

Changes in flow-mediated dilatation in patients with femoropopliteal occlusion receiving conservative and invasive treatment

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Abstract

Background: Although the beneficial effect of revascularisation on reduction of local clinical ischaemic symptoms has been well established, its effect on systemic vascular endothelial function has not been fully explained yet.

Aim: To determine changes in endothelium-dependent flow-mediated dilatation in patients with unilateral femoropopliteal occlusion receiving medical and surgical treatment.

Methods: Seventy-nine patients with symptomatic atherosclerotic ischaemia of lower extremities, treated with endovascular procedures, with femoropopliteal graft, or receiving conservative treatment (21-day controlled treadmill training) were enrolled in the study. Ankle brachial pressure index (ABPI), skin blood flow on the feet, and flow-mediated dilatation (FMD) of brachial arteries were measured in each patient at baseline and after 90 days of follow-up.

Results: The ABPI, vasomotion in the myogenic frequency band, and FMD increased significantly in surgical patients. In patients after femoropopliteal bypass a significant increase of vasomotion in the endothelial frequency band was also observed. In patients receiving conservative treatment (treadmill training), vasomotion in the myogenic frequency band increased whereas the FMD remained unchanged.

Conclusions: It seems that surgical treatment may contribute to reducing the risk of cardiovascular complications in patients with advanced peripheral artery disease, as a result of improving the systemic vascular endothelial function. Limiting treatment to just treadmill training increases pain-free walking distance but does not improve systemic vascular endothelial function.

Key words: endothelial flow-mediated dilatation, endothelial dysfunction, peripheral arterial occlusive disease, treadmill training, flowmotion

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INTRODUCTION

Generalised vascular endothelial dysfunction is one of the key components of an active atherosclerosis [1]. The assessment of endothelial-dependent flow-mediated dilatation (FMD) is one of the methods of monitoring vascular endothelial function [2]. It enables detection of changes in endothelial function secondary to the limited availability of nitric oxide, even if the vascular structural changes are still undetectable in imaging studies. Patients after myocardial infarction or surgical repair

of coarctation of the aorta, as well as individuals with diabetes and arterial hypertension, were shown to have decreased FMD values [1, 3]. Studies support usefulness of FMD measurement in early detection of coronary in-stent restenosis [4, 5].

Published data confirm the beneficial effect of blood flow normalisation after revascularisation procedures on a systemic vascular endothelial function. It involves, for example, faster peripheral perfusion parameter recovery after exercise, as compared to patients with intermittent claudication, and

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Table 1. Patient characteristics in each study group

	Group			P
	1	2	3	
Number of subjects	30	29	20	
Female/male	8/22 (26.7%/73.3%)	7/22 (24.1%/75.9%)	7/13 (35%/65%)	> 0.26
Age	64.6 ± 11.2	66.5 ± 9.7	63.3 ± 11.4	> 0.09
Body mass index	26.5 ± 4.3	25.5 ± 5.5	25.6 ± 3.6	> 0.26
Dyslipidaemia	24 (80%)	25 (86.2%)	18 (90%)	< 0.13
Arterial hypertension	18 (60%)	19 (65.5%)	15 (75%)	0.03
Smoking	22 (73.3%)	21 (72.4%)	13 (65%)	0.02
Diabetes mellitus	8 (26.7%)	10 (34.5%)	5 (25%)	> 0.06

slower progression of new atherosclerotic lesions [6]. These studies were conducted only in cardiac patients undergoing endovascular coronary revascularisation [4, 7]. Only a few studies included patients with atherosclerotic lower extremity ischaemia [8]. Understanding the effect of peripheral revascularisation on the systemic vascular endothelial function may help determine the subsequent course of the disease and plan the treatment accordingly.

The aim of the study was to determine changes in endothelium-dependent FMD in patients with unilateral femoropopliteal occlusion receiving medical and surgical treatment.

METHODS

Patients

Seventy-nine subjects with symptoms of chronic lower extremity ischaemia secondary to peripheral artery disease, Rutherford stage 3, were enrolled in the prospective non-randomised study. Diagnostic imaging confirmed the presence of unilateral, haemodynamically significant stenosis/occlusion of superficial femoral arteries. The inclusion criteria included maintained patency of the popliteal artery along with at least two of three crural arteries in the ischaemic limb and full arterial patency in the fellow lower extremity.

The exclusion criteria involved a history of previous vascular surgery, angioedema, true or dissecting aneurysms of any artery, cancer, neurological disorders, inflammatory disorders, allergies, chronic venous insufficiency, kidney failure requiring kidney replacement therapy, neurogenic diabetic ulcers, poorly controlled or untreated arterial hypertension, extensive skin lesions, and current use of phlebotropic agents, steroids, or immunosuppressants.

The patients were enrolled in one of the three groups, according to treatment method:

- Group 1: 30 subjects treated with endovascular angioplasty with stenting of the superficial femoral artery;
- Group 2: 29 subjects treated with *in-situ* femoropopliteal PTFE bypass with superficial femoral artery ligation in adductor canal;

- Group 3: 20 subjects treated with supervised 45-min treadmill training performed once daily for 21 days in line with TASC II recommendations.

Patient characteristics are shown in Table 1.

All patients received one antiplatelet agent (acetylsalicylic acid at the daily dose of 100–150 mg or clopidogrel 75 mg once-daily) and statins (simvastatin or atorvastatin at the daily dose of 20–40 mg) during the peri- and postoperative period. Additionally, therapies of all comorbidities such as angina pectoris, diabetes mellitus, and arterial hypertension were continued.

