

Relationship between vascular age and classic cardiovascular risk factors and arterial stiffness

Maria Łoboz-Rudnicka¹, Joanna Jaroch¹, Zbigniew Bociąga¹, Ewa Kruszyńska¹,
 Barbara Ciecierzyńska¹, Magdalena Dziuba¹, Krzysztof Dudek²,
 Izabela Uchmanowicz³, Krystyna Łoboz-Grudzień^{1,3}

¹Department of Cardiology, T. Marciniak Hospital, Wrocław, Poland

²Institute of Machine Design and Operation, Technical University of Wrocław, Poland

³Health Science Faculty, Wrocław Medical University, Wrocław, Poland

Abstract

Background: We aimed at establishing if the substitution of vascular age (VA) for chronological age (CA) causes a change in the Framingham Risk Score (FRS) categories. Sex differences in predictors of increased VA among cardiovascular (CV) risk factors and arterial stiffness (AS) parameters were identified.

Methods: In 187 asymptomatic subjects with CV risk factors, classified into 3 FRS categories the VA was derived from the nomograms of the carotid intima-media thickness. Two groups: 1 — subjects whose VA has exceeded CA for at least 5 years and 2 — others were established. Carotid AS parameters were obtained from echo-tracking.

Results: Substitution of VA for CA changed the FRS category into the higher one in 11.8% of subjects. Diabetes mellitus (DM) was the predictor of increased VA in both sexes, while metabolic syndrome (MS) only in women. The cut-off values of AS parameters that allow for prediction of increased VA were determined from the ROC-curve analysis — in men: $\beta > 7.3$, $E_p > 103$ kPa, $AC < 0.61$ mm²/kPa after adjustment for DM, $BMI > 29.1$ kg/m², $WHR > 0.85$ and $CA > 51$ years; in women: $\beta > 9.6$, $E_p > 126$ kPa, $AC < 0.75$ mm²/kPa, $PWV\text{-}\beta > 7.4$ m/s after adjustment for DM, $BMI > 25.8$ kg/m², $WHR > 0.80$ and $CA > 60$ years.

Conclusions: The substitution of VA for CA may increase the FRS category. Sex differences in predictors of increased VA were identified. AS parameters proved to be predictors of increased VA besides the classic risk factors. (Cardiol J 2013; 20, 4: 394–401)

Key words: vascular age, Framingham Risk Score, arterial stiffness

Introduction

Risk algorithms, mostly based on the analysis of the chronological age (CA) and classic cardiovascular (CV) risk factors, have limitations in the precise CV risk assessment of an individual and may cause underestimation of subjects, in whom

aggressive modification of CV disease risk factors should be introduced [1, 2]. Therefore, the concept of evaluating the “vascular age” (VA) — that would reflect the real atherosclerotic damage — has recently drawn a growing attention in the field of the CV risk assessment [3–6]. VA can be investigated by either imaging modalities like ultrasonic measu-

Address for correspondence: Maria Łoboz-Rudnicka, Department of Cardiology, T. Marciniak Hospital, ul. Traugutta 116, 50–420 Wrocław, Poland, tel/fax: +48 71 342 73 05, e-mail: marialoboz@o2.pl

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rement of carotid intima-media thickness (CIMT) and plaque detection or by, so called, physiological methods like pulse wave velocity (PWV) and pulse wave analysis that reflect the arterial stiffness (AS) [7]. AS can be considered a measure of the cumulative influence of CV risk factors with aging on arterial tree and may be regarded as a tissue biomarker [6–8].

We tested the hypothesis that the Framingham Risk Score (FRS) based on traditional CV risk factors does not identify subjects whose VA exceeds the CA for at least 5 years. We aimed at establishing whether the substitution of the VA for the CA in the FRS will cause the change in risk categories, the so called “reclassification”. We investigated which of the traditional CV risk factors enable to predict that the VA exceeds the CA for at least 5 years and establish if there are any sex-specific differences. We examined the relationship between the AS indices and the VA.

Methods

The study group consisted of 187 subjects (mean CA: 53.8 years [52.1–55.5]): 101 women (mean CA: 55.0 years [52.7–57.2]) and 86 men (mean CA: 52.4 years [49.9–54.9]) with CV risk factors and without history of manifest CV disease (coronary, peripheral and cerebral vascular disease was excluded).

