ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.831-005

Factors associated with pathological cardio-ankle vascular indices in patients with acute ischemic stroke: gender differences

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Received 23 November 2015; accepted 19 February 2016.

Abstract

Background. Currently, risk factors of ischemic stroke remain the relevant research object, including gender-dependent arterial stiffness. **Objective.** To study the gender-related differences in factors associated with pathological cardio-ankle vascular index (CAVI) in subjects with acute cerebrovascular accidents (CVA). **Design and methods.** The presence of cardiovascular disease, previous cardiovascular events, types and subtypes of stroke were assessed in all subjects. Color-flow duplex scanning of brachiocephalic arteries and laboratory studies (lipid profile) were performed to assess the presence of atherosclerosis. **Results.** There were no significant differences in intermediate and pathological CAVI values in men and women ($p = 0.59$ and $p = 0.48$, respectively). The factors associated with pathological CAVI differ depending on the gender. The independent predictors of pathological CAVI in men include obesity ($p = 0.04$), intima-media complex thickening ($p = 0.03$); while in women they include obesity ($p = 0.03$), atherogenic index ($p = 0.02$), history of acute cerebrovascular accident ($p = 0.03$), and coronary artery disease ($p = 0.02$). **Conclusions.** Thus, the assessment of CAVI is recommended in patients with ischemic stroke in order to identify increased arterial wall stiffness and to apply preventive approaches in accordance with the gender-related differences.

Key words: cardio-ankle vascular index, gender-related differences, stroke, risk factors, atherosclerosis

For citation: Sumin AN, Kukhareva IN, Kolmykova JA, Ott MV, Vodopyanova NI, Trubnikova OA, Kovalenko AV, Doronin BM. Factors associated with pathological cardio-ankle vascular indices in patients with acute ischemic stroke: gender differences. Arterial'naya Gipertenziya = Arterial Hypertension. 2016;22(1):23–31. ***doi: 10.18705/1607-419X-2016-22-1-23-31.***

Факторы, ассоциированные с патологическим сердечно-лодыжечным сосудистым индексом у больных острым нарушением мозгового кровообращения: гендерные особенности

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Статья поступила в редакцию 23.11.15 и принята к печати 19.02.16.

Резюме

Актуальность. На сегодняшний день остается актуальным вопрос изучения факторов риска развития ишемического инсульта (ИИ). Одним из этих факторов является повышенная жесткость артериальной стенки с учетом гендерных особенностей. **Цель исследования** — изучить гендерные особенности факторов, ассоциированных с патологическим сердечно-лодыжечным сосудистым индексом (СЛСИ) у больных острым нарушением мозгового кровообращения (ОНМК). **Материалы и методы.** У пациентов оценивали наличие сердечно-сосудистых заболеваний, предшествующие сосудистые события, тип и подтип инсульта. Для оценки наличия атеросклероза проведено цветное дуплексное сканирование брахицефальных артерий и лабораторные исследования (липидограмма). **Результаты.** В ходе исследования не было выявлено значимых различий промежуточных и патологических значений СЛСИ у мужчин и женщин (p = 0,59 и p = 0,48 соответственно). Выявлены гендерные различия в факторах, ассоциированных с патологическим СЛСИ. Независимыми предикторами выявления патологического СЛСИ у мужчин были: ожирение (p = 0,04), утолщение комплекса «интима-медиа» (p = 0,03), у женщин — ожирение (p = 0,03), индекс атерогенности (p = 0,02), ОНМК в анамнезе (p = 0,03), наличие ИБС (p = 0,02). **Выводы.** Таким образом, оценка СЛСИ целесообразна у больных ИИ для выявления пациентов с повышенной жесткостью артериальной стенки, что позволит проводить профилактические мероприятия с учетом гендерных особенностей.

Ключевые слова: сердечно-лодыжечный сосудистый индекс, гендерные особенности, инсульт, факторы риска, атеросклероз

Для цитирования: Сумин А. Н., Кухарева И. Н., Колмыкова Ю. А., Отт М. В., Водопьянова Н. И., Трубникова О. А., Коваленко А. В., Доронин Б. М. Факторы, ассоциированные с патологическим сердечно-лодыжечным сосудистым индексом у больных острым нарушением мозгового кровообращения: гендерные особенности. Артериальная гипертензия. 2016;22(1):23–31. ***doi: 10.18705/1607-419X-2016-22-1-23-31.***

