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Large artery stiffness according to different assessment methods in adult population of St.Petersburg☆

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ABSTRACT

Objective: The aim of the present study was to assess the prevalence of increased arterial stiffness by different diagnostic methods and its association with cardiovascular risk in Russian population-based cohort.
Design and methods: In terms of Russian epidemiological study ESSE-RF a random selection of 452 apparently healthy Saint-Petersburg inhabitants aged 25–65 years was performed. Fasting lipids, glucose and blood pressure measurements were performed. We used 3 diagnostic methods of arterial stiffness assessment: pulse wave velocity by applanation tonometry (SphygmoCor - PWV-S) and pulse wave velocity by volumetric sphygmography (VaSera - PWV-V), and cardio-ankle vascular index (CAVI) by VaSera.
Results: 341 (75,4%) had normal parameters of arterial stiffness assessed by all methods. Spearmen's coefficient of correlation and “kappa” coefficient for PWV-S and CAVI were 0,74 and 0,04, for PWV-S and PWV-V - 0,10 and 0,06, for CAVI and PWV-V - 0,28 and 0,03, respectively. There was a significant correlation between cardiovascular risk (defined by SCORE) and PWV-S ($r = 0,38$, $p < 0,001$) and a non-significant trend of increasing CAVI along with cardiovascular risk ($r = 0,35$, $p = 0,14$).
Conclusions: Different methods of arterial stiffness assessment showed a weak correlation with each other. Carotid-femoral pulse wave velocity detected by applanation tonometry is associated with high cardiovascular risk score and might be considered as better additional risk marker for cardiovascular risk stratification.

1. Introduction

Increased arterial stiffness is considered to be one of the possible early markers of arteriolosclerosis and is defined as a surrogate end point for cardiovascular disease. According to Expert consensus on the measurement of aortic stiffness in daily practice 2012 [1], the measurement of carotid-femoral pulse wave velocity (PWV) is recommended as a gold standard for assessing arterial stiffness. Data from Framingham prospective study showed, that increased carotid-femoral PWV was associated with 48% risk elevation of first cardiovascular event and improved by 0,7% the predictive value of traditional risk model in European population [2]. A lot of alternative methods for PWV measurement exist which include assessment of peripheral arteries function as well. The major disadvantage of all methods based on applanation tonometry is blood pressure dependency [3]. Another limitation for wide clinical implication is time-consuming and demand to be performed by trained personnel.

One of the new noninvasive methods is assessment of cardio-ankle vascular index (CAVI), which is positioned as a blood pressure independent marker and is measured by another technique based on volumetric sphygmography [4]. Large epidemiological Japan study revealed correlation between CAVI and traditional risk factors, such as hypercholesterinemia, left ventricular hypertrophy and diabetes mellitus [5]. During the last decade several data about prognostic value of CAVI were published [6], but large prospective

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studies which examine relation of CAVI to cardiovascular risk are still in progress. Previous attempts to compare the above mentioned methods were inconclusive because of small sample size, specific ethnic cohorts of patients or groups with the certain comorbidity [7–9]. The aim of our study was to assess the prevalence of increased arterial stiffness by different diagnostic methods and its association with general cardiovascular risk score in St. Petersburg population-based cohort.

2. Methods

2.1. Participants

This study was based on the data from ESSE-RF study, design described earlier in details [10]. In brief, ESSE-RF is a cross-sectional study in 13 Russian regions to investigate prevalence of risk factors and to evaluate contribution of traditional and new risk factors into morbidity and cardiovascular mortality in the population of Russian Federation. The study was conducted in compliance with current Good Clinical Practice standards and in accordance with the principles set forth under the Declaration of Helsinki (1989). Institutional review board approval of the study protocol was obtained before the initiation of study's participant enrollment. All participants entering the program agreed to and signed informed consent.

Among the participants of Saint-Petersburg population-based sample of ESSE-RF study (1600 Saint-Petersburg inhabitants aged 25–64 years old) 500 patients were selected as a random sample for arterial stiffness assessment.

2.2. Study design

All subjects were invited in the out-patient department of the Almazov Centre during morning hours (from 8 to 11 a.m.) after overnight fasting. Upon arrival, blood tests were performed and medical history was registered. All subjects were interviewed by standard questionnaire including information about social and demographic characteristics of participants, behavior customs (i.e. smoking status) and previous cardiovascular diseases, concomitant medication. Current smoking was defined as having smoked a cigarette in the last 30 days.

