ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

РОССИЙСКИЙ КАРДИОЛОГИЧЕСКИЙ ЖУРНАЛ

Russian Journal of Cardiology

SCIENTIFIC, PEER-REVIEWED MEDICAL JOURNAL

RUSSIAN SOCIETY OF CARDIOLOGY

IN ISSUE:

IN FOCUS:

Hypertension

№ 3 | 2020

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

Russian Society of Cardiology

Scientific peer-reviewed medical journal

Mass media registration certificate № 017388 dated 06.04.1998

Periodicity — 12 issues per year
Circulation — 7 000 copies

The Journal is in the List of the leading scientific journals and publications of the Supreme Examination Board (VAK)

The Journal is included in Scopus, EBSCO, DOAJ

Russian Citation Index:
SCIENCE INDEX (2017) 3,152
Impact-factor (2017) 0,690

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

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Open Access

Printed: OneBook, Sam Poligraphist, Ltd. 129090, Moscow, Protopopovsky per., 6. www.onebook.ru

RUSSIAN JOURNAL OF CARDIOLOGY

№ 25 (3) 2020

founded in 1996

Editorial office:
e-mail: cardiojournal@yandex.ru
Tel. +7 (985) 768 43 18

Publisher:
Silicea-Poligraf
e-mail: cardio.nauka@yandex

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3751

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Machine learning for predicting the outcomes and risks of cardiovascular diseases in patients with hypertension: results of ESSE-RF in the Primorsky Krai

Nevzorova V. A.[1], Plekhova N. G.[1], Priseko L. G.[1], Chernenko I. N.[1], Bogdanov D. Yu.[2], Mokshina M. V.[1], Kulakova N. V.[1]

Aim. To assess the prospects of using artificial intelligence technologies in predicting the outcomes and risks of cardiovascular diseases (CVD) in patients with hypertension (HTN).

Material and methods. A software application was created for data mining from respondent profiles in a semi-automatic mode; libraries with data preprocessing were analyzed. We analyzed the main and additional parameters (35) of CVD risk factors in 2131 people as a part of ESSE-RF study (2014-2019). To create a forecasting model, a high-level language Python 2.7 was used using object-oriented programming and exception handling with multithreading support. Using randomization, learning (n=488) and test (n=245) samples were formed, which included data from patients with an established diagnosis of HTN.

Results. The prevalence of HTN among subjects was 34,39%. There were following significant factors for predicting CVD: anthropometric parameters, smoking, biochemical profile (total cholesterol, ApoA, ApoB, glucose, D-dimer, C-reactive protein). As a result of a 5-year follow-up, CVD was found in 235 people (32,06%) with HTN and 187 people (13,38%) without HTN; mortality rates were 1,27% in subjects with HTN and 1,12% — without HTN. The absolute mortality risk among participants with HTN (0,037) was significantly higher ($p<0,05$) than in patients without HTN (0,017). To create a neural network (NN), the basic Sequential model from the Keras library was used. During machine learning, 26 variables important for the CVD development were used as input and 9 neurons — as output, which corresponded to the number of established cardiovascular events. The created NN had a predictive value of up to 97,9%, which exceeded the SCORE value (34,9%).

Conclusion. The data obtained indicate the importance of risk factor phenotyping using anthropometric markers and biochemical profile for determining their significance in the top 20 predictors of CVD. The Python-based machine learning provides CVD prediction according to standard risk assessments.

Key words: cardiovascular risk factors, hypertension, artificial intelligence.

Relationships and activities: the study was supported by the grant of Russian Foundation for Basic Research (№ 19-29-01077).

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Received: 13.02.2020
Revision Received: 21.02.2020
Accepted: 12.03.2020

For citation: Nevzorova V. A., Plekhova N. G., Priseko L. G., Chernenko I. N., Bogdanov D. Yu., Mokshina M. V., Kulakova N. V. Machine learning for predicting the outcomes and risks of cardiovascular diseases in patients with hypertension: results of ESSE-RF in the Primorsky Krai. *Russian Journal of Cardiology*. 2020;25(3):3751. (In Russ.)
doi:10.15829/1560-4071-2020-3-3751

Most often, to predict the risk of cardiovascular diseases (CVD), multivariate regression analysis models are developed, which combines data on a limited number of established risk factors (RF). Such an algorithm assumes that all included RF are linearly associated with CVD outcomes and are characterized by limited interaction between each other or its absence. Due to such a limitative approach to modeling and predictors, these algorithms, in particular, the Framingham, SCORE, and DECODE equations, demonstrate insufficient prognostic efficiency [1]. In various areas, including in medicine, the most effective prognostic approach is data mining, especially, deep neural networks (DNN). For now, there are many libraries ready for use, on the basis of which it is possible to use DNN in practice. Such a methods based on machine learning (ML) increase the efficiency of risk prediction through the use of data warehouses with the independent identification of new risk predictors and complex interactions between them. There is a small number of studies on the prospects of using ML to predict CVD risk. Some studies showed that, compared with the above equations, ML significantly increases the accuracy of CVD risk prediction and, as a result, the number of patients who could benefit more from preventive measures before the onset of severe manifestations [2-4].

The current study presents the potential value of using ML to develop a model for CVD risk prediction using blood pressure (BP) data. We prospectively analyzed data obtained by a cross-sectional examination of 2800 residents of the Primorsky Krai without CVD. This examination was conducted from 2014 to 2019 as a part of ESSE-RF study. To develop a risk prediction model, we used the modern automated high-level language Python and open-source neural-network library Keras. Learning and optimization of DNN were carried out using the Adam algorithm. The prognostic value of DNN in healthy general population, including a clinically significant subgroup of patients with hypertension (HTN), was assessed.

The aim of the study was to assess the prospects of using artificial intelligence technologies in predicting the outcomes and risks of CVD in patients with HTN.

Material and methods

As a part of the ESSE-RF study (2014-2019), cross-sectional examination of Primorsky Krai residents was performed [5]. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. To form a representative sample, we used the continuous method by an individual invitation of participants. There were following inclusion criteria: signed informed consent, age 24-65 years, full completion of the questionnaire, available data on cardiovascular RF. The exclusion criteria were refusal to participate and active cancer. A total of 2,800 people were included in the study; 2131 of them (76,1%) completed the program by 2019. Patterned sampling using the data adjustment algorithm was carried out in a computer program for extracting data from respondents' questionnaires in a semi-automatic mode (Figure 1).

We analyzed the prevalence of main RF: overweight with body mass index (BMI) calculation, waist circumference (WC), BP and pulse pressure (PP) levels; heart rate (HR), smoking, sedentary lifestyle; SCORE 10-year mortality risk (in individuals ⩾40 years old and ⩽65 years old) based on gender, age, systolic blood pressure (SBP), total cholesterol (TC) and smoking status. BP levels were evaluated in accordance with the guidelines [6], where BP ⩾140/90 mm Hg belongs to HTN. Family history of heart

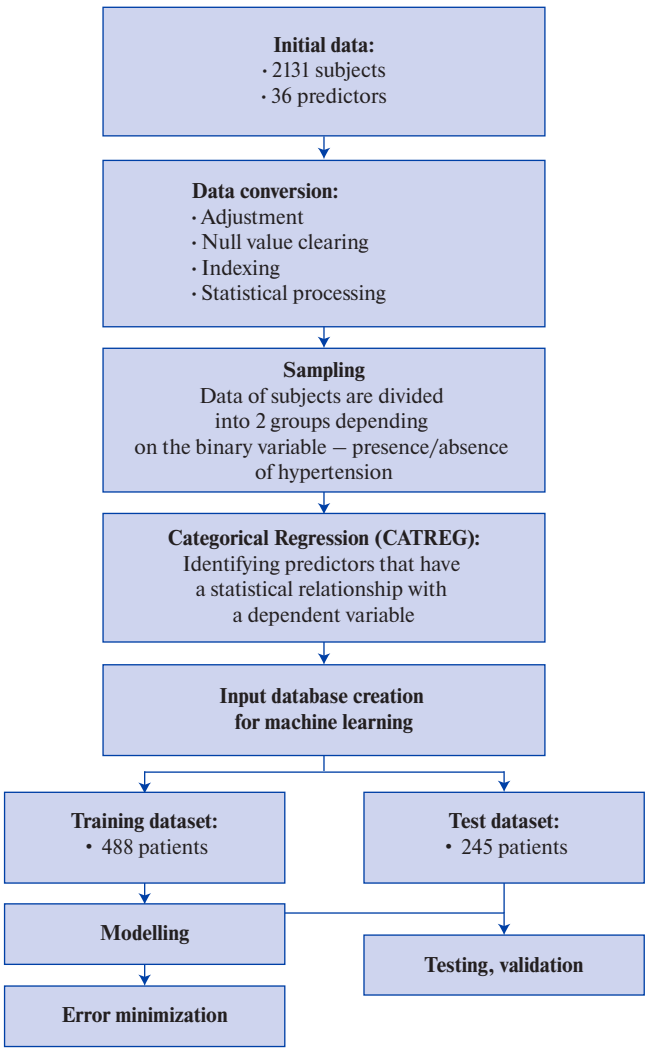


Figure 1. Study design flowchart.

Table 1

Clinical and laboratory characteristics of the subjects

Parameters (M±m)	Group of healthy individuals (n=1398)	Group of hypertensive patients (n=733)
Mean age, years	42,68±11,45	51,56±9,82*
Height, cm	168,82±0,25	168,02±0,36
Weight, kg	75,62±0,44	85,44±0,63*
Body mass index, kg/m^2	26,47±0,14	30,35±0,22*
Waist circumference, cm	85,97±0,39	96,71±0,53*
Mean SBP, mm Hg	123,87±0,27	156,48±0,58*
Mean DBP, mm Hg	75,39±0,22	89,19±0,39*
Mean PP, mm Hg	48,49±0,22	67,29±0,50*
Mean HR, bpm	74,91±0,32	77,75±0,68*
Total cholesterol, mmol/L	5,49±0,03	5,87±0,05*
LDL, mmol/L	3,49±0,03	3,76±0,04*
HDL, mmol/L	1,45±0,01	1,4±0,01*
Triglycerides, mmol/L	1,24±0,02	1,67±0,04*
LP(a), mg/dl	20,19±0,65	20,62±0,92
ApoA, g/l	1,76±0,01	1,81±0,02*
ApoB, g/l	0,82±0,01	0,89±0,01*
Glucose, mmol/L	5,23±0,03	5,86±0,08*
Creatinine, μmol/L	69,12±0,44	71,55±0,77*
Uric acid, μmol/L	315,87± 2,71	356,38±4,01*
D-dimer, μg/L	212,30±7,16	186,05±4,93*
C-reactive protein, mg/L	2,63±0,16	3,78±0,25*

Note: differences are significant at * — p<0,05.

Abbreviations: PP — pulse pressure, LP(a) — Lipoprotein(a), ApoA — apolipoprotein A, ApoB — apolipoprotein B, DBP — diastolic blood pressure, HDL — high density liproproteins, LDL — low density liproproteins, SBP — systolic blood pressure, HR — heart rate.

disease, smoking and alcohol status was determined by anamnesis collection. The parameters of lipid profile (TC, triglycerides (TG), low density lipoproteins (LDL) and high density lipoproteins (HDL), lipoprotein(a) (LP(a)), apolipoprotein A (ApoA), apolipoprotein B (ApoB)), glucose, creatinine, uric acid, D-dimer, C-reactive protein (CRP) levels were determined.

For neural network data analysis, a high-level language Python 2.7 (Python Software Foundation License) was used based on object-oriented programming with exception handling mechanism and multithreading support. After analysis of Python libraries (TensorFlor, Keras), Keras was used to initiate ML. Learning and optimization of the DNN were carried out according to the Adam algorithm (adaptive moment estimation) with the calculation of adaptive learning rate for each parameter. Adam also keeps an exponentially decaying average of past squared gradients AdaDelta and past gradients m_t, similar to momentum.

Statistical processing was carried out using the software package Stata 11.2 and R 3.2.1 (StataCorp LP, USA). Continuous variables are represented as medians with interquartile intervals; the comparison was carried out using the Student's t-test. To compare discrete variables, the Chi-squared test or the Fisher's exact test were used. The cumulative probabilities for CVD were estimated using the Kaplan-Meier method and compared using a log rank test. To assess the impact of various variables on the CVD risk, univariate and multivariate regression models (Cox proportional-hazards model) were used. Hazard ratios and 95% confidence intervals with corresponding p-values are presented. The differences were considered significant at p<0,05. The effectiveness of ML prediction algorithms was assessed using a validation coefficient.

The study was supported by the grant of Russian Foundation for Basic Research (№ 19-29-01077).

Results and discussion

Characteristics of the study population. Complete information on 2131 participants was determined using a randomized algorithm for computer data adjustment (Table 1). The mean age of participants at

Table 2

Parameters included in the machine learning algorithm (data from hypertensive patients)

Risk Factors (M±m)	CVD (n=293)	Without CVD (n=440)	P
Women, %	67,8	42,65	-
Mean age, years	52,67±0,85	52,16±0,50	0,61
Smoking, %	33,9	39,53	-
Height, cm	165,87±0,94	167,48±0,52	0,02*
Weight, kg	85,12±1,57	85,25±0,91	0,94
Body mass index, kg/m^2	31,03±0,55	30,42±0,30	0,33
Waist circumference, cm	97,33±1,35	97,47±0,79	0,92
Thigh circumference, cm	107,43±0,95	107,40±0,56	0,97
Mean SBP, mm Hg	156,29±1,59	157,55±0,85	0,48
Mean DBP, mm Hg	87,52±0,91	89,64±0,58	0,05
Mean PP, mm Hg	67,91±0,73	69,08±1,43	0,46
Mean HR, bpm	76,83±1,27	77,26±0,62	0,76
Glucose, mmol/L	5,77±0,13	5,96±0,13	0,31
Total cholesterol, mmol/L	5,92±0,12	6,01±0,07	0,51
HDL, mmol/L	1,40±0,03	1,40±0,02	1
LDL, mmol/L	3,83±0,10	3,86±0,06	0,79
Triglycerides, mmol/L	1,66±0,09	1,68±0,06	0,85
LP(a), mg/dl	20,09±0,4	20,22±0,2	0,77
ApoA, g/l	1,84±0,04	1,85±0,02	0,82
ApoB, g/l	0,89±0,02	0,92±0,01	0,18
C-reactive protein, mg/L	3,34±0,61	3,78±0,34	0,52
Creatinine, μmol/L	68,93±0,95	72,04±1,30	0,05
Uric acid, μmol/L	353,56±8,98	354,29±5,56	0,94
D-dimer, μg/L	178,99±9,82	185,92±6,16	0,55

Note: differences are significant at * — p<0,05.

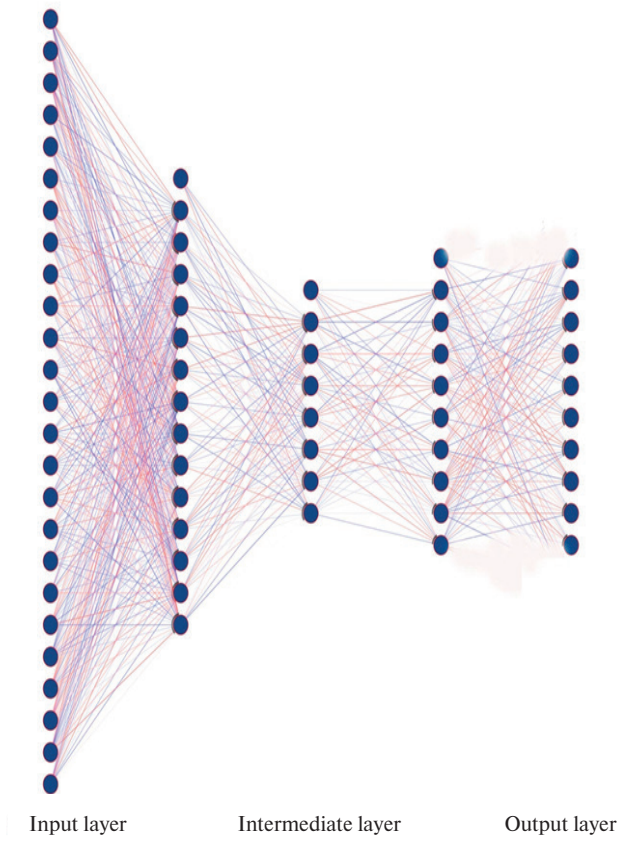
Abbreviations: PP — pulse pressure, LP(a) — Lipoprotein(a), ApoA — apolipoprotein A, ApoB — apolipoprotein B, DBP — diastolic blood pressure, HDL — high density liproproteins, LDL — low density liproproteins, SBP — systolic blood pressure, HR — heart rate.

the study beginning was 45,75 (11,7) years (men — 874 (41%)). During the 5-year follow-up (5-95th percentile: 3,4-4,7 years), 422 cases of CVD were detected in the age range of 60,2±5,6 years for men and 61,1±4,8 years for women. In the group of people without HTN (n=1398), CVD was established in 13,38% (n=187), while among HTN people (n=733) — in 32,06% (n=235). According to the International Classification of Diseases (ICD-10), angina was detected in 51,06% of HTN people; atrial fibrillation and flutter — in 11,06% and 14,44% of people with and without HTN, respectively; old myocardial infarction — in 5,53% and 9,09% of people with and without HTN, respectively; unspecified stroke — in 6,81% of people with HTN. In the HTN group, the absolute mortality risk was significantly higher than in individuals without HTN (0,037 vs 0,017, respectively; p <0,05); the relative mortality risk was 2,146.

CVD risk predictors. The revealed statistical differences in the studied RF between HTN (experimental) and non-HTN (comparison) groups are presented in Table 1.

All participants had excess body weight. Among people with HTN, the mean BMI was higher compared with non-HN individuals (p=0,00001). WC in men did not exceed the recommended value (highest value — 98,5±0,67 cm). Compared with comparison group, women of the experimental group had higher WC (95,13±0,78 cm vs 82,89±0,49 cm; p<0,0001).

The PP level exceeded the threshold level among HTN participants, while the maximum value (68,88±0,71 mm Hg) was observed in women. The



Fugure 2. Neural network model.

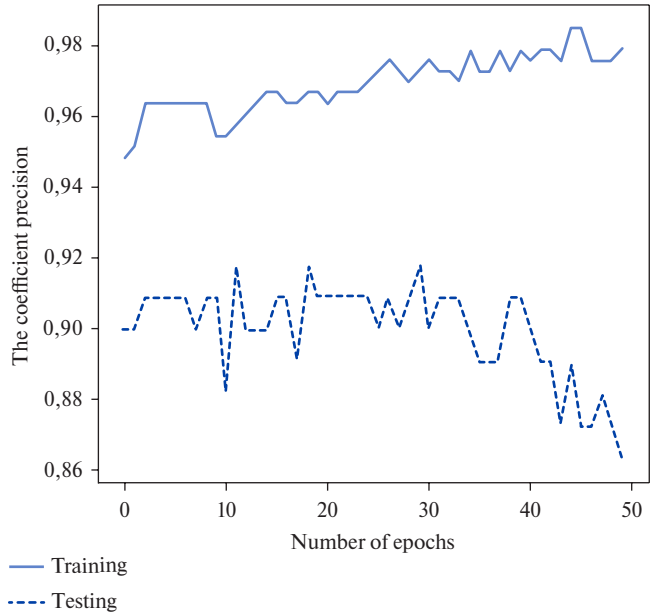


Figure 3. Changes of neural network accuracy in the learning and testing processes (fragment of 50 epochs).

mean HR in the groups was within the acceptable range.

