Uniwersytet Jagielloński
Collegium Medicum

Paweł Kaczmarczyk

Ocena funkcji śródbłonka oraz parametrów przepływu krwi u pacjentów poddanych zabiegom wewnątrznaczyniowym

Endothelial function and blood flow parameters in patients undergoing endovascular treatment

Praca doktorska

Promotor: Prof. UJ dr hab. n. med. Paweł Maga

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im. Profesora Andrzeja Szczeklika, Uniwersytet Jagielloński Collegium Medicum
w Krakowie
Kierownik Kliniki: Prof. UJ dr hab. n. med. Paweł Maga
Kierownik II Katedry: Prof. dr hab. n. med. Krzysztof Sładek

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2. WSTĘP I UZASADNIENIE PODJĘTEJ TEMATYKI

Miażdżyca jest najczęściej stwierdzaną chorobą naczyń krwionośnych. Jedną z jej manifestacji klinicznych jest miażdżyca zarostowa tętnic kończyn dolnych (*peripheral arterial disease* – PAD). Choroba ta dotyczy 20–30% populacji w wieku powyżej 60. roku życia. W 60% przypadków współwystępuje z chorobą niedokrwienną serca i jest samodzielnym czynnikiem ryzyka nagłych incydentów sercowych [1-3]. Liczba chorych na PAD ciągle wzrasta, co w głównej mierze wynika z procesu starzenia się naszej populacji oraz z powodu zwiększającej się stale liczby pacjentów z cukrzycą i otyłością. Nieleczona lub nieprawidłowo leczona PAD może skutkować amputacją kończyny, będącą predyktorem wysokiej śmiertelności [2].

Aktualny stan wiedzy wskazuje na związek pomiędzy dysfunkcją śródbłonka tętnic a zwiększoną liczbą incydentów sercowo-naczyniowych, takich jak: zawał serca, udar mózgu, amputacje kończyny czy zgon. Zaburzenia funkcji śródbłonka odgrywają istotną rolę w patogenezie miażdżycy. Dotyczy to zarówno procesu powstawania blaszki miażdżycowej, jak i jej progresji oraz destabilizacji. Dysfunkcja śródbłonka wpływa na proces rozwoju blaszki miażdżycowej poprzez zaburzenie funkcji rozkurczowej naczynia, przesunięcie równowagi krzepnięcie–fibrynoliza w kierunku procesów krzepnięcia oraz ku zwiększeniu migracji komórek do ścian naczyń [4].

Najczęściej wymienianymi czynnikami ryzyka miażdżycy są: cukrzyca, nadciśnienie tętnicze, palenie tytoniu, hiperlipidemia. Zaprzestanie palenia tytoniu, kontrolowanie powyższych chorób oraz zwiększenie aktywności fizycznej mogą poprawić funkcję śródbłonka, a co za tym idzie – znacząco zmniejszyć ryzyko sercowo-naczyniowe [5]. Poprawa dotyczy głównie odpowiedzi motorycznej naczynia oraz powrotu stanu równowagi pomiędzy procesami krzepnięcia i fibrynolizy. U chorych bezobjawowych lub z długim dystansem chromania przestankowego stosuje się leczenie zachowawcze. W przypadku objawów upośledzających w znacznym stopniu codzienne funkcjonowanie oraz u chorych z krytycznym, przewlekłym niedokrwieniem

zagrażającym kończynie (CLTI) zalecana jest rewaskularyzacja. Jedną z metod rewaskularyzacji jest przezskórna angioplastyka wewnątrznaczyniowa (*percutaneous transluminal angioplasty* – PTA). U pacjentów poddanych skutecznej PTA w zakresie tętnic kończyn dolnych zwiększa się aktywność fizyczna, zmniejszeniu ulega katabolizm organizmu, następuje gojenie się zmian troficznych, co wpływa na poprawę kontroli glikemii, bólu, a także zmniejsza się częstotliwość występowania incydentów niedokrwienie–reperfuzja. Wykazano również znaczącą odpowiedź immunologiczną śródbłonka tętnic poddanych PTA [6].

W oparciu o powyższe spostrzeżenia sformułowano pytanie o wpływ PTA na wskaźniki funkcji śródbłonka tętnic oraz o to, czy stan śródbłonka sprzed rewaskularyzacji może być predyktorem odległych wyników leczenia pacjentów z miażdżycą tętnic kończyn dolnych. Pytania te znajdują szczególne uzasadnienie w kontekście niezadowalających odległych efektów klinicznych po PTA w następstwie nawrotu zwężenia lub niedrożności tętnic. To niepowodzenie występuje u około 30% chorych w pierwszym roku po PTA, bez względu na metodę leczenia. Dotychczas nie wyjaśniono w pełni jego patomechanizmu [7]. Poszukiwanie biomarkerów będących predyktorami niepowodzeń terapii po PTA, takich jak poziom leukotrienów czy tromboksanów, nadal pozostaje w fazie badawczej [8].

W kontekście odległych wyników leczenia pacjentów z PAD, brak jest również obiektywnej metody oceniającej dynamikę przepływu krwi w tętnicach podudzia po PTA. Opracowana do oceny wyników chirurgicznego pomostowania naczyniowego skala *runoff grade* [9] oraz kardiologiczna skala TIMI (*thrombolysis in myocardial infarction*) stosowana do oceny wyników rewaskularyzacji tętnic nasierdziowych są proste w użyciu, lecz w dużej mierze obarczone subiektywną interpretacją operatora, a ponadto o niskiej czułości i swoistości metody. Doniesienia w literaturze wskazujące na związek pomiędzy obiektywnie ocenionym przepływem krwi w kończynach dolnych a wynikami klinicznymi w odległej obserwacji są znikome.

Pacjenci z miażdżycą tętnic kończyn dolnych stanowią – pod względem stopnia zaawansowania i manifestacji klinicznej oraz współwystępowania chorób towarzyszących –

heterogenną populację. Pacjenci z chromaniem przestankowym znacząco różnią się od chorych z CLTI, zarówno z uwagi na wczesne i odległe efekty rewaskularyzacji, jak i występowanie poważnych incydentów sercowo-naczyniowych. Chorzy z CLTI są bardziej narażeni na powikłania okołozabiegowe [10-12] i często wymagają odmiennych procedur terapeutycznych oraz farmakoterapii. Powyższe wyodrębnienie subpopulacji chorych z CLTI i niekrytycznym niedokrwieniem kończyn dolnych nie zawsze znajduje odzwierciedlenie w pracach badawczych. Większość autorów analizuje wyniki badań i efekty leczenia obu grup łącznie. Brak jest danych w piśmiennictwie na temat różnic w dysfunkcji śródbłonka tętnic po PTA w tych odmiennych grupach chorych.

Mimo postępu metod diagnostycznych i terapeutycznych wynikającego z nowoczesnych technologii nadal odczuwalny jest brak narzędzi ułatwiających klinicystom podejmowanie optymalnych decyzji o wyborze formy leczenia w kontekście przewidywania jego odległych efektów u chorych z PAD. Niezbędne w tym celu jest lepsze poznanie wpływu PTA na wskaźniki funkcji śródbłonka tętnic i próba ich skorelowania z odległymi wynikami klinicznymi.

3. CELE PRACY

1. Ocena związku między wskaźnikami funkcji śródbłonka i odległymi wynikami klinicznymi u pacjentów z miażdżycą tętnic kończyn dolnych poddanych wewnątrznaczyniowej angioplastyce balonowej (PTA).

2. Analiza porównawcza parametrów śródbłonka u pacjentów z przewlekłym niedokrwieniem zagrażającym kończynie i niekrytycznym niedokrwieniem kończyn dolnych w rocznej obserwacji po PTA.

3. Ocena dynamiki przepływu krwi w tętnicach kończyn dolnych u pacjentów poddanych PTA z powodu miażdżycy obwodowej – jako potencjalnego czynnika prognostycznego odległych wyników klinicznych.

4. MATERIAŁ I METODY

Dotyczy pracy: „The relationship between pulse waveform anlysis indices, endothelial function and clinical outcomes in patients with peripheral artery disease treayed using percutaneous transluminal angioplasty during one-year follow-up period"

Badanie przeprowadzono jako prospektywną obserwację, oceniającą korelację przedzabiegowej czynności śródbłonka względem częstości występowania incydentów sercowo-naczyniowych oraz ponownych interwencji naczyniowych podczas obserwacji rocznej po PTA tętnic kończyn dolnych. Badaniem objęto 72 pacjentów zakwalifikowanych i poddanych PTA z powodu objawowej miażdżycy tętnic kończyn dolnych w skali Rutherforda 3–6. Wśród nich 42,8% prezentowało CLTI. Przed zabiegiem PTA oraz w trakcie wizyt miesiąc i 6 miesięcy po PTA wykonywano pomiary funkcji śródbłonka:

- badanie przepływozależnego rozszerzenia tętnicy ramiennej (*flow-mediated dilatation* – FMD) – standardowa metoda oceny czynności śródbłonka na podstawie rozszerzalności tętnicy ramiennej pod wpływem zwiększonego przepływu;

- ocena wskaźnika reaktywnej hyperemii (*reactive-hyperemia index* – RHI) – pomiar czynności śródbłonka na podstawie zmian obwodowego napięcia tętniczego na końcu palca, w warunkach reaktywnego przekrwienia, za pomocą pneumatycznego pletyzmografu dokonującego pomiaru zmian objętości;

- pomiar fali tętna (*pulse wave analysis* – PWA) – przy wykorzystaniu przetwornika fotopulsoksymetrycznego zakładanego na palec mierzona jest krzywa fali tętna w czasie rzeczywistym oraz wartości uśrednione, co pozwala obliczyć współczynnik sztywności tętnic przewodzących (*stiffness index* – SI) oraz napięcie małych tętnic – wskaźnik odbicia (*reflection index* – RI);

- ocena grubości kompleksu błony środkowej i wewnętrznej (*intima-media thickness* – IMT) – badanie wykonywane na tętnicach szyjnych przy pomocy aparatu ultrasonograficznego; parametr ten jest wykładnikiem rozwoju zmian miażdżycowych i pozwala oszacować ryzyko incydentów sercowo-naczyniowych.

Ponadto, w trakcie rocznej obserwacji oceniano stan kliniczny kończyn według skali Rutherforda oraz parametry hemodynamiczne ukrwienia kończyn za pomocą wskaźników: kostka–ramię (ABI) oraz paluch–ramię (TBI). Punkty końcowe badania obejmowały: zawał serca, amputację kończyny, zgon, udar i ponowną interwencję naczyniową.

Dotyczy pracy: „Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment"

Prospektywne, jednoośrodkowe badanie obserwacyjne. Badaniem objęto 70 pacjentów z miażdżycą tętnic kończyn dolnych, w tym 30 z objawami krytycznego niedokrwienia i 40 z niedokrwieniem niekrytycznym (z chromaniem przestankowym), u których wykonano PTA w zakresie tętnic kończyn dolnych. Wszyscy uczestnicy badania poddani zostali rocznej obserwacji – wizyty kontrolne po miesiącu, 3, 6 i 12 miesiącach od PTA. Oceniano stan kliniczny uczestników badania, wskaźniki ABI i TBI oraz badano funkcje śródbłonka za pomocą wskaźników: FMD, RHI, PWA, IMT.

Po PTA u wszystkich uczestników badania stosowano przez 4 tygodnie podwójną terapię przeciwpłytkową (aspiryna w dawce 75 mg/dobę oraz klopidogrel w dawce 75 mg/dobę) w połączeniu ze statyną (atorwastatyna w dawce 40–80 mg lub rosuwastatyna w dawce 20–40 mg), która była kontynuowana długotrwale z jednym lekiem przeciwpłytkowym.

Dotyczy pracy: „Dynamics of below-the-knee arterial blood flow after endovascular revascularization of peripheral arteries as a potential predictor of clinical outcomes during a one-year follow-up period”

Do badania włączono 287 pacjentów, u których wykonano 302 zabiegi PTA w zakresie tętnic poniżej więzadła pachwinowego. 162 zabiegi PTA przeprowadzono u pacjentów CLTI, a 140 u chorych z chromaniem przestankowym. Po każdym zabiegu oceniano przepływ krwi w zakresie tętnic podudzia – z wykorzystaniem cyfrowej angiografii subtrakcyjnej, za pomocą liczby klatek (*frame count* – FC). Procedura badania była ujednolicona dla wszystkich uczestników. Wielkość pola ekspozycji, SID (*source-to-image distance*), środek cieniujący i sposób jego podania były stałe dla wykonanych pomiarów. Obrazy angiograficzne rejestrowane były z częstotliwością 6 klatek na sekundę. Dla każdej drożnej tętnicy podudzia (piszczelowej przedniej, tylnej i strzałkowej) odrębnie obliczano liczbę klatek podczas przepływu środka cieniującego pomiędzy najbardziej oddalonymi punktami naczynia objętymi polem ekspozycji (ramką).

Następnie pacjenci objęci byli roczną obserwacją – wizyty kontrolne po miesiącu, 3, 6 i 12 miesiącach po PTA. Każdorazowo oceniano stan kliniczny kończyny (skala Rutherforda), wskaźniki ABI i TBI oraz rejestrowano zdarzenia niepożądane, jak: konieczność reinterwencji z powodu nawrotu zwężenia lub okluzji tętnicy oraz amputacje.

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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

Authors: Paweł S. Kaczmarczyk, Paweł Maga, Rafał Niżankowski, Rafał Januszek, Marzena Frołow, Mikołaj Maga, Jolanta Kościelniak, Andrzej Belowski

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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

Short title: Pulse waveform analysis indices, endothelial function and clinical outcomes in patients with PAD

Paweł S. Kaczmarczyk[1], Paweł Maga[1,2], Rafał Niżankowski[2], Rafał Januszek[3,4], Marzena Frołow[2], Mikołaj Maga[2], Jolanta Kościelniak[1,2], Andrzej Belowski[1,2]

[1]Angio-Medicus Treatment Facility, Krakow, Poland
[2]Department of Angiology, Jagiellonian University Medical College, Krakow, Poland
[3]2nd Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland
[4]Department of Clinical Rehabilitation, University of Physical Education, Krakow, Poland

Address for correspondence: Paweł Kaczmarczyk, MD, Department of Angiology and Cardiology, University Hospital in Krakow, ul. Skawińska 8, 31–066 Kraków, Poland, tel: +48 12 430 52 66, fax: +48 12 430 51 80, e-mail: kaczmarczyk_pawel@wp.pl

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 one-year follow-up period.

Methods: The study included 72 individuals with PAD at amean 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 one-year follow-up.
Key words: endothelial function, percutaneous transluminal angioplasty, arterial pulse waveform analysis, clinical outcomes

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 one-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 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 ankle-brachial index (ABI), tibial-brachial index (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 aspirin (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 s 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°C 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, 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 intima–media thickness.

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 ration (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 one-year follow-up (Fig. 1A) 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 one 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. 1C). 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 SBP ($r = 0.27$, $p = 0.04$), 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) 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 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 subendocardial viability ratio (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 peripheral artery disease 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 one-year follow-up period compared to patients with claudication.

Conflict of interest: None declared

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Table1. Gene characteristics of individuals included in the study at baseline, pharmacological therapy and family history.