The body weight was obtained in light clothing and without shoes by medical scales VEM-150–“Massa-K” (Russia), height was measured by medical stadiometer (Russia). The body mass index (BMI) was calculated according to Quetelet formula. BMI$\geq$30 kg/m^2 was classified as obesity.

Peripheral brachial blood pressure was recorded on the right arm three times after 5 min rest by an automated sphygmomanometer (OMRON M3 Expert, Japan) with mean BP calculation. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of medication prescribed for hypertension. Electrocardiography was performed on device PADSY («Medset Medizintechnik GmbH», Germany). Patients with atrial fibrillation (permanent or paroxysmal) according to ECG signs didn't undergo arterial stiffness measurements and were excluded from data analysis (n = 7).

2.3. Blood tests

Biospecimen collection was performed by the qualified personnel using the standard venopunction technique. Fasting blood lipids (total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG)), serum creatinine and plasma glucose were detected by Abbot Architect c8000 (USA) with «Abbot Diagnostic» kits (USA). Glomerular filtration rate (GFR) calculation was performed by CKD-EPI formula [11]. Patients with GFR<60 ml/min/1,73 m^2 (n = 3) were excluded from data analysis. Patients with glucose level 5,6 - 6,9 mmol/l were referred to impaired fasting glycaemia group. Diabetes mellitus was defined as glucose level $\geq$7,0 mmol/l, or use of medication prescribed for diabetes. Groups of patients with high level of TG (>1,7 mmol/l), LDL (>3,0 mmol/l) and low level of HDL (<1,0 mmol/l in men and <1,2 mmol/l in women) were formed according to use of lipid-lowering therapy.

2.4. Instrumental investigation

After acclimatization in supine position (standardized conditions, quiet atmosphere, temperature maintained at 24 °C) arterial stiffness measurement was performed, comprising determination of PWV by SphygmoCor (Atcor, Australia - PWV-S) and then CAVI, PWV by VaSera (Fukuda, Japan – PWV-V) within 10 min of each other on the same bed without changing supine position. Caffeine and smoking were not allowed within 3 h before measurements.

2.5. Arterial stiffness measurement by SphygmoCor

The carotid-femoral distance was measured according to a formula, recommended by Expert Consensus (2012): (common carotid artery – common femoral artery) × 0,8 [1]. A special pencil sized tonometer was placed on the carotid artery to capture steady pulse waveforms for at least 10 s. Then the tonometer was placed on the femoral artery and pulse waveforms were captured for at least 10 s. Then, according to patient data, such as height, weight, brachial blood pressure before the procedure, the software automatically calculated the PWV-S, using the mean time difference (⌂T) among the R-wave and the pressure wave and the arterial path length between the two recording sites: [PWV-S = distance (meters)/time (seconds)]. The current cut-off value for PWV-S, proposed in 2012, was 10 m/s [1].

2.6. Arterial stiffness measurement by VaSera

ECG electrodes placed on both wrists and a phonocardiogram electrode placed at the right sternal border in the 2nd intercostal space. 4 cuffs with sensors at all four limbs to generate plethysmograms were applied to both upper arms and ankles. The two amorphous probes were placed at projection of common carotid and femoral artery pulsation. PWV was obtained by dividing the vascular length by the time taken for the pulse wave to propagate from the aortic valve to the ankle. These measurements and calculation system were automatically done using the VaSera VS-1000. The cut-off value for PWV-V was also adopted as 10 m/s.

To be compatible with the aortic PWV method established by Hasegawa et al. scale conversion constants were determined to match CAVI with the aortic PWV method. The mean value of CAVI was calculated as arithmetic mean of right CAVI and left CAVI. The reference value of CAVI was <9,0 [12].

2.7. Cardiovascular risk assessment

10-year risk of fatal and non-fatal cardiovascular events was calculated by the SCORE algorithm [13]. According to the results all patients were divided into low ($\leq$1%), intermediate (1–5%), high (5–10%) and very high (>10%) risk groups. 38 patients from 500 participants had previous cardiovascular events (ischemic heart disease – 27, myocardial infarction – 17, stroke – 25 patients) were excluded from the data analysis.

