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Association between peripheral arterial disease and cardiovascular risk factors: role of ultrasonography versus ankle-brachial index

L. SANTORO[1], A. FLEX[1], A. NESCI[1], P.M. FERRARO[2], G. DE MATTEIS[1], A. DI GIORGIO[1], B. GIUPPONI[1], L. SAVIANO[1], G. GAMBARO[2], F. FRANCESCHI[1], A. GASBARRINI[1], R. LANDOLFI[1], A. SANTOLIQUIDO[1]

[1]Department of Internal Medicine, Catholic University of Rome, Rome, Italy
[2]Division of Nephrology and Dialysis, Catholic University of Rome, Rome, Italy

Abstract. – OBJECTIVE: Most studies on atherosclerotic processes include peripheral arterial disease diagnosis only if patients report symptoms suggestive of peripheral arterial disease and/or an instrumental demonstration of lower limbs perfusion deficit is provided, rather than the sole presence of atherosclerotic lesions localized at lower limbs, this attitude leading to ignore early stages of the disease. To overcome these limitations, we have proposed a new ultrasonographic semiquantitative score to better identify all disease stages. The aim of this study is to compare ultrasonography versus ankle-brachial index in the association between peripheral arterial disease and cardiovascular risk factors.

PATIENTS AND METHODS: This cross-sectional observational study included subjects undergoing lower limbs evaluation through ultrasonography and ankle-brachial index determination because of symptoms suggestive of peripheral arterial disease or presence of known cardiovascular risk factors. Associations between ultrasonography and ankle-brachial index with cardiovascular risk factors were assessed by first fitting logistic regression models and then comparing the respective areas under the Receiver Operating Characteristic and 95% confidence intervals.

RESULTS: The areas under the Receiver Operating Characteristic for each cardiovascular risk factors were consistently larger in magnitude for ultrasonography compared with ankle-brachial index, this comparison being statistically significant for age, male gender, smoking status, hypertension, diabetes mellitus and previous cardiovascular events.

CONCLUSIONS: Our study demonstrates that ultrasonography is a better method to screen peripheral arterial disease respect to ankle-brachial index in order to identify all disease stages. These findings are useful in particular when including peripheral arterial disease as organ damage marker in cardiovascular risk stratification.

Key Words
Ultrasonography, Ankle-brachial index, Peripheral arterial disease, Cardiovascular risk factors, Diagnosis.

Introduction

Peripheral arterial disease (PAD) is a worldwide disease with a significant impact on healthcare and a high economic burden[1]. Epidemiological data about its incidence and prevalence are controversial, maybe due to difficulties to get together studies including different definition of the disease, with first studies focusing only on critical limb ischemia or intermittent claudication and the latest one including patients with ankle-brachial index (ABI) alterations. However, it is estimated that more than 200 million people have PAD worldwide[2].

It is well known that PAD progression is very slow, with most patients that remain stable across a follow-up period of 5 years[3]. Instead, the importance of PAD lies in its common association with the other cardiovascular (CV) diseases, like myocardial infarction and stroke, with risk of major CV events more than doubled in patients with PAD[4]. Also for this reason, more and more importance has to be given to PAD as organ damage marker, especially in early stages as happen for carotid intima-media thickness (cIMT) and left ventricular hypertrophy[5,6].

Nowadays, most studies about PAD include ABI evaluation as a screening test. This measurement is simple, noninvasive, risk-free and inexpensive, but results abnormal only in the presence of advanced arterial lesions able to reduce ankle systolic blood pressure, so that early atherosclerotic lesions of the lower limbs cannot be detected by ABI measurement.

Corresponding Author: Luca Santoro, MD; e-mail: luca.santoro@policlinicogemelli.it

We recently introduced a new ultrasonographic lower limbs atherosclerosis score (ULLA score) to better categorize PAD in all stages of diseases, including early ones[7].

The aim of this study is to compare ULLA score versus ABI evaluation in the association between PAD and CV risk factors.