Variables	**Number of individuals, n (%)** **Overall group of patients (n = 72)**
Age [years]	66.3 ± 7.2 65 [61.75÷72]
Gender, males	57/72 (79.1%)
Critical limb ischemia	30/70 (42.8%)
Smoking: Current Previous Whenever Years Cigarettes per day Pack years	 12/72 (16.7%) 52/72 (72.2%) 64/71 (90.1%) 31.4 ± 12.8 30 [20÷40] 18.3 ± 7.5 20 [15÷20] 30.0 ± 19.0 30 [19÷40]
Hypertension	50/72 (69.4%)
Dyslipidemia	34/72 (47.2%)
Diabetes mellitus: Years of treatment	27/72 (37.5%) 15.8 ± 7.9 15 [10÷20]
Coronary artery disease: Myocardial infarction	26/72 (36.1%) 10/72 (13.9%)
Kidney failure	4/72 (5.5%)
Stroke	6/72 (8.3%)

Family history:	
Hypertension	1/72 (1.4%)
Dyslipidemia	0/72 (0%)
Diabetes mellitus	2/72 (2.8%)
Coronary artery disease	0/72 (0%)
Myocardial infarction	1/72 (1.4%)
Cerebral stroke	0/72 (0%)
Peripheral artery disease	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%)
Aspirin	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 inhibitors; LMWH — low molecular weight heparin

Table 2. Characteristics of culprit lesion and distribution of lower limb atherosclerotic lesions

Variables	**Number of individuals, n (%)** **Overall group of patients (n = 72)**
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: a b c d	44/72 (61.1%) 5/44 (11.4%) 13/44 (29.5%) 10/44 (22.7%) 16/44 (36.4%)
TASC Ao-iliac: a b c d	19/72 (26.4%) 6/19 (31.6%) 7/19 (36.8%) 4/19 (21%) 2/19 (10.5%)
Graziani's morphologic categorization of disease severity: 1 2a 2b 3 4 5 6 7	32/72 (44.4%) 1/32 (3.1%) 6/32 (18.7%) 2/32 (6.2%) 3/32 (9.4%) 12/32 (37.5%) 1/32 (3.1%) 6/32 (18.7%) 1/32 (3.1%)
Number of stenoses > 50%: 1 2 3 4 5 Occlusions: 1 2	70/72 (97.2%) 38/70 (54.3%) 18/70 (25.7%) 11/70 (15.7%) 2/70 (2.8%) 1/70 (1.4%) 10/70 (14%) 7/10 (70%) 3/10 (30%)

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

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
Central augmentation pressure 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]	79.5 ± 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].

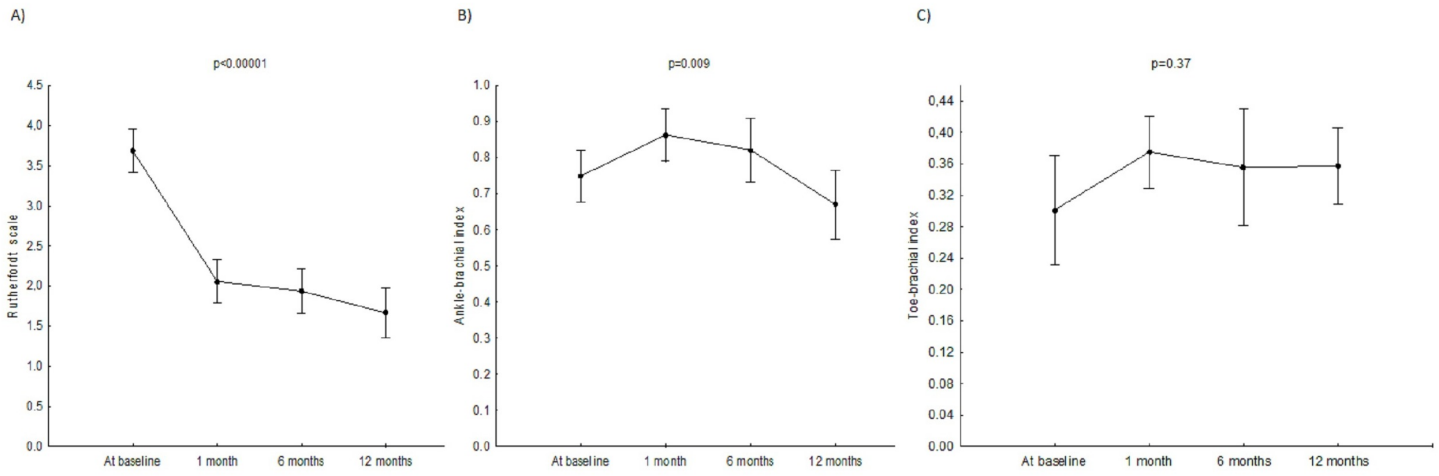
*The value one month after PTA was significantly different from that assessed before PTA by the Wilcoxon signed-rank test.

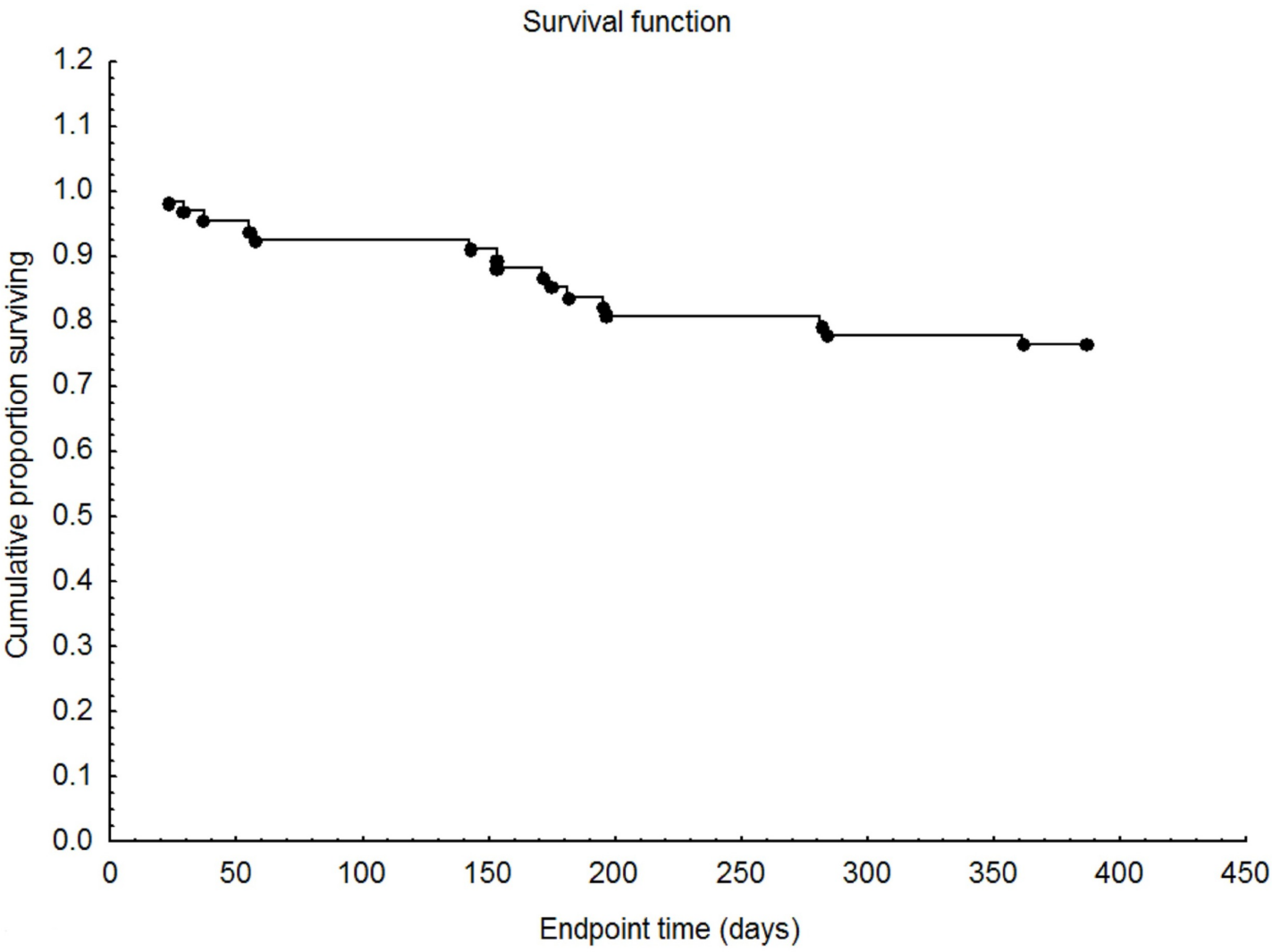
**The value six months after PTA was significantly different from that assessed one month after PTA by the Wilcoxon signed-rank test.

FIGURE LEGEND

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.


A)
p<0.00001
Rutherfordt scale
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
At baseline
1 month
6 months
12 months
B)
p=0.009
Ankle-brachial index
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
At baseline
1 month
6 months
12 months
C)
p=0.37
Toe-brachial index
0,44
0,40
0.36
0.32
0.28
0.24
0.20
0.16
0.12
0.08
0.04
0.00
At baseline
1 month
6 months
12 months


Survival function
Cumulative proportion surviving
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
250
300
350
400
450
Endpoint time (days)

ORIGINAL ARTICLE

Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment

Paweł Kaczmarczyk[1], Marzena Frołow[1, 4], Rafał Januszek[2, 3], Andrzej Belowski[1], Iwona Gregorczyk-Maga[6], Stefan Chlopicki[4, 5], Paweł Maga[1]

[1]Department of Angiology, Jagiellonian University Medical College, Kraków, Poland
[2]2nd Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
[3]Department of Clinical Rehabilitation, University of Physical Education, Kraków, Poland
[4]Jagiellonian Centre for Experimental Therapeutics, Jagiellonian University, Kraków, Poland
[5]Chair of Pharmacology, Jagiellonian University Medical College, Kraków, Poland
[6]Institute of Dentistry, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Paweł Maga, MD, PhD, Department of Angiology, Jagiellonian University Medical College, Jakubowskiego 2, 30–688 Kraków, Poland, phone: +48 124 003 262, e-mail: maga.pawel@gmail.com

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ABSTRACT

Background: Critical limb ischemia (CLI) is the most advanced stage of peripheral arterial disease. CLI patients, compared to non-CLI, achieve worse treatment outcomes and generate higher costs.

Aims: The aim of the study was to compare endothelial function and clinical outcomes in CLI and non-CLI patients after percutaneous transluminal angioplasty (PTA).

Methods: In this prospective, follow-up study, 30 CLI patients and 40 non-CLI patients underwent PTA. Endothelial function was assessed based on flow mediated dilatation (FMD), reactive-hyperemia index (RHI), while the ankle-brachial index, toe-brachial index and the Rutherford scale were used for peripheral artery disease progression evaluation. The results were assessed before PTA, as well as 1, 3, 6 and 12 months after the procedure.

Results: There were no differences at the baseline regarding to endothelial function between both groups. Neither FMD nor RHI changed after PTA in any of the groups, although there was a difference in median RHI value between CLI and non-CLI patients regarding the 1st and 6th month of the follow-up (RHI6–RHI1 = 0.08 in CLI and –0.15 in non-CLI; $P = 0.01$). The larger baseline intima-media thickness (IMT) in the CLI group allowed to predict a greater number of re-intervention ($P = 0.01$) and major adverse event rates ($P = 0.03$). CLI patients presented larger decrease in the Rutherford scale compared to non-CLI ($P < 0.001$).

Conclusions: Baseline IMT was predictive for re-interventions and major adverse event rates. Although neither of groups exhibited significant changes in endothelial function, we proved differences between them regarding to changes in RHI.

Key words: critical limb ischemia, endothelium, endovascular treatment, peripheral artery disease, revascularization

Kardiol Pol 2021; 79, 7–8: 804–812

INTRODUCTION

Peripheral artery disease (PAD) is characterized by ischemia in the lower limbs due to narrowing of the arteries because of atherosclerotic plaque accumulation [1]. Critical limb ischemia (CLI) is the most advanced stage of PAD associated with macro- and microcirculatory, as well as rheological disorders. The Inter-Society Consensus for the Management of PAD estimates that 25% of patients diagnosed with CLI will die within 1 year and an additional 30% will undergo limb amputation [2]. CLI patients typically present a spectrum of symptoms including pain during rest, non-healing ulcers, and tissue necrosis with gangrene [3]. Limb revascularization is considered the first line of treatment for CLI because it significantly reduces the rate of limb amputation and mortality [4, 5]. Comorbidities are more frequent in CLI patients, who require faster treatment access and more advanced procedural strategies. These facts make them more vulnerable to procedural complications [6–8]. Despite clinical differences between patients with CLI and those with limb claudication (non-CLI), they both exhibit

WHAT'S NEW?

In the majority of clinical studies related to peripheral arterial disease, critical limb ischemia (CLI) patients were analyzed together with non-critical limb ischemia (non-CLI) patients. Thus, it is unknown whether endothelial function after endovascular procedures changes in a similar way among CLI and non-CLI patients. To our knowledge, we are the first to investigate if there are any significant differences regarding endothelial function (flow mediated dilatation), intima-media thickness, or clinical outcomes separately in these 2 groups. It is suggested in the present study that CLI patients had better clinical response to revascularization than non-CLI patients (larger drop in the Rutherford scale, better increase in toe-brachial index [TBI]), however, there was no improvement in endothelial function after revascularization in either group.

endothelial dysfunction, the hallmark of atherosclerosis pathogenesis. In fact, endothelium-dependent vasodilation is impaired in coronary artery disease patients [9, 10]. Interventions proven to reduce cardiovascular risk also reverse endothelial dysfunction and failure of the endothelium to respond to therapy [11]. Endothelial dysfunction is also present in PAD patients. The loss of nitric oxide-dependent regulation regarding flow in the lower limbs may worsen the vasoconstrictor effects of catecholamines and impair flow mediated dilatation (FMD), which, in consequence, may worsen stenosis severity while increasing resistance to blood flow during exercise [12].

Understanding the heterogeneity of these two groups, we should expect many differences concerning clinical aspects between patients with claudication and critical limb ischemia, especially after revascularization. Nevertheless, in the majority of clinical studies related to PAD, CLI patients were analyzed together with non-CLI patients. It is not known whether endothelial function after endovascular procedures changes in a similar way in CLI and non-CLI patients.

Therefore, here, we compared endothelial function and clinical outcomes in CLI and non-CLI patients after percutaneous transluminal angioplasty (PTA) during a 12-month follow-up period.

METHODS

Study design

The study was conducted as a prospective, single-center follow-up evaluation. Patients with critical limb ischemia as well as those with stable PAD (Rutherford class from 2 to 3), due to iliac, femoropopliteal, or below–the-knee disease, were eligible for the study. Exclusion criteria were history of end-stage kidney disease, age above 85, and pain related to limb ischemia not allowing to maintain a horizontal position. Patients with incompressible tibial arteries were not eligible for the study.

All subjects provided their written and informed consent before beginning the trial. The study complies with the 1964 Declaration of Helsinki and was approved by the local ethical committee.

Endovascular procedures

Endovascular treatment was performed in a routine manner. A 4 French (F) to 6F sheath was introduced into the artery and diagnostic angiography was performed. Each individual received 5 000 International Units 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 or expandable cobalt-chromium balloon stents. Post-interventional therapy lasted 4 weeks and consisted of both aspirin (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 baseline assessment for all patients and were maintained throughout the study, although compliance was not monitored. Follow-up visits were conducted 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 ankle-brachial index (ABI) improvement of at least 0.1.

