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The relationship between pulse waveform analysis indices, endothelial function and clinical outcomes in patients with peripheral artery disease treated using percutaneous transluminal angioplasty during a one-year follow-up period

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Abstract

Background: *Several predictors of clinical outcomes after percutaneous transluminal angioplasty (PTA) interventions in patients with peripheral arterial disease (PAD) have been investigated. Indices of endothelial function, arterial pulse waveform analysis (aPWA) and markers of peripheral artery ischemia were among the most commonly examined. The aim of the current study was to assess the relationship between potential predictors of clinical outcomes after peripheral artery PTA during a 1-year follow-up period.*

Methods: *The study included 72 individuals with PAD at a mean age of 66.3 ± 7.2 (79.1% males). All patients underwent PTA of the peripheral arteries. Among them, 42.8% presented critical limb ischemia (CLI). During the first visit and at 1 month and 6 months after PTA, endothelial function and aPWA measurements were taken. Ankle-brachial index (ABI), toe-brachial index (TBI) and physical evaluation of the limbs took place during the first visit and at 1, 6 and 12 months after the PTA. The study endpoints included myocardial infarction, amputation, death, stroke and reintervention. All subjects included in the study were observed for 386 days after the PTA.*

Results: *A significant improvement was noted in walking distance after PTA at the following time points, as well as transient improvement of ABI and flow-mediated dilatation (FMD) and no significant change in aPWA indices and reactive-hyperaemia index (RHI). The mean ABI, TBI, FMD and RHI values did not correlate with each other at baseline. There were 25 study endpoints which occurred in 16 patients during the follow-up period (22.2%). Patients with CLI, hypercholesterolemia, lower diastolic blood pressure, higher subendocardial viability ratio, a greater number of pack-years and lower TBI at baseline presented significantly poorer clinical outcomes in terms of endpoint events.*

Conclusions: *Endothelial function assessed as FMD and reactive hyperemia–peripheral arterial tonometry (RH-PAT) before PTA in patients with advanced PAD do not predict clinical outcomes during the 1-year follow-up.* (Cardiol J 2020; 27, 2: 142–151)

Key words: endothelial function, percutaneous transluminal angioplasty, arterial pulse waveform analysis, clinical outcomes

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Introduction

The incidence of peripheral artery disease (PAD) increases are due to the aging population. Early diagnosis and adequate treatment could improve clinical outcomes. Several tools have been proven to accurately indicate peripheral atherosclerosis, beginning with markers of endothelial dysfunction expressed as flow-mediated dilatation (FMD), reactive-hyperemia index (RHI) or arterial pulse-waveform analysis (aPWA) indices and ending in clinically apparent lower limb atherosclerosis assessed by the ankle-brachial index (ABI) or toe-brachial index (TBI), finally proven by arterial angiography or arterial computed tomography [1–5]. Nowadays, most patients with clinically symptomatic lower limb atherosclerosis are treated with percutaneous transluminal angioplasty (PTA). Likewise, predictors of clinical outcomes after PTA are of great interest to scientists. Improving the knowledge of predictors and their associated mechanisms may improve PTA outcomes. Among the proven prognostic factors that may influence PTA results we may find selected endothelial function and aPWA indices, as well as clinical comorbidities, clinical presentation of PAD estimated by the Rutherford scale or ABI and the angiographic image of culprit lesions [6–10].

The aim of the current study was to assess the relationships between aPWA, endothelial function indices and clinical outcomes in patients with PAD following PTA of lower limb arteries during a 1-year follow-up period.

Methods

Study design

The study was conducted as a prospective, single-center follow-up evaluation, assessing the influence of initial endothelial function on the number of clinical cardiovascular events (death, myocardial infarction, stroke, amputation) and the number of reinterventions in patients with symptomatic PAD assessed during a 12 month follow up. Patients with critical limb ischemia (CLI) as well as those with stable PAD (Rutherford class 2 to 3) due to iliac, femoropopliteal or below the knee disease were eligible for the study. Exclusion criteria were a history of end stage kidney disease, age above 85 and pain related to limb ischemia not allowing to obtain a horizontal position. Patients with incompressible tibial arteries were not eligible for the study.

