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HYPERTENSION MANAGEMENT IN METABOLIC SYNDROME

Abstract:

Hypertension is one of the key risk factors for cardiovascular morbidity and mortality. Metabolic syndrome (synonyms: syndrome X, insulin resistance syndrome) is characterized by increased visceral fat mass, decreased sensitivity of peripheral tissues to insulin (insulin resistance) and hyperinsulinemia, which cause disorders of carbohydrate, lipid, and purine metabolism. Hypertension is an integral component of the metabolic syndrome. The severity of hypertension in patients with metabolic syndrome is higher in comparison with patients without metabolic disorders. In patients with metabolic syndrome, the probability of cardiac and brain damage increases fivefold, kidney damage threefold, and the vessels twofold. The presence of diabetes reduces the likelihood of achieving effective control of blood pressure by 1.4 times, hypercholesterolemia — by 1.5 times, obesity — by 1.7 times. In the presence of any three factors, the effectiveness of treatment is reduced twofold. In this article, approaches to the management of patients with hypertension and metabolic syndrome, aspects of non-drug therapy, target blood pressure levels, and the choice of drugs are presented in accordance with evidence-based medicine and current recommendations.

Key words: *hypertension, metabolic syndrome, syndrome X, combined treatment, risk of cardiovascular events, 24-hour blood pressure monitoring, home blood pressure monitoring, drugs of choice, comorbidity, hypertensive crisis*

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β-blockers — beta-blockers, BP — blood pressure, AO — abdominal obesity, ARBs — angiotensin receptor blockers, CCB — calcium channel blockers, LVH — left ventricular hypertrophy, home BPM — home BP measurement, ACE inhibitors — angiotensin converting enzyme inhibitors, CMS — cardiometabolic syndrome, MS — metabolic syndrome, DT — drug therapy, TOD –target organ damage, RAAS — renin-angiotensin-aldosterone system, DM — diabetes mellitus, 24-hour BPM — 24-hour blood pressure monitoring, SNS — sympathetic nervous system, CVR — cardiovascular risk, Tg — triglycerides, HDL cholesterol — high density lipoprotein cholesterol, LDL cholesterol — low-density lipoprotein cholesterol, CKD — chronic kidney disease, HR — heart rate

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Introduction

Hypertension is one of the key risk factors for cardiovascular morbidity and mortality. Currently, more than 1 billion people worldwide have hypertension [15]. Globally, the prevalence of hypertension among the adult population is 30–45%; and in Russia it amounts 40–47% [6]. As the population ages and the sedentary lifestyle becomes common, an enormous increase in the number of patients with hypertension to 1.5 billion people is expected by 2025 [15].

At the end of the last century, the concept of the metabolic syndrome (MS; its synonyms: syndrome X, insulin resistance syndrome) was proposed for people with several risk factors united by the same pathogenetic basis [1]. MS is characterized by an increase in visceral fat mass, a decrease in the sensitivity of peripheral tissues to insulin (insulin resistance) and hyperinsulinemia, which cause disorders of carbohydrate, lipid, purine metabolism and hypertension [1, 6]. Globally, the prevalence of MS among the adult population is 10–30%; in Russia it amounts 20–35%, and in women it is 2.5 times more common. The incidence increases with age [1].

Hypertension is an integral component of metabolic syndrome [1]. The combination of carbohydrate, lipid and purine metabolic disorders with hypertension increases mortality, therefore MS is also called the deadly quartet. Since MS increases the risk of cardiovascular diseases (CVD) by 3 to 6 times, its successor and one more synonym is cardiometabolic syndrome (CMS) [5]. The severity of hypertension in patients with MS is higher compared to patients without metabolic disorders. In patients with MS, the probability of cardiac and brain damage increased fivefold, kidney damage — threefold, and vascular damage — twofold [6]. Diabetes mellitus (DM) reduces the likelihood of effective control of blood pressure (BP) by 1.4 times, hypercholesterolemia by 1.5 times, and obesity by 1.7 times. If there are any three risk factors, the effectiveness of treatment decreases twofold [6]. In this regard, hypertension treatment in patients with MS is an urgent problem. The article is dedicated to this problem.

Diagnostic Criteria for Cardiometabolic Syndrome

Currently, there are at least 7 alternative guidelines on MS diagnosis: WHO — World Health Organization; EGIR — European Group for the Study of Insulin Resistance; NCEP-ATP III — National Cholesterol Education Program-Adult Treatment Panel III; AACE — American Association of Clinical Endocrinologists; IDF — International Diabetes Federation; International Institute of Metabolic Syndrome; and the Recommendations for the Diagnosis and Treatment of Metabolic Syndrome of the Russian Society of Cardiology. At the same time, there are not enough prognostic data concerning the advantages of different diagnostic criteria for MS [1].

In accordance with the Russian recommendations, the **main criterion for diagnosis of MS/CMS** is central (abdominal, AO) obesity with the waist circumference (WC) >80 cm in women and >94 cm in men [1].

Additional Diagnostic Criteria for MS:

1. BP level >140/90 mm Hg or antihypertensive drug use
2. Triglycerides level (Tg) >1.7 mmol/L
3. High density lipoprotein cholesterol (HDL cholesterol) <1.0 mmol/L in men, and <1.2 mmol/L in women
4. Low density lipoprotein cholesterol (LDL cholesterol) >3.0 mmol/L
5. Impaired fasting glycemia (IFG) — fasting blood plasma glucose >6.1 and <7.0 mmol/L, provided that plasma glucose after 2 hours via Oral Glucose Tolerance Test (OGTT) — the load with 75 g of anhydrous glucose — is less than 7.8 mmol/L

6. Impaired glucose tolerance (IGT) — blood plasma glucose 2 hours after OGTT is within the range of >7.8 and < 11.1 mmol/L, provided that fasting plasma glucose level is less than 7.0 mmol/L.
7. Combined IFG/IGT; fasting plasma glucose is ≥6.1 and <7.0 mmol/L, and plasma glucose level via OGTT in 2 hours is ≥7.8 and <11.1 mmol/L.

Abdominal obesity with any two additional criteria serves as the basis for diagnosis of CMS in a patient [1].

Hypertension in Patients with Metabolic Syndrome

Several pathogenetic mechanisms of insulin resistance lead to the development of hypertension. First, it promotes the activation of the sympathetic nervous system (SNS): with insulin blood concentration increase, a dose-dependent norepinephrine increase is revealed. This leads to vasoconstriction, increased systemic vascular resistance (SVR) and cardiac output. In addition, insulin increases sodium reabsorption in the kidneys by 30–40%, and therefore, hyperinsulinemia accompanying insulin resistance in MS has an antinatriuretic effect with an increase in water retention, blood volume (BV) and blood pressure [3].

Clinical Pattern of Hypertension in Patients with MS

Features of hypertension in MS are: frequent refractoriness to treatment, and early target organ damage — the development of left ventricular hypertrophy (LVH), which rapidly leads to myocardial dysfunction, renal hyperfiltration and albuminuria, and arterial stiffness [1]. The severity of hypertension in patients with CMS directly depends on its components. In patients with CMS, the probability of cardiac and brain damage increased fivefold, kidney damage — threefold, and vascular damage — twofold, compared to patients without metabolic disorders [6]. According to 24-hour BP monitoring, patients with hypertension and MS had more pronounced circadian rhythm disturbances, higher pressure load at night and increased variability compared to hypertensive patients without metabolic disorders [1].

Diagnosis of Hypertension

Diagnosis of hypertension in patients with MS is carried out in accordance with the procedure in all other conditions. The primary methods of detecting hypertension are office BP measurement by the Korotkov's method, measurement of BP at home (a synonym for self-monitoring of BP — self-BPM), and 24-hour BPM [1]. For timely and accurate diagnosis of hypertension, it is necessary to strictly follow the BP measurement rules.

BP measurement rules:

- BP is measured in the morning at the same time
- BP should be measured on the same arm using a precisely calibrated tonometer
- It is necessary to use a cuff of the appropriate size and to mark the use of a different size cuff and all other changes in the BP measurement procedure
- The patient should be seated while measuring BP, the patient's arm should lie on the armrest approximately at the level of the heart
- The patient should rest for at least 5 minutes before BP measurement
- Patients should not smoke or consume caffeine-containing beverages at least 30 minutes before BP measurement
- Repeated BP measurement is carried out after 3–5 minutes
- If the difference between BP in these two measurements is <5 mm Hg, the third BP measurement is performed, and the average value between the three measurements is recorded in the individual medical record

- If the difference between BP in the first two measurements is > 5 mm Hg, the measurement should be repeated after the patient has rested for at least 15 minutes
- At the first visit, BP is measured on both arms in a standing and sitting position
- The blood pressure cuff is placed on the arm with the highest value of BP if there are significant differences in this parameter at the arms [1].

According to the new American guidelines of 2017, hypertension should be diagnosed for BP >130/80 mm Hg. (Table 1) [14]. This criterion is based on the SPRINT study results, in which the achievement of target BP value below 120/80 mm Hg leads to a decrease in the risk of myocardial infarction, stroke and death in high-risk patients [11]. Hence, it was suggested to consider normal BP level <120/80, elevated level — 120–129 / 80 mm Hg, grade 1 hypertension at 130–139 / 80–89 mm Hg, and grade 2 hypertension at ≥140/90 mm Hg. [14].

Using the new American diagnostic criteria, the prevalence of hypertension in the USA increased from 32% to 46%; in absolute terms — from 72.2 to 103.3 million people, i. e. by 31.1 million people [13]. Since the criteria for initiating treatment in these recommendations were revised less radically, the need to prescribe drug therapy (DT) increased in only 4.2 million people [8]. In this regard, when developing the European recommendations in 2018, after long discussions it was decided that it would not be advisable to diagnose hypertension in a large number of patients without DT prescription. Thus, the classification of BP and the definition of hypertension in these recommendations did not change in comparison with the recommendations of 2013 [12, 14, 15].

According to European recommendations, normal BP is considered to be <130/85, high normal level is 130–139 / 85–89, grade 1 hypertension is 140–159 / 90–99, grade 2 hypertension is 160–179 / 100–109, and grade 3 hypertension is ≥180 / 110 mm Hg. Thus, hypertension is

Table 1. *Classification of office blood pressure and determining the degree of hypertension in accordance with the 2018 ESC/ESH and 2017 ACC/AHA recommendations [4, 14,15]*

Blood Pressure Classification	2018 ESC/ESH			Blood Pressure Classification	2017 ACC/AHA		
	SBP, mm Hg		DBP, mm Hg		SBP, mm Hg		DBP, mm Hg
Optimal	<120	and	<80				
Normal	120–129	and/or	80–84	Normal	<120	and	<80
High normal	130–139	and/or	85–89	High normal	120–129	and	<80
Grade 1 hypertension	140–159	and/or	90–99	Grade 1 hypertension	130–139	or	80–89
Grade 2 hypertension	160–179	and/or	100–109	Grade 2 hypertension	≥140	or	≥90
Grade 3 hypertension	≥180	and/or	≥110				
Isolated systolic hypertension	≥140	and	<90				

Note: BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension is graded as 1, 2, or 3 according to SBP values in the ranges indicated; BP — blood pressure; SBP — systolic blood pressure, DBP — diastolic BP, ACC — American College of Cardiology, AHA — American Heart Association, ESH — European Society of Hypertension, ESC — European Society of Cardiology

Table 2. *Hypertension diagnosis based on office BP, 24-hour BPM, home BPM in accordance with the 2018 ESC/ESH and 2017 ACC/AHA recommendations [4, 12, 14, 15]*

Category	2018 ESC/ESH			2017 ACC/AHA		
	SBP, mm Hg		DBP, mm Hg	SBP, mm Hg		DBP, mm Hg
Office BP	≥140	and/or	≥90	≥130	and/or	≥80
Home BPM, mean	≥135	and/or	≥85	≥130	and/or	≥80
24-hour BPM:						
Daytime (or awake), mean	≥135	and/or	≥85	≥130	and/or	≥80
Nigh (or asleep), mean	≥120	and/or	≥70	≥110	and/or	≥65
24-hour, mean	≥130	and/or	≥80	≥125	and/or	≥75

Note: BP — blood pressure; SBP — systolic BP, DBP — diastolic BP

an increase in office systolic BP (SBP) ≥140 and/or diastolic BP (DBP) ≥90 mm Hg [15].

In addition to office blood pressure measurement, home and 24-hour BP measurement can be used for primary diagnosis [12, 14]. Normal BP values and diagnostic criteria for home and 24-hour BP measurement somewhat differ from BP office figures. In accordance with the European recommendations, it is necessary to diagnose hypertension with mean daily BP values for 24-hour BPM ≥130/80 mm Hg and for home BPM ≥135/85 mm Hg (Table 2) [12, 15]. According to the American guidelines, it is necessary to diagnose hypertension with mean daily BP values for 24-hour BPM ≥125/75 mm Hg and for home BPM ≥130/80 mm Hg. When determining the degree of hypertension, office BP values should be used.

The advantage of home BPM is that it enables to monitor blood pressure for a long time in conditions that are familiar for the patient. It is very important that the patient or his/her relatives are trained in BP measurement rules, the tonometer is calibrated, and the cuff size is correctly selected. At present, it is not recommended to use wrist-cuff devices, except for patients with obesity, for whom it is difficult to choose a cuff for the arm.

Twenty-four-hour BPM allows to determine daily BP variability and the presence/absence of nocturnal BP decrease. Normally, BP decreases by 10–20 mm Hg at night. Patients with normal nocturnal BP decrease are called dippers. Patients without adequate BP decrease at night are called non-dippers. The main reasons for the absence of BP decrease are obstructive sleep apnea (OSA), obesity, diet high in salt, diabetic nephropathy, chronic kidney disease (CKD), old age, orthostatic hypotension, and autonomic dysregulation. However, the effect of BP decrease at night is not 100% reproducible. For example, sleep disorder can lead to the absence of BP decrease at night. According to studies, BP values obtained using 24-hour BPM are more correlated with the prognosis of patients (risk of death, stroke and other CVD) than with measurements at the doctor's office. Moreover, the measurement of BP at night has maximum correlation with the patients' prognosis.

Assessment of the Hypertension Risk

Over 20 years, the main international guidelines on hypertension have focused on the fact that treatment should be carried out taking into account individual CVR [10, 15]. In the European

Recommendations 2018, uric acid increase (which is often found in patients with MS), early menopause and heart rate >80 beats per minute are added to the risk factors (Table 3). In the new European and American recommendations, low-mobility and low socioeconomic status of a person are indicated as risk factors. In the American recommendations, unhealthy diet and OSA are also listed as risk factors [12, 14, 15].

In order to assess individual CV risk, ESC/ESH recommends to use the standard SCORE System (https://www.escardio.org/static_file/Escardio/Subspecialty/EACPR/Documents/score-charts.pdf), which allows to calculate the risk of a fatal CV event within 10 years based on 5 risk factors: gender, age, SBP, total cholesterol and smoking. Regardless of SCORE values, patients with diagnosed CVD, CKD, DM, LVH or a significant increase in any risk factor are considered to be patients of high or very high risk (e. g, total cholesterol ≥8 mmol/L, LDL cholesterol ≥6 mmol/L, or BP ≥180/110 mm Hg) (Table 4) [15].

In the American guidelines, a calculator is available to evaluate the individual 10-year risk of atherosclerotic CVD; the calculator is available at http://tools.acc.org/ASCVD-Risk-Estimator. The estimation is based on a large number of risk factors: gender, age, race, SBP, DBP, total cholesterol, HDL and LDL cholesterol, DM, smoking, antihypertensive treatment, statins, and aspirin [14].

Table 3. *Risk factors in patients with hypertension in accordance with 2018 ESC/ESH and 2017 ACC/AHA [4, 12, 14, 15]*

2017 ACC/AHA	2018 ESC/ESH
Male	Male
Age	Age (≥55 years in male, ≥65 years in female)
Smoking (current or past history)	Smoking (current or past history)
Dyslipidemia, hypercholesterolemia	Total cholesterol and HDL-C
	Blood uric acid
Diabetes mellitus	Diabetes mellitus
Overweight or obesity	Overweight or obesity
Family history of premature CVD	Family history of premature CVD (men aged <55 years and women aged <65 years), family or parental history of early-onset hypertension
	Early menopause
Sedentary lifestyle	Sedentary lifestyle
Psychological stress, low socioeconomic level	Psychosocial and socioeconomic factors
	Heart rate (resting values >80 beats/min)
Unhealthy diet	
Obstructive sleep apnea	

Note: CVD — cardiovascular diseases, HDL-C — high density lipoprotein cholesterol

Table 4. *Evaluation of cardiovascular risk in patients with hypertension by 2018 ESC/ESH [15]*

Risk category	People with any of the following
Very high risk	1. IHD: acute myocardial infarction, postinfarction cardiosclerosis, acute coronary syndrome, coronary or other arterial revascularization, stroke, and TIA 2. History of ischemic stroke, TIA 3. eGFR <30 mL/min / 1.73 m² (4–5 stage CKD) 4. Significant (≥50% stenosis) plaques in the coronary and/or carotid arteries 5. Aortic aneurysm 6. Diabetes mellitus with target organ damage, e. g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolemia 7. Peripheral artery disease 8. A calculated 10-year SCORE of ≥10%
High risk	1. Significantly pronounced one risk factor (for example, total cholesterol ≥8 mmol/L, LDL cholesterol ≥6 mmol/L or blood pressure ≥180/110 mm Hg) 2. Diabetes mellitus without target organ damage and without a major risk factor who may be at moderate-risk 3. LV hypertrophy 4. eGFR 30–59 mL/min / 1.73 m²(4–5 stage CKD) 5. A calculated 10-year SCORE of 5–10%
Moderate risk	1. A calculated 10-year SCORE of ≥1% to <5% 2. Grade 2 hypertension 3. Many middle-aged people belong to this category
Low risk	1. A calculated 10-year SCORE of <1%

Note: BP — blood pressure, LV — left ventricle; IHD –ischemic heart disease; LDL — low-density lipoproteins, eGFR — estimated glomerular filtration rate; TIA — transient ischemic attack

In most patients with MS, the risk is high and very high, which requires immediate initiation of the necessary treatment.

Treatment of Hypertension

Treatment of hypertension in patients with CMS is not an easy task. DM reduces the probability of achieving effective control of BP by 1.4 times, hypercholesterolemia — by 1.5 times, and obesity — by 1.7 times. If there are any three risk factors, the effectiveness of treatment decreases twofold [6].

Drug-Free Hypertension Treatment

The cornerstone in the treatment of MS, including in hypertension, are drug-free methods that involve lifestyle changes, including proper diet, avoidance of bad habits, increased physical activity, and weight loss until normal weight is achieved (Table 5) [15]. ACC/AHA recommends the DASH (Dietary Approaches to Stop Hypertension) diet and elevated potassium content for patients with hypertension, except patients with CKD and receiving medication that reduces potassium excretion [14].

The effect of garlic, dark chocolate, tea or coffee consumption for stress relief has not been sufficiently proven. Behavioral therapy, including controlled breathing, yoga, transcendental meditation, and biofeedback, do not have conclusive evidence of long-term BP decrease [14].

Drug-free hypertension treatment is recommended for all patients, regardless of BP value [14, 15]. It is of particular importance in patients with MS, because weight loss itself leads to BP decrease [3].

Table 5. *Non-drug therapy for hypertension with MS [15]*

Recommendation	Class	Level
Salt restriction to <5 g per day is recommended	I	A
It is recommended to restrict alcohol consumption to: • Less than 14 units per week for men • Less than 8 units per week for women (1 unit = 125 ml wine or 250 ml beer) *	I	A
Avoid binge drinking	III	C
Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended	I	A
Body-weight control is indicated to avoid obesity (BMI >30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women), as is aiming at healthy BMI (about 20–25 kg/m^2) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk	I	A
Regular aerobic exercise (e. g. at least 30 min of moderate dynamic exercise on 5–7)	I	A
Smoking cessation, supportive care, and referral to smoking cessation programs are recommended	I	B

*** Note:** ACC/AHA recommends less than 2 "drinks" (1 "drink" = 14 g of ethanol, which corresponds to 5 oz of wine (usually 12%), 12 oz of beer (usually 5%) and 1.5 oz of purified alcohol (usually 40%)) per day for men, less than 1 "drink" per day for women [14].

Drug Therapy of Hypertension

Principles of drug therapy in patients with hypertension and MS are the same as in all patients with hypertension [3]. The main practical issues of antihypertensive treatment are:

1. Initiation of drug therapy
2. Target BP values
3. Selection of drugs for BP control

Initiation of Drug Antihypertensive Treatment in Hypertension and MS

In accordance with the 2018 ESC/ESH recommendations, drug therapy (DT) can be considered at high normal BP level (130–139 / 85–89 mm Hg) at very high CVR due to diagnosed CVD, especially IHD (Table 6) [15]. DT (the optimal combination of two antihypertensive drugs) should be recommended for patients with high or very high risk or target organ damage (TOD) at BP ≥140/90 mm Hg. Consequently, most patients with MS require DT. For patients with BP level 140–159 / 90–99 mm Hg, without TOD and with low or moderate risk monotherapy is recommended in case of ineffectiveness of lifestyle changes (Fig. 1) [15].

In patients aged 65–80 years, according to the 2018 ESC/ESH guidelines, MT should be initiated at BP level >140/90 mm Hg; in patients older than 80 years — with BP level ≥160/90 mm Hg. The focus should be on biological, rather than chronological age. Frailty (fragility, poor health), patient's self-support and treatment tolerability should be considered. Treatment should not be unavailable or canceled based on age, provided that it is necessary and permitted [15].

According to the recommendations of ACC/AHA 2017, the choice of treatment depends on the severity of hypertension and does not

Table 6. *Drug therapy start in hypertension [4, 12, 14, 15]*

	2017 ACC/AHA	2018 ESC/ESH
BP 130–139/ 85–89	DT recommended at very high risk (≥10%)	DT can be assigned to patients with very high CVR, established in connection with the presence of CVD*, especially CHD
CVR	DT for primary prevention is recommended • Patients with very high ≥10%) risk with mean SBP ≥130 mm Hg and average DBP ≥80 mm Hg • Patients* at risk <10% are recommended with mean SBP =140 mm Hg and average DBP = 90 mm Hg	• At high / very high CV risk or TOD ** DT recommended for BP 140–159 / 90–99 • Low/moderate risk at BP 140–159 / 90–99 mm Hg without TOD it is recommended that monotherapy with inefficiency change of the LF. • MT* recommended for any with risk if BP =160/100 mm Hg
BP	• DT for secondary prevention of CV events is recommended for patients with CVD and mean SBP = 130 mm Hg and average DBP = 80 mm Hg • Rest — when SAD ≥140 mm Hg, DBP ≥90 mm Hg	• DT is recommended immediately at BP = 160/100 mm Hg at any risk and at BP 140–159 / 90–99 mm Hg at high / very high risk or TOD • With BP 140–159 / 90–99 mm Hg with low and moderate risk without TOD, monotherapy is recommended if inefficiency change of the LF
Elderly and senile age	DT in elderly and senile patients does not differ from therapy in the General population, even at the age of >80 years, but it is necessary to take into account the risk of orthostatic hypotension and falls	• For safe patients >65, for <80 years, DT is recommended for BP >140/90 mm Hg with its good tolerability • Safe patients over 80 years of age DT is recommended for SBP ≥160 mm Hg

Note: LF — lifestyle, DT — drug therapy, BP — blood pressure, SBP — systolic BP, DBP — diastolic BP, HNBP — high normal BP, 24-hour BPM — 24-hour BP monitoring, HBPM — home BP monitoring, TOD — target organ damage, CV — cardiovascular, CVD — CV disease, CVE — CV event

*CVD diagnosis — cerebrovascular disease: ischemic, hemorrhagic stroke, TIA; ischemic heart disease: myocardial infarction, angina, revascularization; atherosclerotic plaque imaging; heart failure, including HFpEF; peripheral arterial disease; atrial fibrillation

** TOD includes pulse BP (in the elderly) ≥60 mm Hg; carotid-femoral PWV >10 m/s; ankle-brachial index of <0.9; LVH in ECG: Sokolov-Lyon index >3.5 mV, RaVL >1.1 mV, Cornell index >244 mV×MS; LVH in Echocardiography: LVMMI: >115 g/m² in men and 95 g/m² in women; albuminuria (30–300 mg/day) or the ratio of albumin to creatinine (30–300 mg/g; 3.4–34 mg/mmol, preferably in the morning portion of urine), CKD with GFR >30–59 mL/min/1.73m² or severe CKD with GFR <30 mL/min /1.73m², progressive retinopathy: hemorrhages or exudates, optic disk swelling

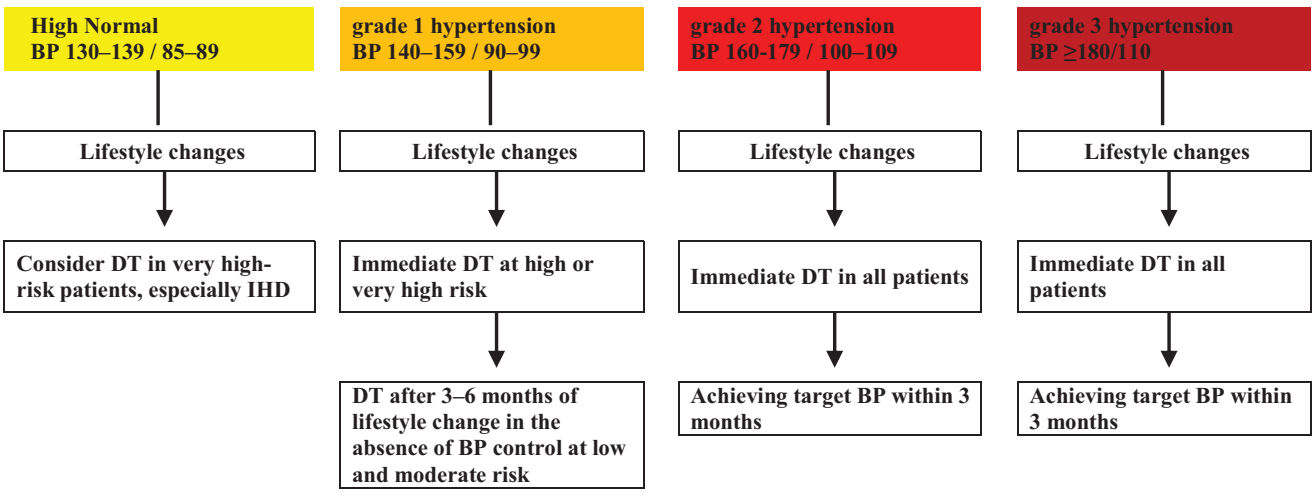

Figure 1. *Lifestyle changes and the onset of antihypertensive drug therapy in different degrees of hypertension according to 2018 ESC/ESH*

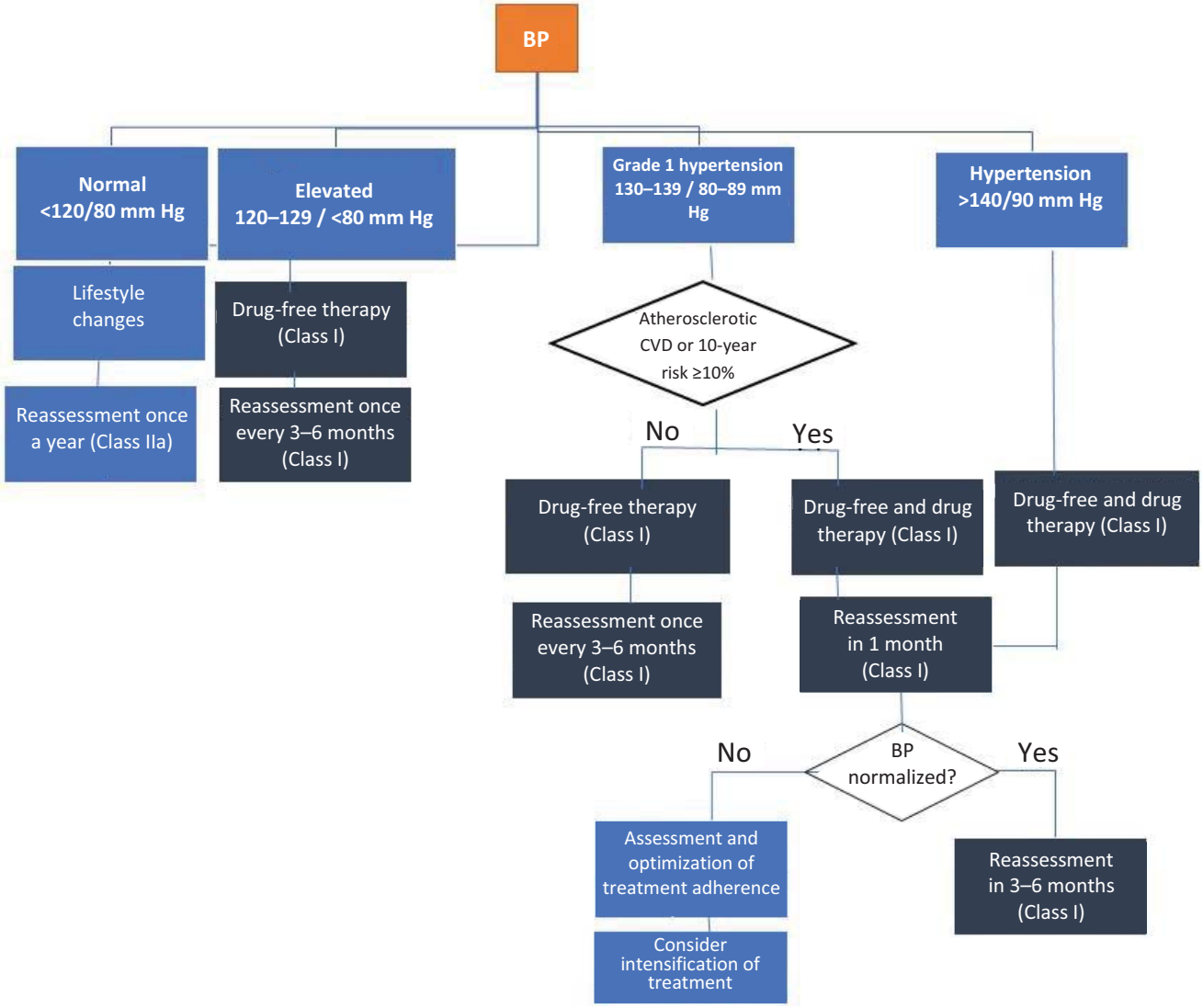

Figure 2. *Management of patients with hypertension according to 2017 ACC/AHA [12]*

depend on age (Figure 2) [14]. In the presence of elevated BP (SBP 120–129 mm Hg), drug-free therapy is recommended [14]. At BP level 130–139 /80–89 mm Hg drug-free therapy is recommended, mainly, lifestyle changes [14]. Drugs at BP of 130–139 / 80–89 mm Hg shall be prescribed to patients with CVD or in at least 10% of 10-year CVR. At BP ≥140/90 mm Hg, regardless of the 10-year risk or CVD [14].