Assessment of FMD

The study was performed on the basis of current FMD assessment guidelines [13]. Patients were examined in fasting state, in supine position. They were asked to refrain from smoking, as well as alcohol and caffeinated beverage consumption in the 12 hours preceding the trial. All vasoactive drugs were discontinued 24 hours before the procedure. FMD was performed in a quiet, temperature-controlled room (21°C to 24°C). Measurements were performed on the dominant forearm. A B-mode brachial artery image was obtained using a 14-MHz linear-array transducer with the Siemens Accuson 2000 ultrasound. The longitudinal segment above the antecubital fossa was used to measure brachial artery diameter.

At baseline, a 10-second clip was recorded to measure the baseline artery diameter. Then, a blood pressure cuff was inflated on the forearm to 40 mm Hg above systolic pressure for 5 minutes. Immediately after cuff deflation, maximal blood velocity was measured for 15 seconds to evaluate arterial flow. Next, a 120-second video clip of the brachial artery in B-mode was recorded to calculate the post-occlusion brachial artery diameter. Continuous analysis of changes in the artery diameter were performed during post-processing at the authors' laboratory by means of a wall-tracking computer system developed by Zieliński et al. [14]. The maximal diameter (maximal FMD — % FMD) was obtained using a semi-automatic technique, operating on the basis of the two regions of interest (ROI), indicating

the anterior and posterior artery wall marked by the operator on the first frame of the ultrasound clip. The algorithm for tracking the borders of the arterial walls was based on the active contour method.

Assessment of the Reactive Hyperemia Index (RHI)

Digital pulse amplitude was measured simultaneously with FMD in a fasting state and supine position using a portable appliance testing (PAT) device comprising a pneumatic plethysmograph measuring digital pulse volume changes (Endo-PAT2000, Itamar Medical, Caesarea, Israel) [15]. The digital pulse amplitude was acquired continually during the examination and digitally recorded to a laptop. Data were analyzed by a computerized algorithm (Itamar Medical), which automatically and operator-independently calculates Assessment of RHI.

Pulse Wave Analysis (PWA)

Arterial pulse waveform 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. AP was defined as the maximal systolic pressure minus pressure at the inflection point. We measured pulse pressure (PP), augmentation index (AI), central augmentation index (CAI), ejection duration (ED), subendocardial viability ration (SEVR), central augmentation pressure (CAP), CAP normalized for the heart rate of 75 beats per minute (CAP-HR75), stiffness index (SI), and reflection index (RI).

Assessment of lower limb ischemia

ABI was calculated with the patient in supine position. The highest systolic pressure of the anterior or posterior tibial artery was measured in each limb and then divided by the highest brachial artery pressure. The mean ABI value for the two legs was included in statistical analysis. Toe-brachial index [TBI] was also calculated with the patient in supine position. The systolic pressure on the big toe was obtained for each limb using a photoplethysmograph (Nicolet VasoGuard; VIASYS Healthcare, Madison, WI, USA), and was divided by the highest brachial artery pressure. Pain-free walking distance and maximal walking distance were measured in each patient before PTA and at every follow-up visit using a treadmill exercise test.

Measurements of intima-media thickness (IMT)

To measure carotid 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 hypoechogenic space. The distance between the leading edge of the first, far wall bright line (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the IMT.

Follow-up of patients

All of the treated patients were followed at the University Hospital Angiology Outpatient Clinic for a period of 12 months following the procedure. Endothelial function was assessed before as well as 1, 3, and 6 months after PTA based on FMD and the reactive-hyperemia index (RHI), while arterial stiffness was evaluated using arterial PWA. Clinical status was evaluated before as well as 1, 3, 6, and 12 months following PTA using the ABI or TBI. The carotid artery was examined before and 1, 3, and 6 months after PTA via IMT measurement. The outcomes were analyzed separately. The primary outcome measures of the study were changes in endothelial function (FMD, RHI, arterial PWA), clinical status (ABI, TBI), and IMT after PTA. The secondary outcome measures were freedom from major adverse limb events (MALE; including occurrence of death, stroke, myocardial infarction, major amputation, and/or re-intervention). Secondary study endpoints were assessed as composite effect (MALE) and solely, all the outcomes separately.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean (standard deviation, [SD]) or median (lower quartile [Q1] — upper quartile [Q3]), where applicable. Normality was assessed via the Shapiro-Wilk test. Equality of variance was evaluated using the Levene's test. Differences between the two groups were compared using the Student's or Welch's t-test, depending on the equality of variances for normally distributed variables. The Mann-Whitney U test was applied for non-normally distributed continuous variables. Categorical variables were compared with the Pearson's chi-squared or Fisher's exact tests if 20% of cells had an expected count of less than 5 (Monte Carlo simulation for Fisher's test using tables of higher dimensions than 2×2). The Wilcoxon matched pair test was used for the comparison of two dependent samples. Friedman's non-parametric ANOVA was used to compare repeated measures of more than two groups and between the groups with more than two measurements. Re-intervention rates and MALE rates in the CLI and non-CLI groups were compared using the log-rank test. Kaplan-Meier estimate curves were generated for MALEs and re-interventions according to the CLI status. MALEs was defined as a composite clinical endpoint including: occurrence of death, stroke, myocardial infarction, major amputation, and/or re-intervention. For comparison of relative changes in endothelial and clinical parameters between measurements at given time periods after PTA in the CLI and non-CLI groups, the Benjamini–Hochberg

Table 1. Baseline patient characteristics

Variables	Number of individuals, n (%)		*P*-value
	CLI (n = 30)	Non-CLI (n = 40)	
Age, years	65.6 (7.5)	67.0 (7.0)	0.57
Gender, males	24 (80)	31 (77.5)	0.8
Smoking, pack years	24 (82.7) 30 (10.4–37.5)	38 (95) 30 (17.5–40)	0.05 0.49
Hypertension	18 (60)	32 (80)	0.06
Dyslipidemia	15 (50)	19 (47.5)	0.83
Diabetes mellitus, years of treatment	11 (36.7) 16.3 (8.4)	16 (40) 15.4 (7.8)	0.77 0.79
Coronary artery disease	11 (36.7)	15 (37.5)	0.94
Myocardial infarction	3 (10)	7 (17.5)	0.37
Kidney failure (GFR <60 ml/min/1.73 m^2)	3 (10)	1 (2.5)	0.18
Cerebral stroke	2 (6.7)	4 (10)	0.62
Pharmacotherapy before intervention			
Statins	4 (13.3)	2 (5)	0.21
Acetylsalicylic acid	5 (16.7)	5 (12.5)	0.62
Insulin	3 (10)	0 (0)	0.04
ACEIs/ARBs	1 (3.3)	2 (5)	0.73
Ca-blockers	2 (6.67)	3 (7.5)	0.89
β-blockers	1 (3.3)	1 (2.5)	0.83

Data are expressed as mean (SD), median (IQR) and numbers (percentages).

Abbreviations: ACEIs, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; Ca-blockers, calcium channel blockers; CLI, critical limb ischemia; GFR, glomerular filtration rate

procedure was used to adjust the *P*-value [16]. Spearman correlation coefficient was calculated for comparison between selected indices. A *P*-value of <0.05 was considered statistically significant. STATISTICA for Windows Release 10 (Statsoft Inc., 2011) was used for data analysis.

RESULTS

Patient characteristics

Clinical characteristics of the patients included in the present study are shown in Table 1. The mean age of the CLI patients was 65.6 (7.5) years, while for non-CLI patients this totaled 67 (7) years. There were no differences in age between these two groups.

There were also no differences in pharmacological treatment or family medical history between the groups (Table 1). At the time of admission, less than 20% of patients were on statins, anti-platelet, or angiotensin converting enzyme inhibitor/ angiotensin receptor blockers-based therapy. After PTA, all patients were prescribed treatment based on aspirin with clopidogrel and high-doses of statins. Kidney failure was defined when glomerular filtration rate was less than 60 ml/min/1.73 m^2. Blood pressure higher than 140/90 mm Hg was defined as abnormal. Since we did not measure in this study serum glucose and LDL levels, we had to accept diagnoses of diabetes and hypercholesterolemia from patients' medical history.

Considering the observational period, the mean length of the follow-up was 406.1 (209.7) days in the CLI group and 471.7 (179.2) days in the non-CLI group ($P = 0.17$). Then, the follow-up period in both groups was limited to 12 months in order to objectify the comparative analysis of follow-up results. During the 12-month follow-up, there were no amputations in the non-CLI group, but 2 amputations in the CLI group (6.7%). There were 9 (30%) re-interventions in the CLI group and 4 (10%) in the non-CLI group ($P = 0.03$). During the follow-up period, 1 patient (2.5%) from the non-CLI group died, while no cases of death were noted in the CLI group during that time. Summarizing, there were 11 (36.7%) MALEs in the CLI group and 5 (12.5%) in the non-CLI group ($P = 0.02$). CLI and non-CLI groups also displayed differences in outcomes based on Kaplan-Meier survival analysis for MALE and re-interventions (Figure 1).

Walking distance

Pain-free walking distance and maximal walking distance improved only in the non-CLI group ($P = 0.02$ and $P = 0.01$, respectively), however, there were no differences between the groups ($P = 0.13$ and $P = 0.11$, respectively; Table 2).

IMT

The relationship between clinical outcomes and baseline IMT

The IMT value >0.9 mm was found in 36 patients (50.7%) from the overall group. The re-interventions occurred in 10 patients with IMT >0.9 mm out of 13 found in the whole group (76.9%), while considering MALEs there were 11 patients with IMT >0.9 mm out of 16 found in the overall group (68.7%). The relationship between baseline IMT and clinical outcomes showed that CLI patients with higher initial mean IMT (thicker than 0.9 mm) value experienced the need for a larger number of re-interventions ($r = 0.45$; $P = 0.01$) and larger number of MALEs ($r = 0.45$; $P = 0.01$).

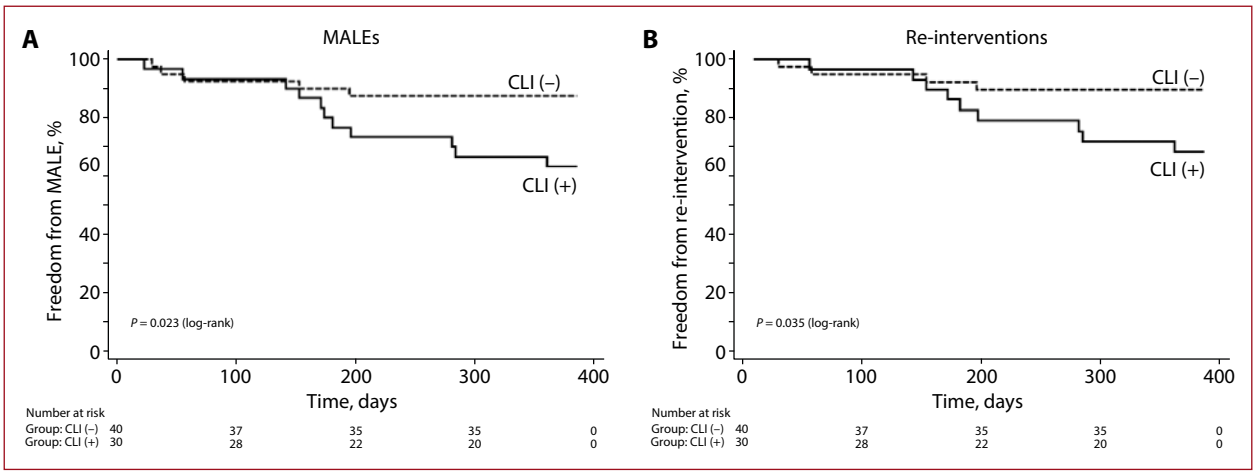

Figure 1. A. Kaplan-Meier survival curves according to critical limb ischemia (CLI) and non-CLI status for major adverse lower limb events. **B.** Kaplan-Meier survival curves according to CLI and non-CLI status for re-interventions

Abbreviations: MALE, major adverse limb events

Table 2. Changes of endothelial function parameters in critical limb ischemia (CLI) and non-CLI patients during the 6-month follow-up period following angioplasty

Variable	CLI			*P*-value	Non-CLI			*P*-value	*P*-value[a]
	At baseline	1 month	6 months		At baseline	1 month	6 months		
FMD	3.0 (1.7–4.7)	5.2 (3.3–6.4)	2.9 (1.9–5.3)	0.16	4.4 (2.1–6.6)	3.9 (2.6–6.5)	2.4 (1.3–4.4)	0.08	0.26
PP	66 (56–76)	63 (56–80)	72 (56–80)	0.88	71 (69–75)	66 (58–78)	62 (53–70)	0.4	0.74
AI	100.5 (88–115)	92.5 (82–107)	98 (83–105)	0.65	94 (85–110)	94 (87–109)	93.5 (88–99.5)	0.23	0.74
Central AI	149 (138–178)	148 (130–165)	151 (133–170)	0.79	156 (135–172)	163 (142–168)	148 (138–158.7)	0.12	0.85
ED	323 (289–337)	322 (294–342)	336 (294–346)	0.6	308 (290–330)	305 (292–329)	314.5 (301.7–330)	0.58	0.81
SEVR	154 (133–171)	145 (118–156)	148 (131–160)	0.61	144.5 (132–165.5)	149 (126–160)	144.5 (133–162.5)	0.89	0.99
CAP	17 (13.5–26)	18 (14–23.5)	18 (12–27)	0.91	17 (13–27)	20 (13–23)	15.5 (12.2–21.5)	0.25	0.89
CAP HR75	17 (11.5–19.5)	14.5 (13.2–19.5)	14 (10–20.5)	0.77	16 (14–21)	16 (14–21)	13 (11–17.2)	0.03	0.61
SI	20 (20–20)	20 (19–20)	20 (20–20)	0.93	20 (18–20)	20 (17–20)	20 (20–20)	0.66	0.15
RI	100 (100–100)	100 (97–100)	100 (100–100)	0.94	100 (94–100)	100 (80.1–100)	100 (100–100)	0.58	0.07
RHI	1.46 (1.19–1.81)	1.37 (1.08–1.62)	1.44 (1.16–1.98)	0.66	1.59 (1.22–2.26)	1.68 (1.32–2.22)*	1.46 (1.32–1.73)	0.16	0.69
PFWD, m	50 (8.75–200)	100 (50–200)	125 (82.5–200)	0.39	50 (27.5–100)	200 (47.5–500)	100 (35–400)	0.02	0.13
MWD, m	100 (10–250)	200 (70–200)	200 (87.5–300)	0.27	100 (30–150)	300 (50–500)	150 (82.5–500)	0.01	0.11
SBP, mm Hg	143.8 (18.2)	145.6 (16.3)	149.4 (18.6)	0.56	150 (14.8)	146 (19.3)	142.2 (16.7)	0.18	0.35
DBP, mm Hg	77.1 (9.2)	78.1 (7.6)	79.8 (7.0)	0.52	81.9 (6.8)[b]	80.2 (7.0)	79.1 (10.5)	0.41	0.1
IMT, mm	0.94 (0.3)	—	0.91 (0.26)	0.055	0.97 (0.29)	—	0.94 (0.26)	0.23	0.88

Data are expressed as mean (SD) and median (IQR).

[a]Comparison between CLI and non-CLI with ANOVA Friedman's test for two groups with repeated measurements (2-way repeated measures ANOVA test).