All subjects provided written and informed consent before the study began. The study complies with the Declaration of Helsinki and was approved by the local ethics committee.

Endovascular procedures

Assessment before the intervention included clinical examination, calculation of the ABI, TBI, color duplex sonography and tonometry. Endovascular treatment was performed in a routine manner. A 4 F to 6 F sheath was introduced into the artery and diagnostic angiography was performed. Each individual received 5000 IU of unfractionated heparin that was injected intra-arterially. The affected artery was treated using over the wire balloon catheters, and wherever necessary, nitinol self-expanding stents or cobalt-chromium balloon expandable stents were implanted. Post-interventional therapy lasted 4 weeks and consisted of both acetylsalicylic acid (75 mg/d) and clopidogrel (75 mg/d). High dose statins (atorvastatin 40 mg to 80 mg or rosuvastatin 20 mg to 40 mg) were initiated at the baseline assessment to all patients and maintained for life. Follow-up visits were done 1, 6 and 12 months after the intervention. Successful angioplasty was defined by a final angiogram with residual stenosis of 30% or less and post-interventional ABI improvement of at least 0.1.

Endothelial function tests

FMD

The study was performed on the basis of current FMD assessment guidelines [11]. The study was performed between 8 and 10 a.m. in a temperature-controlled room (20° to 22°C) with subjects resting in a supine position. Brachial diameter was imaged using a high-resolution (14-MHz line array) transducer ultrasound system (Siemens, Erlangen, Germany) equipped with electronic callipers, vascular software for two-dimensional imaging, color and spectral Doppler, and an internal electrocardiogram. The brachial artery was imaged at a location 2–5 cm above the cubital fossa. A sphygmomanometer cuff was placed on the forearm. The cuff was inflated at least 50 mmHg above systolic pressure to occlude artery inflow for 5 min. All vasodilation measurements were made from 60 to 90 s after deflation. Measurements were performed on a personal computer using brachial reactivity analysis software (Siemens). The response of the vessel diameter to reactive hyperemia was calculated and expressed as a percentage change relative to the diameter immediately before cuff inflation.

RHI

Digital pulse amplitude was measured in a standardized setting (i.e., a quiet, dark, temperate environment [21 to 24°C]) with a Peripheral Arterial Tone (PAT) device that comprises a pneumatic plethysmograph measuring digital pulse volume changes (Endo-PAT2000, Itamar Medical, Caesarea, Israel). Patients were in a fasting state.

The digital pulse amplitude was acquired continually during the examination and digitally recorded to a laptop. Data was analyzed by a computerized algorithm (Itamar Medical), which automatically and operator-independently calculates RHI.

The assessment of the extent of lower limb ischemia

The ABI was calculated with the patient in a supine position. The highest systolic pressure of the anterior or posterior tibial artery was measured in each limb and was divided by the highest brachial artery pressure. The mean ABI value of the two legs were included in statistical analysis. The TBI was calculated with the patient supine. The systolic pressure on the big toe was obtained using a photoplethysmograph (Nicolet VasoGuard; VIASYS Healthcare, Madison, WI, USA) in each limb and was divided by the highest brachial artery pressure.

IMT

To measure carotid intima–media thickness (IMT), ultrasonography of the common carotid artery, carotid bifurcation, and internal carotid artery of the left and right carotid arteries was performed with a 7.5-MHz linear-array transducer (Siemens, Erlangen, Germany). On a longitudinal, two-dimensional ultrasound image of the carotid artery, the anterior and posterior walls of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the IMT.

aPWA analysis

Arterial pulse waveform analysis assessment of arterial stiffness was performed non-invasively with the commercially available SphygmoCor system (AtCor Medical). Peripheral pressure waveforms were recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms had been acquired, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform. Aortic pressure was the maximum systolic pressure minus pressure at the inflection point. Pulse pressure was measured (PP), also augmentation index (AI), central augmentation index (CAI), ejection duration (ED), subendocardial viability ratio (SEVR), central augmentation pressure (CAP), central augmentation pressure normalized for a heart rate of 75 bpm (CAP-HR75), stiffness index (SI) and reflection index (RI) were measured [12].