The data concerning medical history of the study population, their risk factors, family history of CV disease and current pharmacological medication was obtained with the use of a questionnaire. Laboratory tests were performed, including: fasting glucose serum level and lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides) serum level.

All study participants were classified into three FRS risk categories: low (< 6%), intermediate (6–20%) and high (> 20%) according to the 10-year Framingham General Cardiovascular Disease Risk algorithm. The algorithm takes into account the following factors: CA, total cholesterol serum level, HDL-C serum level, the value of systolic blood pressure (with regard if it is treated or not), current smoking and diabetes mellitus (DM) [9].

Metabolic syndrome (MS) was defined according to the IDF definition [10].

The B-mode ultrasound measurement of the mean CIMT was performed with Aloka ProSound Alpha 10 machine in accordance with the Mannheim Protocol recommendations [11]. The VA was

determined with the use of the regression model in accordance with the concept of JH Stein who used the gender- and race-specific nomograms of the distribution of the CIMT values in different age groups (the nomograms were derived from the Atherosclerosis Risk in Communities Study) and defined the VA as “the age at which the composite CIMT value for an individual of a given race and gender would represent the median value (50th percentile)” [12–14].

The AS parameters were calculated with the application of the high-resolution echo-tracking (eT) system incorporated in Aloka ProSound Alpha 10 machine. After obtaining a clear image of the intima-media complex of both anterior and posterior wall of the right common carotid artery (CCA) in its longitudinal axis, the eT gate for the measurement of arterial diameter changes along the cardiac cycle was positioned at the boundaries between the intima and media of the anterior and posterior wall of the right CCA, 1–2 cm proximal to the bifurcation [15]. The proper identification of the stages of the cardiac cycle was provided by the ECG monitoring. The systolic and diastolic blood pressure entered into the system was measured during the eT procedure (the patient in a supine position for at least 15 min) at the left brachial artery. Three to five beats were averaged to obtain a representative waveform. The following AS parameters were calculated automatically [16]:

- β — beta, beta stiffness index [U]:
$$\beta = \ln(Ps/Pd)/[(Ds - Dd)/Dd];$$
- E_p — Peterson’s modulus [kPa]:
$$E_p = (Ps - Pd)/[(Ds - Dd)/Dd];$$
- AC — arterial compliance [mm²/kPa]:
$$AC = \pi(Ds \times Ds - Dd \times Dd)/[4 \times (Ps - Pd)];$$
- PWV- β — one-point pulse wave velocity [m/s]:
$$PWV-\beta = \sqrt{(\beta \times Ps/2 \times \rho)},$$

where: \ln — the natural logarithm, Ps — systolic blood pressure, Pd — diastolic blood pressure, Ds — arterial systolic diameter, Dd — arterial diastolic diameter, ρ — blood density (1.050 kg/m³) (Fig. 1).

Reproducibility of these measurements has been reported elsewhere [17].

All participants provided written informed consent. The study was approved by the ethics committee of Medical University of Wrocław.

Statistical analysis

The statistical analysis of the collected results has been performed using the software package STATISTICA v.9. The analysis included: for quantitative features — accuracy of normal distribution has been verified with Shapiro-Wilk’s and χ^2 tests,