The mean TC level exceeded the normal value in all subjects. The highest mean LDL value (3,88±0,05 mmol/L) was noted in women with HTN. A significant difference in HDL levels was found between HTN and non-HTN women (p=0,007). The mean TG level exceeded the norm only in HTN men (1,77±0,08 mmol/L).

Fasting glucose >5,6 mmol/L is considered to be the RF for diabetes and CVD. Significant differences between the groups were found (p<0,001). Exceeding the threshold level was observed in all HTN participants.

The mean creatinine level did not exceed acceptable values in 100% of cases. However, the studied groups had significant differences in terms of this RF (p=0,006). The highest mean creatinine level was 318,80±4,96 μmol/L in HTN women.

LP(a) is an atherogenic lipid variant, which has a high prognostic value for atherosclerosis and CVD, in particular, coronary artery disease. Acceptable values of LP(a) are in the range of 5-18 mg/dl. There were no significant differences of this RF between HTN and non-HTN groups (20,62±0,93 vs 20,19±0,65 mg/dl, respectively; p=0,704). Non-HTN men had slightly higher mean value of LP(a) (20,70±1,09 mg/dl) compared with HTN men (18,16±1,28 mg/dl), but this difference was not significant.

It is assumed that ApoA and ApoB levels may be decisive in determining the atherosclerosis risk, especially when other lipid parameters do not exceed the norm and/or there are no manifestations of vascular damage [7]. There were significant differences between experimental and comparison groups in ApoA (p=0,025) and ApoB (p=0,00001) levels.

Compared with the experimental group, non-HTN patients had higher levels of D-dimer (Table 1) (p=0,0026). Also, a significant (p=0,0001) difference was found between non-HTN (236,51±1,56 μg/L) and HTN women (190,51±5,72 μg/L).

The mean values of CRP were higher in HTN individuals compared with non-HTN individuals, regardless of gender. The differences between groups were significant (p=0,0001).

Thus, statistical processing revealed following significant factors: anthropometric parameters — height, weight, BMI, WC; blood biochemical parameters — levels of TC, fasting glucose, ApoA and ApoB, D-dimer and CRP.

ML model for predicting CVD outcomes in HTN patients. Various programming languages are used to create DNN, where basic mathematical operators and multidimensional arrays are supported. These include such interpreted C languages as Python, which we used for ML. To develop the DNN, we used the basic sequential model from the Keras

Table 3

Stratification of hypertensive subjects aged 24-65 years without CVD at the study beginning, depending on the presence of first cardiovascular event after a 5-year follow-up

№	№ ICD-10 code	Disease	Number of persons	Specific weight
1	I20.8	Other forms of angina pectoris	120	51,06%
2	I48	Atrial fibrillation and flutter	26	11,06%
3	I25.2	Old myocardial infarction	13	5,53%
4	I64.0	Unspecified stroke	16	6,81%
5	I70.2	Atherosclerosis of native arteries of the extremities	26	11,06%
6	I20.1	Angina pectoris with documented spasm	14	5,96%
7	I69.3	Sequelae of cerebral infarction	7	2,98%
8	I69.4	Sequelae of stroke, unspecified	6	2,55%
9	I20.0 + I21.9	Acute coronary syndrome (unstable angina and acute myocardial infarction)	7	2,98%

Abbreviation: ICD-10 — International Classification of Diseases.

library, which is represented by multiple layers combining to a Rumelhart multilayer perceptron. Using the randomization function X_train, X_test, y_train, y_test=train_test_split (X,Y,test_size=0,40, random_state=42), 2 samples were formed from the total data array: learning (n=488) and test (n=245, Figure 1). These included data from patients with established HTN. Of all the subjects with HTN (n=733), 144 participants were smokers, 170 — former smokers, 419 — non-smokers. Input layer of the prediction model included 26 most important variables (Table 2, Figure 2). Hidden layers were determined empirically: the first layer, where the matrix of weighting coefficients and the matrix of input data of previous neurons are multiplied (15 neurons); the second layer contained the result of minimizing the error (8 neurons), and the third layer was used to refine the prognosis (10 neurons). The output layer consisted of 9 neurons, each of which corresponded to the number of events belonging to the ICD-10 diagnosis (Table 3).

Learning and optimization of DNN were carried out according to the Adam algorithm, which calculates adaptive learning rates for each parameter. Adam keeps an exponentially decaying average of past squared gradients AdaDelta and past gradients m_t, similar to momentum. The Adam algorithm differs from other adaptive methods in the rapid learning rate and efficiency. Changes of the DNN accuracy in the learning and testing processes are presented in Figure 3.

The sample size for the ML was 66,6% of all HTN subjects. Learning and optimization of DNN was carried out in 1000 epochs. As a result of testing using the Adam algorithm, the DNN accuracy reached 97,9%, and the loss value was in the range 10-7-10-8 (Figure 3). During testing, accuracy decreased to 95,5% (Figure 3).

Classification analysis. To assess the clinical significance of our results, we compared our model with the SCORE model in predicting CVD risk. At this operating point, the basic SCORE model correctly predicted 145 CVD out of 465 cases (sensitivity — 61,7%, predictor coefficient — 1,5%). Our ML model correctly predicted 230 CVD out of 733 subjects (sensitivity — 97,9%). The resulting difference is 36,2% of increase in the accuracy of predicting CVD using ML methods.

Conclusion

The study showed that ML methods can be effectively used for cardiovascular risk prediction. The Python-based method provides CVD prediction using standard risk assessments. The use of the randomization function for selecting variables, followed by use of Cox regression methods allows improving prediction. The results also indicate the importance of advanced phenotyping of the subjects using anthropometric markers and blood biochemical parameters, when determining the top-20 predictors for CVD.

The Multi-Ethnic Study of Atherosclerosis (MESA) showed that indicators such as age, inflammation, and vascular diseases prevails in death prognosis. It is also indicated that impaired glucose metabolism an HTN is associated with stroke prognosis, and markers of subclinical atherosclerosis are central to the prognosis of various CVD [8]. The ML method used by us is unique in that it demonstrates the patterns of predictor changes that differ for specific disease outcomes. Relatively high accuracy values (from 86 to 98%) indicate the acceptability of

using this ML method in cardiovascular risk estimation. The advantage of current study is the consideration of anthropometric data, the results of laboratory tests and other important predictors of CVD. Thus, combination of ML and advanced phenotyping increases the accuracy of predicting cardiovascular events in HTN population. The developed approaches allow to more accurately understand markers of subclinical diseases without a priori guess on their nature.

Relationships and activities: the study was supported by the grant of Russian Foundation for Basic Research (№ 19-29-01077).

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3712

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Assessment of glomerular and tubulointerstitial apparatus state depending on the level of the natriuretic peptide in hypertension patients

Chernyavina A. I.

Aim. To assess the state of the glomerular and tubulointerstitial apparatus depending on the level of the N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with hypertension (HTN).

Material and methods. The study included 119 patients with stage I-II HTN. We determined the cystatin C level, glomerular filtration rate (GFF) using the CKD-EPI equation, neutrophil gelatinase-associated lipocalin (NGAL) and NT-proBNP levels; echocardiography and sphygmoplethysmography was performed. In the first analysis, patients were divided into two groups depending on the NT-proBNP level. Group 1 (n=32) consisted of patients with NT-proBNP level >125 pg/ml, group 2 (n=87) — with NT-proBNP level <125 pg/ml. Empirically, the NT-proBNP cutoff point (75 pg/ml) was found to assess the role of cystatin C. The first group included 41 patients with NT-proBNP level >75 pg/ml, the second group — 78 patients with NT-proBNP level <75 pg/ml.

Results. In the group 1 (NT-proBNP >125 pg/ml) the NGAL concentration was significantly higher than in the group 2: 2,50 [1,90; 2,85] vs 1,30 [0,9; 2,0] ng/ml, respectively (p=0,022). Patients in the groups did not significantly differ in the cystatin C levels and GFR (p=0,099 and p=0,090, respectively). When dividing patients according to the NT-proBNP cutoff point (75 pg/ml), the following data were obtained. The concentration of cystatin C in the first group with NT-proBNP >75 pg/ml was 1041,50 [995,00; 1185,00] vs 964,30 [801,00; 1090,00] ng/ml in the second group (p=0,034). Patients in the groups significantly differed in GFR (p=0,027). A correlation analysis revealed a moderate, direct relationship of NT-proBNP with cystatin C (r=0,32; p<0,005) and NGAL levels (r=0,36; p<0,05), as well as a moderate, inverse relationship with GFR (r=-0,35; p<0,005).

Conclusion. NT-proBNP determination can be used as an integrative risk stratification tool for glomerular and tubulointerstitial injury in HTN patients.

Key words: natriuretic peptide, glomerular and tubulointerstitial apparatus.

Relationships and Activities: not.

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Received: 09.01.2020
Revision Received: 19.01.2020
Accepted: 19.01.2020

For citation: Chernyavina A. I. Assessment of glomerular and tubulointerstitial apparatus state depending on the level of the natriuretic peptide in hypertension patients. *Russian Journal of Cardiology*. 2020;25(3):3712. (In Russ.)
doi:10.15829/1560-4071-2020-3-3712

The most important aspect of cardiovascular risk assessment in patients with hypertension (HTN) is the diagnosis of hypertension-mediated organ damage (HMOD). HMOD is defined as structural and/or functional changes in target organs associated with increased BP, such as the heart, arteries, brain, eyes, and kidneys [1, 2].

HTN is the second most important cause of kidney damage after diabetes. In HTN patients, kidney damage is often asymptomatic. In routine practice, renal function changes are usually associated with an increase in serum creatinine [2]. However, recent studies have shown that creatinine and creatinine-based estimated glomerular filtration rate (eGFR) do not accurately reflect the state of glomerular filtration, especially in the early stages [3]. Cystatin C and cystatin C-based eGFR equations are described as more sensitive and early markers of glomerular injury, as well as unfavorable predictors in patients with HTN [3, 4].

One of the debatable issues is the tubulointerstitial assessment in patients with cardiovascular diseases (CVD). The most commonly used markers of tubular dysfunction are neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases 2 (TIMP-2), kidney injury molecule 1 (KIM-1). NGAL is a member of lipocalin protein family and is highly expressed in the renal tubules, especially after ischemic or nephrotoxic damage. Identification of elevated blood and urine NGAL levels in some kidney diseases can be used as an early marker of tubular damage, including in CVD [5].

It is well known that an increase in N-terminal pro-brain natriuretic peptide (NT-proBNP) level allows not only to diagnose and evaluate the severity of heart failure (HF), but also is associated with HTN and increased BP [6]. It was also described that NT-proBNP levels may increase in patients with GFR decrease [7-9]. However, these studies mainly relate to patients with acute kidney injury and chronic kidney disease, where, first of all, the filtration function was studied, which was assessed by the level of creatinine, creatinine-based eGFR or albuminuria level. The relationship between NT-proBNP and cystatin-associated glomerular damage and tubulointerstitial impairment in patients with CVD and risk factors such as HTN remains poorly understood and debatable. Therefore, the study of this problem is a clinically important and promising area of cardiology, the solution of which will not only allow timely verification of renal dysfunction, but also develop algorithms to prevent kidney damage in patients with HTN and CVD.

The aim of this study was to assess the state of glomerular and tubulointerstitial apparatus depending on NT-proBNP level in HTN patients.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee approved this study. All patients signed informed consent.

The study included patients meeting the following inclusion criteria: the presence of stage I-II GB without symptoms and signs of chronic heart failure (CHF), continuous antihypertensive and lipid-correcting therapy at the time of inclusion, signing of informed consent. Stage III patients with secondary hypertension, with oncological and other diseases requiring specific ongoing treatment and monitoring, acute inflammatory and infectious diseases were n.

The study included 119 working-age patients with HTN: 72 (60,5%) men and 47 (39,5%) women. The mean age was 45,96±8,54 years. The mean duration of HTN was 4,17 [2; 6] years.

HTN was established in accordance with Russian (2010) and European (2018) guidelines.

Inclusion criteria were stage I-II HTN without symptoms and signs of heart failure (HF), continuous antihypertensive and lipid-lowering therapy at the inclusion, signed informed consent. There were following exclusion criteria: stage III or secondary HTN; cancer and other diseases requiring specific permanent treatment and monitoring, acute inflammatory and infectious diseases; mental disorders.

To assess cardiac stress, we determined the blood NT-proBNP concentration using an enzyme-linked immunosorbent assay (ELISA) and Vector-Best (Russia) reagent kit on the Expert Plus microplate reader (Biochrom, UK). NT-proBNP >125 pg/ml were considered diagnostic criterion for asymptomatic HF.

To assess renal filtration function, serum creatinine levels was determined by ELISA, and GFR was estimated using creatinine-based SKD-EPI equation; serum cystatin C levels were determined by ELISA using the BioVendor (Czech Republic) reagent kit on the IMMULITE® 1000 system (DPC, USA), and GFR was also estimated using cystatin C-based CKD-EPI equation. The reference values of serum cystatin C concentration were 1043,1±107,5 ng/ml.

To assess the condition of renal tubules, serum NGAL levels was determined by ELISA using the BioVendor (Czech Republic) reagent kit on the IMMULITE® 1000 system (DPC, USA). Reference values of NGAL were 1,2-2,6 ng/ml.

To assess the cardiac structure and function, echocardiography was performed according to the guidelines of American Society of Echocardiography and European Association of Cardiovascular Imaging using the Vivid S5 ultrasound system (General

Table 1

Glomerular and tubulointerstitial parameters in patients depending on NT-proBNP level (n=119)

Parameter	Patients with NT-proBNP >125 pg/ml, (n=32)	Patients with NT-proBNP <125 pg/ml, (n=87)	p
Cystatin C, ng/ml	1039,50 [990,00;1170,00]	970,00 [851,90;1090,00]	0,099
Cystatin C-based eGFR, ml/min/1,73 m^2	74,00 [63,00;89,00]	82,00 [69,00;106,00]	0,090
Serum creatinine, μmol/L	74,75 [72,85;82,90]	71,85 [63,60;80,95]	0,400
Creatinine-based eGFR, ml/min/1,73 m^2	94,85 [85,35;106,40]	100,00 [87,60;107,85]	0,744
NGAL, ng/ml	2,50 [1,90;2,85]	1,30 [0,9;2,0]	0,025

Abbreviations: NT-proBNP — N-terminal pro-brain natriuretic peptide, GFR — glomerular filtration rate, NGAL — neutrophil gelatinase-associated lipocalin.

Electric, USA). Left ventricular ejection fraction (LVEF) (Simpson's biplane) and LV diastolic function were assessed.

To assess the artery condition, sphygmoplethysmography was performed on the VaSeraVS-1000 (Fucuda Denshi, Japan). Cardio-ankle vascular index (CAVI1) in the range from 7,4±0,63 to 8,0±0,67 and ankle-brachial index (ABI) <0,9 were considered criterion for arterial damage.

To assess the condition of glomeruli and tubules depending on the NT-proBNP concentration, all patients were divided into 2 groups. The first group consisted of 32 (26,9%) patients with NT-proBNP >125 pg/ml, the second group — 87 (73,1%) patients with NT-proBNP <125 pg/ml.

Statistical processing was carried out using the software package STATISTICA 10.0. For normally distributed quantitative traits, the mean (M) ± standard deviation (SD) were calculated; for non-normally traits — the median with lower and upper quartiles (Me [LQ;UQ]). For qualitative traits, the absolute manifestation frequency and manifestation frequency percentage (%) or 95% confidence interval (CI) were calculated. An analysis of distribution type was carried out using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Most of the traits were non-normally distributed, and for their statistical analysis, nonparametric statistics were used: for quantitative traits — the Mann-Whitney test; for qualitative traits — chi-squared test. Student's t-test and chi-squared test were used for normally distributed quantitative and qualitative traits, respectively. The differences were considered significant at p<0,05. To study the relationship between the parameters of glomeruli and tubules and NT-proBNP concentration, 2x2 contingency tables were compiled and Yates's chi-squared test, odds ratios (OR), relative risk (RR) and 95% CI for OR and RR were determined.

Results

Patients in the groups were comparable in age, gender, cardiovascular risk factors, HTN duration, achievement of target BP, heart rate (HR) at rest, comorbidities and antihypertensive therapy.

According to echocardiography, LVEF was preserved in all patients an d 30,3% of patients had LV hypertrophy, estimated by LV mass index; 8,4% of patients had LV diastolic dysfunction (LV DD). There were no significant differences between the groups with respect to parameters of cardiac structure and function.

By CAVI1, arterial damage was detected in 57,1% of patients, by ABI — in 5,9%. The groups did not significantly differ in the frequency and severity of arterial changes.

Table 1 shows that patients, depending on the NT-proBNP concentration, did not significantly differ in the creatinine and cystatin C levels, creatinine-based and cystatin C-based eGFRs.

The NGAL level in group 1 was significantly lower than in group 2, and amounted to 1,30 [0,9; 2,0] and 2,50 [1,90; 2,85] ng/ml (p=0,022), respectively. The OR and RR of the tubular damage, assessed by NGAL, in NT-proBNP >125 pg/ml were 3,25 and 1,91, respectively (95% CI for OR=1,30-8,20; for RR=1,17-2,88). Sensitivity and specificity were 64,3% and 74,4%, respectively.

A correlation analysis revealed a moderate direct relationship of NT-proBNP with cystatin C (r=0,32; p<0,005) and NGAL levels (r=0,36; p<0,05), as well as a moderate inverse relationship with cystatin C-based eGFR (r=-0,35; p<0,005).

To assess the NT-proBNP effect on the filtration function, the NT-proBNP cutoff point was found empirically and amounted to 75 pg/mg. The distribution of patients in groups depending on the NT-proBNP cutoff point was as follows: group 1 — 41

Table 2

Glomerular and tubulointerstitial parameters in patients depending on NT-proBNP cut-off point (n=119)

Parameter	Patients with NT-proBNP >75 pg/ml, (n=32)	Patients with NT-proBNP <75 pg/ml, (n=87)	p
Cystatin C, ng/ml	1041,50 [995,00;1185,00]	964,30 [801,00;1090,00]	0,034
Cystatin C-based eGFR, ml/min/1,73 m^2	73,00 [63,00;84,50]	83,00 [69,00;106,00]	0,027
Serum creatinine, μmol/L	74,75 [72,30;89,10]	71,85 [64,10;80,60]	0,400
Creatinine-based eGFR, ml/min/1,73 m^2	94,85 [84,70;101,60]	100,00 [89,50;107,90]	0,744
NGAL, ng/ml	2,40 [1,50;2,70]	1,30 [0,9;2,0]	0,056

Abbreviations: NT-proBNP — N-terminal pro-brain natriuretic peptide, GFR — glomerular filtration rate, NGAL — neutrophil gelatinase-associated lipocalin.

patients (34,5%) with NT-proBNP >75 pg/ml, group 2 — 78 patients (65,5%) with NT-proBNP level <75 pg/ml.