Statistical analysis

The data are expressed as means, standard deviation, medians and interquartile range (IQR) when appropriate. The test choice depended on the distribution of particular data. To compare measurable variables (or to assess the statistical significance of the observed differences), parametric tests were used: the two-sided Student *t* test and Spearman linear correlation. In case of missing mentioned assumptions, non-parametric tests were used (Friedman ANOVA, Mann-Whitney U-Test, Wilcoxon signed-rank and χ^2). A p-value of < 0.05 was considered significant. STATISTICA for Windows Release 10 (StatSoft Inc., 2011) was used for data analysis.

Results

General characteristics

Clinical characteristics, family history and pharmacological therapy of patients included into the present study are demonstrated in Table 1, whereas culprit artery characterization is presented in Table 2.

Clinical outcomes

The pain-free walking distance (PFWD) and maximal walking distance (MWD) increased significantly after PTA during 6 months of the follow-up period ($p = 0.04$ and $p = 0.02$, respectively; Table 3). The improvement of MWD after 6 months of follow-up was significantly poorer in patients with kidney failure ($p = 0.01$). Neither the PFWD change nor the MWD change during the follow up period was related to baseline indices of endothelial function, clinical picture of PAD and pulse waveform indices. Also the mean PFWD and MWD assessed at baseline was not connected with clinical outcomes expressed as study endpoints during the 12-month follow-up period. The mean Rutherford grade decreased significantly at the following time points after the PTA during the 1-year follow-up (Fig. 1A)

Table 1. Gene characteristics of individuals included in the study at baseline, pharmacological therapy and family history. Overall group of patients — n = 72.

Variables	Number of individuals, n (%)
Age [years]	66.3 ± 7.2 65 [61.75÷72]
Gender, males	57/72 (79.1%)
Critical limb ischemia	30/70 (42.8%)
Smoking:	12/72 (16.7%)
Current	52/72 (72.2%)
Previous	64/71 (90.1%)
Whenever	31.4 ± 12.8
Years	30 [20÷40] 18.3 ± 7.5
Cigarettes per day	20 [15÷20] 30.0 ± 19.0
Pack years	30 [19÷40]
Hypertension	50/72 (69.4%)
Dyslipidemia	34/72 (47.2%)
Diabetes mellitus:	27/72 (37.5%)
Years of treatment	15.8 ± 7.9 15 [10÷20]
Coronary artery disease:	26/72 (36.1%)
Myocardial infarction	10/72 (13.9%)
Kidney failure	4/72 (5.5%)
Stroke	
Family history:	6/72 (8.3%)
Hypertension	1/72 (1.4%)
Dyslipidemia	0/72 (0%)
Diabetes mellitus	2/72 (2.8%)
CAD	0/72 (0%)
Myocardial infarction	1/72 (1.4%)
Cerebral stroke	0/72 (0%)
PAD	1/72 (1.4%)
Kidney failure	0/72 (0%)
Pharmacological therapy:	
Statin	7/72 (9.7%)
ARB	3/72 (4.2%)
Beta-blockers	2/72 (2.8%)
Calcium channel blockers	5/72 (6.9%)
Diuretics	3/72 (4.2%)
LMWH	1/72 (1.4%)
Acetylsalicylic acid	11/72 (15.3%)
Insulin	3/72 (4.2%)
Oral anticoagulants	2/72 (2.8%)
Thyroid hormones supplements	1/72 (1.4%)

Data are presented as arithmetic means ± standard deviation; median [lower÷upper quartile]. ARB — angiotensin receptor blockers; CAD — coronary artery disease; LMWH — low molecular weight heparin; PAD — peripheral artery disease

Table 2. Characteristics of culprit lesion and distribution of lower limb atherosclerotic lesions. Overall group of patients — n = 72.