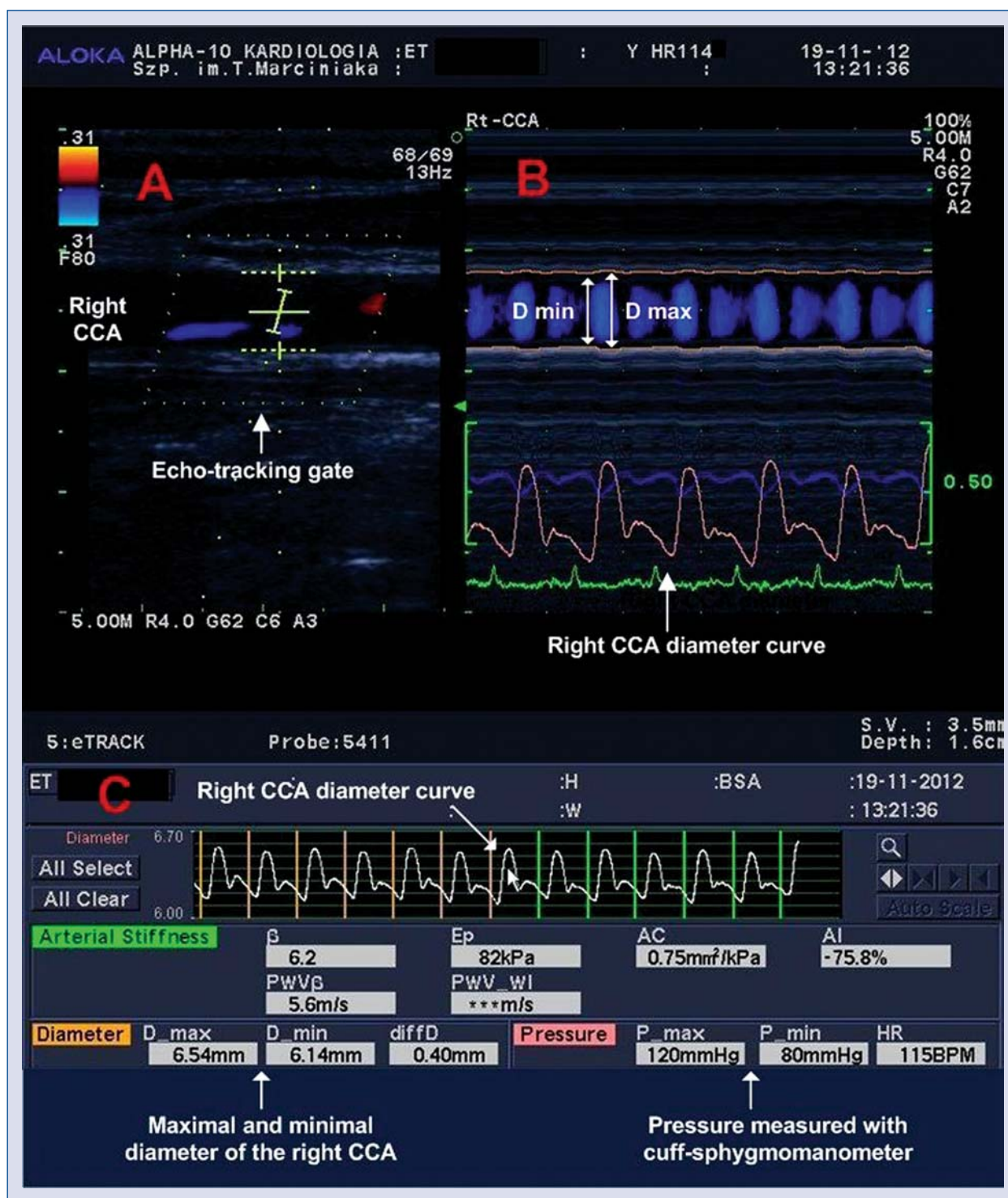


Figure 1. Measurement of arterial stiffness parameters with echo-tracking; **A.** Positioning of the echo-tracking gate in the right common carotid artery (CCA); **B.** The curve of the right CCA diameter changes obtained with the echo-tracking system; D min — minimal arterial diameter; D max — maximal arterial diameter; **C.** Arterial stiffness parameters: β — beta stiffness index; E_p — Peterson's modulus; AC — arterial compliance; AI — augmentation index; PWV_{β} — one-point pulse wave velocity; PWV_{WI} — pulse wave velocity wave intensity.

basic statistics have been calculated (mean, 95% confidence interval [CI]); for qualitative (nominal) features — occurrence frequency (fractions)

has been calculated; significance of differences between means in two groups (differed in sex or differed in calendar age CA and vascular age VA)

Table 1. Patient clinical characteristics.