Target BP Levels

According to the 2017 ACC/AHA recommendations, the target values of BP in all patients should be less than 130/80 mm Hg (Table 7) [14].

In the 2018 ESH/ESC guidelines in the general population of patients with hypertension, the target BP was <140/90 mm Hg, with good tolerability — <130/80 mm Hg. The target level of systolic BP in patients with DM, IHD, and with history of stroke/TIA is 120–130 mm Hg, in CKD and in patients ≥65 years — 130–140 mm Hg [15]. It is noteworthy that the BP level has been specified, below which decrease is impractical due to the risk of acute kidney injury. Previously, it was specified only in the guidelines on kidney disease (Table 8). The target DBP level for all patients is 70–80 mm Hg. According to 24-hour BPM, the target mean SBP is 125 mm Hg, and home BPM is 130 mm Hg [15].

Table 7. *Target levels of blood pressure [4, 12, 14, 15]*

Patient group	2017 ACC/AHA	2018 ESC/ESH
Population	<130/80 mm Hg	<140/90 mmHg (<130/80 if tolerated)
Diabetes mellitus	<130/80	120 — <130/70 — <80
IHD	<130/80	120 — <130/70 — <80
CKD	<130/80	130 — <140
Stroke/TIA	<130/80	120 — <130
Heart failure	<130/80	
Peripheral artery disease	<130/80	
Older patients (aged ≥65 years)	<130 in patients ≥65 years	SBP 120 — <130 in patients <65 years SBP 130 — <140 in patients ≥65 years

Table 8. *Age-dependent target level of office BP according to 2018 ESC/ESH [15]*

Age	SBP, mm Hg					DBP, mm Hg
	Hypertension	+Diabetes	+CKD	+IHD	+Stroke/TIA	
18–65 years	Target to 130 or lower, if tolerated, not <120		Target <140 to 130, if tolerated		Target to 130 or lower, if tolerated, not <120	<80 to 70
65–79 years	Target <140 to 130, if tolerated					<80 to 70
>80 years	Target to <140 to 130, if tolerated					<80 to 70
DBP, mm Hg	<80 to 70	<80 to 70	<80 to 70	<80 to 70	<80 to 70	<80 to 70

Selection of Drugs for BP Control

In accordance with the 2013 ESH/ESC recommendations, the benefits of antihypertensive treatment are caused by the result of a decrease in BP itself, and do not depend on the drugs prescribed for this purpose. The following drug groups are suitable for monotherapy and combined treatment of hypertension: diuretics (including thiazide and thiazide-like chlorthalidone, indapamide), β-blockers, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and other antihypertensive agents (direct renin inhibitors — DRIs, central action drugs, α-blockers) [12]. Depending on the clinical situation, certain groups of antihypertensive agents should be preferred (Table 9) [12]. In patients with hypertension and MS, preference is given to the administration of ACEIs, ARBs and CCBs, in the presence of DM — ACEI and ARBs [15].

In accordance with the 2018 ESH/ESC guidelines, the basis of hypertension treatment should be drugs that in RCTs have proven able to reduce BP and the risk of CV events — ACE inhibitors, ARBs, CCBs and thiazide / thiazide-like diuretics [15]. There is no emphasis on patients with MS in this section of recommendations.

The 2017 ACC/AHA guidelines recommend to start treatment with first-line drugs, which include thiazide / thiazide-like diuretics, ACEIs, ARBs and CCBs (Table 10) [14]. The optimal DT in MS is not defined; there are concerns about thiazide diuretics and β-blockers due to their ability to increase insulin resistance and dyslipidemia. Study data on chlorthalidone showed improvement in cardiovascular and kidney outcomes. Newer vasodilating β-blockers (labetalol, carvedilol, and nebivolol) have a neutral or beneficial effect on metabolic profiles. In DM, first-line antihypertensive agents (diuretics, ACE inhibitors, ARBs, CCBs) are effective and useful [15].

Contraindications to certain groups and individual medicines must be considered in the decision-making process (Table 11).

Table 9. *Selection of antihypertensive drug groups in certain clinical situations [4, 12, 14, 15]*

Situation	2013 ESC/ESH	2017 ACC/AHA	2018 ESC/ESH
LVH	ACEI, CCB, ARB		
Asymptomatic atherosclerosis	CCB, ACEI		
CKD: albuminuria, decreased kidney function	ACEI, ARB	Hypotensive first-line agents; CKD ≥3 stage or CKD 1–2 stage with albuminuria ≥300 mg/day (mg/g) — ACEI, with their intolerance — ARB	ACEIs or ARB + CCB or ACEIs or ARB + loop diuretic
ESRD / kidney transplant	ACEI, ARB	CCB	
Stroke, history of TIA	Any drug that effectively reduces BP	Thiazide diuretics, ACEI, ARB or a combination of thiazide diuretic with ACEI	
History of myocardial infarction	β-blocker, ACEI, ARB	β-blocker is advisable to continue for 3 years after MI/ACS; β-blocker and/or CCB can be considered 3 years after MI/ACS	ACEI or ARB + β-blocker or CCB or CCB + diuretic or β-blocker + diuretic Monotherapy can be considered at low risk of 1-degree hypertension or in elder patients (≥80 y. o.)
Angina	β-blocker, CCB	β-blocker, ACEI / ARB; in failure of target BP achievement and preservation of pain — dihydropyridine CCB; in failure of target BP achievement and absence of pain — dihydropyridine CCB, thiazide diuretic, and/or ARB	

Table 9. (The ending)

Situation	2013 ESC/ESH	2017 ACC/AHA	2018 ESC/ESH
Heart failure with reduced LV EF	Diuretic, β-blocker, ACEI, ARB, mineralocorticoid receptor antagonists	Non-dihydropyridine CCB are not recommended	
Heart failure with preserved LV EF		In congestion — diuretics; in hypertension preservation after congestion elimination — ACEIs / ARB and β-blocker	
Aortic aneurysm	β-blocker	β-blocker	
Atrial fibrillation, prevention	ARB, ACEI, β-blocker or mineralocorticoid receptor antagonists	ARB	
Atrial fibrillation, ventricular rhythm control	β-blocker, non-dihydropyridine CCB		
Peripheral artery disease	ACEI, CCB	Treatment approach same as in absence of peripheral artery disease	
ISH (elderly and senile age)	Diuretic, CCB		
Metabolic syndrome	ACEI, ARB, CCB	Optimal DT has not been determined; there are concerns about thiazide diuretics and beta-blockers due to their ability to increase insulin resistance and dyslipidemia. However, chlorthalidone improved CV and renal outcomes. Newer vasodilating beta-blockers (labetalol, carvedilol and nebivolol) have neutral or beneficial effects on metabolic profiles	
Diabetes mellitus type 2	ACEI, ARB	Hypotensive first-line agents (diuretics, ACEI, ARB, CCB) are useful and effective	
Pregnancy	Methyldopa, β-blocker, CCB	Methyldopa, nifedipine and/or labetalol	
Negroid race	Diuretic, CCB	Initial therapy in patients without HF and CKD should include thiazide diuretics or CCB	
Aortic stenosis		There is no evidence that hypotensive therapy leads to excessive hypotension. Although there are no specific studies comparing different classes of antihypertensive drugs in this group, ACEIs and ARBs may have benefits due to regression of LV fibrosis, shortness of breath and improvement of exercise tolerance. Low initial dose, slow titration	
Aortic insufficiency		Avoid heart rate lowering drugs, including β-blocker	

Table 10. *2017 ACC/AHA first- and second-line antihypertensive agents [14]*

Drug group	Drug	Dosage (mg/day) *	Dosage Frequency	Comments
First-Line Treatment				
Thiazide or thiazide-like diuretics	Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	12.5–25 25–50 1.25–2.5 2.5–10,0	1 1 1 1	Chlorthalidone is a drug of choice based on its prolonged half-life and proven reduction of CVE Hyponatremia, hypokalemia, uric acid and calcium monitoring Use with caution in patients with history of acute gout unless patient receives uric acid–lowering drugs
ACEI	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	10–40 12.5–150 5–40 10–40 10–40 7.5–30 4–16 10–80 2.5–10 1–4	1 or 2 2 or 3 1 or 2 1 1 1 or 2 1 1 or 2 1 or 2 1	Do not use in combination with ARBs or direct renin inhibitor Risk of hyperkalemia, especially in patients with CKD or receiving potassium supplements or potassium-sparing drugs Risk of acute kidney injury in patients with severe bilateral renal artery stenosis Avoid in pregnancy
ARB	Azilsartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan	40–80 8–32 600–800 150–300 50–100 20–40 20–80 80–320	1 1 1 or 2 1 1 or 2 1 1 1	Do not use in combination with ACEIs or direct renin inhibitor Risk of hyperkalemia, especially in patients with CKD or receiving potassium supplements or potassium-sparing drugs Risk of acute kidney injury in patients with severe bilateral renal artery stenosis Do not use in patients with a history of ARB-induced angioedema. Patients with a history of ACEI-induced angioedema can receive ARB 6 weeks after ACEI withdrawal Avoid in pregnancy
CCB—dihydropyridines	Amlodipine Felodipine Isradipine Nicardipine SR Nifedipine SR Nisoldipine	2.5–10 5–10 5–10 5–20 60–120 30–90	1 1 2 1 1 1	Avoid in patients with CHF with reduced EF; amlodipine or felodipine may be used as required Dose-dependent lower extremity edema may occur, more common in women
CCB—non-dihydropyridines	Diltiazem SR Diltiazem ER Verapamil IR Verapamil SR Verapamil-delayed onset ER (various forms)	180–360 120–480 40–80 120–480 100–480	2 1 3 1 or 2 1 (in the evening)	Avoid use with beta blockers because of increased risk of bradycardia and heart block Do not use in patients with CHF with reduced EF Drug interactions with diltiazem and verapamil may occur (CYP3A-mediated)
Second-Line Treatment				
Loop diuretics	Bumetanide Furosemide Torasemide	0.5–4 20–80 5–10	2 2 1	Preferred in patients with symptomatic HF. Preferred over thiazides in patients with moderate-to-severe CKD (GFR <30 mL/min / 1.73 m^2)

Table 10. (Continued)

Drug group	Drug	Dosage (mg/day) *	Dosage Frequency	Comments
Potassium sparing diuretics	Amiloride Triamterene	5–10 50–100	1 or 2 1 or 2	Used as monotherapy; has minimal antihypertensive effect. Combination with thiazides can be considered in hypokalemia on thiazide monotherapy Avoid in severe CKD (GFR <45 mL/min / 1.73 m²)
Aldosterone antagonists	Eplerenone Spironolactone	50–100 25–100	1 or 2 1	Drug of choice in primary aldosteronism and resistant hypertension. Spironolactone is associated with higher risk of gynecomastia and impotence compared with eplerenone; use in resistant hypertension polytherapy. Avoid use with potassium supplements, potassium-sparing diuretics, or in severe kidney disease. Eplerenone often requires twice-daily dosing for adequate BP lowering
β-blocker—cardioselective	Atenolol Betaxolol Bisoprolol Metoprolol tartrate Metoprolol succinate	25–100 5–20 2,5–10 100–400 50–200	1 or 2 1 1 2 1	Not recommended as first-line treatment unless in IHD or HF. Preferred in patients with bronchospasm requiring a beta blocker Bisoprolol and metoprolol succinate are preferred in HF with reduced EF. Avoid abrupt discontinuation.
β-blocker—cardioselective and vasodilating	Nebivolol	5–40	1	Cause nitric oxide–induced vasodilation. Avoid abrupt discontinuation.
β-blocker—non-cardioselective	Nadolol Propranolol IR Propranolol SR	40–120 160–480 80–320	1 2 1	Avoid in airway obstruction. Avoid abrupt discontinuation.
β-blocker—intrinsic sympathomimetic activity	Acebutolol Carteolol Penbutolol Pindolol	200–800 2,5–10 10–40 10–60	2 1 1 2	Generally avoid, especially in IHD or HF. Avoid abrupt discontinuation.
αβ-blocker	Carvedilol Carvedilol phosphate Labetalol	12,5–50 20–80 200–800	2 1 2	Carvedilol is preferred in patients with HF with reduced EF. Avoid abrupt discontinuation.
Direct renin inhibitor	Aliskiren	150–300	1	Do not use in combination with ACEI or ARB. Very long acting drug. Increased risk of hyperkalemia in CKD or in patients on potassium supplements or potassium-sparing drugs. May cause acute kidney injury in severe bilateral renal artery stenosis. Avoid in pregnancy.
α_1-blocker	Doxazosin Prazosin Terazosin	1–8 2–20 1–20	1 2 or 3 1 or 2	Cause orthostatic hypotension, especially in older patients. May be used as a second-line agent in BPH.

Table 10. (The ending)

Drug group	Drug	Dosage (mg/day) *	Dosage Frequency	Comments
Central-acting agents	Clonidine oral Clonidine patch Methyldopa Guanfacine	0,1–0,8 0,1–0,3 250–1000 0,5–2	2 1 weekly 2 1	Last-line treatment because of significant CNS adverse effects, especially in older patients. Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis, especially in older patients; clonidine must be tapered to avoid rebound hypertension
Direct vasodilators	Hydralazine Minoxidil	250–200 5–100	2 or 3 1–3	Cause sodium and water retention and reflex tachycardia; use in combination with beta-blockers and diuretics. Hydralazine in high doses can cause drug-induced lupus. Minoxidil is associated with hirsutism; should be combined with loop diuretics. May induce pericardial effusion.

Table 11. *Absolute and relative contraindications to the use of specific antihypertensive drugs [15]*

Drug	Contraindications	
	Absolute	Relative
Diuretics (thiazides/ thiazide-like, e. g. chlorthalidone and indapamide)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalemia
β-blocker	Asthma Any high-grade sinoatrial or atrioventricular block Bradycardia (heart rate <60 bpm)	Metabolic syndrome Glucose intolerance Athletes and physically active patients
Calcium antagonists: dihydropyridines		Tachyarrhythmia Heart failure (HF with reduced EF, NYHA class III or IV) Pre-existing severe leg edema
Calcium antagonists: verapamil, diltiazem	Severe LV dysfunction (LV ejection fraction <40%) Any high-grade sinoatrial or atrioventricular block Bradycardia (heart rate <60 bpm)	Constipation
ACE inhibitors	Pregnancy Previous angioedema Hyperkalemia (potassium >5.5 mmol/L) Bilateral renal artery stenosis	Women of reproductive age without reliable contraception
ARB	Pregnancy Hyperkalemia (potassium >5.5 mmol/L) Bilateral renal artery stenosis	Women of reproductive age without reliable contraception
MCA	eGFR <30 ml/min/1.73 m^2 Hyperkalemia (potassium >5.5 mmol/L)	

Justification of the Choice of Treatment in Hypertension and MS

Selection of antihypertensive agents in patients with hypertension and MS should be especially careful, since some of them can enhance metabolic disorders [3, 7]. It is advisable to use drugs that can improve or at least not worsen the sensitivity of tissues to insulin. These include blockers of the renin-angiotensin-aldosterone system (ACEI, ARBs) and CCBs (both dihydropyridine and non-dihydropyridine) [3].

Favorable metabolic effects accompany the RAAS block: an increase in tissue sensitivity to insulin, insulin secretion, glucose uptake by tissues due to decreased SNS activity and improved blood flow in skeletal muscles, an improvement in signal transduction via insulin receptors, an influence on the level of free fatty acids and on adipose tissue, and activation of PPARγ receptors. In this regard, in ACEIs and ARBs are key in the treatment of hypertension in patients with MS [6].

The undoubted advantage of these drugs is the absence of negative effect on carbohydrate, lipid and purine metabolism. These drugs have an organic protective effect: LVH reduction, myocardium remodeling and fibrosis delay, albuminuria and proteinuria reduction, nephroangiosclerosis and terminal CKD prevention [6]. In addition, they prevent cardiovascular complications in high and very high-risk patients, including patients with hypertension, MS and type 2 DM.

There are 3 groups of ACEIs, depending on their chemical structure: containing sulfhydryl (captopril, zofenopril), carboxyl (enalapril, quinapril, ramipril, perindopril, trandolapril, spirapril, cilazapril, lisinopril), and phosphoryl group (fosinopril). Since fatty tissue growth often occurs in hypertension and metabolic disorders, the choice of a particular ACEI should consider its lipophilicity, because a higher level of lipophilicity determines greater tissue affinity for the drug (i. e., the ability to influence ACE activity both in plasma and directly in tissues). The active metabolites of fosinopril, quinapril, trandolapril, ramipril and perindopril are highly lipophilic; enalapril, moexipril and captopril have moderate lipophilicity; and lisinopril belongs to hydrophilic compounds. The kidneys eliminate the majority of ACEIs; only 4 agents (zofenopril, fosinopril, trandolapril, spirapril) are eliminated via both liver and kidneys.

The effect of angiotensin II receptor blockers (ARBs), or sartans, is also associated with the suppression of RAAS activity, but they do not affect the kinin-kallikrein system. Antihypertensive efficacy of ACEIs and ARBs is equivalent, but the latter have a better tolerability profile: do not cause cough and angioedema. ARBs provide higher adherence to treatment among patients with hypertension due to better tolerability profile and absence of "escape" of hypotensive effect [6].

ARBs do not affect lipid and purine metabolism, except for losartan, which has been proven to reduce uric acid levels. In addition, lipophilic ARBs improve tissue sensitivity to insulin, carbohydrate and lipid metabolism due to interaction with PPARg- receptors.

CCBs, or calcium antagonists, have a significant vasodilating effect due to inactivation of potential-dependent calcium channels and blocking of the flow of calcium fluxes into vascular smooth muscle cells. Depending on the chemical structure, 3 groups of CCBs are distinguished: dihydropyridines (nifedipine, amlodipine, felodipine, etc.), phenylalkylamines (verapamil), and benzodiazepines (diltiazem). Non-dihydropyridine calcium blockers have negative ino- and dromotropic effects. Dihydropyridine CCBs have a significant vasodilating effect on peripheral arteries, do not affect the cardiac conduction system, and mostly do not reduce myocardial contractility.

To treat hypertension in patients with MS, as well as with type 2 DM, both non-dihydropyridine (verapamil, diltiazem) and long acting dihydropyridine CCBs are used. CCBs do not adversely affect lipid, carbohydrate, and purine metabolism. Reduction of new cases of type 2 DM in long-term treatment with CCBs in combination with ACEIs was established in the ASCOT (amlodipine + perindopril) and INVEST (verapamil + trandolapril) trials.

Nitrenedipine has the most significant preventive effect on cognitive disorders (by 55%) [3].

β-blockers (other than vasodilating ones) and diuretics should be considered only as additional agents in MS. However, in case of high SNS activity and the need in this drug group, it is advisable to use only cardioselective β-blockers (nebivolol, bisoprolol, extended release metoprolol succinate) or vasodilating agents (nebivolol, carvedilol — non-cardioselective αβ-blocker) in order to avoid a negative effect on carbohydrate and lipid metabolism. Carvedilol reduces SPR, improves glomerular filtration and reduces insulin resistance [3].

Thiazide diuretics can adversely affect carbohydrate and lipid metabolism. However, hypervolemia that develops in MS due to increased reabsorption of sodium and water often leads to the need for diuretics. Chlorthalidone and indapamide are the drugs of choice among thiazide-like diuretics. Loop diuretics are not recommended in the treatment of MS: they can cause IGT, glucosuria, and hyperosmolar conditions [3].

I_2-imidazoline receptors agonists (moxonidine, rilmenidine) can be used in MS due to the fact that they improve tissue sensitivity to insulin and promote weight loss [3].

α-antibodies also reduce insulin resistance, improve carbohydrate and lipid metabolism. But they can cause postural hypotension, and therefore they should be combined with β-blockers [3].

Mono- and Combined Hypertension Treatment

The 2018 ESC/ESH guidelines in the majority of cases suggest initiating treatment with a combination of two agents and not with monotherapy (Table 12). At the first treatment stage, a double combination of ACEI (or ARB) with CCB (or thiazide/thiazide-like or looped diuretic in CKD) should be prescribed. Monotherapy can be considered in low-risk patients with BP level 140–159 / 90–99 mm Hg, or in senile (>80 years) or frail patients. If the double combination is ineffective, the second treatment stage is switched to, and a triple combination is prescribed: ACEI (or ARB) with CCB and diuretic (thiazide / thiazide-like or looped in CKD). If the triple combination is ineffective, the third treatment stage is switched to, and 25–50 mg/day of spironolactone or other diuretics, alpha-blockers or β-blockers are added to the triple combination [15].

Monotherapy can be considered in case of low CVR at BP 140–159 / 90–99 mm Hg, or in senile (>80 years) or frail patients [15].

The 2018 ESH/ESC guidelines recommend the addition of β-blockers to the hypertension treatment at any stage in the presence of indications: HF, angina, history of MI, AF or in young women with a planned pregnancy [15]. The American recommendations specify that β-blockers are the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease [14]. In contrast, in patients with chronic aortic insufficiency systolic hypertension should be treated with agents that do not slow heart rate, and β-blockers should be avoided. This is due to the fact that when the heart rate decreases, the diastolic filling time increases and, consequently, aortic regurgitation increases [14].

The 2017 ACC/AHA guidelines also recommend to prescribe two agents of different first-line drug groups (fixed combination, or individual

Table 12. *Therapy choice in hypertension according to 2018 ESH/ESC [15]*

	Drug groups	Comments
Step 1 (initial therapy) — dual combination	ACEI or ARB + CCB or diuretic (loop in CKD)	Consider monotherapy in low risk grade 1 hypertension (systolic BP <150 mmHg), or in very old (80 years) or frail patients
Step 2 — triple combination	ACEI or ARB + CCB + diuretic	
Step 3 — triple combination + spironolactone or another drug	Resistant hypertension: add spironolactone (25–50 mg o. d.) or other diuretic, alpha-blocker or beta-blocker	Referral to a medical specialist as required

medications) as the onset of antihypertensive DT in adults with BP level ≥140/90 mm Hg and mean BP level ≥20/10 mm Hg above target [14]. Hypertension monotherapy is indicated in patients with BP of 130/80 mm Hg, followed by dose titration or addition of other drugs to achieve target BP [14].

The course of hypertension in patients with MS is characterized by refractoriness to treatment, therefore it is advisable to use combined therapy immediately after hypertension diagnosis in this group of patients. In this case, two-component treatment with diuretic and β-blocker should be avoided [3, 7]. When using diuretics, an additional potassium-sparing agent should be prescribed, because hypokalemia may impair glucose tolerance [15].

The 2018 ESH/ESC 2018 guidelines emphasize low adherence to treatment as the main reason for poor BP control [15]. In this regard, the use of the so-called "single pill combination" (SPC) and "polypill" was proposed. SPC is a fixed combination of two or more drugs that affect a particular risk factor (for example, fixed combinations of antihypertensive agents). SPCs are preferred for most patients. A simplified procedure for drug hypotensive treatment includes SPC (ACEI or ARB with CCB or/and thiazide / thiazide-like diuretic) as the main treatment strategy for most patients; in case of specific indications the addition of β-blockers should be considered [15]. Polypill is a combination of two or more agents that affect various risk factors. For example, a combination of antihypertensive agents with antiplatelets and statins [15].

In both the European and American guidelines, single administration of medicines is preferable, since in this case the adherence to treatment increases. In addition, adherence to treatment when taking fixed combinations is better than when taking drugs separately [14, 15].

Hypertension and MS Treatment in Order to Reduce CVR

Isolated antihypertensive treatment does not sufficiently reduce CVR in patients with moderate- or higher-risk hypertension, as well as in patients with established CVD. In these patients, treatment with statins leads to the decrease of MI risk by 1/3 and of stroke by 1/4 even with optimal control of BP [15].

In this regard, in the presence of dyslipidemia, patients with MS should be prescribed statins at the maximum or maximum tolerated doses. In case of intolerance to statins, ezetimibe or bile acid sequestrants, or their combination, should be prescribed [2, 9].

The main goal of dyslipidemia treatment in MS is the correction of LDL cholesterol level. Its target level for very high-risk patients is <1.8 mmol/L

or a decrease of 50% at the baseline level of 1.8–3.5 mmol/L; for high-risk patients it is <2.6 or decrease by ≥50% of the baseline [2, 9]. If the target LDL cholesterol is not achieved, a combination of statin and ezetimibe should be prescribed [2, 9].

Antiplatelet treatment, especially low doses of aspirin, is recommended for the purpose of secondary prevention in patients with hypertension, but is not recommended for primary prevention (in patients without CVD) [15]. This is specified in the 2018 ESH/ESC recommendations. In the American guidelines, almost no attention is paid to aspirin and statins [14]. The Russian recommendations for the management of comorbid patients indicate that prescribing antiplatelets as the primary prevention of CVD in MS has not yet been resolved. In very high-risk patients with hypertension and MS, administration of acetylsalicylic acid should be considered in case of good BP control [3]. In the presence of risk factors for erosive and ulcerative lesions of the gastrointestinal tract, acetylsalicylic acid can be administered under the "cover" of proton pump inhibitors and/or rebamipide, a universal gastroprotective agent. Clopidogrel is recommended as an alternative antiplatelet treatment in patients with ASA intolerance [3].

Conclusion

Hypertension in patients with MS is therefore an extremely urgent problem. In patients with MS, it is necessary to diagnose hypertension in a timely manner with an increase in office systolic BP ≥140 and/or diastolic BP ≥90 mm Hg; and/or at mean daily BP according to 24-hour BPM >130/80 mm Hg; and/or at mean BP values according to home BPM ≥135/85 mm Hg. Most patients with MS have a high or very high cardiovascular risk, which requires immediate initiation of drug antihypertensive treatment. The target BP level in the majority of patients with MS is 120–130 / 70–80 mm Hg. Treatment of most patients with hypertension should be started with a combination of two agents. At the first treatment stage, a double combination of ACEI (or ARB) with CCB (or thiazide / thiazide-like or looped diuretic in CKD) should be prescribed. Monotherapy can be considered in low-risk patients with BP level 140–159 / 90–99 mm Hg, or in senile (>80 years) or frail patients. If the double combination is ineffective, the second treatment stage is switched to, and a triple combination is prescribed: ACEI (or ARB) with CCB and diuretic (thiazide / thiazide-like or looped in CKD). If the triple combination is ineffective, the third treatment stage is switched to, and 25–50 mg/day of spironolactone or other diuretics, α-blockers or β-blockers are added to the triple combination. In patients with MS and dyslipidemia, statins should be prescribed to reduce CVR. In patients with MS, BP stabilization and dyslipidemia correction are extremely important for the prevention of life-threatening complications.

References:

1. Recommendations for the management of patients with metabolic syndrome: clinical guidelines. Ministry of Health of the Russian Federation. 2013; 42 p. [Electronic resource]. URL: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwjuybvrh9DfAhURp4sKHcYnDJoQFjAAegQIChAC&url=http%3A%2F%2Fwww.gipertonik.ru%2Ffiles%2Frecommendation%2FRecommendations_metabolic_syndrome.doc&usg=AOvVaw0OlaDnVqEqE_s6p37JaUFm (date of the application: 03.01.2019) [In Russian]
2. Yezhov M. V., Sergienko I. V., Aronov D. M. et al. Diagnosis and correction of lipid metabolic disorders for the prevention and treatment of atherosclerosis. Russian recommendations. VI revision. Atherosclerosis and Dyslipidemia. 2017; 3: 5–22. [In Russian]
3. Oganov R. G., Denisov I. N. Comorbid Pathology in Clinical Practice. Clinical guidelines. Cardiovascular Therapy and Prevention. 2017; 16(6): 5–56. [In Russian] https://doi.org/10.15829/1728-8800-2017-6-5-56
4. Reznik E. V., Nikitin I. G. New ACC/AHA and ESC/ESH recommendations on arterial hypertension.

Cardiovascular therapy and prevention. 2018; 17(5): 99–119 [In Russian]
5. Rotar O. A. Prevalence of cardiometabolic disorders, target organ damage and mechanisms of their progression in office workers. dis. ... Dr. med Sciences, St. Petersburg. 2016; 250 p. [in Russian].
6. Chazova I. E., Nedogod S. V., Zhernakova Yu. V. et al., Recommendations for the management of patients with arterial hypertension with metabolic disorders. // Kardiologicheskij Vestnik. 2014; 9(1): 3–57. [in Russian].
7. Chazova I. E., Oshchepkova E. V., Zhernakova Yu. V., Clinical recommendations. Hypertension in adults. 016; 70 p. [Electronic resource]. URL: http://webmed.irkutsk.ru/doc/pdf/fedhypert.pdf. (date of the application: 03.01.2019) [In Russian]
8. Bakris G., Sorrentino M., Redefining Hypertension — Assessing the New Blood-Pressure Guidelines. N Engl J Med. 2018; 378 (6): 497–499.
9. Catapano A. L., Graham I., De Backer G. et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016; 37 (39): 2999–3058.
10. Cuspidi C., Tadic M., Grass, G. et al. Treatment of hypertension: The ESH/ESC guidelines recommendations. Pharmacol Res. 2018; 128: 315–321.
11. Group S. R., Wright J. T., Jr., Williamson J. D. et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015; 373 (22): 2103–16.
12. Mancia G., Fagard R., Narkiewicz K. et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Journal of Hypertension 2013; 31(7):1281–1357
13. Muntner P., Carey R. M., Gidding S. et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation. 2018; 137 (2): 109–118.
14. Whelton P. K., Carey R. M., Aronow W. S. et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71 (6): e13–e115.
15. Williams B., Mancia G., Spiering W. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39 (33): 3021–3104.

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CURRENT VIEW ON ANTICOAGULANT AND THROMBOLYTIC TREATMENT OF ACUTE PULMONARY EMBOLISM

Abstract

The presented review concerns contemporary views on specific aspects of anticoagulant and thrombolytic treatment of venous thromboembolism and mostly of acute pulmonary embolism. Modern classifications of patients with acute pulmonary embolism, based on early mortality risk and severity of thromboembolic event, are represented. The importance of multidisciplinary approach to the management of patients with pulmonary embolism with the assistance of cardiologist, intensive care specialist, pulmonologist, thoracic and cardiovascular surgeon, aimed at the management of pulmonary embolism at all stages: from clinical suspicion to the selection and performing of any medical intervention, is emphasized. Anticoagulant treatment with the demonstration of results of major trials, devoted to efficacy and safety evaluation of anticoagulants, is highlighted in details. Moreover, characteristics, basic dosage and dosage scheme of direct (new) oral anticoagulants, including apixaban, rivaroxaban, dabigatran, edoxaban and betrixaban are described in the article. In particular, the management of patients with bleeding complications of anticoagulant treatment and its application in cancer patients, who often have venous thromboembolism, is described. Additionally, modern approaches to systemic thrombolysis with intravenous streptokinase, urokinase and tissue plasminogen activators are presented in this review. The indications, contraindications, results of clinical trials devoted to various regimens of thrombolytic therapy, including treatment of pulmonary embolism with lower doses of fibrinolytic agents, are described.