Introduction

Decrease of arterial wall elasticity is an integral parameter of cardiovascular risk [1, 2]. In recent years a new indicator of the arterial stiffness has been widely investigated. It is cardio-ankle vascular index (CAVI) [3] which is independent of blood pressure (BP) level or operator, can be reproduced easily and is suitable for repeated measurements in contrast to parameters studied previously [4]. In healthy persons, association of increased CAVI with such risk factors as arterial hypertension (HTN), age [5], hyperlipidemia [6], low physical activity [7], and increased level of psychoemotional stress [8] was found. The link between CAVI and prevalence of coronary [9] and non-coronary [10] atherosclerosis was shown, as well as relation between CAVI and affection of small cerebral vessels was found [11]. So far only few studies assessed this index in neurological patients. However, it has not been studied so far in patients with an acute cerebrovascular accident (ACVA).

Stroke is the second most frequent cause of death and the third most frequent cause of disability [12]. Females are at greater risk than males [13–15]. Previous studies showed that there were gender differences in etiology, prevalence, and severity of strokes that were due to physiological differences between males and females. Although age-specific stroke prevalence and mortality are larger in males, total number of strokes is higher and the results of treatment are worse in females since they live longer, and stroke risk increases with age [16, 17]. There are also known gender differences in the risk factors of stroke [18, 19]; one of them is the increased arterial wall stiffness [20–22]. Previous studies also demonstrated differences in CAVI values in males and females [23, 24]. Therefore, the **objective** of the present work was the assessment of gender characteristics of the factors associated with pathological CAVI in patients with ACVA.

Design and methods

Altogether 375 patients (200 males aged 64.2 ± 11.9 years old and 175 females aged 63.5 ± 12.2 years old) diagnosed with ACVA, who received treatment in the neurological department of Kemerovo cardiologic dispensary in 2012–2013, were enrolled in this study. All the patients underwent routine neurological and instrumental examinations (multispiral computed tomography of the brain for verification of the stroke type and assessment of vascular system involvement). The severity of neurological symptoms was assessed according to NIHSS (National Institutes of Health Stroke Scale). Pathogenetic subtype of ischemic stroke (IS) was defined using the TOAST classification of IS subtypes (Adams H. P. et al., 1993). Modifiable (HTN, diabetes mellitus — DM, rhythm disturbances, education, smoking, hypodynamia) and non-modifiable (sex and age) risk factors of IS development were assessed.

BP was measured on the right arms of sitting patients by an automatic tonometer after a 5-minute rest. BP was measured twice with a 2–3-minute interval. The average of two measurements was used for the analysis. HTN was determined as BP 140/90 mm Hg and more or BP less than 140/90 mm Hg in the course of antihypertensive therapy. Height and body mass measurements were carried out with the help of a height meter within the accuracy of 1 cm and floor electronic medical scale within the accuracy of 100 g, subjects of the study wearing no footwear or outdoor clothes. Obesity was determined as body mass index (BMI) ≥ 30 kg/m^2; BMI was calculated according to the formula: weight (kg) / height^2 (m^2) (Quetelet index). A person was considered regularly smoking if he/she smoked 1 cigarette daily or more.

Assessment of brachiocephalic arteries (BCA) was carried out with the help of color duplex ultrasonography (Hewlett-Packard, USA) with the assessment of BCA stenosis degree and intima-media complex thickness (IMT) in the arteria carotis communis. IMT > 1.0 mm was considered abnormal. All kinds of stenosis and separately stenosis of BCA > 50 % were registered.

All patients underwent the examination of peripheral arteries with the device VaSera VS-1000 (Fukuda Denshi, Japan). Ankle-brachial index (ABI) was calculated, values less than 0.9 were considered as a sign of peripheral atherosclerosis of lower extremity arteries. CAVI was also assessed, it was calculated automatically on the basis of the plethysmogram of 4 extremities, electrocardiogram, and phonocardiogram with the help of a special calculation algorithm (Bramwell–Hill formula). CAVI values of 9.0 and more were considered abnormal.

The patients were divided into two groups according to their gender. Patients with ABI < 0.9 (males: 37.0 %, n = 74; females: 42.3 %, n = 74) were excluded from the analysis causing the change in the number of members of study groups (126 males and 101 females). The groups were matched for main demographic and anthropologic characteristics, risk factors of atherosclerosis, comorbidities, prevalence of history of atherothrombotic events, laboratory and instrumental findings.