Variables	Number of individuals, n (%)
De-novo lesion:	54/70 (77.1%)
Right lower limb	27/70 (38.6%)
Left lower limb	27/70 (38.6%)
Re-intervention:	16/70 (22.8%)
Right lower limb	10/70 (14.3%)
Left lower limb	6/70 (8.6%)
Past PTA of lower limb arteries	30/70 (42.8%)
Past PTA of carotid arteries	1/70 (1.4%)
Localization of culprit artery:	
Aorto-iliac segment (Ao-IL):	19/70 (27.1%)
One artery	13/19 (68.4%)
Two arteries	6/19 (31.6%)
Femoro-popliteal segment (Fem-Pop):	44/70 (62.8%)
One artery	31/44 (70.4%)
Two arteries	12/44 (27.3%)
Three arteries	1/44 (2.3%)
Below the knee artery (BTK):	24/70 (34.3%)
One artery	8/24 (33.3%)
Two arteries	9/24 (37.5%)
Three arteries	4/24 (16.7%)
Four arteries	3/24 (12.5%)
Single-segmental involvement:	53/70 (75.7%)
Ao-IL	17/53 (32.1%)
Fem-Pop	27/53 (50.9%)
BTK	9/53 (17%)
Dual-segmental involvement:	17/70 (24.3%)
Ao-IL and Fem-Pop	2/17 (11.8%)
Fem-Pop and BTK	15/17 (88.2%)
TASC Fem-pop:	44/72 (61.1%)
a	5/44 (11.4%)
b	13/44 (29.5%)
c	10/44 (22.7%)
d	16/44 (36.4%)
TASC Ao-iliac:	19/72 (26.4%)
a	6/19 (31.6%)
b	7/19 (36.8%)
c	4/19 (21%)
d	2/19 (10.5%)

→

Table 2 (cont.). Characteristics of culprit lesion and distribution of lower limb atherosclerotic lesions. Overall group of patients — n = 72.

Variables	Number of individuals, n (%)
Graziani's morphologic categorization of disease severity:	32/72 (44.4%)
1	1/32 (3.1%)
2a	6/32 (18.7%)
2b	2/32 (6.2%)
3	3/32 (9.4%)
4	12/32 (37.5%)
5	1/32 (3.1%)
6	6/32 (18.7%)
7	1/32 (3.1%)
Number of stenoses > 50%:	70/72 (97.2%)
1	38/70 (54.3%)
2	18/70 (25.7%)
3	11/70 (15.7%)
4	2/70 (2.8%)
5	1/70 (1.4%)
Occlusions:	10/70 (14%)
1	7/10 (70%)
2	3/10 (30%)

PTA — percutaneous transluminal angioplasty; TASC — Trans Atlantic Inter-Society Consensus

and was more significant after 12 months of follow-up in patients with CLI at baseline compared to those individuals with non-CLI (p = 0.00005).

ABI, TBI and IMT

The mean IMT value decreased significantly 6 months after the PTA procedure compared to the baseline value (Table 3). The mean ABI value increased 1 month after PTA, however, without statistical significance and at following time points it dropped significantly, even below baseline value when assessed after 12 months of follow-up (Fig. 1B). The mean TBI value increased immediately after PTA (but without statistical significance) and remained in favorable balance during the 12 month follow-up (Fig. C). The mean ABI value at baseline was lower in patients treated with calcium channels blockers (p = 0.02). It was greater in patients with grade A of Trans-Atlantic Inter-Society Consensus classification (p = 0.04) and was unexpectedly higher in patients with the greater mean grade on the Rutherford scale (p = 0.03). Also patients with a longer history of smoking were related with lower mean ABI values at baseline (r = –0.26; p = 0.04). ΔABI after 6 months of follow-up was higher in patients with the IMT value lower than 0.9 mm compared to those individuals with the IMT > 0.9 mm at baseline (p = 0.005). No relationship was found between IMT and clinical outcomes after PTA during the 12-month follow-up period.

Endothelial function

The mean FMD value increased insignificantly after PTA, and dropped after 6 months of follow-up below the baseline value (the change was statistically significant in ANOVA analysis; p = 0.04). The baseline mean FMD value correlated positively with ΔAI assessed at baseline and after the 6-month follow-up period (r = 0.54; p < 0.0001). ΔFMD was higher 1 month after PTA in patients with resting pain at baseline compared to those without it (p = 0.01).

No relationship was found between the study endpoint events noticed during follow-up and the value of FMD at baseline or ΔFMD.