2.8. Data analysis

Statistical analysis was performed by SPSS Statistics 17.0 (USA). The sex-specific characteristics of the sample were obtained by simple tabulations and descriptive statistics. Biomedical parameters were calculated from the weighted data, using post-stratification weights adjusted for European standard. Correlations were reported as Spearmen's coefficients of correlation and agreement coefficient “kappa”.

3. Results

3.1. Subject characteristics

Table 1 summarizes the characteristics of the subjects recruited for the study. Prevalence of hypertension, hypertriglyceridemia, hyperglycemia and elevated LDL-C was significantly higher in men, while women had elevated total cholesterol more often.

3.2. Subclinical vascular damage prevalence

The mean values of PWV-S and PWV-V were significantly higher in males compared to females, while there was no gender difference in prevalence of increased arterial stiffness markers (Table 2).

Most of patients 341 (75,4%) did not have subclinical vascular damage by any of methods. The subclinical vascular damage detected by PWV-V assessment was not found out significantly more often 37 (8,2%)) in comparison with assessment by CAVI (33 (7,3%)) and PWV-S (21 (4,6%)). According to both PWV-S and PWV-V, the vascular damage was found out just in 6 (1,3%) patients, PWV-S and CAVI – in 3 (0,7%) patients.

3.3. Arterial stiffness assessment methods agreement

There was no significant correlation between different methods of arterial stiffness assessment. Spearmen's coefficient of correlation for PWV-S and CAVI was 0,07, coefficient of agreement “kappa” was 0,04. Spearmen's coefficient of correlation for PWV-S and PWV-V was 0,10, coefficient of agreement “kappa” was 0,06. Spearmen's coefficient of correlation for CAVI and PWV-V was 0,28, coefficient of agreement “kappa” was 0,03.

Table 2
Arterial stiffness parameters among men and women.

	Men (n = 199)	Women (n = 253)	p
CAVI	7,02 (6,35; 7,98)	7,23 (6,43; 8,13)	0,45
CAVI≥9, n (%)	18 (9,1%)	22 (8,7%)	0,51
PWV-S, m/s	7,6 (6,8; 8,7)	7,1 (6,4; 8,0)	0,001
PWV-S>10 m/s, n (%)	15 (7,5%)	16 (6,3%)	0,37
PWV-V, m/s	7,6 (6,6; 8,5)	7,3 (6,2; 8,3)	0,006
PWV-V>10 m/s, n (%)	11 (5,5%)	37 (14,6%)	0,84

n- number, CAVI - cardio-ankle vascular index, PWV-S - pulse wave velocity by SphygmoCor.
PWV-V - pulse wave velocity by VaSera.

3.4. Association of arterial stiffness with cardiovascular risk

The number of participants with subclinical vascular damage detected by PWV-S assessment increases in proportion to the growing level of cardiovascular risk according to SCORE. Significant correlations of the SCORE risk with PWV-S ($r = 0,38$, $p < 0,001$) was observed. PWV-V's was not associated with the level of cardiovascular risk (Fig. 1).

4. Discussion

The present study was primary aimed to assess the prevalence of increased arterial stiffness in Russian population. This is highly important as well as vascular damage is believed to be one of the explanations of high cardiovascular morbidity in Russia. The second issue was to find an optimal and reliable method of vascular stiffness assessment and check if new technique based on volumetric sphygmography can be equivalent to gold standard being less expensive and easily to perform.

Our study showed rather low prevalence of increased arterial stiffness in Russian population. Only few studies concerning vascular damage in Russian population have been previously published. The study by Rogoza A. and co-authors [14] demonstrated the prevalence of subclinical arterial damage in healthy sample of

Table 1
Characteristics of the sample depending on gender.