Statistical analysis of the study results was carried out using the program package STATISTICA 6.1. Normality of distribution was assessed with the help of Shapiro–Wilk test. Since all values of quantitative variables had distribution differing from the normal one, the results are shown as median and interquartile range (Me ± Q). For comparison of groups in qualitative parameters, χ^2 (chi square) test was used. For assessment of correlation between abnormal CAVI (CAVI > 9.0) and one or several quantitative or qualitative parameters, logistic regression analysis was used. One-way regression analysis included such parameters as age, higher education, stress, smoking and its duration, HTN and its duration, history of myocardial infarction (MI) and stroke (ACVA), atrial fibrillation, angina pectoris, chronic heart failure (CHF), coronary heart disease (CHD), increased body mass index (BMI ≥ 30 kg/m2), DM. Multivariate regression analysis included variables for which values of the test for significant changes during the one-way analysis were less than 0.1, relative risk (RR) and 95 % confidence intervals (95 % CI) were assessed. Firstly, possible correlations between assumed predictors were determined, then several regression models with regard to found correlations were formed. Differences were considered statistically significant at $p < 0.05$.

Results

The examined groups were comparable by age (Table 1). Males more often than females were employed (47.6 and 22.8 %, respectively, p = 0.0001) and had higher education (37.3 and 21.8 %, respectively, p = 0.01). In the female group the proportion of unemployed pensioners was higher (73.3 and 36.5 %, respectively, p = 0.0001) as well as the number of subjects with elementary education (10.9 and 2.4 %, respectively, p = 0.008), hypodynamia was found more often (29.7 and 11.9 %, respectively, p = 0.0008). No differences in the prevalence of HTN, its duration, history of MI and ACVA in males and females were found. In the female group more often than in the male group

Table 1

RISK FACTORS, CLINICAL AND ANAMNESTIC CHARACTERISTICS IN MALES AND FEMALES WITH ACUTE CEREBROVASCULAR ACCIDENT AT ADMISSION

Characteristics	Males (n = 126)	Females (n = 101)	p
Age, years	65.1 ± 11.3	62.2 ± 12.9	0.98
HTN, n (%)	109 (86.5)	91 (90.1)	0.40
HTN duration, years	10.3 ± 7.4	12.1 ± 8.1	0.07
CHD, n (%)	39 (30.9)	47 (46.5)	0.02
Angina pectoris, n (%)	23 (18.3)	35 (34.6)	0.005
Atrial fibrillation, n (%)	18 (14.3)	22 (21.8)	0.03
CHF, n (%)	41 (32.5)	49 (48.5)	0.02
Obesity, n (%)	29 (23.6)	28 (28.6)	0.04
DM, n (%)	9 (7.2)	12 (11.9)	0.01
History of stroke, n (%)	24 (19.1)	22 (21.8)	0.61
Low physical activity, n (%)	15 (11.9)	30 (29.7)	0.0008
History of myocardial infarction, n (%)	11 (8.7)	8 (7.9)	0.82
Smoking, n (%)	37 (29.4)	3 (2.9)	< 0.001
Duration of smoking, years	25.2 ± 8.1	18.3 ± 7.6	0.009
Elementary education, n (%)	3 (2.4)	11 (10.9)	0.008
Higher education, n (%)	47 (37.3)	22 (21.8)	0.01

Note: HTN — arterial hypertension; CHD — coronary heart disease; CHF — chronic heart failure; DM — diabetes mellitus.

Table 2

CHARACTERISTICS OF ISCHEMIC STROKE TYPES AND SUBTYPES AND NEUROLOGICAL IMPAIRMENT IN MALES AND FEMALES WITH HISTORY OF ACUTE CEREBROVASCULAR ACCIDENT

Characteristics	Males (n = 126)	Females (n = 101)	p
Stroke type			
Ischaemic stroke, n (%)	110 (87.3)	89 (88.1)	0.85
Cerebral haemorrhage, n (%)	16 (12.7)	12 (11.9)	0.85
Subtype of ischaemic stroke			
Atherothrombotic, n (%)	91 (72.3)	75 (74.3)	0.73
Cardioembolic, n (%)	19 (15.1)	20 (19.9)	0.34
Hemodynamic, n (%)	6 (4.7)	3 (2.9)	0.49
Hemorheological, n (%)	10 (7.9)	3 (2.9)	0.10
NIHSS, points	6.0 (3.0; 9.0)	4.0 (2.0; 7.0)	0.003

Note: NIHSS — National Institutes of Health Stroke Scale.