The mean RHI value decreased directly after PTA and at 6 months of follow-up, however, without statistical significance (Table 3). The baseline values of RHI correlated positively with baseline values of systolic blood pressure (r = 0.27, p = 0.04), PP (r = 0.29; p = 0.03), CAP (r = 0.35, p = = 0.01) and CAP-HR75 (r = 0.3; p = 0.02). The ΔRHI after 6 month follow-up was significantly greater in patients with past myocardial infarction (p = 0.008). No relationship was found between RHI and clinical outcomes after PTA during the 12-month follow-up period.

Pulse waveform analysis

The mean PP, AI, CAI, CAP, and CAP-HR75 values decreased after PTA and continued to decrease at 6 month follow-up visit, however without statistical significance. The mean ED, SEVR, SI and RI values decreased insignificantly after PTA. They increased above the baseline value during the 6-month follow-up, with the exception of the mean SEVR value, and the trend was statistically non-significant when assessed using ANOVA analysis. No significant relationships were found between baseline values of PWA indices (except for SEVR) and baseline values of endothelial function parameters, markers of clinical progression of lower limb atherosclerosis and the frequency and distribution of endpoint events during the 12-month-long follow-up period. SEVR was related to the endpoint events; higher values at baseline corresponded with significantly poorer outcomes expressed as study endpoint events (p = 0.04). Also, the decrease of the mean ED value (ΔED)

Table 3. The impact of percutaneous transluminal angioplasty (PTA) of lower limb arteries on selected indices at following time-points.

	At baseline	After 1 month	After 6 months	P
Flow-mediated dilatation	4.1 ± 2.9 3.7 [1.8÷5.8]	4.88 ± 2.9 4.7 [2.6÷6.4]	3.4 ± 2.5 2.9 [1.6÷4.5]	0.04
Pulse pressure	67.4 ± 12.9 67.5 [60.2÷74.7]	66.6 ± 15.4 65.5 [57.7÷76.5]	65.6 ± 15.6 65 [55.5÷73]	0.8
Augmentation index	99.2 ± 17.6 95 [85.7÷112.5]	98.4 ± 17.9 94 [84.7÷108]	94.8 ± 14.6 94 [85.5÷101]	0.3
Central augmentation index	156.1 ± 25.9 150 [137.2÷174.2]	155.8 ± 27.9 152.3 [137.5÷167.1]	149.4 ± 20.3 148.7 [136÷161.2]	0.28
Ejection duration	312.8 ± 26.6 310 [290.2÷332.7]	310.4 ± 27.7 309.5 [292÷334.5]	318.3 ± 27 319 [302.5÷337.5]	0.32
Subendocardial viability ratio	149.9 ± 30.5 146 [133÷167.7]	144.5 ± 28.2 146.5 [125.5÷158.5]	148.6 ± 24.3 147 [133.5÷162]	0.6
Central augmentation pressure	19.4 ± 9.1 17 [13÷26]	18.7 ± 8.6 18.5 [13.7÷22.2]	17.7 ± 8.5 16 [12÷22]	0.57
CAP-HR75	16.3 ± 5.7 16.5 [13÷20]	16.3 ± 5.8 16 [13.7÷18.5]	14.2 ± 5.6** 13[10.5÷18]	0.08
Stiffness index	19.2 ± 1.6 20 [20÷20]	18.8 ± 2.0 20 [18÷20]	19.2 ± 1.7 20 [20÷20]	0.57
Reflection index	97.5 ± 5.1 100 [100÷100]	96.2 ± 6.8 100 [94÷100]	97.6 ± 5.5 100 [100÷100]	0.52
Reactive hyperemia index	1.7 ± 0.7 1.5 [1.2÷2.0]	1.7 ± 0.9 1.4 [1.2÷1.8]	1.6 ± 0.5 1.5 [1.3÷1.8]	0.62
Pain-free walking distance [m]	91.0 ± 142.4 50 [20÷100]	292.3 ± 440.2* 150 [50÷300]	394.1 ± 953.3 100 [50÷200]	0.04
Maximal walking distance [m]	120.4 ± 150.0 100 [30÷175]	337.5 ± 486.8* 200 [55÷300]	535.8 ± 1244.3 175 [100÷300]	0.02
Systolic blood pressure [mmHg]	147.3 ± 16.3 150 [139÷158]	145.8 ± 17.6 147 [137÷154.2]	145.1 ± 17.3 145 [133.5÷156]	0.79
Diastolic blood pressure [mmHg]	79.8 ± 8.2 80 [76÷84]	79.2 ± 7.2 79 [74÷84]	9.5 ± 9.1** 80 [75.5÷84]	0.92
Intima–media thickness [mm]	0.96 ± 0.29 0.9 [0.77÷1.07]	–	0.93 ± 0.26 0.86 [0.76÷0.98]	0.006