[b]*P* <0.05 when comparing particular indices at corresponding time points in the CLI and non-CLI groups.

Abbreviations: AI, coronary augmentation index; CAP, central augmentation pressure; CAP HR75, CAP normalized for the heart rate of 75 beats per minute; DBP, diastolic blood pressure; ED, ejection duration; FMD, flow mediated dilatation; IMT, intima-media thickness; MWD, maximal walking distance; PFWD, pain-free walking distance; PP, pulse pressure; RHI, reactive-hyperemia index; RI, reflection index; SBP, systolic blood pressure; SEVR, subendocardial viability ratio; SI, stiffness index

Clinical outcomes

Changes in Rutherford scale and TBI after PTA in CLI and non-CLI patients

Clinical outcomes assessed as the Rutherford grade revealed that during the follow-up, the Rutherford grade decreased significantly in the CLI group and did not change in the non-CLI (Figure 2). TBI did not change at the following time points in the CLI and non-CLI groups, and did not differ between either of the groups (Figure 2).

Endothelial function

Changes in FMD after PTA in CLI and non-CLI patients

The FMD measurements did not change during the following time points of the observational period in the CLI or non-CLI group ($P = 0.16$ and $P = 0.08$). FMD response to PTA did not differ between these groups (Table 2). Analyzing the measurements at given time points following PTA, we noted no significant differences (Figure 2).

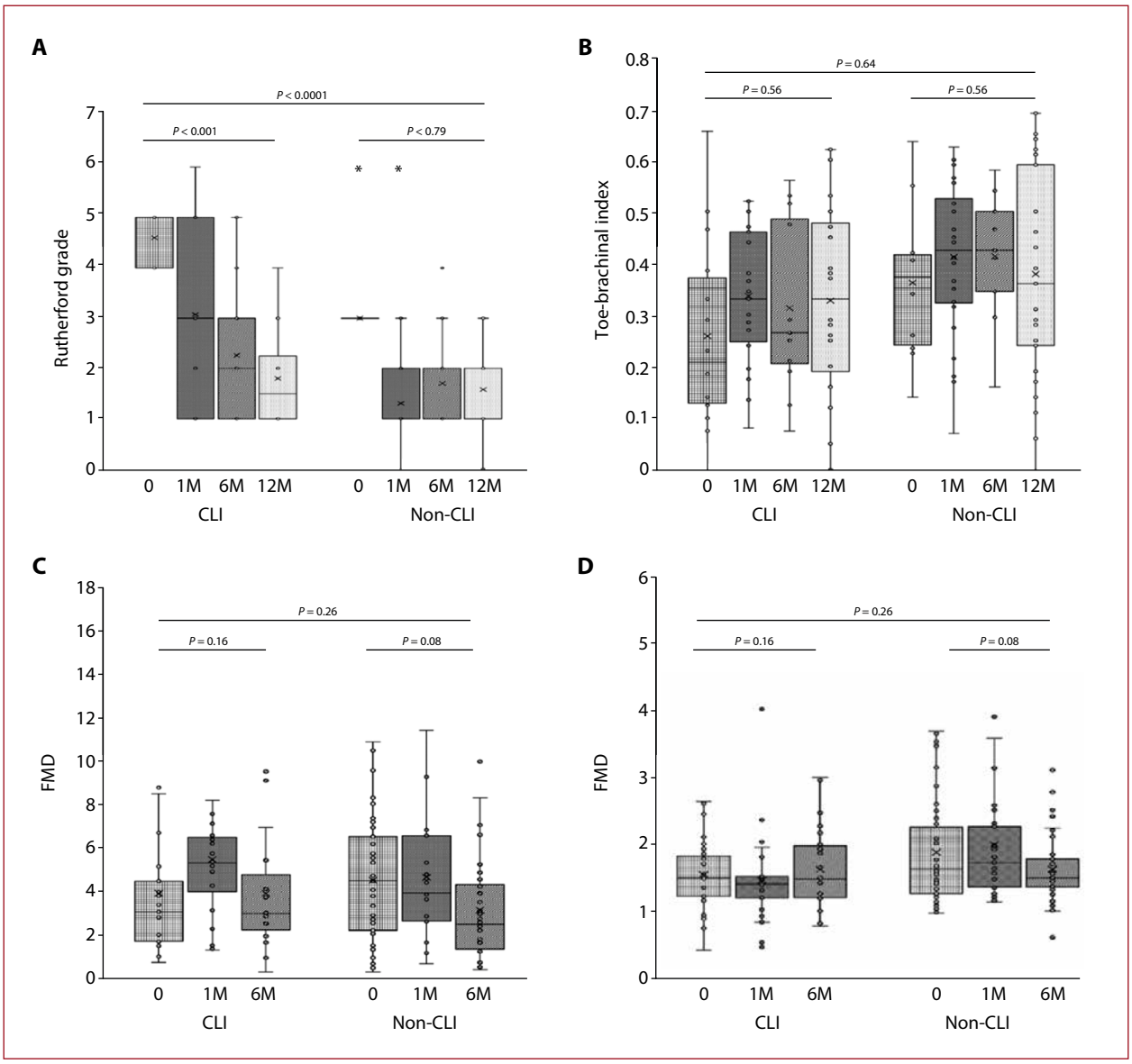

Figure 2. A. Rutherford grade in critical limb ischemia (CLI) and non-CLI patients at selected time points. **B.** Toe-brachial index in CLI and non-CLI patients at selected time points. **C.** Flow mediated dilatation in CLI and non-CLI patients at selected time points. **D.** Reactive-hyperemia index in CLI and non-CLI patients at selected time points. The horizontal line in the box indicates the median, the boxes indicate lower and upper quartiles, the cross in the box indicates the mean, the whiskers indicate standard deviation. M denotes month

Changes in RHI after PTA in CLI and non-CLI patients

Similarly to FMD, RHI did not change during the follow-up period in the CLI or non-CLI groups (Table 2). In contrast to FMD, calculating relative changes between measurements at given time points following PTA, changes in RHI (ΔRHI) were negligible in the CLI and non-CLI groups (Table 2, 3 and Figure 2). However, ΔRHI 1–6 differed between the CLI and non-CLI groups ($P = 0.01$).

Changes in PWA after PTA in CLI and non-CLI patients

No significant changes were observed for PWA indices when considering the following time points in the CLI and non-CLI group, or comparing both groups (Table 2).

DISCUSSION

In the present study, we compared changes within endothelial function and clinical outcome after PTA in a group of 30 patients with CLI symptoms and a group of 40 patients with limb claudication. With regard to the clinical aspects of our study, we noted a significant increase in walking distance after PTA among patients with limb claudication as well as improved wound healing in the CLI patients. In the latter group, the Rutherford scale improved considerably ($P < 0.001$), and thus improvement remained longer, than in non-CLI patients.

We also used ABI and TBI to improve assessment regarding the clinical status of PAD patients. In CLI patients, we focused on TBI since it has been shown to present better accuracy in CLI diagnosis than ABI [7–9]. In this study, the

Table 3. Comparison of relative changes in endothelial and clinical parameters between measurements at given time periods after percutaneous transluminal angioplasty in the critical limb ischemia (CLI) and non-CLI groups

Variable	CLI (n = 30)	Non-CLI (n = 40)	*P*-value	*P*-value[a]
ΔFMD 0–1	1.5 (–1.74–3.55)	0.82 (–2.06–2.95)	0.75	0.91
ΔFMD 0–6	0 (0–0.29)	0 (0–0.31)	0.3	0.9
ΔFMD 1–6	–5.11 (–6.43– –2.04)	–4.18 (–6.45– –3.31)	0.91	0.91
ΔRHI 0–1	–0.07 (–0.31–0.17)	0.1 (–0.55–0.75)	0.31	0.31
ΔRHI 0–6	0.18 (–0.45–0.41)	–0.18 (–0.91–0.24)	0.14	0.21
ΔRHI 1–6	0.08 (–0.13–0.58)	–0.15 (–0.5–0.01)	0.01	0.03
ΔABI 0–6	0.12 (–0.17–0.23)	0.09 (–0.005–0.25)	0.66	0.79
ΔABI 0–12	–0.1 (–0.31–0.12)	0.005 (–0.1–0.14)	0.2	0.4
ΔABI 1–6	–0.07 (–0.16–0.06)	0.05 (–0.07–0.14)	0.03	0.12
ΔABI 1–12	–0.11 (–0.2–0.01)	–0.04 (–0.26–0.12)	0.79	0.79
ΔTBI 0–6	0.09 (–0.08–0.16)	0.005 (–0.19–0.19)	0.69	0.75
ΔTBI 0–12	–0.04 (–0.24– –0.003)	0.02 (–0.16–0.12)	0.25	0.62
ΔTBI 1–6	0.01 (–0.05–0.04)	–0.04 (–0.08–0.008)	0.31	0.62
ΔTBI 1–12	–0.03 (–0.13–0.09)	–0.05 (–0.19–0.11)	0.75	0.75
ΔRutherford 0–6	–3 (–3.25– –1.75)	–2 (–2– –1)	<0.001	<0.007
ΔRutherford 0–12	–3 (–4– –2)	–2 (–2– –1)	<0.001	<0.001
ΔRutherford 1–6	0 (–3–0)	0 (0–1)	0.004	0.004
ΔRutherford 1–12	–1 (–4–0)	0 (–1–1)	<0.001	<0.001
ΔIMT 0–6	–0.07 (–0.42– –0.002)	–0.03 (–0.17–0.06)	0.07	0.07

Data are expressed as median (IQR); 0–1 indicates the difference between the first month following the procedure and baseline value; 0–6 — the difference between the sixth month following the procedure and baseline value; 0–12 — the difference between the twelfth month following the procedure and baseline value.

[a]*P* — after adjustment by Benjamini–Hochberg procedure.

Abbreviations: ABI, ankle-brachial index; TBI, toe-brachial index; other: see Table 1 and 2

post-procedural increase in ABI and TBI was observed both in the CLI and non-CLI groups. However, based on the analyzed results, the TBI was the factor that improved predominantly in CLI patients. In contrast with non-CLI patients, the improvement in CLI group was observed till the end of the follow-up.

Another interesting finding of this study was achieved by the analysis of IMT. We noted that CLI patients with higher mean baseline IMT had significantly poorer clinical outcomes ($P = 0.01$ for re-interventions and $P = 0.03$ for major adverse events). Indeed, IMT has significant predictive value in assessing the risk of cardiovascular and cerebrovascular events [12, 17–20]. In several studies, a strong correlation has been shown between increased IMT and peripheral artery occlusive disease [21–23]. It is presumed that by reducing the IMT, we reduce vessel stiffness, which may directly translate into improved claudication distance. Improved blood supply to the arteries of the lower limbs (increased blood flow to the peripheral parts of the lower limbs), directly translates into a longer claudication distance and increased patient mobility (a kind of walking training), which has been shown to reduce arterial stiffness and improve endothelial function.

Endothelial function in CLI and non-CLI patients was measured on the basis of FMD and RHI measurements, which are well-established methods used in the assessment of endothelial dysfunction in patients with cardiovascular disease in conduit and resistance vessels, respectively [24]. In previous studies using FMD and RHI, it has been shown that the FMD response and RHI score reflect endothelial status and, to some degree, NO-bioavailability [18]. The RHI correlates with the measurement of endothelial vasodilator function in the coronary arteries and with brachial FMD, although it has been suggested in other studies that FMD and RHI do not always correlate [25, 26]. Nevertheless, both endothelial function tests significantly predicted cardiovascular events [27, 28].

In the present work, neither FMD nor RHI significantly improved during the follow-up in CLI or non-CLI patients. ΔFMD improved during the first month of observation in both groups, however, this improvement did not sustain as ΔFMD decreased between the first and sixth month following PTA. Similarly in RHI measurements, ΔRHI displayed only transient improvement after the first month of PTA in CLI patients, and there were no significant differences between the first and sixth month in CLI and non-CLI group.

These results indicate that improvement of endothelial function after revascularization was transient and lasted only up to the first month following PTA. After that time, endothelial function deteriorated, even though patients displayed clinical benefits from revascularization.

Some previous reports confirmed the beneficial effects of peripheral artery revascularization on all-cause and

cardiovascular mortality as well as improvement of global endothelial [29–32]. On the other hand, Budzyński et al. [33] reported that superficial femoral artery (SFA) stenting and classical pharmacotherapy did not significantly modify systemic endothelial function, as assessed by FMD in patients with adequately controlled individual risk factors of atherosclerosis. In contrast, among patients who did not reach treatment targets before SFA stenting, in those who underwent intensification of pharmacotherapy prior to the endovascular procedure, noticeable improvement in endothelial function markers (FMD, IMT) was observed within 3–6 months of observation.

The results of the present work suggest that neither PTA nor newly introduced pharmacological treatment (aspirin, clopidogrel, statin) had significant and sustained impact on post-PTA endothelial function. This may be due to several reasons. Firstly, we did not record compliance with the newly prescribed medications. We did not evaluate the level of control of patients' comorbidities, such as hypertension or diabetes. Furthermore, the follow-up period might have been too short, since most of the CLI patients required several months for the wounds to heal (up to 6 months). Based on the study, we may presume that a possible positive response of endothelial function to PTA and treatment was too weak, so intensification of pharmacological treatment would be needed to afford sustained improvement of endothelial function and more sustained benefits in PAD patients. Accordingly, endothelial-guided therapy may provide a tool to improve the efficacy of vascular pharmacotherapy that may be greater in non-CLI then CLI patients given the advanced disease in the latter group [34, 35].

Study limitations

The major study limitation of the present work was a relatively low number of patients included in the study. Furthermore, a modification of treatment (all patients were treated with statin, aspirin, and clopidogrel after PTA), improvement of patient compliance, modification of lifestyle (e.g. reduction in the number of cigarettes smoked, quitting smoking, or increasing physical activity) could also improve endothelial function after PTA, thus, it is difficult to interpret if endothelial function changes reported here were strictly related to endovascular procedure or could be the consequence of lifestyle changes, or medications.

Article information

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Dynamics of below-the-knee arterial blood flow after endovascular revascularization of peripheral arteries as a potential predictor of clinical outcomes during a one-year follow-up period

Authors: Paweł Kaczmarczyk, Marek Krzanowski, Ewelina Szybiak, Mikołaj Maga, Agnieszka Wachsmann, Katarzyna Tyrak, Rafał Januszek, Andrzej Belowski, Łukasz Partyka, Paweł Maga

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Dynamics of below-the-knee arterial blood flow after endovascular revascularization of peripheral arteries as a potential predictor of clinical outcomes during a one-year follow-up period

Short title: Frame count and clinical outcomes after PTA of lower limb arteries

Paweł Kaczmarczyk[1,2], Marek Krzanowski[1,2], Ewelina Szybiak[3], Mikołaj Maga[3], Agnieszka Wachsmann[4], Katarzyna Tyrak[4], Rafał Januszek[6,7], Andrzej Belowski[1,2], Łukasz Partyka[1,2], Paweł Maga[3,4]

[1]Angio-Medicus Treatment Facility, Krakow, Poland
[2]University Hospital, Krakow, Poland
[3]Jagiellonian University Medical College, Krakow, Poland
[4]Department of Angiology, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Dermatology, Jagiellonian University Medical College, Krakow, Poland
[6]Department of Clinical Rehabilitation, University of Physical Education, Krakow, Poland
[7]2nd Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland

Address for correspondence:
Rafał Januszek, MD, PhD, 2nd Department of Cardiology and Cardiovascular Interventions, University Hospital in Krakow, ul. Kopernika 17, 31–501 Kraków, Poland, tel: +48 12 424 71 70, fax: +48 12 424 71 80, e-mail: jaanraf@interia.pl

Abstract

Background: Patients with advanced lower limb ischemia are at present, mainly treated using revascularization.