Key words: *pulmonary embolism, venous thromboembolism, thromboembolism of pulmonary artery, treatment, risk stratification, anticoagulant therapy, direct oral anticoagulants, systemic thrombolysis, fibrinolysis, bleeding complications*

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ESC — European Society of Cardiology, FDA — Food and Drugs Administration, MOPPET — moderate pulmonary embolism treated with thrombolysis, PEITHO — pulmonary embolism thrombolysis study, PERT — Pulmonary Embolism Response Team, PESI — Pulmonary Embolism Severity Index, tPA — tissue plasminogen activator, VKA — vitamin K antagonists, ACD — anticoagulant drug, ACT — anticoagulant therapy, APTT — activated partial thromboplastin

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time, VTE — venous thromboembolism, CI — confidence interval, PE — pulmonary embolism, INR — international normalized ratio, LMWH — low molecular weight heparin, UFH — unfractionated heparin, HR — hazard ratio, DOAC — direct oral anticoagulants, PTT — prothrombin time, PTS — post-thrombotic syndrome, RCT — randomized clinical trial, STL — systemic thrombolysis, DVT — deep vein thrombosis, CTEPH — chronic thromboembolic pulmonary hypertension

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease [1, 2]. The incidence of the first acute event of VTE is 0.7–1.4 per 1 thousand people/years, and is most common in people aged over 55 years [2, 3]. In persons, aged 70 years and older, VTE rate reaches 7 cases per 1 thousand people [4]. At the same time, though DVT rate remains constant over time, the hospitalization for PE in the United States increased more than twofold in recent decades, mainly due to the widespread introduction of sensitive imaging that can determine small emboli [5].

With the obvious success of modern diagnostic methods, the management of patients with PE presents significant challenges. This is due to the diverse clinical presentation and different hemodynamic response to the embolization of pulmonary vasculature, which in turn is associated with the massiveness of the emboli, the state and compensatory capabilities of the heart, the presence and severity of concomitant diseases. Therapeutic measures include the use of anticoagulant drugs (ACD), thrombolytics, interventional approaches described earlier [6], surgical embolectomy and maintenance therapy. In addition, if the use of endovascular therapeutic methods, unfortunately, is limited to large medical centers, the basic therapy of VTE, including anticoagulant therapy (ACT) and systemic thrombolysis (STL), as a rule, is available in almost all specialized hospitals. The purpose of this review was to discuss modern approaches to the treatment of patients with acute PE with ACT and STL.

Clinical classification of pulmonary embolism severity

Assessment of the massiveness of PE or calculation of the mortality risk in this event is a crucial step in determining the principles and sequence of treatment strategy stages. The clinical classification of PE severity is based on the calculated risk of early (up to 30 days) mortality due to thromboembolic event [1]. This distribution (or stratification), which is important both diagnostically and therapeutically, is based on an assessment of the patient's clinical status at the time of presentation. High-risk PE is assumed or confirmed in the presence of shock or persistent hypotension, and non-high-risk PE (intermediate or low) — in their absence (Table 1) [1].

Classification of PE severity based on massiveness (scope) of the thromboembolism case was previously widely used. However, even in the recommendations of the European Society of Cardiology (ESC) 2008 it was noted that PE severity should be understood more as an individual assessment

Table 1. *Classification of patients with acute pulmonary embolism based on early mortality risk*

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI > I	Sign of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate-	**High**	–	+	Both positive	
	Low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

Note: PESI — Pulmonary Embolism Severity Index; RV — right ventricular; sPESI — simplified Pulmonary Embolism Severity Index; sPESI ≥1 point(s) indicates high 30-day mortality risk. Adapted from S.V. Konstantinides et al. [1]

of early mortality due to PE [7], rather than the anatomical volume, shape and disposition of the intrapulmonary embolus assessment. Therefore, in ESC Guidelines for the diagnosis and treatment of acute PE 2008 it was proposed to replace the incorrect, according to experts, terms of massive, submassive and non-massive PE with the corresponding risk categories of early mortality presented in Table 1 [7]. However, in the literature, especially in North America, there are widespread definitions of massive, submassive PE, which correspond to cases of high and intermediate risk, respectively [8–11]. The assessment of the lesion massiveness should ideally take into account the angiographic control of the scale and distribution of the embolic material using the Miller index [12].

In addition to assessing the risk of early mortality (or massiveness) for PE after diagnosis, it is considered extremely important to calculate the prognosis of the disease using the clinical index of PESI (**P**ulmonary **E**mbolism **S**everity **I**ndex) in the original [13] and **s**implified versions — sPESI [14].

Interdisciplinary approach

Timely diagnosis, accurate risk stratification, and adequate use of reperfusion techniques are crucial measures to ensure the earliest possible favorable outcome in patients with high or intermediate-high risk PE [15]. Hospitalization of patients with suspected or already diagnosed PE outside the working hours of the main specialists (at night or on weekends) is combined with the worst prognosis due to the lack of timely, specialized medical care by experienced doctors. In recent years, in the United States and most recently in Europe, a new coordinated approach for the management of patients with PE — with the help of a multidisciplinary team of specialists called PERT (**P**ulmonary **E**mbolism **R**esponse **T**eam) [16], competent in the treatment of PE and including, at least, pulmonologist, interventional radiologist, cardiologist and thoracic surgeon, was developed [17]. PERT provides highly professional care focused on the treatment of PE at all its stages, from clinical suspicion of PE to selection and implementation of any medical intervention: ACT, STL, interventional methods of treatment, surgical embolectomy, etc. Therapeutic strategy should optimally integrate all of the available range of therapeutic techniques in compliance with, albeit multidisciplinary, a unified approach to the management of such patients [18].

Anticoagulant therapy

The clinical study by D.W. Barritt and S.C. Jordan published in *The Lancet* [19] in 1960 was of fundamental importance in the development of modern guidelines for the management of patients with PE based on PE treatment with ACT [20]. ACT is the main method of treatment for the majority of patients with acute PE and, in addition, represents the basis of therapy for the prevention of acute and chronic complications, including relapses of PE (leading to hemodynamic insufficiency), lower limb DVT, which is often a source of PE and post-PE syndrome [15, 21]. The ACT is usually considered in the management of hemodynamically stable patients [22].

The ACT plays one of the key roles, if not the basis of the therapeutic strategy in VTE and, in particular, acute PE [23]. There are 3 phases of VTE treatment: initial (first 5–10 days), long-term (from the end of the initial phase to 3–6 months) and extended (>3–6 months) [2]. The duration of the ACT should not be less than 3 months. During this period, traditional modes of acute phase therapy are represented by parenteral administration of ACD (unfractionated heparin (UFH) i. v., subcutaneous injections of low molecular weight heparins (LMWH) or fondaparinux) in the first 5–10 days, layered on or replaced by vitamin K antagonists (VKA), which are selected until the therapeutic range of the international normalized ratio (INR) 2.0–3.0 is reached [4, 21, 24]. LMWH are preferable in comparison with UFH, as their use is associated with a lower rate of massive bleeding, a more reliable therapeutic effect and a lower probability of heparin-induced thrombocytopenia [23].

The benefits of ACT, including prevention of thrombus enlargement, reduction of VTE recurrence, hemodynamic collapse and death, should be carefully weighed against the risk of bleeding to determine the choice of ACT and the duration of

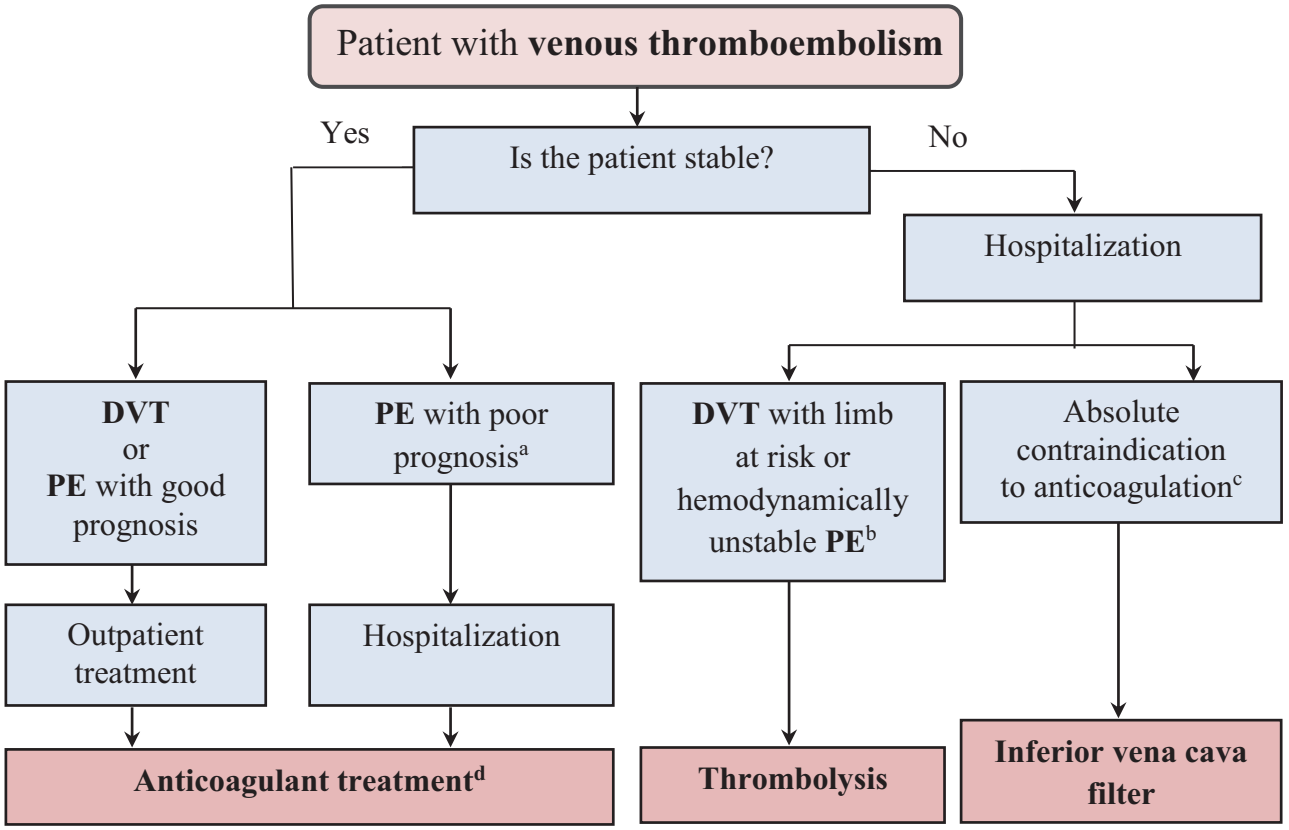

Figure 1. *Approach to initial treatment of venous thromboembolism*

Notes: DVT — deep vein thrombosis; PE — pulmonary embolism. a — assessment of 30-day mortality risk with the Pulmonary Embolism Severity Index score or its simplified version or the Hestia criteria. b — catheter-directed thrombolysis for DVT and systemic thrombolysis for PE. c — active bleeding, high risk of bleeding, or other contraindication to anticoagulant therapy. d — initiate treatment with direct oral anticoagulants (rivaroxaban or apixaban, or initial low molecular weight heparin followed by dabigatran or edoxaban). Modified from T. Tritscher et al. [2]

treatment (Fig. 1) [2]. In order to determine the risk of VTE recurrence and duration of the ACT, thromboembolic events are distinguished between provoked (transient, caused by any identifiable factors) and unprovoked (in the absence of any identifiable risk factor for the development of VTE) [23, 25].

Prior to the introduction of direct (or new) oral anticoagulants (DOAC), urgent therapy of PE began with parenteral administration of anticoagulants, usually LMWH, as transitional treatment with VKA, reaching full activity only after 5-7 days [15, 24]. In the latest ESC Guidelines 2014 for the diagnosis and treatment of acute PE, immediate intravenous administration of UFH to high-risk patients (with shock or hypotension, class I, level of evidence C) is recommended [1]. The mode of transitional treatment with VKA is quite effective and safe in patients with PE and DVT: the 3-month rate of VTE relapses during VKA therapy is 3.4 % (up to 20 % in patients not receiving treatment) with massive bleeding rate of 1.6 % [26]. However, the practical application of therapy with VKA is problematic, since it requires frequent determination of INR and fractional selection of the optimal dosage to ensure the presence of the drug in the effective therapeutic range. Moreover, there are many interactions between VKA and other drugs, including allopurinol, amiodarone, selective serotonin reuptake inhibitors, antibiotics and antiepileptic agents, as well as various vitamin K-rich products, such as broccoli, grapefruit, cauliflower, etc. [15].

Despite treatment with ACT, a substantial portion of survivors after DVT or PE is at risk of consequences, such as post-thrombotic syndrome (PTS), recurrent DVT or chronic thromboembolic pulmonary hypertension (CTEPH). In the fall of 2018, the American Society of Hematology published recommendations for the management of VTE using ACT, which are of undisputed interest

to practitioners [27]. Recommendations, suggesting that the choice of anticoagulant by doctors has already been made, mainly relate to the selection of the initial dosage of ACD; drug-drug interactions; evaluation of INR in close proximity to the patient; revision of the term for re-determination of INR; switch to another ACD; organized training of patients; improving compliance with the ACT regimen, etc. [27].

Patients with provoked events, having a removable or treatable cause (e. g., immobilization after injury or surgery), should receive anticoagulants for a period of 3 months [2, 23]. Patients who experienced the first unprovoked episode of VTE are at high risk of relapse (10 % after 1 year and 30 % — 5 years) and should thus receive the ACT indefinitely, until a high risk of hemorrhagic complications is reached [28].

Direct oral anticoagulants

The introduction of DOAC in 2012 greatly simplified the conduct of ACT in patients with VTE. DOAC can be prescribed in fixed dosages without the need for regular determination of INR and, in addition, have fewer interactions with other drugs [29]. Currently, there are 4 drugs for the treatment of PE: dabigatran (specific thrombin inhibitor) and three Xa factor blockers: apixaban, rivaroxaban and edoxaban (Table 2) [4]. In addition, the US FDA approved betrixaban,

Table 2. *Direct oral anticoagulant agents in the treatment and secondary prevention of VTE*

	Dosage and Interval			Not recommended or contraindicated
	Initial Phase	**Long-Term Phase**	**Extended Phase**	
Rivaroxaban	15 mg twice a day with food for 21 days	20 mg once daily with food		• CrCl <30 ml/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers
Dabigatran etexilate	Initial therapy with parenteral anticoagulation for 5–10 days should precede administration of dabigatran etexilate	150 mg twice daily		• CrCl <30 ml/min • Concomitant treatment with P-gp inhibitors in patients with CrCl <50 ml/min • Concomitant treatment with P-gp inducers (i. e., rifampin)
Apixaban	10 mg twice a day for 7 days	5 mg twice daily	2.5 mg twice daily after at least 6 months of treatment	• CrCl <15 ml/min Severe hepatic impairment (Child-Pugh C), or hepatic disease associated with coagulopathy • Strong dual inhibitors or inducers of CYP3A4 and P-gp
Edoxaban	Initial therapy with parenteral anticoagulation for 5–10 days should precede administration of edoxaban	60 mg once daily 30 mg once daily can be considered in patients with ≥1 of the following factors: CrCl 15–50 ml/min; body weight ≤60 kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole		• CrCl <15 ml/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant treatment with rifampin

Note: CrCl — creatinine clearance; CYP3A4 — cytochrome P450-3A4; P-gp — P-glycoprotein; VTE — venous thromboembolism. Adapted from S.V. Konstantinides et al. [4]

another Xa factor inhibitor with a very low dependence on renal clearance (7–14 %), but it has not yet been studied in the treatment of PE [15]. To date, there has been one large, international, double-blind, randomized clinical trial (RCT) to investigate the efficacy and safety of betrixaban in patients for the prevention of VTE [30]. Prolonged use of betrixaban (35–42 days) was accompanied by a decrease in events caused by VTE, including PE, without increasing massive bleeding rate based on a modified analysis of all patients who underwent randomization.

Permission to use DOAC in the treatment of PE was based on the results of phase III studies of initial therapy, as well as prolonged treatment, which showed that DOACs are as effective as traditional drugs, but unlike the latter, treatment with them is associated with a lower rate of massive bleeding (Table 3) [31]. In the first meta-analysis, the rate of recurrent VTE and VTE-related deaths after 6 months was 2.0 % in patients receiving DOAC and 2.2 % in the group of patients treated with VKA. Massive bleeding was reported in 1.1 % of patients in the DOAC group and in 1.7 % of patients in the VKA group.

Table 3. *Overview of phase 3 trials using DOACs for the treatment of acute VTE*

Trial	Intervention	Study duration; number of patients	Study design	Efficacy outcome	Safety outcome
			Dabigatran		
RE-COVER [35]	Dabigatran[a] versus warfarin[a]	6 months; 2,539 patients with acute VTE	Double blind	Recurrent VTE or fatal PE: 2.4 % for dabigatran versus 2.1 % for warfarin	Massive bleeding: 1.6 % for dabigatran versus 1.9 % for warfarin
RE-COVER II [36]	Dabigatran[a] versus warfarin[a]	6 months; 2,589 patients with acute VTE	Double blind	Recurrent VTE or fatal PE: 2.3 % for dabigatran versus 2.2 % for warfarin	Massive bleeding: 1.2 % for dabigatran versus 1.7 % for warfarin
			Rivaroxaban		
EINSTEIN-DVT [37]	Rivaroxaban versus warfarin[a]	3–12 months; 3,449 patients with acute DVT	Open label	Recurrent VTE or fatal PE: 2.1 % for rivaroxaban versus 3.0 % for warfarin	Massive bleeding or CRNM bleeding: 8.1 % for rivaroxaban versus 8.1 % for warfarin
EINSTEIN-PE [38]	Rivaroxaban versus warfarin[a]	3–12 months; 4,832 patients with acute PE with or without DVT	Open label	Recurrent VTE or fatal PE: 2.1 % for rivaroxaban versus 1.8 % for warfarin	Massive bleeding or CRNM bleeding: 10.3 % for rivaroxaban versus 11.4 % for warfarin
			Apixaban		
AMPLIFY [39]	Apixaban versus warfarin[a]	6 months; 5,395 patients with acute DVT and/or PE	Double blind	Recurrent VTE or fatal PE: 2.3 % for apixaban versus 2.7 % for warfarin	Massive bleeding: 0.6 % for apixaban versus 1.8 % for warfarin
			Edoxaban		
Hokusai-VTE [40]	Edoxaban combined with LMWH versus UFH or LMWH with warfarin	3–12 months; 8,240 patients with acute DVT and/or PE	Double blind	Recurrent VTE or fatal PE: 3.2 % for edoxaban versus 3.5 % for warfarin	Massive bleeding or CRNM bleeding: 8.5 % for edoxaban versus 10.3 % for warfarin

Note: In the trials, dabigatran (twice a day) and edoxaban (once a day) in intensive regimen were started after a minimum 5-day period of therapeutic dose of LMWH, which was followed by a direct oral anticoagulant (DOAC) in a fixed dose for both drugs, whereas apixaban (twice a day) and rivaroxaban (once a day) were given in a higher loading dose (for 7 days for apixaban and for 21 days for rivaroxaban) followed by a lower fixed dose. CRNM — clinical-relevant non-massive; DVT — deep vein thrombosis; LMWH — low molecular weight heparin; PE — pulmonary embolism; UFH — unfractionated heparin; VTE — venous thromboembolism. [a] — combined with enoxaparin. Adapted from M.V. Huisman et al. [15].

Compared with patients treated with VKA, patients taking DOAC showed a significant decrease (62 %) in massive bleeding in a critical area (e. g., brain or pericardium), as well as intracranial bleeding (61 %), overall — fatal hemorrhages (64 %) [32]. Based on the results and practical advantages of DOAC (fixed dosage, oral administration, no need for monitoring), recent recommendations of the American College of Thoracic Physicians included the use of DOAC, not VKA, in patients with PE who do not have an active cancer [28]. The use of Xa factor antagonists and direct thrombin inhibitors is likely to increase as they are added to the general guidelines as a first-line therapy.

Despite the advantages of DOAC over VKA, there are subgroups of patients with PE, for whom VKA administration is preferred [33]. First, these are patients suffering from end-stage renal failure or with creatinine clearance of <30 ml/l, since the majority of DOAC and LMWH are eliminated mainly through the kidneys [2, 23]. Secondly, for some patients who do not comply with the drug regimen, the need for serial measurement of INR acts as a kind of "guarantor" in terms of VKA intake. Thirdly, some patients' insecurity with insurance coverages when taking DOAC, as VKAs mainly are cheap products and are covered by insurance programs. Finally, VKAs are preferred in patients with antiphospholipid syndrome [23, 33].

At this time, there are practically no data on direct comparative analysis of individual drugs in the DOAC group and the choice of one of them is based on the difference in therapeutic regimens, characteristics of the patient and his/her preferences [23]. Although in early 2019, there were results of comparative analysis of apixaban and rivaroxaban prescribed for the prevention of repeated VTE episodes [34]. The total VTE recurrence rate in the group treated with apixaban was 3 per 100 person-years, and in the group of rivaroxaban — 7 per 100 person-years. The rate of massive bleeding was 3 per 100 person-years in the apixaban group and 6 per 100 person-years in the rivaroxaban group. When using the multivariate Cox regression model, apixaban compared to rivaroxaban was associated with a reduced risk of repeated VTE episodes (HR 0.37, 95 %, CI 0.24-0.55; p<0.0001) and massive hemorrhagic events (0.54 [0.37–0.82]; p=0.0031) [34].

DOACs should be avoided in case of simultaneous use of cytochrome P450 3A4 inhibitors or inducers (Table 2), including azole antifungals (e. g., ketoconazole), some protease inhibitors used in the treatment of HIV (e. g., ritonavir) and antiepileptic agents (in particular, phenytoin and carbamazepine), since these drugs can affect serum concentrations of DOAC [2].

The choice — whether or not to start DOAC therapy in a patient with PE in the acute phase — is determined by the clinical situation and the presence of comorbidity. Patients at high risk with hemodynamic instability usually receive UFH or LMWH, and it is also allowed to start treatment with DOAC prior to the stabilization of hemodynamic parameters [1]. Only patients with severe kidney injury, determined by creatinine clearance <15 ml/min^{-1} for apixaban, rivaroxaban, edoxaban and <30 ml/min^{-1} for dabigatran, as well as with severe liver dysfunction should not be prescribed with DOAC. Moreover, DOACs are contraindicated in pregnant and lactating women due to the fact that all drugs of this group penetrate the placenta and breast milk, and safety data in these categories of patients are not available [15]. Given the lack of data on the safety of DOACs in patients with antiphospholipid syndrome and arterial thrombosis, these drugs should also not be used in the above groups of patients. Finally, patients weighing >120 kg should be excluded from treatment with DOACs due to insufficient information about their efficacy in people with increased weight [41]. Analyzing prospectively the experience of DOAC administration according multicenter registry in France (2012–2017), R. Chopard et al. [21] noted the widespread use of this group of anticoagulants (in 70 % of patients with acute PE), especially after DOACs became available on the market. Among the factors limiting administration of DOACs, researchers note active cancer and impaired renal function in patients.

Prevention and treatment of hemorrhagic complications during anticoagulant therapy

Patients with VTE receiving ACT differ from other categories of patients on treatment with ACD (in particular, with atrial fibrillation) by rare simultaneous administration of antiplatelet drugs, a higher frequency of concomitant cancer, as well as an intensive mode of ACT at the beginning of treatment [42].

Prior to the administration of ACD all available information about the patient should be carefully collected, in particular: 1. Does patient currently receive ACD? 2. When was the last time the drug was used and in what dosage? 3. Does the patient take aspirin or another drug that inhibits platelet function? 4. Does the patient have kidney disease?

The main therapeutic measures in the development of anticoagulant-associated hemorrhagic complications match the same principles on which the management of patients with bleeding of other etiology is based (Fig. 2).

Immediate measures to stop or slow bleeding include local hemostasis (compression of the available bleeding artery, tamponade of the nasal cavity, installation of an intraesophageal Sengstaken-Blakemore tube to stop bleeding from esophageal veins, etc.) and mitigation of blood loss consequences (oxygen, intravenous fluids, hemodynamic support, blood transfusion) [42].

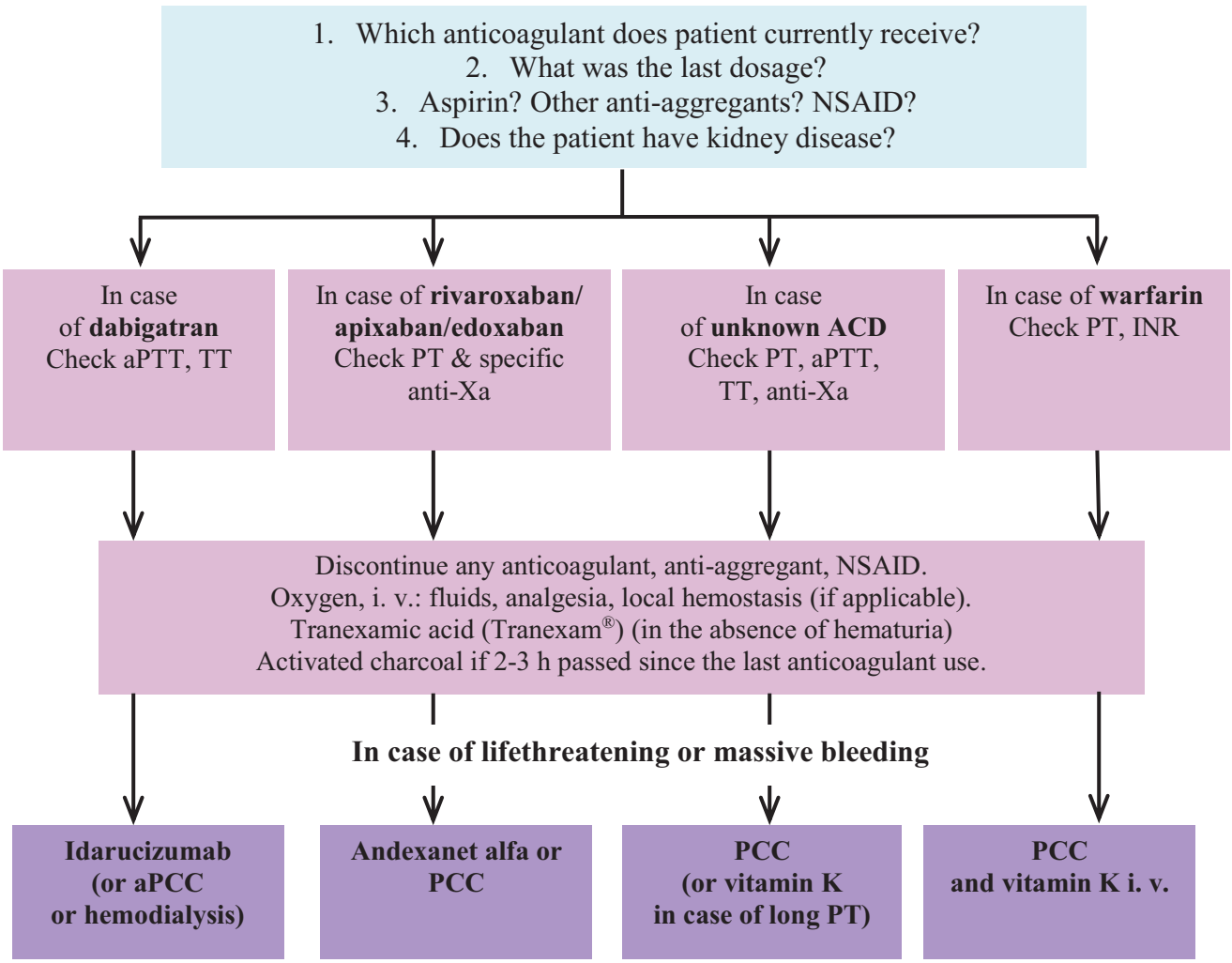

Figure 2. *Algorithm for management of anticoagulant associated massive bleeding*

Note: NSAID — nonsteroid anti-inflammatory drug; aPTT — activated partial thromboplastin time; TT — thrombin time; PT — prothrombin time; aPCC — activated prothrombin complex concentrate; PCC — prothrombin (plasma) complex concentrate; i. v. — intravenous. Adapted from S. Piran and S. Schulman [42]

Table 4. *Reversal strategies for different anticoagulants*

Anticoagulant type	Half-life, h	Route of elimination	Reversal strategy
VKA	20–60 (warfarin)	Liver metabolism; metabolites are primarily eliminated in the urine (warfarin)	Vitamin K, PCC, plasma
UFH	1–2	Therapeutic dose: hepatic elimination; very high doses: possible renal contribution	Protamine sulfate
LMWH	3–7	Renal	Protamine sulfate: partial reversal; rFVIIa: life-threatening bleeding
Fondaparinux	17–21	Renal	rFVIIa (high dose, 90 mcg/kg): life-threatening bleeding
Dabigatran	12–17	Renal (80 %)	Idarucizumab, aPCC
Apixaban	8–15	Renal (25 %)	4F-PCC, andexanet alfa
Betrixaban	19–27	Renal (11 %)	4F-PCC, andexanet alfa
Edoxaban	9–11	Renal (35 %)	4F-PCC, andexanet alfa
Rivaroxaban	9–13	Renal (66 %)	4F-PCC, andexanet alfa

Note: PCC — prothrombin complex concentrate; rFVIIa — recombinant activated factor VII; aPCC — activated prothrombin complex concentrate; 4F-PCC — four-factor prothrombin complex concentrate. Adapted from S. Piran and S. Schulman [42]

Tranexamic acid (in Russia: Tranexam®) should be used for bleeding caused by trauma or surgery [43]. This effective hemostatic drug is contraindicated in hematuria due to the risk of blood clots in the ureter and the development of hydronephrosis. Treatment with any antiplatelet, nonsteroidal anti-inflammatory drugs or ACD should be interrupted [42]. Charcoal enhances the elimination of DOAC and thus can be used for several hours if bleeding is caused by an overdose of anticoagulants or their accidental intake.

Evaluation of the level of anticoagulant effect is a useful and necessary method for optimal management of patients with hemorrhagic complications. In some cases, therapy may be interrupted for a few days until the anticoagulant effect disappears and the treatment should be aimed at stopping bleeding from the source. When waiting for the end of the anticoagulant effect, it is necessary to remember the values of the half-life periods of the main ACD (Table 4) [42].

On the other hand, if the patient developed acute kidney damage, there is a significant delay in the elimination of any DOAC. If the patient took VKA, a quick and accurate assessment is possible due to the measurement of INR in the immediate proximity of the patient. For patients taking DOAC, a global assessment of parameters such as thrombin time (TT), prothrombin time (PTT), or activated partial thromboplastin time (APTT) may, at best, provide a rough estimate of the effect, but less for apixaban and edoxaban than for dabigatran (with TT or APTT) or rivaroxaban (with PTT), as recently demonstrated in the review [44].

While TT is a fairly sensitive marker and will be able to determine the content of dabigatran in low concentrations, this indicator is not able to distinguish the content of anticoagulant in clinically acceptable or toxic levels. The APTT values for dabigatran and PTT for rivaroxaban in therapeutic doses are usually increased, but their sensitivity usually varies depending on the reagents used.

