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Clinical utility of digital volume pulse analysis in prediction of cardiovascular risk and the presence of angiographic coronary artery disease

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Abstract *Background:* Stiffness Index (SI), assessed by finger photoplethysmography (digital volume pulse analysis), has been suggested as a simple and easy measure of arterial stiffness. However, its potential association with cardiovascular risk and coronary artery disease (CAD) has been little studied. The aims of the study were to investigate the relation of SI with classical risk factors and established arterial stiffness indices and its ability to predict cardiovascular risk and the presence of angiographic CAD.
Methods: We enrolled 126 consecutive patients (mean age 61 years, 74% males) with suspected stable CAD undergoing diagnostic coronary angiography. Cardiovascular risk was assessed using Framingham risk score (FRS) and the European Heart score. Carotid-femoral (PWVcf) and carotid-radial (PWVcr) pulse wave velocity and augmentation index, using applanation tonometry, and SI using finger photoplethysmography, were measured in all patients.
Results: SI was positively correlated with PWVcr ($p = 0.017$) but not with PWVcf. Increased SI (R^2 0.19, $p < 0.001$) was independently associated with higher diastolic blood pressure and male gender. Increased SI and PWVcf were associated with higher FRS and Heart score ($p < 0.05$ for all), while only higher PWVcf was associated with the presence of angiographic CAD ($p = 0.007$).
Conclusions: SI, easily derived using finger photoplethysmography, was related to classical risk factors and peripheral arterial rather than aortic stiffness. SI and PWVcf were the only vascular indices associated with cardiovascular risk, but only PWVcf was related to the presence of

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coronary atherosclerosis. Further research is needed to clarify the value of this useful index of arterial stiffness in risk stratification.

Introduction

Cardiovascular disease (CVD) is one of the most common causes of mortality and morbidity in the western world.[1] Atherosclerosis is the leading cause of CVD and the identification of individuals at high CVD risk has been an important priority of modern medicine. The assessment of CVD risk in clinical practice is currently based on the calculation of "risk scores" such as the Framingham Risk Score (FRS)[2] and the European Heart Score[3] that take into consideration the presence of various established cardiovascular risk factors i.e. age, gender, smoking, blood pressure, lipids and diabetes status. However, in several occasions the estimated risk may be misguiding[4] leading to the search of novel markers that could refine risk stratification. Indices of subclinical atherosclerosis have been suggested to improve prediction of cardiovascular events.[5]

Increased arterial stiffness is thought to occur early in the atherosclerotic process and established measures of arterial stiffness, such as aortic pulse wave velocity (PWV) and augmentation index (AIx), have been shown to be associated with cardiovascular prognosis in several studies and large meta-analyses.[6–11] Increased carotid-femoral PWV (PWVcf)[12–15] and central AIx[12,16] have also been associated with the presence of coronary atherosclerosis in patients undergoing coronary angiography. Digital volume pulse (DVP) analysis using finger photoplethysmography is a non-invasive method for evaluating arterial stiffness with high reproducibility and low inter-observer variability.[17] Stiffness index (SI), derived by contour analysis of the digital pulse, is considered to be a measure of arterial stiffness[17] and has been previously associated with aortic PWV.[18,19] However, very few data exists associating this index to cardiovascular risk scores,[20–22] while its usefulness for risk stratification and the prediction of the presence of coronary atherosclerosis, especially in comparison to established arterial stiffness indices, has not been previously studied.

The aims of the present study were to investigate the association of SI with i) classical risk factors, ii) established arterial stiffness indices such as PWV and AIx derived by arterial tonometry and iii) cardiovascular risk (as assessed by FRS and Heart Score) and the presence of significant angiographic coronary artery disease (CAD), in high risk patients with suspected stable CAD undergoing diagnostic coronary angiography.

