total cholesterol and LDL cholesterol levels were detected. By the end of the study (in 6 months) changes increased according with rosuvastatin dose titration, in addition to this triglycerides serum levels decreased significantly (23% decrease, $p<0.05$) and HDL cholesterol levers increased (6% increase, $p<0.05$). In the end of

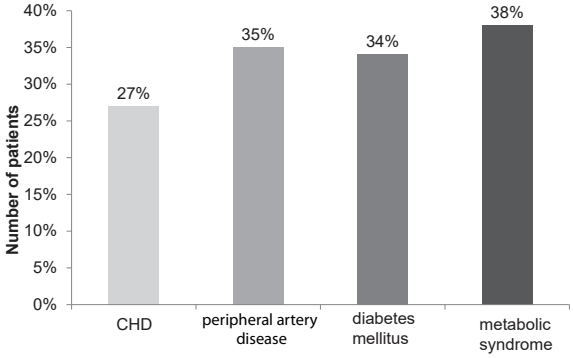

Figure 1. Frequency of concomitant complications in ROZALIA study

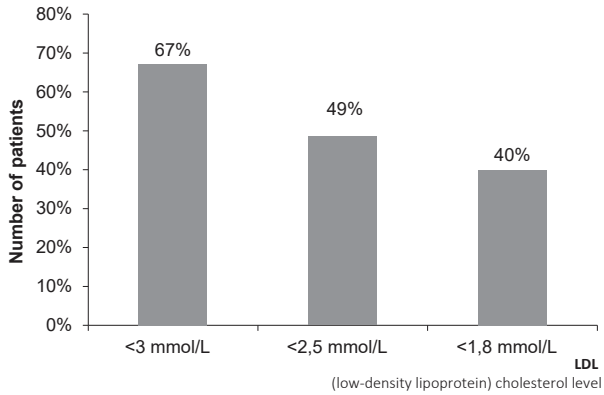

Figure 3. Achievement of target LDL cholesterol levels in the ROZALIA study

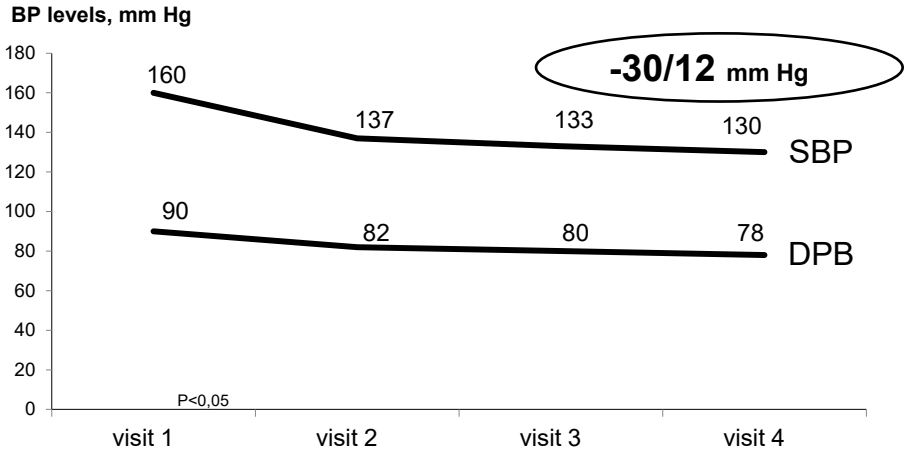

Figure 2. BP dynamics in the ROZALIA trial

the study LDL cholesterol target levels<.3.0 mmol/L, <2.5mmol/L and <1.8 mmol/L were achieved in 67%, 49% and 40% of patients respectively. Efficacy of lipid-correcting therapy didn't change in the groups of patients with diabetes mellitus and metabolic syndrome. It is worth to mention that apparent effect was achieved in 48% of patients who received statins but didn't reach target levels of LDL cholesterol before. In addition, levels of such prognostically important markers like C-reactive protein, uric acid, serum glucose and microalbuminuria were decreased. It is known that combination of ACE inhibitor and dihydropyridine calcium antagonist is able to reduce the frequency of new cases of diabetes mellitus comparing with beta blocker and diuretic combination [16].

Increase of creatine phosphokinase and transaminases levels have been detected in 0.92% and 0.9% of patients, respectively. Majority of patients demonstrated excellent and good tolerability of treatment and observed improvement of life quality. There were no reports about severe adverse effects: dry cough was present in 3.1% of patients, lower leg edema – in 2.2% of patients , muscle pain – in 1.1% of patients. Authors concluded that fixed drug combination of lisinopril and amlodipine together with rosuvastatin is safe and effective for patients with mild and moderate AH, hypercholesterolemia and high/very high CVR.

In Russia the combination of lisinopril/amlodipine together with administration of rosuvastatin was investigated in TRIUMVIRAT study [26–28]. This study pointed out safety and efficacy of fixed combination of amlodipine/lisinopril together with administration of lipid-lowering drug rosuvastatin in patients with uncontrollable AH and hypercholesterolemia in the outpatient setting [28]. This trial involved patients older than 18 years with essential AH both with the new-onset (untreated) AH≥160/100 mm Hg. and with insufficient BP control – BP levels ≥140190 mm Hg. in spite of antihypertensive drug administration including combination of 2 and 3 medicines. Patients involved in this program, received fixed combination amlodipine/lisinopril once per day in the morning in one one of the following doses. Previously untreated patients or patients who received one drug before

were administered with 5/10 mg, patients who previously used to take two or three drugs were administered with 5/20 mg or 10/20 mg respectively. Patients with LDL cholesterol higher than target levels for existing risk degree received also rosuvastatin [29]. Dose of rosuvastatin was chosen according with the target and initial levels of LDL cholesterol. Dose of rosuvastatin varied from 5 mg/day to 40 mg/day in different patients. Rosuvastatin in the dose of 20–40 mg/day reduced LDL cholesterol levels by ⩾ 50%. After three months of treatment target levels of BP (<140/90 mm Hg.) were achieved in 80% of patients. Combined therapy of amlodipine/lisinopril with addition of rosuvastatin not only considerably improved control of BP and lipid levels but also significantly reduced the risk of cardiovascular complications development.

It is well known that in Russia patient adherence to antihypertensive therapy or to statins remains poor. It is reasonable to think that serious simplification of dosage schedule (ideally one pill for a day), reduction of drugs' number and medication's cost due to use of effective generic drugs altogether would help to increase patient adherence.