Aim: The aim of the study was to investigate whether the dynamics of blood flow in below-the-knee (BTK) arteries assessed at angiogram completion correlate with clinical outcomes after a 12-month follow-up period among patients with severe leg ischemia treated percutaneously.

Methods: The current study enrolled 287 consecutive patients who underwent 302 endovascular procedures on the infra-inguinal arteries. The mean age of the included

participants was 67.4 ± 10.4 years. After the procedure, blood flow of all patent BTK arteries was assessed using frame count (FC). Patients were then evaluated after 1, 3, 6 and 12 months. During the follow-up visits, clinical condition was evaluated based on the Rutherford scale, ankle-brachial index, the need for reintervention and amputation.

Results: Clinical improvement at the end of the follow-up period was observed in 242 cases (80.1%) and no improvement or worsening in 42 (13.0%). In total, 66 reinterventions (21.8%) and 18 (6%) amputations during the follow-up period were recorded. Patients with higher FC on the tibial anterior artery experienced significantly better clinical improvement within the 12-month follow-up period ($p = 0.02$). Lower FC predisposed to worse clinical outcomes after angioplasty. Similar tendencies were found for the tibial posterior and fibular artery, however, without statistical significance.

Conclusions: The results suggest a negative relationship between FC seen on the final angiogram and clinical outcomes in patients undergoing endovascular treatment of the peripheral arteries.

Key words: peripheral arterial disease, endovascular treatment, clinical end-points, frame count, predictors

WHAT IS NEW?

Several predictors of clinical outcomes after percutaneous interventions of the infra-inguinal arteries have been demonstrated. The status of blood flow velocity regarding below-the-knee (BTK) arteries after intervention assessed in angiography is not sanctioned. The aim of the study was to investigate whether the dynamics of blood flow in the BTK arteries correlates with clinical outcomes after a 12-month follow-up period among patients with severe leg ischemia treated percutaneously. The study enrolled 287 patients. After the procedure, blood flow of all patent BTK arteries was assessed using frame count (FC). During the 12-month-long follow-up clinical condition, reinterventions and amputation rates were observed. Patients with higher FC on the tibial anterior artery experienced significantly better clinical improvement within the follow-up period. Lower FC predisposed to worse clinical outcomes after angioplasty. The results suggest better clinical outcomes during the follow-up in patients with slower blood flow assessed by FC after endovascular interventions of the infra-inguinal arteries.

INTRODUCTION

Patients with advanced lower limb ischemia are at present, mainly treated using revascularization. While percutaneous treatment is becoming increasingly popular due to lower periprocedural risks than open vascular surgery, it seems that the long-term effects of any type of revascularization are far from optimal [1]. Recently, significant improvement of devices used for endovascular treatment (ET) and tactics of revascularization have been introduced. The development of a system that is able to predict clinical outcomes in patients with peripheral arterial disease (PAD), such as amputation-free survival or overall survival, could help clinicians in decision-making and guiding the appropriate usage of health care resources. To date, a number of studies have been published demonstrating predictors of clinical outcome in patients after percutaneous transluminal angioplasty (PTA) of the infra-inguinal arteries [2,3]. Among others, biochemical indices such as the urinary leukotriene E4 or thromboxane were found to be associated with long-term results [4]. Apart from biomarkers and clinical scoring systems, clinical outcomes could also be predicted based on angiographic findings including runoff grade [5]. The runoff grade was designed to evaluate treatment results after bypass surgery. Despite its subjective form, it was proven to predict clinical outcome [6,7]. There are cardiological scoring systems that can predict clinical outcomes in patients who have undergone percutaneous coronary interventions. The Thrombolysis In Myocardial Infarction (TIMI) flow grade and corrected TIMI frame count (CTFC) are among the most commonly used methods. Despite their subjectivity, they are simple, easy-to-use and not time-consuming tools to assess the dynamics of blood flow in the epicardial coronary arteries [8,9]. Currently used scoring systems are not sufficient and there is still a need to create more objective scoring systems dedicated to the peripheral vessels that could predict immediate and long-term clinical outcomes.

Therefore, the aim of the current study was to investigate whether the dynamics of blood flow in below–the-knee (BTK) arteries assessed at angiogram completion are associated with clinical outcome within the 12-month follow-up period among patients with severe leg ischemia, treated percutaneously.

METHODS

Study population, design and definitions

The current study enrolled 287 consecutive patients who underwent 302 ET on the infra-inguinal arteries at a relatively large angiology centre. The patient recruitment lasted from

March until October 2015. The mean age of the included participants was 67.4 ± 10.4 years (Table 1). There were 162 procedures performed in critical limb ischemia (CLI) patients and 140 procedures in patients with limb claudication (Table 2). After the procedure, blood flow of all patent BTK arteries was assessed using the frame count (FC) evaluation method adapted to the purposes of the present study. Patients were then evaluated after 1, 3, 6 and 12 months. During the follow-up visits, clinical condition was evaluated based on the Rutherford scale, ankle-brachial index (ABI), reintervention and amputation rates. The medical therapy after percutaneous interventions remained along with the current recommendations. Chronic kidney disease (CKD) was defined as impaired kidney function expressed as decreased glomerular filtration rate (<60 mL/min/1.73 m^2) for 3 months or more irrespective of cause, estimated using the Cockcroft-Gault formula. Hypercholesterolemia, hypertension, diabetes, coronary artery disease and heart failure were defined according to the European Society of Cardiology guidelines and previous diagnoses from prior hospital discharge cards [10-14]. Other diagnoses were taken into account on the basis of previous ones found on prior hospital discharge cards. This study complies with the Declaration of Helsinki. All subjects provided written and informed consent for participation prior to enrolment.

Frame count

Blood flow rate in the BTK arteries was assessed by means of digital subtraction angiography using the Integris V 3000 angiography unit (Philips, Eindhoven, Netherlands). Patients were examined in supine position. The source-to-image distance was kept at a constant 100 cm. A 31 cm diameter field of view was used, the image intensifier was positioned against the calf of the patient. The intensifier was positioned in such a way that the maximal length of the calf was visualized, with intercondylar prominence of the tibia maintained at the uppermost point of the image. The contrast medium (Ultravist 370, Schering Pharma AG, Germany) was manually injected into the sheath, positioned into the ipsilateral common femoral artery. Images were recorded at a rate of 6 frames per second. The number of frames between the contrast first arriving at the proximal part of the image and when reaching the most distal part of each of the axial calf arteries, i.e. the tibial arteries, and the fibular artery (FA), it was measured for each of the vessels and used for further analysis. The first frame was defined as the one in which the contrast dye fully enters the artery, fulfilling all criteria: a) a column of fully concentrated dye must be extended across the entire width of the origin of the artery, b) dye must touch both borders of the origin of the artery, c) there must be antegrade motion to the dye. The last frame was defined as the one in which the dye first entered the artery at the

distal edge of the image. Full opacification of the artery was not required. Often, the final frame is best determined by running the cine film past the initial opacification of the end-point branch and then moving frame-by frame in reverse until the end-point branch disappears [9]. We did not correct the BTK FC for the length of the arteries because the purpose of the study was to assess the speed of blood flow in the BTK arteries, regardless of the length of the vessels that supply blood to them, and consequently, the height and surface area of the patients.

Statistical analysis

The schedule frequency characteristics were measured on a nominal or ordinal scale, and for continuous variables, using descriptive statistics including arithmetic mean, standard deviation, median and interquartile range, where applicable. Normal distribution was checked with the Shapiro-Wilk test. The Student t-test or the Mann-Whitney U test were used when applicable for the comparison of continuous variables, while the Chi^2 test was applied for categorical variables. ANOVA analysis was used to assess trend significance at following time-points. We also performed multivariate analysis and to assess this, a model based on the retrograde correction method was constructed. The model included anthropometric indices, concomitant diseases, smoking status, age, gender, kidney function parameters, clinical presentation of PAD at baseline, location of the culprit artery and PTA, number of occluded arteries, ABI and Rutherford class at baseline. Receiver operator characteristic (ROC) curve analysis was performed to determine optimal cut-off values when the sensitivity approximates specificity, as well as their relationship between TIMI FC and study end-points. A probability of $p < 0.05$ was considered statistically significant. Due to the fact that the results of the current study were not a primary outcome we did not calculate the power of the study. However, the power analysis after the study, which is often criticized, for the alpha coefficient of 2.5% and almost 100 patients with a composite study endpoint and 200 patients without it, the power was calculated at 80%, which is a standard result and should be sufficient to determine the relationship with particular factors between two groups. Statistical analyses were performed using the Statistica 10.0 software (Dell Software, Inc, Round Rock, TX, USA) and SPSS STATISTICS 24 (IBM, USA).

RESULTS

Clinical characteristics of all participants (Table 1), characteristics of PTA procedures, including lesion location and type (stenosis vs. occlusion), number of occluded BTK and

pedal arteries, as well as the FC (Table 2) show, besides baseline information, interesting differences between the CLI and non-CLI patients. Clinical improvement at the end of the follow-up period was observed in a total of 242 cases (80.1%), no improvement or worsening in 42 (13.0%) (Figure 1 and 2). Altogether, 66 reinterventions (21.8%) and 18 (6%) amputations during the follow-up period were recorded (Table 3). In the group of patients that required reinterventions, 40 cases clinically improved (60.6%), 13 presented stable clinical symptoms (19.7%), 3 cases clinically worsened (4.5%) and 10 underwent amputation (15.5%). While in the group of patients without reinterventions (236 procedures; 78.1%), clinical improvement was noted in 202 cases (85.6%), no improvement in 25 (10.6%), worsening in 1 (0.4%) and amputation in 8 (3.4%). The end-point was lower by 16 patients: 3 patients died during the follow-up period and 13 withdrew without giving a specific reason. While assessing the distribution of FC on particular BTK arteries, most patients were placed in the group with FC lower than 6, between 5 and 10, and between 10 and 20 (Figure 2).

Dynamics of blood flow

The dynamics of blood flow were assessed concerning the anterior tibial artery (ATA), posterior tibial artery (TPA) and FA. Larger FC (slower blood flow) was found in younger patients (ATA: $p = 0.052$, $r = -0.13$) (FA: $p = 0.02$, $r = -0.15$), and those with less advanced clinical symptoms - lower Rutherford class (ATA: $p < 0.001$, $r = -0.28$); (TPA: $p = 0.001$, $r = -0.21$); (FA: $p < 0.001$, $r = -0.38$). Similar findings were attributed to patients with less advanced angiological findings such as lower TASC grade (ATA: $p = 0.01$, $r = -0.16$) (TPA: $p = 0.01$, $r = -0.2$) (FA: $p = 0.01$, $r = -0.16$) and a larger number of patent BTK vessels (ATA: $p = 0.01$, $r = -0.17$) (FA: $p < 0.0001$, $r = -0.28$). We found larger frame count in non-CLI patients (ATA: $p < 0.0001$, $r = -0.26$; TPA: $p = 0.009$, $r = -0.21$; FA: $p < 0.0001$, $r = -0.37$) and in those who underwent superficial femoral artery treatment in comparison to other locations (ATA: $p = 0.03$, $r = 0.14$) and patients with better ABI compared to those with lower mean ABI value (TPA: $p = 0.001$, $r = 0.25$). This trend was similar when the group of patients with CLI and those with claudication were analysed separately. The relationship between the level of PTA, clinical study end-points and FC according to particular BTK arteries is presented in Table 4.

FC and clinical outcomes

Patients with higher FC (slower blood flow) on ATA had significantly better clinical improvement (based on the Rutherford scale) within the 12-month follow-up period ($p =$

0.02). The lower FC (faster blood flow) predisposed to worse clinical outcomes after PTA (Figure 3A). Similar tendencies were found for TPA and FA, however, without statistical significance.

FC and ABI

We found no relationship between FC of particular BTK arteries and ABI (calculated as changes in ABI values measured directly before and after the procedure, as well as the ABI value after 12 months of follow-up and at baseline). There was significant improvement of ABI values after PTA at following time-points ($p < 0.001$). This is presented in Figure 1A.

Study end-points

The overview of clinical study end-points is presented in Table 3 and Table 4.

Amputations

We found no relationship between the frame count regarding BTK arteries and the number of amputations: ATA, TPA and FA. Amputation rate during the follow-up period was almost two-times greater in patients with occluded ATA after PTA compared to those with patent ATA, but without statistical significance (8.33% vs. 4.85%, $p = 0.23$). There were no relationships between TPA, FA and FA. The amputation rate was greater in patients who had at least two occluded BTK arteries compared to those with one occlusion or none, but without statistical significance (7.78% vs. 5.66% and 3.77%, $p = 0.6$). The amputation rate was more than twice as great as in patients with occluded BTK arteries undergoing PTA compared to those with stenosed arteries, however, without statistical significance (7.45% vs. 3.51%, $p = 0.16$).

Reinterventions

Amputation rate was significantly greater in patients requiring reinterventions during the follow-up period compared to others (15.1% vs. 3.3%, $p < 0.001$). Patients with smaller frame count assessed on ATA presented significantly greater reintervention rates during the follow-up period (11.8 ± 12.4 vs. 9.4 ± 10.6 frames, $p = 0.02$, Figure 3B). This relationship was not significant for TPA and FA. Occlusion of ATA, TPA and FA after PTA was not related to higher reintervention rate during the follow-up period. The percentage of reinterventions was not connected with the number of occluded arteries nor the lesion type.

CLI vs. non-CLI patients

Patients with CLI were associated with a significantly lower number of FC (faster blood flow) when compared to claudicants. Patients who improved or had stable symptoms after PTA within the 12 months of follow-up, those initially non-CLI, achieved better clinical outcomes ($p = 0.005$). Amputation rate during the 12-month follow-up period was significantly higher in CLI patients. Based on the Rutherford scale (from Rutherford 2 to 6), the amputation rate was 0%, 0.7%, 2.1%, 11.8% and 26.6%, respectively ($p < 0.001$). Similarly, the reintervention rate reached the greatest percentage in CLI patients compared to non-CLI ones ($p = 0.03$).

Multivariate and ROC analysis

Multivariate analysis revealed that PTA performed on the popliteal artery was an independent predictor of better clinical outcome after 12-months of follow-up expressed as a combination of amputation rate and lack of clinical improvement in comparison to PTA of other infra-inguinal arteries (hazard ratio [HR] = 0.46; 95% confidence interval [CI]: 0.23-0.89; $p = 0.02$), while PTA of the BTK arteries was an independent predictor of increased amputation (HR = 7.4; 95% CI: 2.1-25.6; $p = 0.002$) and reintervention rates (HR = 2.1; 95% CI: 1.2-3.7; $p = 0.008$). PTA of the popliteal (HR = 1.8; 95% CI: 1.1-2.9; $p = 0.01$) and BTK artery (HR = 1.9; 95% CI 1.2-3.2; $p = 0.008$) were found to be independent predictors regarding combinations of no clinical improvement and reinterventions in comparison to other locations. The ROC curves assessing relationships between FC measured on the BTK arteries after PTA did not meet the study end-points. Our attempts to determine cut-off points for frame count that best display risk of poorer clinical outcomes failed.