Patients in the groups did not significantly differ in clinical, anamnestic and routine laboratory parameters, comorbidities and antihypertensive therapy. According to echocardiography, the groups were comparable in cardiac structure and function and, according to sphygmoplethysmography — in artery condition.

Table 2 presents the data on glomerular and tubular assessment in the groups. There were significant differences between group 1 and 2 in the cystatin C level (1041,50 [995,00; 1185,00] ng/ml vs 964,30 [801,00; 1090,00] ng/ml (p=0,034), respectively) and cystatin C_2-based eGFR (73,00 [63,00; 84,50] ml/min/1,73 m^2 vs 83,00 [69,00; 106,00] ml/min/1,73 m^2 (p=0,027), respectively). According to cystatin C concentration, the OR and RR of glomerular dysfunction at NT-proBNP >75 pg/ml increased 3 times (OR=3,1, 95% CI=1,27-7,31) and 2 times (RR=2,0 95% CI=1,17-3,31), respectively. Sensitivity and specificity were 64,1% and 82,2%, respectively.

There were following study limitations: small sample size; to confirm tubular damage more accurately, 2 or more methods for determining tubular dysfunction are required; to determine NT-proBNP predictor value for kidney damage in HTN patients more accurately, a ROC analysis should be performed in a larger population.

Discussion

It is well known that NT-proBNP can act not only as a biomarker of myocardial injury in HF. Its relationship with target organ damage, in particular the kidneys, in patients with HTN, chronic kidney disease, and type 2 diabetes without symptoms and signs of HF [9]. In studies, conventionally, kidney damage is assessed by the concentration of serum creatinine, creatinine-based eGFR and/or albuminuria level. However, earlier markers of glomerular and tubulointerstitial kidney damage are not evaluated. It was suggested that, using more accurate and earlier markers of renal dysfunction, assessing the effect of NT-proBNP levels on glomerular and tubular damage in HTN patients will predict the dysfunction in the early stages.

According to our study, in HTN patients without HF symptoms, NT-proBNP >125 pg/ml was associated with kidney damage. In study by Takahama H, et al., it was shown that NT-proBNP increase is a predictor of kidney damage in patients with acute decompensated HF [8]. Moreover, NT-proBNP levels were significant in patients who had HTN-related HF.

Glomerular damage, assessed by cystatin C level, was recorded in our study at a lower NT-proBNP level (75 pg/ml). The obtained data can be explained by the fact that BNP increases GFR in the kidneys by relaxing mesangial cells and inhibits fractional sodium reabsorption. This enhances natriuresis and decreases BP. BNP also reduces vascular resistance by relaxing smooth muscle cells. Therefore, many studies showed that lower initial concentrations of BNP and NT-proBNP in HTN patients are associated with a higher risk of HF and target organ damage [10, 11]. Nevertheless, there is no doubt that renin-angiotensin-aldosterone system (RAAS) and sympathoadrenal system (SAS) play an important role in the pathogenesis of target organ damage. But BNP acts as a compensator only in the early stages by reducing the activity of these systems [10]. As the disease progresses, RAAS and SAS activity increases, and there is imbalance in BNP system, and despite high levels, endogenous BNP becomes resistant and is no longer able to compensate it. Then an increase

in release and level of BNP and NT-proBNP is already considered not as compensatory mechanisms, but as a dysfunction of the changed organ, including tubular and glomerular damage. It should be noted that BNP release, which is more associated with positive and compensatory effects, is under genetic control, and with an increase in RAAS and SAS activity, it is stimulated by mechanical stretching of cardiac myocytes, i.e., myocardial stress. Therefore, the final serum concentration of NT-proBNP and BNP is specified by the balance between production, degradation and renal clearance. Changes in cardiac, arterial, and renal function associated with HTN can affect serum BNP concentration.

In our study, NT-proBNP >75 pg/ml was associated with cystatin C increase. Some studies showed that changes in circadian BP profile in HTN patients and nondecrease of nocturnal BP compared with daytime values are closely related to kidney damage, assessed by the cystatin C concentration, as well as to the progression of its dysfunction [12]. Therefore, it can be assumed that NT-proBNP level may reflect an increase of nighttime BP, which leads to impaired renal filtration function and cystatin C increase. In our study, 24-hour BP profile was not evaluated, and this hypothesis requires further study. Another confirmation of the relationship between cystatin C and NT-proBNP is the fact that cystatin C correlates with left ventricular (LV) concentric remodeling in patients with chronic kidney disease [13]. Therefore, in patients with HTN, LV remodeling leads to myocardial stress even in normal NT-proBNP values for HF, which, in turn, leads to glomerular dysfunction. Thus, observed NT-proBNP increase >75 pg/ml can be considered as an additional predictor of glomerular damage.

We also obtained data on tubulointerstitial damage in HTN patients with NT-proBNP >125 pg/ml. The data obtained can also be explained by the fact that when the compensatory effect of BNP on the renal function is reduced, it becomes resistant and all positive effects are withdrawn. But given the evidence that BNP is localized in the distal tubules [10], it can be assumed that BNP and NT-proBNP increase can reflect tubular dysfunction.

There is literature evidence that NGAL is not only a marker of decreased tubular function, but can be a predictor of cardiovascular events in patients with chronic kidney disease [5]. Recent studies have also shown that NGAL level associated with NT-proBNP was a predictor of cardiovascular events and mortality in patients with HF [14]. At the same time, studies showed that the level of NGAL was higher in HTN patients.

Шn the study by Kim IY, et al., it was shown that NGAL is an independent predictor of LV hypertrophy and LV DD in patients with chronic kidney disease [15].

Conclusion

The results obtained indicate that NT-proBNP can be used for risk stratification of glomerular and tubulointerstitial damage in HTN patients without symptoms and signs of HF. The OR and RR of the tubular lesion, assessed by NGAL, with an increase in NT-proBNP >125 pg/ml were 3,25 and 1,91, respectively (95% CI for OS=1,30-8,20; for RR=1, 17-2,88). The OR and RR of glomerular dysfunction, estimated by cystatin C concentration, with NT-proBNP >75 pg/ml, were 3,1 and 2,0, respectively (95% CI for OR=1,27-7,31; 95% CI for RR=1,17-3,31). Therefore, an early glomerular and tubulointerstitial changes in HTN patients occurs not only due to an increase and inadequate control of BP, but may also be due to myocardial stress, which is reflected in NT-proBNP levels even in the normal range.

Relationships and Activities: not.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3736

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Clinical outcomes in hypertension patients after coronary stenting due to exertional angina

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Aim. To study clinical outcomes in hypertension patients after coronary stenting due to exertional angina.

Material and methods. The study included 214 patients with class 3 stable angina and hypertension. All patients underwent coronary angiography followed by elective stenting. Clinical outcomes were assessed on average after 44 months of outpatient follow-up.

Results. During the follow-up period, 43% of patients retained class III angina; the decrease in systolic (SBP) and diastolic blood pressure (DBP) was 18- and 14-mm Hg, respectively. There were 35 cases of myocardial infarction (MI) in this category of subjects. We revealed that 57% of patients had a progression of angina: from class III to class IV; the decrease in SBP and DBP was 10- and 18-mm Hg, respectively. There were 110 cases of MI and 10 cases of acute cerebrovascular accident in these patients.

Conclusion. Inadequate control of SBP in patients after stenting due to stable exertional angina leads to a greater number of complications, mainly myocardial infarction.

Key words: hypertension, exertional angina, systolic blood pressure, myocardial infarction.

Relationships and Activities: not.

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Received: 02.02.2020
Revision Received: 09.02.2020
Accepted: 17.02.2020

For citation: Akhtereyev R. N., Galyavich A. S., Baleeva L. V., Galeeva Z. M. Clinical outcomes in hypertension patients after coronary stenting due to exertional angina. *Russian Journal of Cardiology*. 2020;25(3):3736. (In Russ.)
doi:10.15829/1560-4071-2020-3-3736

Hypertension (HTN) is one of the most important independent risk factors of coronary artery disease (CAD). At the same time, patients with CAD and HTN belong to a very high cardiovascular risk [1]. The combination of these diseases is common — according to the REACH registry, 80% of patients with CAD had HTN [2].

The combination of these diseases also significantly worsens the prognosis. According to a meta-analysis of 22672 patients with stable CAD, 5-year blood pressure (BP) increase >140 and 80 mm Hg is associated with a high risk of cardiovascular events [3]. BP decrease can significantly reduce the risk of major cardiovascular events, including those associated with CAD. A meta-analysis demonstrated that a decrease in systolic BP (SBP) for every 10 mm Hg can reduce the CAD risk by 17% [4]. Current guidelines for HTN management emphasize that BP decrease <130 mm Hg is associated with a favorable outcome and is the target [5].

There is a close hemodynamic relationship between HTN and CAD: an increase in afterload and pulse wave velocity leads to an increase in pulse pressure, which rises the myocardial oxygen demand. Similar hemodynamic mechanisms are responsible for target organ damage, including coronary arteries and myocardium. Increased oxidative stress, endothelial dysfunction, and hyperactivity of the sympathetic nervous and renin-angiotensin systems modulate the atherogenic potential of high BP [6].

There is much data on the prevalence of CAD and HTN combination and their common pathogenesis, but there is little data on the CAD progression in stented patients depending on the extent of BP decrease.

The aim was to study the clinical outcomes of HTN patients stented for stable angina depending on the extent of SBP and diastolic BP (DBP) decrease.

Material and methods

The study included 214 patients aged 45 to 75 years (mean age 61,35±8,2 years). There were following inclusion criteria: age <75 years, CCS class III stable angina, HTN with BP ⩽180/110 mm Hg, sinus rhythm, signed informed consent. The exclusion criteria were: age >75 years, not signed informed consent, stage ⩾2 heart failure, a history of cerebrovascular accident, severe kidney (creatinine >160 μmol/L) and liver failure (transaminase levels ⩾3 times the normal range), any heart rhythm disorders requiring treatment; second- and third-degree atrioventricular block; bradycardia (⩽50 bpm); sinoatrial block; respiratory failure (⩾II degree); ineffective contraception in women of reproductive age; pregnancy and lactation; alcoholism and drug addiction; history of cancer.

We assessed the following parameters in all patients: a complete blood count; lipid profile; levels of creatinine, glucose, and blood potassium. Electrocardiography, echocardiography, and coronary angiography (CA) were performed. All patients underwent coronary stenting followed by dual antiplatelet and statin therapy. Conventional antihypertensive therapy was chosen taking into account the individual response of patients and was continued after hospitalization.

The clinical course of angina was evaluated by the questioning patients. BP changes was assessed using patient self-monitoring data. The dynamics of angina class and extent of BP decrease were evaluated on average 44 months after hospitalization by telephone survey.

Statistical processing was carried out using software package Statistica 6.0 (StatSoft Inc., USA). The differences in quantitative traits was evaluated by the Mann-Whitney U test, and in qualitative traits — by the Pearson's chi-squared test.

Results

During the follow-up period, 92 patients (43%) retained class III angina. The decrease of SBP and DBP in these patients was 18 and 14 mm Hg, respectively. According to CA, coronary stenosis >70% was found in all above-mentioned patients (n=92). In this subgroup, 35 cases of myocardial infarction (MI) were recorded. In 122 patients (57%), there was an increase in the angina severity — from class III to IV. The decrease in SBP and DBP in this subgroup was 10 and 18 mm Hg, respectively. According to the CA, coronary stenosis >70% was found in all these patients (n=122). In this subgroup, 110 cases of MI and 10 cases of acute cerebrovascular accident (CVA) were recorded during the follow-up (Table 1).

Table 1

Angina class and blood pressure levels at the beginning and end of the study

Angina class and cardiovascular events	Number of patients	Δ SBP, mm Hg	Δ DBP, mm Hg
Class III → class III	92	18*	14
IM	35		
CVA	0		
Class III → class IV	122	10*	18
IM	110		
CVA	10		

Notes: * — p<0,05, Δ — difference between the BP at the beginning and end of the study.

Abbreviations: DBP — diastolic blood pressure, MI — myocardial infarction, CA — coronary angiography, CVA — cerebrovascular accident, SBP — systolic blood pressure.

Discussion

There is a close relationship between CAD and HTN, since they are both related to the heart function as a pump. The BP level depends on the efficiency and tension of cardiac muscle. In turn, myocardial contractility depends on its filling (mainly in diastole) and coronary permeability. An obstruction in the coronary arteries (mainly due to atherosclerotic plaques) reduces the cardiac muscle efficiency.

This paper was devoted to the study of clinical outcomes of HTN patients stented for stable angina depending on the extent of SBP and DBP decrease.

It is known that angina is associated with a high risk of cardiovascular events [7]. The CLARIFY registry included 32,105 patients from 45 countries. The follow-up was on average 24 months. According to non-invasive testing, 4056 patients (20%) had angina symptoms, and 5242 (25,8%) patients had symptoms of myocardial ischemia. In the group of patients with angina symptoms, cardiovascular death or MI was recorded in 12,2% of cases. The presence/absence of HTN in this group was not determined. In our study, for 44 months of follow-up, among 214 patie nts after coronary stenting, 145 cases of MI and 10 cases of CVA were recorded (72,4% of hard endpoints). Such a large number of cardiovascular events can be explained by several reasons: 1) the severity of coronary atherosclerosis (all patients had coronary stenosis >70%); 2) all patients had severe angina manifestations (class III angina); 3) concomitant HTN in all patients significantly increased myocardial oxygen demand and aggravated myocardial ischemia.

Attention should be paid to the relationship of angina and the extent of BP decrease. In patients without angina class change, significant SBP decrease by an average of 18 mm Hg was noted, while in patients with angina progression, the SBP decrease was less pronounced — by 10 mm Hg ($p<0,05$). Our results are to some extent consistent with meta-regression analysis, which included 123 studies and 613815 patients [8]. The authors showed that a decrease in the relative risk of cardiovascular events is proportional to BP decrease. SBP decrease for every 10 mm Hg led to a significant reduction in the relative risk of cardiovascular events, CAD, and CVA by 20%, 17%, 27%, respectively.

Our data have something in common with widely discussed ISCHEMIA study, which demonstrated that coronary revascularization does not significantly influence on the prognosis of patients with stable angina [9, 10].

The data obtained showed that patients with more pronounced SBP decrease had less cardiovascular events (MI). DBP decrease, despite the fact that the coronary filling is performed mainly in diastole, did not have the same effect.

Study limitations: small sample; telephone survey.

Conclusion

The combination of severe coronary atherosclerosis and clinical manifestations of angina in patients with HTN leads to unfavorable outcomes, despite coronary stenting. Inadequate control of SBP in patients with stable angina leads to a greater number of events (mainly MI).

Relationships and Activities: not.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3258

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Comorbidity of hypertension and chronic venous disease in men

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Aim. To study the clinical manifestations and characteristics of lower extremity chronic venous disorders (CVD) in working-age men with hypertension (HTN).

Material and methods. The study included 74 men with HTN at the age of 30-50 years and 41 men without HTN. HTN duration and regularity of antihypertensive medication intake were studied. We analyzed complaints and objective signs associated with CVD, their severity, structural and functional parameters of superficial, deep and perforator veins of the lower extremities using the triplex ultrasound. The prevalence and severity of cardiovascular risk factors among patients with HTN and CVD and patients with HTN and without CVD were analyzed.

Results. Men aged 30-50 with HTN showed a high prevalence of complaints (68%) associated with CVD: evening heaviness and fullness in the legs; pain decrease at rest; a combination of pain, spasm and swelling in long-time standing. Objective signs of CVD were recorded in 83,8% of men with HTN (most often — telangiectasia (38%) and swelling (24%)). Men with HTN were diagnosed with more severe manifestations of CVD than men without HTN. In patients with HTN, episodic pain and evening perimalleolar swelling were 1,8 and 4 times more likely, respectively, than in men without HTN. The presence of CVD and HTN was not associated with cardiovascular risk factors. HTN men was characterized by a large-diameter veins, pathological reflux, vein tortuosity, the presence of thrombotic masses and post-thrombotic lesions. In these patients, along with an increased blood flow velocity in the deep and perforator veins of the lower leg, a low velocity in the deep femoral veins was observed. This indicates venous insufficiency even at rest. Orthostasis in men with HTN increased the frequency of reflux in superficial veins by 2-4 times, which indicates latent venous insufficiency.

Conclusion. HTN is characterized by an increase in the frequency and severity of symptoms and signs of CVD, which indicates their comorbidity.

Key words: men, comorbidity, hypertension, chronic vein disorders.

Relationships and Activities: not.

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Received: 13.04.2019
Revision Received: 28.05.2019
Accepted: 24.06.2019

For citation: Baev V. M., Vagapov T. F., Shmeleva S. A. Comorbidity of hypertension and chronic venous disease in men. *Russian Journal of Cardiology*. 2020;25(3):3258. (In Russ.)
doi:10.15829/1560-4071-2020-3-3258

Hypertension (HTN) today remains one of the most urgent research and practical problems due to the high incidence and common cardiovascular, cerebrovascular and renal complications, which are recognized as the leading causes of death in the Russian Federation [1]. Comorbidities in HTN patients increases the risk of complications and mortality, which, in turn, increase socio-economic losses for society and the state as a whole due to disability of patients, expensive diagnostics and treatment [2]. Of particular importance is the comorbidity of hypertension and chronic vascular diseases, including venous disorders, since vessels are considered as one of the main target organs for HTN [3-5]. It was previously shown that lower extremity chronic venous disorders (CVD) in men with HTN significantly reduces their working ability and quality of life [6]. However, at present, the comorbidity of HTN and lower extremity CVD remains poorly studied, even despite the fact that the arterial and venous systems are a common circulatory complex, and the adult population in Russia has a high prevalence of CVD (women — 63%, men — 37%) [7].

The aim was to study the clinical manifestations and characteristics of lower extremity CVD in working-age men with HTN.

Material and methods

The study included 115 men who were divided into two groups: experimental (n=74) — patients with HTN, control (n=41) — patients without HTN [8]. The inclusion criteria for the experimental group were male gender, age 30-50 years, the presence of HTN. Further, to identify the dependence of CVD on cardiovascular risk factors, the 1st (62 patients with hypertension and objective signs of CVD) and the 2nd groups (12 patients with hypertension and without CVD) were selected from the experimental group.

