

Markers of vascular damage depending on the blood pressure level: data of the population study ESSE-RF

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Aim. To evaluate the relationship of prehypertension (preHTN) with vascular wall damage and decreased renal function depending on cardiovascular risk in a representative sample of Russian population.

Material and methods. As a part the ESSE-RF study in 4 regions (St. Petersburg, Tomsk, Tyumen, the Republic of North Ossetia), 7042 participants aged 25-64 were additionally examined for state of vessels. All participants signed informed consent and completed the approved questionnaires. Anthropometry, fasting glucose and blood pressure (BP) levels were assessed. BP was measured by the OMRON monitor (Japan) twice on the right hand in a sitting position; average BP was calculated. The optimal BP was considered 120/80 mm Hg, preHTN — 120-139/80-89 mm Hg, HTN — \geq 140/90 mm Hg or antihypertensive therapy. The 10-year risk of fatal cardiovascular diseases was determined according to the SCORE charts. Glomerular filtration rate (GFR) was calculated using the CKD-EPI equation. Investigation of vessels was performed using a vascular screening system VaSera, Fukuda Denshi. Cardio-ankle vascular index (CAVI) and ankle-brachial index (ABI) was determined. Statistical analysis was performed using SPSS Statistics 20.

Results. The analysis included data of 6906 participants, among which women predominated ($n=4531$; 65,6%). An increase in the prevalence of subclinical vascular lesion according to CAVI was detected with a BP increase from optimal to preHTN and HTN (0,06, 0,19 and 0,75, respectively). According to ABI, this pattern was not observed (0,24, 0,22 and 0,54, respectively). The prevalence of ABI $<0,9$ was greatest in the HTN group and did not significantly differ between patients with preHTN and optimal BP. After the exclusion of 1610 patients belonging to the groups of high and very high cardiovascular risk, the prevalence of subclinical vascular lesion was reevaluated. With a BP increase from optimal to preHTN and HTN in the low-risk groups of cardiovascular events, an increase in the prevalence of subclinical vascular lesions was also observed only according to CAVI (0,11, 0,28 and 0,62, respectively). Due to the low prevalence of chronic kidney disease (CKD) in the general population ($n=7$), the analysis of CKD prevalence in groups by BP

level was not carried out. According to linear regression analysis (adjusted for sex, age, body mass index, total cholesterol level), significant associations of systolic BP with GFR, CAVI, and ABI were not detected in the groups of optimal BP, preHTN, and HTN.

Conclusion. Regardless of cardiovascular risk grade, an increase in the prevalence of subclinical vascular lesions was detected with an increase in BP from optimal to preHTN and HTN only according to CAVI. The prevalence of decreased ABI did not significantly differ between patients with preHTN and optimal BP. No association of GFR reduction with preHTN has been identified. No association of GFR reduction with preHTN has been identified.

Key words: prehypertension, vascular lesion, cardio-ankle vascular index, vascular index.

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In 2003, the Joint National Committee for Prevention, Detection, Evaluation and Treatment of High Blood Pressure (BP) (JNC 7) introduced the concept of “prehypertension” (preHTN). PreHTN includes a range of systolic BP (SBP) of 120-139 mm Hg, diastolic BP (DBP) of 80-89 mm Hg and is considered a risk factor for hypertension (HTN) [1]. It is known that the association of BP and cardiovascular mortality is significant with blood pressure of 115/75 mm Hg and more. With an increase in BP for every 20/10 mm Hg the risk of cardiovascular death doubles [2].

Over the past 15 years, with the results of new studies, the standing of preHTN has been reinforced as a condition associated with target organ damage (TOD), cardiovascular morbidity and mortality. In the National Health and Nutrition Examination Survey, preHTN is defined as a risk factor for cardiovas-

cular disease and stroke, especially in case of one or more other risk factors (hypercholesterolemia, obesity, diabetes and/or smoking) [3]. Qureshi AI, et al. analyzed the data of the Framingham Heart Study and determined the relationship of preHTN with the risk of myocardial infarction (MI) and coronary artery disease (CAD), and did not revealed associations between preHTN and stroke [4]. However, the Women’s Health Initiative study demonstrated the association of preHTN with fatal cardiovascular events and strokes in postmenopausal women [5].

