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Cardiovascular event risk in relation to arterial stiffness in patients with subclinical peripheral atherosclerosis

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Abstract. Introduction: Arterial stiffness is an independent predictor for general and cardiovascular morbidity and mortality. Peripheral atherosclerotic disease is more frequently associated with systolic hypertension, therefore wider pulse pressure is suggestive to arterial stiffness. Our study evaluates the relationship between arterial stiffness and cardiovascular event risk, estimated by the Framingham risk score, in patients with infraclinic peripheral atherosclerosis. Material and method: A total of 43 subjects with multiple cardiovascular risk factors and peripheral atheromatosis were evaluated. The Framingham risk score was calculated and the arterial stiffness was assessed by using brachial pulse pressure (PP) and digital volume pulse analysis, which determines the stiffness index (SI_{DVP}). Results: We found that 20.93% of patients had less then 5% risk of cardiovascular events during 10 years, although atherosclerotic disease was already present at peripheral level. We also found strong correlation ($p<0.05$) between PP and SI_{DVP}, although the relationship with risk factors was different. Thus, the arterial stiffness was correlated with age ($p=0.012$) and with the presence of hypertension ($p=0.005$), if appreciated by PP, respectively with smoking ($p=0.003$), if appreciated by SI_{DVP}. Between subgroups composed by sex criteria, there were statistically significant differences in Framingham risk scores ($p=0.001$), but no differences in arterial stiffness. Both PP and the SI_{DVP} had a progressive growth in risk levels, with a statistically significant correlation with the Framingham score ($p=0.04$ for PP, $p=0.002$ for SI). Conclusion: In subclinical stage of peripheral atherosclerotic disease, the cardiovascular event risk, estimated by the Framingham risk score, is correlated with the level of arterial stiffness.
Key Words: arterial stiffness, cardiovascular risk, peripheral atherosclerosis, digital volume pulse analysis.

Rezumat. Introducere: Rigiditatea arterială este un factor predictiv independent pentru morbiditatea şi mortalitatea de cauză cardiovasculară şi generală. Boala arterială aterosclerotică periferică este mai frecvent asociată cu forma sistolică de hipertensiune arterială, sugerând rigiditate arterială crescută. Studiul nostru a evaluat relaţia între rigiditatea arterială şi riscul de evenimente cardiovasculare, apreciat prin scor Framingham, la pacienţi cu ateroscleroză periferică în etapa infraclinică. Material şi metodă: Au fost evaluaţi 43 de subiecţi cu multiplii factori de risc cardiovasculari şi boală aterosclerotică periferică prezentă, în stadiul infraclinic. S-au determinat scorul de risc pentru evenimente cardiovasculare Framingham şi rigiditatea arterială (prin presiunea pulsului la brahială şi indicele de rigiditate prin fotopletismografie digitală). Rezultate: 20.93% dintre pacienţi au un risc <5% de evenimente cardiovasculare la 10 ani, deşi boala aterosclerotică este deja prezentă la nivel periferic. Există o corelaţie puternică între cele două metode de apreciere a rigidităţii ($p<<0.05$), chiar dacă relaţia cu factorii de risc este diferită. Astfel, rigiditatea arterială se corelează cu vârsta ($p=0.012$) şi prezenţa hipertensiunii ($p=0,005$), dacă se apreciază prin presiunea pulsului, respectiv cu fumatul ($p=0.003$), dacă se apreciază prin indicele de rigiditate. Între subloturile alcătuite pe criteriul sexului există diferenţe semnificative de risc Framingham ($p=0.001$ pentru un nivel de semnificaţie de 0.05), nu însă şi de rigiditate arterială. Atât presiunea pulsului, cât şi indicele de rigiditate, au avut o creştere progresivă cu nivelele de risc, realizând o relaţie statistic semnificativă cu scorul Framingham ($p=0.04$ pentru un nivel de semnificaţie de 0.05 pentru PP, respectiv $p=0.002$ pentru SI, pentru un nivel de semnificaţie de 0.01). Concluzie : În stadiul infraclinic de boală aterosclerotică periferică, riscul de evenimente cardiovasculare, apreciat prin scorul Framingham, se corelează cu nivelul de rigiditate arterială.
Cuvinte cheie: rigiditate arterială, risc cardiovascular, ateroscleroza periferica.