Methods

Study patients and design

One hundred thirty seven consecutive subjects referred for diagnostic coronary angiography due to suspected stable CAD were enrolled in the current study. Anginal symptoms on exertion and/or a positive non-invasive stress test indicating a high risk for stable CAD were the main reasons for referral. Patients with suspected or documented acute coronary syndrome, any history of previously established cardiovascular disease (including CAD, cerebrovascular and symptomatic peripheral vascular disease), valvular heart disease, prosthetic valves, congenital heart disease, hypertrophic obstructive cardiomyopathy, atrial fibrillation, as well as those on hemodialysis were excluded from the study.

Upon enrollment all subjects were asked about their medical history, presence of cardiovascular risk factors and use of any medication. A complete physical examination was performed before coronary angiography. Blood samples were drawn from all patients early in the morning after an overnight fast and just before coronary angiography. Measurement of vascular indices was performed in the morning before coronary angiography. Subjects whose pulse wave recordings could not be adequately assessed ($n = 11$) were excluded from the final analysis.

The study protocol was approved by the Ethics Committee of the University Hospital of Ioannina, Greece. The study complied with the Declaration of Helsinki and all participants provided written informed consent.

Cardiovascular risk factor assessment

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). The minimum waist circumference between the pelvic brim and the costal margin was measured. Smokers were defined as those who were smoking at the time of enrollment or those who had stopped for less than 12 months. Office blood pressure (BP) was measured in the sitting position after 5 min of rest using an automated brachial sphygmomanometer (Omron M7, Omron Healthcare Co, Kyoto, Japan) and the mean of three consecutive measurements by a trained operator was reported. Hypertension was defined as office measured systolic blood pressure (SBP) $>$ 140 mmHg and/or diastolic blood pressure (DBP) $>$ 90 mmHg or administration of anti-hypertensive medications. Hypercholesterolemia was defined as low density lipoprotein cholesterol (LDL-c) $>$ 115 mg/dl or administration of anti-cholesterolemic medications. Diabetes mellitus was defined as a fasting blood glucose concentration $\geq$ 126 mg/dl or administration of anti-hyperglycemic medications. Creatinine clearance was estimated using the Modification in Diet in Renal Disease (MDRD) formula.[23] Fasting plasma glucose, serum lipids and creatinine were measured using standard methodology.

FRS is a multivariate risk function that predicts 10-year risk of developing coronary events[2]; a risk score of $<$10%, 10–20% and $>$20% indicates low, intermediate and high risk respectively. The risk factors included in FRS are age, gender, smoking, blood pressure, total and high density

lipoprotein (HDL) cholesterol and diabetes. Accordingly, the European Heart Score predicts 10-year risk for developing a fatal cardiovascular event[3]; a risk score of <1%, 1—<5%, 5—10% and ≥10% indicates low, intermediate, high and very high risk respectively. Risk factors included in the Heart Score are age, gender, smoking, systolic blood pressure, total and HDL cholesterol. Patients with diabetes are considered to be at high risk according to the European Society of Cardiology guidelines on cardiovascular prevention.[24]

Coronary angiography

Coronary angiography was performed according to the standard Judkins technique. Significant CAD was defined as ≥50% stenosis in the internal diameter of at least one coronary artery (≥30% for the left main coronary artery). All coronary angiograms were visually assessed by two experienced angiographers and a consensus was reached. Reviewers were blinded to the results of vascular indices.

Measurement of vascular indices

All measurements were performed following an overnight fast (subjects were also asked to refrain from smoking and caffeine use for at least 6 h) and before the administration of scheduled medications. Measurements were taking place in a quiet, temperature controlled room (~22 °C) after a brief period of rest by a single operator who was blinded to the results of coronary angiography and other findings.

