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Prognostic Significance of Arterial Stiffness Parameters in the Identification of very High-Risk Patients

Aim	To study contribution of arterial wall stiffness indexes (cardo-ankle vascular index, CAVI; augmentation index, AI) to the predictive probability of identifying patients of very high risk groups (after myocardial infarction, MI)
Material and methods	The study included 288 men aged 40 to 60 years (mean age, 51.6±6.2 years). Among them, 133 patients belonged to the group of very high risk for cardiovascular complications (CVC) since they have had MI not earlier than five years before inclusion into this study, whereas 155 patients had no history of CVC. CAVI and AI were determined with a Fukuda denshi VS-1500 VaSera sphygmograph. A multifactorial logistic regression model was constructed, and a ROC analysis was performed for evaluating the probability of assigning a patient to the very high risk group.
Results	The study demonstrated a significant role of CAVI and AI in prediction of patient assignment to the group of very high risk for CVC development (after MI). According to results of the ROC analysis the predictive role of CAVI (area under the curve, AUC=0.70) was somewhat inferior to the predictive role of the age (AUC=0.75) but was superior to that of AI (AUC=0.641). The proportion of variance in the probability of assigning patients to the very high risk group due to the effects of studied factors was 31%. Total quality of the predictive model can be rated as good (AUC=0.77). Recommended cut-off points in assigning patients to the group of very high risk for CVC were 8.0 for CAVI and 0.99 for AI.
Conclusion	Indexes of arterial wall stiffness, such as CAVI and AI, determine the patient assignment to groups of very high risk for development of CVC (after MI) with a good quality of the predictive model.

Keywords	Arterial wall stiffness; risk of cardiovascular complications; cardio-ankle index; augmentation index
For citation	Nosov A. E., Gorbushina O. Yu., Vlasova E. M., Alekseev V. B. Prognostic Significance of Arterial Stiffness Parameters in the Identification of very High-Risk Patients. Kardiologiia. 2020;60(10):27–32. [Russian: Носов А. Е., Горбушина О. Ю., Власова Е. М., Алексеев В. Б. Прогностическая значимость параметров жесткости артериальной стенки в выявлении пациентов из группы очень высокого риска. Кардиология. 2020;60(10):27–32]
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Cardiovascular complications (CVCs) play a key role in modern medical science. The continuous improvement of prognostic scores, including social and lifestyle factors, biochemical and clinical indicators, enables increasingly accurate predictions of adverse outcomes in patients. In the past few decades, much attention has been paid to studies of the properties of the vascular wall and its role in the prognosis of CVCs [1]. To date, of the numerous parameters that characterize arterial stiffness, carotid-femoral pulse wave velocity (PWV) more than 10 m/s and ankle-brachial index (ABI) less than 0.9, have been included in the risk stratification guidelines [2, 3]. Other indicators of arterial stiffness are subjected to intense clinical testing to assess their prognostic value. In 2006, Japanese researchers proposed a new arterial stiffness index, the cardio-ankle vascular index (CAVI), which is based on the β-stiffness index independent of blood pressure (BP) at the time of measurement. The formula also includes cardio-femoral PWV [4, 5]. The study of this index made it possible to establish a statistically significant association between the effects of several risk factors (RFs) of developing CVCs (age, arterial hypertension (AH), diabetes mellitus, dyslipidemia, obesity, chronic kidney disease) and the development of CVCs, such as myocardial infarction (MI) and stroke [6]. The augmentation index (AI), based on contour analysis of the sphygmogram, is also actively studied as a prognostic indicator. Despite numerous studies on the prognostic role of these indicators, they have not yet been included in validated risk stratification systems. This makes it relevant to continue to investigate their association with the risk of developing CVCs.

Objective

The objective was to study the contributions of the arterial stiffness indicators, CAVI and AI, to the prognostic probability of identifying patients at very high risk due to having a history of MI.