Table 3

INSTRUMENTAL AND LABORATORY EXAMINATIONS IN MALES AND FEMALES WITH ACUTE CEREBROVASCULAR ACCIDENT

Characteristics	Males (n = 126)	Females (n = 101)	p
Carotid wall thickening (IMT > 0.9 mm), n (%)	112 (88.8)	91 (90.1)	0.76
Stenosis of BCA with one side, n (%)	21 (16.6)	17 (16.8)	0.97
Stenosis of BCA on both sides, n (%)	27 (21.4)	12 (11.9)	0.001
Stenosis of CA > 50%, n (%)	24 (19.1)	9 (8.9)	0.03
LDL cholesterol, mmol/L	2.9 (2.3; 3.53)	3.2 (2.4; 3.86)	0.06
HDL cholesterol, mmol/L	0.9 (0.77; 1.28)	1.1 (0.94; 1.40)	0.01
AI, mmol/L	3.4 (2.50; 4.30)	3.1 (2.38; 3.70)	0.07
Total cholesterol, mmol/L	4.8 (4.1; 5.78)	5.1 (4.23; 6.21)	0.09
Triglycerides, mmol/L	1.4 (1.19; 1.89)	1.3 (1.03; 1.98)	0.25
Urea, mmol/L	4.8 (3.96; 5.84)	4.54 (3.70;6.47)	0.91
Creatinine, μmol/L	0.08 (0.07; 0.09)	0.03 (0.07; 0.09)	0.71

Note: IMT — intima-media thickness; BCA — brachiocephalic arteries; CA — carotid arteries; LDL cholesterol — low-density lipoprotein cholesterol; HDL cholesterol — high-density lipoprotein cholesterol; AI — atherogenic index.

CHD was diagnosed (46.5 and 30.9 %, respectively, p = 0.02) as well as angina pectoris (34.6 and 18.3 %, respectively, p=0.005), atrial fibrillation (21.8 and 14.3 %, respectively, p = 0.03), CHF (48.5 and 32.5 %, respectively, p = 0.02), DM (11.9 and 7.2 % respectively, p = 0.01), and obesity with BMI ≥ 30 kg/m2 (28.6 and 23.6 %, respectively, p = 0.04). Smoking and long smoking history were more often registered in the male group than in the female group (29.4 and 2.9 %, respectively, p < 0.001, p = 0.009). No significant differences in the prevalence of lower extremity atherosclerosis between males and females were found (p = 0.90).

Ischemic type of ACVA (87.3 and 88.1 %, respectively, p = 0.85), as well as hemorrhagic type of ACVA (12.7 and 11.9 %, respectively, p = 0.85), has the same prevalence in male and female groups (Table 2). The predominant type of ischemic ACVA is atherothrombotic subtype (72.3 and 74.3 % in males and females, respectively, p = 0.73). The prevalence of cardioembolic ACVA subtype was the same in both groups (p = 0.25). Neurological impairment according to NIHSS was more profound in males than in females: 6.0 (3.0; 9.0) and 4.0 (2.0; 7.0) points, respectively (p = 0.003).

The thickening of intima-media complex (IMC) was equally prevalent in males and

Table 4

ANKLE-BRACHIAL INDEX AND CARDIO-ANKLE VASCULAR INDEX VALUES IN MALES AND FEMALES WITH ACUTE CEREBROVASCULAR ACCIDENT AT ADMISSION

VASERA at admission	Males (n = 200)		Females (n = 175)		p
ABI < 0.9, n (%)	74 (37.0)		74 (42.3)		0.29
ABI > 0.9, n (%)	126 (63.0)		101 (57.7)		0.29
Side	L	R	L	R	
ABI	1.0 (0.88; 1.10)	1.1 (0.91; 1.13)	0.9 (0.86; 1.09)	1.0 (0.84; 1.09)	p_{1-2} = 0.05 p_{3-4} = 0.07 p_{1-3} = 0.19 p_{2-4} = 0.03
Gender	**Males (n = 126)**		**Females (n = 101)**		
CAVI > 9.0, n (%)	71 (56.3)		52 (51.5)		0.53
CAVI 8.0–9.0, n (%)	20 (15.9)		18 (17.2)		0.69
CAVI < 8.0, n (%)	35 (27.8)		31 (30.7)		0.63
Side	L	R	L	R	
CAVI	8.8 (7.6; 10.3)	9.2 (7.9; 10.5)	8.7 (7.4; 10.0)	8.9 (7.6; 10.0)	p_{1-2} = 0.07 p_{3-4} = 0.17 p_{1-3} = 0.41 p_{2-4} = 0.20

Note: Ankle-brachial index (ABI); CAVI — cardio-ankle vascular index.