Characteristic	All (n = 452)	Men (n = 203)	Women (n = 249)	p (Men vs women)
Age, years	43,9 ± 10,3	43,1 ± 10,3	44,6 ± 10,1	0,11
Height, sm	–	178,5 ± 7,4	164,8 ± 6,3	NA
Weight, kg	–	88,7 ± 15,3	72,3 ± 16,4	NA
BMI, kg/m2	27,1 ± 5,2	27,8 ± 4,2	26,6 ± 5,8	0,01
BMI ≥30 kg/m^2, n (%)	115 (25,4%)	52 (26,1%)	63 (24,9%)	0,42
Current smokers	112 (24,8%)	72 (35,4%)	47 (18,9%)	<0,001
SBP, mmHg	128,5 ± 18,6	134,0 ± 16,0	124,0 ± 19,3	<0,0001
DBP, mmHg	78,8 ± 12,4	81,8 ± 11,9	76,3 ± 12,2	<0,0001
Hypertension, n (%)	162 (36,0%)	80 (40,3%)	80 (31,8%)	0,03
Total cholesterol, mmol/l	5,47 ± 1,12	5,43 ± 1,06	5,50 ± 1,18	0,03
Total cholesterol >4,9 mmol/l, n (%)	245 (54,4%)	115 (58,4%)	130 (51,4%)	0,08
Statins therapy, n (%)	7 (1,5%)	0	7 (2,8%)	0,02
LDL, mmol/l	3,58 ± 1,02	3,63 ± 0,94	3,53 ± 1,08	NA
LDL >3,0 mmol/l*, n (%)	319 (70,9%)	155 (78,7%)	164 (64,8%)	0,001
HDL, mmol/l	1,33 ± 0,32	1,19 ± 0,26	1,44 ± 0,32	NA
HDL <1,0 in men and <1,2 mmol/l in women*, n (%)	141 (31,2%)	53 (26,9%)	88 (34,8%)	0,04
TG, mmol/l	1,30 ± 0,86	1,47 ± 1,00	1,16 ± 0,70	<0,0001
TG >1,7 mmol/l*, n (%)	90 (19,9%)	59 (29,9%)	31 (12,3%)	<0,0001
Glucose, mmol/l	5,40 ± 1,04	5,62 ± 1,31	5,23 ± 0,72	<0,0001
Glucose 5,6-6,9 mmol/l, n (%)	101 (22,3%)	58 (29,3%)	43 (17,0%)	0,001
Diabetes mellitus, n (%)	23 (5,2%)	12 (6,6%)	10 (4,1%)	0,22

n-number, * - adjusted for statin therapy, NA – not applicable, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, LDL – low density lipoproteins, HDL – high density lipoproteins, TG – triglycerides.