Material and methods

This cross-sectional study was carried out in the Professional Pathology Department, Federal Scientific Center of Medical Preventive Technologies for Public Health Risk Management. The study included 288 subjects. Inclusion criteria: male sex, age from 40 to 60 yrs (mean age 51.6±6.2 yrs) with or without a history of MI. Exclusion criteria: ABI<0.9, since hemodynamic stenosis of the lower extremity arteries makes it impossible to interpret CAVI correctly; glomerular filtration rate<60 ml/min/1.73 m^2.

Among the subjects included in the study, 133 were at very high risk of developing CVCs since they had had MI within the previous 5 yrs. 155 subjects had no history of MI, and thus, they were not in the group with a very high risk of developing CVCs. The mean age of subjects with a history of MI was 54.5±5.0 yrs, and that of subjects without a history of MI was 49.1±6.1 yrs (p<0.001). Of the subjects with a history of MI, 89.5% had AH, 6.8% had type 2 diabetes mellitus, and their body mass index was 28.4±2.5 kg/m^2. Of those without a history of MI, 84.5% had AH (p=0.22), 7.7% had type 2 diabetes mellitus (p=0.75), and their body mass index was 27.8±2.2 kg/m^2 (p=0.35). Most of the subjects with a history of MI received standard drug therapy, e.g., acetylsalicylic acid, statins, beta-blockers, angiotensin-converting enzyme inhibitors. Subjects with AH received combined, mostly two-component, antihypertensive therapy.

Indicators of arterial stiffness were estimated using a Fukuda denshi VS-1500 VaSera sphygmograph (Japan). CAVI and AI were calculated for each subject. CAVI is an arterial stiffness index based on the β-stiffness index, independent of BP at the moment of measurement. This indicator reflects arterial stiffness from the aortic root to the ankle arteries and is determined as follows:

$$CAVI = a\,(\beta\text{-stiffness index}) + b = a\left[2\,(\rho/\Delta P) \times \ln(Ps/Pd) \times haPWV^2\right] + b \quad \textbf{(1)}, \text{ where}$$

CAVI, cardio-ankle vascular index; haPWV, cardio-ankle pulse wave velocity; Ps, systolic BP; Pd, diastolic BP; ΔP, Ps – Pd; ρ, blood viscosity=1.05 g/ml; a and b are constants. AI, the ratio of the reflection peak pressure to the systolic peak pressure, is determined as follows:

$$AI = P2/P1 \quad \textbf{(2)}, \text{ where}$$

P1, systolic peak pressure; P2, reflection peak pressure.

This study was preformed according to the ICH/GCP guidelines, the Declaration of Helsinki (2008), and the National Standard of the Russian Federation GOST-R 52379–2005 Good Clinical Practice. The ethics committee of the Federal Scientific Center of Medical Preventive Technologies for Public Health Risk Management approved the study protocol (Protocol No. 105 dated 17.06.2019). All subjects were informed of the study's objective and gave voluntary, informed consent.

Statistical processing was performed using SPSS 22.0. A model of multivariate logistic regression was constructed, which is described as:

$$p\ probability = \left[1 + e^{-(b_0 + b_1 x)}\right]^{-1}, \quad (3), \text{ where}$$

p is the probability of a history of MI; x is an independent factor; b0, b1, bi are coefficients of the multivariate mathematical model. The model included CAVI, AI, and the subject's age. For the model, the probability of 0.5 was the cut-off point for the binary classification of history of MI/no history of MI.

The construction of a logistic regression model involved the calculation of the chi-square (used to assess the statistical significance of the model), as well as the criterion – 2 LogLikelihood (is analogous to sum of squares of residuals in linearregression, it shows how much unexplained information left afteruse of the model for actual data). The criterion R^2 Nagelkerke was calculated that shows the proportion of variability in the value of the dependent variable due to the influence of the tested variables. Hosmer-Lemeshow goodness-of-fit test shows quality of description of real data by the model.

A receiver operating characteristic (ROC) – curve was constructed for each factor tested, and the prognostic probability was determined using the multivariate logic model to assess the quality of the binary classification. The area under the ROC-curve (AUC) was calculated. The model's quality was assessed by AUC as follows: 0.9–1.0 – excellent; 0.8–0.9 – very good; 0.7–0.8 – good; 0.6–0.7 – average; 0.5–0.6 – unsatisfactory. Correlation analysis was performed using Spearman's coefficient. The significance level of p<0.05 was used.