	Women (n = 101)	Men (n = 86)	Total (n = 187)	P
Chronological age [years]	55.0 (52.7–57.2)	52.4 (49.9–54.9)	53.8 (52.1–55.5)	0.129
Hypertension	47 (46.5%)	45 (52.3%)	92 (49.2%)	0.520
Diabetes mellitus type 2	37 (36.6%)	46 (53.5%)	83 (44.4%)	0.030
Smoking	35 (34.7%)	36 (41.9%)	71 (38.0%)	0.389
Hypercholesterolemia	63 (62.4%)	53 (61.6%)	116 (62.0%)	0.963
Metabolic syndrome	48 (47.5%)	15 (17.4%)	37 (33.7%)	< 0.001
Heart rate [min ⁻¹]	73.4 (71.5–75.3)	68.7 (66.6–70.8)	71.2 (69.8–72.7)	0.001
Systolic BP [mm Hg]	132 (128–136)	133 (130–136)	133 (130–135)	0.354
Diastolic BP [mm Hg]	77 (75–79)	75 (73–77)	76 (74–77)	0.181
Pulse pressure [mm Hg]	55 (52–59)	59 (56–61)	57 (55–59)	0.026
Fasting glucose [mg/dL]	97 (94–101)	100 (95–105)	98 (95–101)	0.403
Total cholesterol [mg/dL]	217 (208–226)	205 (196–213)	211 (205–217)	0.082
LDL-C [mg/dL]	129 (121–137)	127 (119–135)	128 (122–134)	0.942
HDL-C [mg/dL]	62 (58–65)	50 (47–53)	56 (54–59)	< 0.001
Triglycerides [mg/dL]	150 (132–169)	146 (126–165)	148 (135–161)	0.704
Total/high density lipoprotein ratio	3.76 (3.51–4.00)	4.38 (4.06–4.69)	4.04 (3.84–4.24)	< 0.001
Body mass index [kg/m ²]	27.9 (26.9–29.0)	28.8 (27.9–29.7)	28.3 (27.7–29.0)	0.128
Waist circumference [cm]	87 (84–91)	102 (98–106)	93 (90–96)	< 0.001
Waist to hips ratio	0.82 (0.80–0.84)	0.94 (0.92–0.97)	0.87 (0.85–0.89)	< 0.001
FRS [%]	11.1 (9.3–13.0)	20.4 (18.1–22.7)	15.4 (13.8–17.0)	< 0.001
FRS category low	30 (29.7%)	10 (11.6%)	40 (21.4%)	0.005
FRS category intermediate	48 (47.5%)	29 (33.7%)	77 (41.2%)	0.078
FRS category high	23 (22.8%)	47 (54.7%)	70 (37.4%)	< 0.001

BP — blood pressure; LDL-C — low density lipoprotein cholesterol; HDL-C — high density lipoprotein cholesterol; FRS — Framingham Risk Score

has been verified with Mann-Whitney's nonparametric test or t-test for independent variables; significance of differences in occurrence frequency of specified nominal or categorized variables subgroups has been verified with Pearson's χ^2 test or with Fisher's exact test. Both values of odds ratio and their 95% CI have been estimated. For quantitative variables that showed a statistically significant difference between the two groups, receiver-operating characteristic (ROC) curves were obtained to calculate the cut-off values optimized to reach the best compromise in the prediction of the increased VA. Optimal cut-off was defined as a threshold where the sum of sensitivity and specificity was maximum. Value $p < 0.05$ has been accepted as a critical level for all statistical tests.

Results

The detailed patient clinical characteristics have been presented in Table 1. The prevalence of the traditional CV risk factors like: hypertension, smoking and hypercholesterolemia did not differ

between men and women, while DM occurred more frequently in men and MS in women.

Framingham Risk Score: Reclassification

The 10-year FRS was higher in men than in women (20.4% vs. 11.1%, $p < 0.001$) and the analysis of the risk categories revealed that more women than men were classified in a low-risk group (29.7% vs. 11.6%, $p = 0.005$), while more men — in comparison to women — belonged to a high-risk group (54.7% vs. 22.8%, $p < 0.001$). The mean VA of the whole population significantly exceeded the mean CA (59.9 years; 56.0–63.8 vs. 53.8 years; 52.1–55.5; $p < 0.05$), and the mean difference value was about 6.1 years. An analogous trend, even more pronounced, was observed in men (61.9 years; 56.5–67.4 vs. 52.4 years; 49.9–54.9; $p < 0.001$), with a mean difference about 9.5 years. In women the difference between VA and CA did not reach the statistical significance.

The study material was divided into two groups: group 1 — individuals whose VA exceeded

Table 2. Relationship between the Framingham Risk Score (FRS) categories and vascular age.