Unlike optimal BP, preHTN increases the risk of both chronic kidney disease (CKD) [6] and end-stage kidney disease [7]. Literature data on the vascular wall characteristics in patients with preHTN are contradictory. An analysis of the Framingham Heart Study did not reveal an association of a decrease in the ankle-brachial index (ABI) with the preHTN risk [4]. In later

Table 1

Sex-specific characteristics of the subjects

Parameter	Total (n=6906)	Men (n=2375)	Women (n=4531)	p (men vs women)
Age, years	50,0 [38,0;57,0]	54,0 [42,0;57,0]	48,0 [36,0;58,0]	<0,0001
Smoking, n (%)	2526 (36,7%)	1607 (67,7%)	919 (20,3%)	<0,0001
BMI, kg/m ²	28,3±5,8	27,6±4,7	28,6±6,3	<0,0001
BMI, kg/m ²	27,1 [24,4;33,7]	27,0 [23,4;36,7]	27,3 [24,5;34,0]	
BMI ≥30 kg/m ² , n (%)	2360 (34,3%)	660 (28,0%)	1700 (37,7%)	<0,0001
WC ≥102 cm for men and ≥88 cm for women, n (%)	2638 (38,3%)	660 (27,9%)	1978 (43,8%)	<0,0001
SBP, mm Hg	132,5±19,6	135,6±18,3	130,8±20,0	<0,0001
DBP, mm Hg	81,8±11,2	83,8±11,7	80,8±10,8	<0,0001
Antihypertensive therapy, n (%)	2183 (31,6%)	575 (24,2%)	1608 (35,5%)	<0,0001
Total cholesterol, mmol/l	5,5±1,2	5,4±1,2	5,6±1,2	<0,0001
Total cholesterol >4,9 mmol/L*, n (%)	4327 (69,4%)	1286 (65,1%)	3041 (71,4%)	<0,0001
Reception of statins, n (%)	208 (3,1%)	62 (2,7%)	146 (3,3%)	0,08
Diabetes, n (%)**	470 (7,5%)	149 (7,5%)	321 (7,5%)	0,51
Creatinine, mmol/l	66,5 [60,4;73,3]	72,6 [65,9;81,0]	63,4 [58,8;71,0]	
GFR, ml/min/1,73 m ²	104,1 [91,7;115,3]	91,0 [81,5;101,2]	110,0 [97,4;117,9]	
GFR ≤60 ml/min/1,73 m ² , n (%)	7 (0,1%)	5 (0,3%)	2 (0,04%)	<0,0001

Note: * — lipid-lowering therapy, ** — blood glucose ≥7,1 mmol/l and/or glucose-lowering therapy.

Abbreviation: WC — waist circumference.

Table 2

Prevalence of patients with high and very high risk of CVE depending on BP levels

Parameter	Optimal BP (n=1380)	PreHTN (n=2098)	HTN (n=3428)	Total (n=6906)	P
Diabetes, n	20 (1,6%)	65 (3,6%)	385 (12,3%)	470 (7,5%)	<0,0001
History of stroke, n	9 (0,7%)	18 (0,9%)	91 (2,7%)	118 (1,7%)	<0,0001
History of MI, n	6 (0,4%)	17 (0,8%)	90 (2,6%)	113 (1,6%)	<0,0001
SCORE ≥5%, n	28 (2,2%)	168 (9,1%)	987 (31,5)	1183 (18,9%)	<0,0001
Total of patients with high and very high risk, n	62 (4,8%)	243 (13,2%)	1305 (41,3%)	1610 (25,7%)	<0,0001

publications by Indian and Scandinavian authors, the relationship between preHTN both with a decrease in ABI [8] and an increase in the cardio-ankle vascular index (CAVI) was determined [9]. In the Russian population, the association of preHTN with renal dysfunction and vascular wall damage has not been previously analyzed.