DISCUSSION

During the previous decade, angioplasty and stent placement have become an accepted, and in many situations, preferred alternative of surgical treatment in patients with symptomatic limb ischemia [1]. Despite its safety and effectiveness, the number of reinterventions related to endovascular procedures still remains high. In the femoro-popliteal region, restenosis rates in some groups of patients following endovascular procedures are described as higher than after traditional bypass surgery [15]. Thus, improvement of patency is one of the major challenges for endovascular procedures.

In the past several years, many studies have been conducted focusing on factors that could influence the clinical outcome of endovascular treatment. Based on the BASIL study,

factors that contributed to the survival model were age, presence of tissue loss, serum creatinine, ABI, prior myocardial infarction, history of stroke, BMI, smoking status and Bollinger angiogram score [2]. The FINNVASC and PREVENT III studies evaluated the post-procedural risk level based on variables such as age, tissue loss, coronary artery disease, diabetes mellitus or dialysis [3]. It was confirmed that hemodialysis alongside with cilostazol administration, stent fracture and TASC lesion type were independent predictors of successful femoro-popliteal stenting with nitinol stents [16]. Research performed among patients with end-stage kidney disease and their coronary arteries revealed the reduction in blood flow velocity assessed using the FC method [17]. Based on this, it was concluded that some co-morbidities inducing decreased blood flow in the arteries could certainly impact clinical outcomes following PTA of the peripheral arteries. There have been many reports stating that vessel runoff could be a strong predictor of clinical outcomes after ET [7,18,19]. Conventionally, evaluation of vessel runoff has been estimated based on the Society for Vascular Surgery (SVS) runoff score or the number of patent tibial vessels [18]. The SVS runoff score was, in fact, an effective tool in predicting treatment outcomes, but its complexity in the evaluation process made it too sophisticated for daily medical practice. There are some reports stating that the SVS runoff score was not reproducible among observers [20]. Based on the experience taken from interventional cardiology, the idea of using flow grades as a predictor of clinical outcomes in patients after endovascular procedures on the peripheral vessels was introduced. Hiramori et al. evaluated the runoff grade by final angiogram after endovascular therapy [6]. Also, Davies et al. have proven that in patients presenting resting pain and tissue loss treated with endovascular techniques, patency is negatively affected by compromised and poor runoffs [7]. Although the runoff grade was shown to be an independent predictor of endovascular treatment outcome, opinions were still based on the subjective evaluation of vessel blood flow, making it vulnerable to potential errors [21]. Therefore, in the current study, we aimed to investigate the relationship between the number of frames counted in the final angiogram and factors that may influence the clinical outcome after endovascular treatment. Statistically significant correlations have been found between the number of counted frames for the BTK arteries and age, the Rutherford scale, number of occluded BTK arteries, TASC classification, level of treated vessel and the presence of critical limb ischemia. Also, slower blood flow in the calf vessels was generally detected among the healthier population. Multiple studies have proven that improvement of clinical symptoms is related to the acceleration of peripheral blood flow after endovascular treatment compared to preoperative condition [22]. It has also already been stated that patients

without significant blood flow after endovascular treatment have worse cumulative outcomes [6]. Salapura et al. stated that faster blood flow after endovascular treatment has better prognostic value only within the first month of observation [23]. He found that clinical improvement in the 12-month follow-up was significantly related to slower blood flow in the calf arteries. Slower blood flow in the calf vessels was generally detected within a healthier population. What is more, the lower FC (faster blood flow) predisposed to worse clinical outcomes after PTA. These finding were observed most significantly with regard to the anterior tibial artery, but the same phenomena was also present for TPA and PA. The current study demonstrated that PTA performed on the popliteal and BTK artery is a prognostic factor of poorer clinical outcomes during follow-up. This was not significantly related to the FC, despite the fact that the relationship between FC and the PTA level was initially observed. Furthermore, univariate analysis also showed such a relationship, which turned out to be statistically significant in the case of amputation, no-clinical improvement and composite study endpoints. However, the relationship between FC, PTA and clinical outcomes proved to be too weak to be confirmed using multivariate analysis. Based on MR angiography, Prince et al. found that female patients with type-2 diabetes mellitus and cellulitis or ulcerations on the legs tended to have faster blood flow within the lower limb arteries [24]. It has been hypothesized that faster blood flow is a result of vascular calcifications and decreased arterial compliance, which forces faster flow velocity. More advanced clinical condition (higher Rutherford scale) is frequently related to the presence of peripheral ulcers that can result in vasodilatation and increased demand for flow, thereby, causing its acceleration. Another possible explanation for the presence of faster blood flow in patients with more advanced PAD is the fact that with peripheral vessel occlusions, the velocity of blood flow can be related to the smaller cross-sectional diameter of collateral vessels compared to the main arteries. It may also relate to distal ischemia, which stimulates vasodilation distal to occlusions. The FC technique presented in the current study is a simple and objective method created to predict clinical outcomes after endovascular procedures on the peripheral arteries.

The FC could be influenced by additional factors such as coronary perfusion pressure (including the severity of heart failure expressed as left ventricle ejection fraction), pressure of the contrast injection, vessel size, the length of lower limb arteries above the BTK arteries, the number of branches, stenosis severity, heart rate (including atrial fibrillation), the use of some medications and other factors related to endothelial function and coagulation system.

In conclusion, the results suggest a negative relationship between FC seen on the final angiogram and clinical outcomes in patients undergoing endovascular treatment of the

peripheral arteries. FC should be considered as a simple and effective index that can be used in the future to predict vessel patency in this group of patients.

Conflict of interest: None to declare

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Table 1. Patients' general characteristics

	Overall group (n = 302)	CLI (n = 162)	Non-CLI (n = 140)	P-Value
Male : Female	180 : 122	90 : 72	92 : 48	0.07
Age, years	67.4 ± 10.4	69.4 ± 10.2	65.0 ± 10.1	< 0.001
Current smokers Ex-smokers	52 (17.2) 119 (39.4)	29 (17.9) 56 (34.5)	23 (16.4) 63 (45)	0.69 0.07
Prior cerebral stroke/TIA	32 (10.6)	21 (13.0)	11 (7.8)	0.14

Glomerular filtration rate, ml/min/m^2	72.3 ± 24.3	69.4 ± 25.7	75.7 ± 22.1	0.02
Kidney failure Dialysis therapy	39 (12.9) 6 (1.9)	26 (16.0) 5 (3.1)	13 (9.3) 1 (0.7)	0.07 0.13
Heart failure	25 (8.3)	19 (11.7)	6 (4.3)	0.01
Coronary artery disease Prior myocardial infarction	142 (47.0) 56 (18.5)	77 (47.5) 31 (19.1)	65 (46.4) 25 (17.8)	0.76 0.73
Hypertension	232 (76.8)	124 (76.5)	108 (77.1)	0.94
Diabetes Insulin therapy	143 (47.3) 96 (31.8)	92 (56.8) 67 (41.3)	51 (36.4) 29 (20.7)	< 0.001 < 0.001
Hypercholesterolemia	85 (28.1)	48 (29.6)	37 (26.4)	0.49

Data are presented as arithmetic means ± standard deviation for continuous and numerical variables (percentages).

Abbreviations: CLI, critical limb ischemia; TIA, transient ischemic attack.

Table 2. Atherosclerotic lesion characteristics and frame count

	Overall group (n = 302)	CLI (n = 162)	Non-CLI (n = 140)	P-Value
Level of PTA, n (%):				
Superficial femoral artery	215 (71.2)	97 (59.9)	118 (84.3)	< 0.001
Popliteal artery	130 (43.0)	78 (48.1)	52 (37.1)	0.054
Below-the-knee artery	148 (49.0)	112 (69.1)	36 (25.7)	< 0.001
Occluded BTK arteries, n (%):				
none	55 (18.2)	24 (14.8)	31 (22.1)	0.09
one	158 (52.3)	78 (48.1)	80 (57.1)	0.0004
two	89 (29.4)	60 (37.0)	29 (20.7)	0.002
Lesion type before PTA, n (%):				
stenosis	114 (37.7)	48 (29.6)	66 (47.1)	0.0017
occlusion	188 (62.2)	114 (70.4)	74 (52.8)	0.0017
Occluded foot arteries, n (%):				
none	89 (29.5)	40 (24.7)	49 (35)	0.05
one	142 (47.0)	77 (47.5)	65 (46.4)	0.84
two	71 (23.5)	45 (27.8)	26 (18.6)	0.059
TASC classification, n (%):				
0	42(13.9)	36 (22.2)	6 (4.3)	0.039
A	37(12.2)	14 (8.6)	23 (16.4)	< 0.001
B	76 (25.1)	20 (12.3)	56 (40)	< 0.001
C	64 (21.2)	33 (20.4)	31 (22.1)	0.7
D	83 (27.5)	59 (34.4)	24 (17.1)	0.0002

Frame count (frames per artery):				
Anterior tibial artery	11.3 ± 12.1	8.0 ± 7.7	14.4 ± 14.4	< 0.001
	8 (5 ÷ 12,7)	6 (4 ÷ 9)	11 (6 ÷ 17)	
Tibial posterior artery	11.3 ± 10.0	9.1 ± 7.8	13.4 ± 11.3	0.009
	8 (5 ÷ 15)	6 (4.2 ÷ 10)	10 (5.5 ÷ 17)	
Fibular artery	11.7 ± 8.3	8.8 ± 4.9	15.1 ± 10.0	< 0.001
	9 (6 ÷ 14.2)	7 (6 ÷ 11)	12 (8 ÷ 20)	

Data are presented as arithmetic means ± standard deviation and medians ÷ interquartile range for continuous and numerical variables (percentages).

CLI - critical limb ischemia; PTA - percutaneous transluminal angioplasty; TASC - Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease.

Table 3. Study end-points after 12 months of follow-up

	Overall group (n = 302)	CLI (n = 162)	Non-CLI (n = 140)	P-Value
Reinterventions	66/302 (21.8)	46/162 (28.4)	20/140 (14.3)	0.003
Amputations	18/302 (6.0)	17/162 (10.5)	1/140 (0.7)	< 0.001
No clinical improvement	60/302 (19.9)	35/162 (21.6)	25/140 (17.8)	0.41
Composite study end-point	98/302 (32.4)	61/162 (37.6)	37/140 (26.4)	0.03

Data are presented as numerical variables (percentages).

CLI, critical limb ischemia; PTA, percutaneous transluminal angioplasty. No clinical improvement means that after 12 months of follow-up, the Rutherford grade was the same as before PTA or worse with the inclusion of amputation patients.

Table 4. Study end-points after 12 months of follow-up and frame count according to the location of treated lesion

	Superficial femoral artery (n = 215)	Popliteal artery (n = 130)	Below-the knee artery (n = 148)	P-Value
Reinterventions	43/215 (20)	35/130 (26.9)	42/148 (28.4)	0.13
Amputations	7/215 (3.2)	8/130 (6.1)	17/148 (11.5)	0.007
No clinical improvement	34/215 (15.8)	33/130 (25.4)	40/148 (27)	0.02
Composite study end-point	63/215 (29.3)	52/130 (40)	60/148 (40.5)	0.04
Frame count (frames per artery)				
Anterior tibial artery	12.5 ± 13.7 8 (5 ÷ 14.7)	8.1 ± 5.8 6 (4 ÷ 10)	9.5 ± 8.9 7 (4 ÷ 10)	0.002
Tibial posterior artery	11.9 ± 10.4 9 (5 ÷ 15.7)	8.7 ± 6.6 6 (5 ÷ 10)	9.9 ± 7.9 7 (5 ÷ 12)	0.051
Fibular artery	12.3 ± 8.8 9.5 (6 ÷ 17)	9.2 ± 5.8 7 (5 ÷ 11)	10.5 ± 7.3 8 (6 ÷ 12)	0.06

Data are presented as arithmetic means ± standard deviation and medians ÷ interquartile range for continuous and numerical variables (percentages).

No clinical improvement means that after 12 months of follow-up, the Rutherford grade was the same as before PTA or worse with the inclusion of amputation patients, while clinical improvement means that after 12 months of follow-up, the Rutherford grade has improved (decreased).

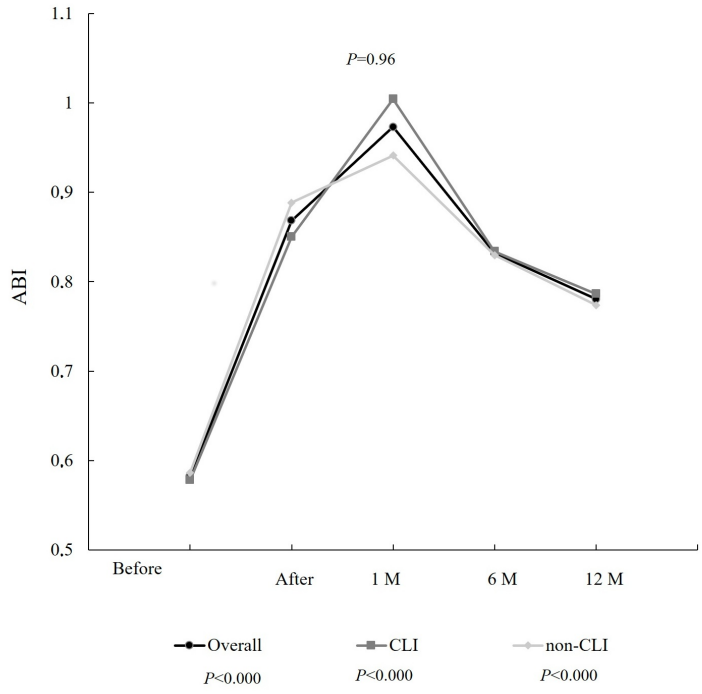
Figure 1. A. The ABI mean values at following time-points of the study; B. The Rutherford class mean values at following time-points of the study

Abbreviations: ABI, ankle-brachial index; PTA, percutaneous transluminal angioplasty

Figure 2. Quantitative distribution of the number of patients depending on frame count range

Figure 3. A. The relationship between frame count at anterior tibial artery (ATA) and clinical outcomes in patients with clinical improvement and stable clinical symptoms during the follow-up period vs. individuals with worsening clinical symptoms, reinterventions and amputations; **B.** The relationship between frame count at anterior tibial artery (ATA) and reinterventions in patients with clinical improvement and stable clinical symptoms during the follow-up period vs. individuals with worsening clinical symptoms, reinterventions and amputations.