Results

At step 0 of the analysis, where the prognosis is based only on a constant without introducing factors into the model, all subjects are assigned to the category that included most of the subjects, «no history of MI,» with 53.8% of cases being correctly classified. As for the factors not included in the model at step 0, i.e., age, CAVI, AI, the residual value of χ^2 was 66.9 with p<0.0001, indicating a statistically significant improvement in the model quality when these factors were taken into account. When the above factors were simultaneously introduced into the model (step 1), the value of χ^2 was 74.6 with p<0.0001. When estimating the function likelihood, the –2Log likelihood value for the model was 323.0, and the Nagelkerke R2 was 0.31. The Hosmer-Lemeshow

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1239

Table 1. Parameters of the multivariate logistic regression model of the probability of assigning a patient to the group of a very high risk of cardiovascular complications

Variables	B	Standard error	Wald	p	Exp (B)	95% confidence interval for Exp (B)	
						Lower limit	Upper limit
Age	0.129	0.025	26.03	<0.001	1.138	1.083	1.196
CAVI mean	0.348	0.131	7.02	0.008	1.417	1.095	1.833
AI	1.892	0.850	4.95	0.026	6.631	1.253	35.079
Constant	-11.6	1.602	52.87	<0.001	0.000	–	–

CAVI, cardio-ankle vascular index; AI, augmentation index; B regression coefficient;Wald - significance criterion coefficient B for the corresponding independent variable; Exp (B) – the change odds ratio when changing predictor per unit.

Table 2. Results of ROC-analysis of regression model parameters

Variable	Area under ROC-curve (AUC)	Standard error*	p**	Asymptotic 95% confidence interval	
				Lower limit	Upper limit
CAVI mean	0.700	0.031	<0.001	0.640	0.761
AI	0.641	0.032	<0.001	0.578	0.704
Age	0.750	0.029	<0.001	0.693	0.806
Prognostic probability	0.777	0.027	<0.001	0.724	0.830

*, in accordance with a non-parametric assumption; **, zero hypothesis is rejected if the area under ROC-curve is statistically significantly greater than 0.5. CAVI, cardio-ankle vascular index; AI, augmentation index.

goodness-of-fit test was 0.41, i.e., the model reflected the actual data satisfactorily.

The logistic regression model classified 70.1% of the cases correctly. The model identified correctly in 66.9% of cases that subjects with a history of MI belonged to the group of very high risk of developing CVCs (sensitivity), and in 72.9% of the cases to the group without this risk (specificity).

The main coefficients of the regression model are provided in order of significance in Table 1. All of them significantly increase the likelihood of belonging to the group of subjects with a history of MI, i.e., having a very high risk of developing CVCs. Age was the most significant factor in the model, followed by CAVI. AI was the least significant factor.

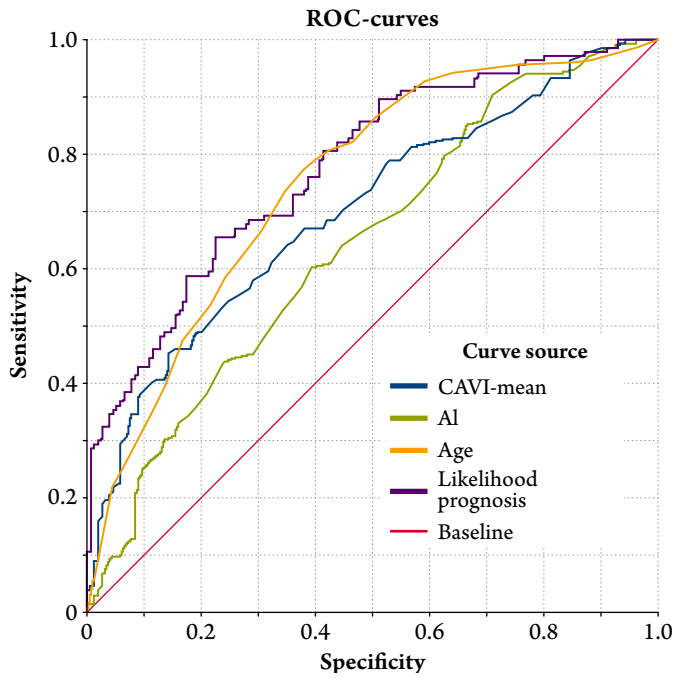
The collinear test of the indicators included in the model showed no correlation with r>0.9. The greatest correlation coefficient (0.51; p<0.01) was between the subjects' age and CAVI. The resulting equation of logistic regression was:

$$p\ probability = [1+e^{-(-11.6+0.129 \times Age + 0{,}348 \times CAVI\ mean + 1.892 \times AI)}]^{-1} \quad (4).$$

The results of the ROC analysis are provided in Table 2 and Figure 1). The largest AUC characterizing the prognostic ability of an indicator was 0.750 for age, 0.70 for CAVI, and 0.641 for AI. Thus, the quality can be characterized as good of the age and CAVI models and as average for AI. The inclusion of prognostic probability in the ROC analysis allowed to achieve AUC=0.777 for the overall model, i.e., the overall model's quality was good.

According to the ROC analysis matrix, the cut-off point for CAVI 8.0 had 64% sensitivity and 65% specificity in case of the very high risk; and 31% and 93%, respectively, for CAVI 9.0. The cut-off point of AI more than 0.99

Figures 1. Results of ROC-analysis of regression model parameters



CAVI, cardio-ankle vascular index; AI, augmentation index.

determined 64% sensitivity and 55% specificity for the very high-risk group.

Discussion

The search for non-invasive indicators to characterize fairly accurately the prognosis of subjects at risk of various categories is a prominent issue in current cardiology. The vascular wall elasticity depends on several RFs, which is why arterial stiffness can be roughly considered an integral result of all damaging effects on the artery wall [7]. The indicators of arterial stiffness, including the pulse wave velocity in different vascular segments, are considered to have different prognostic values, requiring an individual statistical justification for each indicator of stiffness. CAVI, developed by the Japanese scientists and implemented in VaSera VS-1500N sphygmometers, allows obtaining, in the screening mode, several indicators characterizing the state of the arterial bed (CAVI, AI, ABI). The enables clinicians to take further diagnostic and preventive measures [7, 8]. The main data set for the prognostic value of CAVI was obtained for the Asian population; however, the method has been tested in Russia [9, 10]. A Japanese trial, including more than 32,000 subjects, found that those with cardiovascular diseases had higher CAVI values than healthy subjects [11]. The review by Bonarjee provides data showing that CAVI is significantly correlated with the severity of coronary atherosclerosis as detected by coronary angiography, and that CAVI is significantly higher in subjects with angina [8]. By computed tomography, Park et al. [12] confirmed the association of CAVI with the coronary calcium index and with the degree of coronary artery atherosclerotic stenosis. The Japanese researchers found a positive correlation of CAVI with the number of coronary arteries involved [13]. Similar data are presented in the review by Trifonova et al. [10], according to which CAVI >9 predicted the presence of hemodynamically significant coronary stenosis with 75% sensitivity and 93% specificity. According to Tanaka et al. [14], CAVI >7.41 may be indicative of developing coronary atherosclerosis, CAVI >8 may indicate the presence of coronary stenosis.

Only few studies concerning the prognostic value of CAVI for severe CVCs (MI, stroke) were conducted, mainly in the Asian population [15–17]. Satoh-Asahara et al. [17] showed CAVI to be a significant factor associated with the incidence of CVCs in obese subjects. In the Cox regression model, the odds ratio (OR) per unit of increase in CAVI was 1.44 (95% confidence interval (CI) 1.02–2.02; p=0.037) [17]. Gohbara et al. [15] described CAVI >8.325 as an independent RF of developing CVCs (OR 18; p=0.005) and ischemic stroke (OR 9.37; p=0.034) after suffering acute coronary syndrome. Chung et al. [18] provided data on statistically significant differences in the odds ratios (OR) of developing CVCs in subjects with type 2 diabetes mellitus and CAVI ≤9 and >9 (OR 1.18; p=0.049).