Clinical data on anticoagulant therapy in cancer

It is believed that patients with malignant tumors who have had at least one episode of VTE in their history should receive the ACT as long as the underlying disease is in the active stage or active antitumor therapy is being carried out [23].

LMWH is considered to be the standard in the treatment of VTE associated with tumor process [45]. Supporting data on the benefits of LMWH over

VKA were obtained in two large RCTs. In the initial study of 676 cancer patients with acute episodes of VTE, 6-month treatment with dalteparin significantly reduced the incidence (by 52 %) of VTE recurrences without affecting massive bleeding or mortality rate compared to VKA [46]. A while later, it was noted in 900 cancer patients with acute VTE that treatment with tinzaparin in comparison with warfarin was accompanied by a slight decrease in the risk of recurrent VTE events (7.6 % and 10.5 %; p=0.07), did not affect massive bleeding or mortality rates and significantly reduced non-massive bleeding rate (10.9 % and 15.3 %; p=0.004) [47].

The results of a direct comparative study of DOAC and LMWH were published. The Hokusai-VTE-Cancer study was an open-label RCT devoted to the study the efficacy of daily intake of oral Xa inhibitor edoxaban compared with dalteparin in symptomatic or accidental episodes of VTE in 1,050 cancer patients over a period of 6 and 12 months [48]. Edoxaban turned out to be just as effective as dalteparin with respect to total relapses of VTE and massive bleeding rate (12.8 % and 13.5 %). The rate of VTE relapses decreased with edoxaban compared with dalteparin (7.9 % and 11.3 %), but the number of cases of massive bleeding (6.9 % and 4.0 %) increased due to a higher level of hemorrhagic complications in patients with tumors of the gastrointestinal tract (13.2 % and 2.4 %) [48]. In an open-label RCT of 406 patients with cancer, treatment of VTE for 6 months showed that rivaroxaban reduced the risk of VTE relapses compared to dalteparin (4 % and 11 %), but increased the risk of clinically significant non-massive bleeding (13 % and 2 %) [49].

The data obtained, including Hokusai-VTE-Cancer trial, suggest that DOACs may be more effective than LMWH for preventing recurrence of VTE in patients with malignant tumors, although due to an increased risk of massive bleeding, in comparison with patients receiving LMWH [50, 51]. Therefore, the recommendations of the International Society for Thrombosis and Hemostasis 2018 proposed to use DOACs for the treatment of cancer patients with VTE and low risk of bleeding with the consideration of LMWH as an effective alternative. In patients with high risk of hemorrhagic complications, the use of LMWH remains the preferred therapy [52].

Clinical studies on the comparative evaluation of DOAC and LMWH in the treatment of VTE are ongoing, and they should provide additional data on the complex efficacy and safety of the drug-specific and class-specific effects of DOAC used in cancer patients.

Reperfusion therapy

Despite the fact that the basic therapy of acute PE is ACT, in patients with massive or submassive PE more aggressive treatment, including thrombolysis (or fibrinolysis), catheter or surgical embolectomy, should be considered [53]. Reperfusion therapy of acute PE involves induction of STL with intravenous thrombolytic agents to restore blood flow [15].

Systemic thrombolysis

The decision on the use of thrombolytic therapy in acute PE should be based on the results of a careful calculation of the "risk-benefit" for each patient [53]. Modern guidelines recommend the immediate start of reperfusion therapy in patients with high-risk PE (massive embolism, class I, level of evidence B), if there are no absolute and relative contraindications for its implementation [1, 8, 28, 54]. These recommendations are mainly based on minor studies that demonstrated rapid improvement of surrogate hemodynamic parameters (the ratio of right and left ventricular end-diastolic sizes) after thrombolysis [55] and are supported by epidemiological data [56].

Fibrinolytic drugs are enzymes that convert native, circulating plasminogen into plasmin, and are represented by three main classes: tissue plasminogen activators (tPA), streptokinase and urokinase [57]. In turn, tissue plasminogen activators include alteplase, reteplase and tenecteplase. In addition, if heparin causes a passive reduction in the size of the thrombus, thrombolytics accelerate the process of hydrolysis of fibrin molecules [8, 57].

Thrombolytic therapy of acute PE restores pulmonary perfusion faster than isolated ACT [1, 58].

Early elimination of pulmonary obstruction leads to rapid decrease of pressure and resistance in the pulmonary artery with simultaneous improvement of right ventricular function [59]. However, hemodynamic benefits of thrombolysis are limited to a few days; survivors do not have a significant difference at the end of the first week [60].

In a minor prospective study of the outcome in patients with massive PE, the use of STL (streptokinase) demonstrated a decrease in mortality compared with the group receiving heparin only [61]. In addition, it is noted that STL reduces the risk of CTEPH and improves quality of life [62]. The meta-analysis showed that systemic thrombolytic therapy also reduces mortality in patients with submassive PE (HR 0.48; 95 % CI 0.25–0.92) [63]. However, such results are achieved with the risk of significant hemorrhagic complications (HR 2.91; 95 % CI 1.95–4.36), including intracranial hemorrhages (HR 3.18; 95 % CI 1.25–8.11). It is noteworthy that the use of STL in patients with sudden cardiac arrest due to PE and not subjected to shock therapy, admitted to clinics before cardiac arrest, was also associated with improved survival [64]. The most favorable effect is observed if the treatment is started in the first 48 hours after the symptoms onset. However, STL may be acceptable among patients with a duration of symptoms of 6–14 days [1]. According to a study by M. Zuin et al. [65], STL used during the first 8.5 hours after the onset of symptoms was associated with a decrease in 30-day mortality among patients with high-risk PE compared with patients who received thrombolytic therapy after 8.5 hours. Dosages of the main thrombolytic agents used for the treatment of PE are presented in Table 5 [66].

Meta-analysis of 15 studies with a total of 2,057 patients showed that fibrinolysis reduced overall mortality (HR 0.59; 95 % CI: 0.36–0.96) and contributed to a significant reduction in the composite end-point of death or treatment intensification (HR 0.34; 95 % CI: 0.22–0.53), mortality due to PE (HR 0.29; 95 % CI: 0.14–0.60), and relapse of PE (HR 0.50; 95 % CI: 0.27–0.94) [55]. However, the favorable effects of STL are noted along with an increased risk of massive hemorrhagic events (HR 2.91; 95 % CI: 1.95–4.36), intracranial and fatal bleeding (HR 3.18; 95 % CI: 1.25–8.11).

It should be noted that the interpretation of the results of meta-analyses should be carried out with extreme caution, given the pronounced heterogeneity of: 1. Scope of study and criteria for selection of patients (assessment of PE severity); 2. Fibrinolytic drugs, their dosages, modes of testing, and 3. Modes of treatment with fibrinolytics and duration of treatment [4]. These differences can become even more pronounced and even critical if studies with complete and reduced doses of fibrinolytics, as well as the method of administration (systemically or locally administered) are analyzed [63]. Table 6 presents the main studies on the results of the use of thrombolytic drugs in patients with acute PE [15].

Table 5. *Thrombolytic agents and doses for high-risk pulmonary embolism*

Agent	Infusion treatment 12–24 h	Short infusion treatment
Urokinase (plasminogen activator)	4,400 IU/kg (bolus/30 min) + 4,400 IU/kg per hour 12–24 h	3 mln IU/2 h
Streptokinase (polypeptide derived from cultures of beta-hemolytic streptococci, binds to plasminogen and converts it to plasmin)	250,000 IU (bolus/15 min) + 100,000 IU/h 12–24 h	1.5 mln IU/2 h
Tenecteplase (binds to fibrin, increasing affinity for plasmin)	Not applicable	30–50 mg in bolus, adjusted by weight (5 mg for each 10 kg, from 60 to 90 kg)
Alteplase (binds to fibrin, increasing affinity for plasmin)	Not applicable	100 mg/2 h (10 mg in bolus, 50 mg in the first hour, and 40 mg in the second hour)

Note: IU — international unit. Modified from C. J. C. S. Fernandes et al. [66]

Table 6. *Prospective and cohort studies investigating thrombolytic agents and regimens in patients with acute PE*

Reference and/or trial	Population	Groups	Outcome	Time of outcome assessment	Thrombolysis group	Control group	P-value
PEITHO [8, 67]	Intermediate-risk PE (n=1,005)	Tenecteplase plus ACT versus ACT only	Death or hemodynamic collapse	7 days	2.6 %	5.6 %	0.02
			CTEPH	38 months	2.1 %	3.2 %	NS
			NYHA III–IV	38 months	12 %	10.9 %	NS
			Echo parameters of RV dysfunction	38 months	–	–	NS
			Death	38 months	20.3 %	18.0 %	NS
TOPCOAT [68]	Intermediate-risk PE (n=83)	Tenecteplase plus ACT versus ACT only	NYHA III–IV	90 days	5.4 %	20.5 %	NS
			RV dilatation or hypokinesis	90 days	33.3 %	37.8 %	NS
			6-minute walking distance <330 m	90 days	16 %	28 %	NS
TIPES [60]	Intermediate-risk PE (n=58)	Tenecteplase plus ACT versus ACT only	Reduction of RV/LV ratio, mean (s.e.)	24 hours	0.31	0.10	NS
			Hypokinesia of the RV free wall (s.e.)	7 days	0.47	0.34	NS
MAPPET-3 [69]	Intermediate-risk PE (n=256)	Alteplase plus ACT versus ACT only	Death or hemodynamic collapse	30 days	11 %	24.6 %	0.006
			Death	30 days	3.4 %	2.2 %	NS
MOPETT [70]	"Moderate PE" (n=121)	Half-dose of tPA versus ACT only	sPAP (mm Hg), mean (s.d.)	6 months	31	49	<0.001
			sPAP (mm Hg), mean (s.d.)	28 months	28	43	<0.001
			Death	28 months	1.6 %	5.0 %	NS

Note: LV — left ventricular; MAPPETT-3 — Management Strategies and Prognosis of Pulmonary Embolism-3 Trial; MOPETT — Moderate Pulmonary Embolism Treated with Thrombolysis; NS — not significant; NYHA — New York Heart Association; PEITHO — Pulmonary Embolism Thrombolysis; RV — right ventricular; RV/LV ratio — right-to-left ventricular diameter ratio; sPAP — systolic pulmonary artery pressure; TIPES — Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT — Tenecteplase or Placebo: Cardiopulmonary Outcomes at Three Months. Adapted from M.V. Huisman et al. [15]

Patients at high risk with hemodynamic instability represent only a minority of all patients with PE (about 5 %). In turn, hemodynamically stable patients make up a much larger group (>95 %) [51, 66, 67], in which the use of STL in standard dosages is associated with the expectation of favorable hemodynamic and clinical effects [55, 71, 72]. In patients with high-risk acute PE the probability of death is high, which facilitates the decision in favor of STL, compared with patients who are hemodynamically stable [58]. Mortality among hemodynamically unstable patients varies from 35 to 58 % [12, 69].

Before carrying out STL, it is necessary to make sure that the patient does not have relative or absolute contraindications presented in the ESC Guidelines for diagnosis and treatment of acute PE 2014 [1] and modified by H.U. Virk et al. [58] (Table 7).

Absolute contraindications to STL may become relative in patients at the time of onset of the life-threatening condition of high-risk PE. In general, up to 2/3 of patients with acute PE do not receive thrombolytic therapy due to various contraindications [58]. Given the often decisive role of STL in the treatment of PE, which can save the life of the patient, balanced and individual approach to the assessment of absolute and relative contraindications is required.

The undesirable "risk-benefit" ratio in favor of the high probability of severe and potentially fatal hemorrhagic complications was the reason why

Table 7. *Contraindications to systemic thrombolysis in patients with acute pulmonary embolism*

Absolute contraindications	Hemorrhagic stroke or stroke of unknown origin at any time
	Ischemic stroke in the preceding 6 months
	Central nervous system damage or neoplasms
	Recent major trauma/surgery/brain injury in the preceding 3 months
	Gastrointestinal bleeding within the last month
	Active bleeding (excluding menses)
	Suspected aortic dissection Known malignant intracranial neoplasm
Relative contraindications	Transient ischemic attack in the preceding 6 months
	Oral ACT therapy
	Pregnancy, or period within one week postpartum
	Non-compressible puncture site
	Trauma or prolonged cardiopulmonary resuscitation >10 min
	Severe uncontrolled hypertension (systolic >180 mm Hg, diastolic >110 mm Hg)
	Advanced liver disease
	Infective endocarditis
	Active peptic ulcer
	Pericarditis
	Age >75 years
	Recent invasive procedure

Note: Adapted from S. V. Konstantinides et al. [1] and H. U. Virk et al. [58]

scientific societies removed the recommendation for routine use of STL in groups of patients with intermediate and intermediate-high risk [1, 8, 28]. Most scientific societies agree that immediate reperfusion therapy with systemic (intravenous) thrombolytics is indicated for a (small) group of patients with massive PE or high-risk PE, who have stable hypotension or shock (Table 8) [54]. On the other hand, from the point of view of the risk of potentially life-threatening bleeding associated with STL, its use in clearly "stable" patients with submassive PE or intermediate-risk PE is not recommended until hemodynamic decompensation or collapse developing during the ACT [54].

In 2014, the results of the largest to date study (PEITHO) conducted in 1,005 patients with intermediate-high risk PE [73] were published. The results indicate that intravenous use of tPA tenecteplase was accompanied by low levels of mortality or hemodynamic collapse (2.6 % compared to 5.6 % in the group of patients receiving heparin). However, treatment with tenecteplase was associated with significantly increased rates of hemorrhagic strokes and major extracranial bleeding. In particular, in the group of patients with tenecteplase treatment extracranial bleeding was noted in 6.3 % of cases (approximately in one of 16 patients), and among patients receiving anticoagulant — in 1.2 % of cases (in one of 83, $p<0.001$). Thus, the use of STL is indicated in patients who have a massive PE (or high risk), that is, have stable hypotension or shock [1, 8, 28]. This approach contradicts the ideas that existed until recent times regarding the possible clinical benefit of fibrinolysis in apparently stable patients with submassive PE (or intermediate risk) [4]. It should be noted that there are no combined data on the safety of other thrombolytic drugs to date, so the results of a study in 256 patients with intermediate-risk PE treated with alteplase, which did not reveal an increased risk of intracranial or fatal bleeding, are interesting [69]. Obviously, and this is noted by almost all experts, it is necessary to conduct additional studies to improve scientific understanding regarding the use of thrombolytic therapy in hemodynamically stable patients [74].

Table 8. *Recommendations of scientific societies and organizations regarding thrombolytic treatment of acute pulmonary embolism*

Guidelines	Populations	Recommendations	Strength/ class	Level of evidence
AHA, 2011 [8]	Massive PE	Thrombolysis reasonable for patients with acceptable risk of bleeding	IIa	B
	Submassive PE	Thrombolysis considered if there is a clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe right ventricular dysfunction, or major myocardial necrosis) and low risk of bleeding	IIb	C
	Candidates for thrombolysis	Catheter embolectomy and fragmentation or surgical embolectomy for patients with contraindications to fibrinolysis	IIa	C
		Catheter embolectomy and fragmentation or surgical embolectomy for patients who remain unstable after receiving fibrinolysis	IIa	C
ESC, 2014 [1]	High-risk PE	Intravenous anticoagulation with UFH to be initiated without delay	I	C
		Thrombolytic therapy	I	B
		Surgical embolectomy for patients in whom STL is contraindicated or has failed	I	C
		Percutaneous CDT as an alternative to surgical pulmonary embolectomy for patients in whom full-dose STL is contraindicated or has failed	IIa	C
	Intermediate-high risk PE	Routine primary STL not recommended	III	B
		Close monitoring to permit early detection of hemodynamic decompensation	I	B
		Thrombolytic therapy in presence of clinical signs of hemodynamic decompensation	IIa	B
		Surgical embolectomy or percutaneous CDT may be considered if the anticipated risk of bleeding under thrombolytic treatment is high	IIb	C
ACCP, 2016 [28]	With hypotension	In the absence of high bleeding risk: STL	2	B
		In the presence of high bleeding risk or if STL has failed: surgical embolectomy	2	C
	Without hypotension	STL not recommended	1	B
	Acutely deteriorating during ACT	STL	2	C
	Candidates for STL	STL via a peripheral vein or as CDT	2	C

Note: ACCP — American College of Chest Physicians; AHA — American Heart Association; CDT — catheter-directed thrombolysis; ESC — European Society of Cardiology. Green highlights indication for STL, and yellow — the recommendation to consider STL. Adapted from S.V. Konstantinides et al. [54]

The possible effects of STL on the long-term clinical outcome in patients after acute PE are not yet clear. It is believed that treatment with STL in the acute phase of PE can reduce residual or progressive thromboembolic obstruction in the lungs, thereby preventing the development of post-PE syndrome [75, 76]. A prospective cohort study that divided 121 patients with extensive PE (determined by detection of a large thrombus) into two groups: receiving reduced doses of systemic thrombolytic drugs or only anticoagulants, demonstrated that STL was accompanied by a lower rate of pulmonary hypertension after 28 months [70]. However, patients with intermediate-risk PE included in the PEITHO study were followed up for an average period of 38 months, and there were

no differences in long-term survival when comparing groups receiving thrombolytic therapy or only heparin [77].

Systemic thrombolysis with reduced doses of fibrinolytics

As we noted above, intravenous thrombolysis can be associated with life-threatening hemorrhagic complications, in particular intracranial hemorrhage [55]. Unfortunately, the rates of serious bleeding have not decreased over the past 40 years [73] and due to understandable fears there has been a sharp decline in the popularity of this method of treatment in clinical practice, even in patients with cardiogenic shock [54, 56, 78]. In order to improve the safety of fibrinolysis, efforts have been made to explore alternative methods, in particular whether reduced dosages of STL can be safe while maintaining normal perfusion of pulmonary vasculature. A randomized pilot study conducted in 118 patients with high- or intermediate-risk PE provided data that a half-dose of tPA resulted in fewer hemorrhagic complications than the full dose and was just as effective in terms of improving pulmonary vascular obstruction [79]. Unfortunately, the study was terminated prematurely for reasons not related to the protocol, and so the results are not conclusive.

In 2013, the results of the MOPETT trial [70], which studied the efficacy of a half dose ("safe dose") of alteplase (50 mg or 0.5 mg/kg i. v. for 2 h in patients less than 50 kg) in comparison with a group of 121 patients receiving only the ACT with symptomatic so-called "moderate" PE, were published. The authors found that a half dose of alteplase reduced the rate of pulmonary hypertension after 28 months ($P < 0.001$), duration of hospitalization ($P < 0.001$), rate of total mortality and relapses of PE ($P = 0.0489$) without hemorrhagic complications. However, study data again do not allow its complete interpretation due to the lack of study registration, the inclusion of eligibility criteria that do not meet the standard criteria, extremely high level of persistent pulmonary hypertension in the control group, which caused concern whether such a design can be representative based on non-selective selection of patients with really acute PE [54].

The results of a study by T.H. Kiser et al. recently became available [80], and they concern the comparative efficacy and safety of two dosages for the treatment of PE: half (50 mg) and full dose (100 mg) of alteplase. At baseline, patients receiving alteplase at half dose were less likely to require vasopressor therapy (23.3 % vs 39.4 %; $p < 0.01$) and invasive lung ventilation (14.3 % vs 28.5 %; $p < 0.01$) than patients in the group receiving a full dose of alteplase. Half-dose treatment was associated with a higher rate of intensification of therapy (53.8 % and 41.4 %; $p < 0.01$), mainly due to the need for repeated thrombolysis and catheter thrombus fragmentation. At the same time, hospital mortality was comparable (13 % vs 15 %). There was no difference in the level of cerebral hemorrhages, gastrointestinal bleeding, acute anemia due to blood loss [80]. It should be noted that in this study stratification of patients with high- and intermediate-risk PE was performed only on the basis of the need for vasopressors, which certainly increased the number of patients with high-risk PE [81].

In the treatment of 45 patients with PE of intermediate-high risk using reduced thrombolytic dosage (initially, infusion of 50 mg of alteplase for 2 h was performed followed by systemic administration of heparin for at least 24 h), excellent clinical outcome indicators were noted with a low rate of further hemodynamic deterioration, a short period of stay in the intensive care unit (4.2 days) and in hospital (7.4 days), excellent survival at the time of discharge (97.8 %) and on the 30th day of the disease (95.6 %) [82]. Unfortunately, despite the "half" thrombolytic therapy in the group of patients with low risk of hemorrhagic complications the authors often observed moderate or massive bleedings (in 5 patients, 11 %).

Although systemic fibrinolytic therapy in "half-dose" is more attractive for many doctors, the evidence in its favor should be considered preliminary at best, and such unapproved regimes cannot be recommended at the present stage [54, 81, 83]. Catheter techniques can be considered as an alternative option for patients with PE requiring active reperfusion treatment due to initial or developing hemodynamic decompensation, but in the presence of absolute or relative contraindications to systemic fibrinolysis [4, 6, 83].

References:

1. Konstantinides S. V., Torbicki A., Agnelli G., et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) endorsed by the european respiratory society (ERS). European Heart Journal. 2014; 35(43): 3033–69, 3069a-3069k. DOI:10.1093/eurheartj/ehu283.
2. Tritschler T, Kraaijpoel N, Le Gal G, Wells PS. Venous thromboembolism: advances in diagnosis and treatment. JAMA. 2018 Oct 16;320(15):1583-1594. doi: 10.1001/jama.2018.14346.
3. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med. 2013;126(9): 832.e13-832. doi:10.1016/j.amjmed.2013.02.024
4. Konstantinides S. V., Barco S., Lankeit M., Meyer G. Management of pulmonary embolism: an update. J Am Coll Cardiol. 2016 Mar 1;67(8):976-90. doi: 10.1016/j.jacc.2015.11.061.
5. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications: a systematic review and meta-analysis of the management outcome studies. J Thromb Haemost. 2010;8(8):1716-1722. doi:10.1111/j.1538-7836.2010.03938.x
6. Vatutin N. T., Taradin G. G., Kanisheva I. V., et al. The role of interventional methods in treatment of pulmonary embolism. The Russian Archives of Internal Medicine. 2018;8(5):346-360. [In Russian] doi: 10.20514/2226-6704-2018-0-5-346-360
7. Torbicki A, Perrier A, Konstantinides S, et al.; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008 Sep;29(18):2276-315. doi: 10.1093/eurheartj/ehn310.
8. Jaff M. R., McMurtry M. S., Archer S. L., et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a Scientific Statement from the American Heart Association. Circulation 2011;123(16):1788-830. doi: 10.1161/CIR.0b013e318214914f.
9. Sekhri V, Mehta N, Rawat N, et al. Management of massive and nonmassive pulmonary embolism. Arch Med Sci. 2012 Dec 20;8(6):957-69. doi: 10.5114/aoms.2012.32402.
10. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol. 2013 Spring;18(2):129-38.
11. Corrigan D, Prucnal C, Kabrhel C. Pulmonary embolism: the diagnosis, risk-stratification, treatment and disposition of emergency department patients. Clin Exp Emerg Med. 2016 Sep; 3(3): 117–125. doi: 10.15441/ceem.16.146
12. Miller G. A., Sutton G. C., Kerr I. H., et al. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br Med J. 1971;2:681– 684.
13. Aujesky D., Obrosky D. S., Stone R. A., et al. Derivation and validation of a prognostic model for pulmonary embolism. Am. J. Respir. Crit. Care Med. 2005; 172: 1041–1046.
14. Jiménez D, Aujesky D, Moores L, et al.; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010 Aug 9;170(15):1383-9. doi: 10.1001/archinternmed.2010.199
15. Huisman M. V., Barco S., Cannegieter S. C., et al. Pulmonary embolism. Nat. Rev. Dis. Primers. 2018 May 17;4:18028. doi: 10.1038/nrdp.2018.28.
16. Kabrhel C., Jaff M. R., Channick R. N., et al. A multidisciplinary pulmonary embolism response team. CHEST Journal. 2013; 144(5):1738-1739.
17. Root C. W., Dudzinski D. M., Zakhary B., et al. Multidisciplinary approach to the management of pulmonary embolism patients: the pulmonary embolism response team (PERT). J Multidiscip Healthc. 2018 Apr 5;11:187-195. doi: 10.2147/JMDH.S151196.
18. Petriş AO, Konstantinides S, Tint D, et al. Therapeutic advances in emergency cardiology: acute pulmonary embolism. Am J Ther. 2019 Mar/Apr;26(2):e248-e256. doi: 10.1097/MJT.0000000000000917.
19. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. Lancet 1960;275(7138):1309–12.
20. Jolly M., Phillips J. Pulmonary embolism: current role of catheter treatment options and operative thrombectomy. Surg. Clin. North. Am. 2018 Apr;98(2):279-292. doi: 10.1016/j.suc.2017.11.009.
21. Chopard R, Andarelli JN, Humbert S, et al. Prescription patterns of direct oral anticoagulants

in pulmonary embolism: A prospective multicenter French registry. Thromb Res. 2019 Feb;174:27-33. doi: 10.1016/j.thromres.2018.12.013.
22. Stein PD, Dalen JE, Matta F, et al. Optimal therapy for unstable pulmonary embolism. Am J Med. 2019 Feb;132(2):168-171. doi: 10.1016/j.amjmed.2018.09.018.
23. Borohovitz A, Weinberg MD, Weinberg I. Pulmonary embolism: Care standards in 2018. Prog Cardiovasc Dis. 2018 Mar — Apr;60(6):613-621. doi: 10.1016/j.pcad.2017.12.005.
24. Hepburn-Brown M, Darvall J, Hammerschlag G. Acute pulmonary embolism: a concise review of diagnosis and management. Intern Med J. 2019 Jan;49(1):15-27. doi: 10.1111/imj.14145
25. Kearon C, AgenoW, Cannegieter SC, et al.; Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14(7):1480-1483. doi:10.1111/jth.13336
26. Carrier M., Le G. G., Wells P. S., et al. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann. Intern. Med. 2010 May 4;152(9):578-89. doi: 10.7326/0003-4819-152-9-201005040-00008.
27. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018 Nov 27;2(22):3257-3291. doi: 10.1182/bloodadvances.2018024893.
28. Kearon C., Akl E. A., Ornelas J., et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315-352. doi: 10.1016/j.chest.2015.11.026.
29. Heidbuchel H., Verhamme P., Alings M., et al. EHRA practical guide on the use of new oral anticoagulants in patients with nonvalvular atrial fibrillation: executive summary. Eur Heart J. 2013 Jul; 34(27): 2094-2106. doi: 10.1093/eurheartj/eht134.
30. Beyer-Westendorf J., Verhamme P., Bauersachs R. Betrixaban for prevention of venous thromboembolism in acute medically ill patients. Eur Heart J Suppl. 2018 May;20(Suppl E):E16-E22. doi: 10.1093/eurheartj/suy017
31. van Es N., Coppens M., Schulman S., et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014; Sep 18;124(12):1968-75. doi: 10.1182/blood-2014-04-571232.
32. van der Hulle T., Kooiman J., den Exter P. L., et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J. Thromb. Haemost. 2014;12(3):320-8. doi: 10.1111/jth.12485.
33. Arcadi FA, Portaro S, Giorgianni R, et al. New versus old oral anticoagulants: how can we set the scale needle? Considerations on a case report. Medicina (Kaunas). 2019 Mar 17;55(3). pii: E71. doi: 10.3390/medicina55030071
34. Dawwas GK, Brown J, Dietrich E, et al. Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. Lancet Haematol. 2019 Jan;6(1):e20-e28. doi: 10.1016/S2352-3026(18)30191-1.
35. Schulman S., Kearon C., Kakkar A. K., et al.; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52. doi: 10.1056/NEJMoa0906598.
36. Schulman S., Kakkar A. K., Goldhaber S. Z., et al.; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764-72. doi: 10.1161/CIRCULATIONAHA.113.004450
37. Bauersachs R., Berkowitz S. D., Brenner B., et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-510. doi: 10.1056/NEJMoa1007903.
38. Büller H. R., Prins M. H., Lensin A. W., et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012; 366(14):1287-97. doi: 10.1056/NEJMoa1113572
39. Agnelli G., Buller H. R., Cohen A., et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808. doi: 10.1056/NEJMoa1302507.
40. Büller H. R., Décousus H., Grosso M. A., et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406-15. doi: 10.1056/NEJMoa1306638.
41. Martin K., Beyer-Westendorf J., Davidson B. L., et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the

ISTH. J. Thromb. Haemost. 2016 Jun;14(6):1308-13. doi: 10.1111/jth.13323.
42. Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. Blood. 2019;133(5):425-435. doi:10.1182/blood-2018-06-820746
43. Shakur H, Roberts I, Bautista R, et al.; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010; 376(9734):23-32. doi: 10.1016/S0140-6736(10)60835-5.
44. Douxfils J, Gosselin RC. Laboratory assessment of direct oral anticoagulants. Semin Thromb Hemost. 2017 Apr;43(3):277-290. doi: 10.1055/s-0036-1597296
45. Mosarla RC, Vaduganathan M, Qamar A, et al. Anticoagulation strategies in patients with cancer: JACC Review Topic of the Week. J Am Coll Cardiol. 2019 Mar 26;73(11):1336-1349. doi: 10.1016/j.jacc.2019.01.017
46. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003 Jul 10;349(2):146-53.
47. Lee AYY, Kamphuisen PW, Meyer G, et al.; CATCH Investigators.. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA. 2015 Aug 18;314(7):677-686. doi: 10.1001/jama.2015.9243.
48. Raskob GE, van Es N, Verhamme P, et al.; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018; 378:615–24. doi: 10.1056/NEJMoa1711948
49. Young A, Marshall A, Thirlwall J, et al. Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism: results of the Select-D Pilot Trial. Blood 2017; 130:625.
50. Li A, Garcia DA, Lyman GH, et al. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. Thromb Res 2018: doi:10.1016/j.thromres.2018.02.144.
51. Peacock WF, Singer AJ. Reducing the hospital burden associated with the treatment of pulmonary embolism. J Thromb Haemost. 2019 Mar 9. doi: 10.1111/jth.14423
52. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018 Sep;16(9):1891-1894. doi: 10.1111/jth.14219.
53. Bartel B. Systemic thrombolysis for acute pulmonary embolism. Hosp. Pract. 2015;43(1):22-7. doi: 10.1080/21548331.2015.1001302.
54. Konstantinides S. V., Barco S. Systemic thrombolytic therapy for acute pulmonary embolism: who is a candidate? Semin. Respir. Crit. Care Med. 2017 Feb;38(1):56-65. doi: 10.1055/s-0036-1597560.
55. Marti C., John G., Konstantinides S., et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2015; 36(10):605-14. doi: 10.1093/eurheartj/ehu218.
56. Stein P. D., Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med. 2012; 125(5):465-70. doi: 10.1016/j.amjmed.2011.10.015.
57. Murphy E, Lababidi A, Reddy R, et al. The role of thrombolytic therapy for patients with a submassive pulmonary embolism. Cureus. 2018;10(6):e2814. doi:10.7759/cureus.2814
58. Virk HUH, Chatterjee S, Sardar P, et al. Systemic thrombolysis for pulmonary embolism: evidence, patient selection, and protocols for management. Interv Cardiol Clin. 2018 Jan;7(1):71-80. doi: 10.1016/j.iccl.2017.08.001.
59. Nikitina O. V., Mikhailov I. P., Kudryashova N. Y., et al. Thrombolytic and anticoagulant therapy for pulmonary embolism: an effect on pulmonary perfusion (part 2). Russian Sklifosovsky Journal of Emergency Medical Care. 2018; 7(2): 134–143. DOI: 10.23934/2223-9022-2018-7-2-134-143 [in Russian].
60. Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010;125(3):e82–e86. doi: 10.1016/j.thromres.2009.09.017
61. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. J Thromb Thrombolysis. 1995;2(3):227-229.
62. Kline J. A., Steuerwald M. T., Marchick M. R., et al. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. Chest 2009;136:1202-10.
63. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014 Jun 18;311(23):2414-21. doi: 10.1001/jama.2014.5990