Introduction. During last years, more and more proofs have been accumulated that support the idea that arterial stiffness is an independent predictor for cardiovascular and general morbidity and mortality (Laurent & Boutouynie 2007). These findings were initially made on patients with essential hypertension (HT), type II diabetes mellitus (DM) and end-stage renal disease (Laurent et al 2006). Recently, these observations were also extended to older people and even in general population (Shokawa et al 2005; Willum-Hausen et al 2006).

Among all localizations of atherosclerotic disease, the peripheral atherosclerotic disease (PAD) is best characterized by the association with higher levels of systolic blood pressure (SBP), modified arterial stiffness, and alteration of the reflected pulse wave (Van Popele 2001; Safar 2007; Makin et al 2001). Researches on patients with PAD proved that these patients usually present higher levels of blood pressure (BP) when compared with subjects the same age without PAD. At the moment when PAD is diagnosed, 35-55% of subjects are hypertensive (Makin et al 2001). While systolo-diastolic HT is more often identified with coronary heart disease and cerebrovascular disease, PAD is associated with isolated systolic HT (Safar et al 2008).

With ageing, there is a natural amplification of the pulse wave in the entire arterial tree. The growth of central pulse pressure (PP) is more important when it is compared with brachial PP (Hamilton et al 2007; Oliver & Webb 2003). Thus, in a sample of mid-life patients with PAD, the detection of a high level of SBP and PP at brachial level is suggesting even a more important increase at central level, with implications for the cardiovascular risk.

There are researches concerning altered viscoelastic properties at femoral and carotid level in patients with PAD. These results, corroborated with morphologic modifications of the intima-media complex at carotid and/or femoral level, suggests that there are bidirectional implications between arterial stiffness and atherosclerosis (ATS) (Safar et al 2003).

Therefore, we formulated the hypothesis that, in the subclinical phase of PAD, the study of arterial stiffness could bring new informations on a more aggressive evolution of atherosclerotic disease, by inter-conditioning between ATS and arterial stiffness.

The goal of our study was to evaluate the relation between arterial stiffness and risk of cardiovascular events, evaluated by the Framingham risk score, in patients with subclinical PAD. At the same time, by using two different methods to assess arterial stiffness (brachial PP and stiffness index through digital volume pulse analysis-SI_{DVP}), we evaluate their relationship with traditional risk factors (RF) in predictability for cardiovascular events.

Material and Method

Selection of patients. We conducted a study on hospitalized patients in the 5th Medical Clinic, part of Municipal Clinic Hospital of Cluj-Napoca, from October 2007 to March 2008. Patients with multiple risk factors, but no history of cardiac disease or symptoms for peripheral arterial disease were assessed, using vascular ultrasound and ankle-brahial index. The patients, who had DM as RF for ATS were excluded, because in DM a particular PAD form, can develop (association of macroangiopaty, medial calcinosis and microangiopaty), with consequence in the arterial stiffness and ankle-brahial index level.

Finally, 43 non-diabetic patients with peripheral subclinical atherosclerosis and normal ankle-brahial index were selected. In the selected group, clinical and laboratory data for traditional RF (age, sex, family history, body-mass index-BMI, smoking, total cholesterol and serum lipid fractions) were collected.