Clinical practitioners are expecting creation of polypill containing lisinopril, amlodipine, rosuvastatin that are proved to have high efficacy in primary and secondary prevention of cardiovascular disorders and their complications.

Conflict of interest: None declared.

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The features of cardiovascular lesions in patients with pulmonary tuberculosis

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Summary
In this report, we observed 39 patients suffering from different forms of severe progressing pulmonary tuberculosis, as well as from cardiovascular disease (CVD), and studied their CVD factors. Severe myocardial ischemic changes of left ventricle were revealed in 67.5% of patients without history of coronary artery disease (CAD) while studying their electrocardiography (ECG), coagulation hemostasis and clinical presentation parameters. Having active bronchopulmonary pathology on the background, they also had hemostasis coagulation component impairment (68% of cases) in the form of blood coagulation system activation and its fibrinolytic activity decrease. The obtained data show that toxic infectious impact on the myocardium, followed by myocardiodystrophy and decreased heart function, is the lead in causing cardiovascular alterations in patients with acute pulmonary tuberculosis. Dystrophic changes of left ventricle myocardium can be observed quite early and are indicated primarily by T wave inversion.

Keywords
Tuberculosis, coagulation hemostasis, cardiovascular complications, myocardiodystrophy, electrocardiography

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Cardiovascular lesions can be detected even during early stages of pathological process. It is well known that cardiovascular system is highly vulnerable to tubercular intoxication. [2, 10].

Combination of active tubercular process and cardiovascular lesion causes a lot of problems due to necessity of complex antibacterial therapy against tuberculosis altogether with treatment of concomitant diseases including vascular pathologies.

Aim of this work: to investigate the features of cardiovascular lesions in patients with pulmonary tuberculosis during different stages of disease. Analysis of changes that occur in left and right parts of the heart arouses particular interest when clinical, radiologic and electrocardiogram examination does not reveal signs of hypertension.

Combination of active tubercular process and cardiovascular lesions creates additional problems because of necessity to make combined antibacterial therapy against MBT together with treatment of cardiovascular diseases.

It is well known that during last years the number of patients with severe, rapidly progressing course of tuberculosis has increased. These forms of tubercular infection are classified as "Rapidly progressing pulmonary tuberculosis" (RPPT). This term includes different clinical forms of pulmonary tuberculosis with similar manifestations.

Even being different from pathogenetic point of view all these clinical forms of tuberculosis have acute onset, severe intoxication and bronchopulmonary manifestations that can be combined differently with respiratory failure, concomitant nonspecific infections, haemoptysis, pulmonary hemorrhage and other complications. Typical clinical course of this tuberculosis form is gradual development of progressing and disabling dyspnea with alveolar hyperventilation. This group of patients is at the highest risk of cardiovascular complications' development. When exudative reaction prevails such types of dystrophy and necrosis like caseous necrosis and myocard dystrophy develop fast.

Materials and methods

We observed 39 patients (29 male and 10 female) with RPPT. Average age of patients is 36 years. All patients underwent full clinical, laboratory and radiological examination. We investigated hemostasis/coagulation system, plasma concentration of fibrinogen and fibrinogen B as a sign of fibrinogen degradation, thrombin time test as a screening coagulation test aimed to observe intensity of fibrin clot formation [9].

Results and discussion

Results of this investigation showed MBT bacterioexcretion in all patients. 60% of patients were diagnosed with drug-resistant tuberculosis with MBT resistance to main antituberculosis drugs. In case of bronchial obstruction cough, acute asphyxia manifested as bronchial asthma attacks and mild fever were the most prominent symptoms that can be considered as a sign of chronic pulmonary lesions. Pulmonary auscultation revealed both fine and coarse crackles and dry rales. In case of focal tubercular process rales were found in distinct localization. It is known that opportunistic microorganisms together with MBT are the most frequent causative agents of bronchial inflammation. Addition of secondary bronchopulmonary infection presented with Gram-negative cocci, Gram-positive bacilli and fungi causes formation of big and giant caverns with signs of abscesses and consequent lung destruction. New-onset patients were treated with combined therapy consisted of 5 main drugs except cases with MBT resistant to several drugs. We used to change therapy to second-line antibacterial drugs in case of MBT drug resistance detection. Apart of etiological treatment patients received bronchodilators, mucolytic and anti-inflammatory medicines, cardiac glycosides, angiotensin-converting enzyme inhibitors and selective beta-blockers.

Analysis of ECG of 29 patients with caseous lesions of pulmonary tissue in RPPT demonstrated ST segment depression (average value 0,2±0,13 mV (M±σ)) in 11 cases (40%), ST segment elevation (average value 0,18±0,09 mV) in 8 cases (27.5%). These data show evident ischemic changes of left ventricle myocard in these patients (67.5%) who had no history of coronary heart disease. The average duration of QRS complex in these patients was 0,08±0,017 second (M±σ), and PQ interval duration was 0,15±0,11 second (M±σ) that indicate the absence of significant conduction abnormalities.

Toxic-allergic lesions in tuberculosis are characterized with microcirculatory vessels' changes. In case of prevailing exudative tissue reaction dystrophic and necrotic lesions of vessels develop fast causing different vasomotor abnormalities, endothelial dysfunction. Recent investigations demonstrate that vascular endothelial cells produce potent vasodilating substances: prostacyclin, endothelium-derived

relaxing factor (EDRF), endothelium-derived hyperpolarizing factor, it brought new insights into pathogenesis of pulmonary hypertension as a main cause of cor pulmonale [1]. Data about EDRF as a modulator of smooth muscle in lung vessels changed its role in regulation of pulmonary circulation, pulmonary artery pressure and pulmonary vascular resistance. Vasodilating factors of endothelial cells are strongly connected with smooth muscle elements of lung vessels. In case of pulmonary hypoxia and decrease of alveolar pO_2 release of relaxing factor from endothelial cells slows down and it has hemoregulatory effect on vessels.

Dysfunction of this system can be the cause of pulmonary vessels constriction and pulmonary hypertensia. Microcirculation impairment is accompanied with tissue hypoxia and metabolic acidosis. Increased vascular permeability, extravasation of blood, erythrocyte sludging, activation of platelets and tissue factors of blood coagulation with further formation of fibrin clots are also very important.

Hemostasis abnormalities have different phases. In the beginning they are characterized with hypercoagulation due to hyperfibrinogenemia and suppressed fibrinolysis. Abnormal microcirculation, tissue and platelet factors' release in blood, platelets' activation cause formation of microclots. Intravascular changes are presented with congestion and slowing-down of blood flow. Functional insufficiency of platelets and erythrocytes causes their aggregation and increase of adhesion [6, 8]. Pneumosclerosis develops in the parts of lungs characterized with vascular paralysis in places of tubercular lesions.