A)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1
0,9
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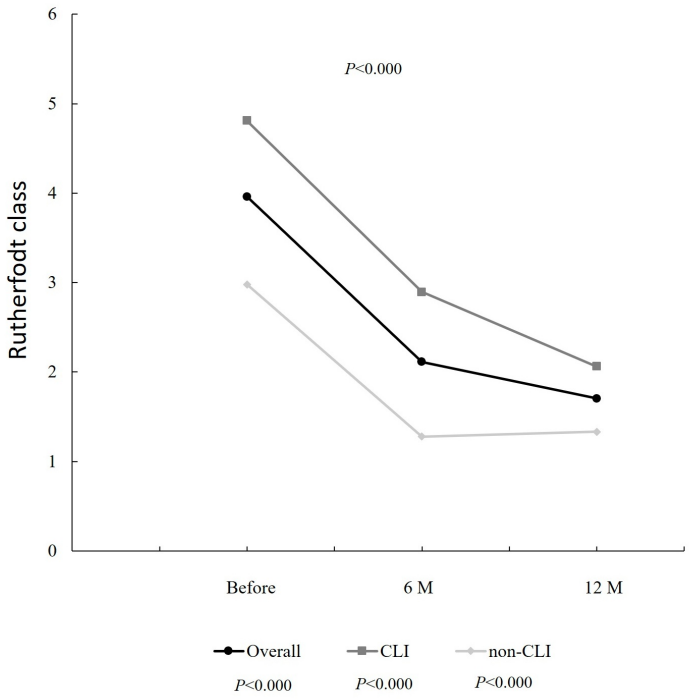
0,7
0,6
0,5
ABI
P=0.96
Before
After
1 M
6 M
12 M
Overall
CLI
non-CLI
P<0.000
P<0.000
P<0.000

B)


6
5
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2
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Rutherfodt class
P<0.000
Before
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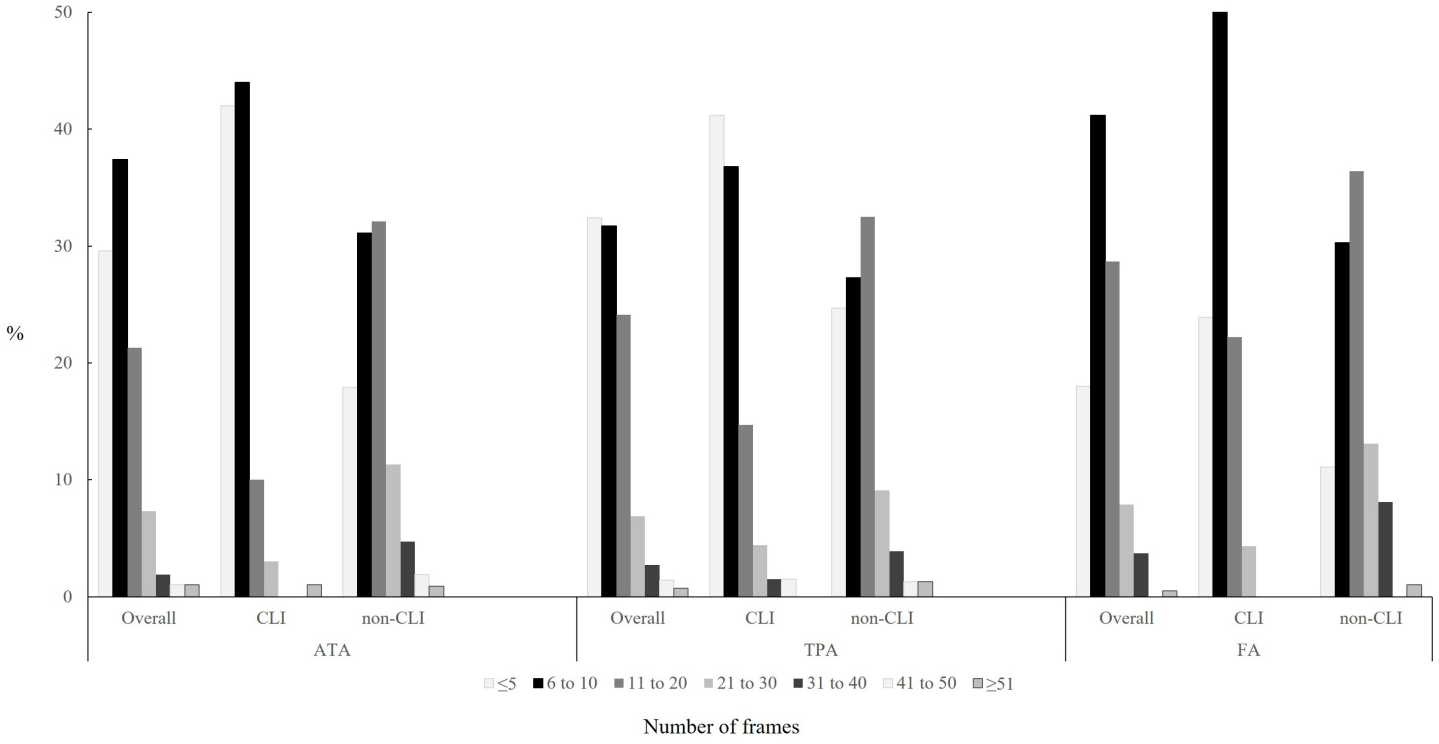
12 M
Overall
CLI
non-CLI
P<0.000
P<0.000
P<0.000


50
40
30
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10
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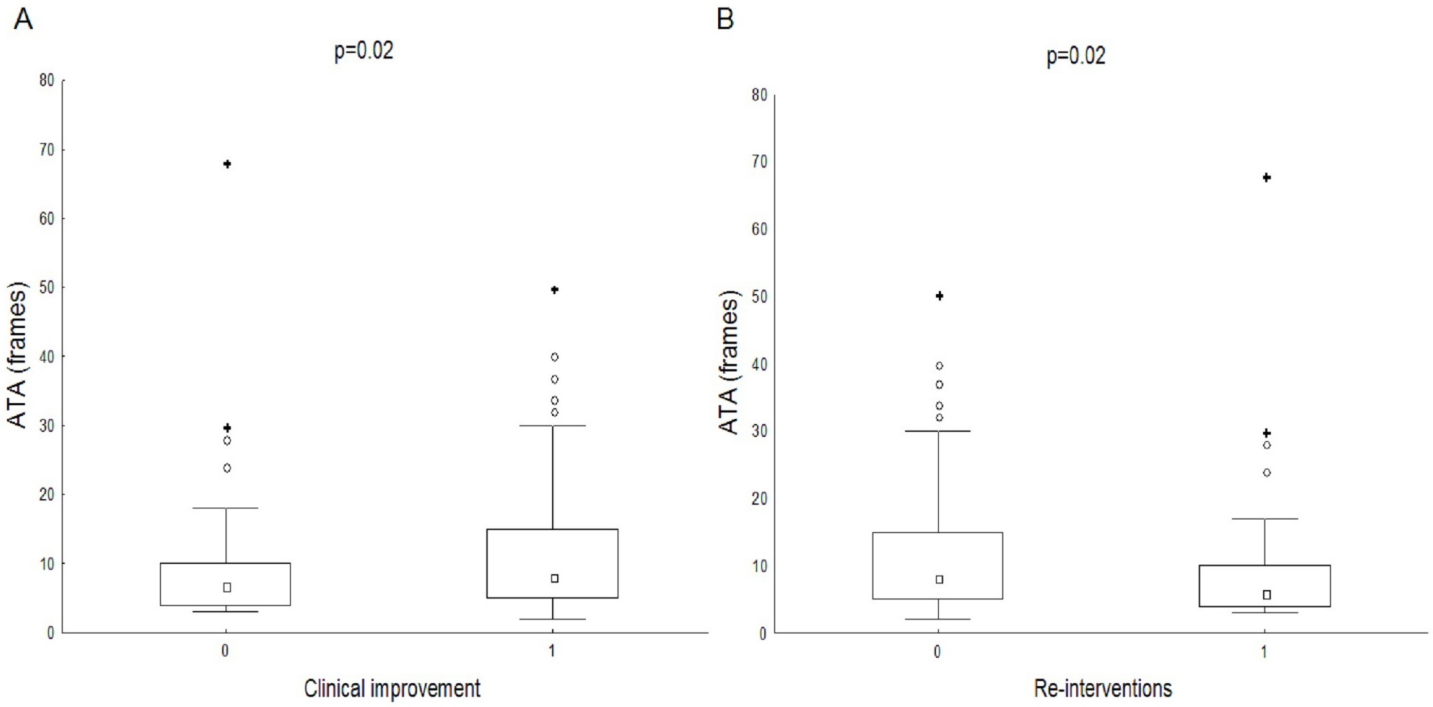
%
Overall
CLI
non-CLI
ATA
Overall
CLI
non-CLI
TPA
Overall
CLI
non-CLI
FA
≤5
6 to 10
11 to 20
21 to 30
31 to 40
41 to 50
≥51
Number of frames


A
p=0.02
ATA (frames)
80
70
60
50
40
30
20
10
0
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1
Clinical improvement
B
p=0.02
ATA (frames)
80
70
60
50
40
30
20
10
0
0
1
Re-interventions

8. PODSUMOWANIE WYNIKÓW I WNIOSKI

Artykuł nr 1

- Wykazano, że średnia wartość IMT uległa istotnemu statystycznie zmniejszeniu w obserwacji 6-miesięcznej po PTA.
- Nie uwidoczniono istotnej statystycznie poprawy wartości FMD, RHI oraz parametrów sztywności naczyń po PTA w obserwacji 6-miesięcznej.
- SEVR (*subendocardial viability ratio*) – jako jeden z parametrów sztywności naczyń – związany był z wystąpieniem istotnie statystycznie większej liczby osiągniętych punktów końcowych, takich jak: liczba reinterwencji, zgonów, zawałów serca, amputacji oraz udarów mózgu. Wyższe wyjściowe wartości SEVR wiązały się z większą liczbą tych zdarzeń.
- Wyjściowe wartości FMD, RHI oraz IMT nie miały związku z liczbą punktów końcowych w obserwacji rocznej.
- Większa liczba osiągniętych punktów końcowych w obserwacji rocznej wiązała się z występowaniem hypercholesterolemii, paleniem tytoniu, niższym ciśnieniem rozkurczowym krwi i niższym wyjściowym wskaźnikiem TBI.

Artykuł nr 2

- Stwierdzono statystycznie więcej reinterwencji naczyniowych oraz innych zdarzeń niepożądanych u pacjentów z CLTI oraz z wyższym wyjściowym IMT w porównaniu z pacjentami z chromaniem przestankowym.
- Nie stwierdzono istotnej poprawy po PTA w zakresie parametrów FMD i RHI w obu grupach chorych w obserwacji rocznej.

- Zaobserwowano poprawę wskaźnika FMD w pierwszym miesiącu po PTA, jednak poprawa ta nie była trwała, ponieważ ΔFMD zmniejszyło się między pierwszym a szóstym miesiącem po PTA.
- Podobnie w pomiarach RHI – ΔRHI wykazywał jedynie przejściową poprawę po pierwszym miesiącu od PTA u pacjentów z CLTI i nie zaobserwowano istotnych różnic w okresie między pierwszym a szóstym miesiącem po PTA w grupach pacjentów z CLTI i bez CLTI.

Wyniki te wskazują, że poprawa funkcji śródbłonka po rewaskularyzacji była przejściowa i utrzymywała się tylko przez pierwszy miesiąc po PTA. Po tym okresie funkcja śródbłonka uległa pogorszeniu, mimo że pacjenci wykazywali kliniczne korzyści z rewaskularyzacji.

Artykuł nr 3

- Pacjenci z wolniejszym przepływem krwi w zakresie tętnic podudzia (wyższym wskaźnikiem FC) po PTA prezentowali w rocznej obserwacji znamienną istotnie statystycznie poprawę kliniczną: lepsze gojenie ran, wydłużenie dystansu chromania.
- Zaobserwowano, że szybszy przepływ krwi (niższy wskaźnik FC) w zakresie tętnicy piszczelowej przedniej istotnie statystycznie predysponował do gorszych efektów klinicznych oraz do większej liczby reinterwencji naczyniowych.

- Wolniejszy przepływ krwi w zakresie tętnic podudzi po PTA obserwowano u młodszych pacjentów (dla tętnicy piszczelowej przedniej: $p = 0,05$; dla tętnicy strzałkowej: $p = 0,02$) oraz u chorych z mniej zaawansowaną klinicznie chorobą (dla tętnic: piszczelowej przedniej, piszczelowej tylnej i strzałkowej – $p < 0,001$).
- Wolniejszy przepływ krwi obserwowano u pacjentów z mniej zaawansowanymi zmianami morfologicznymi w obrazowaniu angiograficznym (dla tętnic: piszczelowej przedniej, piszczelowej tylnej i strzałkowej – $p = 0,01$) oraz u chorych posiadających większą liczbę drożnych tętnic na podudziu (dla tętnicy piszczelowej przedniej: $p = 0,01$, dla tętnicy strzałkowej: $p < 0,001$).

- Wolniejszy przepływ krwi obserwowano u pacjentów z chromaniem przestankowym w porównaniu z pacjentami z CLTI (dla tętnic: piszczelowej przedniej, piszczelowej tylnej i strzałkowej – $p < 0{,}001$) oraz u chorych, u których zanotowano wyższe wyjściowe wartości wskaźnika kostka–ramię (dla tętnicy piszczelowej tylnej: $p = 0{,}001$).

Wyniki tego badania wskazują na odwrotną zależność między FC obserwowanym na końcowym angiogramie a odległymi wynikami klinicznymi u pacjentów poddawanych PTA tętnic kończyn dolnych.

Podsumowanie

Wyniki przedstawionych badań sugerują, że zabieg PTA oraz zastosowane leczenie farmakologiczne (aspiryna, klopidogrel, statyna) nie miały istotnego i trwałego wpływu na funkcję śródbłonka tętnic. Można zatem wnioskować, że krótkotrwała pozytywna odpowiedź funkcji śródbłonka na PTA była zbyt mała i konieczna jest intensyfikacja leczenia farmakologicznego, aby uzyskać trwałą poprawę funkcji śródbłonka po PTA, a przez to lepsze odległe wyniki leczenia pacjentów z PAD. W związku z powyższym – terapia pod kontrolą funkcji śródbłonka może stanowić narzędzie do poprawy skuteczności farmakoterapii naczyniowej.

FC należy traktować jako prosty i skuteczny wskaźnik, który można w przyszłości wykorzystać do przewidywania drożności tętnic u pacjentów z PAD leczonych wewnątrznaczyniowo.

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10. STRESZCZENIE W JĘZYKU POLSKIM

Wstęp

Miażdżyca zarostowa z roku na rok dotyczy coraz większej liczby pacjentów. Głównie z powodu ogólnego starzenia się naszej populacji, ale również z powodu stale zwiększającej się liczby pacjentów z cukrzycą czy otyłością. Zaburzenia funkcji śródbłonka mają duże znaczenie w patogenezie rozwoju miażdżycy zarostowej. Dlatego markery dysfunkcji śródbłonka są istotnymi narzędziami, które w udowodniony sposób pomagają w diagnostyce i monitorowaniu miażdżycy. Należą do nich: FMD (*flow-mediated dilatation*), RHI (*reactive-hyperemia index*) oraz aPWA (*arterial pulse-waveform analysis*). Inne narzędzia, jak ocena dynamiki przepływu krwi, zostały stworzone głównie do oceny wyników jej leczenia. Obecnie większość pacjentów z objawową miażdżycą zarostową tętnic kończyn dolnych jest leczona z wykorzystaniem technik wewnątrznaczyniowych. Najbardziej zaawansowanym stadium miażdżycy zarostowej, związanej z zaburzeniami mikro- oraz makrokrążenia, jest krytyczne niedokrwienie kończyn dolnych (CLTI). W oparciu o dokument TASC II (*Inter-Society Consensus for the Management* of *PAD*) wiadomo, że 25% pacjentów z krytycznym niedokrwieniem umrze w przeciągu roku, a u dodatkowych 30% wykonana zostanie amputacja kończyny. Chorzy z krytycznym niedokrwieniem kończyn są znacząco bardziej obciążeni klinicznie (mają więcej chorób towarzyszących) w porównaniu z chorymi z chromaniem przestankowym, wymagają ponadto pilnej rewaskularyzacji z zastosowaniem bardziej zaawansowanych technik leczenia. To wszystko sprawia, że ta grupa chorych jest bardziej narażona na powikłania okołozabiegowe. Pomimo wspomnianych różnic między pacjentami z chromaniem przestankowym a chorymi z krytycznym niedokrwieniem kończyn, obie grupy chorych wykazują dysfunkcję śródbłonka.