64. Bougouin W., Marijon E., Planquette B., et al.; on behalf from the Sudden Death Expertise Center. Pulmonary embolism related sudden cardiac arrest admitted alive at hospital: Management and outcomes. Resuscitation. 2017;115:135-140. doi: 10.1016/j.resuscitation.2017.04.019.
65. Zuin M, Rigatelli G, Carraro M, et al. Systemic thrombolysis in haemodynamically unstable pulmonary embolism: The earlier the better? Thromb Res. 2019 Jan;173:117-123. doi: 10.1016/j.thromres.2018.11.029.
66. Fernandes CJCDS, Jardim CVP, Alves JL Jr, et al. Reperfusion in acute pulmonary thromboembolism. J Bras Pneumol. 2018 Jun 7:0. doi: 10.1590/S1806-37562017000000204.
67. Becattini C., Agnelli G., Lankeit M., et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur. Respir. J. 2016;48(3):780-6. doi: 10.1183/13993003.00024-2016.
68. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost. 2014 Apr;12(4):459-68. doi: 10.1111/jth.12521.
69. Konstantinides S., Geibel A., Heusel G., et al.; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002 Oct 10;347(15):1143-50.
70. Sharifi M., Bay C., Skrocki L., et al.; "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol. 2013;111(2):273-7. doi: 10.1016/j.amjcard.2012.09.027.
71. Riva N., Puljak L., Moja L., et al. Multiple overlapping systematic reviews facilitate the origin of disputes: the case of thrombolytic therapy for pulmonary embolism. J Clin Epidemiol. 2018;97:1-13. doi: 10.1016/j.jclinepi.2017.11.012.
72. Teleb M, Porres-Aguilar M, Anaya-Ayala JE, et al. Potential role of systemic thrombolysis in acute submassive intermediate risk pulmonary embolism: review and future perspectives. Ther Adv Cardiovasc Dis. 2016;10(2):103–110. doi:10.1177/1753944716630694
73. Meyer G., Vicaut E., Danays T., et al.; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370(15):1402-11. doi: 10.1056/NEJMoa1302097.
74. Miranda CH. Use of thrombolytic agents in the treatment of acute pulmonary thromboembolism: things are not as simple as you might think. J Bras Pneumol. 2019 Feb 11;45(1):e20180297. doi: 10.1590/1806-3713/e20180297.
75. Klok F. A., Dzikowska-Diduch O., Kostrubiec M., et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J. Thromb. Haemost. 2016;14(1):121-8. doi: 10.1111/jth.13175
76. Goldhaber S. Z. PEITHO Long-Term Outcomes Study: Data Disrupt Dogma. J Am Coll Cardiol. 2017 Mar 28;69(12):1545-1548. doi: 10.1016/j.jacc.2017.01.027.
77. Konstantinides S. V., Vicaut E., Danays T., et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol. 2017;69(12):1536-1544. doi: 10.1016/j.jacc.2016.12.039.
78. Jiménez D, de Miguel-Díez J, Guijarro R, et al; RIETE Investigators. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE Registry. J Am Coll Cardiol. 2016;67(2):162–170 doi: 10.1016/j.jacc.2015.10.060.
79. Wang C, Zhai Z, Yang Y, et al.; China Venous Thromboembolism (VTE) Study Group. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest 2010; Feb;137(2):254-62. doi: 10.1378/chest.09-0765.
80. Kiser TH, Burnham EL, Clark B, et al. Half-dose versus full-dose alteplase for treatment of pulmonary embolism. Crit Care Med. 2018 Oct;46(10):1617-1625. doi: 10.1097/CCM.0000000000003288.
81. Jin Q, Luo Q, Zhao Z, et al. Half-dose versus full-dose alteplase therapy in pulmonary embolism: does half dose really lose? Crit Care Med. 2018 Dec;46(12):e1223-e1224. doi: 10.1097/CCM.0000000000003384
82. Rothschild DP, Goldstein JA, Bowers TR. Low-dose systemic thrombolytic therapy for treatment of submassive pulmonary embolism: Clinical efficacy but attendant hemorrhagic risks. Catheter Cardiovasc Interv. 2019 Feb 15;93(3):506-510. doi: 10.1002/ccd.28042.
83. Halaby R, Giri J. Keep it simple? Half-dose systemic thrombolysis or catheter-directed thrombolysis for pulmonary embolism. Vasc Med. 2019 Mar 5:1358863X18824653. doi: 10.1177/1358863X18824653.

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EPIDEMIOLOGICAL INDICATOR VALUE IN THE IODINE AVAILABILITY ASSESSMENT — EVIDENCE FROM THE REGIONS OF THE RUSSIAN FEDERATION

Abstract

Background: In the Russian Federation, newborn screening comprises thyroid stimulating hormone determination to exclude primary congenital hypothyroidism. Screening is carried out throughout Russia. Neonatal TSH can be used to assess iodine deficiency and monitor iodine prevention programs.

Objective: To assess and compare official statistical data on congenital hypothyroidism, the prevalence of hypothyroidism and iodine deficiency syndrome in children, as well as urinary iodine in the Russian regions.

Materials and methods: The level of neonatal TSH was determined in 97.69% of children born in the Russian Federation in 2017. This article represents the results on the prevalence of hypothyroidism in the regions with various iodine availability. The correlation analysis was used to assess the relationship of CH incidence in newborns and iodine availability.

Results: The calculated correlation coefficient, which was 0.2, reflects a weak relationship between the degree of iodine deficiency in the region and the number of newborns diagnosed with congenital hypothyroidism.

Conclusions: In the Russian Federation, a law on universal salt iodization does not exist, and many regions are still in conditions of moderate or severe iodine deficiency. To assess the iodine status in these particular regions, we could use the results of newborn TSH screening.

Key words: *congenital hypothyroidism, newborn screening, iodine deficiency, thyroid-stimulating hormone*

Conflict of Interests

The authors declare no conflict of interests.

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Search and analytical work on the preparation of the manuscript was carried out as part of the state task: a scientific assessment of the need for additional regulatory and other measures to eliminate iodine deficiency in pilot regions with severe iodine deficiency.

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CH — congenital hypothyroidism, IDD — iodine deficiency disorders, Me — median, fT4 — free thyroxine, TSH — thyroid stimulating hormone

Introduction

Iodine deficiency, detected in the environment, as well as related disorders (IDD) form a wide range of medical and social problems around the world due to high prevalence and serious clinical consequences [1].

Newborn screening for thyroid-stimulating hormone is carried out throughout the Russian Federation.

Based on these results, we can assume the presence of factors in this environment that affect the thyroid, namely the availability of iodine. In newborns, pituitary thyroid-stimulating hormone (TSH) is inversely related to the level of urinary iodine [2]. The results of newborn screening for hypothyroidism are used to assess the prevalence and severity of iodine deficiency disorders [3]. Maternal iodine deficiency is the most common cause of increased TSH levels in infants in iodine-deficient areas. In 1994, the World Health Organization (WHO) established criteria for neonatal hyperthyrotropinemia for regions with mild, moderate and severe iodine deficiency. According to the recommendations, neonatal TSH levels above 5 μIU/L are determined in no more than 3% of newborns in areas with high iodine availability, in regions with mild iodine deficiency this figure is 3–19.9%, with moderate — 20–39.9% [4]. For those countries where the universal salt iodization program is implemented, newborn screening may be a relevant indicator of iodine deficiency and related diseases. Neonatal TSH above 5 μIU/L has financial advantages for the assessment of iodine deficiency, because it covers all newborns in this area, and does not require additional studies [5]. Iodine deficiency is the most common but preventable cause of mental retardation worldwide. This condition can be prevented if you start taking iodine prophylactically before pregnancy [6]. The problem of endemic cretinism is of high relevance for regions with severe iodine deficiency.

Objective

To evaluate and compare the official statistics on congenital hypothyroidism, statistical reporting of the prevalence of hypothyroidism and iodine deficiency syndrome in children, as well as urinary iodine in the regions of the Russian Federation.

Materials and Methods

Study Design

The study was conducted using statistical data received from FSBI Research Centre of Medical Genetics (data of federal screening for congenital hypothyroidism). The Table presents the number and percentage of children with TSH >20 μU/mL. Data on the incidence of hypothyroidism in older age and congenital iodine deficiency syndrome were obtained from f. 12 of Rosstat of Russia. Data on median urinary iodine were obtained from studies conducted by FSBI Endocrinology Research Centre of the Ministry of Health of Russia in the regions of the Russian Federation. The study is observational, continuous, and multicenter.

Eligibility Criteria

The study enrolled 97.69% of all newborns (in absolute numbers — 1 632 801 newborns) in the Russian Federation in 2017. In addition, children and adolescents in the Russian Federation, male and female, living in different regions of the Russian Federation and suffering from diseases primarily caused by iodine deficiency in the diet were included.

Description of Medical Intervention

Determination of thyroid-stimulating hormone in a whole-blood sample of newborns was carried out via immunofluorescence method using DELFIA Neonatal TSH reagent kit (PerkinElmer, Inc., USA.) The threshold value for the detection

of congenital hypothyroidism was TSH >20 μU/mL. At the stage of primary screening congenital and transient hypothyroidism was not differentiated, but it can be noted that transient hypothyroidism is accompanied by relatively high levels of TSH (9–40 of μU/mL) than congenital one (TSH level in most cases is more than 40 μU/mL). Such conditions can be distinguished at the 2nd stage of screening in outpatient settings by detecting serum TSH and fT4 [6].

Subgroup Analysis

Patients were divided into two groups according to age: newborns and children under 14 years. Prevalence is estimated for the following diseases (statistical reporting names are presented in accordance with ICD-10): congenital iodine deficiency syndrome, subclinical hypothyroidism due to iodine deficiency and other forms of hypothyroidism.

Ethical Review

The Local Ethical Committee of FSBI Endocrinology Research Centre of Ministry of Health of Russia approved this study on 13.02.2019.

Statistical Analysis

Sample size calculation principles: The study was conducted on the principle of a continuous, rather than a sample study, which may be justification for not calculating the minimum sample size.

Methods of statistical data analysis: To assess the relationship between the number of newborns diagnosed with CH in regions with different iodine levels, a correlation analysis was performed using the non-parametric Spearman method. The correlation coefficient for median urinary iodine and percentage of newborns with CH was calculated using Statistica data analysis software system, version 13, TIBCO Software Inc. (2017). This correlation coefficient r is significant for $\rho < 0.05000$

Results

Data on the sample of patients were obtained on the basis of official statistics. The sample included persons of both sexes living in different regions of the Russian Federation.

Table 1 presents the results of comparing data on the incidence and prevalence of hypothyroidism in different regions of the Russian Federation with different iodine availability. In these regions, epidemiological studies were conducted jointly with FSBI Endocrinology Research Centre of the Ministry of Health of Russia.

Table 2 presents the results of statistical processing.

The calculated correlation coefficient, which was 0.2, reflects a weak relationship between the degree of iodine deficiency in the region and the number of newborns diagnosed with congenital hypothyroidism. This may be due to various factors. First, attention is drawn to possible inaccuracies in official statistics, which is seen in the analysis of the number of newborns with CH and the number of children 0–14 years old diagnosed with hypothyroidism.

Discussion

Discussion of Main Study Result

Newborn screening for TSH is primarily aimed at detecting congenital hypothyroidism due to congenital thyroid dysgenesis and, in rare cases, genetic factors. For the assessment of iodine availability in the regions, it may be necessary to use a more sensitive indicator, for example, neonatal TSH >5 μU/mL. However, as many neonatal TSH studies have shown, newborn screening may be useful for detecting moderate to severe iodine deficiency, but should be cautiously recommended for assessment in regions with mild iodine deficiency. For example, in Georgia, where Me of urinary iodine is 297 μg/L in schoolchildren and 211 μg/L in pregnant women, in some areas, the percentage of newborns with TSH >5 μU/mL was 4.4%, which can be falsely interpreted as moderate iodine deficiency [7]. In Austria, despite the relatively low median of urinary iodine (85 μg/L in pregnant women), the percentage of newborns with elevated TSH levels was much lower — 2.2% [8]. In Belgium, there is a mild iodine deficiency in pregnant women, but the incidence of increased

Table 1. *Data on congenital hypothyroidism and urinary iodine in the Russian regions*

Regions	Urinary iodine median (μg/L) [min; max]	Number of newborns	CG (abs)	CG (%)	Hypothyroidism incidence (0–14)	Congenital iodine deficiency syndrome (0–14)
Moscow	104.5 [70.9; 135.5]	128,826	67	0.05	0	0
Moscow Region	74.2 [47.3; 129]	84,448	41	0.04	783	103
Belgorod Region	57.3 [49; 86.0]	14,918	3	0.02	281	302
Ivanovo Region	105.4 [36; 624]	10,320	1	0.009	42	3
Kaluga Region	66.2 [46.3; 94.2]	10,720	5	0.04	52	7
Smolensk Region	61 [12; 400]	8,560	2	0.023	102	7
Ulyanovsk Region	81.9 [58.9; 156]	11,901	2	0.016	714	12
Voronezh Region	152.4 [69.8; 209]	22,550	8	0.035	421	21
Komi Republic	57.2 [43.1; 108]	9,484	2	0.021	228	12
Murmansk Region	41.6 [4.7; 68.4]	7,715	2	0.025	259	2
Arkhangelsk Region	63.7 [39; 84]	11,502	3	0.026	94	1
Volgograd Region	52.8 [38.9;79]	24,512	2	0.008	447	13
Astrakhan Region	25.9 [18.8; 32.2]	12,189	4	0.03	60	0
Krasnodar Region	79.3 [47.3; 126]	65,942	22	0.03	741	149
Kabardino-Balkaria	141.1 [109; 168]	9,234	2	0.021	179	32
Republic of Tatarstan	72.1 [46.9; 88.9]	48,120	15	0.03	805	172
Udmurtia	68.3 [30.8; 125]	17,903	11	0.06	189	10
Chuvash republic*	38.2 [6.8; 250]	14,044	1	0.007	180	0
Penza Region	70 [23; 308]	11,836	1	0.008	494	17
Nizhniy Novgorod Region	70.9 [46; 129]	33,575	13	0.03	210	0
Kirov Region	65.9 [43.8; 101]	13,503	8	0.05	683	0
Perm Region	95.5 [16.3; 351]	31,663	7	0.022	1137	29
Sverdlovsk Region	96 [55; 144.7]	53,443	14	0.026	1339	39
Khanty-Mansi Autonomous Area	229.7 [5.6; 837]	22,752	7	0.03	1396	54
Tuva Republic	123 [23; 436]	6,989	3	0.04	165	15
Samara Region	100.8 [23; 326]	34,258	10	0.029	684	47

*iodine deficiency of moderate severity according to Me of urinary iodine

Table 2. *Statistical data*

Indicator	Result
r — correlation coefficient	0.261
ρ — validity of the correlation coefficient	0.198
t — significance of the correlation coefficient	4.98

TSH during follow-up was low, and the authors also note a low sensitivity of this indicator for populations with mild iodine deficiency or optimal iodine intake [9]. In the regions of the Russian Federation, studies on the possibility of using neonatal TSH as a marker of iodine deficiency were also conducted. In the Tyumen Region the TSH levels of above 5 μU/mL were analyzed. According to the results of the study, a reduction in the rate of hyperthyrotropinemia up to 5% was shown, which indicates an improvement of the iodine status on the back of preventive measures. Analysis of various parameters of iodine deficiency severity showed that in the region with iodine prevention among pregnant women, monitoring of iodine deficiency disorders via hyperthyrotropinemia detection is limited to pregnant women themselves, because the iodine consumption is monitored in this group only [5]. In the Krasnoyarsk Region, TSH levels in the whole blood of newborns were analyzed. The rate of neonatal TSH >5 μU/mL corresponded to mild iodine deficiency and moderate one in some regions, which generally reflects the improving iodine availability in regions with severe environmental iodine deficiency [10]. A study conducted in Moscow found that with the implementation of measures to prevent iodine deficiency, the rate of neonatal hyperthyrotropinemia significantly decreased and amounted to 0.44% in 2000 and 0.60% in 2006 [11]. Considering all the above, neonatal TSH above 5 μU/mL can be used to assess iodine status in pregnant women in a population with moderate and severe iodine deficiency. For the general population, in future it is possible to assess thyroglobulin in both newborns and school-age children as a marker of iodine deficiency in the regions [12]. Thyroglobulin is negatively associated with urinary iodine and significantly elevated in children with severe iodine deficiency. Since there are practically no anti-thyroglobulin antibodies in children, its concentration may reflect the true pattern of iodine deficiency in the region [13].

Study Limitations

It is impossible to completely exclude the human factor when assigning a diagnosis according to ICD-10, which can significantly distort the statistical reporting data.

Conclusions

The level of thyroid stimulating hormone in newborns may be a sensitive marker of iodine deficiency when using a threshold TSH level >5 μU/mL. TSH >20 μU/mL should be used to detect primary congenital hypothyroidism associated with genetic factors. Given the absence of a law on universal salt iodization in Russia, many regions are still in conditions of moderate or severe iodine deficiency, and the use of newborn screening for TSH in these regions is possible to assess the iodine status of the population. In regions with mild iodine deficiency or optimal iodine availability, it is necessary to use other markers, including thyroglobulin.

References:

1. Dedov I. I., Mel'nichenko G. A., Troshina E. A. et al. Iodine deficiency is a threat to the health and development of Russian children. Ways to solve the problem: National Report. M.: UN Children's Fund (UNICEF) in the Russian Federation. 2006; 123 p. [in Russian]
2. Gusina N. B., Zinovik A. V., Kolkova T. V. The results of population neonatal screening for congenital hypothyroidism reflect the effect of iodine prophylaxes in Belarus. Clinical and experimental thyroidology. 2010; 6(2): 40–45. [in Russian]. doi.org/10.14341/ket20106240-45
3. Delange F. M. Neonatal screening for congenital hypothyroidism: results and perspectives. Horm. Res. 1997; 48: 51–61. doi.org/10.1159/000185485
4. World Health Organization. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers. 3rd ed. Geneva; 2007.
5. Suplotova L. A., Makarova O. B., Koval'zhina L. S. Neonatal gipertireotropinemiya — an indicator of the severity of iodine deficiency in the population? Clinical and experimental thyroidology. 2015; 11(3): 47–53. [in Russian]. doi: 10.14341/ket2015347-53
6. Chikulaeva O. A. The federal clinical recommendations on diagnostics and treatment of congenital hypothyroidism in the children. Problems of endocrinology. 2014; 60(6): 53–66 [in Russian]. doi:10.14341/probl201460653-66
7. Barnabishvilli N., Gerasimov G. A., Azikuri T. The results of neonatal TSH screening do not agree with indicators

of the optimal iodine status of pregnant women in the Republic of Georgia. Clinical and experimental thyroidology. 2018; 14(2): 81–85. doi: 10.14341/ket9777
8. Travers C. A., Guttikonda K., Norton C. A. et al. Iodine status in pregnant women and their newborns: are our babies at risk of iodine deficiency? Med J Aust. 2006; 184(12): 617–620
9. Vandevijvere S., Coucke W., Vanderpas J. et al. Neonatal thyroidstimulating hormone concentrations in Belgium: a useful indicator for detecting mild iodine deficiency? PLoS One. 2012; 7(10): e47770. doi: 10.1371/journal.pone.0047770
10. Osokina I. V., Osokina D. E., Manchouk V. T. Monitoring of iodine deficiency in Central Siberia according the results of neonatal TSH-screening. Clinical and experimental thyroidology. 2013; 9(2): 41–44 [in Russian]. doi.org/10.14341/ket20139241-44
11. Duhareva O. V., Antsiferov M. B. Results of monitoring iodine deficiency in Moscow children. Pediatria. 2007; 86(3): 44–47 [in Russian].
12. Ma Z. F., Skeaff S. A. Thyroglobulin as a biomarker of iodine deficiency: a review. Thyroid. 2014; 24(8): 1195–1209. doi: 10.1089/thy.2014.0052
13. Zimmermann M. B., Aeberli I., Andersson M. et al. Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100-299 mug/L: a UNICEF/ICCIDD study group report. J Clin Endocrinol Metab. 2013; 98(3): 1271–1280. doi: 10.1210/jc.2012-3952.

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THE ASSOCIATION BETWEEN INTRACARDIAC HEMODYNAMICS AND LUNG FUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Abstract

Study objective. To assess the association between intracardiac hemodynamics and airway obstruction with pulmonary hyperinflation in patients with chronic obstructive pulmonary disease. **Materials and methods.** Ninety-six patients with chronic obstructive pulmonary disease, aged 40 to 75 years, without concomitant cardiovascular disease, were examined and divided into 4 groups according to the severity of the disease. The patients underwent general clinical examination, spirometry, 24-hour pulse oximetry and echocardiography with assessment of linear and volumetric parameters, as well as diastolic function of left and right ventricles. **Results.** Linear and volumetric parameters of the left ventricle, LV myocardial mass and geometry in the examined patients with chronic obstructive pulmonary disease matched threshold values. The progression of the severity of chronic obstructive pulmonary disease was accompanied by decrease of the end-diastolic size of the left ventricle, ratio of peak early to late diastolic filling velocity for the left ventricle (E/A) without significant changes in the left ventricle isovolumetric relaxation time (IVRT). Moderate correlations of the inspiratory capacity with the end-diastolic size of the left ventricle (r=0.612; p=0.001) and the left ventricle E/A (r=0.464; p=0.001); forced expiratory volume in 1 second (FEV_1) with the left ventricle E/A (r=0.600; p=0.011) were established. As a result of the logistic regression performed, the predictor value of the inspiratory capacity was confirmed (Wald χ^2 — 5.795; p=0.024). Impairment of left ventricular diastolic function of grade I was revealed in 12 (31.6 %) patients in group 2, in 7 (24.1 %) patients in group 3, and in 9 (56.2 %) patients in group 4. **Conclusion.** Airway obstruction severity and pulmonary hyperinflation progression in patients with chronic obstructive pulmonary disease and without concomitant cardiovascular disease is associated with a decrease of left ventricular size and diastolic filling, contributes to the development of the left ventricular diastolic dysfunction, predominantly due to the decrease in filling velocity parameters.

Keywords: *COPD, pulmonary hyperinflation, inspiratory capacity, left ventricle diastolic dysfunction*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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TAPSE — tricuspid annular plane systolic excursion; ABP — arterial blood pressure; RVBD — right ventricle basal diameter, DBP — diastolic blood pressure; IC — inspiratory capacity; LVPW — left ventricular posterior wall thickness; LVMMR — left ventricular myocardial mass ratio; EDS — end diastolic size; LV — left ventricle; LA — left atrium; LAVI/BSA — left atrial volume index/body surface area; FEV_1 — forced expiratory volume in 1 second; RA — right atrium; RA/BSA — right atrial volume index/body surface area; BSA — body surface area; SBP — systolic blood pressure; PASP — pulmonary artery systolic pressure; RVW — right ventricular wall thickness; COPD — chronic obstructive pulmonary disease; DT — early diastolic filling deceleration time; E/A — ratio of peak early to late diastolic filling velocity; LV E/e' — ratio of early transmitral flow velocity (E) to average mitral annular velocity (e'); LV-IVRT — isovolumetric relaxation time of the left ventricle; SpO_2 — average daily saturation

The results of a number of recent studies indicate an adverse effect of pathophysiological features of chronic obstructive pulmonary disease (COPD) on diastolic function of the right and left ventricle in the absence of cardiovascular diseases, significant risk factors for their development, and chronic pulmonary hypertension. It was shown that besides the traditional factors (age, hypertension, diabetes mellitus, obesity) affecting the left ventricle (LV) diastolic function, bronchial obstruction and pulmonary hyperinflation also lead to hemodynamic disorders [1–6]. The results of the prospective, observational COSYCONET study (COPD and Systemic Consequences — Comorbidities Network) to assess COPD progression over time and interactions with comorbidities demonstrated the predictor value of the pulmonary hyperinflation (intrathoracic lung volume) and bronchial obstruction (forced expiratory volume in 1 second — FEV_1) parameters for development of LV diastolic filling impairment [3]. It should be recognized that studies on the association between intracardiac hemodynamics and lung function parameters in patients with COPD are rare and controversial.

The objective of our study is to assess the association between intracardiac hemodynamics and parameters of airway obstruction and pulmonary hyperinflation in patients with COPD.

Materials and methods

Comparative cross-sectional study was conducted in 96 patients with COPD at the state outpatient clinic. The Study Protocol was approved by the Ethics Committee of the Federal State Budgetary Institution of Higher Education "State University of Medicine and Dentistry named after A.I. Evdokimov" of the Ministry of Health of Russia.

Inclusion criteria:
1. Men and women aged 40 to 75 years;
2. Stage 1–4 COPD (GOLD);
3. Informed patient consent to participate in the study.

Exclusion criteria:
1. Exertional angina pectoris;
2. History of myocardial infarction/acute cerebrovascular accident;
3. Cardiac rhythm disturbances;
4. Chronic heart failure;
5. Grade 2–3 hypertension;
6. Type 1 or 2 diabetes mellitus;
7. Chronic kidney disease;
8. Body mass index ≥ 30 kg/m^2;
9. Moderate/severe COPD exacerbation in the previous 30 days;
10. Malignancy.

COPD pharmacotherapy included long-acting bronchodilators (anticholinergic and/or β_2-agonists), the patients received monotherapy with angiotensin-converting enzyme inhibitors, angiotensin I receptor antagonists or diuretic for concomitant arterial hypertension grade 1.

Anthropometric parameters (height, weight, Kettle body mass index — BMI), as well as office blood pressure (BP) by Korotkoff's method, and cholesterol, creatinine and fasting glucose in plasma were measured in all patients. COPD Assessment Test (CAT)

and Modified Medical Research Council Dyspnea Scale (mMRC) were used for comprehensive assessment of symptoms and severity of dyspnea.

Lung ventilation function was assessed on a Master Lab instrument, a volume-constant body plethysmography system, manufactured by the Erich Jaeger company, Germany, using spirography methods with computer-based calculation of parameters. The parameters obtained were assessed in accordance with GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease) of 2018. Twenty-four-hour pulse oximetry monitoring was performed to assess the average daily oxygen saturation using a MIROxi pulse oximeter (made in Italy).

Echocardiography was performed on Vivid 7 Expert, a cardiovascular ultrasound system manufactured by GE Medical Systems. Left ventricular structural and functional parameters were assessed: end-diastolic size (LV-EDS), end-systolic size (LV-ESS), end diastolic size (LV-EDS), left ventricular posterior wall thickness (LVPW), left ventricular myocardial mass ratio (LVMMR), ejection fraction (LVEF) by modified Simpson's biplane method. Left atrial (LA) parameters were estimated: LA size and LA volume index: LA/body surface area (BSA). When evaluating the right heart chambers, the following parameters were analyzed: right atrial minor diameter index (RA/BSA), right ventricular basal diameter (RVBD), right ventricular wall thickness (RVWT), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP) [7]. To assess RV and LV diastolic function the following parameters were evaluated: mitral ratio of peak early to late diastolic filling velocity (E/A); isovolumetric relaxation time of the LV (LV IVRT); deceleration time of early diastolic filling of the LV (LV DT); ratio of early transmitral flow velocity (E) to average mitral annular velocity (e') (LV E/e'); ratio of peak early to late diastolic filling velocity (RV E/A); deceleration time of early diastolic filling of the RV (RV DT) [7].

To exclude coronary heart disease, 24-hour Holter ECG monitoring on the Astrocard E2bp, exercise stress echocardiography on the Vivid 7 Expert manufactured by GE Medical Systems, and treadmill testing on the Schiller BP-200 plus tester were performed.

Data analysis was performed using the statistical software package SPSS 22.0. Before calculations, the distribution normality was checked using the Kolmogorov-Smirnov two-sided goodness-of-fit test and a test for equality of variances using the Levene's method. Most samples did not pass the normality tests, therefore nonparametric statistical methods were used. The Mann-Whitney test was used to evaluate statistical differences among the comparison groups. Data are presented by median, 25th and 75th quartiles. Multiple correlation analysis was performed with adjustment for gender, age, and ABP, using Spearman's rank correlation coefficient (r). Logistic regression was used, the dependent variables were reduced to a dichotomized type. Differences were considered statistically significant at $p < 0.05$.

Results

Depending on COPD severity, the patients were divided into 4 groups (Table 1). When comparing the clinical and demographic parameters of the studied groups, a statistically significant increase in age was revealed in group 2 compared with groups 1 and 4 ($p=0.041$; $p=0.007$. respectively). Age parameters in patients of group 3 significantly exceeded those in group 1 ($p=0.01$). Group 2 patients had higher body mass index values than those in groups 3 and 4 ($p=0.015$; $p=0.003$, respectively).

Besides the typical significant intergroup differences in FEV_1, statistically significant differences in inspiratory capacity (IC) were revealed, the value of which was minimal in group 4 patients compared with other groups ($p < 0.001$). Average daily pulse oximetry values (SpO_2) in the groups were comparable, except for group 4 patients, who had values lower than those in group 1 ($p=0.02$). The severity of symptoms and dyspnea in patients in group 4, according to the CAT and mMRC questionnaires, significantly exceeded those in groups 1, 2, and 3. Maximum comparable frequency of COPD exacerbations was observed in groups 2 and 4, significantly exceeding those in groups 1 and 3.