Scintigraphic study results in patients with tuberculosis demonstrated that initially capillary reduction is not typical for fresh lesions but it aggravates with time[5]. After clot formation pulmonary changes transform to pneumosclerosis. It can explain further microcirculatory abnormalities, increase of pulmonary artery systolic pressure (PASP). In case of big lesions involving ⩾ 50% of capillary system generalized increase of small arteries tone occurs on the affected side and it causes development of pulmonary arterial hypertension.

Abnormalities in hemostasis system that lead to increased risk of thrombosis and thromboembolism were identified in 68% of cases. It is worth to mention that patients with RPPT had some abnormal blood coagulation tests. Analysis of blood coagulation profiles demonsrtrated that hypercoagulation in these patients has similar mechanism and is caused by active pulmonary tuberculosis regardless of its clinical form [3].

Increased fibrinogen concentration (up to 5.5-6.6 g/l) and detection of abnormal fibrinogen are the signs of blood prethrombotic state development. In 66% cases high rate of thrombotest (rate of VI-VII indicates hypercoagulability) was detected. Activation of blood coagulation system and decrease of fibrinolysis are evidences of latent intravascular blood clotting [10]. We administered anticoagulants (heparin subcutaneously) and antiplatelet therapy.

Heart failure in patients with RPPT can develop without cardiac hypertrophy that can be explained by early dystrophic changes of myocardium caused by infection, intoxication, continuous hypoxia and impaired intracardiac haemodynamics.

In case of inflammatory process with undulating course cor pulmonare is manifested as "subacute cor pulmonare" and in the beginning these changes can be reversible in some patients.

In case of repeated exacerbation these symptoms become constant and aggravate with time. Most frequently myocardium dystrophy is manifested as insufficiency of myocardial contractility, abnormalities of cardiac rhythm an conductivity. Elimination of infection and inflammatory process causes decrease of toxic effect on cardiac muscle and is supposed to me one of the ways to treat myocardium dystrophy. These patients require pathogenetic therapy aimed to preserve vessels and to treat myocardium dystrophy, together with continuous tuberculosis specialist and cardiologist observation. In case of absence of positive results after several months of chemotherapy or in case of pulmonary hemorrhage and spontaneous pneumothorax surgical treatment should be considered.

Undulating course of long-term pulmonary tuberculosis causes pneumosclerosis expansion that creates background for opportunistic infections. Well-timed therapy consisted of anti-inflammatory drugs, antibiotic, bronchodilators, taking into account occupational hazards and smoking history can significantly decrease toxic effect of tuberculosis on myocardium. Therefore these patients require pathogenetic therapy aimed to preserve vessels and to improve microcirculation.

Clinical and laboratory examination of 26 patients with uneffective initial treatment demonstrated that between these patients prominent and mild intoxication and bronchopulmonary symptoms prevailed. Statistic analysis of ECG in this group of patients

demonstrated no significant signs of right atrium hypertrophy (P wave amplitude: 0.168±0.05 mV(M±s), reference values – up to 0.25 mV with amplitude >0.25 mV in case of hypertrophy).

At the same time some signs of right ventricle hypertrophy and incomplete right bundle-branch block were presented. Amplitude of S1 wave was 0,13±0,15 mV (M±σ) (normal values) and Rv1 + Sv5,6 sum was 0,53±0,34 mV (in case of hypertrophy > 1,05mV). However increase of Rv1 wave was detected (0,25±0,34 mV (M±σ) (1 mV= 10 mm, so 2,5±3,4 mm) that corresponds to rSR pattern; broad QRS complex – 107,4±23,24 mc (reference value – not longer than 90 mc) (M±σ) was presented. ECG signs of ischemic myocardial lesions were identified: ST segment elevation >0.1 mV or 1 mm (according with ECG results it was detected in all 26 patients, average value 1.2±0.6 mm) without ST interval depression > 0.05 mV or 0.5 mm in all 26 patients (average value 0.3±0.3 mm). We also found out inverted T wave in most leads in all patients (we didn't take into account inverted T wave in aVR and V1 leads) with average value of 0.8±0.6 mm (M±σ), comparing with positive T wave in other leads with average value of 5.3±2.3 mm (M±σ).

Therefore we found out both signs of right ventricle hypertrophy and signs of myocardial ischemic lesions represented as ST segment elevation > 0.1 mV or 1 mm – 1.2±0.6 mm (M±σ) and inverted T vawe in standard limb and chest leads with average value of 0.8±0.6 mm (M±σ).

Typically performing of Holter monitor test, ECG, echocardiogram, multislice computer tomography, MRI of cardiovascular system is recommended in this group of patients for differential diagnosis of ischemic and pulmonary causes of cardiovascular pathology.

During manifestation of pulmonary hypertensia and right ventricle myocardial hypertrophy patients had complaints on weakness, arrhythmias during coughing, feeling fear, change of body position. During examination it was possible to find subtle edema of dorsal surfaces of hands and feet. Right ventricular failure combined with pulmonary hypertension indicate the development of cor pulmonare.

Works of Ershov A.I. (1996), Laricheva K.A. (2010) [4, 7] dedicated to investigation of tissue perfusion demonstrate that during formation of chronic cor pulmonare the role of active mechanisms of haemodinamics regulation decreases, whereas the role of passive ones increases. Decrease of vasomotor activity of microcirculatory vessels and capillary reserve leads to impairment of the main regulator of pulmonary circulation – hypoxic pulmonary vasoconstriction (Euler-Lijestrand mechanism).

With further progressing of tubercular process peripheral vasoconstriction changes to vasodilatation of venules and venous portion of capillaries and depositing blood inside them. This leads to decrease of circulating blood volume and blood pressure and consequently – to decompensation of circulation. Before antimycobacterial drugs had been invented people suffering from RPPT had "collapse" variant of decompensation caused by toxic paralysis of vasomotor nerves. Clinically it manifested with cyanosis, impairment of myocardial contractility. During auscultation muffled heart sounds were detected. Opening of arteriovenous anastomoses reduces after load on right ventricle (decreasing pulmonary artery pressure), on the other hand it impairs arterial blood saturation with oxygen. It has bad impact on myocardium and causes further decrease of peripheral vascular resistance and aggravation of collapse. Delay of intensive care, use of uneffective drugs can lead to slow regression of pathological process and aggravate myocardial and vascular dystrophic changes. Inadequate interventions can make all efforts and costs of pathogenetic and symptomatic therapy unreasonable.