Data are presented as arithmetic means ± standard deviation; median [lower÷upper quartile]. CAP-HR75 — central augumentation pressure normalized for a heart rate of 75 bpm

*The value one month after PTA was significantly different from that assessed before PTA by the Wilcoxon signed-rank test.

**The value six months after PTA was significantly different from that assessed 1 month after PTA by the Wilcoxon signed-rank test.

after the 1-month follow-up was significantly lower in males compared to females (p = 0.001).

Follow-up analysis

During the follow-up period lasting 386 days, occurrence of the study endpoints were noted in 16 individuals. Considering those 16 individuals, the overall number of endpoint events was 25 and included: 20 reinterventions, 1 myocardial infarction, 2 deaths and 2 amputations. The Kaplan-Maier survival curve is presented in Figure 2. The probability of endpoint events was increased in patients with hypercholesterolemia at baseline (p = 0.03), individuals with CLI before PTA (p = 0.04), those with lower diastolic blood pressure at baseline (p = 0.03), in individuals with higher subendocardial viability ratio at baseline (p = 0.04), those with greater number of pack-years before PTA (p = 0.03) and with lower TBI before the procedure (p = 0.02).

Clinical presentation of PAD before PTA

The current study population included 72 patients. Out of these, 30 patients presented with CLI and 40 patients were without CLI (non-CLI). The remaining two individuals were not classified. A significant relationship was noticed between study endpoints and clinical presentation at baseline (CLI vs. non-CLI; p = 0.04). The percentage of