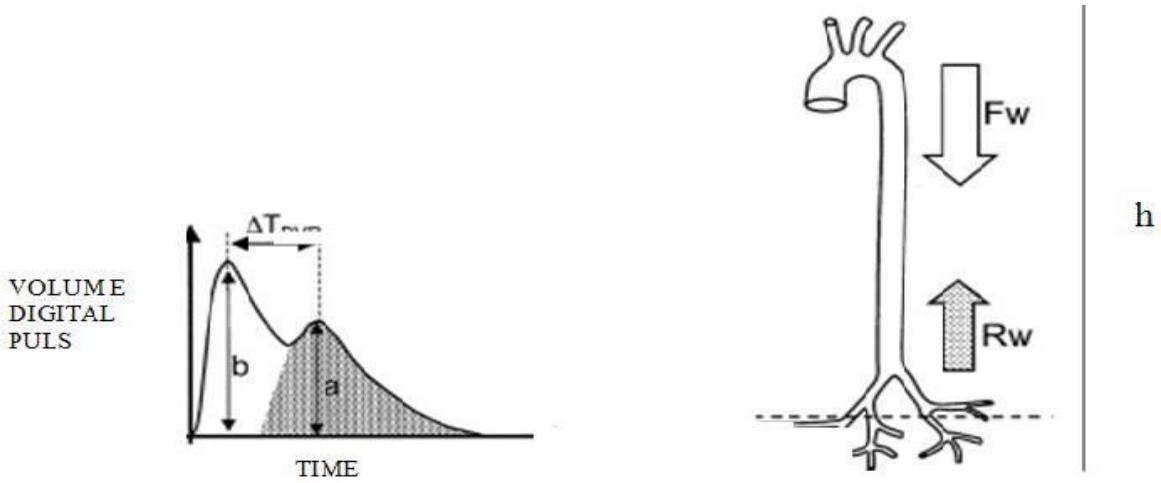
Eco-Doppler arterial evaluation. Arterial ultrasound evaluation was conducted with an Aloka SSD 4000 unit, using a linear transducer with variable frequency 7-10 MHz. The presence of ATS plaques in femoral, popliteal or diffuse infrainguinal arteries was identified. The ATS plaque was defined as the focal thickening of the wall at least 50% or greater than 1.5 mm than that of the surrounding wall. (Roman et al 2006). Also, using a continuous Doppler Siemens device and a sphygmomanometer with calibrated mercury,

arterial pressures were detected at the level of extremities arteries. The ABI was determined, as ratio between pressures at the level of tibial and radial artery. If the ratio was between 0.9–1.3 the patient was considered eligible for inclusion into the sample.

Arterial stiffness evaluation. Two methods were used in evaluation of arterial stiffness for patients included: PP and SI_{DVP}.

PP was determined based on the values of SBP and DBP at the level of brachial artery, using the formula PP=SBP-DBP. A sphygmomanometer with calibrated mercury was used, at the level of right arm. The cuff of the sphygmomanometer was addapted to the circumference of the arm. After 10-minutes rest, three determinations were made, taking into account the average value.

SI_{DVP} was determined using a digital photopletismograph (Pulse Trace PCA2, Micro medical, Rochester, UK). Pulse Trace PCA2 estimates large arteries stiffness, analysing digital volume pulse obtained by measuring infrared light transmission through the finger (photoplethysmography). This device uses an optimization system of transmission, so that determination is independent of the variation of the volume of blood from finger and the dimension of person's finger.



Time variation of digital pulse volume

Anterograde (Fw) and retrograde (Rw) pulse wave

Figure 1. Parameters used to calculate SI_{DVP}

SI_{DVP} results from the formula $SI_{DVP} = h/\Delta T$ [where h is the height of the patient, andΔT is the time between the systolic peak (b) and the diastolic peak (a) of pulse wave at the finger level] (fig.1). SI_{DVP} by digital photopletismography was obtained by analyzing 10 consecutive cardiac cycles, with the patient in the supine position, after 10-minutes rest. SI_{DIV} is an estimate of the pulse wave velocity (PWV) in large arteries, and is regarded as a measure of large artery stiffness (Millaseau et al 2002; Wikretowicz 2009).

This method is extremely easy, operator independent, with excellent tolerance. The expert consensus document on arterial stiffness in 2006 has appreciated this method as having epidemiological applicability (Laurent et al 2006).

Determination of the risk score for coronaries events. For the patients included into the study, based on RF determinations, we established the Framingham risk score for cardiovascular events.