Conclusion

Our results demonstrate that the most important cause of cardiovascular lesions in patients with RPPT is toxic-allergic effect on myocardium with consequent development of myocardium dystrophy. Dystrophic changes of myocardium develop quite fast, and it correlates with T wave changes in ECG.

Hypertrophy of right ventricle doesn't occur in all the cases of tubercular process with undulating course because normal vascular patency of anastomoses relieves heart action and if hypertrophy of both ventricles develops ECG signs of right ventricle hypertrophy disappear. So even in case of severe respiratory failure and cor pulmonare decompensation pulmonary hypertension doesn't reach high levels.

Conflict of interest: None declared.

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Valvular lesions in connective tissue dysplasia: clinical manifestations characteristics, the prognosis of the course

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Summary

Objective

To conduct a prospective study of young patients with undifferentiated form of connective tissue dysplasia (CTD) and analyze their valve syndrome course.

Materials and methods

Five hundred forty nine (549) patients aged 18-45 years (men = 330, 60.11%; women = 219, 39.89%) were enrolled in the study. They all had symptoms of CTD. Valve syndrome was indicated in 281 patients (51.18%; 95% CI 46.91-55.43) combined with arrhythmic (71.89%) and vascular (63.35%) CTD syndromes.

Results

Subjective status of patients with valve syndrome was characterized by numerous cardiovascular and other, less informative adverse effects.

The severity of CTD predicted valve syndrome formation. Low tolerance to physical activity and subsequent formation of dystonic reactions and left ventricle diastolic dysfunction were revealed more often among patients with valve syndrome. Valve syndrome progression was revealed in 2.85% of cases (8/281), average age of progression

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detection – 27.13±3.94 years. Arachnodactyly, combined valve pathology, bicuspid mitral valve prolapse, valve myxomatous degeneration were found more often among patients with severe form of valve syndrome and CTD.

Conclusion

Valve syndrome was revealed in 51% of young patients with undifferentiated CTD and is often combined with congenital subvalvular anomalies, arrhythmic and vascular CTD disorders. Valve syndrome is characterized with diverse and nonspecific complaints. It's associated with greater CTD severity, exerts regular influence on formation of left ventricle diastolic dysfunction and maladaptive reactions to physical activity. Combined valve pathology, bicuspid mitral valve prolapse, mitral valve myxomatous degeneration and arachnodactyly are predictors of progressive form of valve syndrome.

Keywords

Connective tissue dysplasia, valve syndrome, course of disease

Introduction

Cardiovascular symptoms of connective tissue dysplasia (CTD) including valve, vascular and arrhythmic syndromes can directly threaten health and life of patients because of progressive course with development of clinically significant unfavorable manifestations like aorta and other arteries aneurisms or dissections, life-threatening arrhythmias, myxomatously changed left ventricle cord avulsion, progressive insufficiency of heart valves, early and sudden death [1-3]. Course of disease and unfavorable outcomes of cardiovascular lesions are studied better for syndromal forms of CTD: Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome and others [4. 5]. Recently published data indicate that undifferentiated forms of CTD can manifest as the same cardiovascular syndromes and complications with increased frequency of early and sudden death comparing with general population. It does not go along with the idea of unambiguously benignant course of undifferentiated CTD and implies prognostic heterogeneity of this patients' group. There is a contradiction between contemporary knowledge about imperative clinical significance of CTD cardiovascular manifestations in definition of individual life and health perspectives and lack of possibility to make prognosis of cardiovascular syndromes course because of insufficient knowledge about factors that are associated with their formation and course.

The aim of this study is to make analysis of valve syndrome course in CTD during prospective observation of young patients with undifferentiated CTD.

Materials and methods

This research has been done of Western Syberian medical center, Omsk Regional Clinical Hospital, during the period of 2004–2013 years. We performed screening study of 752 patients, after which we selected 549 patients who had signs of dysmorphogenesis of connective tissue in the age of 18–45 years, (330 (60.11%) males and 219 (39.89%) females) according with inclusion/exclusion criteria.

We used the following inclusion criteria: presence of undifferentiated CTD, age of 18–45 years, signed informed consent. Presence of disorders underlying aorta lesions: atherosclerosis, syphilitic aortitis, We chose the following conditions as an exclusion criteria: Takayasu arteritis, giant cell arteritis, mycotic aneurism, chest trauma or/and cerebral arteries (craniocerebral trauma), use of narcotic drugs, alcohol abuse at the moment of inclusion, hereditary syndromes of connective tissue dysplasia in patient or in its first generation relatives. Patients were included with the trial during examination after independent appealing for medical help, during follow-up observation or being referred for advice of medical specialist. CTD was diagnosed according with the complex of phenotypic signs of connective tissue dysmorphogenesis[6]. Average age of patients was 23.51±8.67 years (95% CI: 22.78–24.24).

Methods of examination included physical examination, laboratory and instrumental techniques including electrocardiography (ECG), Holter ECG monitoring with analysis of cardiac rhythm variability, 2D and 3D Doppler- echocardiography (Echo-CG), veloergometry, Doppler ultrasonography of intracranial and extracranial arteries supplying the brain, transcranial Doppler ultrasonography with functional tests, magnetic resonance imaging and magnetic resonance angiography.

Dynamic observation required making of actual medioprophylactic activities [7-9].

Statistical methods included descriptive and analytic statistics: parametric t-test, analysis of contingency tables – Fisher's exact test, χ^2,, dispersion analysis – single-factor dispersion analysis of quali-

tative (binary) characters. =Statistical tests like relative risk (RR), sensitivity (Se), specificity(Sp) were used for estimation of different factors' and clinical outcomes interrelations. The borderline of RR clinical significance for risk factor was 1.2, for a factor with protective action – 0.8. Estimation of information capability and prognostic (diagnostic) coefficient was performed with the use of summary prognostic table according with the Kullback test and statistic procedure of heterogeneous consequent recognition [10]. Statistical tests were performed using Microsoft Excel, Statistica 10,0 (StatSoft Inc., USA) software.

Results

Cardiovascular lesions took second position among registered dysplastic changes after musculoskeletal manifestations (table 1).