Pulse wave velocity and central augmentation index

Assessment of PWVcf, carotid-radial (PWVcr) and AIx was performed in the supine position non-invasively with the commercially available Sphygmocor system (Version 7.01, At Cor Medical, Sydney, Australia) using applanation tonometry as previously described[15,25,26] by a single operator who was blinded to the results of coronary angiography and other findings. Pressure waveforms were recorded from the carotid and femoral arteries for the measurement of PWVcf (and from the carotid and radial arteries for the measurement of PWVcr) and wave transit time (t) was calculated by the system software, using the R wave on the simultaneously recorded electrocardiogram as reference frame. PWV was calculated as distance/transit time and the distance traveled by the pulse wave was estimated as the distance between the two recording sites measured over the body surface minus the distance from the suprasternal notch to the carotid. Central aortic pressure waveforms were generated from the right radial artery pressure waveform using a previously validated transfer function. The central pressure waves were analyzed to calculate augmentation index (AIx). AIx was calculated as the difference between the second and first systolic peaks observed on the central pulse waveform and expressed as a percentage of the central pulse pressure corrected for heart rate (AIx@75). Only high quality recordings with acceptable curves on visual inspection and quality index ≥ 80% as provided by the software were included in the analysis. In studies performed on two separate days (8—12 days apart) in 12 subjects by a single operator, the within-subject coefficient of variation of PWVcf, PWVcr and AIx@75 were 5.6%, 5.1% and 12.0% respectively.

Stiffness index (digital volume pulse contour analysis)

Digital volume pulse (DVP) contour analysis was performed after rest in a supine position with the PulseTrace device (Micro Medical, Gillingham, Kent, UK), a system that uses a high-fidelity photoplethysmography finger probe. The amount of light transmitted is indirectly proportional to the blood volume in the finger pulp; changes in blood finger blood volume with pulse wave produce relevant changes in light transmission. The DVP waveform consists of a systolic peak and a second diastolic peak which is formed by the reflection of the pulse wave from the small arteries in the lower body distally.[18] The time delay between the systolic and diastolic peaks [peak-to-peak time (PPT)] is expected to depend on the speed of the pressure waves traveling-from the root of the subclavian artery to the sites of reflection and back to the subclavian artery and the path length of the travelling waves that has been assumed to be proportional to the individual's height (h). Stiffness Index (SI), calculated as h/PPT, has therefore been proposed as an index of large artery stiffness. Each person had at least three measurements (recorded for 30 s) taken 1 min apart and an average was calculated and used for the analysis. Subjects whose DVP recordings could not be adequately assessed or had highly variable measurements were excluded. In studies performed on two separate days (8—12 days apart) in 15 subjects by a single operator, the within-subject coefficient of variation of SI was 6.9%.

Statistical analysis

Continuous variables are presented as mean ± SD. Kolmogorov—Smirnov Z-test was used to determine the normal distribution of continuous variables; glucose levels were not normally distributed and data are presented as median (min, max). Univariate associations of vascular indices with cardiovascular risk factors (or between the various vascular indices) were assessed using Pearson's and Spearman's correlation coefficients. Stepwise linear regression analysis was used to identify independent predictors of vascular indices; variables whose univariate associations with vascular indices achieved near statistical significance (i.e. $p < 0.1$) were used in multivariate analysis. Logistic regression analysis was used to assess associations of vascular indices with cardiovascular risk estimates and the presence of significant CAD. The Area Under the Curve (AUC) of regression models were calculated and their predictive accuracy was compared using the methodology described by Hannley and McNeil (c-statistic).[27] p values were always two-sided and a value of $p < 0.05$ was considered significant. The SPSS statistical software package (version 15.0 for Windows, SPSS Inc. Chicago, IL, USA) was used.

Results

Table 1 shows the characteristics and cardiovascular profile of the 126 subjects included in the final analysis. Of these patients, 74% were males, 36% were currently smoking, 38% had type 2 diabetes, 75% had hypertension and 86% had hypercholesterolemia. According to the FRS and European Heart score, 37% and 25% of our population respectively was classified as high or very high risk for future CAD events (FRS $>$ 20%) or cardiovascular death (Heart score $>$ 5%) in the next 10 years. Presence of significant angiographic CAD was found in 41% of our patients.