females (88.8 and 90.1 %, respectively, p = 0.76) (Table 3). Bilateral BCA stenosis (21.4 and 11.9 %, respectively, p = 0.001) and coronary artery stenosis > 50 % (19.1 and 8.9 %, respectively, p = 0.03) was more often registered in the male group than in the female group. Lipidogram analysis (including low-density lipoproteins, atherogenic index — AI, total cholesterol, triglycerides) showed no differences between the groups (p > 0.05). No relevant differences between males and females were found regarding the number of cases with abnormal CAVI > 9.0 (56.3 and 51.5 %, respectively, p = 0.53) or ABI < 0.9 (37.0 and 42.3 %, respectively, p = 0.29) (Table 4).

For the evaluation of factors associated with the increase of CAVI > 9.0, the variables shown in the tables were included in the logistic regression analysis. In the male sample (Table 5) the one-way analysis showed association of increased CAVI with age, obesity, IMC thickening, LDL and AI increase. In the female sample (Table 6) the association of increased CAVI with age, obesity, CHD, and increase of AI was found. Based on the one-way analysis, models for the multiple regression analysis were developed.

The multiple logistic regression analysis showed the following associations with increased CAVI: in males — obesity (RR 3.57; p = 0.04), IMC thickening (RR 4.11; p = 0.03), in females — obesity (RR 3.22; p = 0.03), AI (RR 1.67; p = 0.02), history of ACVA (RR 2.77; p=0.03), CHD (RR 2.42; p = 0.02).

Discussion

In the present study no significant differences in CAVI between males and females with IS were found. Independent factors associated with abnormal CAVI (> 9.0) in males were obesity and IMC thickening, and in females — obesity, AI, CHD, and history of ACVA.

Impacts of gender on clinical signs and severity of stroke can be seen not in all studies [17, 25, 26], although gender differences in risk factors of stroke are rather clear [26]. Therefore, in females more often than in males more severe strokes was registered (17.20 versus 12.54 %) as well as more frequent HTN (76.42 versus 66.39 %), dyslipidemia (30.35 versus 22.76 %), and obesity (18.40 versus 9.32 %) (p < 0.05). Compared to the females, the males had higher rate of intracardiac artery stenosis (23.11 versus 17.45 %), smoking (29.60 versus 13.05 %) and alcohol abuse (12.15 versus 0.47 %) (p < 0.05) [19]. In the present study, smoking was more often found in males, while females had

Table 5

FACTORS ASSOCIATED WITH ABNORMAL CARDIO-ANKLE VASCULAR INDEX IN MALES WITH ACUTE CEREBROVASCULAR ACCIDENT AT ADMISSION

Characteristics	HR	95% CI	p
Univariate analysis			
Age	1.00	0.97–1.03	0.72
HTN duration	1.05	0.99–1.12	0.08
CHF	1.87	0.91–3.86	0.08
Obesity	2.77	1.16–6.66	0.02
Smoking	1.85	0.89–3.85	0.09
Atherothrombotic IS	1.82	0.88–3.74	0.09
NIHSS at admission	1.06	0.99–1.13	0.08
Carotid wall thickening (IMT > 0.9 mm)	3.48	1.00–12.00	0.04
LDL cholesterol	1.40	1.01–1.93	0.03
AI	1.32	0.99–17.6	0.05
Total cholesterol	2.15	1.09–4.27	0.08
Urea	1.36	1.05–1.76	0.02
Multivariate analysis			
Model 1, regardless of the age, duration of HTN, atherothrombotic subtype IS, LDL cholesterol, NIHSS and level of urea at admission p = 0.01 for the model			
Age	1.03	0.99–1.06	0.24
Obesity	3.57	1.02–12.5	0.04
Model 2, regardless of age, smoking and AI p = 0.02 for model			
Age	1.01	0.98–1.04	0.61
Carotid wall thickening (IMT > 0.9 mm)	4.11	1.12–15.02	0.03

Note: HR — hazard ratio; CI — confidence interval; HTN — arterial hypertension; CHF — chronic heart failure; NIHSS — National Institutes of Health Stroke Scale; IMT — intima-media thickness; AI — atherogenic index; LDL cholesterol — low-density lipoprotein cholesterol; IS — ischaemic stroke.