In absolute majority of patients (88,71%; n=487) CTD manifestations involved 2-4 systems: two systems were affected in 35.52% of patients (n=195), three systems – in 36.43% of patients (n=200), four systems – in 16.76% of patients (n=92). Lesions of one and five systems were registered in 6.16% (n=34) and in 4.74% (n=26) of patients respectively. Involvement of 6 systems mentioned above occurred significantly more rarely (0,36%; n=2). Involvement of each system had the following pattern: musculoskeletal system – 3.00 (2.00–4.00) symptoms, cardiovascular system – 1.00 (1.00-2.00) symptoms. Number of respiratory symptoms ranged from 0 to 3, gastrointestinal symptoms – from 0 to 4, ophthalmic symptoms – from 0 to 2, urogenital symptoms – from 0 to 1. Average diagnostic coefficient in general group of patients was 28,84±10,76 (95% CI – 27,94–29,74). It was detected that patients with severe form of CTD (n=339, 61,75%). Average diagnostic coefficient in mild CTD subgroup of patients was 20,12±2,07 (n=210, 38,25%, 95% CI: 34,19-42,48), the same rate for severe CTD was 34,25±10,65 (95% CI 33,10-35,39; t-value 19,321; p=0,000). System involvement score was 3.00 (2.00-4.00). Estimation of CTD symptoms according with National Guideline (2012) revealed that the most frequent manifestations are: increased dysplastic stigmatization/ increased mainly visceral dysplastic stigmatization (59.19%), mitral valve prolapsed syndrome (28.23%). Such signs right benignant hyper mobility of joints (8.93%), Marfan-like appearance (1.46%), Ehlers-like phenotype (1.46%), unclassified phenotype (0.55%), MASS-phenotype (0.18%).

Table 1. **Distribution of CDT manifestations**

System/organ	Number. (n)	%
Musculoskeletal system	549	100,00
Cardiovascular system	413	75,23
Skin manifestations	169	30,78
Respiratory system	119	21,68
Ophtalmic manifestations	120	21,86
Urogenital system	87	15,85
Gastrointestinal tract	81	14,75

Valve syndrome was diagnosed in 281 patients (51, 18%, 95% CI 46.91-55.43). Mitral valve prolapse (MVP) was the most frequent CTD valve manifestation (98.53% of all valves' prolapses), in 47.76% of cases (n=96) was combined with anomalous left ventricle cords, and in 35.32% (n=71) of cases – with myxomatous degeneration of valve (1–2 stage). In absolute majority of patients 1stage MVP was registered / (n=181; 90,05%), MVP of 2 stage occurred considerably less frequently (n=20, 9.95. Intensity of regurgitation didn't exceed 2 grade in all regurgitation variants: mitral, tricuspid and aortic (table 2).

Subjective health status of CTD patients with valve syndrome was characterized with numerous complaints related to cardiovascular system (cardialgia, undefined discomfort in heart area, palpitation, intermittence, etc) and general complaints (general weakness, fatigability, bad tolerance of physical activity, headache, non-rotatory vertigo) with poor level of informativity (0.52–0.80), significant diagnostic threshold wasn't achieved, total diagnostic coefficient was less than +13.

Table 2. **Clinical manifestations of valve syndrome, n=281**

	Number, (n)/%
Prolapses of heart valves	204/72,60
Mitral valve prolapse, classic	77/27,40
Mitral valve prolapse, non-classic	124/44,13
Tricuspid valve prolaps	20/ 7,12
Aortic valve prolapse	1/0,36
Combined prolapses	18/6,41
Myxomatous degeneration of valve	106/37,72
Isolated myxomatous degeneration	29/10,32
Associated with valve prolapse	77/ 27,40
Valvular regurgitation	157/55,87
MV: regurgitation (grade 1).	69/24,56
MV: regurgitation (grade 2).	11/3,91
Tricuspid valve: regurgitation (grade 1).	54/19,22
Tricuspid valve: (grade 2).	1/0,36
Aortic valve: regurgitation (grade 1).	28/ 9,96

Comment: MV – mitral valve

In majority of cases (n=202; 71,89%) patients with valve syndrome had arrhythmias, in 63.35% (n=178)

of cases vascular manifestations of CTD were detected. There were no gender differences between patients with valvular manifestations and without them: male – n=166, 59,07%, female – n=164, 61.19% in corresponding groups (χ^2 0,18; p=0,675). Presence of valve syndrome didn't affect significantly the development of orthostatic reactions in patients (n=47; 16,73%); (χ^2 2,641: p=0,104). At the same time patients with valve syndrome demonstrated significantly poorer tolerability of physical exercise (veloergometry) comparing with patients without valve syndrome: 79/28.11% and 46/17.16% respectively ((χ^2 8,74; p=0,003). Presence of valve syndrome increased the possibility of reducing physical exercise tolerability and/or development of distonic reactions to physical exercise by two times (χ^2 8,741; p=0,004); OR 1,89 (95%CI 1,23-2,91); Se 0,63 (95%CI 0,55-0,71); Sp 0,52 (95%CI 0,50-0,55). Valve syndrome was identified as a significant factor for diastolic dysfunction development — (χ^2 110,406; p=0,001); OR 10,06 (95%CI 6,13–16,56); Se 0,77 (95%CI 0,69-0,83); Sp 0,75 (95%CI 0,73-0,77) with sufficiently strong influence on formation of resultant sign diversity – 25,7% (F=140,486, p=0,000; df1=1; df2=547; η^2=0.257). Valve syndrome formation was predicted with severity of CTD, sign "involvement ≥3 systems" (F=25.777, p=0,000; η^2=0.045, "DC≥23" (F=27,091, p=0,000; η^2=0.047).