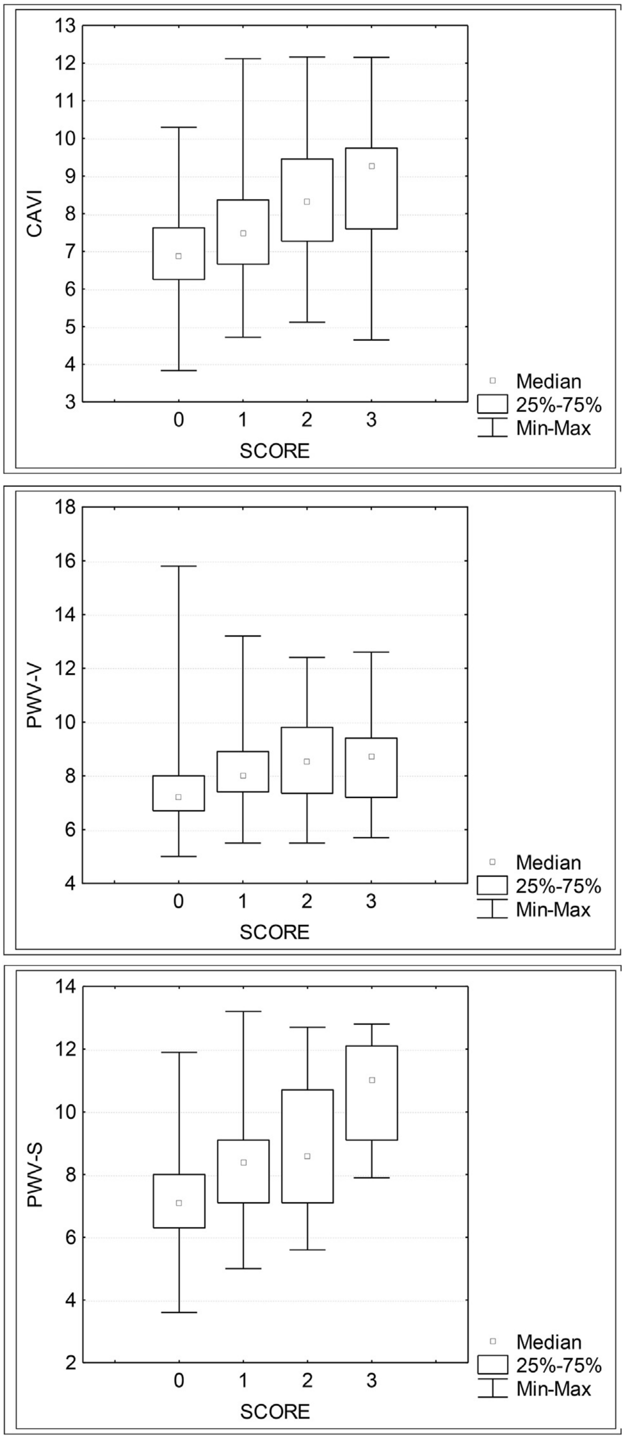

Fig. 1. Trends in prevalence of subclinical vascular damage patients according to SCORE risk groups.

Tomsk inhabitants (1348 subjects). Increased arterial stiffness was documented in 37,8% of participants according to PWV-V assessment, in 16,6% - according to CAVI measurement, these numbers being significantly higher than obtained in our investigation. At the same time, both methods detected increased arterial stiffness in 14,6% only [14]. These discrepancies can be partly explained by possible regional trends, indicating need for further investigations in different geographical parts of the Russian Federation. Direct comparison of the new technique with applanation tonometry was not performed in the above mentioned study. According to another cohort from Smolensk, the average values of CAVI were 7,8 ± 1,1 in the sample of healthy people (447 participants) in the age from 19 to 90 years [15]. In 2015 data from Russian sample of 114 young people (median age 21 years) was published – mean values of CAVI (5,87 ± 0,80) were significantly higher in comparison with the data in patients from Japan of the similar age and gender (5,36 ± 0,52); deviations from reference range wasn't determined [16]. All mentioned above Russian studies included subjects with different age and sex distribution, so the data cannot be compared directly. Other studies assessed arterial stiffness in patients with existing cardiovascular diseases and cannot be used as reference value.

The VaSera device was better tested in Japanese population where a study performed in 2011 was done in a sample of 5969 free of cardiovascular diseases subjects, threshold values of CAVI were calculated, taking into account age and gender differences [5], while the prevalence of increased arterial stiffness wasn't calculated. Later, in 2014 data appeared from small Korean population (110 subjects from 20 to 69 years) [17]. Significant association of PWV-V values with age was found, the average values of PWV were 9,34 ± 2,13 m/s in men and 8,15 ± 1,69 m/s in women, what is slightly higher than levels reported in our study.

The problem of comparison of arterial stiffness data obtained by different technologies and devices is still under investigation. One of the comparative studies of arterial stiffness measurement by SphygmoCor and VaSera was performed in a small sample of 20 healthy volunteers. Study showed moderate reproducibility of the results of these technologies, and significant correlation of technologies between each other [18]. In 2008 according to the data of A. Takaki and co-authors, a significant connection between CAVI and PWV-V values was also reported [19]. However, this study was performed in patients after coronary angiography due to chest the pain and does not reflect general population. In the present study low agreement of different diagnostic methods was shown in population-based sample. This can indicate that the substitution of techniques for screening PWV and risk calculation is not possible, and we need first to understand the place and diagnostic accuracy of new method in risk estimation.

Association of arterial stiffness and cardiovascular risk was previously estimated by classic methods of stiffness measurements. Thus, in 2010 Sehestedt et al. published results of large cohort study with a follow-up of 12,8 years in 1968 subjects without cardiovascular diseases. PWV-S was shown to have better prognostic value in patients with risk lower than 5% by SCORE in comparison with left ventricular hypertrophy, presence of atherosclerotic plaques and microalbuminuria. Besides, there was a significant correlation between PWV-S and SCORE ($p = 0{,}008$), indicating a stronger prognostic importance of PWV-S in subjects with SCORE<5% [20]. However, in 2017 Japanese researches published results of a big meta-analysis from the data in 14 673 Japanese participants without a history of cardiovascular disease: increased PWV-V was significantly associated with a higher risk of CVD, even after adjustment for conventional risk factors ($p < 0{,}001$) [21]. Few years earlier another big Asian study enrolled 1391 patients aged 31–88 years old, where adding CAVI into the cardiovascular risk score RAMA-EGAT improved the prediction of CAD incidence, increasing C-statistics from 0,72 to 0,85 and resulting in a net reclassification improvement of 27,7% ($p < 0{,}0001$) [22]. According to our cross-sectional data, in Russian population PWV-S positively correlated with cardiovascular risk level according to SCORE, while both CAVI and PWV-V did not demonstrate any association. As we didn't perform follow-up of this cohort yet, we cannot make a conclusion about prognostic value of all indexes, but is seems that PWV-S is better related to general risk in Russian population.