Univariate associations of various vascular indices with cardiovascular risk factors are shown in Table 2. In multivariate analysis, 1) SI (R^2 0.19, $p < 0.001$) was independently associated with diastolic blood pressure (B 0.08, $p < 0.001$) and male gender (B 1.17, $p = 0.004$), 2) PWVcf (R^2 0.29, $p < 0.001$) was independently associated with age (B 0.07, $p < 0.001$) and systolic blood pressure (B 0.03, $p = 0.004$), 3) PWVcr (R^2 0.19, $p < 0.001$) was independently associated with diastolic blood pressure (B 0.03, $p = 0.001$) and male gender (B 0.44, $p = 0.033$) and 4) AIx (R^2 0.34, $p < 0.001$) was independently associated with height (B −0.24, $p = 0.016$), male gender (B −5.47, $p = 0.007$), systolic blood pressure (B 0.12, $p = 0.003$) and waist circumference (B −0.14, $p = 0.04$).

SI was positively correlated with PWVcr (r 0.212, $p = 0.017$), while a trend for a significant association with AIx (r 0.163, $p = 0.069$) was also found. SI did not correlate with PWVcf (p = NS). PWVcf was positively correlated with PWVcr (r 0.280, $p = 0.002$) and AIx (r 0.188, $p = 0.036$) while PWVcr was also positively correlated with AIx (r 0.197, $p = 0.028$).

Associations of vascular indices with cardiovascular risk estimates and the presence of CAD are shown in Table 3. Increased SI and PWVcf were associated with higher estimated risk for CAD events (OR 1.59, 95% CI 1.08, 2.35, $p = 0.020$ and OR 1.68, 95% CI 1.14, 2.47, $p = 0.009$ per 1 SD increase for SI and PWVcf respectively) as assessed by FRS and with higher estimated risk for cardiovascular mortality (OR 1.61, 95% CI 1.07, 2.43, $p = 0.023$ and OR 1.78, 95% CI 1.18, 2.69, $p = 0.006$ per 1 SD increase for SI and PWVcf respectively) as assessed by Heart score. The accuracy of SI and PWVcf for identifying high risk individuals according to FRS (AUC 0.658 vs 0.624 respectively for SI and PWVcf) and Heart score (AUC 0.662 vs 0.654 respectively for SI and PWVcf) did not differ significantly ($p > 0.05$ for both comparisons). Presence of angiographic CAD was associated only with increased PWVcf (OR 1.72, 95% CI 1.16, 2.54, $p = 0.007$ per 1 SD increase); none of the other vascular indices was associated with the presence of CAD.

Table 1 Characteristics of the study population ($n = 126$).

Age, years	61 ± 10
Male gender, *n* (%)	93 (74)
Smoking, *n* (%)	45 (36)
Hypertension, *n* (%)	94 (75)
Hypercholesterolemia, *n* (%)	108 (86)
Diabetes mellitus, *n* (%)	48 (38)
Body mass index, kg/m^2	28.9 ± 4.0
Height, cm	168 ± 9
Waist circumference, cm	104 ± 11
Systolic blood pressure, mmHg	142 ± 17
Diastolic blood pressure, mmHg	81 ± 10
Estimated GFR, ml/min/1.73 m^2	74.3 ± 12.4
Glucose, mg/dl	106 (71, 348)
Total cholesterol, mg/dl	208 ± 49
HDL cholesterol, mg/dl	48 ± 13
Triglycerides, mg/dl	130 ± 59
LDL cholesterol, mg/dl	134 ± 45
High risk patients, *n* (%)	
Framingham risk score $>$ 20%	47 (37)
Heart score $\geq$ 5%	32 (25)
Heart rate, beats/min	67 ± 9
Pulse wave velocity carotid-radial, m/sec	7.5 ± 1.1
Pulse wave velocity carotid-femoral, m/sec	9.7 ± 2.2
Augmentation index, %	22.5 ± 9
Stiffness index, m/sec	9.9 ± 2.2
Presence of coronary artery disease, *n* (%)	52 (41)

Continuous data are presented as mean ± standard deviation or median (range).
GFR = glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein.