Systolic blood pressure (SBP) values in the study groups corresponded to the target level; SBP values in the group 2 patients significantly exceeded those in groups 3 and 4 (p=0.05; p=0.012). Smoking index and blood glucose level had no significant intergroup differences between the studied groups. The highest cholesterol level was observed in group 1, the lowest level — in group 3, with no clinically significant increase in all groups. The average daily heart rate (HR) in group 4 patients

Table 1. *Demographic, clinical and functional characteristics of the patients examined*

Parameter	GOLD 1	GOLD 2	GOLD 3	GOLD 4	p	p	p	p	p	p
	1	2	3	4	1-2	1-3	1-4	2-3	2-4	3-4
Number of patients, n (%)	13 (13.5)	38 (39.6)	29 (30.2)	16 (16.7)						
Age, years	59.0 [56.0; 61.0]	68.0 [67.0; 70.0]	65.0 [60.0; 69.0]	61.5 [56.0; 64.0]	0.041	0.01	ns	ns	0.007	ns
Men/women, n	12/1	27/11	29/0	16/0						
BMI, kg/m^2	24.8 [22.6; 28.2]	28.55 [24.4; 29.1]	23.05 [19.4; 29.1]	22.51 [21.4; 25.7]	ns	ns	ns	0.015	0.003	ns
Smoking index, pack-year	50.0 [40.0; 50.0]	40.0 [15.0; 45.00]	50.0 [45.0; 75.0]	40.00 [39.38; 44.0]	ns	ns	ns	ns	ns	ns
FEV_1, % of normal value	85.5 [82.0; 89.0]	61.0 [52.0; 68.0]	43.0 [34.0; 46.0]	26.0 [25.75; 30.0]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Inspiratory capacity, % of normal value	99.6 [98.0; 102.0]	88.5 [84.0; 97.0]	69 [59.0; 81.0]	58.0 [50.0; 55.0]	0.002	<0.001	<0.001	<0.001	<0.001	0.001
$SpO_{2,\%}$	96.0 [92.6; 96.5]	93.55 [92.7; 94.8]	93.5 [92.4; 94.5]	92.6 [90.28; 93.6]	ns	ns	0.02	ns	ns	ns
mMRC, points	0.0 [0.0; 1.0]	1.0 [1.0; 2.0]	1.0 [1.0; 1.0]	2.0 [1.75; 3.0]	<0.001	<0.001	<0.001	ns	0.028	0.012
CAT, points	13.0 [9.3; 21.3]	19.0 [13.0; 26.0]	16.0 [13.0; 26.0]	25.0 [17.0; 32.8]	ns	ns	0.007	ns	0.039	0.004
COPD exacerbations/ year, n	1.0 [1.0; 2.0]	2.0 [1.0; 2.5]	1.0 [1.0; 2.0]	2.0 [1.0; 2.5]	0.03	ns	<0.05	0.005	ns	0.007
Hypertension grade 1, n (%)	4 (30.8)	20 (52.6)	8 (27.6)	5 (31.2)						
SBP (office), mm Hg	127.0 [121.0; 130.0	130.0 [128.0; 137.0]	123.0 [118.0; 131.0]	120.5 [110.0; 133.0]	ns	ns	ns	0.05	0.012	ns
DBP (office), mm Hg	82.0 [80.00; 84.00]	77.0 [73.0; 82.0]	79.0 [76.0; 82.0]	72.0 [69.0; 75.0]	ns	ns	ns	ns	ns	ns
Glucose, mmol/L	4.8 [4.5; 4.8]	5.05 [4.6; 5.6]	4.8 [4.5; 5.2]	4.9 [4.6; 5.3]	ns	ns	ns	ns	ns	ns
Cholesterol, mmol/L	5.2 [5.0; 6.9]	4.95 [4.7; 6.3]	4.2 [4.1; 6.0]	4.9 [4.8; 5.15]	ns	0.035	ns	0.001	ns	0.005
HR, bpm	77.0 [67.0; 80.0]	77.0 [67.0; 80.0]	72.0 [68.0; 88.5]	82.5 [75.5; 89.75]	ns	ns	0.015	ns	0.008	0.023

Note: the data are presented as median, first and third quartiles (Me; Q25; Q75). Significance of intergroup differences (p) was evaluated using the Mann-Whitney test; ns — not significant

was significantly higher compared with patients in groups 1, 2, and 3 (p=0.015; p=0.008; p=0.023, respectively).

The LA and LV linear and volumetric parameters, as well as LV geometry were studied in patients with COPD, the medians of the analyzed parameters corresponded to the threshold values (Table 2).

The comparative intergroup analysis of the hemodynamic parameters revealed a significant decrease in LA size in patients in group 2 compared with group 1 (p=0.04), and in patients in group 4 compared with groups 1 and 2 (p=0.001; p=0.011, respectively). LAVI/BSA in groups 3 and 4 was significantly lower than that in group 1 (p=0.011; p=0.04, respectively).

In group 4 patients, there was a decrease of LV EDS compared with groups 1, 2, and 3 (p<0.001; p<0.001; p=0.003, respectively), and LV EDV decrease compared with groups 1 and 2 (p=0.006; p=0.014). When assessing LV ESV in group 4 patients, a decrease was observed compared with groups 1 and 2 (p=0.006; p=0.013, respectively).

There were no intergroup differences of the LVPW thickness and LVMMR, except for the LVMMR parameter in patients in groups 3 and 4 (p=0.026): the values of this parameter corresponded to normal values.

Table 2. *Echocardiography parameters in patients with COPD*

Parameter	GOLD 1	GOLD 2	GOLD 3	GOLD 4	p	p	p	p	p	p
	1	2	3	4	1-2	1-3	1-4	2-3	2-4	3-4
LA, cm	3.8 [3.5; 3.8]	3.5 [3.2; 3.8]	3.5 [3.1; 3.9]	3.15 [3.0; 3.5]	0.04	ns	0.001	ns	0.011	ns
LAVI/BSA, mL/m²	32.1 [21.7; 32.8]	29.3 [26.0; 34.3]	28.4 [22.3; 31.2]	26.9 [23.0; 29.8]	ns	0.011	0.04	ns	ns	ns
RAVI/BSA, mL/m²	1.5 [1.4; 1.5]	1.6 [1.2; 2.2]	1.3 [1.2; 1.3]	1.5 [1.3; 1.7]	ns	ns	ns	ns	ns	ns
LV EDS, cm	5.0 [4.8; 5.3]	4.8 [4.4; 5.4]	4.7 [4.7; 4.9]	4.2 [4.1;4. 5]	ns	ns	<0.001	ns	<0.001	0.003
LV EDV, mL	111.0 [95.0; 124.0]	101.0 [93.0; 121.0]	96.0 [87.0; 122.0]	94.0 [78.0; 97.0]	ns	ns	0.006	ns	0.014	ns
LV ESV, mL	29.0 [23.0; 36.0]	32.0 [31.0; 37.0]	36.0 [32.0; 43.0]	39.0 [34.0; 51.0]	ns	ns	0.006	ns	0.013	ns
RVBD, cm	2. 4 [2.4; 2.8]	2. 6 [2.4; 2.8]	2.6 [2.5; 2.8]	2.7 [2.2; 2.9]	ns	ns	0.035	ns	ns	ns
LVPW, cm	0.95 [0.95; 1.2]	0.98 [0.9; 1.1]	0.94 [0.9; 1.2]	0.98 [0.93; 1.1]	ns	ns	ns	ns	ns	ns
RVWT, cm	0.5 [0.5; 0.6]	0.5 [0.5; 0.6]	0.5 [0.5; 0.6]	0.6 [0.5; 0.8]	ns	ns	<0.05	ns	ns	ns
LVMMR, g/m²	101.9 [79.7; 119.6]	100.7 [87.1; 116.9]	93.9 [81.4; 116.8]	83.2 [69.1; 102.8]	ns	ns	0.026	ns	0.038	ns
LVEF, %	66.5 [65.0; 68.0]	64.0 [62.0; 66.0]	60.0 [58.0; 65.0]	62.0 [60.0; 67.0]	ns	<0.05	0.011	ns	ns	ns
TAPSE, cm	2.2 [1.91; 2.43]	2.0 [2.0; 2.0]	1.95 [1.9; 2.0]	1.8 [1.8; 2.0]	ns	ns	0.001	0.018	0.02	0.02
PASP, mm Hg	25.7 [22.5; 31.9]	26.7 [22.1; 22.0]	27.8 [22.95; 28.5]	31.3 [28.5; 34.0]	ns	ns	0.001	ns	0.028	0.002

Note: See Table 1.

Despite that LV global systolic function (ejection fraction) in patients in the study groups was in the normal range, a decrease in this parameter was observed in patients in groups 3 and 4 compared with patients in group 1 (p <0.05; p=0.011, respectively).

RAVI/BSA values in all groups were comparable. When assessing RVBD, a significant increase in group 4 compared with group 1 was observed (p=0.035). PASP in patients in groups 1, 2, and 3 did not exceed normal values, moderate pulmonary hypertension was observed in group 4: PASP = 31.3 mm Hg. RVWT in group 4 exceeded 0.5 cm, which was significantly different from group 1 (p <0.05).

In group 4 patients, a significant decrease in the TAPSE value was discovered, compared with other groups (p=0.018; p=0.02; p=0.02, respectively). TAPSE changes in the study groups varied within normal range.

Analysis of the parameters of the LV diastolic function (Table 3) in the study group patients revealed that the LV E/A decreased as COPD severity increased. A minimal value of this parameter was observed in patients in group 4; the differences between groups 1 and 3 were significant (p <0.01; p <0.01, respectively). There were no significant intergroup differences in the LV IVRT. The LV DT value increased as COPD severity increased. Differences in this parameter between all groups were statistically significant, except for LV DT values in patients in groups 2 and 3, where these values were comparable. LV diastolic dysfunction presented with the I grade (impaired relaxation) according to the European Association of Cardiovascular Imaging guidelines and American Society of Echocardiography guidelines [7], was revealed in 12 (31.6 %) patients in group 2, in 7 (24.1 %) patients in group 3, and in 9 (56.2 %) patients in group 4. As the severity of COPD progressed, a tendency to decrease in the LV E/e' was observed, which values did not differ from normal values.

As regards RV, a significant decrease in RV E/A was observed in patients in group 4 compared with groups 1, 2, and 3 (p=0.002; p=0.001; p=0.016). RV DT changes were diverse: there was a significant increase in this parameter in patients in group 2 compared with group 1 (p=0.017) with its subsequent decrease in groups 3 and 4 (the differences with group 4 were significant (p=0.009).

To reveal the association between lung function and hemodynamics parameters, correlation analysis was performed (Table 4). As a result, moderate direct correlation of IC with LV EDS (r=0.612; p=0.001) (Fig. 1) and with LAVI/BSA (r=0.433; p <0.001) was discovered, and moderate inverse

Table 3. *Parameters of left and right ventricular diastolic function in patients with COPD*

Parameter	GOLD 1	GOLD 2	GOLD 3	GOLD 4	p	p	p	p	p	p
	1	2	3	4	1-2	1-3	1-4	2-3	2-4	3-4
LV E/A, units	0.93 [0.85; 1.22]	0.81 [0.72; 0.99]	0.81 [0.74; 0.87]	0.77 [0.69; 1.07]	ns	0.01	0.01	ns	ns	ns
LV IVRT, ms	87.0 [84.5; 92.5]	100.0 [89.0; 114.0]	94.0 [90.0; 113.5]	100.0 [90.0; 111.0]	ns	ns	ns	ns	ns	ns
LVDT, ms	206.0 [142.5; 290.3]	233.0 [206.0; 244.0]	242.5 [200.0; 268.0]	265.0 [208.5; 280.0]	0.007	<0.001	0.01	ns	0.049	<0.01
LV E/e', units	6.9 [5.7; 7.4]	6.3 [5.5; 7.7]	7.0 [5.9; 9.6]	5.2 [3.3; 8.5]	ns	ns	ns	ns	ns	ns
RV E/A, units	1.35 [0.99; 1.41]	1.15 [0.99; 1.25]	1.08 [0.85; 1.2]	0.90 [0.74; 1.1]	ns	ns	0.002	ns	0.001	0.016
RVDT, ms	207.0 [200.8; 248.3]	247.5 [217.8; 302.8]	230.0 [203.0; 277.0]	222.0 [189.0; 256.0]	0.017	ns	ns	ns	0.009	ns

Note: See Table 1.

correlation of IC with RVBD (r=-0.533; ρ=0.042) was found.

Moderate direct correlation of FEV_1 with LAVI/BSA (r=0.380; ρ <0.001) and LV EDS (r=0.350; ρ=0.005) was discovered. The relationship between the FEV_1 and structural and functional RV parameters was inverse for RVBD (r=-0.465; ρ=0.022), PASP (r=-0.575; ρ=0.003), and RVWT (r=-0.406; ρ=0.003).

A moderate negative relationship between the average daily SpO_2 and PASP (r=-0.546; ρ=0.006), as well as a moderate direct relationship between the average daily SpO_2 and TAPSE (r=0.379; ρ=0.002) were discovered.

Correlation analysis of the relationship between IC and LV diastolic function parameters demonstrated a moderate direct relationship with LV E/A (r=0.464; ρ=0.001) (Fig. 2) and a moderate inverse relationship with LV DT (r=-0.599; ρ<0.001). A relationship with FEV_1 was discovered for LV E/A (r=0.600; ρ=0.011).

Due to the correlations discovered, logistic regression was used to assess the impact of functional characteristics of COPD on the parameters of the LV diastolic function. A mathematical model with the agreement percent of 81.6 % was built, which included IC and FEV_1 parameters besides the traditional factors (age, BMI, SBP, DBP) that contribute to the LV diastolic dysfunction (LV E/A <0.8).

Table 4. *Correlation of intracardiac hemodynamics and lung functional parameters*

Parameter	IC, % of normal value		FEV_1, % of normal value		SpO_2, %	
	r	ρ	r	ρ	r	ρ
LAVI/BSA, mL/m²	0.433	<0.001	0.380	<0.001	0.503	0.058
LV EDS, cm	0.612	0.001	0.350	0.005	0.305	ns
RVBD, cm	-0.533	0.042	-0.465	0.022	ns	ns
RVWT, cm	ns	ns	-0.406	0.003	ns	ns
TAPSE, cm	ns	ns	ns	ns	0.379	0.002
PASP, mm Hg	ns	ns	-0.575	0.003	-0.546	0.006
LV E/A, units	0.464	0.001	0.600	0.011	ns	ns
LVDT, ms	-0.599	<0.001	ns	ns	0.132	ns

Note: the correlation coefficient was calculated using the Spearman rank method

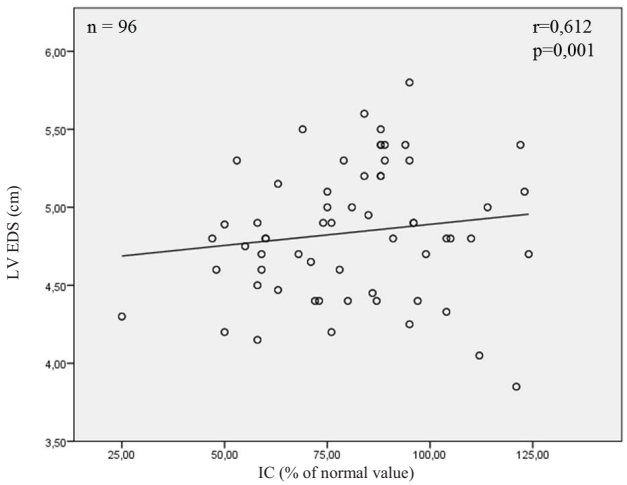

Figure 1. *Correlation between IC and LV EDS*

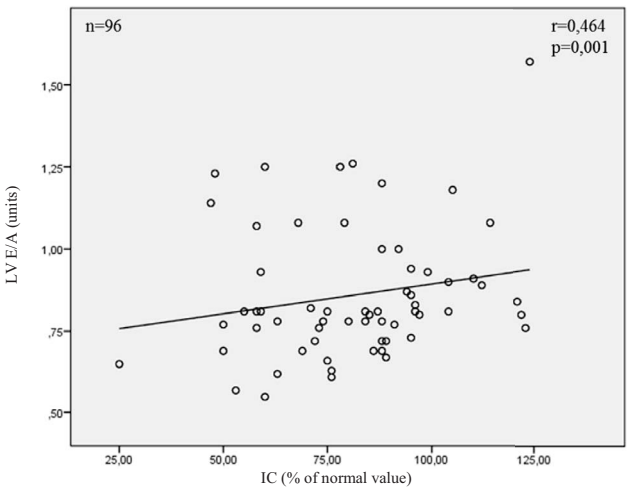

Figure 2. *Correlation between IC and LV E/A*

According to the results obtained, the contribution of IC (Wald χ^2=5.795; p=0.024) was discovered, in addition to the significant influence of DBP (Wald χ^2=10.872; p=0.002), SBP (Wald χ^2 =10.264; p=0.003), BMI (Wald χ^2=8.546; p=0.008), and age (Wald χ^2=6.696; p=0.020) to the LV diastolic function.

Discussion

We conducted a comparative study of the intracardiac hemodynamics parameters in 96 patients with COPD of varying severity (GOLD 1–4) and without any significant cardiovascular diseases. All parameters, except for RVWT and PASP, corresponded to normal values [7]. It was discovered that the progression of COPD severity was associated with significant decrease in the LV EDS value. Minimal values of LV EDS were observed in patients in group 4 (GOLD 4), and moderate direct correlation of this parameter with IC and FEV_1 was found. IC parameter characterizes the maximum air volume that a patient can inspire after expiration at rest; it corresponds to the difference between total lung capacity and functional residual capacity and can be used as a surrogate marker of static pulmonary hyperinflation [8].

When the LV diastolic function parameters were assessed, a significant decrease in LV E/A in patients in groups 3 and 4 compared with group 1 was found, as well as statistically significant LV DT prolongation with increase in COPD severity. Among all patients examined impairment of the LV diastolic function of grade I was observed in 28 individuals. The maximum number of patients with diastolic dysfunction (56.2 %) was in group 4. Correlation analysis demonstrated a moderate positive relationship of LV E/A with IC and FEV_1, a moderate negative relationship of LV DT with IC was found. The results of the logistic regression allowed to discover the impact of IC on the development of LV diastolic dysfunction along with age, BMI, SBP, and DBP.

The results obtained are consistent with published data on the negative impact of chronic obstruction and pulmonary hyperinflation on structural and functional cardiac parameters in the absence of cardiovascular diseases, hypertension, diabetes mellitus, dyslipidemia, and significant remodeling of the right heart chambers due to chronic pulmonary hypertension [1–6. 9]. It was found that an increase in pulmonary volumes contributes to redistribution of pulmonary blood flow with decrease in filling of pulmonary veins, intrathoracic blood volume and LV preload, which in turn can lead to decrease in the left heart chamber sizes [2, 4].

Impairment of normal breathing mechanics in COPD due to prolongation of expiration with pronounced increase in internal positive end expiratory pressure also leads to decrease in venous return and LV diastolic filling [10]. The decrease in LV E/A as COPD severity increases, revealed in this study, as well as the positive relationship of this parameter with IC and FEV_1 indicates impairment of the LV filling due to the reduction the preload in the absence of significant changes in LV relaxation, which is consistent with published data [11, 12]. It can be assumed that the decreased LV preload leads to a decrease in LV filling velocity parameters, predominantly due to early diastolic filling velocity.

The revealed RV parameter changes (increase in RVWT and RVBD in group 4 patients, inverse correlations of RVBD, RVWT and PASP with SpO_2) demonstrate the known processes of RV remodeling in the presence of chronic pulmonary hypertension [9].

The revealed negative correlation between RVBD and IC can reflect the compression effect of pulmonary hyperinflation on pulmonary blood flow with an increase in the RV afterload. A tendency to decrease in TAPSE in the study groups and a direct correlation with SpO_2 is consistent with the concept of the RV systolic function impairment in early stages of COPD [13].

Conclusion

The results of the comparative study conducted indicate that bronchial obstruction and pulmonary hyperinflation contribute to the RV remodeling, that is manifested by a decrease in its size

and diastolic filling in patients with COPD who do not have significant cardiovascular diseases and severe chronic pulmonary hypertension. The progression of bronchial obstruction and pulmonary hyperinflation severity contributes to the formation of LV diastolic dysfunction, predominantly due to the decreased filling velocity.

References:

1. Watz H., Waschki B., Meyer T. et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest. 2010; 138(1):32-38. doi: 10.1378/chest.09-2810.
2. Smith B., Prince M., Hoffman E. et al. Impaired Left Ventricular Filling in COPD and Emphysema: Is It the Heart or the Lungs? The Multi-Ethnic Study of Atherosclerosis COPD Study. Chest. 2013; 144(4):1143–1151. doi: 10.1378/chest.13-0183.
3. Altera P., Watz H., Kahnertc K. et al. Airway obstruction and lung hyperinflation in COPD are linked to an impaired left ventricular diastolic filling. Respiratory Medicine. 2018; 137: 14–22. doi: http://dx.doi.org/10.1016/j.rmed.2018.02.011.
4. https://doi.org/10.1371/journal.pone.0176812.
5. Schoos M., Dalsgaard M., Kjærgaard J. et al. Echocardiographic predictors of exercise capacity and mortality in chronic obstructive pulmonary disease. BMC Cardiovascular Disorders. 2013; 13:84. doi:10.1186/1471-2261-13-84. 9.
6. Vasudeva A., Sudhakar Mugula R., Seshadris S. Assessment of Diastolic Dysfunction Pa-rameters and Cardiac Chamber Size in Smokers with COPD: A Case Control Study. J Clin Diagnos Res. 2018; 12(1): 10-13. doi:10.7860/JCDR/2018/29204.11137.
7. Nagueh S., Smiseth O., Appleton C. et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29: 277-314. http://dx.doi.org/10.1016/j.echo.2016.01.011
8. Aisanov Z. R., Kalmanova E. N. Bronchial Obstruction and Pulmonary Hyperinflation in Patients with Chronic Obstructive Pulmonary Disease. Practical Pulmonology. 2016; 2: 9-18. [In Russian]
9. Sumin A. N., Arkhipov O. G. Right ventricular diastolic function in patients with lung diseases in the absence or presence of pulmonary hypertension. Therapeut. arch. 2017; 3: 54-60. doi: 10.17116/terarkh201789354-60. [In Russian]
10. Kubota Y., Asai K., Murai K. et al. COPD advances in left ventricular diastolic dysfunc-tion. Int J Chron Obstruct Pulmon Dis. 2016; 11: 649–655. doi:http://dx.doi.org/10.2147/COPD.S101082
11. Gajanan S. Gaude, Gautam Suresh, Vinay Mahishale. Left ventricular dysfunction and its correlates in chronic obstructive pulmonary disease patients. Afr J Med Health Sci. 2015; 14: 87-91. doi: 10.4103/2384-5589.170165
12. Mayr A., Urban M., Schmidt I., et al. Effects of dynamic hyperinflation on left ventricular diastolic function in healthy males — a randomized study. Eur Respir J. 2018; 52: PA3349; doi: 10.1183/13993003.congress-2018.PA3349
13. Hilde J., Skjørten I., Grøtta O et al. Right Ventricular Dysfunction and Remodeling in Chronic Obstructive Pulmonary Disease Without Pulmonary Hypertension. J Am Coll Cardiol. 2013; 62 (12): 1103-1111. http://dx.doi.org/10.1016/j.jacc.2013.04.09

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MOBILE HEALTH TECHNOLOGY: ORGANIZATIONAL, MEDICAL AND PHARMACOEPIDEMIOLOGICAL APPROACHES FOR CSD PREVENTION IN PRE-PRIMARY CARE

Abstract

Objective: to evaluate the innovative organizational, medical and pharmacoepidemiological approaches for the prevention of circulatory system diseases in pre-primary care using mobile health technologies.

Materials and methods: 3,694 people went through preventive consultation (questionnaires, anthropometry, body fat and blood pressure evaluation, electrocardiography, glucose and blood cholesterol) at equipped medical sites in shopping centers and rural health posts.

Results. Among the surveyed, there were both healthy people and patients cardiovascular diseases and diabetes mellitus. Behavioral (insufficient consumption of fruits and vegetables, adding more salt without trying food, physical inactivity, smoking and alcohol abuse) and nutritional (obesity, hypertension, hypercholesterolemia and glycaemia) risk factors of chronic non-communicable diseases were detected that contribute to high mortality from circulatory system diseases in the Tver region. This is associated with low adherence to drug therapy and its lack of efficacy in patients with hypertension, ischemic heart disease and cerebrovascular diseases.

Conclusion: to assess the effectiveness of CSD prevention in pre-primary care, it is possible to use mobile medical sites in shopping centers and rural health posts.

Key words: *prevention of circulatory system diseases, mobile health, shopping centers*

Conflict of Interests

The authors declare no conflict of interests

Source of Financing

The authors states that no finding for the study has been received

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mHealth — mobile health technologies, CSD — circulatory system diseases, RF — risk factors, NCDs — noncommunicable diseases, EH — essential hypertension, DM — diabetes mellitus, IHD — ischemic heart disease, CVDs — cerebrovascular diseases, BP — blood pressure, ECG — electrocardiogram

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Introduction

In Russia, CSD mortality [1] despite its decline significantly exceeds the one in European countries, which requires the introduction of effective programs for the prevention and treatment of circulatory system diseases (CSDs) [2, 3]. This includes the Tver Region, which for many years has been an outsider in terms of both overall and CSD mortality. At the same time, low detection of risk factors (RF) of noncommunicable diseases (NCDs) is noteworthy. According to the data of the Ministry of Health of the Tver Region for January–May 2016, during regular check-up of the population the following RFs were registered: low physical activity in 143 patients (16%) out of 8,933; smoking in 95 (13%) out of 7,316 patients; overweight in 167 patients (17%) out of 9,811; hypertension in 765 (12%) of 6 373 patients; hypercholesterolemia in 344 (10%) out of 3,444 patients, and hyperglycemia in 45 (3%) out of 1,487 patients. This raises the need exist to develop new organizational, medical and pharmacoepidemiological approaches to the prevention of CSDs and ways to assess their effectiveness, including the use of mobile health technologies (mHealth). mHealth allows to deliver medical care even outside the medical institution. At the same time, the conditions of care are determined by the actual location of a patient [4]. mHealth requires the use of mobile devices (phones, gadgets, wireless medical devices for monitoring the functional body state, personal handheld computers, etc.) [5], which makes it a good platform for assisting in the implementation of healthcare programs [6]. This allows quick monitoring of the main parameters of the patient's health, change in RF, correct implementation of the doctor's recommendations, and the use of innovative technologies for both creating a healthy lifestyle among the population and increasing adherence of patients with CSDs to secondary prevention.

Accordingly, the "Mobile Health in Tver" project was developed and tested though the efforts of the staff of the Federal State Budgetary Institution of Higher Education "Tver State Medical University" of the Ministry of Health of the Russian Federation (TSMU) and the Ministry of Health of the Tver Region.

The Objective was to assess the use of innovative organizational, medical and pharmacoepidemiological approaches for CSD prevention in pre-primary care.

Materials and Methods

From November 2015 to December 2018, 3,686 people went through preventive consultation at equipped medical sites in shopping centers and rural health posts.

All applicants filled a questionnaire to identify behavioral and nutritional RF of NCDs [7]. The first included the consumption of fruits and vegetables (less than 400 g); adding more salt without trying food; smoking; low physical activity (walking less than 30 minutes a day); alcohol abuse (over 20 g/day for males, and over 10 g/day for females). The second were overweight (BMI is 25–29.9 kg/m^2); obesity (BMI 30 kg/m^2 or higher); hypertension (140/90 mm Hg or higher); hyperglycemia (blood glucose level 7.8 mmol/L and higher two hours after meals); and hypercholesterolemia (5.0 mmol/L and higher). In addition, previously diagnosed essential hypertension (EH), diabetes mellitus (DM), ischemic heart disease (IHD) and cerebrovascular diseases (CVDs) were considered. Genetic predisposition to the development of IHD, DM, and use of hypotensive and lipid lowering therapy two weeks before preventive consultation were considered.

In all of the applicants, anthropometry (height, weight) was carried out, body mass index (Quetelet index) was calculated, the measurement of blood pressure (BP) and I-lead electrocardiography (ECG) in the patient seated using virtual technologies were performed. Two grades were used in the evaluation of ECG: normal and pathology (disorders of ventricular repolarization and cardiac rhythm disorders). Blood glucose and blood cholesterol levels were determined in some of the examined persons using test strips.

In-depth preventive consultation lasted no less than 40 minutes. It involved detailed information on the detected NCD risk factors, methods and the need for their timely correction to perform adequate

primary, secondary and tertiary NCD prevention in every patient. Specially trained 5th- and 6th-year students of the Departments of General Medicine and Pediatrics of TSMU, as well as students of medical colleges under the supervision of the teacher conducted the interviews. After the in-depth preventive consultation, leaflets containing a summary of recommendations on the correction of NCD risk factors were given to all patients. For the same purpose, the use of a personal medical online account was suggested to every patient, which was demonstrated at the medical site (website: https://своездоровье.рф; demo login: pat3, password: pat31111).

If follow-up was required, patients were referred to medical institutions in Tver (TSMU Diagnostic Center, Tver Regional Cardiology Hospital, and Regional Outpatient Clinic) and the Tver Region (outpatient departments of Central District Hospitals).

Statistical processing of the study results was carried out using the WinPepi statistical software package (using Fisher's and χ^2 tests).

Study design: single-point, cross-sectional study of a convenience sample [8]. It enrolled everyone interested in preventive consultation at mobile medical sites in shopping centers and rural health posts.

Results and Discussion

Over the last decade, much attention was paid to mHealth worldwide [5, 6]. mHealth enables delivery of new forms of medical care: within walking distance care, including through offline clinics and distance learning programs that will increase awareness of the population about health and its determinants, which will improve morbidity and premature mortality [2].

Among the 3,686 examined at medical sites in shopping centers and rural health posts, there were half as many men as women (1,206 (33%) and 2,480 (67%), respectively). The analysis of age groups showed that older women (from 46 years old) were more likely to refer to the medical site. In contrast, in men, the highest rate of this parameter was between the ages of 20 and 35 years. This phenomenon in men requires further study to analyze its possible causes: onset of health problems, lack of time to visit a doctor, wives' concern, etc. In general, it should be noted that 69.9% of those who came to the medical site were people of working age (from 20 to 60 years), which confirms its relevance among the working-age population.

Among the adult visitors to the shopping centers and rural health posts of Tver and the Region, the following behavioral RFs of NCDs were most often detected: inadequate intake of fruits and vegetables (2,161; 58.6%); physical inactivity (2,103; 57.1%) was less common; alcohol abuse (1,197; 32.5%), adding more salt without trying food (922; 25.0%) and smoking (768; 21.3%) were even less common. Detectability analysis of behavioral RFs depending on gender and age allowed us to establish the following.

In men (Table 1), at the age of 20–35 years, 36–45 years, 46–69 years and older than 60 years, compared with persons aged 20 years and younger, insufficient intake of fruits/vegetables was detected. In contrast, physical inactivity increased with age, while smoking was more common in young adults compared with elderly people. In men, there were no differences in age with regard to both alcohol abuse and adding more salt without trying food.

In women (Table 2), the age-related difference in the insufficient intake of vegetables/fruits and physical inactivity was not detected. However, they were more likely to abuse alcohol at the age of 20 to 45 years; less likely to add more salt without trying food at the age of 36–60 years; and 20 to 45 y. o. women were more likely to smoke compared to other age groups.

Against the background of the presence of a rather large amount of behavioral RFs of NCDs, the surveyed also had nutritional RFs. Among the latter, hypercholesterolemia was most often (567 of 996; 56.9%); then hypertension (in 1,555 of 3,676; 42.3%), more rarely — obesity (in 1,000 of 3,518; 28.4%) and hyperglycemia was rare (in 51 of 954; 5.7%). Analysis of the detection of nutritional RFs depending on gender and age allowed us to establish the following.