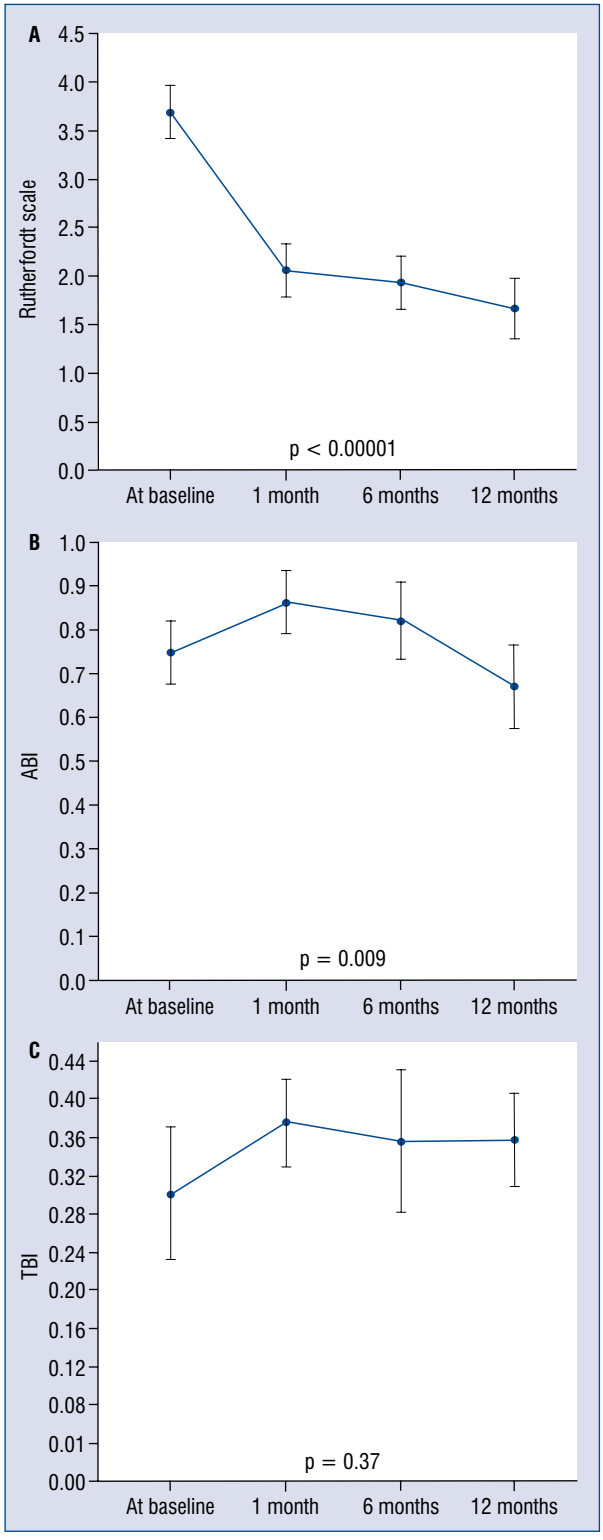

Figure 1. The change in ankle-brachial index (ABI), toe-brachial index (TBI) and Rutherford scale at following time points after percutaneous transluminal angioplasty (PTA) in comparison to baseline values; **A.** The change in the mean Rutherfordt grade value at following time points after PTA; **B.** The change in mean ABI value at following time points after PTA; **C.** The change in the mean TBI value at following time points after PTA

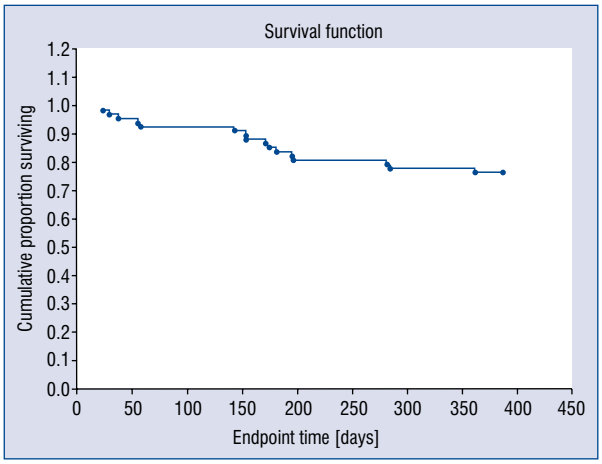

Figure 2. Kaplan-Meier survival analysis.

patients with CLI among those in which the study endpoints occurred was 68.7%, while in individuals without CLI at the baseline, the incidence of study endpoint events was significantly lower 35.2% ($p = 0.04$).

Discussion

Studies of brachial artery FMD have been reported since 1992, and today, it is the most widely used method in clinical research [13]. Apart from FMD, several other noninvasive tests for the assessment of endothelial function have been developed. In 2002, reactive hyperemia–peripheral arterial tonometry (RH-PAT) was reported to be the test for peripheral vascular endothelial function, and since then, its use has rapidly increased [14]. The RH-PAT technique is less operator-dependent and uses a contralateral arm as its internal control to correct systemic changes during testing. FMD assesses the endothelial response to shear stress in the brachial artery as a result of hyperemia, whereas RH-PAT measures the actual hyperemia. However, these methods differ in target vasculature: the brachial artery diameter in FMD versus a finger arterial pulse wave in RH-PAT. The Framingham Heart Study reported no statistically significant relationships between signals obtained with RH-PAT and FMD, suggesting that these reflect distinct aspects of vascular function [15]. Several published studies have investigated the relationship between cardiovascular events and endothelial function, nonetheless, the number of studies comparing FMD and RH-PAT as predictors of cardiovascular events is limited [16–18]. In a systematic review and meta-analysis, Matsuzawa

et al. [19] found that both brachial FMD and digital RHI-PAT have significant predictive value for future cardiovascular events after adjustment for other risk factors. The present analysis did not confirm that dependence indicating no significant relationship between the main indices of endothelial function (FMD, IMT, RHI) and study endpoints.