Discussion

Stiffness Index, assessed by DVP analysis using photoplethysmography, has been previously suggested as a measure of arterial stiffness.[18] Its simple, easy and rapid acquisition in the finger would make it a very appealing tool in the evaluation of cardiovascular risk via the assessment of arterial stiffness. However, the use of SI in clinical practice is very limited compared to other indices of arterial stiffness. Applanation tonometry has been widely used for several decades to derive PWVcf and PWVcr, indices of aortic and peripheral arterial stiffness, and AIx, a more complex index determined both by the aortic stiffness and the reflections of the pulse wave from the peripheral circulation. PWVcf and AIx have been extensively studied in relation to cardiovascular risk factors and independently associated with cardiovascular prognosis.[9,10]

In the present study, increased SI was associated with higher blood pressure (especially diastolic blood pressure) and male gender. The association of blood pressure (systolic, diastolic or mean blood pressure) with SI has been previously reported[18,28] and depicts the major effect of blood pressure on arterial stiffness indices. This effect was also confirmed by our results; an independent association of PWVcf and AIx was found with systolic blood pressure, while PWVcr was associated with diastolic blood pressure. Higher SI in male patients may be attributed to higher stature compared to women since height is the nominator in the formula used to calculate SI, while males were also found to have higher PWV in peripheral muscular arteries (PWVcr). Interestingly, in contrast to previous studies,[18,28]

Table 2 Univariate and multivariate associations of vascular indices with cardiovascular risk factors.

		Univariate analysis		Multivariate analysis	
		Correlation coefficient (r)	p value	B coefficient (95% CI)	p value
SI, m/sec	Diastolic blood pressure, mmHg	0.368	<0.001	0.08 (0.05, 0.12)	<0.001
	Systolic blood pressure, mmHg	0.239	0.007	–	–
	Male gender, yes/no	0.211	0.018	1.17 (0.38, 1.96)	0.004
	Smoking, yes/no	0.191	0.032	–	–
PWVcf, m/sec	Systolic blood pressure, mmHg	0.355	<0.001	0.03 (0.01, 0.05)	0.004
	Heart rate, beats/min	0.350	<0.001	–	–
	Age, years	0.337	<0.001	0.07 (0.03, 0.10)	<0.001
	Hypertension, yes/no	0.275	0.002	–	–
	Glucose, mg/dl*	0.156	0.082	–	–
	Diabetes, yes/no	0.153	0.087	–	–
	LDL cholesterol, mg/dl	−0.151	0.090	–	–
AIx, %	Height, cm	−0.490	<0.001	−0.24 (−0.44, −0.05)	<0.016
	Male gender, yes/no	−0.460	<0.001	−5.47 (−9.45, −1.50)	0.007
	HDL cholesterol, mg/dl	0.327	<0.001	–	–
	Age, years	0.258	0.004	–	–
	Systolic blood pressure, mmHg	0.224	0.012	0.12 (0.04, 0.20)	0.003
	Waist circumference, cm	−0.225	0.013	−0.14 (−0.26, −0.01)	0.04
	Diastolic blood pressure, mmHg	0.202	0.024	–	–
	Smoking, yes/no	−0.173	0.054	–	–
	Heart rate, beats/min	0.172	0.055	–	–
PWVcr, m/sec	Diastolic blood pressure, mmHg	0.336	<0.001	0.03 (0.02, 0.05)	0.001
	Heart rate, beats/min	0.286	0.001	–	–
	Systolic blood pressure, mmHg	0.227	0.01	–	–
	Age, years	−0.192	0.031	–	–
	Male gender, yes/no	0.168	0.060	0.44 (0.04, 0.85)	0.033

*Natural logarithm used in analysis. Only variables with a $p < 0.1$ in the univariate analysis are shown.
AIx = augmentation index, CI confidence interval; PWVcf = pulse wave velocity carotid-femoral; PWVcr = pulse wave velocity carotid-radial; SI stiffness index.