The aim of this study was to assess the association of preHTN with vessel wall lesions and decreased renal function depending on cardiovascular risk (CVR) in a representative sample of the Russian population.

Material and methods

As a part of the multicenter observational study ESSE-RF, in 2012-2013 a sex- and age-stratified,

random sample of people 25-64 years old was formed. In 4 regions, 7042 participants underwent an additional examination of blood vessels. Data of 6906 participants were suitable for analysis (St. Petersburg — 1596 people, Tomsk — 1560, Tyumen — 1631, Republic of North Ossetia — 2119). All participants signed informed consent. Respondents were interviewed using a standard questionnaire consisting of 12 modules containing information on lifestyle, comorbidity and therapy.

BP was measured with an Omron automatic monitor (Japan) on the right hand in a sitting position, after a 5-minute rest. BP was measured twice with an interval of 2-3 minutes; the analysis includes the average of two measurements.

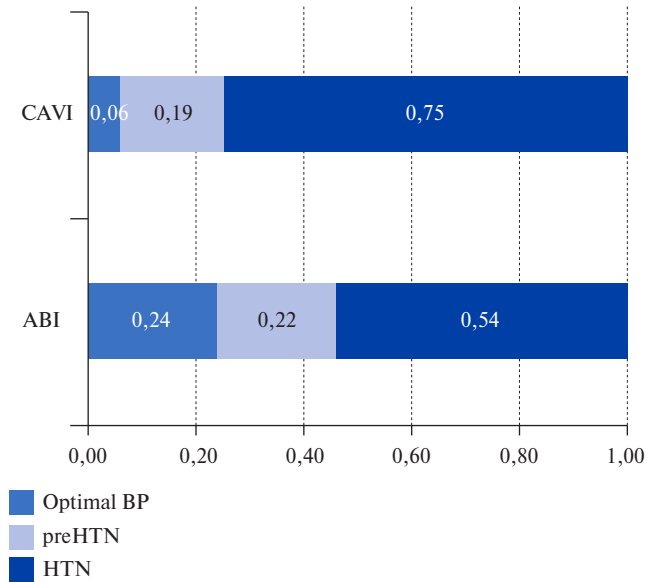


Figure 1. Prevalence of subclinical vascular injury (CAVI ≥ 9 and ABI $< 0,9$) in the general population depending on BP levels.

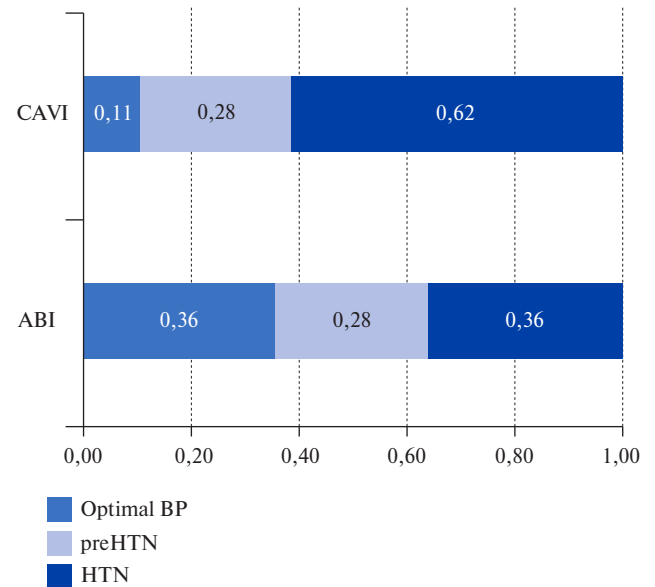


Figure 2. Prevalence of subclinical vascular injury (CAVI ≥ 9 and ABI $< 0,9$) in patients with low and moderate risk of CVE depending on BP levels.

Depending on the BP level and use of antihypertensive therapy, the following groups were identified according to the 2013 ESH/ESC guidelines for the management of arterial hypertension: optimal BP (BP $< 120/80$ mm Hg), preHTN ($120/80 \leq$ BP $< 140/90$ mm Hg) and HTN (BP $\geq 140/90$ mm Hg and/or antihypertensive therapy) [10]. This classification of BP levels was used to increase the statistical significance of the calculations. PreHTN included groups of normal and high-normal BP.