In general group of CTD patients 217 clinically significant unfavorable cardiovascular manifestations were detected in 156 (28.42%) cases with average duration of observation 7,49±3,44 years, 95%CI 7,21–7,79. Average age of patients during control visit was 31,01±8,58 years, 95%CI 30,29–31,73. The most frequent unfavorable cardiovascular manifestations were dilatation/aneurism of thoracic aorta (27.19%), symptomatic vascular lesions of brain: arteriovenous malformations, intracranial arterial aneurisms (26.73%), clinically significant arrhythmias (23.04%). Valve syndrome progressing, progression of mitral valve prolapse grade and mitral valve insufficiency, spontaneous cord avulsion were registered in 2.85% (8/281) of cases, average age of progression detection was 27,13±3,94 years, 95% CI – 23,7–27,3. Estimation of CTD manifestation revealed that the patients with unfavorable course of CTD valve syndrome have some lesions more often comparing with the other patients with valvular manifestations:combined valvular lesions (4/50,00% and 14/4,98%, respectively(χ^2 19,155; df=1; p=0,001)), bicuspid mitral valve prolapse (2/25,00% and 4/1,47%, respectively (χ^2 10,878; df=1; p=0,002)), myxomatous valve degeneration (6/75,00% and 59/21,61%, respectively (χ^2 9,637; df =1; p=0,003)), arachnodactyly – (2/25,00% and 4/1,47%, respectively (χ^2 10,880; df =1; p=0,001)). The risk of valve syndrome unfavorable course increased in case of associated valvular lesions in the form of prolapses by 10 times: RR 9,97 (95%CI 1,88-70,85); Se 0,75 (95%CI 0,36-0,96); Sp 0,78 (95%CI 0,77-0,79); mitral valve myxomatous degeneration – by 15 times – RR 14,61 (95% CI 3,22-65,24); Se 0,50 (95%CI 0,18-0,82); Sp 0,95 (95%CI 0,94–0,96); bicuspid mitral valve prolapse – by 15 times: – RR 15,28 (95% CI 2,22-54,75); Se 0,25 (95% CI 0,05–0,54); Sp 0,98 (95%CI 0,98–0,99), and also "aracnodactyly RR 33,81 (95%CI 4,45–179,25); Se 0,33 (95%CI 0,06–0,72); Sp 0,99 (95%CI 0,98–0,99). To define the effect of factors mentioned above (validity and power of influence) we performed one-factor dispersion analysis for qualitative (binary) symptoms. factor «combined valvular lesions» had the biggest impact on valve syndrome progressing: 11,30% (F=61,988, p=0,000; df1=1; df2=547; η^2=0.113); factor "bicuspid mitral valve prolapse" took the second position – 8,50% (F=46,396, p=0,000; df1=1; df2=547; η^2=0.085); "arachnodactyly" – 8,5% (F=46,396, p=0,000; df1=1; df2=547; η^2=0.085); «myxomatous valve degeneration» – 5,9% (F=32,767, p=0,000; df1=1; df2=547; η^2=0.059). Chosen complex of independent factors had summarized impact on the formation of the diversity of the resultant sign "valve syndrome progression" around 34.2%. Such components of valve syndrome like myxomatous degeneration of heart valves and associated CTD valvular manifestations were identified as potent predictors of clinically significant arrhythmias development: risk of arrhythmia onset increased twice in case of myxomatous degeneration of heart valves (– χ^2 6,619; p=0,011; RR 2,15; 95% CI 1,18–3,82) and in case of associated CTD valvular manifestations it had three-fold increase (χ^2 5,679; p=0,018; RR 3,28; 95% CI 1,20–6,85).

Discussion

Studying of systemic dysmorphogenesis morphofunctional cardiovascular manifestations has always been one of important research topics because of evident impact on patient's life and health prognosis. Valve syndrome is one of the most frequent cardiovascular manifestations of CTD [11–15]. Many works are dedicated to prevalence, clinic and laboratory signs, ultrastructural and immunohistochemical characteristics of heart valves as in syndromal CTD as in undifferentiated CTD [11, 12, 14, 16-18]. Factors determining CTD development in the form of heart valves lesions

remain poorly undertood. Some data propose that development of mitral valve prolapse is associated with magnesium deficiency [19, 20]. This research identified some factors with predictor role in severe CTD development: "involvement of more than 3 systems", and "diagnostic coefficient CTD ⩾23" that can be a prove of already known CTD characteristics like system involvement and similarity of connective tissue dysmorphogenesis in different organs. Results of this observation proved existing ideas about non-specific complaints of patients with CTD because subjective manifestations of valve syndrome have low informative value. From the one side, it is possible to talk about overdiagnosis problem at the stage of anamnesis and complaints estimation that, on the one part, goes along with specific psychological condition (increased anxiety, lowered self-esteem) that brings them down to their disease, from the other side, complaints of young patients are often considered as vegetative dysfunction and overstrain and lead to ill-timed diagnostics and prevention and development of negative consequences related to dysplastic-dependent conditions and associated pathology. They can threaten patient's health and even life. Clinical significance of CTD valvular manifestations is defined by their involvement into formation of left ventricle diastolic dysfunction, deconditioning reactions to physical exercise and progressing in a few percent of cases. Impact of valve syndrome in dysplastic dysfunction can be determined by the changes of blood pressure inside atria and the volume of transmitral blood flow that changes the phase of early diastolic filling. The presence of anomalous left ventricle cords can interfere with synchronous contraction and relaxation of left ventricle, increase the volume of mitral regurgitation and worsen its consequences [21, 22]. The majority of works investigating the prognosis of CTD course are dedicated to studying of mitral valve prolapse natural course, that demonstrated the crucial role of TNFβ in pathogenesis of matrix remodeling, fibrosis and oxidative stress [23–26]. It gives future prospects to the components of TNFβ-signaling pathway as predictors of myxomatous valve degeneration formation and progressing. Nevertheless some authors consider clinical symptoms more informative for estimation of the prognosis of mitral valve prolapse progression [17, 27]. According with these data dysmorphogenetic symptom arachnodactyly and non-modifiable factors describing morphofunctional condition of heart valves (myxomatous degeneration in mitral valve prolapsed), prolapsed of both valvular cusps, association with other heart valves' prolapses are the predictors of dysplastic-dependent valvular lesions.

Conclusion

The results of this study demonstrate that valve syndrome is present in 51% of young patients with undifferentiated CTD and it manifests as heart valve prolapse: mitral valve prolapse 1–2 grade prevails with functional insufficiency 1–2 grade or without it in 72.6% of patients, myxomatous degeneration of valves, isolated or combined with prolapse, is present in 37.72% of patients, often it is also combined with congenital anomalies of subvalvular structures (50.89%), arrhythmic (71.89%) and vascular syndromes (63.35%) of CTD. Valve syndrome is characterized with diverse and non-specific patient's complaints; it is associated with more severe forms of CTD. It has an impact on the formation of left ventricle diastolic dysfunction, causes low tolerability of physical exercises and distonic reaction on it. Combined lesions of heart valves, bicuspid mitral valve prolapse, myxomatous degeneration of mitral valve and arachnodactyly are found to be predictors of valve syndrome progressive course.

Conflict of interest: None declared.