Table 6

FACTORS ASSOCIATED WITH ABNORMAL CARDIO-ANKLE VASCULAR INDEX IN FEMALES WITH ACUTE CEREBROVASCULAR ACCIDENT AT ADMISSION

Characteristics	HR	95% CI	p
Univariate analysis			
Age	1.00	0.97–1.03	0.88
CHD	2.06	0.98–4.31	0.05
Obesity	3.03	1.19–7.69	0.02
DM	3.05	0.91–10.23	0.06
History of stroke	2.12	0.86–5.26	0.09
AI	1.48	1.00–2.19	0.04
Multivariate analysis			
Model 1. regardless of age. history of stroke. carotid wall thickening (IMT >0.9 mm) p = 0.02 for the model			
Age	1.01	0.98–1.04	0.96
Obesity	3.22	1.15–9.09	0.03
AI	1.67	1.08–2.56	0.02
Model 2. regardless of age. carotid wall thickening (IMT > 0.9 mm) p = 0.04 for the model			
Age	1.01	0.98–1.04	0.96
History of stroke	2.77	1.05–7.69	0.03
CHD	2.42	1.11–5.31	0.02

Note: HR — hazard ratio; CI — confidence interval; CHD — coronary heart disease; DM — diabetes mellitus; AI — atherogenic index; IMT — intima-media thickness.

higher frequency of CHD, DM and obesity; no differences between males and females in the age, HTN, peripheral atherosclerosis and arterial wall stiffness was found.

In other cohorts, CAVI was usually higher in males than in females, as shown both in healthy individuals and in population studies [23]. For example, the prevalence of abnormal CAVI was 12.74 % in males and 9.91 % in females among 18,336 persons examined in China [24]. In more evident disease (as in the present study) gender differences might be less obvious as well as possible impact of other risk factors [4].

In neurological patients no gender characteristics were assessed previously with regard to correlation between CAVI, risk factors and clinical signs. For example, in the study conducted in China positive correlation was found between CAVI and carotid atherosclerosis among all the subjects. Compared to the persons with CAVI values in the lower tertile (5.15–7.40), those with the values in the middle (7.41–8.65) and upper (8.66–13.60) tertiles had higher risk of carotid atherosclerosis ($p = 0.007$ for the trend). The authors concluded that CAVI ≥ 8.0 may be an optimal predictor of carotid atherosclerosis [27]. In our study the correlation between CAVI and manifestations of subclinical atherosclerosis (IMC thickening) was found only in males, but not in females.

The assessment of clinical values revealed an association between CAVI and small cerebral vessels lesions according to the brain magnetic resonance imaging (RR 1.889; $p = 0.002$) in young and middle-aged asymptomatic patients [10]. In patients without stroke or history of transient ischemic attack, values of CAVI ≥ 9.2 were associated with the asymptomatic brain infarctions (RR 2.34; 95 % CI 1.16–5.02) [19]. In addition, in patients with cerebrovascular diseases, CAVI values were higher than in controls, linear regression analysis also showed a significant correlation between CAVI and severity of atherosclerotic carotid artery lesions in patients with cerebrovascular diseases ($p < 0.05$) [20].

Examination of 842 patients with atherothrombotic subtype of IS showed that CAVI was the lowest in the control group, higher in patients with minor stroke and the highest in patients with massive stroke. CAVI values more than 9.5 were associated with the risk of atherosclerotic IS (RR 1.44; $p < 0.001$) [21]. In addition, CAVI was higher in the group of ACVA patients with microhemorrhages (10.5 versus 8.6, $p < 0.001$). High CAVI was independently associated with microhemorrhages in patients with acute IS [28].

In this work we did not intend to study the impact of sex on the correlation between arterial wall stiffness values and neurological symptoms in patients with stroke, it should be done in the next studies.

Conclusions

In patients with ACVA, abnormal CAVI was found in 56.3 % of males and 51.5 % of females. Despite the differences in cardiovascular risk factors (in males smoking was found more often, whereas in females obesity, DM, and hypodynamia were more frequent), arterial stiffness level did not differ between the groups. Independent predictors of the increased risk of abnormal CAVI in males were obesity (RR 3.57, $p = 0.04$), IMC thickening (RR 4.11, $p = 0.03$), while in females obesity (RR 3.22, $p = 0.03$), AI (RR 1.67, $p = 0.02$), history of ACVA (RR 2.77, $p = 0.03$), and CHD (RR 2.42; $p = 0.02$) were the main predictors.

CAVI assessment is reasonable in patients with IS in order to determine subjects with increased arterial wall stiffness in order to further planning of rehabilitation procedures with regard to gender characteristics and to evaluate their effectiveness.

Conflict of interest

The authors declare no conflict of interest.

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