SI was not related to age. However, our population consisted mostly of patients >50 years old (>90%), while previous studies included healthier and younger patients and increasing SI with aging was more prominent in age groups <55 years old.[18]

Regarding the applanation tonometry derived indices, our results are in accordance with previous studies. The main determinants of PWVcf were age and systolic blood pressure,[29] while AIx was associated with systolic blood pressure[30,31] and female gender,[32] and inversely with height[33] and central obesity probably due to decreased peripheral wave reflections.[15] PWVcr was mainly determined by diastolic blood pressure and gender as discussed above; these associations have not been previously reported.[34]

In the current study, SI was found to be associated with peripheral arterial stiffness of the upper limb (PWVcr), while there was a trend for a significant association with AIx. SI was not related to aortic stiffness (PWVcf), although previous studies have reported a modest correlation of SI with PWVcf ($r = 0.54–0.65$).[18,19] Furthermore, SI shared common determinants with PWVcr. As both SI and PWVcr are recorded using the upper limb, this finding may be expected, but has not been previously reported. These results indicate that SI may not be an appropriate method for the evaluation of central aortic stiffness as has been previously suggested,[19] at least in populations similar to ours (i.e. older and high risk populations), and may be a more complex index of vascular stiffness than originally thought. A strong association of SI with AIx ($r = 0.80$) and small artery elasticity ($r = -0.65$) has been previously reported,[19] supporting our suggestion that peripheral artery stiffness and peripheral pulse wave reflections may be important determinants of SI. Further studies in larger populations are needed to clarify this association.

SI and PWVcf were the only vascular indices associated with higher cardiovascular risk estimates as assessed by both FRS and European Heart score. Although the prognostic value of PWVcf is well established[6,8,9] and its use for cardiovascular risk assessment is recommended in clinical practice according to current guidelines,[35] SI has been associated with cardiovascular risk estimates only in few small studies.[21,22] The results of the present study showed that increasing SI and PWVcf by 2.2 m/sec (i.e. 1 SD, same for both indices) led to ca. 60% and 70% respectively higher probability of being at high risk for future cardiovascular events. Furthermore, we showed that SI and PWVcf could identify high risk individuals with a similar accuracy. On the other hand, SI was not found to be associated with the presence of coronary atherosclerosis, an association not previously studied. Only PWVcf was found to be associated

Table 3 Univariate associations of vascular indices with cardiovascular risk estimates and the presence of coronary artery disease.

	High risk FRS, yes/no	High/very high risk heart score, yes/no	Coronary artery disease, yes/no
SI, m/sec	OR 1.59	OR 1.61	OR 0.99
	p = 0.020	***p = 0.023***	$p = 0.952$
PWV carotid-femoral, m/sec	OR 1.68	OR 1.78	OR 1.72
	p = 0.009	***p = 0.006***	***p = 0.007***
PWV carotid-radial, m/sec	OR 1.18	OR 1.14	OR 1.00
	$p = 0.382$	$p = 0.516$	$p = 0.996$
AIx, %	OR 0.89	OR 1.04	OR 0.87
	$p = 0.527$	$p = 0.867$	$p = 0.460$

Data are presented as OR per 1 standard deviation of vascular indices.
AIx = augmentation index; FRS = Framingham risk score; OR = odds ratio; PWV = pulse wave velocity; SI = stiffness index.
Bolditalics represent significant associations (i.e. $p < 0.05$).

with the presence of significant angiographic CAD in our population, an association reported by other studies,[12–15] further supporting the established value of aortic stiffness in the prediction of cardiovascular risk. These findings indicate that SI, an easily measured and highly reproducible vascular index, could prove to be helpful in the prediction of cardiovascular risk, but larger studies are needed to investigate its potential prognostic role.

In conclusion, the digital volume pulse analysis-derived SI was found to be related to peripheral arterial rather than aortic stiffness suggesting that SI may not be an appropriate index for the evaluation of aortic stiffness, at least in older high risk patients. Both SI and PWVcf were found to have a similar accuracy in the discrimination of patients at high cardiovascular risk, but only PWVcf was associated with the presence of significant angiographic CAD in our population. More research is needed to define the role of this potentially useful index of arterial stiffness in the prediction of cardiovascular risk.

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Conflict of interest

None of the authors has any conflict of interest related to this article.

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