The inclusion criteria for the control group were male gender, age 30-50 years, absence of HTN. There were following exclusion criteria for patients of both groups: drug use; cancer; endocrinopathies (diabetes, hypothyroidism, adrenal gland disorders); acute and chronic respiratory diseases; history of upper respiratory tract infections in last two weeks; acute infectious diseases; acute and chronic kidney diseases (pyelonephritis, glomerulonephritis); differentiated connective tissue disorders; anemia; hepatitis; cirrhosis; pancreatitis; gastric and duodenal ulcers; professional athletes; lower extremity fractures and surgery; spine and brain injuries; organic diseases of the central nervous system and spinal cord disorders; heart failure.

The ethics committee of E. A. Wagner Perm State Medical University approved this study. All patients signed informed consent.

Clinical characteristics of men with HTN. Participants of the experimental group had different severity of HTN: 42 patients — stage 1 HTN, 26 patients — stage 2 HTN, 6 patients — stage 3 HTN. Fifty-eight patients from the experimental group know that they have HTN, but only 17 (23%) take antihypertensive therapy. The median duration of HTN in this group was 5 (3-10) years. In 16 (22%) people, HTN was a newly diagnosed. Patients with HTN were characterized by high body weight, BMI, waist circumference, plasma glucose and total cholesterol levels (Table 1).

Clinical analysis. Health assessment was carried out according to the medical history data: HTN duration and adherence to antihypertensive therapy.

Table 1

Comparative analysis of men from the experimental and control groups

Parameter	Experimental group, n=74	Control group, n=41	P
	Me (Q_1-Q_3)		
Age, years	41 (36-44)	40 (36-45)	0,76
Weight, kg	92 (84-100)	82 (75-87)	0,001
SBP, mm Hg	146 (140-153)	120 (110-122)	0,001
DBP, mm Hg	96 (90-100)	80 (72-82)	0,001
Heart rate, bpm	74 (67-78)	70 (64-74)	0,025
Total cholesterol, mmol/L	5,05 (4,50-5,68)	4,60 (4,20-5,30)	0,039
Fasting glucose, mmol/L	5,30 (4,80-5,60)	4,80 (4,50-5,40)	0,035
BMI, kg/m^2	30,0 (28,0-32,0)	26,0 (24,0-29,0)	0,001
Waist circumference, cm	100 (92-106)	90 (86-99)	0,001

Note: P — probability value.

Abbreviations: BMI — body mass index, DBP — diastolic blood pressure, SBP — systolic blood pressure.

Table 2

Comparative analysis of subjective signs of CVD between patients of from the experimental and control groups

Question	Experimental group, n=74	Control group, n=41	P
	Abs. (%)		
Do you feel the heaviness and fullness in the legs at the end of the day, intensifying in hot weather or in a hot room?	33 (45%)	9 (22%)	0,027
Does the pain and heaviness in the legs decrease or gone after resting in a horizontal position or when using compression stockings?	50 (68%)	16 (39%)	0,012
Do you have oedema in the lower legs and feet at the end of the day?	25 (34%)	6 (6%)	0,046
Do pain in legs, spasm, and oedema aggravated in long-time standing?	28 (38%)	7 (17%)	0,035

Note: P — probability value.
Abbreviation: CVD — chronic venous disorders.

Cardiovascular parameters were assessed by BP using a sphygmomanometer A&D UA-777. We recorded the prevalence and severity of cardiovascular risk factors, which were evaluated using the anamnesis data, instrumental and laboratory tests: blood and urine tests, chest x-ray, electrocardiography (ECG), echocardiography, Doppler ultrasound of peripheral arteries, fundoscopy [1, 2].

Assessment of CVD symptoms. To assess the subjective signs, we used a questionnaire based on the CEAP classification, which included the main complaints and clinical manifestations of CVD [9]. Lower limb examination was carried out in a standing. We assessed the following objective signs: telangiectasia, varicose veins, swelling, trophic changes in the skin and subcutaneous tissue, healed venous ulcer, open venous ulcer. The severity of CVD was assessed using the Venous Clinical Severity Score (VCSS) [10]. Lower limb venous ultrasound was performed using triplex ultrasound of different modes [11]: B-mode was used to assess venous architecture; color Doppler mapping was used for rapid evaluation of blood flow. Ultrasound was carried out together with certified ultrasound specialist S.V. Letyagina using a iU22 xMatrix system (Phillips, USA, 2014).

Lower limb venous ultrasound was performed according to anatomical localization, using anatomical nomenclature, terminology of the International Union of Phlebology, and CEAP classification [9, 11] — superficial venous system: great saphenous vein (GSV), small saphenous vein (SSV), saphenopopliteal junction (SPJ); — deep venous system: common femoral vein (CFV), posterior tibial vein (PTV), muscular (soleal and gastrocnemius) veins (MV); — perforator veins: Dodd's and Cockett's perforators. We evaluated the location, diameter, lumen area, wall thickness of veins. Peak flow velocity, venous reflux and its duration, the presence of thrombotic masses and post-thrombotic lesions, tortuosity of deep and/or superficial veins were also assessed. Not intensified blood flow during distal compression and retrograde flow during proximal compression were identified. We also used following functional tests: Valsalva maneuver; proximal compression; distal compression; orthostatic test.

Statistical processing was carried out in the software package Statistica 6.1 (StatSoft-Russia, 2009) using nonparametric statistics. Descriptive statistics data are presented as median (Me) and first (Q1) and third (Q3) quartiles. Comparison of variational series of two independent groups was performed using the Mann-Whitney U-test, and the comparison of proportions and discrete data using the Chi-squared test. The dynamics of the proportions' comparison between groups were evaluated by the McNemar's test. Differences were considered significant at $p<0,05$.

Results

Patients in the experimental and control groups had many complaints associated with CVD. However, some complaints were recorded more often in the experimental group (Table 2).

Compared with the control group, patients of the experimental group were 6 times more likely to have evening swelling. These patients also 2 times more often had complaints of evening heaviness and fullness in the legs, pain decrease at rest, a combination of pain, spasm and swelling in long-time standing.

Physical examination of lower extremities revealed CVD signs of C1-C4 in the experimental group, while in the control group — C1-C3. In the experimental group, objective signs of CVD were recorded in 62 patients (83,8%), which is 2,5 times more often than in the control group — 14 patients (34,1%) (p=0,001). In the experimental group, telangiectasias

Table 3

Comparative analysis of objective signs of CVD between patients of from the experimental and control groups

Objective sign	Experimental group, n=74	Control group, n=41	P
	Abs. (%)		
C_0 — no visible or palpable signs	12 (16,2%)	28 (68,2%)	0,001
C_1 — telangiectasias or reticular veins	28 (37,8%)	7 (17,1%)	0,035
C_2 — varicose veins	15 (20,3%)	3 (7,3%)	0,11
C_3 — oedema	18 (24,3%)	3 (7,3%)	0,045
C_4 — secondary skin alterations	1 (1,4%)	0 (0,0%)	0,76
C_5 — healed ulcer	0 (0,0%)	0 (0,0%)	-
C_6 — open ulcer	0 (0,0%)	0 (0,0%)	-

Note: P — probability value.
Abbreviation: CVD — chronic venous disorders.

Table 4

Analysis of contingency table between the experimental and control groups

Symptoms	Experimental group, n=74				Control group, n=41				P
	Severity (points)								
	0	1	2	3	0	1	2	3	
	Abs. number of cases								
Pain	32	42	0	0	28	13	0	0	0,017
Varicose veins	59	8	7	0	38	2	1	0	0,117
Oedema	50	21	2	0	38	3	0	0	0,012
Hyperpigmentation	72	2	0	0	41	0	0	0	0,751

Note: P — probability value.
Abbreviation: CVD — chronic venous disorders.

and oedema were recorded more often than in the control group (Table 3).

Using the VCSS, we conducted a comparative analysis, which showed significant differences between the groups in terms of severity of pain and oedema (Table 4).

Patients with HTN had pain in the legs 1,8 times more often than patients of the control group (57% vs 32%, respectively). Patients with HTN also experienced perimalleolar oedema 4 times more often (28% vs 7%). Severe manifestations of CVD such as inflammation, induration, ulcers, and cases of compression therapy were not recorded.

A comparative analysis of the prevalence of cardiovascular risk factors between hypertensive patients with and without objective signs of CVD did not reveal differences. This suggests that CVD in patients with HTN is not associated with the prevalence and severity of risk factors. CVD development does not depend on the duration of HTN. The prevalence of obesity as the main risk factor of CVD was also the same.

Venous ultrasound did revealed differences in qualitative traits of the experimental and control groups. For example, the prevalence of pathological refluxes (>0,5 sec) in the superficial veins reached 10%, in the deep veins — 1,4%, in perforator veins — 33%. Venous reflux was detected 3-4 times more often in the experimental group than in the control group, but the differences was not reliable. Post-thrombotic lesions of the superficial and deep veins and thrombotic masses were revealed in 1,4% of cases; similar findings were not detected in perforator veins. In the experimental group, we observed vein tortuosity of the superficial veins in 6,8% of cases, deep veins — in 8,1%, perforator veins — in 17,8-33%.

In HTN patients, there were differences in quantitative traits: blood flow velocity, vein diameter and area (Table 5).

Table 5

Comparative analysis of quantitative traits of venous structure and function between the experimental and control groups

Parameter	Experimental group, n=74	Control group, n=41	P
	Me (Q_1-Q_3)		
SSV, right			
Diameter, mm	2,3 (2,0-2,7)	2,1 (1,7-2,5)	0,042
CFV, left			
Blood flow velocity, cm/sec	28,1 (22,8-35,8)	31,4 (25,5-38,0)	0,01
PTV, left			
Blood flow velocity, cm/sec	12,6 (10,4-14,5)	11,2 (9,3-13,8)	0,049
Cockett's perforators, right			
Blood flow velocity, cm/sec	9,4 (6,7-12,5)	5,7 (5,1-7,3)	0,013
Cockett's perforators, left			
Lumen area, mm^2	5,4 (2,49-7,55)	3,0 (2,0-3,2)	0,04

Note: P — probability value.
Abbreviations: CFV — common femoral vein, PTV — posterior tibial vein, SSV — small saphenous vein.

HTN patients had a larger diameter of superficial veins and a larger lumen area of perforator veins than in the control group. Along with the increased blood flow velocity in the deep and perforator veins of lower leg, low blood flow velocity in the main deep veins of the thigh was characteristic for patients with HTN. This indicates venous insufficiency even at rest.

In orthostasis, refluxes in superficial and deep veins was recorded 2-4 times more often. However, a significant increase was noted only in the superficial veins — from 8% to 18%, while in the experimental group — from 3% to 10% (p=0,027 according to the McNemar's test).

Discussion

Previous few studies of HTN patients showed that venous and arterial blood flow have common pathogenesis of arterial and venous pressure increase, changes in regulation of vascular tone and capacitance, and microcirculatory alterations [12-14]. The study of venous circulation in HTN patients showed a relationship between HTN and venous flow changes, including in the lower extremities, related mainly to the tone and capacitance changes [15]. Changes in the veins of the lower extremities, characteristic of hypertension, were revealed — weakening of extensibility and capacitive response due to the weakened response of the venoconstrictor to unloading of the baroreceptor [11]. The possible association of hypertension and varicose veins was indicated by Mäkivaara LA, who found a higher prevalence of venous lesions in people with cardiovascular diseases, including hypertension [16]. In 2016, B. Matić revealed common risk factors in patients with hypertension and chronic venous insufficiency of the lower extremities [17]. Thus, our data indicate that hypertension is more often combined with signs of CVD and impaired venous blood flow in the lower extremities. The results actually indicate a high probability of comorbidity of hypertension and chronic hepatitis B. AH is combined with a more pronounced clinical picture of CVD. This comorbidity increases the risk of a negative prognosis of the life and health of men of working age, which requires the development of new strategies in assessing cardiovascular risks and new approaches in choosing treatment methods for this comorbidity.

Conclusion

1. Hypertensive men aged 30-50 years had high prevalence of complaints (68%) associated with CVD: evening heaviness and fullness in the legs, pain decrease at rest, a combination of pain, spasm and oedema in long-time standing. Objective signs of CVD were recorded in 83,8% of men with HTN (most often — telangiectasia (38%) and swelling (24%)).

2. Hypertensive men were diagnosed with more severe manifestations of CVD than men without HTN. In patients with HTN, episodic pain and evening perimalleolar swelling were 1,8 and 4 times more likely, respectively, than in men without HTN. The presence of CVD and HTN was not associated with cardiovascular risk factors.

3. Hypertensive men was characterized by a large-diameter veins, pathological reflux, vein tortuosity, the

presence of thrombotic masses and post-thrombotic lesions. In these patients, along with an increased blood flow velocity in the deep and perforator veins of the lower leg, a low velocity in the deep femoral veins was observed. This indicates venous insufficiency even at rest. Orthostasis in men with HTN increased the frequency of reflux in superficial veins by 2-4 times, which indicates latent venous insufficiency.

Relationships and Activities: not.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3774

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Early structural and functional left ventricular disorders in young patients with hypertension: a role of insulin resistance

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Cardiac remodeling refers to factors that increase the risk of cardiovascular events in patients with hypertension (HTN). Changes in myocardial structure and function can be caused not only by hemodynamic causes, but also a number of metabolic disorders.

Aim. To analyze the associations of insulin resistance and left ventricular (LV) remodeling in a cohort of young patients with untreated uncomplicated hypertension and high normal blood pressure (BP).

Material and methods. The presented cohort cross-sectional study included 105 subjects. We analyzed clinical, demographic and anthropometric characteristics, performed a biochemical panel (creatinine, potassium, lipid profile, glucose, insulin, uric acid) with the estimation of insulin resistance scores (HOMA-IR, METs-IR, TyG), a glycosylated hemoglobin test. Urine albumin-to-creatinine ratio was determined. Office and 24-hour ambulatory BP measurement and two-dimensional speckle-tracking echocardiography were performed in all patients.

Results. The median age was 23 years (men — 85%); 51% of participants were overweight or obese, 39% had dyslipidemia, 21% — insulin resistance. Signs of LV remodeling were observed in 38 (40%) subjects: 32 (34%) — concentric remodeling, 5 (5%) — concentric LV hypertrophy (LVH), 1 (1%) — eccentric LVH. Defects of LV systolic global longitudinal strain (GLS) were observed in 44 (47%) young patients with HTN and preHTN. Stepwise multivariate regression analysis revealed that the TyG index was an independent predictor of LV GLS defects (b=0,38, p=0,001).

Conclusion. In a cohort of young patients with HTN and high normal blood pressure, there is a high prevalence of insulin resistance, metabolic disorders, and early signs of LV remodeling and subclinical systolic dysfunction. The TyG index, available for estimation by routine biochemical tests, is an independent factor affecting the LV GLS.

Key words: hypertension, young patients, prehypertension, insulin resistance, left ventricular hypertrophy, left ventricular strain, left ventricular systolic global longitudinal strain, two-dimensional speckle-tracking echocardiography.

Relationships and Activities: not.

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Received: 01.03.2020
Revision Received: 09.03.2020
Accepted: 13.03.2020

For citation: Shavarova E. K., Kobalava J. D., Yezhova N. E., Khomova I. A., Bazdyreva E. I. Early structural and functional left ventricular disorders in young patients with hypertension: a role of insulin resistance. *Russian Journal of Cardiology*. 2020;25(3):3774. (In Russ.)
doi:10.15829/1560-4071-2020-3-3774

The high prevalence of hypertension (HTN) in young people and little evidence of a decrease in the absolute risk of cardiovascular events (CVE) with long-term antihypertensive therapy in young people require further study of this issue and search for a favors of early drug use. In 2018, an analysis of the prospective cohort study CARDIA with long-term follow-up (median — 19 years) was published, which included people <40 years of age. This work confirmed the increased risk of CVE in people with blood pressure (BP) >130/80 mm Hg compared with normotension individuals [1]. One of the independent predictors of unfavorable prognosis is left ventricular hypertrophy (LVH). The Framingham study showed that an increase in left ventricular (LV) mass for every 50 g increases the relative cardiovascular risk in women by 49%, and in men by 57% [2]. Not only hemodynamic, but also metabolic factors contribute to the development of LVH. Both in experimental and in clinical studies, the contribution of insulin resistance to development of myocardial structural and functional changes has been confirmed. The American Association of Clinical Endocrinologists has created a concept for dysglycemia-based chronic disease, where insulin resistance is defined as the first stage, followed by prediabetes, type 2 diabetes, and vascular complications. [3].

Since LVH is more likely associated with LV diastolic dysfunction, and LV contractility are usually not impaired [4], special attention should be paid to more sensitive methods for diagnosing a decrease in LV systolic function. The prognostic value of LV strain changes, estimated by speckle tracking echocardiography, as well as the search for effective preventive strategies in young people with HTN and preHTN, remain the debating point. Cardiac magnetic resonance imaging (MRI) remains the gold standard technique for assessing myocardial strain, but its practical use is limited by cost and low availability. The use of 2D speckle tracking echocardiograpy allows to quantify the global and regional contractile function of the myocardium. This technique has already been introduced into current guidelines on examination of patients with cardiomyopathies, patients after heart transplant, in case of chemotherapy-induced cardiotoxicity. However, the prospects of its use in young HTN patients requires further study. The aim of this study was to analyze the associations of insulin resistance and LV remodeling in a cohort of young patients with untreated uncomplicated HTN and preHTN.

Material and methods

During the medical screening, students and employees of the RUDN University aged 18 to 45 years (n=965) were doubly measured for office BP with 2-week interval. Fifty-seven (5,9%) individuals were diagnosed with HTN, 64 (6,6%) participants had high normal BP. The study was approved by the ethics committee of the RUDN University. Of the 121 people mentioned, 105 agreed to continue participating in the study and signed informed consent. They underwent 24-hour ambulatory BP monitoring. White-coat HTN was revealed in 11 patients who were excluded from further follow-up. Laboratory and instrumental examinations was performed for 94 patients with uncomplicated essential HTN diagnosed by office and 24-hour ambulatory BP measurement. The inclusion criteria were clinic BP ⩾140/90 mm Hg and/or average 24-hour BP ⩾130/80 mm Hg and/or average daytime BP ⩾135/85 mm Hg and/or average nocturnal BP ⩾120/70 mm Hg. There were following exclusion criteria: history of CVD (myocardial infarction or unstable angina, stroke, hospitalization due to heart failure); atrial fibrillation; glomerular filtration rate <45 ml/min (CKD-EPI equation); secondary HTN; white coat HTN; exacerbation/decompensation of chronic diseases; type 2 diabetes; limb amputation.

We collected anamnestic, demographic, and anthropometric data. Assessment of salt, fast food, and alcohol consumption was carried out by a structured questionnaire. Levels of creatinine, potassium, lipids, glucose, insulin, and uric acid were determined. We also assessed glycated hemoglobin (HbA_{1c}), as well as urine albumin/creatinine ratio.