Patients and Methods

Patients

Subjects >18 years undergoing lower limbs vascular evaluation and submitted to ultrasonographic evaluation of the lower limb arteries and ABI determination between 1 Jul 2014 and 30 Jun 2015 because of symptoms suggestive of PAD or presence of known CV risk factors were enrolled in this cross-sectional observational study.

CV risk factors included in the statistical model were age, gender, diabetes mellitus status, arterial hypertension status, dyslipidemia status, body mass index (BMI), cigarette smoking modeled as both number (packs/year) and smoking status ("never", "former" and "active"), sedentary lifestyle, previous CV events and family history of CV disease. The presence of diabetes mellitus status, arterial hypertension and dyslipidemia were diagnosed based on relative guidelines[8-10].

Ultrasound Lower Limb Evaluation

Ultrasonographic examination was performed as previously described[7]. Briefly, the femoropopliteal and run-off segments were continuously scanned from the subinguinal region to the paramalleolar region with axial and sagittal scans. All segments were examined for their parietal characteristics, especially the presence of vessel wall calcifications and/or atherosclerotic plaques. In addition, flow-velocity measurements using spectral Doppler imaging and color Doppler imaging were obtained. Arteries were grouped into femoropopliteal or proximal (common, superficial and deep femoral arteries, popliteal artery) and infrageniculate or distal (tibiofibular trunk, anterior and posterior tibial arteries, fibular artery) districts.

ULLA (Ultrasonographic Lower Limbs Atherosclerosis) score was calculated to assess disease severity as previously described[7].

Ankle-Brachial Index Evaluation

The ABI was calculated from the highest systolic ankle pressure to the highest brachial systolic pressure ratio for each leg. The ankle systolic pressure was measured after the patients rested supine for 5 minutes, placing a 10-12 cm sphygmomanometer cuff just above the ankle and using a Doppler probe to evaluate the systolic pressures of the posterior and anterior tibial arteries of each leg[11].

ABI values from 1.00 to 1.40 were considered normal, whereas values less than or equal to 0.90 were considered abnormal; values ranging from 0.91 to 0.99 suggested a "borderline" ABI and values >1.40 indicated non-compressible arteries. After comparing the two legs, the lowest measured ABI value was chosen for the analysis.

A semiquantitative measure of the ABI has been also performed and classified in four grades: *grade 0* (ABI 0.91-1.40) were considered normal, *grade 1* (ABI 0.41-0.90) indicated mild-moderate PAD, *grade 2* (ABI $\leq$ 0.40) indicated severe PAD, *grade 3* (ABI > 1.40) indicated non-compressible arteries.

Statistical Analysis

Continuous variables were summarized as means and standard deviations; categorical variables as frequencies and percentages. Associations between continuous variables were assessed with the Spearman test. Associations between ULLA and ABI scores with CV risk factors were assessed by first fitting logistic regression models with each CV risk factor as dependent variable and the ULLA and ABI scores as continuous predictors. Then, the respective areas under the Receiver Operating Characteristic (AUROCs) and 95% confidence intervals (CI) were compared using the *roccomp* program in Stata 13.1 (StataCorp, TX, USA). A two-tailed p-value < 0.05 was regarded as statistically significant.

Ethical Approval

Written informed consent was obtained from all participants before their enrollment in the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Catholic University of Rome (Ethics Committee reference number: l4725/2014).

Results

A total of 319 participants had all the data available for analysis. The characteristics of the study participants are reported in Table I.

Overall, 36 patients (11.3%) were classified as ULLA grade 0, 85 (26.7%) as grade 1, 89 (27.9%) as grade 2, 27 (8.5%) as grade 3, 63 (19.8%) as

Table I. Demographic and clinical characteristics of the study participants.

Age, mean (SD)	69 (10)
BMI*, mean (SD)	27.2 (4.3)
Gender	
F	173 (54.2%)
M	146 (45.8%)
Smoking status (ever vs never)	
No	126 (39.5%)
Yes	193 (60.5%)
Hypertension	221 (69.3%)
Diabetes	105 (32.9%)
Dyslipidemia	193 (60.5%)
CV# family history	251 (78.7%)
Sedentary	86 (27.0%)
CV# events	76 (23.8%)

Variables are reported as mean (standard deviation) and as frequencies (percentages).
*BMI: body mass index. #CV: cardiovascular.

grade 4 and 19 (6.0%) as grade 5. The Spearman's rho for the correlation between ULLA and ABI scores was 0.48 ($p < 0.001$).