FRS category	Men (n = 86)		Women (n = 101)		Total (n = 187)	
	Group 1 VA-CA ≥ 5 N = 47	Group 2 Others N = 39	Group 1 VA-CA ≥ 5 N = 38	Group 2 Others N = 63	Group 1 VA-CA ≥ 5 N = 85	Group 2 Others N = 102
Low	6 (12.8%)	4 (10.3%)	11 (28.9%)	19 (30.2%)	17 (20.0%)	23 (22.5%)
Intermediate	12 (25.5%)	17 (43.6%)	17 (44.7%)	31 (49.2%)	29 (34.1%)	48 (47.1%)
High	29 (61.7%)	18 (46.2%)	10 (26.3%)	13 (20.6%)	39 (45.9%)	31 (30.4%)
	χ ² test: χ ² = 3.12; df = 2; p = 0.210		χ ² test: χ ² = 0.45; df = 2; p = 0.800		χ ² test: χ ² = 4.60; df = 2; p = 0.100	

VA — vascular age; CA — chronological age

Table 3. Reclassification — change of the Framingham Risk Score (FRS) category into the higher one after the substitution of the vascular age for the chronological age.

	Total (n = 187)	Men (n = 86)			Women (n = 101)			P
Calendar age [years]	53.8 (52.1–55.5)	52.4 (49.9–54.9)			55.0 (52.7–57.2)			0.129
Vascular age [years]	59.9 (56.0–63.8)	61.9 (56.5–67.4)			58.1 (52.5–63.6)			0.202
Reclassification	22 (11.8%)	16 (18.6%)			6 (5.9%)			0.0142
		Group 1 (n = 47)	Group 2 (n = 39)	P	Group 1 (n = 38)	Group 2 (n = 63)	P	
FRS category low → intermediate	9	15 (31.9%)	1 (2.6%)	0.0005	6 (15.8%)	0 (0%)	0.0022	
FRS category intermediate → high	13	4 (8.5%)	1 (2.6%)		4 (10.5%)	0		
		11 (23.4%)	0		2 (5.3%)	0		

the CA for at least 5 years, and group 2 — others, separately for sex. To group 1 belonged 85 (45%) subjects: 47 (55%) men and 38 (38%) women. The statistical analysis revealed that men belonged to group 1 more frequently than women (p = 0.029).

The important observation was that in both sexes the FRS category did not differentiate between individuals who belonged to group 1 and to group 2 (Table 2).

The upgrade into the higher CV risk category — the so called “reclassification” occurred in 22 subjects (11.8% of the whole population; Table 3). The sex analysis revealed that men underwent reclassification more frequently than women (18.6% vs. 5.9%, p = 0.0142); Twenty one (95%) of the individuals who underwent reclassification belonged to group 1.

Predictors of subjects in whom the VA exceeded the CA for at least 5 years: Sex differences

The analysis of the predictors of the VA exceeding the CA for at least 5 years performed

separately for men and women revealed that DM was a predictor in both sexes, although a stronger one in women (women: OR 3.63, p = 0.005; men: OR 2.54, p = 0.058). To the additional predictors in women belonged: MS (OR 4.01, p = 0.009), waist to hip ratio (WHR) > 0.80 (OR 17.3, p = 0.003) and body mass index (BMI) > 25.8 (OR 3.52, p = 0.012; Table 4). The cut-off values were determined from the ROC curve.

Relationships between arterial stiffness parameters and vascular age

The AS parameters in men, except for the arterial compliance, showed linear correlation with the CA. In women almost all AS parameters correlated positively linearly with the VA (except for the arterial compliance that showed negative correlation), while in men it was only β and Ep (Table 5).

The cut-off values of the AS parameters that allow for the prediction of increased VA were determined from the ROC-curve analysis (Table 6). Of noteworthy is that the cut-off values in men were lower than in women.

Table 4. Predictors of the vascular age exceeding the chronological age for at least 5 years in men and women.