All participants underwent anthropometry. Fasting blood tests of the lipid profile, glucose, and creatinine (Abbott Architect 8000 analyzer (USA), reagents manufactured by Roche-diagnostics) was carried out. Body mass index (BMI) was calculated using the Quetelet's equation; glomerular filtration rate (GFR) was estimated using the CKD EPI equation.

Based on age, sex, levels of SBP, total cholesterol, and smoking status, a 10-year risk of fatal cardiovascular diseases was determined according to the SCORE risk charts.

Vascular examination was performed using a VaSera screening system (Fukuda Denshi); CAVI and ABI was estimated. The vascular examination technique was described in detail in a previous publication [11].

For data processing, standard descriptive statistics were used (mean, standard error of the mean in case of normal distribution and median, 25 and 75 percentiles in case of nonnormal distribution). To assess associations, multivariate models of binary logistic

regression and multiple linear regression were used. Mathematical and statistical data analysis was performed using the software package SPSS 20.0 (SPSS Inc., USA).

The study was supported by the Grant of President of Russian Federation on state support of leading scientific schools of the Russian Federation NS-5508.2018.7 (agreement № 075-15-2019-161 dated 23.05.2019).

Results

The analysis included data of 6906 participants (women — 4531; 65,6%). The characteristics of participants with an assessment of sex differences are presented in Table 1.

The men smoked more often, took antihypertensives less often, and had significantly lower values of GFR. Among women, obesity and hyperlipidemia were significantly more often diagnosed.

The prevalence of patients with a high and very high risk of cardiovascular events (CVE) (diabetes, stroke, history of MI or SCORE $\geq 5\%$) depending on BP levels is presented in Table 2. Due to the low prevalence of CKD in the general population ($n=7$), analysis of CKD prevalence depending on BP levels was not performed.

With an increase in BP from optimal to preHTN and HTN, the prevalence of diabetes, stroke, MI, and the number of patients with high risk of CVE increases. In patients with preHTN, a high risk is approximately 3 times more likely than in participants with optimal BP.

Table 3

**Association of HTN with a high risk of cardiovascular diseases and TOD
(binary logistic regression; results are presented as odds ratio [95% confidence interval])**

Parameter	HTN
SCORE \geq 5%	3,34 [2,72;4,10], p=0,0001
Diabetes	2,30 [1,76;3,01], p=0,0001
History of stroke	1,97 [1,19;3,26], p=0,009
History of MI	1,95 [1,11;3,40], p=0,02
CAVI \geq 9	1,84 [1,51;2,25], p=0,0001
ABI <0,9	1,40 [0,98;2,01], p=0,07

The prevalence of subclinical vascular injury in the general population depending on the BP levels is shown in Figure 1.

An increase in the prevalence of subclinical vascular lesion according to the CAVI was detected with BP increase from optimal to preHTN and HTN; according to the ABI, this pattern was not observed. The prevalence of ABI <0,9 was highest in the HTN group and does not significantly differ between patients with preHTN and optimal BP.

After the exclusion of 1610 subjects, belonging to high and very high-risk groups of CVE, the prevalence of subclinical vascular injury was reevaluated. The results are presented in Figure 2.

With an increase in BP from optimal to preHTN and HTN in the low-risk groups of CVE, there is an increase in the prevalence of subclinical vascular damage only according to CAVI.

According to linear regression adjusted for sex, age, BMI, and total cholesterol, SBP in the preHTN and HTN groups was associated with SCORE risk ($\beta=0,03$ [0,02; 0,04] and 0,08 [0,07; 0,08], respectively). No significant associations of SBP with GFR, CAVI, and ABI were found in the groups of optimal BP, preHTN, and HTN.

Table 3 presents the results of a binary logistic regression adjusted for sex, age, smoking, obesity (BMI \geq 30 kg/m²) and hypercholesterolemia (total cholesterol \geq 4,9 mmol/l).