Table 1. *Detection of behavioral risk factors in men depending on age (abs. and %)*

Risk factor	Age (years)										Total		Total surveyed
	<20		20 — 35		36 — 45		46 — 60		>60				
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	
Inadequate consumption of fruits and vegetables (χ^2 = 10,7; ρ = 0,030)	35 44,3%	44 55,7%	255 61,3%	161 38,7%	116 63,7%	66 36,3%	201 62,6%	120 37,4%	132 63,5%	76 36,5%	733 60,8%	473 39,2%	1206
Hypodynamia (χ^2 = 18,4; ρ = 0,001)	60 67,4%	29 32,6%	259 60,8%	167 39,2%	93 48,7%	98 51,3%	141 50,0%	141 50,0%	119 54,6%	99 45,5%	672 55,7%	534 44,3%	1206
Alcohol abuse (χ^2 = 7,2; ρ = 0,124)	24 30,8%	54 69,2%	171 41,1%	245 58,9%	88 48,4%	94 51,6%	133 41,3%	189 58,7%	87 41,8%	121 58,2%	503 41,7%	703 58,3%	1206
Add food without tasting it (χ^2 = 2,5; ρ = 0,643)	20 26,3%	56 73,7%	115 27,6%	302 72,4%	61 33,7%	120 66,3%	91 28,4%	230 71,6%	63 28,5%	148 71,5%	350 29,0%	856 71,0%	1206
Smoking (χ^2 = 22,2; ρ = 0,000)	31 39,7%	47 60,3%	145 34,9%	270 65,1%	67 36,8%	115 63,3%	103 31,7%	221 68,3%	39 18,8%	168 81,2%	385 31,9%	921 68,1%	1206

Table 2. *Detection of behavioral risk factors in women depending on age (abs. and %)*

Risk factor	Age (years)										Total		Total surveyed
	<20		20 — 35		36 — 45		46 — 60		>60				
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	
Inadequate consumption of fruits and vegetables (χ^2 = 5,7; ρ = 0,223)	50 54,9%	41 45,1%	293 61,0%	187 39,0%	201 57,3%	150 42,7%	485 58,6%	342 41,4%	399 54,6%	332 45,4%	1428 57,6%	1052 42,4%	2480
Hypodynamia (χ^2 = 3,1; ρ = 0,541)	49 53,8%	42 46,2%	278 57,6%	205 42,4%	197 56,4%	152 43,6%	467 56,5%	359 43,5%	440 60,2%	291 39,8%	1431 57,7%	1049 42,3%	2480
Alcohol abuse (χ^2 = 70,5; ρ = 0,000)	15 16,5%	76 83,5%	173 35,8%	310 64,2%	138 39,3%	213 60,7%	227 27,6%	597 72,4%	141 19,3%	590 80,7%	694 28,0%	1786 72,0%	2480
Add food without tasting it (χ^2 = 10,9; ρ = 0,028)	24 26,4%	67 73,6%	120 25,0%	361 75,0%	73 20,8%	278 79,2%	164 19,9%	660 80,1%	191 26,1%	542 73,9%	572 23,1%	1908 76,9%	2480
Smoking (χ^2 = 157,0; ρ = 0,000)	20 22,0%	71 78,0%	135 27,9%	349 72,1%	83 23,9%	264 76,1%	119 14,4%	709 85,6%	28 3,8%	702 96,2%	383 15,4%	2097 84,6%	2480

In men (Table 3), obesity and hypertension increased with age, while hypercholesterolemia and hyperglycemia did not depend on age. In women (Table 4), obesity, hypertension, hypercholesterolemia, and hyperglycemia increased with age.

When conducting preventive counseling in crowded areas and at rural health posts, it was also found that only in 2,028 (54.9%) of the patients no changes were registered on the ECG, while the rest of them reported impaired repolarization

Table 3. *Detection of alimentary-dependent risk factors in men depending on age (abs. and %)*

Risk factor	Age (years)										Total		Total surveyed
	<20		20 — 35		36 — 45		46 — 60		>60				
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	
Obesity (χ^2= 105,7; ρ = 0,000)	3	73	50	343	59	117	126	184	75	123	313	840	1153
	3,9%	96,1%	12,7%	87,3%	33,5%	66,5%	40,6%	59,4%	37,9%	62,1%	27,1%	72,9%	
Arterial hypertension (χ^2= 226,2; ρ = 0,000)	9	80	95	331	94	97	181	101	150	68	529	667	1196
	10,1%	89,9%	22,2%	77,8%	49,2%	50,8%	64,2%	35,8%	68,8%	31,2%	44,2%	55,8%	
Hypercholesterolemia (χ^2= 7,2; ρ = 0,125)	3	4	11	26	12	12	42	34	39	35	107	111	218
	42,9%	57,1%	29,7%	70,3%	50,0%	50,0%	55,3%	44,7%	52,7%	47,3%	49,1%	50,9%	
Hyperglycemia (χ^2= 3,7; ρ = 0,451)	1	7	0	36	1	21	4	74	2	67	8	205	213
	12,5%	87,5%	0,0%	100,0%	4,5%	95,5%	5,1%	94,9%	2,9%	97,1%	3,8%	96,2%	

Table 4. *Detection of alimentary-dependent risk factors in women depending on age (abs. and %)*

Risk factor	Age (years)										Total		Total surveyed
	<20		20 — 35		36 — 45		46 — 60		>60				
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	
Obesity (χ^2= 229,8; ρ = 0,000)	1	85	32	425	69	266	299	489	286	413	687	1678	2365
	1,2%	98,8%	7,0%	93,0%	20,6%	79,4%	37,9%	62,1%	40,9%	59,1%	29,0%	71,0%	
Arterial hypertension (χ^2= 491,5; ρ = 0,000)	1	90	33	447	88	263	347	480	468	263	1026	1454	2480
	1,1%	98,9%	6,7%	93,2%	25,1%	74,9%	42,0%	58,0%	64,0%	36,0%	41,4%	58,6%	
Hypercholesterolemia (χ^2= 19,50; ρ = 0,001)	2	7	30	47	33	53	139	127	188	136	392	370	762
	22,2%	77,8%	39,0%	61,0%	38,4%	61,6%	52,3%	47,7%	58,0%	42,0%	51,4%	48,6%	
Hyperglycemia (χ^2= 10,2; ρ = 0,037)	0	9	2	75	2	86	11	239	28	289	43	698	741
	0,0%	100,0%	2,6%	97,4%	2,3%	97,7%	4,4%	95,6%	8,8%	91,2%	5,8%	94,2%	

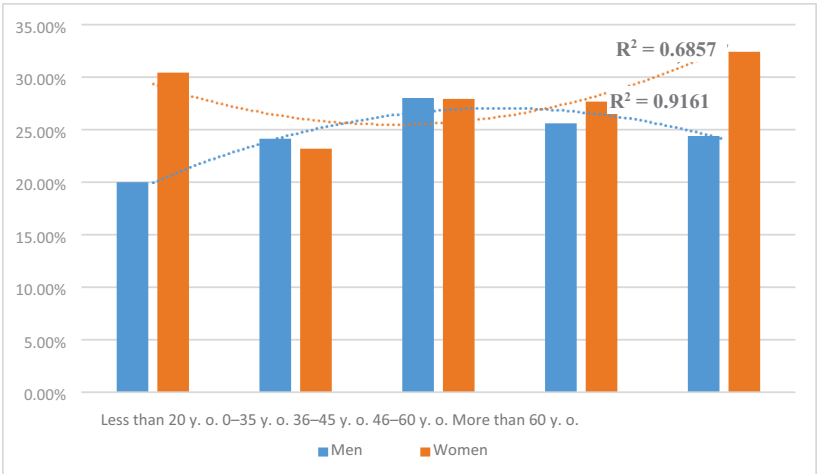

Figure 1. *Age-dependent incidence of repolarization process impairment in men and women*

processes (783; 21.2%), cardiac rhythm disorders (691; 18.7%) or in the form of their combinations (192; 5.2%). The incidence of ECG disorders depending on gender and age is presented in Fig. 1 and 2.

In men (Table 5), there was no age-related significant difference among repolarization processes, cardiac rhythm disorders and combined disorders. On the contrary, in women (Table 6), impairment of repolarization was more common in persons younger than 20 years and at the age of 60 years and older, while the incidence of cardiac rhythm and combined disorders was almost the same in persons of different ages.

Another positive point in the interest of the Tver population in mHealth at shopping centers and rural health posts is that among the surveyed, there were not only those with previously diagnosed EH (1,053; 28.5%), IHD (505; 13.7%) with its various signs and CVD (118; 3.2%), but also

Table 5. *Frequency of registration of changes in the electrocardiogram in men depending on age (abs. and%)*

ECG indicators	Age (years)										Total	
	<20		20 — 35		36 — 45		46 — 60		>60			
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not
Without pathology	28	27	182	192	66	98	138	151	96	97	510	565
	50,9%	49,1%	48,7%	51,3%	40,2%	59,8%	47,8%	52,2%	49,7%	50,3%	47,4%	52,6%
Disorders of repolarization processes (χ^2= 1,8; ρ = 0,769)	11	44	90	284	46	118	74	215	47	146	268	807
	20,0%	80,0%	24,1%	75,9%	28,0%	72,0%	25,6%	74,4%	24,4%	75,6%	24,9%	75,1%
Heart rhythm disorders (χ^2= 3,0; ρ = 0,555)	14	41	85	289	45	119	60	229	42	151	246	829
	25,5%	74,5%	22,7%	77,3%	27,4%	72,6%	20,8%	79,2%	27,8%	78,2%	22,9%	77,1%
Combined Disorders (χ^2= 1,4; ρ = 0,841)	2	53	12	362	6	158	13	276	5	188	38	1037
	3,6%	96,4%	3,2%	96,8%	3,7%	96,3%	4,5%	95,5%	2,6%	97,4%	3,5%	96,5%

Table 6. *Frequency of registration of changes in the electrocardiogram in women depending on age (abs. and%)*

ECG indicators	Age (years)										Total	
	<20		20 — 35		36 — 45		46 — 60		>60			
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not
Without pathology	39	40	234	189	155	153	345	407	280	387	1053	1176
	49,4%	50,6%	55,3%	44,7%	50,3%	49,7%	45,9%	54,1%	42,0%	58,0%	47,2%	52,8%
Disorders of repolarization processes (χ^2= 11,3; ρ = 0,023)	24	55	98	325	86	222	208	544	216	451	632	1597
	30,4%	69,6%	23,2%	76,8%	27,9%	72,1%	27,7%	72,3%	32,4%	67,6%	28,4%	71,6%
Heart rhythm disorders (χ^2= 7,1; ρ = 0,131)	11	68	69	354	50	258	157	595	134	533	421	1808
	13,9%	86,1%	16,3%	83,7%	16,2%	83,8%	20,9%	79,1%	20,1%	79,9%	18,9%	81,1%
Combined Disorders (χ^2= 1,8; ρ = 0,780)	5	74	18	405	13	295	30	722	23	644	89	2140
	6,3%	93,7%	4,3%	95,7%	4,2%	95,8%	4,0%	96,0%	3,4%	96,6%	4,0%	96,0%

healthy individuals. The age of the surveyed with diagnosed CSD is of additional interest in terms of rapid assessment of the implementation of secondary prevention. Therefore, more detailed information on the gender- and age-dependent incidence of CSD in the medical history is provided in the Tables 7 and 8.

In men, the incidence of EH and IHD increased with age, while the CVD detection remained almost the same. In women, only the frequency of history of EH increased with age, while the incidence of IHD and CVD did not depend on age.

Another important piece of information was obtained on the mobile medical site regarding adherence to drug therapy. It turned out that only 75% of the examined patients with EH took antihypertensive drugs in the last two weeks, but 83% of them had elevated BP at the time of the examination. At the same time, only one in five (19.4%) of respondents with IHD or CVD took lipid lowering drugs in the last two weeks before preventive consultation, but target cholesterol values were detected only in a quarter (26.8%) of the examined patients. It should be added that almost half of those examined with diagnosed CSD had changes on the ECG, which indirectly indicated insufficient effectiveness of the follow-up of these patients.

Thus, not only behavioral, but also nutritional RFs of NCD are detected both in the surveyed men and women quite often. Their frequency is determined by both gender and age, which should be considered in preventive measures. At the same time, it is noteworthy that the detectability of RFs of NCD

Table 7. *Detection of diseases of the circulatory system in men depending on age (abs. And%)*

Circulatory system diseases	Age (years)										Total	
	<20		20 — 35		36 — 45		46 — 60		>60			
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not
Hypertonic disease	1	67	14	344	18	138	60	214	37	151	130	914
(χ^2= 63.037 P = 0.000	**1,5%**	98,5%	**3,9%**	96,1%	**11,5%**	88,5%	**21,9%**	78,1%	**19,7%**	80,3%	**12,5%**	87,5%
Coronary heart disease	2	66	15	343	7	148	16	255	20	168	60	980
(χ^2= 11.298 P = 0.023)	**2,9%**	97,1%	**4,2%**	95,8%	**4,5%**	95,5%	**5,9%**	94,1%	**10,6%**	89,4%	**5,8%**	94,2%
(χ^2= 3.353 P = 0.501)	0	68	2	355	1	154	1	270	3	183	7	1030
	0,0%	100,0%	**0,6%**	99,4%	**0,6%**	99,4%	**0,4%**	99,6%	**1,6%**	98,4%	**0,7%**	99,3%

Table 8. *Detection of diseases of the circulatory system in women, depending on age (abs. and%)*

Risk factor	Age (years)										Total	
	<20		20 — 35		36 — 45		46 — 60		>60			
	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not	Yes	Not
Hypertonic disease	1	77	7	411	31	252	136	539	166	463	341	1742
χ^2= 109.858 P = 0.000	**1,3%**	98,7%	**1,7%**	98,3%	**11,0%**	89,0%	**20,1%**	79,9%	**26,4%**	73,6%	**16,4%**	83,6%
Coronary heart disease	6	73	22	395	28	254	52	617	56	575	164	1914
χ^2= 6.397 P = 0.171	**7,6%**	92,4%	**5,3%**	94,7%	**9,9%**	90,1%	**7,8%**	92,2%	**8,9%**	91,1%	**7,9%**	92,1%
Cerebrovascular disease	0	78	4	413	2	277	6	659	5	619	17	2046
χ^2= 0.834 P = 0.934	**0,0%**	100,0%	**1,0%**	99,0%	**0,7%**	99,3%	**0,9%**	99,1%	**0,8%**	99,2%	**0,8%**	99,2%

in the visitors of shopping centers and rural health posts in the Tver Region was, on the one hand, significantly higher than detectability during health check-up of the population of the Tver Region in 2016, and, on the other, was comparable with the results of other authors [9]. Such dissonance in the RFs of NCD detection in conditions of pre-primary care and health check-up can be explained by the low effectiveness of the latter, which requires the use of additional organizational approaches for the correction of RFs of NCD. This is due to the fact that, according to the authors [10, 11, 12, 13], RFs contribute to high NCD prevalence and mortality. Concerning the latter, it should be noted that according to data for 2018 [14], CSD mortality rates in the Tver Region are the highest and remain 1.5 times higher than the national average. There is an opportunity to improve the situation in the Tver Region, since 79% of individuals who went through preventive consultation in shopping centers and rural health posts expressed the desire to correct the RFs of NCD. It is only necessary to improve organizational and medical approaches in the CSD prevention, including using mHealth.

Of course, within the framework of this study of the pharmacoepidemiological situation in the outpatient treatment of CSD it is difficult to determine the main reasons for its low effectiveness, but we can assume the following: doctors conduct insufficient explanatory work on the need to take antihypertensive and lipid lowering agent, and patients have low adherence to their intake.

The above unfavorable situation with the outpatient treatment of EH, IHD and CVD may have a negative impact on CSD mortality in the Tver Region. Taking into account the results of other studies [15], it can be assumed that a detailed analysis of the pharmacoepidemiological situation of outpatient treatment of EH, IHD and CVD in Tver and its subsequent correction will increase not only patient adherence to drug therapy, but also its effectiveness in terms of achieving target BP and cholesterol levels. As demonstrated [16], the latter circumstance is important in reducing CSD mortality.

To solve the identified problems during CSD prevention, a number of measures can be implemented. Firstly, perform in-depth preventive consultation not only in the outpatient clinic (prevention unit) as currently provided for in adult health check-up [7], but also in shopping centers, in order to increase adherence to the doctor's recommendations for correction of RFs of NCD, including antihypertensive and lipid-lowering therapy. Secondly, use information technology capabilities (patient's online account) for prolonged virtual contact with patients, thus increasing their adherence to the doctor's recommendations for correction of RFs of NCD. Moreover, the vast majority of visitors of shopping centers who went through preventive consultation expressed the desire to change their lifestyle for the better. Finally, introduce wide use of virtual ECG registration technologies in both outpatient and home conditions, in order to objectify the processes occurring in the myocardium under the influence of correction of the RFs of NCD.

Conclusions

1. More than half of the visitors at the mobile medical site were people of working age.
2. The majority of patients who underwent preventive consultation had both behavioral and nutritional RFs of NCDs; one-third had CSD.
3. The absolute majority of patients with CSD did not take antihypertensive or lipid lowering agents in the last two weeks before preventive consultation; in most cases, they did not achieve target BP and cholesterol levels.
4. In order to improve the effectiveness of NCD prevention, it is possible to use mobile health technologies in crowded places that allow not only to conduct in-depth preventive consultation outside medical institutions, but also to provide patients with an individual online account to self-monitor the correction of RFs of NCD.

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References:

1. Healthcare in Russia. 2017. The Federal State Statistics Service. [Electronic resource]. URL: http://www.gks.ru/bgd/regl/b17_34/Main.htm http://www.gks.ru/bgd/regl/b17_34/Main.htm (date of the application: 24.05.2019). [In Russian]
2. Drapkina O. M, Samorodskaya I. V., Starinskaya M. A. et al. Comparison of Russian regions in terms of standardized death rates from all causes and diseases of the circulatory system in 2006–2016. Preventive medicine. 2018; 21 (4): 4–12. https://doi.org/10.17116/profmed20182144. [In Russian]
3. Chestnov O. P., Kulikov A. A. Noncommunicable diseases as a priority for global health. Preventive medicine. 2013; 16 (4): 3–7. [In Russian]
4. Order of the Ministry of Health of the Russian Federation of November 30, 2017 N 965n «On approval of the procedure for the organization and provision of medical care using telemedicine technologies». [Electronic resource]. URL: https://normativ.kontur.ru/document?moduleId=1&documentId=306114 (date of the application: 24.05.2019). [In Russian]
5. M-Health: new horizons for health through mobile technologies: second global survey on eHealth. WHO, 2011. [Electronic resource]. URL: www.who.int/goe/publications/goe_mhealth_web.pdf date of the application: 24.05.2019).
6. Chestnov O. P., Boytsov S. A., Kulikov A. A. et al. Mobile health: international experience and prospects. Preventive medicine. 2014; 4: 3–9. [In Russian]
7. Order of the Ministry of Health of Russia dated 13.03.2019 N 124n «On approval of the procedure for conducting preventive medical examination and clinical examination of certain groups of the adult population». [Electronic resource]. URL: http://p27spb.ru/wp-content/uploads/2018/07/124n.pdf (date of the application: 24.05.2019). [In Russian]
8. Epidemiological dictionary edited by John M. Last for the International epidemiological Association. [Electronic resource]. URL: http://osdm.org/wp-content/uploads/2014/05/epid_dict.pdf http://osdm.org/wp-content/uploads/2014/05/epid_dict.pdf(date of the application: 24.05.2019). [In Russian]
9. Balanova Yu. A., Kontsevaya A. V., Shalnova S. A. et al. Prevalence of behavioral risk factors of cardiovascular diseases in the Russian population the research results of the ESSE-RF. Preventive medicine. 2015; 5: 42–52. [In Russian]
10. Boytsov S. A., Chuchalin A. G. et al. Recommendations Prevention of chronic non-communicable diseases. State Research Center for Preventive Medicine of the Ministry of Health of the Russian Federation. 2013. [Electronic resource]. URL: http://webmed.irkutsk.ru/doc/pdf/prevent.pdf. (date of the application: 24.05.2019). [In Russian]
11. Oganov R. G., Maslennikova G. Ya. The Epidemic of cardiovascular diseases can be stopped by strengthening prevention. Preventive medicine. 2009; 6: 3–7. [In Russian]
12. Boytsov S. A., Oganov R. G. A Quarter century in the search for the best ways to prevent non-communicable diseases and new challenges for the future. Preventive medicine. 2013; 5: 3–8. [In Russian]
13. Dolgalev I. V., Karpov R. S. The Stability of risk factors of cardiovascular disease according to the results of 17 years of observation. Russian cardiology journal 2015; 1 (117): 67–71. [In Russian]
14. Fisenko V. S., Rogina N. I., Korochkin A. V. Implementation of the main targets to reduce deaths from diseases of the circulatory system in the constituent entities of the Russian Federation (according to the results of Supervisory activities of Roszdravnadzor). Vestnik Roszdravnadzora 2015; 5: 26–32. [In Russian]
15. Leonova M. V., Steinberg L. L., Belousov Yu. B. et al. The Results of pharmacoepidemiological study of arterial hypertension PYTHAGORAS IV: commitment of doctors. Russian cardiology journal 2015; 1: 59–66. [In Russian]
16. Lyusov V. A., Kharchenko V. I. Kakorin V. A. et al. The Determination of target levels of blood pressure during antihypertensive therapy in patients with severe, resistance to therapy, arterial hypertension. Russian cardiology journal 2008; 2; 67–82. [In Russian]

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VASCULAR STIFFNESS AND LEFT VENTRICLE REMODELING IN PATIENTS WITH HYPERTENSION RECEIVING RENAL REPLACEMENT THERAPY

Abstract

Objective. The objective of our study was to compare vascular stiffness and left ventricular remodeling in patients with hypertension receiving renal replacement therapy and in patients with essential hypertension.

Materials and methods. The study enrolled 158 patients, divided into 4 comparable in age groups: 32 patients on planned hemodialysis, 37 recipients of renal transplant, 69 patients with essential hypertension and 20 healthy volunteers. All the patients underwent 24-hour blood pressure monitoring with an assessment of VS and central BP. Mean 24-hour, night and daytime SBP, DBP, PBP, SBP_{ao}, PWV_{ao}, RWTT and PTIN, and the decrease degree of SBP and DBP were determined. M- and B-mode echocardiography was performed in all patients.

Results. No significant difference was detected in central and peripheral BP between patients on PH and after KT. Comparing patients on RRT with the group of essential hypertension, the office systolic and diastolic BP values did not differ significantly. However, significantly higher night DBP and SBP_{ao} values were detected in patients on RRT, and in the patients after KT night SBP and PBP levels were also increased. PWV_{ao} increase of more than 10 m/s was detected only in patients on RRT. In the groups of patients with hypertension 24-hour VS differed significantly from the group of healthy volunteers. PTIN showed more obvious difference: in the healthy volunteers, it was in the range of 80–90%, in the patients with essential hypertension — 50–60%, and in the patients on PH and after KT it was 20–40%. In all groups of patients with hypertension, the mean LV posterior wall thickness and the interventricular septum thickness were close to the upper limit of the norm. In these groups, the LV relative wall thickness was also increased. In both groups on RRT, LVMI was increased compared to the norm (≤116 g/m^2 in males and ≤ 96 g/m^2 in females). All patients showed normal LV systolic function and LV dimensions. LVEDD was significantly higher in patients on PH, and LVPWT — in patients after KT, compared to the group of essential hypertension. Furthermore, significantly higher values of LVMI and IVST were detected the group of PH in comparison with after KT. In addition, in all the groups of patients with hypertension, there was a tendency to LV spherification in comparison with healthy volunteers, and in the group of essential hypertension the difference was more significant compared with the group on RRT.

Conclusion. In patients with hypertension, receiving renal replacement therapy, higher mean 24-hour aortic pulse wave velocity, central pressure, and longer period of aortic pulse wave velocity increase are recorded than in patients with essential hypertension with comparable values of office BP.

Key words: *renal transplantation, planned hemodialysis, vascular stiffness, pulse wave velocity, 24-hour blood pressure monitoring, PTIN*

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Aix — index of augmentation, PTIN — Pulse Time Index of Norm, RWTT — Reflected Wave Transit Time, BP — blood pressure, LVH — left ventricular hypertrophy, (d) — mean daily values, DBP — diastolic blood pressure, RRT — renal replacement therapy, ACEI — angiotensin converting enzyme inhibitors, LVMI — left ventricular mass index, LVEDD — end-diastolic diameter of the left ventricle, LVESD — end systolic diameter of the left ventricle, LV — left ventricle, LVM — left ventricular mass, (n) — mean values, LVRT — relative thickness of left ventricular walls, PBP — pulse blood pressure, PH — planned hemodialysis, (s) — mean 24-hour values, SBP — systolic blood pressure, SBP_{ao} — central blood pressure, VS — vascular stiffness, GFR — glomerular filtration rate, 24-hour BPM — 24-hour blood pressure monitoring, PWV_{ao} — pulse wave velocity in the aorta, CVC — cardiovascular complications, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, KT — kidney transplantation, EF — ejection fraction, CKD — chronic kidney disease, Echo — Echocardiography

Introduction

The problem of early and non-invasive diagnosis of target organ damage in hypertension remains extremely topical. Pulse wave velocity in the aorta (PWV_{ao}) is considered one of the methods, which can be used for this purpose [1–3]. In addition to the standard single-step registration of carotid-femoral PWV_{ao}, there is now an opportunity to conduct a 24-hour estimation of vascular stiffness (VS) using the oscillometric method [4–6]. It is important that the study of fluctuations and mean 24-hour PWV_{ao} values enables to provide more complete estimation of the vascular wall state than single measurements. At present, the results of the study of 24-hour VS using single-cuff oscillometry in healthy volunteers and patients with essential hypertension are known [7–9]. In patients on planned hemodialysis (PH) and in patients after kidney transplantation (KT), the features of 24-hour heart rate changes remain poorly understood. However, cardiovascular complications (CVCs) play a leading role among the causes of mortality among these patients [10, 11]. Therefore, timely identification of signs of vascular wall damage is very important in the context of initiation of prevention of CVC progression and measures to increase life expectancy.

Study objective

To carry out a comparative analysis of vascular stiffness and left ventricular remodeling in patients with hypertension receiving renal replacement therapy and with essential hypertension.

Materials and methods

The study enrolled 158 patients. Patients with secondary renal parenchymal hypertension and terminal chronic kidney disease (CKD) (GFR <15 mL/min) comprised two main groups: 32 patients (18 males and 14 females) receiving PH aged 34.4 [25.5; 48] years (mean duration of PH was 24 [9;52] months) and 37 recipients of a kidney transplant (18 males and 19 females) aged 39 [32; 46] years (mean time after surgery was 19 [10; 36] months, and the mean duration of the previous dialysis period was 24 [8; 48] months). The comparison groups were as follows: 69 patients with essential hypertension selected in pairs with patients with nephrogenic hypertension (gender, age, extent and duration of hypertension, office values of BP and antihypertensive therapy were taken into account); and 20 healthy volunteers (16 males and 4 females) composed the control group. The groups of the examined patients were comparable in age, taking into account the fact,

proven as far back as 1964 by N.N. Savitsky, that only age has a decisive effect on VS in both healthy and sick persons [12].

Exclusion criteria for all groups of patients were: Body mass index >30 kg/m² (due to deterioration of quality of recording of the oscillometric curve with an increase in soft tissue thickness above the brachial artery), unstable clinical status, diabetes mellitus, cardiac arrhythmias (atrial fibrillation and flutter, frequent supraventricular and ventricular extrasystoles), confirmed ischemic heart disease, NYHA II-IV chronic heart failure, severe dyslipidemia, acute inflammatory diseases, exacerbation of chronic diseases, cancer, thyroid disease, connective tissue diseases, history of professional sports, and pregnancy. Additional exclusion criteria for patients with CKD were history of KT, chronic transplant rejection, uncorrected calcium and phosphorus metabolism disorders. Twenty-one patients on PH, 34 kidney transplant recipients and 55 patients with essential hypertension received antihypertensive therapy including angiotensin converting enzyme inhibitors (ACEI), β-blockers, calcium channel blockers and centrally acting drugs (moxonidine). After KT, all subjects also received immunosuppressive therapy. All patients underwent 24-hour monitoring of BP using a portable automatic BPLab monitor with assessment of vascular stiffness and aortic pressure (SBP_{ao}) values using Vasotens technology (Petr Telegin OOO, N. Novgorod). Patients receiving PH were measured within the interdialysis period. BP was recorded by the oscillometric method in automatic mode on the brachial artery for 22–24 hours, against the background of normal physical activity with an interval between measurements of 20 minutes during daytime and 40 minutes at night. Throughout the monitoring period, the patients kept a diary, which reflected the duration and quality of night sleep, levels of physical and emotional activity, eating, taking medications, smoking and changes in well-being. The study was considered informative if the number of successful blood pressure measurements was at least 70% of all planned measurements during the day, or at least 21 measurements in the afternoon and at least 7 measurements during sleep [13]. Parameters of SBP_{ao} and VS were obtained by post-processing the oscillometric curve obtained at the brachial artery using mathematical algorithms incorporated into the Vasotens software (BPLab, N. Novgorod). Mean 24-hour (s), daily (d) and night (n) values of systolic and diastolic pressure (SBP (s), SBP (d), SBP (n), DBP (s), DBP (d), DBP (n)), pulse BP (PBP (s), PBP (d), PBP (n)), central arterial pressure (SBP_{ao}(s), SBP_{ao}(d), SBP_{ao}(n)), pulse wave velocity in the aorta (PWV_{ao}(s), PWV_{ao}(d), PWV_{ao}(n)), reflected wave transit time (RWTT (s), RWTT (d), RWTT (n)), augmentation index (Aix) and pulse time index of norm during 24 hours, daytime and at night (PTIN (s), PTIN (d), PTIN (n)), and the degree of systolic and diastolic BP decrease. The quality control of each BP measurement was carried out based on visual assessment of the oscillometric curves on the clinical report screen. To calculate outpatient PWV_{ao} and associated indices, the distance between the jugular fossa and the superior margin of the pubic symphysis — the jugulum — symphysis distance (projection of the aortic length) — was measured in all patients. Assessment of SBP_{ao} was performed by plotting the curve of the average shape of pulsation in the ascending aorta based on the curve of pressure change in the brachial artery using the forward and backward Fourier transform and the transfer function developed by O'Rourke et al. on the basis of a comparison of direct invasive measurement of BP in the aorta and brachial artery, and using the mathematical algorithms integrated in the Vasotens software [14]. At present, there is no doubt that the value of central BP better correlates with the severity of left ventricular hypertrophy (LVH) and cardiovascular outcomes [7, 15, 16]. Therefore, its determination is preferable in the management of hypertensive patients.

PTIN was calculated using the formula:

$$PTIN, \% = (\Sigma T_k) / T_m * 100,$$

where ΣT_k is the sum of all periods during which the PWV_{ao} does not exceed the threshold value of 10 m/s, T_m is the total monitoring time. Normally, the value of the PTIN index is close to 100%. During the study, PWV_{ao} values are recorded both above and below the threshold value of 10 m / s. Twenty-four-hour PTIN indicates the percentage of time when the PWV_{ao} curve is below the line

drawn through the 10 m/s mark. Obviously, there are differences in the clinical status of patients with PWV_{ao} above the threshold value of 0 or 50 or 100 percent of the study time. Accordingly, it is quite appropriate to use the "time index" for PWV_{ao}. It should be noted that in the process of studying the parameters of 24-hour VS, the authors proposed various experimental indices to improve the diagnostic accuracy of 24-hour VS monitoring. However, currently, only the PTIN index confirms its informative value.