Framingham risk score is a tool for calculating the risk for coronary events in 10 years, proposed by the NATIONAL CHOLESTEROL EDUCATIONAL PROGRAM, through the third report of the experts on detection, evaluation and treatment of hypercholesterolemia for adults (ATP III) (NCEP 2002). The score is designed to estimate the risk of coronary events (myocardial infarction and coronary deaths) in adults aged over 20 years, that don't have manifest cardiac disease. We used a Framingham risk

score variant, designed for calculating the risk for coronary events in non-diabetic patients. Determination of this score is possible through an on-line calculator that can be find to the address: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.

Statistical analysis. All statistical calculations and tests were implemented using SPSS 12. The characteristics of the study were converted into statistical variables of quantitative and qualitative type. We had both ordinal and categorical qualitative variables. Thus, to analyze correlations we used Spearmann's rho and Kendall tau correlation tests. To compute the statistical hypothesis regarding comparisons between groups we used the Student t-test for parametric comparisons and Mann-Whitney U-test and Wilcoxon W test for nonparametric situations. In our statistical decisions we needed a parametric test for equality of variances. We computed this using Levene's test. For the parametric indicators of centrality, the confidence intervals were calculated on a 95% level of significance.

Results. In the studied sample, there was a relatively balanced distribution from the point of view of sex (23 men versus 20 women). Most patients were hypertensive and had cardiovascular AHC. The characteristics of the sample can be observed in Table 1.

Table 1

The risk factors in the analyzed group (n=43)

Risk factors	*Value (N +/- standard deviation or %)*
Average age (years)	60.302 $\pm$ 7.787
Sex male/female	23/20
Smoking	17 (39.5%)
Family history	26 (60.4%)
IMC (kg/m^2)	29.36$\pm$4.7157
HTA	39 (90.7%)
Cholesterol total (mg/dl)	227.25$\pm$49.9247
HDL-cholesterol (mg/dl)	55.5348$\pm$14.76
Triglyceride (mg/dl)	145$\pm$75.5

Traditionally, the Framingham levels of risk are divided in three intervals: <10%, 10-20% and >20%. An analysis regarding accuracy of Framingham risk score in predicting coronary events (Brindle 2006) established that this tool provides an underestimated risk in the high risk level, and an overestimate risk in the low risk level. In our study we considered for analysis, as "high level" of risk a Framingham score >15%. Proceeding in this way, we have introduced a degree of favourable error, in the sense of overestimating the risk in the subgroup of high risk. In the same time, we considered as "low risk" Framingham risk as <5% (Scott 2009), introducing in this way a degree of favourable error, in the sense of underestimating risk in the subgroup of low risk.

Table 2

Distribution of the patients in risk levels

	Number of patients		
	Low risk	Medium risk	High risk
Framingham risk score -traditional levels-	19	16	8
Framingham risk score -our levels-	9	21	13

As it can be seen in Table 2, using our risk score levels, in the high-risk category, imposing appropriate prophylactic measures for ATS disease, more patients than accordingly to the traditional Framingham score (>20%) were included (13 vs. 8 patients). Also, in the low-risk category, fewer patients with no prophylactic measures for ATS disease remained (9 vs. 19 patients).

Average values and standard deviations of two parameters of arterial stiffness can be observed in table 3.

Table 3

Average values ± standard deviation for the parameters of arterial stiffness

PP(mmHg)	*59.42 ± 18.3*
SI_{DVP} (m/s)	10.19 ± 2.08

We found a strong correlation, statistically significant between PP and SI_{DVP} ($p<0.05$), as tools for evaluation of arterial stiffness. We found this in the conditions that traditional RF had a variable behaviour in correlation with arterial stiffness, different for the two parameters. Thus:

- PP was statistically significant correlated with age ($p=0.012$) and with the presence of HTA ($p=0.005$),
- SI_{DVP} was statistically significant correlated with smoking ($p=0.003$)

Other analyzed RF, namely lipid fractions, IMC, AHC, had not presented significant correlations with arterial stiffness evaluated by PP and SI_{DVP}.

We have also analyzed the relation of arterial stiffness with the risk levels <5%, 5-15%, >15% of Framingham score. As can be seen in Fig. 2, both PP and SI_{DVP} had a progressive growth in relation with Framingham score, in all three risk levels.