Otsuka et al. [19] showed that the absence of a decrease in CAVI during the treatment for 6 months statistically significantly increased the probability of developing CVCs (p<0.001).

Meta-analysis by Matsushita et al. [20] that included 9 prospective (n=5,214) and 17 cross-sectional (n=7,309) studies of the Asian subjects showed an ambiguous prognostic role of CAVI. With an increase in CAVI by 1 standard deviation, the standardized OR of the CVC development was 1.2 (95% CI 1.05–1.36; p=0.006). When comparing CAVI in subjects with and without a history of CVCs, the mean difference in CAVI was 1.28 (95% CI 0.86–1.70; p<0.001). This systematic review demonstrated a moderate correlation between CAVI and the incidence of CVCs, but there was no correlation between CAVI and total mortality in these studies [20]. Most scientific publications concerning the Asian population provide the recommended cut-off points for CAVI in terms of developing CVCs: CAVI<8 is normal; CAVI ≥8 and <9 is borderline; and CAVI ≥9 is pathological [14, 21]. Kabutoya and Kario [22] showed the ratios of CAVI to brachial-ankle pulse wave velocity (baPWV), which had been previously investigated as an RF of developing CVCs with a normal value<14 m/s. According to regression analysis, baPWV of 14 m/s corresponded to CAVI 8.303, and baPWV 18 m/s to CAVI 9.059 [22, 23]. When providing the CAVI data, most authors recommend obtaining additional data on the role of this indicator in the European population, since there are likely differences with the data obtained for the residents of the Asian region.

The increase in the arterial stiffness results in an early return of the reflected pulse wave, which increases the proximal pressure and causes an increase in AI. This index is a characteristic of arterial stiffness different than velocity i.e., pulse wave velocity, CAVI, and is obtained by analyzing the pulse wave circuit [24, 25]. In population studies, increased AI was associated with higher total mortality and incidence of CVCs in subjects with AH, coronary artery disease, and terminal chronic kidney disease [24, 26]. Patvardhan et al. [27] showed that AI was significantly higher in subjects who had more than 5 RFs of CVCs, as compared to those with less than 3 RFs, and in subjects with cardiovascular diseases, i.e., coronary artery disease, MI, coronary stenosis more than 50%. According to the ROC analysis in this study, AI demonstrated average prognostic capacity for cardiovascular pathologies (AUC=0.604) [27].

Our study has demonstrated a statistically significant role of CAVI in the process of assigning patients to the group of a very high risk of developing CVCs, i.e., those with a history of MI. The increase in OR of assigning patients to this group with a 1-point increase in CAVI is 1.417, which is

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1239

consistent with the literature. According to the ROC analysis, the prognostic role of CAVI (AUC=0.70) is slightly inferior to the prognostic role of age (AUC=0.75) yet superior to the prognostic role of AI (AUC=0.641). Sensitivity and specificity of the applicable, literature-based cut-off points for CAVI were 64% and 65%, respectively, for CAVI=8 and 31% and 93%, respectively, for CAVI=9, with patients being assigned to the very high-risk group. If AI is >0.99, the patient can be assigned to the group of a high risk of developing CVCs with 64% sensitivity and 55% specificity.

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Conclusions

1. Arterial wall stiffness indicators, such as CAVI and AI, in male patients aged 40 to 60 years, are statistically significant, independent markers of a very high risk of developing cardiovascular complications.
2. The rate of variability in the probability of patients being assigned to the very high-risk group due to the effects of the factors studied is 31%. The overall quality of the prognostic model is rated as good.
3. The recommended cut-off points in patients at very high risk of developing cardiovascular complications are 8.0 for CAVI and 0.99 for AI.

No conflict of interest is reported.

The article was received on 20/06/2020

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ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1239