In conclusion, the present study show that arterial stiffness markers weakly correlate with each other and cannot be considered equal measures of cardiovascular risk. Besides, different indexes can measure different properties of arterial wall besides true large artery stiffness. Large prospective studies are required to make a final conclusion, which method can be helpful in reclassified the risk and be a reliable marker of target organ damage.

Conflicts of interest

None declared.

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References

[1] Van Bortel L, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012;30(3):445–8.
[2] Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham heart study. Circulation 2010;121(4):505–11.
[3] Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 2009;54(6):1328–36.
[4] Shirai K, Song M, Suzuki J, et al. Contradictory effects of β1- and α1- aderenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI) – CAVI independent of blood pressure. J Atherosclerosis Thromb 2011;18(1):49–55.
[5] Namekata T, Suzuki K, Ishizuka N, et al. Establishing baseline criteria of cardio-ankle vascular index as a new indicator of arteriosclerosis: a cross-sectional study. BMC Cardiovasc Disord 2011;11(51):1–10.
[6] Yoshiaki K, Daisuke M, Makoto T, et al. Cardio-Ankle Vascular Index is a predictor of cardiovascular events. Artery Res 2011;5:91–6.
[7] Takaki A, Ogawa H, Wakeyama T, et al. Cardio-Ankle Vascular Index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res 2008;31(7):1347–55.
[8] Huck CJ, Bronas UG, Williamson EB. Noninvasive measurements of arterial stiffness: repeatability and interrelationships with endothelial function and arterial morphology measures. Vasc Health Risk Manag 2007;3(3):343–9.
[9] Masayasu I, Shioji K, Kadota S, et al. Relationship of cardio-ankle vascular index (CAVI) to carotid and coronary arteriosclerosis. Circ J 2008;72(1):1762–7.
[10] The rationale for and design of the study Research Organizing Committee of the ESSE-RF project. Epidemiology of cardiovascular diseases in different regions of Russia (ESSE-RF). Prev Med 2013;6:25–34. Russian.
[11] Andrew SL, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12.
[12] Shoda T. Vascular pathology research with pulse wave examination CAVI-VaSera. ME Times; 2005. p. 7.
[13] Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24(11):987–1003.
[14] Rogoza AN, Kaveshnikov VS, Trubacheva IA, et al. Vascular wall in adult population of Tomsk in the framework of the project ESSE-RF. Syst Hypertens 2014;11(4):42–8. Russian.
[15] Miylagina IV, Miylagin VA, Pozdnyakov YuM, et al. Cardio-ankle vascular index — a new cardiovascular risk predictor. Cardiovasc Ther Prev 2008;(7):22–6. Russian.
[16] Sorokin A, Kotani K, Bushueva O, et al. The cardio-ankle vascular index and ankle-brachial index in young Russians. J Atherosclerosis Thromb 2015;22(2):211–8.
[17] Jang S, Ju E, Huh E, et al. Determinants of brachial-ankle pulse wave velocity and carotid-femoral pulse wave velocity in healthy Koreans. J Kor Med Sci 2014;29(6):798–804.
[18] Huck CJ, Bronas UG, Williamson EB, et al. Noninvasive measurements of arterial stiffness: repeatability and interrelationships with endothelial function and arterial morphology measures. Vasc Health Risk Manag 2007;3(3):343–9.
[19] Takaki A, Ogawa H, Wakeyama T, et al. Cardio-Ankle Vascular Index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res 2008;31(7):1347–55.
[20] Sehestedt T, Jeppesen J, Hansen TW, et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J 2010;31(7):883–91.
[21] Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. Hypertension 2017;69(6):1045–52.
[22] Yingchoncharoen T, Limpijankit T, Jongjirasiri S, et al. Arterial stiffness contributes to coronary artery disease risk prediction beyond the traditional risk score (RAMA-EGAT score). Heart Asia 2012;4(1):77–82.