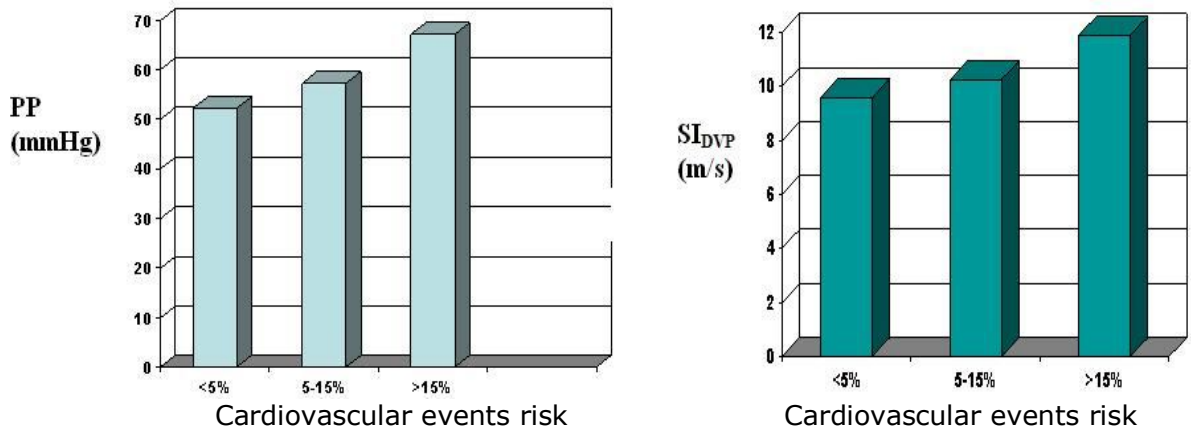


Figure 2. Relation of PP and SI_{DVP} with the groups of risk Framingham

From a functional point of view, the level of arterial stiffness was correlated variably, depending on the method we used, with the presumed incidence of cardiovascular events (Table 4). Thus, the Framingham risk score:

- statistically significant correlated ($p=0.04$) with PP for a significance level 0.05
- statistically significant correlated ($p=0.002$) with SI for a significance level 0.01

The relatively balanced distribution in the sample, from the gender point of view, allowed a division and a comparative analysis between subgroups composed on these criteria.

Thus, in subgroups of women and men we haven't found statistically significant differences between the characteristics of stiffness (PP, SI_{DVP}) taken into study, Table 5.

Table 4

Correlation between the parameters of stiffness and Framingham score

			PP	*SI*	*Framingham*
Speaman's rho	PP	Correlation Coefficient	1.000	.216	.314
		Sig.(2-tailed)		.154	.040
		N	43	43	43
	SI	Correlation Coefficient	.216	1.000	.483
		Sig.(2-tailed)	.164		0.02
		N	43	43	43
	Framingham	Correlation Coefficient	.314*	.483**	1.000
		Sig.(2-tailed)	.040	0.002	
		N	43	43	43

*0.05 level of significance; ** 0.01 level of significance

Table 5

Comparison between subgroups of men/women related to stiffness parameters

		Levene's test for Equality of Variances		*t-test for Equality of Means*						
		F	Sig.	t	df	Sig.(2-tailed)	Mean difference	Std. Erorr Difference	95% Confidence Interval of the Difference	
									Lower	Upper
PP_B_F	Equal variances assumed	0.0	.989	1.031	41	.309	5.7687	5.58997	-5.52831	17.05005
	Equal variances not assumed			1.031	40.281	.309	4.7687	5.58843	-5.53187	17.05361
SI_B_F	Equal variances assumed	2.7	.105	-1.221	41	.229	-.77598	.63527	-2.06894	.50698
	Equal variances not assumed			-1.258	38.111	.216	-.77598	.61704	-2.02499	.47303

In the meantime, the Framingham risk score was statistically significant different between different gender subgroups (p=0.001 for a level of significance 0.05), higher values being registered for the men's subgroup, Table 6.