Assessment of insulin resistance. We used Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) proposed by Matthews DR, et al. (1985) [5]. The HOMA-IR was calculated as follows: HOMA-IR = fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22,5. The threshold of insulin resistance was considered as exceeding the 75th percentile of its cumulative population distribution in non-diabetic adult population aged 20-60 years; HOMA-IR >2,7 was considered confirmation of insulin resistance.

Alternative methods for assessing insulin resistance were:

— Triglyceride-glucose index (TyG) proposed by Simental-Mendía L, et al. (2008) and calculated as ln (fasting triglycerides (mg/dl) × fasting glucose (mg/dl/2)). The threshold for normal glucose tolerance were TyG level of 8,29 [6].

— The Metabolic Score for Insulin Resistance (METS-IR) proposed by Bello-Chavolla O, et al. and calculated as ln ((2*Fasting glucose)+fasting TG)*BMI)/(ln (HDL-Cl), where TG are triglycerides, BMI — body mass index, HDL-C — high density lipoprotein cholesterol [7].

Echocardiography. We myocardial structure and function by standard echocardiography on a

Table 1

Clinical and demographic characteristics of young subjects with uncomplicated essential hypertension

Parameter	n=94
Age, years	23 [21; 25]
Men, n (%)	80 (85)
Race:	
Caucasians, n (%)	85 (90,5)
Negroids, n (%)	5 (5,3)
Mongoloids, n (%)	3 (3,2)
Hispanic/Latino, n (%)	1 (1,0)
Family history of early CVD, n (%)	32 (34)
Family history of HTN, n (%)	67 (71)
Body weight, kg	81,8±17,0
BMI, kg/m^2	25,9±4,8
BMI ⩾25 kg/m^2, n (%)	48 (51)
BMI ⩾30 kg/m^2, n (%)	16 (17)
WC, cm	88,3±13,5
Abdominal obesity, n (%)	30 (32)
TC, cm	100,9±10,9
WC/TC	0,86 [0,78; 0,91]
TC/height	0,48 [0,44; 0,54]
Smoking, n (%)	36 (38)
Fast food ⩾1 time/week, n (%)	45 (48)
Salt >5 g/day, n (%)	45 (48)
eGFR (SKD-EPI), ml/min/1,73 m^2	100,7±15,4
Urine albumin/creatinine ratio, mg/g	4 [0; 7]
TC, mmol/L	4,6±1,0
LDL-C, mmol/L	2,7±0,8
HDL-C, mmol/L	1,3±0,4
TG, mmol/L	0,9 [0,7; 1,4]
Dyslipidemia, n (%)	37 (39)
Uric acid, μmol/L	345,8±70,8
Glucose, mmol/L	4,9 [4,7; 5,3]
Insulin, μU/ml	8,1 [5,4; 12,3]
HOMA-IR	2,0±1,2
TyG	8,3±0,6
METS-IR	38,0±8,3
HbA_{1c}, %	5,1±0,3

Abbreviations: BMI — body mass index, WC — waist circumference, TC — thigh circumference, eGFR — estimated glomerular filtration rate, TC — total cholesterol, LDL-C — low density lipoprotein cholesterol, HDL-C — high density lipoprotein cholesterol, TG — triglycerides.

VIVID-7 ultrasound system (General Electric, USA). We used B-mode, M-mode, pulse wave (PW) and continuous wave (CW) Doppler, colour flow mapping with assessment of end-dastolic and end-systolic LV dimensions, end-diastolic and end-systolic volumes, stroke volume (SV), LV ejection fraction (EF), interventricular septum (IVS) and LV posterior wall (PW) thickness at diastole, left (LA) and right atrial (RA) sizes, LA volume index, RV size, pulmonary artery systolic pressure (PASP). LV mass was calculated by the Devereux R (1986) formula and indexed to body surface area (m^2) [8]. The criteria for LV hypertrophy were LV mass index (LVMI) ⩾95 g/m^2 in women, ⩾115 g/m^2 in men. Classification of LV remodeling types was carried out according to Ganau A (1992) method [9]. To evaluate diastolic function, we determined the peak E, the E/A ratio, average peak e', E/e'avg ratio, left atrial volume index, and tricuspid regurgitation peak velocity. All patients underwent an assessment of LV global longitudinal strain (GLS) using a speckle-tracking echocardiography. Apical four-, two- and three-chamber views were obtained. LV GLS was calculated automatically. Normal values of LV GLS were considered at >-20% [10]

The 24-hour ambulatory BP monitoring was performed according to a standard technique using a BPlab monitor with Vasotens technology (OOO Petr Telegin, Nizhny Novgorod, Russia).

Statistical analysis. Statistical processing was carried out using the software package SPSS 10.0. Normally distributed quantitative variables are presented as m±SD. For non-normally distributed quantitative variables, the median (Me) and 25; 75 percentiles (interquartile range — IQR) were used. Significance of differences was evaluated by Wilcoxon and Mann-Whitney tests. Data comparison in three subgroups was carried out using one-way analysis of variance, as well as the Kruskal-Wallis test with Bonferroni adjustment or Tukey's test. To assess the relationship, the Spearman's Rank or the linear Pearson's correlation coefficients were calculated. Differences were considered significant at $p<0,05$.

Results

The clinical and demographic characteristics of participants are presented in Table 1. The median age was 23 years (men — 85%). More than half of the subjects had overweight or obesity, and an abdominal distribution of excess fat was observed in 32%. We also revealed that 34% of participants had a family history of early CVE. Dyslipidemia was detected in 39%. More than a third of patients were smokers. Two-thirds of patients (67%) had masked HTN. Office systolic BP (SBP) was 133,4±15,7 mm Hg; diastolic BP (DBP) — 77,5±12,7 mm Hg. The average 24-hour SBP were 134,3±14,5 mm Hg, DBP — 77,0 [73,0; 85,5].

Table 2

Comparison of LV structural and functional parameters depending on the distribution between the quartiles of insulin resistance indices

HOMA-IR					
	1st quartile (n=21)	2nd quartile (n=23)	3rd quartile (n=23)	4th quartile (n=22)	p
BMI, kg/m^2	21,2±2,2	23,3±1,6	27,1±2,0	31,9±3,9	<0,001
WC, cm	75,9±7,8	81,3±6,6	90,9±5,9	105,5±9,2	<0,001
LVEF, %	60,3±5,2	60,0±4,6	59,4±5,4	60,8±5,6	NA
IVS thickness, cm	1,0 [0,8; 1,1]	0,9 [0,9; 1,1]	1,0 [0,9; 1,1]	1,0 [0,9; 1,1]	NA
LVPW thickness, cm	1,0 [0,8; 1,1]	1,0 [0,9; 1,1]	1,0 [0,9; 1,1]	1,0 [0,9; 1,1]	NA
LVMI, g/m^2	81,6 [71,4; 87,5]	86,4 [71,6; 95,6]	83,9 [78,0; 104,4]	88,0 [82,8; 100,7]	NA
RWT	0,39±0,05	0,41±0,08	0,45±0,09	0,43±0,11	NA
LV GLS, %	-20,5±1,5	-20,1±1,3	-19,9±2,6	-20,0±3,0	NA
METS-IR					
	1st quartile (n=23)	2nd quartile (n=24)	3rd quartile (n=23)	4th quartile (n=23)	p
BMI, kg/m^2	21,2±2,2	23,3±1,6	27,1±2,0	31,9±3,9	<0,001
WC, cm	75,9±7,8	81,3±6,6	90,9±5,9	105,5±9,2	<0,001
LVEF, %	61,4±5,3	60,3±5,3	59,3±4,7	59,5±4,9	NA
IVS thickness, cm	0,9 [0,8; 1,0]	0,9 [0,8; 1,0]	1,0 [0,9; 1,1]	1,0 [1,0; 1,2]	<0,001
LVPW thickness, cm	0,9 [0,8; 1,0]	0,95 [0,9; 1,1]	1,0 [0,9; 1,1]	1,1 [1,0; 1,2]	<0,001
LVMI, g/m^2	81,5 [63,1; 89,4]	87,5 [71,7; 96,4]	86,8 [80,5; 101,2]	87,0 [78,0; 109,1]	NA
RWT	0,38±0,06	0,41±0,09	0,41±0,05	0,47±0,12	0,003
LV GLS, %	-20,9±2,2	-20,2±2,0	-19,9±1,4	-19,4±2,8	NA
TyG					
	1st quartile (n=23)	2nd quartile (n=23)	3rd quartile (n=25)	4th quartile (n=23)	p
BMI, kg/m^2	23,8±3,5	24,9±5,0	26,9±5,5	27,8±4,0	0,015
WC, cm	82,1±10,2	82,3±11,9	92,2±13,6	95,3±12,9	0,001
LVEF, %	60,6±4,9	60,0±5,4	60,4±5,1	59,6±4,8	NA
IVS thickness, cm	0,9 [0,8; 1,0]	1,0 [0,8; 1,0]	1,0 [0,9; 1,1]	1,0 [0,9; 1,2]	NA
LVPW thickness, cm	0,9 [0,8; 1,0]	1,0 [0,9; 1,1]	1,0 [0,9; 1,1]	1,1 [1,0; 1,2]	0,012
LVMI, g/m^2	87,3 [68,7; 101,9]	81,7 [74,4; 89,7]	86,2 [78,1; 93,8]	88,4 [81,0; 111,9]	NA
RWT	0,37±0,06	0,42±0,07	0,42±0,09	0,45±0,11	0,014
LV GLS, %	-21,1±2,4	-20,5±1,6	-19,9±1,7	-18,6±2,3	0,003

Abbreviations: IVS — interventricular septum, LVPW left ventricular posterior wall, LVMI — LV mass index, RWT — relative wall thickness, LV GLS — left ventricular global longitudinal systolic strain.

LV remodeling were found in 38 (40%) participants: concentric remodeling — 32 (34%), concentric LVH — 5 (5%), eccentric LVH — 1 (1%). In order to assess LV dysfunctional impairment, LVEF was determined. Preclinical LV systolic dysfunction with normal LVEF was observed in 44 (47%) young people with HTN and preHTN.

To identify early disorders of carbohydrate metabolism, HbA_{1c}-level was evaluated; there were subjects with HbA_{1c} >5,7% (prediabetes). Insulin resistance (HOMA-IR >2,7) was diagnosed in 20 (21%) patients. Insulin sensitivity was also determined using TyG and METS-IR. The sample was divided into quartiles for each of three insulin resistance indices (Table 2). In the obtained subgroups, we compared clinical, demographic, anthropometric characteristics, laboratory data and parameters of myocardial structure and function. In subgroups, there were no significant differences in the age and sex patterns, the levels of clinic and average 24-hour

Table 3

Comparison of subgroups depending on insulin resistance and overweight/obesity

	Normal BMI, no IR (n=32)	Increased BMI, no IR (n=18)	Normal BMI, IR (n=14)	Increased BMI, IR (n=30)	p
Age, years	23,5±1,4	24,2±2,1	23,9±3,3	27,1±1,4	NA
Sex, f (%)	7 (22)	2 (11)	2 (14)	3 (10)	NA
BMI, kg/m^2	21,8±0,3	28,7±0,4	22,8±0,6	29,8±0,3	<0,001
WC, cm	77,5±6,4	94,4±9,0	80,2±7,6	99,9±10,6	<0,001
TC, cm	92,7±9,5	106,7±12,3	94,3±6,2	108,0±9,7	<0,001
SBPcl, mm Hg	130,5±14,5	128,7±10,9	136,7±15,1	137,4±17,6	NA
DBPcl, mm Hg	76,5±11,7	73,2±8,6	79,7±14,1	80,2±13,5	NA
SBP24, mm Hg	133,6±12,3	132,8±12,4	134,5±13,9	136,3±16,0	NA
DBP24, mm Hg	82,1±9,2	75,4±4,0	81,3±13,9	80,3±14,0	NA
LVMI, g/m^2	82,0 [69,3; 91,8]	82,6 [77,8; 102,1]	87,0 [75,4; 94,1]	87,0 [79,9; 109,8]	NA
RWT	0,38±0,07	0,41±0,05	0,42±0,09	0,46±0,10	0,007
LV GLS, %	-20,9±2,3	-20,7±1,2	-19,1±1,5	-19,2±2,2	0,005

Abbreviations: BMI — body mass index, WC — waist circumference, TC — thigh circumference, SBPcl — clinic systolic blood pressure, DBPcl — clinic diastolic blood pressure, SBP24 — average 24-hour systolic blood pressure, DBBP24 — average 24-hour diastolic blood pressure, LVMI — left ventricular mass index, RWT — relative wall thickness, LV GLS — left ventricular global longitudinal systolic strain.

Table 4

Correlation of insulin resistance indices with anthropometric and demographic characteristics

	HOMA-IR	TyG	METS-IR
Age, years$^{\#}$	0,012	0,178	0,202
BMI, kg/m^2	0,248*	0,323*	0,928**
WC, cm	0,373**	0,456**	0,852**

Note: $^{\#}$ — ρ (Spearman's), rest — r (Pearson's) * — p<0,05, ** — p<0,01.
Abbreviations: BMI — body body mass, WC — waist circumference.

Table 5

Multivariate regression analysis of the association of LV GLS with clinical, hemodynamic and echocardiographic parameters

	b	p
TyG	0,38	0,001
METS-IR	-0,18	0,49
WC	0,11	0,66
Office SBP	0,12	0,62
Average office BP	0,29	0,22
LVMI	0,13	0,36

Abbreviations: WC — waist circumference, SBP — systolic blood pressure, LVMI — left ventricular mass index.

SBP and DBP, LVEF. In all cases, from the lower quartile to the upper, an increase in BMI, waist circumference (WC), and proportion of individuals with abdominal obesity was noted. Lipid metabolism disorders were more significantly expressed in the upper quartile using HOMA-IR. LVMI, thicknesses of IVS and PW, relative wall thickness (RWT), LV global longitudinal strain (GLS) remained

unchanged depending on the HOMA-IR quartile. No significant differences in LVMI between quartiles were obtained for the other two insulin resistance indices. In this case, the RWT increased from the lower to the upper quartile of METS-IR and TyG. For the latter, more significant LV strain aggravation in the upper quartile was also demonstrated.

Then we identified 4 subgroups depending on the simultaneous presence of two characteristics: insulin resistance (TyG) and overweight or obesity (BMI $\geqslant$25 kg/m^2). For this analysis, we used TyG because it had a more significant relationship with LV remodeling parameters than HOMA-IR and did not show a direct dependence on BMI like METS-IR. In the first group, there were no participants with both insulin resistance and overweight/obesity, in the second and third groups, there were deviations of only one of the characteristics: BMI $\geqslant$25 kg/m^2 without insulin resistance or normal BMI with insulin resistance, respectively. Patients from the fourth subgroup were characterized by both insulin resistance and overweight/obesity. The threshold of the TyG was 8,29. The comparison of subgroups are presented in Table 3.

RWT and LV GLS significantly differed between groups. For LVMI, only a tendency to a larger value in individuals with insulin resistance was recorded. When dividing the sample only by presence of insulin resistance, the differences in LVMI were not significant (p=0,087). Multiple comparison of RWT and LV GLS between subgroups using the Bonferroni adjustment revealed significant differences only between the first and fourth subgroups.

The correlation analysis showed that all three insulin resistance indices had relationships with obesity by BMI and WC (Table 4). Associations of HOMA-IR with LV structural characteristics were significant only in relation to LVPW thickness (r=0,238, p<0,05) and RWT (r=0,235, p<0,05). For TyG and METS-IR, stronger relationships were established with LV remodeling parameters, such as IVS and LVPW thicknesses, RWT, LV GLS. The relationship with LVMI was significant only for METS-IR.

For the variables with strongest relationships, we performed a univariate regression analysis, where one of the insulin resistance indices acted as a predictor variable, and one of LV characteristics — as a dependent variable. TyG was significant predictor of changes in LV GLS (r=0,46, p=0,005), LVMI (r=0,32, p=0,02), IVS thickness (r=0,31, p=0,03), LVPW thickness (r=0,30, p=0,03), and METS-IR — LV GLS (r=0,46, p=0,005), LVMI (r=0,42, p=0,002), IVS thickness (r=0,52, p=0,00006), LVPW thickness (r=0,44, p=0,001), and RWT (r=0,31, p=0,03). The HOMA-IR was not associated with LV GLS, but there were associations with LVMI (r=0,40, p=0,003), IVS thickness (r=0,48, p=0,0004), and LVPW thickness (r=0,38, p=0,006), and RWT (r=0,33, p=0,02).

In order to assess the contribution of anthropometric, metabolic, hemodynamic factors to the subclinical change in LV systolic function, a multivariate regression analysis was performed. Age and sex were not significant predictors of LV GLS changes and were not included in the model. The TyG, METS-IR, HOMA-IR, WC, office SBP, average office BP, and LVMI were used as predictors, and LV GLS was a dependent variable (Table 5). The TyG (b=0,38, p=0,001) was an independent predictor of impaired LV GLS. Thus, after the inclusion of SBP, WC, and LVMI in the regression equation, the TyG remained a significant factor of LV GLS decrease.

Discussion

There is no position statement on the therapy need for young people with uncomplicated HTN, since it is difficult to conduct a study evaluating the prognosis in such patients due to the long waiting time for hard endpoints [11]. Nevertheless, a number of epidemiological studies with a long follow-up period have confirmed that in young patients with BP >130/80 mm Hg, as well as in older age groups, there is a clear relationship between BP and the long-term risk of CVE and mortality [12, 13]. Perhaps the early initiation of therapy can prevent more severe HTN and HTN-mediated organ damage, usually not undergoing a complete regression without timely treatment [14, 15].

In this population, it is necessary to search for indicators of structural and functional disorders caused by HTN, preferably before the LVH — one of the independent factors of an unfavorable prognosis. As one of these indicators, LV GLS can be used. In the study by Navarini S, et al., when comparing the HTN and normotension children and adolescents (mean age — 14 and 11 years) without changes in LV volumetric parameters and LVEF, a significant decrease of LV GLS in the HTN group was revealed [16]. In another study, Sengupta S, et al. found that patients with HTN, compared with non-HTN individuals, have a decrease of LV peak longitudinal strain in the subendocardial and subepicardial regions, and of circumferential strain — in the subepicardium. LV radial strain does not differ between the groups. The subendocardial-to-subepicardial gradient of circumferential deformation correlated with the radial strains. Despite reduced longitudinal shortening, LV wall thickening

in patients with HTN occurs later due to relatively preserved circumferential shortening [17]. In our study, early impairment of systolic function, assessed by reduced LV strain, was detected in almost half of young HTN people with hypertension and high normal BP. Assessment of prevalence of various remodeling types revealed a predominance of RWT increase without LVMI increase, that is, concentric LV remodeling.

One of the interesting findings was the high frequency of masked HTN (67%). This can be explained by the fact that the median age of participants was 23 years, and the prevalence of masked HTN among young patients is higher than among middle-aged people.