	Men (n = 86)		Women (n = 101)	
	P ^a	OR (95% CI)	P ^a	OR (95% CI)
Hypertension	0.694	1.30 (0.56–3.05)	0.940	0.89 (0.40–2.00)
Diabetes mellitus	0.058	2.54 (1.06–6.07)	0.005	3.63 (1.54–8.53)
Smoking	0.606	0.72 (0.31–1.71)	0.249	0.54 (0.22–1.31)
Metabolic syndrome	0.863	1.30 (0.42–4.05)	0.009	4.01 (1.49–10.8)
Hypercholesterolemia	0.836	0.83 (0.34–1.98)	0.174	0.52 (0.23–1.18)
WHR > 0.93 ^b	0.076	4.00 (1.06–15.1)		
WHR > 0.80 ^b			0.003	17.3 (2.10–143)
BMI > 29.1 kg/m ^{2c}	0.319	1.71 (0.72–4.08)		
BMI > 25.8 kg/m ^{2c}			0.012	3.52 (1.39–8.87)

^a χ^2 test; ^bthe cut-off value from the ROC curve: for men AUC = 0.627, for women AUC = 0.662; ^cthe cut-off value from the ROC curve: for men AUC = 0.553, for women AUC = 0.624; OR — odds ratio; CI — confidence interval; WHR — waist to hips ratio; BMI — body mass index

Table 5. Linear correlation between arterial stiffness parameters and chronological and vascular age in men and women.

	Men				Women			
	β	Ep	AC	PWV- β	β	Ep	AC	PWV- β
CA	r = 0.420	r = 0.398	r = -0.180	r = 0.391	r = 0.416	r = 0.441	r = -0.379	r = 0.484
	p < 0.001	p < 0.001	p = 0.096	p = 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
VA	r = 0.304	r = 0.320	r = -0.048	r = 0.150	r = 0.593	r = 0.538	r = -0.229	r = 0.421
	p = 0.005	p = 0.003	p = 0.661	p = 0.167	p < 0.001	p < 0.001	p = 0.022	p < 0.001

CA — chronological age; VA — vascular age; β — beta stiffness index; Ep — Peterson's modulus; AC — arterial compliance; PWV- β — one-point pulse wave velocity

Table 6. The cut-off values of the arterial stiffness parameters in prediction of the vascular age exceeding the chronological age for at least 5 years.

Stiffness parameters	Men		Women		
	P ^a	Odds ratio ^b	P ^a	Odds ratio ^c	
β > 7.3	0.0003	6.46 (4.07–10.2)	β > 9.6	0.0001	6.92 (4.34–11.0)
Ep > 103 kPa	0.0199	3.00 (1.98–4.56)	Ep > 126	0.0032	4.38 (2.86–6.71)
AC < 0.61 mm ² /kPa	0.0463	2.81 (1.85–4.26)	AC < 0.75 mm ² /kPa	0.0439	2.76 (1.83–4.16)
PWV- β > 6.0 m/s	0.0627	2.43 (1.61–3.68)	PWV- β > 7.4 m/s	0.0103	4.28 (2.62–6.99)

^a χ^2 test; ^badjusted odds ratio for diabetes, chronological age > 51 years; WHR > 0.85 and BMI > 29.1 kg/m²; ^cadjusted odds ratio for diabetes, chronological age > 60 years, WHR > 0.80 and BMI > 25.8 kg/m²; β — beta stiffness index; Ep — Peterson's modulus; AC — arterial compliance; PWV- β — one-point pulse wave velocity

Discussion

Nowadays we are witnessing the revival of the idea: “a man is as old as his arteries” in the concept of the “vascular age” [3–7, 13, 14, 18].

Framingham Risk Score: Reclassification

FRS is useful in the population risk assessment but is not helpful in the individual risk evaluation.

Various reports have provided evidence that atherosclerosis in form of increased CIMT, plaques and coronary artery calcium score > 0 can be found in asymptomatic subjects classified as at low — or intermediate CV risk [19, 20]. Framingham CV risk estimates are influenced strongly by the CA. Integrating VA in the risk algorithms could be an attractive concept for subjects whose risk was estimated as low or intermediate according to

the traditional risk scores. In our study the FRS categories did not differentiate between individuals with increased VA and others — the finding consistent with the previous studies [19, 20]. Our results confirmed the thesis that VA represents the atherosclerotic burden which varies between individuals with the same CA despite similar CV risk profiles [18].

In our study 11.8% of the population was reclassified into the higher FRS category after substitution of VA for CA. In the report by Stein et al. [13] the proportion of subjects who underwent reclassification into the higher risk category was comparable (15%). We observed a stronger tendency for reclassification in men. This finding was consistent with the results of the study by Gepner et al. [21] performed on a population of asymptomatic and non-diabetic subjects, in which the male sex belonged to the predictors of the rise in CV risk for at least 5%. This shows that the assessment of the VA helps identify individuals whose CV risk might be underestimated.