In binary logistic regression, the association of optimal BP and preHTN with TOD was not detected. HTN is significantly associated with a high SCORE risk, diabetes, a history of stroke and/or MI, and subclinical vascular injury according to the CAVI.

Discussion

According to the ESSE-RF study (Russian population), with an increase in BP from optimal to preHTN and HTN, the prevalence of patients with high and very high CVR and subclinical vascular lesions increases.

The definition and concept of preHTN was developed after extended discussion and debates of JNC 7 participants. The idea was to consider preHTN as a risk factor for HTN development and recommend not to initiate drug therapy, but emphasize the need for lifestyle modification [1].

Increased BP is often accompanied by impaired carbohydrate metabolism: permeability of the endothelial barrier and oxidative stress contribute to pancreatic β -cell dysfunction and insulin resistance [12]. In Iran from 2009 to 2014, Khosravani A, et al. observed 2941 participants without HTN and diabetes. The five-year incidence rate of diabetes among individuals with preHTN was 12,7%, while the logistic regression results were not significant [13].

Our study revealed an increase in diabetes prevalence with BP increase from optimal to preHTN and HTN. Logistic regression did not reveal a significant relationship between preHTN and diabetes, while the presence of HTN increased the diabetes risk in the Russian population.

The high prevalence of CKD is now recognized as an urgent public health problem worldwide. HTN is one of the main reasons of CKD. A meta-analysis by Garafallo C, et al. revealed a relationship of preHTN and HTN with CKD. At the same time, an increase in SBP and DBP for every 10 mm Hg increases the risk of reducing GFR [6]. According to a meta-analysis of 6 studies with 1003793 participants by Huang Y, et al., preHTN compared with optimal BP significantly increases the likelihood of end-stage kidney disease [7]. According to our data, assessment of CKD prevalence depending on the BP levels and logistic regression analysis did not reveal significant relationships. Perhaps this is due to the low prevalence of CKD (0,1% in the studied Russian population).

In the structure of cardiovascular mortality, stroke and MI take a leading position. Meta-analysis of 17 studies with 591664 subjects by Huang Y, et al. revealed that preHTN increased the risk of CAD [14].

Results were more significant in studies with follow-up >10 years. It is important that the preHTN-associated risk of CAD was higher in Western than in Asian participants. Authors also revealed that 8,4% of CAD cases could be prevented if the predisposition to HTN was removed in Asian patients, and this proportion increases to 24,1% in Western subjects. Huang Y, et al. performed a meta-analysis of 19 studies with 762393 participants, which confirmed an increased risk of stroke in patients with preHTN compared with optimal BP [15]. Significant differences between groups by sex and ethnicity were not identified. In our study, there was an increase in the history of stroke and MI with BP increase from optimal to preHTN and HTN. Association with history of strokes and MI was found only for participants with HTN.

In patients with preHTN, endothelial dysfunction is recorded. According to small study with 53 respondents with optimal BP and 65 with preHTN by Thitiwuthikiat P, et al., association of a combination of hyperuricemia and preHTN with subclinical vascular injury according to CAVI test (≥ 9) was revealed [9]. The prospects of diagnosing subclinical vascular lesions according to ABI test ($< 0,9$) is controversial. In 2005, Qureshi AI, et al. analyzed data of the Framingham Heart Study, according to which a significant relationship between preHTN and ABI $< 0,9$

was not identified [4]. According to a later study with 70 participants by Rubio-Guerra AF, et al. (2017), a relationship was found between preHTN and ABI $< 0,9$ [8].

Conclusion

1. In the Russian population, with an increase in BP from optimal to preHTN and HTN, there is an increase in the number of patients with high and very high risk. In patients with preHTN, markers of high CVR are found about 3 times more often than in subjects with optimal BP.

2. Regardless of CVR grade, an increase in the prevalence of subclinical vascular lesions was detected with an increase in BP from optimal to preHTN and HTN only according to CAVI. The prevalence of decreased ABI did not significantly differ between patients with preHTN and optimal BP.

3. The prevalence of impaired renal function in the Russian population is low. No association of GFR reduction with preHTN has been identified.

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