Echocardiography (Echo) was carried out on the DC-7 device, Mindray (China), in patients receiving renal replacement therapy (RRT and on the Vivid 7 Dimension device, GE (USA), in patients with essential hypertension and healthy volunteers in M- and B-regimens within a few days after 24-hour BPM. The measurements were carried out in standard EchoCG positions with the determination of the ejection fraction (EF) of the left ventricle (LV), diastolic thickness of left ventricular walls (posterior wall thickness (LVPWT) and interventricular septum thickness (IVST), mm), end-diastolic and end-systolic LV diameters (EDD, ESD). Calculation of the left ventricular wall relative thickness (LVRT) and left ventricular mass (LVM) using the Devereux R.B formula, and left ventricular mass index (LVMI), as the ratio of LVM to body surface area, was performed. LVMI ≥116 g/m^2 was considered as threshold value for LV hypertrophy for males, and ≥96 g/m^2 — for females [17].

The study was approved by the Ethical Committee of the FSBHI "Volga District Medical Center" of FMBA of Russia. All study participants gave written informed consent.

Statistical analysis was performed using the STATISTICA 10.0 software package (StatSoft, Inc., USA). In order to automatically calculate 24-hour BPM values, aortic pressure and LV parameters, we used the 05.00.04 version of the BPStat program (BPLab, Russia). Non-parametric statistical methods were used in the calculations. For descriptive statistics, median and deviations estimated for the 25th and 75th percentiles (Me ± SD) were calculated. For comparison of two independent groups, the Mann-Whitney U test was used. The Kruskal-Wallis test was used to compare three independent groups. In the calculation of the correlation between the two signs, the Spearman's correlation analysis was used. The level of statistical significance was assumed to be $p < 0.05$.

Results and discussion

Based on 24-hour BPM results, elevated values of mean daily SBP, DBP and aortic pressure were revealed in all groups of hypertensive patients with both renal and essential hypertension (upper limit of the norm for SBP (d) was 135 mm Hg, DBP (d) — 85 mm Hg, SBP_{ao} — 120 mm Hg). Office values of SBP and DBP and mean night SBP and DBP exceeded the norm only in patients receiving RRT (the upper limit of the norm for office SBP was 139 mm Hg, DBP — 89 mmHg, SBP (n) — 120 mm Hg, DBP (n) — 70 mm Hg). The mean values of PBP in any group of hypertensive patients did not exceed the threshold value of 53 mm Hg. The degree of nocturnal decrease of SBP and DBP was reduced only in groups of patients with kidney disease. The results are presented in Table 1.

As is seen from Table 1, the groups of patients on PH and after KT did not differ significantly in terms of values of central and peripheral blood pressure. Comparison of groups of patients receiving RRT with the essential hypertension group revealed no significant differences in the office SBP and DBP values; but significantly higher values of DBP (n) and SBP_{ao} (n) were detected in patients on RRT, and in patients after KT, SBP (n) and PBP (n) were also increased. Thus, both peripheral and central blood pressure values differed in the groups, which is significant for the development of target organ damage. A significantly lower nocturnal SBP and DBP decrease was observed in patients on PH and after KT (i.e., change in 24-hour BP profile of a non-dipper type). In all groups with hypertension, all 24-hour BPM values significantly differed in comparison with the healthy group.

When considering 24-hour VS parameters, an increase in PWV_{ao} more than 10 m/s was detected only in groups of patients with CKD. Other vascular stiffness indices (Aix and RWTT) also showed a tendency to VS increase in patients receiving RRT,

Table 1. *The results of 24-hour BP monitoring in patients with hypertension of various origin and in healthy volunteers (Me[25р;75р])*

Parameters	Patients with renal hypertension receiving PH (n = 32)	Patients after KT (n = 37)	Patients with essential hypertension (control group) (n = 69)	Healthy persons (n = 20)
Age, years	34.5 [25.5; 48]	39 [32; 46]	39 [29; 48]	32 [27; 40.5]
HR, bpm	74 [64; 83]	69 [61; 80]	65 [59; 78]	69 [63; 80]
office SBP, mm Hg	144 [127; 160][1]	143 [130; 148][1]	138 [127; 144][1]	122 [115; 127]
office DBP, mm Hg	92 [81; 100][1]	91 [82; 98][1]	88 [80; 94][1]	79 [73; 82]
SBP (s), mm Hg	139 [123; 155][1]	138 [125; 143][1]	133 [122; 139][1]	117.5 [108; 122]
SBP (d), mm Hg	140.5 [126.5; 156][1]	137.5 [127; 143][1]	137 [126; 144][1]	119 [109.5; 123.5]
SBP (n), mm Hg	122 [111; 144][1]	129.5 [121; 143][1.2]	117 [110; 123][1]	107 [98; 110.5]
DBP (s), mm Hg	87 [76; 95.5][1]	86 [78; 92][1]	83 [76; 88][1]	74.0 [68; 76]
DBP (d), mm Hg	90 [78; 97][1]	86 [80; 94][1]	87 [79; 93][1]	74.5 [69; 77.5]
DBP (n), mm Hg	76.5 [69; 86][1.2]	79.5 [77; 87][1.2]	71 [65; 76][1]	62.0 [57.5; 68.5]
PBP (s), mm Hg	48 [41; 57.5][1]	51 [42; 56][1]	48 [44; 54][1]	44.0 [40.5; 48]
PBP (d), mm Hg	49.5 [41; 59.5][1]	51 [43; 57][1]	48 [45; 55][1]	44.0 [40.5; 48]
PBP (n), mm Hg	45.5 [42; 55][1]	48.5 [43; 57][1.2]	45 [41; 49][1]	40.5 [39.5; 45.5]
Nocturnal SBP decrease, %	9 [3; 16][1.2]	8 [2; 14][1.2]	12 [9; 19][1]	17 [12; 20]
Nocturnal DBP decrease, %	6 [1; 11][1.2]	8 [1; 12][1.2]	13 [11; 17][1]	18 [13; 19]
Mean 24-hour SBP_{ao}, mm Hg	127.5 [113; 143.5][1]	127 [119; 132][1]	122 [113; 128][1]	105.5 [99; 110]
Mean daily SBP_{ao}, mm Hg	129.5 [116; 145.5][1]	126 [120; 132][1]	126 [117; 133][1]	106.5 [101; 111.5]
Mean night SBP_{ao}, mm Hg	115.5 [100; 135.5][1.2]	119.5 [114; 134][1.2]	109 [102; 114][1]	95 [88; 100]

Note: [1] — significant differences (р <0.05) with a group of healthy persons, [2] — significant differences (р <0.05) with the group of essential hypertension

although they did not exceed the standard values in any of the studied groups. The results are presented in Table 2.

According to the Table 2, almost all VS parameters in groups on RRT during daytime and at night, except for the augmentation index, significantly differed from the group of patients with essential hypertension, which indicates more pronounced changes in the vascular wall in patients with kidney disease. In all groups with hypertension, all 24-hour VS parameters significantly differed in comparison with the healthy group. PWV_{ao} in the healthy group was significantly lower than the upper limit of the norm (10 m/s) (mean 24-hour PWV_{ao} was 6.6 [6.3, 6.9] m/s); in patients with essential hypertension PWV_{ao} was at the upper limit of the norm (mean 24-hour PWV_{ao} was 9.9 [9.2; 10.4] m/s); and in patients with hypertension receiving renal replacement therapy it exceeded 10 m/s by several tenths (mean 24-hour PWV_{ao} in patients on PH was 10.7 [9.5; 11.2] m/s, and in patients after KT — 10.3 [9.7; 11] m/s). PTIN in the study groups differed more clearly: in healthy volunteers, it was in the range of 80–90%; in patients with essential hypertension, it was 50–60%, and in patients on PH and after KT — 20–40%. The augmentation index was within normal limits, but there were differences in this parameter in the groups of patients with hypertension and healthy volunteers.

In all groups of patients with hypertension, the mean IVST and PWT were close to the upper limit of the normal value. In the groups of patients with

hypertension, there was also an increase in the relative thickness of the LV walls. In both groups of patients receiving RRT, an increase in LVMI was observed compared to the normal value (≤116 g/m^2 in males and ≤96 g/m^2 in females). LV systolic function and LV cavity dimensions were recorded within normal values in all of the examined groups. The results are presented in Table 3.

As is seen from Table 3, in all groups of patients with hypertension compared with healthy volunteers, significantly higher values of the LV wall thickness, LVRT, LVMI, and EDD were observed. When comparing patients with hypertension receiving renal replacement therapy and patients with essential hypertension, significantly higher LVMI values were obtained. In addition, significantly higher

Table 2. *The results of 24-hour VS monitoring in patients with hypertension of various origin and in healthy volunteers (Me[25p;75p])*

Parameters	Patients with renal hypertension receiving PH (n = 32)	Patients after KT (n = 37)	Patients with essential hypertension (control group) (n = 69)	Healthy persons (n = 20)
Aix, %	–28 [–42; 5][1]	–29 [–47; 6][1]	–39[1][–52; –27.5]	–52 [–63; –44.5]
RWTT (s), ms	133 [127.5; 140.5][1,2]	135 [129; 143][1,2]	143 [133; 154][1]	156.0 [148, 159.5]
RWTT (d), ms	132.5 [124; 139][1,2]	134.5 [127; 142][1]	141 [131; 153][1]	154.0 [146; 159]
RWTT (n), ms	139 [130.5; 151][1,2]	140 [131; 153][1,2]	149 [138; 162]	163.0 [160; 169]
PWV_{ao} (s), m / s	10.7 [9.5; 11.2][1,2]	10.3 [9.7; 11][1,2]	9.9 [9.2; 10.4][1]	6.6 [6.3; 6.9]
PWV_{ao} (d), m / s	10.8 [9.9; 11.4][1,2]	10.4 [10; 11.3][1,2]	10 [9.3; 10.7][1]	6.6 [6.4; 7]
PWV_{ao} (n), m / s	10.2 [8.6; 11][1,2]	10.2 [8.9; 11][1,2]	9.2 [8.6; 10][1]	6.1 [5.9, 6.8]
PTIN (s), %	27 [9; 69.5][1,2]	22 [1; 50][1,2]	61 [15; 85][1]	89 [47; 99]
PTIN (d), %	17.5 [1.5; 58.5][1,2]	19 [0; 37][1,2]	50 [10; 71][1]	80 [46; 90]
PTIN (n), %	36.5 [6; 99.5][1,2]	17 [0; 75][1,2]	48 [15; 75][1]	78 [57; 100]

Note: [1] — significant differences (p <0.05) with a group of healthy persons, [2] — significant differences (p <0.05) with the group of essential hypertension

Table 3. *The results of echocardiography in patients with hypertension of various origin and in healthy volunteers (Me [25p; 75p])*

Parameters	Patients with renal hypertension receiving PH (n = 32)	Patients after KT (n = 37)	Patients with essential hypertension (control group) (n = 69)	Healthy persons (n = 20)
Age, years	34.5 [25.5; 48]	39 [32; 46]	39 [29; 48]	32 [27; 40.5]
IVST, mm	12.5 [10; 13.5][1,2,3]	11.7 [9; 12.5][1]	11 [10.4; 13][1]	8 [7.8; 9.1]
LVPWT, mm	11 [10; 12.3][1]	12 [11; 12.8][1,2]	10.5 [9.2; 11][1]	8 [7.2; 8.1]
LVRT	0.45 [0.38; 0.46][1]	0.46 [0.44; 0.56][1]	0.47 [0.43; 0.52][1]	0.35 [0.32; 0.38]
LVMI, g / m^2	129 [102; 137][1,2,3]	119 [104; 131][1,2]	95 [83; 105][1]	65 [59; 73]
EDD, mm	51.8 [49; 56.4][1,2]	50 [43; 53][1]	47.4 [43.5; 51.2][1]	45.4 [43.7; 48]
ESD, mm	33 [28; 40.6][1,3]	30.3 [25.2; 32.2]	30.7 [29.6; 32.5][1]	29.4 [28.1; 30.5]
EF, %	59 [58; 74]	61 [52; 76]	64.5 [62; 66]	67 [64; 70]

Note: [1] — significant differences (p <0.05) with a group of healthy persons, [2] — significant differences (p <0.05) with the group of essential hypertensions, [3] — significant differences (p <0.05) with the group of patients after KT

Table 4. *Correlation between LV wall thickness, LVMI, and 24-hour VS monitoring parameters (mean 24-hour PWVao and PTIN)*

Analyzed parameters	Patients on PH (n = 32)		Patients after KT (n = 37)	
	SpearmanR	ρ	SpearmanR	ρ
Age & PTIN	–0.72 *	0.02	–0.64 *	0.01
Age & PWV_{ao}	0.53	0.05	0.58 *	0.02
IVST & PTIN	–0.23	0.52	–0.57 *	0.03
IVST & PWV_{ao}	0.60 *	0.04	0.41	0.13
LVPWT & PTIN	–0.19	0.59	–0.58 *	0.03
LVPWT & PWV_{ao}	0.58 *	0.05	0.43	0.11
LVMI & PTIN	–0.67	0.22	–0.66 *	0.01
LVMI & PWV_{ao}	0.60	0.28	0.61 *	0.02

***** — significant correlation (ρ <0.05)

EDD was recorded in patients on PH in comparison with essential hypertension patients, and in patients after KT there was higher LVPWT. Significant differences were found in LVMI, IVST and LV ESD between the groups of patients on PH and after KT.

Thus, the results of Echo in the examined groups revealed an increase in LVMI in the following series: healthy volunteers < patients with essential hypertension < recipients of kidney transplant < patients on planned hemodialysis. Concomitant LV hypertrophy was detected in patients receiving RRT, and concentric remodeling was observed in patients with essential hypertension. Analysis of linear parameters in all groups of patients with hypertension showed a tendency of LV spherification as compared to the control group; and in the group of essential hypertension, it was more significant compared to the renal hypertension group.

In the groups of patients receiving RRT, the correlation of LV wall thickness, LVMI, and 24-hour VS monitoring parameters (mean 24-hour PWV_{ao} and PTIN) was analyzed. The results are presented in Table 4.

According to the Table 4, in the group of patients receiving PH, significant correlation was found only for mean 24-hour PWV_{ao} and thickness of LV walls. Significant correlation coefficients were found for kidney transplant recipients for PTIN and IVST, LVPWT and LVMI (r = –0.66; ρ = 0.01). Correlation was found for LVMI and PWV_{ao} (r = 0.61; ρ = 0.02), although it was slightly lower than the similar correlation with the PTIN index. This means that with decreasing PTIN, IVST, LVPWT and LVMI increase.

Thus, a decrease in the PTIN index, which reflects a more frequent or longer 24-hour increase of PWV_{ao}, correlates with an increase of hypertensive LV remodeling in patients after KT, whereas in patients on PH, the thickness of LV walls is associated with the mean 24-hour PWV_{ao}.

Conclusion

In patients with hypertension, receiving renal replacement therapy, higher mean 24-hour aortic pulse wave velocity, central pressure, and longer period of aortic pulse wave velocity increase are recorded than in patients with essential hypertension with comparable values of office BP. The best indicator of these differences is PTIN with its significantly lower value in patients with CKD than in patients with essential hypertension.

Higher vascular stiffness, systolic and diastolic night BP values, as well as the frequency of non-dipper and night-picker 24-hour profiles are obtained in patients with hypertension, receiving renal replacement therapy, in comparison with patients with essential hypertension.

In patients with hypertension associated with CKD, higher LVMI values and less pronounced left ventricle spherification are recorded than in patients with hypertension of the same grade. In kidney transplant recipients, LVMI is significantly lower than in patients receiving planned hemodialysis, which may indicate a positive effect of kidney transplantation on the improvement of cardiac remodeling associated with hypertension.

References:

1. Boytsov S. A., Pogosova N. V., Bubnova M. G. et al. Cardiovascular prevention 2017. National guidelines. Russian Journal of Cardiology. 2018; 23(6): 7–122. doi:10.15829/1560-4071-2018-6-7-122 [In Russian]
2. Williams B., Mancia G., Wilko Spiering W. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur. Heart J. 2018; 39: 3021–3104. doi:10.1093/eurheartj/ehy339
3. Van Bortel L. M., Laurent S., Boutouyrie S. P. et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens. 2012; 30(3): 445–448. doi:10.1097/HJH.0b013e32834fa8b0
4. László A., Reusz G., Nemcsik J. Ambulatory arterial stiffness in chronic kidney disease: a methodological review. Hypertens Res. 2016;.39(4):.192–8. doi:10.1155/2012/178078
5. Rogoza A. N., Balakhonova T. V., Chkhladze N. M. et al. Modern methods of the blood vessels state assessing in patients with hypertension. M.: Atmosfera. 2008; 72 p. [In Russian]
6. Posokhov I. N., Kulikova N. N., Starchenkova I. V. et al. The «Pulse Time Index of Norm» highly correlates with the left ventricular mass index in patients with arterial hypertension. Vascular Health and Risk Management. 2014; 10: 139–44. doi:10.2147/VHRM.S58351
7. Omboni S., Posokhov I. N., Parati G. et al. 24-hour central blood pressure is better associated with target organ damage of hypertension than brachial blood pressure: the Vasotens Registry. Journal of Hypertension. 2017; 35: e82–e83. doi: 10.1097/01.hjh.0000523189.57049.80
8. Merezhanova A., Mazalov K., Tarlovskaya E. et al. Evaluation of circadian oscillation of arterial wall stiffness. Journal of Hypertension. 2016; 34: e131. doi:10.1097/01.hjh.0000491687.02726.a1
9. Rogoza A. N., Kuznetsov A. A. Central aortic blood pressure and augmentation index: comparison between Vasotens and SphygmoCor technology. Research Reports in Clinical Cardiology. 2012; 3: 27–33. doi:10.2147/RRCC.S30994
10. Bikbov B. T., Tomilina N. A. The contingent and treatment quality indicators in patients on replacement therapy of end stage renal disease in the Russian Federation in 1998-2013 years. Report of the Register of Renal Replacement Therapy of the Russian Dialysis Society. Part II. Nephrology and dialysis. 2016; 18(2):98–164. [In Russian]
11. United States Renal Data System. 2018 Atlas of CKD & ESRD. [Electronic resource]. URL: https://www.usrds.org/2018/view/Default.aspx. (date of the application: 05.06.2019).
12. Sawicki N. N. Biophysical basis of blood circulation and clinical methods for the study of hemodynamics. M.: Medicine. 1974; 312 p. [In Russian]
13. Parati G., Stergiou G., O'Brien E. et al. European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability: European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014; 32: 1359–1366. doi:10.1097/HJH.0000000000000221
14. Nichols W. W., O'Rourke M. F., Vlachopoulos C. McDonald's. Blood Flow in Arteries, Sixth Edition: Theoretical, Experimental and Clinical Principles, 6th Edition. London: Hodder Arnold. 2011; 768 p.
15. Litwin M., Obrycki Ł., Niemirska A. et al. Central systolic blood pressure and central pulse pressure predict left ventricular hypertrophy in hypertensive children. Pediatr Nephrol. 2019; 34(4): 703–712. doi:10.1007/s00467-018-4136-7.
16. Palatini P., Rosei E. A., Avolio A. et al. Isolated systolic hypertension in the young: a position paper endorsed by the European Society of Hypertension. J Hypertens. 2018; 36(6): 1222–1236. doi:10.1097/HJH.0000000000001726
17. Lang R. M., Bierig M., Devereux R. B. et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am SocEchocardiogr. 2005; 18: 1440–63. doi:10.1016/j.echo.2005.10.005

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CASE OF GUILLAIN—BARRÉ SYNDROME IN A PATIENT WITH PULMONARY LANGERHANS CELL HYSTIOCYTOSIS

Abstract

Langerhans cell histiocytosis is a rare disease characterized by various clinical patterns: from isolated lung lesions to severe involvement of other organs. This clinical case demonstrates a rare combination of pulmonary Langerhans cell histiocytosis and Guillain—Barré syndrome due to possible common mechanisms of the disease development mediated by the CD1A expression.

Key words: *Langerhans cell histiocytosis, Guillain—Barré syndrome, clinical case*

Conflict of Interests

The authors declare no conflict of interests.

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LV — left ventricle, GBS — Guillain—Barré syndrome, PCR — polymerase chain reaction

Introduction

Guillain—Barré syndrome (GBS) (ICD 10 code is G 61.0) is an autoimmune peripheral neuropathy, which is the most common cause of acute tetraparesis. In the Russian Federation, the incidence corresponds to global data and is on average 1.8 per 100,000 per year [1].

Most authors agree that this refers to post-infectious autoimmune peripheral neuropathy. Because of molecular mimicry of lipopolysaccharide

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structures (ganglioside antigens) of microorganisms and nerve cells, antibody- and cell-mediated immunity is triggered, and the latter plays a key role in GBS [2]. CD1 molecules specialize in the capture and presentation of glycoproteins by T-cells. Meanwhile, CD1a+/CD207+ expression is a key histopathological finding typical for Langerhans cell histiocytosis, a disease characterized by proliferation of CD1a+ dendritic cells with local or multiple organ lesions. CD1 gene polymorphism can influence predisposition to the development of Guillain—Barré syndrome, which is widely discussed [3, 4].

Meanwhile, we found no clinical cases of a combination of pulmonary histiocytosis and Guillain—Barré syndrome in the PubMed database using the keywords "Langerhans cell histiocytosis AND Guillain—Barré syndrome".

Case Report

Lung pathology was revealed in patient G., 56 years old, during regular health check-up. For its clarification, we performed chest computer tomography on 3.04.15, and disseminated lung disease of unknown etiology was diagnosed based on the CT results. From 14.04 to 02.05.2015, the patient was in the Ulyanovsk Regional Clinical TB Dispensary, where video-assisted thoracic surgery (VATS) with biopsy of the right lung was performed on 17.04.2015. In the initial study of the lung biopsy, evidence of histiocytosis was obtained: "Lung tissue with granulomatous pattern of inflammation with signs of vasculitis and bronchiolitis with areas of eosinophilic infiltration, with formation of foci of desquamative interstitial pneumonia, with formation of foci of fibrosis with deposition of coal pigment." No signs of tumor growth and specific inflammation were found. To verify the diagnosis, the sample was sent to the Republican Clinical Oncologic Dispensary of the Ministry of Health of the Republic of Tatarstan. The following conclusion was made: CD1A, S100 positive reaction in cell clusters. CD68 slightly positive reaction. Langerhans cell proliferative activity index (ki67) is 8%. Conclusion: Langerhans cell histiocytosis. Based on the obtained data, Langerhans cell histiocytosis with isolated lung lesion was diagnosed.

The patient has hypertension for a long time; antihypertensive drugs are taken irregularly. There are no cardiovascular diseases in family history. He denies having bad habits, including smoking. Negative PCR (polymerase chain reaction) results on Epstein—Barr virus DNA were obtained.

Since 26.04.15, he has noted numbness in fingers, weakness in the legs. Due to increasing weakness and deterioration of sensitivity in the extremities brain, computed tomography was performed on 29.04.15, and moderate hydrocephalus was revealed. The condition worsened: Numbness of lips and dysarthria occurred. On May 2, 2015, the patient was transferred to the Neurological Department of the Central City Clinical Hospital of Ulyanovsk. During examination in the Neurological Department, consciousness was preserved, the patient was in a forced supine position. Body temperature was 36.9 °C. Body mass index was 28.7 kg/m^2. The skin and visible mucous membranes were clear and of normal color. Peripheral lymph nodes were not enlarged. Vesicular breathing over the lungs, and there were no crackles. Respiratory rate was 19 per minute. Heart tones were muted, heart rate — 104 per minute, blood pressure — 140 and 100 mm Hg on both hands. The abdomen during palpation was soft, painless; the lower edge of the liver was 2–2.5 cm below the costal margin. There was no peripheral edema.

Neurological status: Adequate. No meningeal symptoms. Convergent strabismus OU. Diplopia is stopped with monocular vision. Bilateral weakness of facial muscles up to 2.0 points. Lagophthalmos on the left side. Eyelash sign is positive on the right side. Pharyngeal reflexes are reduced. There are some difficulties with swallowing. Dysarthria. Dysphonia. Dysphagia. Strength in the upper extremities is reduced up to 2.0 points, in the feet — up to 0.5 points, and there is plegia in the hips with diffuse hypotonia. Conductive hypesthesia from the level of Th2–Th3 and down, more pronounced in the distal parts of stocking and glove type. Tendon areflexia. Plantar reflexes are not triggered. There are no pathological plantar reflexes.

Complete blood count (04.05.15): hemoglobin — 170 g/L, RBC — 5.1×10^{12}/L, WBC — 19.0×10^{9}/L,

ESR 5 mm/h. Blood chemistry (02.05.15): Creatinine — 72.4 mmol/L, alanine aminotransferase — 86 IU/L, total protein — 71 g/L, albumin — 41.21 g/L, total bilirubin — 8.2 mmol/L, glucose — 8.51 mmol/L, cholesterol — 4.52 mmol/L, potassium — 3.79 mmol/L. Prothrombin index — 88%, activated partial thromboplastin time — 30 s, international normalized ratio — 1.1. Glycemic profile (09.05.15): glucose — 6.7–9.7–9.2–6.3 mmol/L. Cerebrospinal fluid was not examined.

Electrocardiography (02.05.15): Sinus rhythm with a heart rate of 104 bpm. PQ — 160 ms. QRS — 90 ms. QTc — 414 ms.

Echocardiography (04.05.15): concentric left ventricular (LV) hypertrophy (LV myocardial mass index — 126 g/m^2). Systolic LV function is preserved, ejection fraction is 53%. Diastolic LV dysfunction of impaired relaxation pattern.

Chest radiography (04.05.15): A chain of metal clips at the level of the third intercostal space of the right lung. Pulmonary pattern is enhanced in the lower basal regions of the right lung. Sinuses are clear. The mediastinum is not displaced.

Ultrasound of the kidneys and bladder (20.05.15): Coral calculus in the left kidney, 18-mm cystic calculus.

Based on patient's complaints, history, examination data, typical neurological status, laboratory and instrumental data, which can exclude focal pathology of the brain, acute demyelinating polyneuropathy (Guillain—Barré syndrome) was diagnosed. Bulbar palsy. Peripheral tetraparesis. The syndrome of oculomotor disturbances.

Hypertension of the 2nd stage, achieved the 1st degree of HT, risk 4. Left ventricular hypertrophy. Urolithiasis. Coral calculus of the left kidney. Cystic calculus. Hyperglycemia.

In the Neurological Department, treatment was performed, including plasmapheresis, intravenous immunoglobulin, and systemic corticosteroids (pulse therapy with metipred 1,000 mg due to histiocytosis) and oral metipred 40 mg, thioctic acid (Berlithion), anticholinesterases (neostigmine, ipidacrine), B vitamins, and antihypertensive drugs (amlodipine, bisoprolol).

The patient's condition stabilized within 4 days after transfer to the Neurological Department: strength in the hands began to grow, range of motions increased, swallowing restored, strength in the hands increased up to 4.0 points, in the hips — up to 3.0 points, and in the feet — up to 4.0 points. On 20.05.15, the patient was discharged with improvement, and considering high rehabilitation potential, he was referred to the Rehabilitation Department.

It is recommended to take corticosteroids with a gradual daily dose reduction to 8 mg of metipred, thioctic acid, B vitamins, and anticholinesterases.

When the patient was contacted by telephone after 3 years, it was found that he feels himself satisfactory, disturbance of sensitivity in the fingers of the lower extremities remained, and there were no complaints related to the respiratory system. He is socially adapted, works, and performs daily physical activity (running). He is under neurologic follow-up and receives annual health resort treatment. Recommended antihypertensive drugs, unfortunately, are taken irregularly.

Discussion

In recent years, the etiology and pathogenesis of histiocytosis have been actively discussed. In addition to infectious histiocytosis, the malignant nature of the disease has been discussed [5]. The favorable course of the disease within 4-year follow-up of the patient, in our opinion, gives evidence against the oncological etiology. On the other hand, no obvious infection was detected while the patient was in the TB dispensary.

It seems to us that in tour patient activation of CD1A typical for Langerhans cell histiocytosis, regardless of the etiological cause, triggered the immune mechanism of the development of autoimmune peripheral neuropathy (Guillain—Barré syndrome). Anti-ganglioside antibodies play a key

role in the development of histiocytosis, and they are also found in the serum of patients with autoimmune neuropathy — ganglioside complexes play an important role in the pathogenesis of Guillain—Barré syndrome [2].

Damage to the central nervous system in histiocytosis is extremely rare and is an inflammatory process resembling paraneoplastic encephalitis [6]. As a rule, pulmonary histiocytosis is isolated and is not accompanied by a multi-organ lesion [5]; such patients are not classified as high-risk according to the prognosis [1, 7]. However, the presented case suggests that even when mono-organ Langerhans cell histiocytosis exists severe life-threatening complications, such as Guillain—Barré syndrome may develop.

Conclusion

This clinical case is of interest from the perspective of possible general mechanisms of both Langerhans cell histiocytosis and Guillain—Barré syndrome. In addition, the presented case shows that patients with isolated pulmonary Langerhans cell histiocytosis require special attention due to the possible development of multi-organ lesions and the development of life-threatening complications, including Guillain—Barré syndrome.

References:

1. Russian Society of Neurology. Guillain—Barre syndrome in adults. Clinical guidelines. 2016; 23 p. [in Russian].
2. Kaida K, Ariga T., Yu R. K. Antiganglioside antibodies and their pathophysiological effects on Guillain—Barré syndrome and related disorders — A review. Glycobiology. 2009; 19(7): 676–692. doi: 10.1093/glycob/cwp027.
3. Liu H., Xing Y., Guo Y. et al. Polymorphisms in exon 2 of CD1 genes are associated with susceptibility to Guillain—Barré syndrome. J Neurol Sci. 2016; 369: 39–42. doi: 10.1016/j.jns.2016.07.029.
4. Cencioni M. T., Notturno F., Caporale C. M. T cell response in acute motor axonal neuropathy. Int J Immunopathol Pharmacol. 2009; 22(4): 1043–50. doi:10.1177/039463200902200420
5. Zinn D. J., Chakraborty R., Allen C. E. Langerhans Cell Histiocytosis: Emerging Insights and Clinical Implications. Oncology (Williston Park). 2016; 30(2): 122–32, 139.
6. Grois N., Prayer D., Prosch H. et al. Neuropathology of CNS disease in Langerhans cell histiocytosis. Brain. 2005; 128(4): 829–38. doi:10.1093/brain/awh403
7. Guo F., Zhang Y. B. Clinical features and prognosis of patients with Guillain—Barré and acute transverse myelitis overlap syndrome. Clin Neurol Neurosurg. 2019; 181: 127–132. doi: 10.1016/j.clineuro.2019.04.014.