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CLINICAL CASE

A rare cause of variant angina: Single coronary artery arising from right sinus Valsalva

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Abstract

Anomalous origin of a coronary artery from opposite sinus Valsalva is considerably rare. Although intertruncal course, acute take-off angleandco-existing atherosclerosis aremaj or causes of ischemic events in this population, vasospastic angina should also be appreciated. Documenting transient ST segment elevations on ECG and excluding other possible reasons with conventional and CT coronary angiograms may result in this diagnosis. Tothe best of our knowledge this is the first case in the literature reporting Prinzmetal's phenomenon of a single coronary arterya rising from right sinus Valsalva.

Keywords

variant angina, single coronary artery, coronary anomalie

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Introduction

Anomalous origin of a coronary artery from the opposite sinus Valsalva is considerably rare1.Although life-long asymptomatic state is quite possible, -especially in patients with single coronary artery- first clinical presentation might be even sudden cardiac death. Estimating the risk of sudden death and eliminating the potential factors of myocardial ischemia are key points of the management algorithm in this group 2-4.

Case report

A 36-year-old woman admitted to our hospital with typical restangina that had lasted for an hour. She was a current smoker with a family history for coronary artery disease.Initial electrocardiography showed ST segment elevations on leads D1 and aVL along with reciprocal changes on leads D3 and aVF (Figure 1A). Transthoracic echocardiography revealed preserved left ventricular systolic function with mild hypokinesia in posterolateral wall. The patient was referred for coronary angiography following administration of antiplatelet agents and sublingual nitroglycerin. There was a complete relief of pain with normalization of the electrocardiography (Figure 1B) as soon as she had been transferred to cath-lab. The procedure was started with left Judgkins catheter but cannulation of the left main ostium could not be succeeded. Non-selective opaque injection revealed that the left sinus valsalva was free of any coronary ostia. A right-Judkins catheter was successfully used to visualize right coronary, left anterior descending and circumflex arteries originating from the right sinus Valsalva withindividualostia(Figure 1C). No significant stenosiswas detected. However acute angulation in proximal portion of circumflex artery was noteworthy. The patient was diagnosed as having variant angina since the pain and the ST segment elevations were completely resolved after nitroglycerin administration.

A coronary CT angiography was performed in third day to confirm the type of anomalie and to demonstrate the course of left coronary system(Figure 1D). Left anterior descending arterywas passing anterior to right ventricular outflow tract and circumflex arteryhad a retro-aortic course. According to modified Lipton's classification this was a Type RIII-C anomalie and stated to have a benign nature and favorable prognosis1,5. A pharmacological stress test could not be performed in elective conditions due to patient's unwillingness for the second procedure. She was treated with long-acting diltiazem and isosorbide-mononitrate combination and had not experienced an

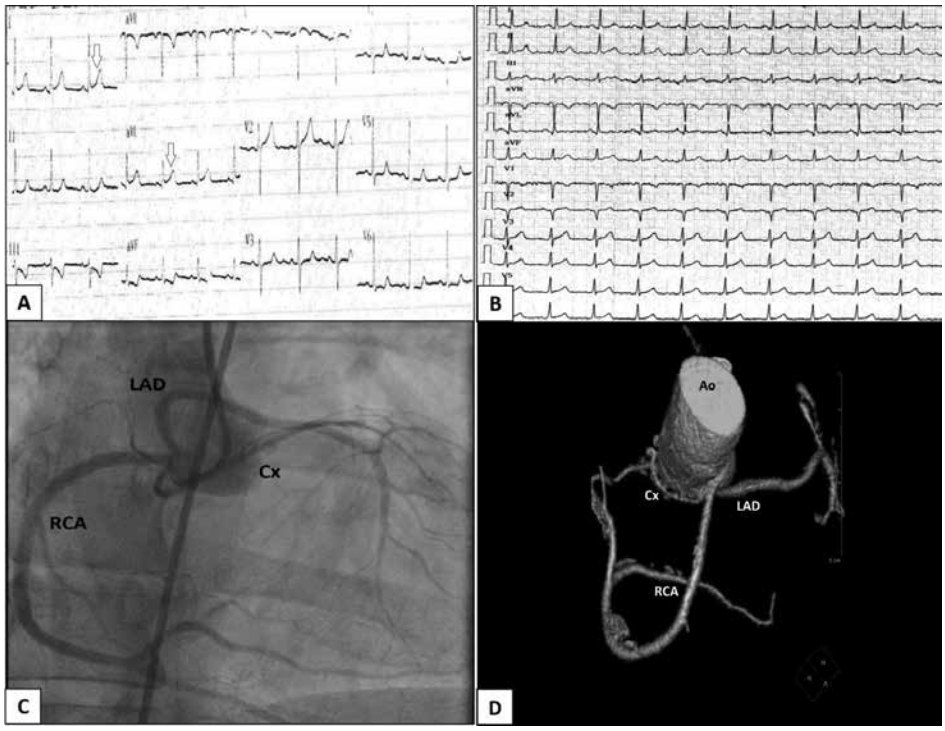

Figure 1: Initial 12-lead ECG of the patient during typical chest pain. Note the ST segment elevations on D1 and aVL (arrows), along with reciprocal changes in D3 and aVF (A). After administration of nitroglycerin, 12-lead ECG demonstrating normalization of the ST segment changes (B).Angiographic view of the whole coronary system originating from the right sinus Valsalva. Note that LAD, Cx and RCA have individual ostia (C).Reconstruction image of CT angiography demonstrating the anomalous origin of the left coronary system and its relationship with aorta.Cx artery passes posterior to the aorta and LAD traverses anterior to RVOT (D). Ao, aorta. Cx, circumflex artery. LAD, left anterior descending artery. RCA, right coronary artery. RVOT, right ventricular outflow tract.

angina episode during in-hospital follow-up thereafter. She was still symptom-free in sixth month visit.

Discussion

Origin of left coronary arteries from right sinus was reported with an incidence of 0.017 at angiographic series which is extremely rare1.Well-known association of this situation with ischemia is due to possible intertruncal course of left main coronary artery or one of its main branches. Other possible routes for anomalous coronary artery can be specified as retro-aortic, pre-pulmonary and septal. Slit-like orifice, intramural course and finally acute take-off angle of relevant coronary artery also stand accused of adverse outcome 4, 6. Classically, significant atherosclerosismay exist inan anomalous coronary artery. Complex percutaneousintervention had been successfully performed in various cases so far 7,8. Aside from anatomical complications and atherosclerotic process, vasospastic events had also been reportedto cause acute myocardial ischemia in the literature 6,9.