Cele pracy

Celem analizy zbioru prac była ocena potencjalnego związku pomiędzy parametrami funkcji śródbłonka oraz dynamiką przepływu krwi a wynikami leczenia wewnątrznaczyniowego pacjentów

z miażdżycą zarostową tętnic kończyn dolnych. Mając na uwadze duże zróżnicowanie wśród chorych z PAD, dokonano ponadto osobnej analizy powyższych wyników u chorych z chromaniem przestankowym oraz u chorych z CLTI w obserwacji rocznej.

Materiały i metody

Badania miały charakter prospektywny, z roczną kontrolą pozabiegową. Do badań włączeni zostali pacjenci z chormaniem przestankowym kończyn dolnych oraz pacjenci z objawami krytycznego niedokrwienia kończyn dolnych, zakwalifikowani do leczenia wewnątrznaczyniowego. Oceniano funkcje śródbłonka, głównie na podstawie FMD (*flow mediated dilatation*) oraz RHI (*reactive-hyperemia index*), natomiast w ocenie klinicznego zaawansowania choroby pomocne były wskaźniki: kostka–ramię (ABI), paluch–ramię (TBI) oraz skala Rutherforda. Po każdym zabiegu rewaskularyzacyjnym oceniano ponadto przepływ krwi w zakresie tętnic podudzi (*frame count* – FC) za pomocą angiografii subtrakcyjnej. Wyniki były oceniane przed zabiegiem, po zabiegu oraz kontrolowane po miesiącu, 3, 6 i 12 miesiącach.

Wyniki i konkluzje

W oparciu o pierwszą pracę, zauważono, że wyjściowe wartości FMD, IMT, RHI nie korespondowały z liczbą punktów końcowych badania (liczbą reinterwencji, zgonów, zawałów serca, amputacji oraz udarów mózgu) u pacjentów z objawową miażdżycą zarostową po leczeniu wewnątrznaczyniowym w obserwacji rocznej.

Wśród wskaźników sztywności naczyń – wysokie przedzabiegowe wartości SEVR (*subendocardial viability ratio*) związane były z wystąpieniem większej liczby reinterwencji, zgonów, zawałów serca, amputacji czy udarów mózgu. Ponadto, większa liczba punktów końcowych dotyczyła pacjentów z hypercholesterolemią, niższym ciśnieniem rozkurczowym krwi czy niższymi wyjściowymi wartościami TBI, palących tytoń. Większa liczba punktów końcowych

badania dotyczyła pacjentów z wyjściowo występującymi objawami krytycznego niedokrwienia kończyn w porównaniu z chorymi z chromaniem.

Na podstawie wyników drugiej pracy udowodniono, że pacjenci z krytycznym niedokrwieniem kończyn dolnych odnieśli większe korzyści z zabiegów rewaskularyzacyjnych w porównaniu z osobami z chromaniem – w kontekście wzrostu wskaźnika TBI czy gojenia ran. Pomimo to nie odnotowano trwałej poprawy w zakresie parametrów śródbłonka w żadnej grupie chorych.

W oparciu o trzecie badanie odnotowano, że szybszy przepływ krwi (mniejsza liczba klatek) w zakresie naczyń podudzia predysponował do gorszych efektów klinicznych w obserwacji rocznej oraz większej liczby reinterwencji. Wolniejszy przepływ krwi w zakresie naczyń podudzi (wyższy wskaźnik FC) po zabiegach wewnątrznaczyniowych obserwowano u młodszych pacjentów oraz chorych prezentujących mniej zaawansowaną klinicznie chorobę.

11. STRESZCZENIE W JĘZYKU ANGIELSKIM

Introduction

The incidence of peripheral artery disease (PAD) is increasing due to the aging population. Early diagnosis and adequate treatment have been shown to improve clinical outcomes. Several tools have been proven to accurately diagnose peripheral atherosclerosis, such as markers of endothelial dysfunction expressed as flow-mediated dilatation (FMD), reactive-hyperemia index (RHI), or arterial pulse waveform analysis (aPWA). Other markers that evaluate the dynamics of blood flow were created to quantify the rate of progression in PAD and predict treatment outcomes. Nowadays, most patients with clinically symptomatic lower limb atherosclerosis are treated with percutaneous transluminal angioplasty (PTA).

The most advanced stage of PAD involving both macro- and microcirculation is called critical limb ischemia (CLI). The Inter-Society Consensus for the Management of PAD estimates that 25% of patients diagnosed with CLI will die within 1 year and an additional 30% will undergo amputation of the limb. CLI patients typically present with a spectrum of symptoms including pain during rest, non-healing ulcers, and tissue necrosis with gangrene. Comorbidities are present more frequent in CLI patients. These patients also require more immediate treatment and require more advanced procedural strategies. Because of this, they are more vulnerable to procedural complications. Despite the clinical differences between patients with CLI and those with limb claudication (non-CLI), they both exhibit the fundamental issue of endothelial dysfunction.

Objective

This study aims to assess the relationships between endothelial function indices, the dynamics of blood flow, and the clinical outcomes in patients with PAD. Given the heterogeneity of patients with PAD, we compared endothelial function, dynamics of blood flow, and clinical outcomes between CLI and non-CLI patients after PTA over a 12-month follow-up period.

Material and methods

In this prospective, follow-up studies we enrolled CLI and non-CLI patients who underwent PTA. Endothelial function was assessed based on FMD and RHI. The progression of PAD was evaluated using the ankle-brachial index, toe-brachial index (TBI), and the Rutherford scale. After the procedure, the blood flow of all patent below-the-knee (BTK) arteries was assessed using frame count (FC). The results of these tests were assessed before PTA, as well as 1, 3, 6, and 12 months after the procedure.

Results and conclusions

Based on the first study, we noted that baseline FMD, intima-media thickness (IMT), and RHI values did not significantly affect the study endpoints in patients with PAD who underwent PTA and completed 12 months of follow-up. Among aPWA indices, higher baseline values of the subendocardial viability ratio (SEVR) corresponded with an increased number of reinterventions, death, myocardial infarction, amputation, and stroke. Furthermore, an increase in these study endpoints was related to a history of hypercholesterolemia, longer history of smoking, lower diastolic blood pressure, and lower baseline TBI. Patients with CLI at baseline had significantly more study endpoint events during the one-year follow-up period compared to patients with claudication.

The second study found patients with CLI had a better clinical response to revascularization than non-CLI patients (larger drops in the Rutherford scale and greater increases in the TBI). However, there was no persistent improvement in endothelial function after revascularization in either group.

In the third study, we noted that patients with reduced blood flow within BTK arteries (higher FC) experienced significantly better clinical improvement during the follow-up period. A lower FC (faster blood flow) predisposed patients to worse clinical outcomes after angioplasty. These results suggest that patients with reduced blood flow as assessed by FC, experience better clinical outcomes after endovascular interventions of infrainguinal arteries.

Kraków, dnia 21.03.2022

lek. med. Andrzej Belowski

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/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„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."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji i monitorowaniu uczestników badania w okresie ich obserwacji objetem projektem badawczym.

Procentowy udział w jego powstanie określam na 3%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

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/podpis współautora/

Kraków, dnia 21.03.2022

dr hab.n.med. Paweł Maga prof.UJ

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

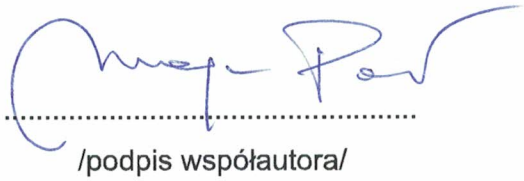
Jako współautor pracy pt.

„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."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: zaproponowanie tematu badawczego, nadzorowanie badań śródbłonka, współudział w interpretacji wyników i w przygotowaniu ostatecznej wersji manuskryptu.

Procentowy udział w jego powstanie określam na 10%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.



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/podpis współautora/

Kraków, dnia 21.03.2022

lek. med. Jolanta Kościelniak

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„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."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji i monitorowaniu uczestników badania w okresie ich obserwacji objetem projektem badawczym.

Procentowy udział w jego powstanie określam na 2%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

Jolanta Satława-Kościelniak

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr n.med. Marzena Frołow

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„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."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w określeniu celu badawczego i w wykonywaniu badań niezbędnych do potwierdzenia celu badawczego oraz nadzór nad wykonaniem wybranych pomiarów badawczych śródbłonka.

Procentowy udział w jego powstanie określam na 10%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

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/podpis współautora/

Kraków, dnia 21.03.2022

lek. Mikołaj Maga

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„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."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji uczestników badania, administrowaniu pozyskanymi wynikami oraz w przygotowaniu wstępnej wersji artykułu.

Procentowy udział w jego powstanie określam na 5%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

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/podpis współautora/

Kraków, dnia 21.03.2022

prof. dr hab. med. Rafał Niżankowski
.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„*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*."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w zaplanowaniu części badań umożliwiających sprawdzenie hipotezy badawczej oraz w interpretacji uzyskanych wyników.

Procentowy udział w jego powstanie określam na 5%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy **wykazuje indywidualny wkład lek med. Pawła Kaczmarczyka** przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

Signed by /
Podpisano przez:
Rafał Niżankowski
Date / Data: 2022-03-22 09:09

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr hab.n.med. Iwona Gregorczyk-Maga

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w katalogowaniu danych oraz w sporządzeniu ostatecznej wersji artykułu.

Procentowy udział w jego powstanie określam na 5%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....

/podpis współautora/

Kraków, dnia 21.03.2022

lek. med. Andrzej Belowski
.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji i monitorowaniu uczestników badania w okresie ich obserwacji,

Procentowy udział w jego powstanie określam na 3%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr hab.n.med. Paweł Maga prof.UJ

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

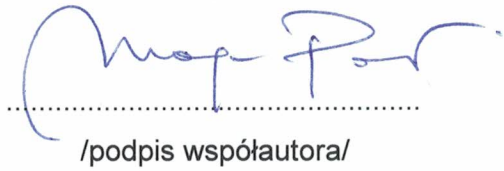
Jako współautor pracy pt.

„Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: zaproponowanie tematu badawczego, nadzorowanie badań śródbłonka, współudział w interpretacji wyników i przygotowaniu ostatecznej wersji artykułu.

Procentowy udział w jego powstanie określam na 10%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników oraz powstaniu manuskryptu.



.....

/podpis współautora/

Kraków, dnia 21.03.2022

dr n.med. Marzena Frołow

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział i nadzór nad wykonaniem badań niezbędnych do potwierdzenia celu badawczego, udział w interpretacji wyników.

Procentowy udział w jego powstanie określam na 7%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....

/podpis współautora/

Kraków, dnia 21.03.2022 r.

Prof. dr hab. n. med. Stefan Chłopicki
.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w zaplanowaniu części badań, umożliwiających sprawdzenie hipotezy badawczej oraz współudział w interpretacji wyników i powstaniu manuskryptu.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Paweł Kaczmarczyk przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr hab. n. med. Rafał Januszek

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Endothelial function in patients with critical and non-critical limb ischemia undergoing endovascular treatment."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w interpretacji wyników i obliczeniach statystycznych oraz pisaniu manuskryptu.
Procentowy udział w jego powstanie określam na 10%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Paweł Kaczmarczyk przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....
/podpis współautora/

dr hab. med. Rafał Januszek
specjalista chorób wewnętrznych
specjalista chorób płuc
specjalista kardiolog
1543440

Kraków, dnia 21.03.2022

dr hab.n.med. Rafał Januszek
.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„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."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w obliczeniach statystycznych, interpretacji wyników i pisaniu wstępnej wersji manuskryptu.

Procentowy udział w jego powstanie określam na 10%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....
/podpis współautora/

dr hab. med. Rafał Januszek
specjalista chorób wewnętrznych
specjalista chorób płuc
specjalista kardiolog
6539/0

Kraków, dnia 21.03.2022

dr hab. n. med. Rafał Januszek

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w obliczeniach statystycznych, interpretacji wyników i pisaniu manuskryptu.

Procentowy udział w jego powstanie określam na 10%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....

/podpis współautora/

dr hab. n. med. Rafał Januszek
specjalista chorób wewnętrznych
specjalista chorób płuc
specjalista kardiolog

Kraków, dnia 21.03.2022

lek. Agnieszka Wachsmann

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji pacjentów oraz w przygotowaniu wstępnej wersji artykułu.

Procentowy udział w jego powstanie określam na 3%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji projektu badawczego, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników oraz powstaniu manuskryptu.

Wachsmann Agnieszka
.....
/podpis współautora/

Kraków, dnia 21.03.2022

lek. med. Andrzej Belowski

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji pacjentów i w sporządzeniu analizy statystycznej

Procentowy udział w jego powstanie określam na 2%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Paweł Kaczmarczyk przy opracowywaniu koncepcji badania, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników oraz redagowaniu manuskryptu.

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr n.med. Katarzyna Tyrak

.....

/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w pozyskiwaniu i dokumentacji danych klinicznych uczestników badania.

Procentowy udział w jego powstanie określam na 2%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Paweł Kaczmarczyk przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

.....

/podpis współautora/

Kraków, dnia 21.03.2022

dr n.med. Łukasz Partyka
.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up.”

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji pacjentów oraz w przygotowaniu ostatecznej wersji artykułu.

Procentowy udział w jego powstanie określam na 5%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Paweł Kaczmarczyk przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr hab. n. med. Paweł Maga prof.UJ
.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: zaproponowanie tematu badawczego, nadzorowanie i udział realizacji projektu badawczego i współudział w przygotowaniu ostatecznego tekstu artykułu.

Procentowy udział w jego powstanie określam na 10%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników oraz powstaniu manuskryptu.

.....
/podpis współautora/

dr n. med. Marek Krzanowski

.....
/tytuł zawodowy, imię i nazwisko/

Kraków, dnia 21.03.2022

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: zaplanowanie części badań umożliwiających sprawdzenie hipotezy badawczej oraz współudział w interpretacji uzyskanych wyników.

Procentowy udział w jego powstanie określam na 10%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników i powstaniu manuskryptu.

.....
/podpis współautora/

Kraków, dnia 21.03.2022

lek. Mikołaj Maga

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w rekrutacji pacjentów oraz w sporządzeniu ostatecznej wersji artykułu.

Procentowy udział w jego powstanie określam na 5%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Paweł Kaczmarczyk przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników oraz powstaniu manuskryptu.

.....
/podpis współautora/

Kraków, dnia 21.03.2022

dr n.med. Ewelina Szybiak

.....
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
„Dynamics of below-the-knee arterial blood flow after endovascular revascularisation of peripheral arteries as a potential predictor of clinical outcomes during one-year follow-up."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: współudział w wykonywaniu obliczeń związanych z określeniem przepływu środka cieniującego w zakresie tętnic podudzia.

Procentowy udział w jego powstanie określam na 3%

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Pawła Kaczmarczyka przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników oraz pisaniu manuskryptu.

Ewelina Szybiak

.....
/podpis współautora/