The results of the comparisons of ULLA and ABI scores with regard to each CV risk factor are reported in Table II. The AUROCs for each CV risk factor was consistently larger in magnitude for ULLA compared with ABI; the comparisons were statistically significant for age, male gender, smoking status, hypertension, diabetes and previous CV events.

Discussion

In the last few years, interest about PAD has grown quickly, with regard not only to the clinical aspects but also its etiopathogenesis, in particular in earlier stages of disease. To this purpose, we have recently introduced a new ultrasonographic score, the ULLA (Ultrasonographic Lower Limbs Atherosclerosis) score, which can classify PAD respect to the presence of atherosclerotic lesions of the lower limbs in all stages of disease, including early, asymptomatic ones[7]. By using this score, it has been possible to identify different CV risk profiles in patients affected by PAD, as evidenced by the association between ULLA score and main traditional CV risk factors[7].

The rationale that brings us to design an ultrasonographic score was to overcome the previous limits due to the fact that most studies on atherosclerotic processes included PAD diagnosis only if patients reported symptoms suggestive of PAD and/or an instrumental demonstration of lower limbs perfusion deficit was provided, rather than the sole presence of atherosclerotic lesions localized at lower limbs. Typically, in these studies diagnosis of PAD was made using ABI evaluation, a test considered simple, noninvasive, risk-free, and inexpensive and with a value <0.90 indicative of PAD, it has acceptable diagnostic performance properties for PAD screening[12-14]. On the other hand, this test results altered only in the presence of advanced arterial lesions able to reduce ankle systolic blood pressure. So, routine use of ABI can be conceived to detect perfusion deficit of PAD, and not to screen the presence of the disease, interpreted as presence of atherosclerotic lesions localized at lower limbs, which remains evidently underdiagnosed by using ABI.

The attitude of considering also early stages of PAD is very important, especially in a time period in which evaluation of subclinical vascular lesions, as a measure of vascular target organ damage, rep-

Table II. Associations between ULLA* and ABI† scores and cardiovascular risk factors.

	*ULLA Score		†ABI		
	OR (95% CI)	AUROC (95% CI)	OR (95% CI)	AUROC (95% CI)	*p*-value
Age ≥ 60 years	1.68 (1.31, 2.16	0.69 (0.61, 0.77)	1.04 (0.65,1.66)	0.51 (0.45, 0.58)	<0.001
Male gender	1.76 (1.48, 2.10)	0.71 (0.66, 0.77)	1.71 (1.17, 2.50)	0.59 (0.54, 0.63)	<0.001
BMI#≥ 25 kg/m^2	0.87 (0.74, 1.02)	0.55 (0.48, 0.62)	0.98 (0.68, 1.42)	0.51 (0.46, 0.56)	0.20
Smoking status	1.43 (1.21, 1.69)	0.64 (0.58, 0.70)	1.40 (0.95, 2.07)	0.56 (0.52, 0.61)	0.010
Hypertension	1.54 (1.27, 1.85)	0.66 (0.60, 0.73)	1.25 (0.83, 1.89)	0.54 (0.49, 0.59)	<0.001
Diabetes	1.38 (1.17, 1.63)	0.63 (0.57, 0.70)	1.23 (0.86, 1.75)	0.55 (0.49, 0.60)	0.003
Dyslipidemia	1.10 (0.94, 1.28)	0.54 (0.48, 0.61)	0.67 (0.47, 0.96)	0.54, 0.49, 0.59)	0.90
CV‡ family history	1.00 (0.83, 1.21)	0.50 (0.42, 0.58)	0.82 (0.55, 1.21)	0.53 (0.47, 0.59)	0.64
Sedentary	1.25 (1.05, 1.48)	0.59 (0.53, 0.66)	0.96 (0.65, 1.43)	0.51 (0.46, 0.56)	0.11
CV‡ events	1.59 (1.32, 1.91)	0.68 (0.61, 0.75)	1.64 (1.13, 2.36)	0.62 (0.56, 0.68)	0.038