Multi-slice CT angiography recently became an invariable diagnostic step in the management algorithm of coronary anomalies not only by demonstrating anatomical relationships but also clearly visualizing luminal patency and some specifications like take-off angle. Just as in our case, it may provide substantial prognosticinformation 2,4.

Conclusion

Regarding to the fact that, significant luminal stenosis and external mechanical compression had been excluded with conventional and CT coronary angiography, the clinical scenario was attributed to coronary vasospasm in this case. To the best of our knowledge, this is the first case in the literature reporting Prinzmetal's angina with documented electrocardiographic changes in a patient with Type RIII single coronary artery.

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The Great Wall International Congress of Cardiology is recognized as a leader among cardiology events of Asian-Pacific region

Great Wall International Congress of Cardiology (GW-ICC) is one of the largest congresses in cardiology in the Asia-Pacific region. Congress was founded in 1990 as a regular technical training course titled "International Training Course on the Great Wall - the China-American Seminar on radiofrequency ablation". Less than 100 doctors attended the first scientific event. In 1995, the GW-ICC has positioned itself as a platform for in-depth training and academic exchange, covering areas such as coronary heart disease, heart failure, hypertension, interventional arrhythmology. According to the organizers, the aim of this project is the rapprochement between China and the international cardiology community. Nowadays the Congress is the largest, most influential and successful scientific event for cardiovascular diseases in the Asia-Pacific region.

The 26th GW-ICC was held in Beijing (China National Convention Center) from October 29 to November 1, 2015 under the theme "Bridging the Gap, Facing the Challenge". The Congress was attended by 17000 delegates from China and 30 other countries. Advanced technologies have been used for the presentation of the program, news and information. Attendees were provided with additional access to academic materials and live presentation through the congress online website, micro-blog, mobile application, mobile text, e-magazine, webinar and other social media.

The scientific program of the Congress covered 16 topic of cardiology. In particular, they discussed a wide range of scientific materials: translational research of cardiovascular diseases, prevention and control of cardiovascular risk, coronary intervention, cardiac electrophysiology and pacemakers, valve disease, heart failure and left ventricular function, clinical studies, as well as inter-regional cooperation research and related subjects

Overall, the Congress has conducted more than 400 different forms of meetings with the participation of over 20 international organizations.

Currently, GW-ICC has formed a strategic alliance to empower cardiology knowledge development and exchange with international associations such as the American College of Cardiology (ACC), World Heart Foundation (WHF), European Society of Cardiology (ESC), American Heart Association (AHA). Every year the Congress expands the collaboration with other influential international medical organizations and groups, including Heart Rhythm Society (HRS), Japanese Circulation Society (JCS), American Society of Echocardiography (ASE), China Committee of Cardio-Cerebral-Vascular Diseases of GSC (GSC), Chinese American Heart Association (CnAHA), Global Chinese College of Cardiology and the University of Minnesota (G3C/UMN), Cardiovascular Information Technologies (CVIT), and Society for Cardiac Angiography and Interventions (SCAI), National

Societies of Italy, England, the Netherlands, Turkey, etc. The scientific program included presentations of Russian scientists.

On the invitation of the organizing committee of the Congress, Professor Mekhman N Mamedov (National Research Center for Preventive Medicine, Moscow) made a presentation on the primary prevention of diabetes in cardiology practice. During discussion the Chinese colleagues recognized this problem utterly important for China and reached an agreement on the coordination of efforts in the implementation of national projects for the primary prevention of cardiovascular disease and diabetes.

Abstracts, summaries of the results of clinical trials and clinical case were accepted online at www.gw-icc.org. Collection of scientific papers published in the Congress can be found in the special issue of the journal BMJ.

Thematic press conferences and distribution of daily updated press releases were organized in the media center of the Congress. The work of the Congress was covered by more than 50 regional and international media.

It is worth to mention that the organizing committee of the GW-ICC supports the initiative of the World Heart Federation for the prevention of cardiovascular disease among woman. Presentation in support of the project "Go Red for Woman" was made during the gala dinner.

According with reached agreements Cardioprogress Foundation actively disseminated the information on the Congress. Articles, photo-report and informational letter about GW-ICC were published on the official website of the Foundation in Russian and English languages. Two issues of the International heart and vascular diseases journal contained advertising banners of the GW-ICC. Preliminary program of the V International forum of cardiologists and internists, English version of the newsletter "Cardioprogress", brochures and the latest issues of the English version of the International heart and vascular diseases journal were spread during the exhibition at the GW-ICC.

For detailed information about GW-ICC check the website http://en.gw-icc.org.

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Journal of the Cardioprogress Foundation

Guidelines for authors

International Heart and Vascular Disease Journal
Requirements for Submission and Publication

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

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

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

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

1. Submission requirements and publishing policy

1.1. A manuscript should be submitted to the following e-mail address: submissions.ihvdj@gmail.com

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

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

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

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

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

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

2. General recommendations for submission of original scientific works

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

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

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

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

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

3. Publication of uncontrolled trials results

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

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

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of "good clinical practice". Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The «Material and methods» section must contain details of the process of obtaining participants informed consent, and notifica-

tion that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

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

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

5. Authorship

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

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

6. Conflict of interests/financing

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

7. Manuscript content

7.1. Title page

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

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

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

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

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

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

7.2. Summary

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

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

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

7.3. List of abbreviations and their definitions

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

7.4. Text

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

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

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

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7.5. Statistics

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

7.6. Acknowledgements

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

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

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

7.7.5. In order to increase the citing of authors, transliteration of sources in Russian are made in the **International Heart and Vascular Disease Journal** using official coding. Names of authors and journals are transliterated by means of coding, and semantic transliteration (translation) is used for the titles of articles. If a source has an original transliteration, the latter is used. The Editors will be grateful if authors provide the transliterated variant of the list of references. You can use online services: http://translit.ru_for making transliteration.

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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.

Please provide initials after the last names of authors. Last names of foreign authors are given in the original transcription. Names of periodicals can be abbreviated. Usually such abbreviations are accepted by the Editors of those periodicals.

These can be found on the Publisher's site or in the list of abbreviations of Index Medicus.

Punctuation in the list of references should be considered. A full stop should be put with a space between the name of the journal and the year of its release. After the year of release a semicolon is put without a space, then a colon follows the volume number, and finally page numbers are given. There are no indications like "volume", "№", "pages". Russian periodicals often have no indication of volume or numbering of pages within a year. In this case the number of an issue should be specified in brackets.

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

Chapters in a book

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

Sources in Russian with transliteration:

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

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

Books

Sources in Russian with transliteration:

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