In routine practice, medical screening of healthy individuals does not require 24-hour BP monitoring, while masked HTN is much more likely associated with disorders of carbohydrate and lipid metabolism and asymptomatic target organ damage compared with true normotension [18, 19]. In this regard, we analyzed the prevalence of insulin resistance by HOMA-IR, which was rather high — every fifth had signs of impaired insulin sensitivity. The determination of insulin levels is not included in the routine examination of a HTN patient, which does not allow the HOMA-IR to be calculated. Therefore, a search for new screening tests is needed to assess insulin sensitivity. These tools are TyG and METS-IR, calculated using the lipids and glycemia levels. The predictive value of the TyG was demonstrated by da Silva A, et al. — the frequency of symptomatic coronary artery disease was 16% higher in the upper TyG tertile (9,9±0,5) compared with the lower one (8,3±0,3) [20].

The effect of insulin resistance on the myocardial structure and function has been confirmed in some clinical studies. Thus, in two cross-sectional population studies, a correlation was found between the extent of insulin resistance increase, estimated by the HOMA-IR, and the severity of LVH estimated by MRI data [21, 22] In another large cross-sectional study, the association of higher HOMA-IR values with LV GLS decrease was observed, and the relationship was not dependent on the obesity [23]. In the study by Lin JL, et al. (2018), a significant relationship between insulin resistance and LV remodeling in the Chinese population was obtained, and there were also no differences in groups and BMIs above and below 23 kg/m^2 [24]. In the CARDIA study, according to echocardiography 25 years after the initial examination, individuals with impaired glucose tolerance compared with normoglycemia subjects had the larger LV RWT and the lower LV GLS [13]. The limitations of the CARDIA study include a comparative statistical analysis of LV remodeling parameters only in groups that differ in the severity of impaired glucose metabolism (normoglycemia, impaired glucose tolerance, diabetes mellitus) without assessing the effect of insulin resistance. A prospective analysis of LV remodeling changes depending on the presence/absence of insulin resistance was performed by Cauwenberghs N, et al. [25]. This study demonstrated that higher levels of insulin and its increase during the 5-year follow-up in middle-aged people were associated with a more severe impairment of LV strain, LVEF decrease, deterioration in LV diastolic function (E/e'), and increased LVMI. Additional studies are needed to confirm the validity of such tendencies in young people with preHTN and HTN.

In our study, dividing the group by METS-IR and TyG quartiles showed an increase in RWT from the group with lowest values to the group with highest values of indices, and a more significant decrease in LV strain was determined in the group of upper TyG quartile. Similar data was also confirmed in the correlation analysis, where associations of IVS and LVPW thicknesses, RWT and LV GLS with METS-IR and TyG were found; HOMA-IR had associations with RWT and LVPW thickness. With a weaker relationship between the TyG and structural parameters, its correlation with LV GLS was found to be stronger with a higher significance compared to METS-IR and, especially, HOMA-IR, which had a slight association with LV GLS. An important question is, what specifies the early LV remodeling in young HTN people to a greater extent — obesity or insulin resistance. In the group without insulin resistance and obesity, the values of RWT and LV GLS were low, significantly increasing from the group of obesity without insulin resistance to the group of insulin resistance without obesity, being the highest in the group with both factors. In group of individuals with preHTN and hypertension, a rather high frequency of abdominal obesity was observed — 32%, while a BMI of $\geqslant$30 kg/m^2 was recorded in 17% of these patients. Moreover, the inclusion of WC in regression model for assessing the TyG role in early LV structural and functional changes did not reduce its prognostic value; the TyG remains an independent predictor of LV GLS decrease in young people with HTN.

The modern model for reducing the CVE risk focuses on the early, preclinical diagnosis of cardiovascular diseases and the primary prevention of complications. Nevertheless, relevant therapeutic algorithms are developed only for patients with already developed diseases. The exceptions are guidelines for smoking cessation and dyslipidemia

treatment, and the lipid-lowering therapy is associated with a decrease in CVE risk by only 30% [26]. A number of researchers explain the maintenance of residual risk with statin therapy by a decrease in insulin sensitivity [27-30]. It is known that long before the development of symptomatic cardiovascular diseases, myocardial remodeling onsets. An important role in the development and progression of myocardial damage (metabolic cardiomyopathy) can be played by insulin resistance. Under the ischemia, increased pressure load, and myocardial damage, insulin-resistant myocytes assimilate glucose worse and caused an impairment of myocardial adaptability [31]. Compensatory enhancement of fatty acid metabolism is accompanied by increased oxygen consumption, decreased cardiac myocyte efficiency, lipotoxicity, free-radical changes, subclinical inflammation, micro- and macrovasculopathy [32, 33]. In this regard, modern clinical guidelines focus on the early detection and prevention of risk factors such as HTN, obesity, and carbohydrate metabolism disorders [34]. Additional prospective studies are required to assess the prospects for non-drug and drug therapy of HTN and insulin resistance in young people with increased BP.

Conclusion

In a cohort of young patients with HTN and high normal blood pressure, there is a high prevalence of insulin resistance, metabolic disorders, and early signs of LV remodeling and subclinical systolic dysfunction. The TyG index, available for estimation by routine biochemical tests, is an independent factor affecting the LV GLS in young people with preHTN and HTN. This index retains its predictive value even with WC use in the regression equation. Since early disorders of carbohydrate metabolism can make a significant contribution to cardiovascular disease progression, they should be taken into account when developing preventive strategies. Prospective studies are required to study the effectiveness of antihypertensive therapy for young people with HTN and impaired LV GLS in order to reduce the CVE risk.

Relationships and Activities: not.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3738

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Atrial fibrillation and CHA_2DS_2VASc score of 1 — is there a problem in clinical practice?

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Aim. To study the incidence of nonvalvular atrial fibrillation (AF) in patients with a CHA_2DS_2VASc score of 1 in actual clinical practice, to determine the major RF for stroke, additional factors for thromboembolic risk modification and the proportion of patients receiving oral anticoagulant therapy.
Material and methods. We performed a retrospective analysis of 6575 medical records of patients hospitalized for five years in a therapeutic inpatient unit. To determine the stroke risk, major and minor modifying factors were assessed.
Results. Of 1160 patients with nonvalvular AF, 93 (8,0%) patients had a CHA_2DS_2VASc score of 1: hypertension (87,1%), heart failure (4,3%), vascular diseases (4,3%), diabetes (2,15%) and age 65-74 years (2,2%); minor modifying factors were as follows: left atrial (LA) dilatation (81,7%), obesity (40,9%), persistent/permanent AF (37,6%), proteinuria (26,9%), chronic kidney disease (3,2%). A combination of minor risk factors was observed in 61,3%, the most common of which were obesity, LA dilatation, persistent/permanent AF. Anticoagulants were prescribed to 72% of patients with a CHA_2DS_2VASc score of 1.
Conclusion. In actual clinical practice, patients with nonvalvular AF with a CHA_2DS_2VASc score of 1 are often found. The most common risk factors for stroke in these patients are hypertension, persistent or permanent AF, LA dilatation, and obesity. The use of anticoagulant therapy in these patients does not contradict current guidelines. However, further prospective follow-up is necessary to determine the effectiveness and safety of this therapy.

Key words: atrial fibrillation, hypertension, CHA_2DS_2VASc score of 1, anticoagulants.

Relationships and Activities: the study was supported by a grant from the Russian Science Foundation (№ 17-75-30052).

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Received: 04.02.2020
Revision Received: 25.02.2020
Accepted: 12.03.2020

For citation: Baranova E. I., Pavlova V. A., Ionin V. A., Petrishcheva E. Yu., Bliznyuk O. I., Zaslavskaya E. L., Ma I., Skuridin D. S., Shlyakhto E. V. Atrial fibrillation and CHA_2DS_2VASc score of 1 — is there a problem in clinical practice? *Russian Journal of Cardiology*. 2020;25(3):3738. (In Russ.) doi:10.15829/1560-4071-2020-3-3738

Atrial fibrillation (AF) is the most common persistent arrhythmia. The AF prevalence in adult population of Western Europe is 3% and it has increased in recent decades [1, 2]. AF significantly increases the thrombotic risk and is the cause of 26% of ischemic strokes, which often leads to disability or death [1].

The anticoagulant therapy is a greatest benefit for patients with AF, which prevents ischemic strokes and systemic embolism [3]. Currently, nonvalvular AF prevails, which is not associated with severe or moderate mitral stenosis and mechanical valve prostheses. To determine the stroke risk in patients with nonvalvular AF, the European Society of Cardiology (ESC) recommends using the CHA_2DS_2VASc score, which considers the main risk factors (RF) for stroke (congestive heart failure, hypertension (HTN), age 65-74 years, age ⩾75 years, diabetes, prior stroke or transient ischemic attack, or systemic embolism, vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque) and female sex [3, 4]). However, there are other stroke factors that are not included in this score: obesity, cardiac remodeling, chronic kidney disease, obstructive sleep apnea, and others.

Current clinical guidelines recommend use of anticoagulants to prevent thrombotic events, preferably direct oral anticoagulants (DOACs) for patients with nonvalvular AF and CHA_2DS_2VASc score of ⩾2 in men and ⩾3 points in women, regardless of the bleeding risk [3, 4]. If a patient with nonvalvular AF has CHA_2DS_2VASc score of 0, then anticoagulants are not indicated, since the stroke risk is low (IIIB) [3]. Patients with nonvalvular AF and CHA_2DS_2VASc score of 1 (without female sex) have a moderate risk of stroke, and ESC guidelines recommends to consider the anticoagulants for these patients (IIaB) [3]. At the same time, the stroke risk in these patients is relatively low, and with the anticoagulant therapy, risk of bleeding can be higher. Currently, there are no randomized clinical trials in patients with CHA_2DS_2VASc score of 1 (in women — score of 2), and the matter of advisability of using anticoagulants in these patients remains open.

In 2019, a document was published containing the opinion of ESC Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Council on Stroke [5]. This document contains the decision-making algorithm for the appointment of anticoagulants in patients with CHA_2DS_2VASc score of 1 (without female sex), based on a comparison of the risk for stroke and bleeding. In patients with a HAS-BLED score ⩾2, i.e., if the risk of bleeding prevails over the risk of stroke, the anticoagulants are not indicated. There is a need to correct potentially modifiable RF for bleeding (HTN, use of nonsteroidal anti-inflammatory drugs, alcohol abuse), and then re-evaluate the risk of bleeding and compare with the risk of stroke [5] (Figure 1).

If a patient with CHA_2DS_2VASc score of 1 has a low risk of bleeding (<2 points), then experts recommends an individual risk stratification considering the main and additional risk factors for stroke. In patients with AF, CHA_2DS_2VASc score of 1 and a low risk of bleeding, it is proposed to single out the major factors, which favor oral anticoagulation and additional factors requiring thromboembolic risk modification [5] (Table 1).

At the same time, the following questions remain unclear: (1) how often AF patients with CHA_2DS_2VASc score of 1 are found, (2) what is the incidence of major stroke RF, additional factors for thromboembolic risk modification, and (3) how often these patients use anticoagulants in actual clinical practice.

The aim of this study was to study the incidence of nonvalvular AF in patients with a CHA_2DS_2VASc score of 1 in actual clinical practice, to determine the major RF for stroke, additional factors for thromboembolic risk modification and the proportion of patients receiving oral anticoagulant therapy.

Material and methods

We studied medical records of 6575 patients hospitalized in a period from 2014 to 2018 in the therapeutic and cardiology departments of the university hospital. All data obtained as a result of a retrospective analysis of medical records was entered into a single original MS Excel database developed for this study. From all records of patients with AF, men with CHA_2DS_2VASc score of 1 and women with CHA_2DS_2VASc score of 2 and nonvalvular AF were selected. The prevalence analysis results are presented as n/tot.n (%), where n is the number of patients diagnosed with certain sign, tot.n is the total number of patients who were evaluated for this sign, and % is the percentage of the total number examined. Normally distributed values are presented as mean and standard deviation (M±SD). Statistical analysis was performed using software package StatPlus: mac Pro (AnalystSoft Inc.), version 7.0. The study was supported by a grant from the Russian Science Foundation (№ 17-75-30052).

Results

In the period from 2014 to 2018, 1203 patients with AF were hospitalized, which amounted to 18,3% of the total number of patients (men — 540/1203 (44,9%); women — 663/1203 (55,1%)). The mean age of patients with AF was 69,9±10,6 years. Most patients had a paroxysmal and permanent AF (538 (44,7%) and 456 (37,9%) patients, respectively). Per-

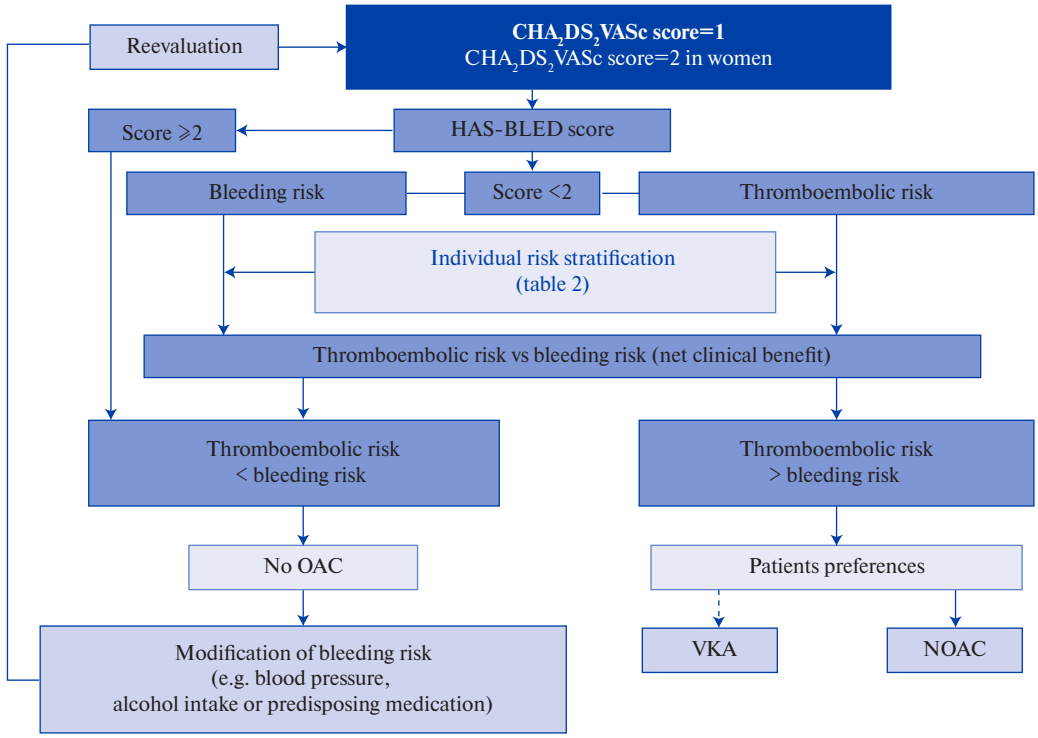

Figure 1. Decision tree for oral anticoagulation in patients with AF and CHA_2DS_2-VASc score of 1 [5].

sistent and long-standing persistent AF were found less frequently (201 (16,7%) and 8 (0,7%) patients, respectively). Valvular AF (mechanical valve prosthesis, moderate and severe mitral stenosis) were found in 43 (3,6%) patients, nonvalvular AF — in 1160 (96,4%) patients. The mean CHA_2DS_2VASc score was 4,3±1,9, HAS-BLED — 1,5±0,9. Among patients with nonvalvular AF, there were 93 (8,0%) men with CHA_2DS_2VASc score of 1 and women with CHA_2DS_2VASc score of 2. The most common single RF was HTN — 81 (87,1%) patients, less common — vascular diseases and diabetes (Table 2).

When analyzing the patients with AF and HTN as the single RF for stroke, it was found that the majority of them (n=70; 86,4%) at the hospitalization had controlled HTN and received antihypertensive therapy: beta-blockers — 49 (52,7%), angiotensin converting enzyme inhibitors — 38 (30,1%) or angiotensin II receptor blockers — 28 (30,1%).

An analysis of additional RF for thromboembolic events in patients with AF and CHA_2DS_2VASc score of 1 [5] revealed the following most common factors: left atrial (LA) dilatation — 76 (81,7%), which was more common in men; obesity — 38 (40,9%); persistent/permanent AF — 35 (37,6%). The combination of several additional RF for thromboembolism in AF patients was recorded in 57 patients (61,3%). In women, the most common were the combination of obesity and LA dilatation (n=14; 24,6%), while in men — permanent/persistent AF and LA dilatation (Table 3).

Table 1
Individual risk stratification factors in patients with AF and CHA_2DS_2-VASc score of 1 (without female sex) [5]

Favors oral anticoagulation (in case of low bleeding risk)
Age (>65 years)
Type II diabetes mellitus
Atrial fibrillation (not atrial flutter)
Persistent/permanent atrial fibrillation
Additional factors for thromboembolic risk modification
Obesity (body mass index ⩾30 kg/m^2)
Proteinuria (>150 mg/24 h or equivalent)
eGFR (<45 ml/h)
NT-proBNP (>1400 ng/l)
Positive cardiac troponin T and I
Enlarged LA volume (⩾73 ml) or diameter (⩾4,7 cm)
LAA emptying velocity (<20 cm/s)
ABC (age/biomarker/clinical history) score

Abbreviations: BMI — body mass index, LA — left atrium, eGFR — estimated glomerular filtration rate, AF — atrial fibrillation.

Despite the minimum CHA_2DS_2VASc score, 48 (51,6%) patients received anticoagulant therapy before hospitalization and 67 (72,0%) patients were

Table 2

RF for stroke in patients with nonvalvular AF and CHA_2DS_2-VASc score of 1 in men and of 2 in women

Parameter	Men 47/526 (8,9%)	Women 46/634 (7,3%)	Overall 93/1160 (8,0%)
Hypertension	41/47 (87,2%)	40/46 (87,0%)	81/93 (87,1%)
Age 65-74 years	1/47 (2,1%)	1/46 (2,2%)	2/93 (2,15%)
Diabetes	0/47 (0%)	2/46 (4,3%)	2/93 (2,15%)
CHF (congestive or LVEF ⩽40%)	3/47 (6,4%)	1/46 (2,2%)	4/93 (4,3%)
Vascular diseases (prior myocardial infarction, peripheral artery disease, aortic plaque)	2/47 (4,3%)	2/46 (4,3%)	4/93 (4,3%)

Abbreviations: CHF — chronic heart failure, LVEF — left ventricular ejection fraction, MI — myocardial infarction.