*ULLA: ultrasonographic lower limbs atherosclerosis. †ABI: ankle-brachial index. #BMI: body mass index. ‡CV: cardiovascular.

resents a topic of great interest, as happened for cIMT and arterial stiffness[5,15-18]. Moreover, the inclusion of all stages of PAD could lead the Authors to reconsider its impact on the development of major CV events, leading to different treatment strategy, respect to what have done till now considering the increased risk of CV mortality and morbidity in these patients[4,19,20].

We have now carried out the present study to specifically compare ULLA score versus ABI evaluation in the association between PAD and CV risk factors, finding that ultrasonography is more strictly associated with main CV risk factors respect to ABI; this difference was statistically significant for age, male sex, smoking status, hypertension, diabetes and previous CV events.

A first important implication of these results is that ultrasonography should be considered superior respect to ABI in the evaluation of CV risk profile, also when considering the distribution of atherosclerotic lesions in different districts of lower limbs. This ability of ultrasonography, especially in identifying early lesions, could also have a role when discoursing about the possible association of PAD with novel biomarkers of the atherosclerosis process, in particular, associated with pathways of inflammation, which importance is often deduced through instrumental methods with different sensitivities[21-24].

Another central prospect of ultrasonography is linked to the possibility to correctly study PAD progression. It is well known that PAD is considered a disease with poor progression and most affected patients show a stable condition along five years; one more time, these data derived from studies that include techniques with poor sensibility, as ABI or angiography[25,26]. So, ultrasonography represents a more sensible and complete technique, able to provide morphologic and functional information certainly useful to better assess PAD progression.

Considering PAD at all disease stages using ultrasonography, rather than ABI evaluation, can have a role also in the recent research revealing the role of PAD involvement in CV risk stratification: patients affected by ABI-assessed PAD have higher CV mortality and morbidity than age-matched controls without PAD, and these findings are similar for individuals with symptomatic and asymptomatic PAD[4,19,20]. For this reason, it has been suggested to add the presence of PAD in the assessment of organ damage, validating a new risk equation incorporating ABI evaluation, to better define the existing CV risk profile. On the other hand, it is well known that the relationship between ABI and CV disease is not linear, with CV risk profile that varies across the range of ABI. This is firstly due to poor arterial compressibility resulting from stiffness and calcifications that is present in particular in patients affected by diabetes. Moreover, it has to be underlined that although widely used in specialist vascular settings, the ABI is rarely applied in routine clinical practice, also because most clinicians would not completely know how to perform this test[27]. So, ultrasonography could change the predictive value of PAD in assessing CV risk, as already recently reported in some studies[28-31].

Finally, exploring the possible presence of subclinical atherosclerosis in the lower limb districts could be of interest because multiple organ damages carries a worse prognosis than single organ involvement[32,33]. In individuals with one or more classical risk factors who do not appear to have a high total CV risk according to current methods of quantification, subclinical organ damage is common. The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT–LLA) demonstrated that treatment of patients with indicators of subclinical CV disease could reduce CV events[34].

Some limitations of the present study have to be addressed: first of all, the sample size is still too small for drawing definitive results, so that our results may serve as a pilot study. Secondly, an economic evaluation is desirable to better understand if ultrasonography can be favorable when PAD suspect is strong, to avoid time loss. Finally, the role of ULLA score in predicting CV events is still unknown, unlike ABI.

Conclusions

In the light of our results, we would like to suggest a new overview of PAD that concerns the sole presence of atherosclerotic lesions localized at lower limbs, and to this purpose to immediately perform ultrasonography if PAD suspect is strong. We think that this new point of view is necessary in particular to identify early stages of PAD that serve as organ damage marker in CV risk stratification.

Conflict of Interest

The Authors declare that there is no conflict of interest regarding the publication of this paper.

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