Carotid-femoral pulse wave velocity (cf-PWV) is another aspect addressed in this study. It is considered as the gold standard for estimation of regional arterial stiffness. Arterial stiffening increases systolic and pulse pressure, promotes left ventricular hypertrophy and dysfunction, and impairs capacity for myocardial perfusion [8]. It has been proven to be an independent predictor of all-cause and cardiovascular deaths in PAD patients [7]. It was revealed that abnormal artery stiffness is associated with major cardiovascular disease endpoints, including heart disease, stroke and chronic kidney disease. The present analysis did not confirm statistically significant dependence between baseline indices of artery stiffness and the study endpoints except for SEVR.

Surprisingly, in this study, higher values of SEVR at baseline were related to poorer clinical outcomes during the 12-month follow-up period. This relation is in conflict with the current understanding of SEVR.

The SEVR is an index of myocardial oxygen supply and demand, which can be assessed non-invasively by applanation tonometry. Low SEVR values indicate reduced subendocardial perfusion [20–22].

Low SEVR has been associated with reduced coronary flow reserve in patients with low ABI [23], microalbuminuria [24, 25], hypertension and cardiac autonomic neuropathy [26, 27] in patients with type 1 diabetes, low fitness in obesity [28, 29] and markers of inflammation in patients with rheumatoid arthritis [30]. Reduced SEVR has been shown to predict cardiovascular mortality in patients with chronic kidney disease [31] and the combined endpoint all-cause mortality and end-stage renal disease in patients with type 1 diabetes [25]. The reason for the described discrepancy remains unknown in our group of patients, but further investigation is planned on this subject.

The higher number of study endpoints was also observed in patients with kidney failure, hypercholesterolemia, lower diastolic blood pressure and TBI values at baseline.

Another finding worth mentioning is the fact that patients with CLI at baseline presented poorer clinical outcomes during the follow-up period compared to patients with intermittent claudication. CLI patients had significantly more episodes of reinterventions and study endpoints such as limb amputation, stroke, myocardial infarction, and death.

Symptomatic PAD in the lower limb presents itself as either intermittent claudication or CLI. CLI represents the most advanced form of PAD and is defined as chronic ischemic resting pain, ulcers or gangrene attributable to arterial occlusive disease [32, 33]. It is well established that CLI, compared to patients with claudication, confers a substantially worse prognosis with regard to both limb salvage and overall survival [34]. Knowing that, one must be aware that CLI patients should be treated very differently from non-CLI patients in terms of time to revascularization, technique of procedures and even pharmacological treatment. These patients require faster diagnosis, frequently multi-stage endovascular procedures, more aggressive pharmacological treatment and what is most important, they require a multidisciplinary approach.

Limitations of the study

The current study is of an observational and explorative nature. In the present population, it was necessary to first identify certain factors that could influence the study endpoints. Knowing these factors, the plan was to investigate them further in future studies.

For that reason, this study should be treated as a pilot study which can explain the relatively low number of patients. Most of the study patients are still under scheduled follow-up and it will be possible to investigate their endothelial function after a longer period of time.

Another study limitation was the fact that there was no coherent group of patients. The need for endovascular procedures was the main factor responsible for inclusion into the study. Patients were admitted to the clinic due to symptomatic PAD from different outpatient clinics. Time from diagnosis to the revascularization procedure was very limited, especially for patients with CLI. Since there was no control group or randomization, it was believed that the patients included better resemble the population.

Finally, FMD alone has some limitations. Because it is measured by ultrasound, it carries a risk for errors. The method is technically demanding, requiring specific training. Furthermore, FMD is very sensitive to a number of intercurrent factors that may influence vascular function transiently but may not have great importance for long-term

atherosclerosis risk. For example, FMD can be acutely lowered by an intercurrent viral illness, can be transiently impaired after a meal and varies in circadian pattern [35].

Conclusions

Baseline FMD, IMT and RHI values were not related to the number of study endpoints in patients with PAD after PTA during 12 months of follow-up. Among aPWA indices, higher baseline SEVR values corresponded with an increased number of study endpoints such as the number of reinterventions, death, myocardial infarction, amputation or stroke. Furthermore, the larger number of study endpoints was related to history of hypercholesterolemia, longer history of smoking, lower diastolic blood pressure and lower baseline TBI. Patients with CLI at baseline had significantly poorer treatment outcomes and a larger number of study endpoints during the 1-year follow-up period compared to patients with claudication.

Conflict of interest: None declared

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