Table 3

Additional factors for thromboembolic risk modification in patients with nonvalvular AF and CHA_2DS_2-VASc score of 1 in men and of 2 in women

Parameter	Men	Women	Overall
LA dilatation (⩾73 ml or ⩾4,7 cm)	46/47 (97,9%)	30/46 (65,2%)	76/93 (81,7%)
Obesity (BMI ⩾30 kg/m^2)	20/47 (42,6%)	18/46 (39,1%)	38/93 (40,9%)
Persistent/permanent AF	23/47 (48,9%)	12/46 (26,1%)	35/93 (37,6%)
Proteinuria (>150 mg/day)	12/47 (25,5%)	13/46 (28,3%)	25/93 (26,9%)
CKD (GFR <45 ml/min/1,73 m^2)	1/47 (2,1%)	2/46 (4,3%)	3/93 (3,2%)
Combination of additional factors	32/93 (68,1%)	25/93 (54,3%)	57/93 (61,3%)
Obesity+LA dilatation	6/32 (18,8%)	8/25 (32,0%)	14/57 (24,6%)
Persistent/permanent AF+LA dilatation	7/32 (21,9%)	2/25 (8,0%)	9/57 (15,8%)
Persistent/permanent AF+obesity	0/32 (0,0%)	1/25 (4,0%)	1/57 (1,8%)
Obesity+proteinuria	0/32 (0,0%)	1/25 (4,0%)	1/57 (1,8%)
Proteinuria+LA dilatation	0/32 (0,0%)	4/25 (16,0%)	4/57 (7,0%)
Persistent/permanent AF+LA dilatation+proteinuria	4/32 (12,5%)	1/25 (4,0%)	5/57 (8,8%)
Obesity+proteinuria+LA dilatation	5/32 (15,6%)	2/25 (8,0%)	7/57 (12,3%)
Persistent/permanent AF+obesity+LA dilatation	6/32 (18,8%)	2/25 (8,0%)	8/57 (14,0%)
Obesity+LA dilatation+CKD	1/32 (3,2%)	1/25 (4,0%)	2/57 (3,5%)
Persistent/permanent AF+obesity+LA dilatation+proteinuria	3/32 (9,4%)	2/25 (8,0%)	5/57 (8,8%)
Persistent/permanent AF+LA dilatation+proteinuria	0/32 (0,0%)	1/25 (4,0%)	1/57 (1,8%)

Abbreviations: CKD — chronic kidney disease, AF — atrial fibrillation, LA — left atrium, BMI — body mass index.

recommended anticoagulant therapy after hospitalization. Two (2,2%) patients, in addition to AF, had other indications for anticoagulant therapy (pulmonary embolism, intracardiac thrombus). Among the RF for thromboembolic events in patients receiving anticoagulants, HTN was more common, and among the additional RF — LA dilatation (Table 4).

Bleeding risk analysis revealed 2 men with HAS-BLED score of 2 and 5 women with HAS-BLED score ⩾2; all other patients had score <2. The drugs prescribed for patients with AF and CHA_2DS_2VASc score of 1 in men and of 2 in women were as follows: warfarin — 18/67 (26,9%), apixaban — 40/67 (59,7%), dabigatran — 6/67 (8,9%) and rivaroxaban — 3/67 (4,5%).

Discussion

ESC guidelines (2016) recommends consideration of anticoagulants in patients with nonvalvular AF and CHA_2DS_2VASc score of 1 in men and of 2 in women (IIaB) [3]. It has been established that even a single RF for stroke in AF patients increases the thromboembolic risk. In a study by Lip GYH, et al. (2015), it was found that CHA_2DS_2VASc score of 1 (without female sex) increases the stroke risk by 3,01 times and death by 3,12 times [6]. Anticoagulant therapy reduces the incidence of stroke and systemic emboli in patients with nonvalvular AF and CHA_2DS_2VASc score of 1 [7].

Current cohort study was conducted for the first time in the Russian population and it was found that

Table 4

Risk factors for thromboembolic events in patients with AF and CHA_2DS_2-VASc score of 1 in men and of 2 in women who received anticoagulant therapy

Parameter	Men	Women	Overall
Number of patients receiving anticoagulants	30/47 (63,8%)	37/46 (80,4%)	67/93 (72,0%)
Hypertension	25/30 (83,3%)	33/37 (89,2%)	58/67 (86,6%)
CHF (congestive or LVEF ⩽40%)	3/30 (10,0%)	1/37 (2,7%)	4/67 (6,0%)
Vascular diseases (prior myocardial infarction, peripheral artery disease, aortic plaque)	2/30 (6,7%)	2/37 (5,4%)	4/67 (6,0%)
Age 65-74 years	0/30 (0,0%)	1/37 (2,7%)	1/67 (1,5%)
LA dilatation (⩾73 ml or 47 mm)	27/30 (90,0%)	24/37 (64,9%)	51/67 (76,1%)
Persistent/permanent AF	19/30 (63,3%)	11/37 (29,7%)	30/67 (44,8%)
Obesity (BMI ⩾30 kg/m^2)	14/30 (46,7%)	15/37 (40,5%)	29/67 (43,3%)
Proteinuria (>150 mg/day)	10/30 (33,3%)	10/37 (27,0%)	20/67 (29,9%)

Abbreviations: CHF — chronic heart failure, LVEF — left ventricular ejection fraction, MI — myocardial infarction, LA — left atrium, BMI — body mass index.

out of 1160 patients hospitalized with nonvalvular AF, there were 8% of patients with CHA_2DS_2VASc score of 1. The proportion of such patients among outpatient population with AF is 15% [8]. Such a difference is due to the fact that hospitalized patients with AF are often older than outpatients and often have comorbidities.

We found that the most common single RF for stroke was HTN (87,1%), other RF were much less common. According to Chao T-F, et al. (2015), among population with CHA_2DS_2VASc score of 1, patients were more likely to have a single RF for stroke — age 65-74 years or HTN [9]. ESC/ESH Guidelines for the management of HTN (2018) note that stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when HTN is the single additional RF (IIa, B) [10]. In a study by Chao T-F, et al. (2015), it was shown that in patients with AF and HTN as a single RF, the frequency of thromboembolic events per 100 patient years is 2,2 in men and 1,9 in women [9]. HTN is of particular importance as a stroke RF in patients older than 50 years [11]. A meta-analysis of 9 clinical trials conducted in 2020 showed that HTN and inadequate control of office blood pressure are predictors of stroke and systemic embolism [12]. Therefore, when considering anticoagulants to AF patients, non-taking into account this important predictor of stroke, in our opinion, is not justified.

In a study conducted in Taiwan, it was found that age 65-74 years or type 2 diabetes are the most significant RF of thromboembolic events; the incidence of strokes or systemic embolism in such patients is on average 3 per 100 patient years [9]. However, in our study, there were little number of patients with type 2 diabetes or 65-74 years of age without additional RF for stroke (without comorbidities). This is probably due to the special characteristics of in-patient population, and the race has lower value.

Currently, there are no data from randomized clinical trials indicating the need for anticoagulant therapy in AF patients and CHA_2DS_2VASc score of 1. At the same time, patients with CHA_2DS_2VASc score of 1 were included in the RE-LY and ARISTOTLE studies [13, 14].

When considering the anticoagulants to AF patients with CHA_2DS_2VASc score of 1, the risks of thrombosis and bleeding should be evaluated [5]. The bleeding frequency in patients with HAS-BLED score of 2 (1,88-3,20% per year) exceeds the thrombotic risk in patients with AF and CHA_2DS_2VASc score of 1 (0,6%-1,3% per year) [5]. According to study by Sulzgruber P, et al. (2019), anticoagulants should not be used in patients with CHA_2DS_2VASc score of 1 and HAS-BLED score ⩾2 [5]. With a low bleeding risk (HAS-BLED score <2) and CHA_2DS_2VASc score of 1, additional RF may affect the considering anticoagulants (Table 1).

We detected LA dilatation in 81,7% of patients with AF and CHA_2DS_2VASc score of 1. This fact should be taken into account, since LA remodeling is an additional factor for thromboembolic risk modification and is easily diagnosed with ultrasound. It is known that LA dilation is a result of not only HTN, but also obesity, and in our study, obesity was detected in 40,9% of patients. LA dilatation favors a persistent and permanent AF, which we found in 37,6% of patients. In 61,3% of patients, a combination of several additional thromboembolic risk modification factors was observed. The most common were combinations of LA dilatation with obesity or with a permanent/persistent AF.

In our study, an analysis of LA appendage peak flow velocity was not performed. However, it was previously established that a decrease of this parameter (<20 cm/sec) is a risk of stroke [15]. Slowing blood flow contributes to blood clot formation in LA appendage, and such patients have a very high risk of cerebral embolism (up to 16% per year) [16]. At the same time, 50% of patients with a thrombus in LA or its appendage have a low CHA_2DS_2VASc score and the risk of cardioembolic events in such patients can be underestimated [16].

According to the meta-analysis of 8 largest studies, CHA_2DS_2VASc score of 1 significantly increases the risk of thromboembolic events, and the age of patients (65-74 years) is of the greatest importance, therefore, these patients should receive anticoagulants [17]. Moreover, the authors believe that even in patients with CHA_2DS_2VASc score of 1 and comorbidity as the single additional RF (HTN, type 2 diabetes, heart failure and atherosclerosis-related diseases), anticoagulants, especially DOACs, are indicated [17].

Our study revealed that 72,0% of patients with CHA_2DS_2VASc score of 1 after hospitalization were prescribed anticoagulants, and most did not have other indications for anticoagulant therapy (pulmonary embolism, deep vein thrombosis, intracardiac trombus). The most common single RF for stroke in these patients was HTN (86,6%). In addition, many of these patients had additional factors for thromboembolic risk modification (LA dilatation, permanent and persistent AF, obesity, and kidney disease).

When choosing management strategy of patients with CHA_2DS_2VASc score of 1, additional RFs in favor of anticoagulants and low risk of bleeding, the matter should be discussed with the patient and jointly resolved [5]. If it is decided not to use anticoagulants, then in such patients it is necessary to monitor and annually calculate CHA_2DS_2VASc score, since the age of patients increases and comorbidities may develop, that is, additional RFs for stroke [11]. If there is CHA_2DS_2VASc score $\geqslant 2$ (without female sex), anticoagulants should be prescribed unless contraindicated, regardless of the HAS-BLED score [3].

Study limitations. We conducted a study of patients hospitalized with nonvalvular AF, which does not fully reflect the incidence of patients with CHA_2DS_2VASc score of 1 in the population; most subjects were not examined for such additional factors of thromboembolic risk modification as the levels of NT-proBNP, troponin T or I, and LA appendage peak flow velocity.

Conclusion

1. Among hospitalized patients, 8,0% had nonvalvular AF and CHA_2DS_2VASc score of 1.
2. The most common single RF for stroke in patients with nonvalvular AF and CHA_2DS_2VASc score of 1 was HTN (87,1%).
3. LA dilatation, obesity, permanent or persistent AF are the most common factors for thromboembolic risk modification; 61,3% of patients have a combination of several additional factors.
4. Anticoagulants were prescribed for 72,0% of patients with CHA_2DS_2VASc score of 1; most of these patients had HTN.

Thus, the problem of detecting and treating patients with nonvalvular AF and CHA_2DS_2VASc score of 1 is relevant in actual clinical practice; such patients are not uncommon, and the most frequent RFs for stroke in these patients are HTN, persistent or permanent AF, LA dilatation, and obesity. Most patients with CHA_2DS_2VASc score of 1 have indications for the oral anticoagulant therapy, and further prospective studies are necessary to determine the effectiveness and safety of this strategy.

Relationships and Activities: the study was supported by a grant from the Russian Science Foundation (№ 17-75-30052).

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3-3729

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Blood pressure phenotypes in young patients with type 1 diabetes

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Aim. To study phenotypes of clinic and 24-hour ambulatory blood pressure (BP), to determine their associations with arterial stiffness parameters, and to assess global cardiovascular risk (CVR) in young patients with type 1 diabetes (T1D).
Material and methods. The presented cross-sectional single-center study included 81 T1D patients without a history of hypertension (HTN) and other cardiovascular diseases (CVD) (men — 39%; median age — 27 years; median duration of T1D — 6 years). All participants underwent a routine clinical and laboratory testing, measurement of clinic and 24-hour ambulatory BP (BPLab Vasotens), assessment of central BP and arterial stiffness parameters using applanation tonometry technique. BP phenotypes were analyzed with diagnostic criteria for HTN by ESC/ESH 2018 guidelines. CVR was assessed using the SCORE 10-year risk calculator (ESC 2019). The differences were considered significant at p<0,05.
Results. The prevalence of true HTN was 6,2%, masked HTN — 38,3%. Isolated nocturnal HTN was revealed in 30,7% of patients with clinic BP <140/90 mm Hg. The subgroup with masked HTN was dominated by patients with normal clinic BP (58,1%) and in most cases was characterized by isolated diastolic BP increase (64,5%). Masked HTN was associated with a higher carotid-femoral pulse wave velocity (PWV) (median — 7,2 versus 6,3 m/s, p=0,002). The most common profiles of nocturnal BP decrease were non-dipper (63,9%) and night-picker (16,6%). High and very high CVR was recorded in 87,7% of patients.
Conclusion. Hypertension occurs in 44,5% of young patients with type 1 diabetes and is characterized by a high prevalence of masked isolated nocturnal HTN and non-dipping. Masked HTN is associated with a higher carotid-femoral PWV. High and very high 10-year CVR was recorded in 87,7% of patients.

Key words: type 1 diabetes, 24-hour ambulatory blood pressure monitoring, masked hypertension, arterial stiffness, cardiovascular risk.

Relationships and Activities: not.

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Received: 29.01.2020
Revision Received: 16.02.2020
Accepted: 11.03.2020

For citation: Kobalava Zh. D., Stavtseva Yu. V., Troitskaya E. A., Safarova A. F., Petrosyan A. E. Blood pressure phenotypes in young patients with type 1 diabetes. *Russian Journal of Cardiology*. 2020;25(3):3729. (In Russ.)
doi:10.15829/1560-4071-2020-3-3729

Type 1 diabetes (T1D) is one of the most common endocrine disorders developing in children and young adults, the prevalence of which has been increasing in recent years [1-3]. T1D is associated with an almost three-fold increase in mortality compared with the general population, which is primarily due to the premature atherosclerosis, and, as a result, cardiovascular events occur at least 10 years earlier [4-5]. The most important risk factor for the development and progression of macro- and microvascular complications in T1D is hypertension (HTN). According to various data, its prevalence ranges from 24 to 43% [6-7] and increases with the duration of diabetes [8].

The features of HTN in T1D patients have not been sufficiently studied, and blood pressure (BP) phenotyping is important. The concept of "phenotype" has firmly come into clinical practice with the development of personalized medicine. Phenotype is defined as a combination of signs characterizing differences in the severity of symptoms, clinical outcomes and mortality in patients with a certain disease [9]. Thus, phenotyping of T1D patients depending on changes in clinic and/or ambulatory BP can be of great importance in risk stratification and treatment strategy. Small studies have shown a relatively high frequency of masked and nocturnal HTN, as well as nondecrease in BP at night in T1D patients, which may explain cardiovascular risk (CVR) increase [10-12]. At the same time, despite guidelines, the frequency of 24-hour ambulatory blood pressure monitoring (ABPM) use in this population is relatively low in actual clinical practice.

The most important features of current clinical guidelines on HTN [13-15] are the orientation of management strategies to global CVR, which significantly changes the approach to treatment, especially in young patients, as well as lowering BP threshold for initiating antihypertensive therapy (AHT). According to ACC/AHA guidelines (2017), pharmacologic treatment is indicated for patients at high risk of atherosclerosis-related cardiovascular disease (CVD) with BP ⩾130/80 mm Hg [15]. According to ESC/ESH guidelines (2018), AHT should be considered in patients with high normal BP (⩾130/85 mm Hg) and very high CVR due to CVD (especially coronary artery disease) [13, 14]. Diabetes, in most cases, is associated with high or very high CVR, which makes early use of lipid-lowering and antihypertensive therapy important. Moreover, CVR in T1D patients may be underestimated, as well as HTN may be untimely diagnosed, which is associated by a high prevalence of masked HTN. This can lead to untimely prescribing of medication and the early development of complications. The prevalence of HTN and its phenotypes, the characteristics of CVR categories in the Russian population of T1D patients remain insufficiently studied. An additional important factor, probably affecting CVR in T1D patients, is an increase of arterial stiffness, which often precedes HTN manifestations and vascular events [16]. The association of arterial stiffness with masked HTN in this population requires further research.

The aim was to study phenotypes of clinic and 24-hour ambulatory BP, to determine their associations with arterial stiffness parameters, and to assess global CVR in young patients with T1D.

Material and methods

The current cross-sectional single-center study included patients aged 18 to 44 years with established T1D, who were monitored from January to December 2018. Exclusion criteria were any cardiovascular and clinically significant non-cardiovascular diseases. The main clinical and demographic characteristics, laboratory and instrumental data were recorded in the research database.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. All patients signed informed consent.

BP was measured in the morning using the oscillometric device HEM-5001 (Omron Health Care, Japan) in accordance with the guidelines [13, 14]. When analyzing the data on clinical measurement, BP ⩾140/90 mm Hg considered threshold for HTN diagnosis. For characterization of clinic BP levels, a standard classification was used [13, 14].

ABPM was performed according to a standard technique from clinical guidelines [17]. To carry out the 24-hour ABPM, a portable BPLab device (OOO Petr Telegin, Russia) was used. The circadian BP

Table 1

24-hour BP classes

Class	Description	Range
Dipper	Normal nighttime BP decrease	10-20%
Non-dipper	Insufficient nighttime BP decrease	⩾0% — <10%
Over-dipper	Excessive nighttime BP decrease	<0%
Night-picker	Steady nighttime BP increase	>20%

Abbreviations: BP — blood pressure, SBP — systolic blood pressure.

Table 2

Determination of BP phenotypes [15, 16]

BP phenotype	Clinic BP, mm Hg		ABPM data, mm Hg				
			24-hour BP		Daytime BP		Nighttime BP
Normotension	<140/<90	and	<130/<80	and	<135/<85	and	<120/<70
True HTN	⩾140/⩾90	and	⩾130/⩾80	and/or	⩾135/⩾85	and/or	⩾120/⩾70
White coat HTN	⩾140⩾90	and	<130/<80	and/or	<130/<85	and	<120/<70
Masked HTN	<140/<90	and	⩾130/⩾80	and/or	⩾135/⩾85	and/or	⩾120/⩾70

Note: standards are presented as follows: 2018 ESC/ESH or 2017 ACC/AHA.
Abbreviations: BP — blood pressure, HTN — hypertension, ABPM — ambulatory blood pressure monitoring.

rhythms in the aorta and brachial artery were analyzed using the standard dipping classification (Table 1) [17]. BP phenotypes were determined by comparing the clinic and ambulatory BP (2018 ESC/ESH criteria were used) (Table 2).

The parameters of central pulse wave and arterial stiffness were determined using a SphygmoCor device (AtCor, Australia), by means of applanation tonometry of radial artery and estimation of carotid-femoral pulse wave velocity (cfPWV). The test was performed according to the standard protocol [18]. An increase in cfPWV was considered at ⩾10 m/s [13, 14].

Ten-year CVR was evaluated in accordance with the clinical guidelines [13, 19]: patients with established HTN-mediated organ damage (HMOD) or three or more risk factors or a diabetes duration >20 years were classified as very high risk; patients with diabetes >10 years without HMOD or with additional risk factor were classified as high risk; patients <35 years of age with diabetes <10 years without other risk factors were classified as moderate risk.