Table 6

Statistical comparison between subgroups men/women related to Framingham score

	factor_gender	*N*	*Mean rank*	*Sum of ranks*
Framingham_group_gender	.00	20	15.770	314.00
	1.00	23	27.48	632.00
	Total	43		
			Framingham_group_gender	
Mann-Whitney U			104.000	
Wilcoxon W			314.000	
Z			-3.333	
Asymp. Sig. (2-tailed)			.001	

Discussion. Cardiovascular diseases represent the main cause of morbidity and mortality in modern society. There are numerous consensuses regarding risk stratification for these diseases. Basically, they all evaluate the traditional RF such as age, smoking, the level of arterial pressure, cholesterol, or glycaemia. However, defining the target of the treatment is dynamic. The proof is the periodical adjustment of the levels for therapeutic target, in the same time with the appearance of a new consensus of the experts.

Actual recommendations, based on the traditional risk scores, impose differential therapeutic sanctions, depending on framing patients into classes of risk. By using the actual risk scores for cardiovascular events, the practician takes into account only traditional RF. Therefore, they have limitations in identifying vulnerable population, especially in early stages of the disease (Scott 2009).

Our study was made on 43 patients with multiple cardiovascular RF and presence of subclinical ATS disease at peripheral arterial level. Based on Framingham score, our analysis included in high risk level (>15%), imposing appropriate prophylactic measures for ATS disease, 13 patients (30.23%) of this sample. For traditional level (>20%), it would include even less, only 8 patients (18.6%). This limit of risk score in identifying ATS disease is important, since patients with PAD, symptomatic or asymptomatic, have three-times more frequent coronary events (Merino 2008).

There are numerous researches on human subjects that prove that there are differences between arterial stiffness determined by age related with gender. Some authors have ascertained that this arterial stiffness determined by age is more obvious to female sex comparing with male sex (Ahimastos et al 2003). Other authors, based on studies on primates, sustain exactly the opposite (Qiu et al 2007). Our study found out, between subsamples elected by the gender criteria, similar levels of stiffness parameters, for risk score statistically different. This suggests that, in the evaluation of cardiovascular risk relating to arterial stiffness, sex as traditional RF, has not influenced significantly the results.

There is not a consensus regarding the ideal method to evaluate arterial stiffness (Oliver & Webb 2003). There are numerous studies that analyze the parameters of arterial stiffness to appreciate the cardiovascular risk on patients with RF for ATS (Simsons et al 1999; Van Popele 2001; Shokawa et al 2005; Willum-Hansen et al 2006; Kovaite et al 2007), PWV being the most frequent method in use. The two parameters of stiffness used in our study, PP and SI, were statistically significant strongly correlated.

Both PP and SI_{DVP} were statistically significant correlated with Framingham score, having the same increasing trend with levels of risk. It must be remarked that this correlation appeared, although different individual relationships exist between parameters of stiffness and RF (HTA, age, smoking).

For HT and age there is a consensus in literature, namely that these RF are direct determinants of arterial stiffness (Oliver & Webb 2003). For smoking, there are controversies concerning the chronic or acute role on the level of arterial stiffness

(Argacha et al 2007; Jatoi et al 2007). Our study distinguished for PP a significant correlation with HT and age, and for SI_{DVP} a significant correlation with smoking.

In the stage of subclinical atherosclerotic disease, arterial stiffness has the potential to realize a stratification of risk, somehow independent from traditional RF. It would be useful to establish the cut-off values for different stiffness parameters. Thus, identification of high levels of arterial stiffness in the case of some patients, even having low traditional risk scores, would impose adequate therapeutically interventions to prevent appearance or attenuate the progress of atherosclerotic disease.

Limits: The main limit of our study is the absence of follow-up for our cohort. We intend to prospectively analyse incident rates of coronary events in this population, and also to assess progression of PAD.

Conclusion. In the studied sample, namely patients with subclinical PAD, the risk for cardiovascular events, estimated by Framingham score, evolves progressively with arterial stiffness, evaluated by PP and $SI_{DVP.}$ PP is correlated with direct determinants of stiffness (age, HTA), while correlation of SI_{DVP} with smoking illustrates, more probably, arterial stiffness ATS-related.

Also, using different levels of risk for Framingham score, a larger amount of atherosclerotic population can be identified.

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