Predictors of the VA exceeding the CA for at least 5 years: Sex differences

The present study revealed a few interesting issues concerning sex differences in predictors of the VA exceeding the CA for at least 5 years. First of all, in our population DM was the only predictor of increased VA common for both men and women (with a stronger influence in females). One of the possible mechanisms that accounts for elevated CV risk and increased VA in individuals with abnormal glucose metabolism leads through increased AS [22]. Then, MS and its components: elevated BMI and WHR were proved to be predictive for increased VA only in females. This could be partly explained by the fact that our female population belonged mainly to the middle-aged group (perimenopausal women) — which is characterized by the clustering of various risk factors. It has been shown in literature that the effect of MS on the development of early atherosclerosis usually expressed by thickened CIMT is more pronounced in women than in men. There have already been a few reports providing evidence that MS accelerates the age-dependent increase in CIMT and AS parameters and that its influence on vascular structure and function is independent of its individual components and results mainly from the clustering of risk factors [23, 24].

In the present study no association between the HDL-C or LDL-C serum levels and VA was established, which might be caused by the fact that

6% of the study population was on lipid-lowering therapy. In the report by Stein et al. [13] HDL-C and LDL-C serum levels were proved to be predictors of the upgrade of the coronary heart disease risk category into the higher one.

The surprising finding of our study was that systolic blood pressure was not a predictor of the VA exceeding the CA for at least 5 years. In the report by Stein et al. [13] systolic blood pressure was proved to be a weak predictor of increased VA (of noteworthy is that in the study by Stein et al. [13] increased VA was the VA exceeding the CA for at least 10 years).

Relationships between AS parameters and VA

Vascular stiffening is an integral part of the “normal” vascular aging. It is mainly caused by the degeneration of elastic lamellae and overproduction of abnormal collagen in the arterial wall [25].

O’Rourke [26] suggests that atherosclerosis should be evaluated in 2 aspects: atherosclerosis which reflects structural changes of the arterial wall and sclerosis — concerned with functional changes. CIMT is a marker of atherosclerosis, while AS reflects sclerosis. The novel high resolution eT method enables simple, noninvasive assessment of the AS and it correlates with the carotid-femoral PWV, which is a gold standard in the assessment of the AS [8]. To our best knowledge, this is the first report concerned with the relationship between AS measured by eT and VA.

In our study AS parameters measured at the CCA correlated with the CA, the finding that was consistent with the literature [27]. One of the strengths of our study was the investigation of the relationship between the AS parameters and CIMT-derived VA. Our novel approach enabled an integrated evaluation of the structural and functional arterial changes. We proved that AS parameters correlated with the VA. Furthermore, we identified the cut-off values of some of the AS parameters that allowed for the prediction of the VA exceeding the CA for at least 5 years (from the ROC curve after adjustment for other risk factors such as: DM, BMI, WHR and CA).

As it was mentioned earlier, AS reflects the process of the physiological vascular aging. However, it can be accelerated by variable damaging factors that interact with the vascular wall throughout the whole life of an individual. The measurement of the AS parameters provides the information on the present condition of the arterial wall. Therefore, the assessment of AS parameters can be a good method for the evaluation of the VA.

Limitations of the study

The present study has an observational, cross-sectional design. The sample was entirely Caucasian. The AS parameters were calculated from algorithms that include the change in CCA diameter and the value of blood pressure measured at the brachial artery not at the CCA, which may affect the measurement of the AS parameters because carotid and brachial pressure is not identical due to the phenomenon of the central to peripheral blood pressure amplification, pronounced especially in young people. Our sample consisted mostly of middle-aged subjects. Because there was no follow-up of the study population, the relationships between the study results and subsequent CV events remains unknown. The significance of the estimation of the VA is still unclear.

Conclusions

The substitution of the VA for the CA may cause the change of the FRS category into the higher one. There are sex-related differences in predictors of increased VA. AS parameters proved to be predictors of increased VA besides the classic risk factors. The results of our study suggest that integrative approach to CV risk assessment — that incorporates markers of structural and functional vascular parameters into risk algorithms — might be beneficial. Future studies will be needed to establish the prognostic value of VA.

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Conflict of interest: none declared

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