For primary data processing, descriptive statistics were used. Intergroup differences for quantitative variables were assessed using the Mann-Whitney and Kraskel-Wallis tests. For qualitative variables, contingency tables were created and the Pearson's chi-squared test was used. Differences were considered significant at p<0,05. For data processing, software package Statistica 10.0 was used.

Results

We analyzed data on 81 patients with T1D (Table 3). At the inclusion in the study, there were no data suggestive of additional CVR, with the exception of hyperlipidemia, which indicates inadequate outpatient management of lipid metabolism disorders (all patients did not receive statins). It should be noted that cfPWV >10 m/s was detected only in 3 patients (3,7%).

The total prevalence of HTN was 44,5% (n=36). The distribution of patients by BP phenotypes is shown in Figure 1. Among patients with normal clinic BP according to ESC/ESH criteria, optimal BP was recorded in 33,3%, normal — in 52%, and high normal in 14,7%. It should be noted that the prevalence of different BP phenotypes did not differ between subgroups with masked HTN and true normal BP. Although in relation to the latter, there was a tendency to a higher frequency of optimal BP (Figure 2).

An additional analysis revealed that patients with high normal BP, compared to patients with optimal BP, were older (31 (28; 35) years vs 27 (21; 28) years, p=0,045) and had higher levels of triglycerides (1,43 (1,16; 1,6) vs 1,08 (1,06; 1,39) mmol/L, p=0,04). There were no significant differences with the normal BP group. There were also no differences in ABPM data, dipping phenotypes, and arterial stiffness parameters.

To compare the clinical characteristics between all BP phenotypes, the Kruskal-Wallis test was used (Table 4). With the exception of obvious differences between clinic and ambulatory BP, higher nocturnal heart rate in patients with masked HTN were noted.

Given the clinical significance of masked HTN for CVR, an additional analysis was performed in this group, accounting for 41% of all patients with normal clinic BP. It was shown that 23 (74,2%) patients with masked HTN had isolated nocturnal HTN, 2 (6,5%) patients — isolated daytime HTN, and 6 (19,4%) patients — masked hypertension according to day- and nighttime measurements. Thus, isolated nocturnal HTN was observed in 30,7% of patients with normal clinic BP. Twenty (64,5%) patients with masked HTN had isolated diastolic HTN, 11 (35,5%) — systolic-diastolic HTN. Patients with masked HTN compared with the group of true normal BP were characterized by a longer duration of diabetes, older age, as well as higher albuminuria, cfPWV, and variability of SBP (Table 5). No other differences were found in arterial stiffness parameters and dipping phenotypes.

Table 3

Characteristics of T1D patients at inclusion in the study*

Parameter	Population (n=81)
Age, years, median	27 (23;34)
Male sex, n (%)	48 (39)
Duration of diabetes, years	6 (2,8;11)
BMI, kg/m^2	21,7 (20,2;24)
Smoking, n (%)	20 (24,7%)
Creatinine, µmol/L	82 (67;97)
GFR CKD EPI, ml/min/1,73 m^2	101 (87;122)
Total cholesterol, mmol/L	5,1 (4,1;5,7)
LDL, mmol/L	3,2 (2,9;4,1)
Triglycerides, mmol/L	1,2 (1,0;1,5)
HbA_{1c},%	6,9 (5,6;7,9)
Albuminuria/Creatinine, mg/g	12 (6;24)
Mean SBP (clinic), mm Hg	120 (110;120)
Mean DBP (clinic), mm Hg	80 (70;80)
Daytime mean SBP, mm Hg	119 (111;126)
Daytime mean DBP, mm Hg	78 (69;81)
Nighttime mean SBP, mm Hg	112 (107;118)
Nighttime mean DBP, mm Hg	69 (62;78)
Central SBP, mm Hg	109 (100;118)
Central DBP, mm Hg	72 (67;76)
Central PP, mm Hg	40 (35;46)
Pulse wave velocity, m/s	6,3 (5,3;6,7)

Note: * — quantitative data are presented as median (interquartile range).

Abbreviations: HbA_{1c} — glycated hemoglobin, DBP — diastolic blood pressure, BMI — body mass index, LDL — low density lipoproteins, PP — pulse pressure, SBP — systolic blood pressure, GFR — glomerular filtration rate.

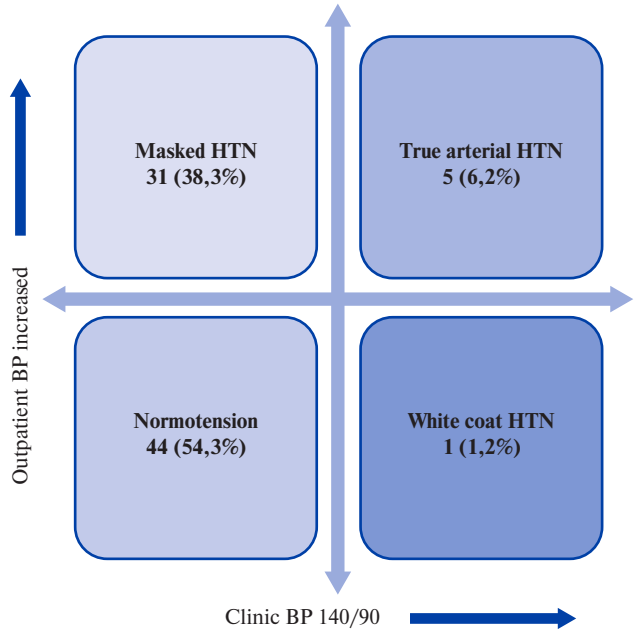

Figure 1. BP phenotypes in young patients with type 1 diabetes (n=81).
Abbreviations: HTN — hypertension, BP — blood pressure.

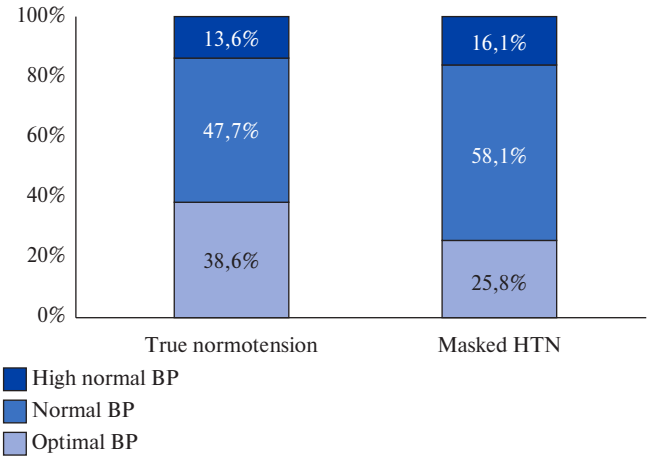

Figure 2. Characteristics of clinic BP phenotypes in patients with true normotension and masked HTN (n=75).
Note: p>0,05 using Pearson's chi-squared test for all phenotypes.
Abbreviations: HTN — hypertension, BP — blood pressure.

Regardless of the thresholds and phenotype of HTN, the most common profiles of nocturnal BP decrease were non-dipper (63,9%) and night-picker (16,6%) (Table 6). This, along with the high frequency of masked nocturnal HTN indicates a potentially higher risk of cardiovascular complications in this category of patients [20].

Assessment of 10-year CVR [19] revealed that 87,7% of patients were in the high and very high-risk categories (Figure 3). Significant differences in clinical, demographic and laboratory data, the level of peripheral and central BP, parameters of ABPM, arterial stiffness between the moderate and high/very high-risk groups have not been established. In the subgroup of masked HTN, there were 85,3% and 4% of patients at high and very high risk, respectively, and in the subgroup with no nighttime decrease in SBP — 82% and 6%, respectively. The distribution of patients with different levels of risk by BP and SBP dipping phenotypes is presented in Figure 4 (A and B).

Discussion

Phenotyping by the levels of clinic and ambulatory BP allows to identify patients with a higher CVR and, accordingly, a less favorable prognosis. This approach is of particular importance for young patients with T1D who may have underestimated risk.

An important result of this study is the confirmation of high frequency of masked HTN in young

Table 4

Intergroup differences for different HTN phenotypes (2018 ESC/ESH diagnostic criteria)*

Parameter	True HTN (n=5)	Masked HTN (n=31)	Normotension (n=44)	P
Age, years	28,0 (26;38)	31,5 (21;38)	27 (23;28)	H3
Male sex, n (%)	4 (80)	15 (50)	29 (63)	H3
Clinic SBP, mm Hg	160 (150;160)	120 (110;120)	120 (110;120)	0,01
Clinic DBP, mm Hg	95 (90;100)	76,5 (70;80)	79 (70;80)	0,01
Nighttime heart rate night, bpm	69 (62;75)	82 (75;88)	78 (71;82)	0,01
Daytime mean SBP, mm Hg	128 (126;134)	124 (119;128)	114 (110;120)	0,0001
Daytime mean DBP, mm Hg	83 (83;84)	79,5 (77;86)	72,5 (67;79)	0,0001
Nighttime mean SBP, mm Hg	117 (115;128)	118 (113;121)	108 (100;113)	0,0001
Nighttime mean DBP, mm Hg	78 (76;78)	79 (74;83)	65,5 (62;69)	0,0001

Note: * — quantitative data are presented as median (interquartile range).
Abbreviations: HTN — hypertension, DBP — diastolic blood pressure, SBP — systolic blood pressure.

Table 5

Characteristics of T1D patients with normal clinic BP depending on the presence of masked HTN*

Parameter	True normotension (n=45)	Masked HTN (n=30)	p
Age, years	26,4±5,5	31±8,6	0,02
Duration of diabetes, years	4 (0,65;8)	6 (3;12,9)	0,009
Urine ACR, mg/g	8 (3;17)	18,5 (11;29)	<0,001
Clinic SBP, mm Hg	120 (108;120)	120 (110;120)	0,78
Clinic DBP, mm Hg	77 (69;80)	78 (70;80)	0,96
Daytime mean SBP, mm Hg	114 (110;121)	124 (118;128)	<0,001
Daytime mean DBP, mm Hg	72 (67;79)	79 (76;86)	<0,001
Nighttime mean SBP, mm Hg	108 (100;114)	118 (110;121)	<0,001
Nighttime mean DBP, mm Hg	64 (62;69)	79 (74;83)	<0,001
Daytime SBP variability, mm Hg	19 (13;22)	14 (10;18)	0,03
Nighttime SBP variability, mm Hg	13 (9;19,5)	20 (11;28)	0,02
24-hour cfPWV, m/s	6,3 (5,8;6,8)	7,2 (6,2;8,2)	0,002

Note: * — quantitative data are presented as median (interquartile range).
Abbreviations: ACR — albumin/creatinine ratio, DBP — diastolic blood pressure, SBP — systolic blood pressure, cfPWV — carotid-femoral pulse wave velocity.

patients with T1D. It is important that 93,6% of patients had nocturnal HTN (74,2% — isolated nocturnal HTN). Thus, the diagnosis of masked HTN in most cases was based on the nocturnal BP, which emphasizes the importance of 24-hour ABPM in this population. To date, a relatively small number of studies on the BP phenotypes in patients with T1D have been published [10-12]. In the study by Rodrigues TC et al. (188 patients with T1D), masked HTN was detected in 7,4% (13,6% in the group with normal clinic BP), and isolated nocturnal HTN — in 23,3% [10]. In another study, among 85 T1D patients, the prevalence of masked HTN was 24% [11]. It should be noted that in both studies, the clinic BP threshold was 130/80 mm Hg, and the daytime BP threshold was 135/85 and 130/80 mm Hg, respectively. Therefore, these results cannot be compared with the data obtained by us. The closest to current work is the study by Lithovius R et al., which included 140 T1D patients, some of whom had a history of HTN and use of AHT. The prevalence of masked hypertension was 23%, true HTN — 33%, true normotension — 38% and white-coat HTN — 6% [12]. In our work, the prevalence of masked HTN according to European criteria was 38,3%, true HTN — 6,2%. Such a pronounced dif-

ference can probably be explained by lower mean age of the participants in our study (27 vs 47,3 years). In addition, we included patients without a history of HTN and AHT.

According to 2017 ACC/AHA guidelines [15], the clinic and ambulatory BP thresholds for HTN are different from those accepted in Russia. When analyzing BP phenotypes using ACC/AHA criteria, there is an increase in the HTN prevalence to 88,9%, mainly due to true hypertension (44,4%). It is interesting that the frequency of masked HTN using the American and European criteria was practically the same (35,8% vs 38,3%, p=0,7), although only 15 patients showed a concordance for this phenotype. It should be noted that when using the threshold proposed in the 2018 ESC/ESH guidelines, compared with 2017 ACC/AHA, there was a greater specificity with respect to HTN diagnosis due to a significant loss of sensitivity (sensitivity — 13,9% and 55,4; specificity — 97,8% and 50%, respectively). The accuracy of the criteria was comparable (60,5% and 54,3%, respectively).

Characteristics of arterial stiffness and pulse wave in T1D patients have been studied in a number of works: in some, higher augmentation index values among T1D patients were recorded [21, 22], in others conflicting data were obtained [23]. In the present study, a deviation from the reference values for PWV was observed in 3,7% of cases, which indicates the need to evaluate cfPWV according to individual standards depending on sex and age [24]. It was shown that, despite the normal mean level of cfPWV, patients with masked HTN

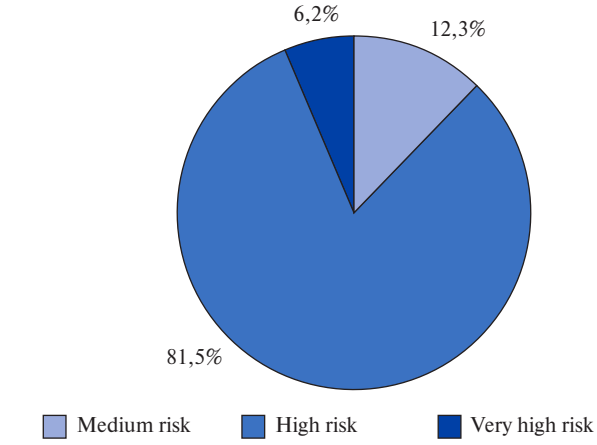

Figure 3. The distribution of T1D patients depending on 10-year CVR.

Table 6

Dipping classes in patients with various BP phenotypes (2018 ESC/ESH criteria)*

BP phenotype	Night-picker	Non-dipper	Dipper	Over-dipper
True HTN	0 (0)	4 (80)	1 (20)	0 (0)
WC-HTN	0 (0)	1 (100)	0 (0)	0 (0)
Masked HTN	6 (19,4)	19 (61,3)	2 (6,5)	4 (12,9)
True normotension	8 (18,2)	28 (63,6)	6 (13,6)	2 (4,5)
All phenotypes	6 (16,6)	23 (63,9)	3 (8,3)	4 (11,1)

Note: * — data are presented as n (%).
Abbreviations: HTN — hypertension, BP — blood pressure, WC-HTN — white coat hypertension.

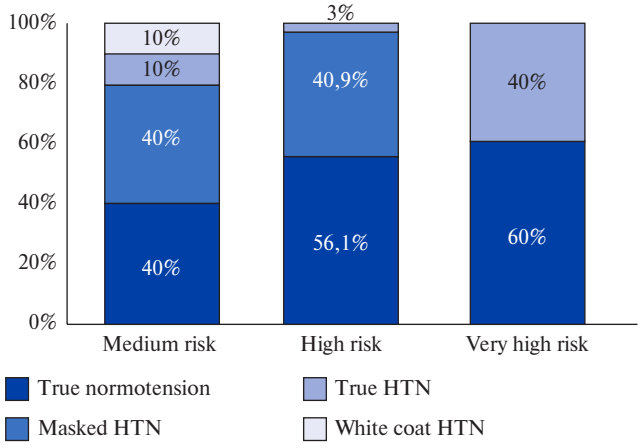

Figure 4 (A). The distribution of T1D patients by BP phenotypes depending on the risk category.

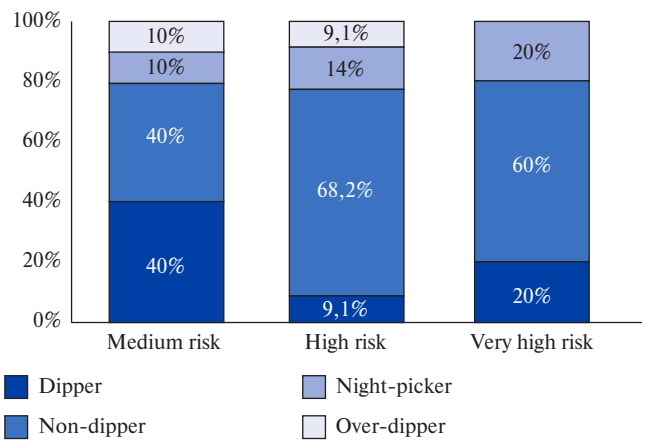

Figure 4 (B). The distribution of T1D patients by dipping classes depending on the risk category.

had its significant increase compared to true normotension. In the study by Lithovius R et al., a similar data was obtained [12]. The tendency to arterial stiffness increase in patients with masked HTN may reflect early arterial changes and, probably, contributes to an increase in CVR.

It is known that circadian BP disorders are associated with an increased risk of cardiovascular events [25]. Diabetes is associated with an increase in the frequency of non-dipping. In this study, the frequency of overall non-dipping BP was 74,5%, indicating a potentially higher risk of unfavorable cardiovascular outcomes.

Estimation of CVR level when choosing the optimal management strategy is a key recommendation of most world cardiology societies [13-15]. Correct assessment of CVR is especially important in young patients without a history of significant CVD, since in this group complex approach to risk evaluation [26] can significantly change the treatment strategy and contribute to earlier drug therapy. Obviously, patients with diabetes cannot be considered a low-risk group, but risk of some T1D patients, due to young age and absence of comorbidities, may be significantly underestimated. In our study, it was shown that almost 90% of patients belonged to high and very high-risk groups, even without HTN history, established cardiovascular and renal diseases. This is due to both the long duration of diabetes (>10 years in 36% of patients) and the high prevalence of dyslipidemia and other risk factors. All patients did not received lipid-lowering therapy or AHT.

Thus, young T1D patients without a history of CVD and AHT often have masked (including isolated nocturnal) HTN and high CVR, which requires a review of treatment and diagnostic strategies and, possibly, use of therapy even with high normal BP. Further studies are required for assessing the impact of such an approach on CVR and outcomes.

Conclusion

Young T1D patients without a history of chronic diseases had HTN (true and masked) in 44,5% of cases. A high frequency of potentially unfavorable BP phenotypes was established — masked HTN, isolated nocturnal HTN, and non-dipping. Masked hypertension is associated with a higher cfPWV compared with the true normotension group. Most patients with T1D have a high and very high 10-year CVR, which requires a revision of diagnostic and treatment strategies.

Relationships and Activities: not.

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