Methods

Location and severity of atherosclerosis was determined based on duplex Doppler ultrasound or angio-computed tomography. The ankle brachial pressure index (ABPI) was measured in all subjects.

All FMD and microcirculatory parameters were measured in the morning, in an air-conditioned room at a constant temperature of 21°C, with patients lying supine after a 15-min rest. Patients were advised to refrain from caffeine- and/or tannin-based as well as alcoholic drinks. They were also requested to avoid walking intensity, which could lead to ischaemic pain. A 12-h interval between drug administration and diagnostic investigations was ensured.

The ABPI, FMD, and flowmotion parameters and transcutaneous pressure of oxygen (T_{cpO₂}) were measured twice — on the day preceding treatment commencement and on day 90 of the follow-up.

Flow-mediated dilatation

Flow-mediated dilatation was measured in line with the recommendations of the International Brachial Artery Reactivity Task Force [2].

After the upper extremity arterial occlusion had been excluded in Doppler ultrasound scan, structural evaluation of brachial arteries was performed using 5–12 MHz broadband line transducers (Logic 7 ultrasound scanner, GE). The

longitudinal cross-section of the vessel at 5–10 cm proximally from the elbow was assessed. Using M-mode, the 5-second sequence of vascular wall movements in time was recorded. The distance between the hyperechoic striations on the endothelial surface of the anterior and posterior vascular wall was considered as the diameter. Each time, five measurement cycles were completed and the mean values were determined for further analysis.

The brachial artery diameter (BAD) was measured three times, i.e. at rest, after reactive hyperaemia, and following nitroglycerin administration.

Reactive hyperaemia was induced by cuff occlusion followed by arterial blood flow restoration. The manometer cuff positioned on the proximal humerus was pressurised to the value exceeding the diastolic pressure by 30 mm Hg. The ischaemia was maintained for 5 min. Fifty seconds after blood flow restoration, the BAD was measured again. The FMD was calculated as the difference in BAD between hyperaemic and resting states.

Another 10 min later, the patients were administered 0.5 mg of nitroglycerin (Glyceroli trinitras, Fa. Lek) sublingually. Three minutes after its administration, the BAD was measured again in order to determine the range of exogenous, non-endothelium-dependant arterial dilation. The differences in BAD between the nitroglycerin administration and resting was the actual nitroglycerin-mediated dilation (NMD).

In order to ensure objective measurement, the obtained FMD and NMD values were correlated with the BAD at rest, thus achieving FMD% and NMD%.

Flowmotion

Skin blood flow (SBF, perfusion units defined as 1 PU = 10 mV) was assessed using a PF 457 laser probe on a Periflux System 5000 (Fa. Perimed, Sweden) attached to the dorsal surface of the foot between the second and third metatarsal bone. Resting measurement was performed (10 min recording at 37°C).

Fourier analysis of the recording was performed using Perisoft PSW software v. 2.50 (Fa. Perimed, Sweden) which enables the time domain flow signal to be transformed into a frequency spectrum, with identification of five frequency

bands: vasomotion of endothelial frequency band, 0.01–0.02 Hz (VFB_E); vasomotion of neurogenic frequency band, 0.02–0.06 Hz (VFB_N); vasomotion of myogenic frequency band, 0.06–0.15 Hz (VFB_M); vasomotion of respiratory frequency band, 0.15–0.40 Hz (VFB_R); and vasomotion of heart beat frequency band, 0.40–1.60 Hz (VFB_H). The obtained results were expressed as power density units [PU/Hz] [9].

Institutional Review Board

The consent of the Institutional Review Board at the Karol Marcinkowski Medical University of Poznan was obtained with decision no. 1071/07 and 1083/08.

Statistical analysis

All obtained data was subjected to statistical analysis using STATISTICA software v.9 (StatSoft, Poland). In order to appreciate the time-related dynamics of variation in the analysed parameters, the relative increments expressed as percentages were determined. As the analysed variables did not follow a normal distribution pattern, the following non-parametric tests were used for the analysis: Mann-Whitney U-test and Spearman rank correlation coefficient, and their statistical significance was determined. $P \leq 0.05$ was considered statistically significant.

RESULTS

Patients enrolled in a given study group were compared in terms of sex, age, body mass index, dyslipidaemia, smoking, diabetes, and arterial hypertension (Table 1).

The mean ABPI values at baseline were 0.57 ± 0.24 ; 0.53 ± 0.23 ; and 0.59 ± 0.15 ($p > 0.78$) in Group 1, Group 2, and Group 3, respectively. The postoperative ABPI increased significantly in Groups 1 and 2 to 0.75 ± 0.1 ($p < 0.049$). However, it remained unchanged in Group 3, i.e. 0.61 ± 0.18 ($p = 0.198$) (Tables 2–4).

The preoperative FMD values were comparable across the three groups ($p > 0.294$). Postoperatively, FMD values increased significantly in patients from Group 1 and 2 (3.88 ± 1.92 to 6.69 ± 2.23 ; $p < 0.01$ and 4.27 ± 2.14 to 4.8 ± 2.26 ; $p = 0.049$, respectively). FMD value in Group 3 remained unchanged (4.41 ± 1.88 at

Table 2. Analysed parameters at baseline (first measurement — on the day preceding Day 1 of the study)

	Group			P		
	1	2	3	1 vs. 2	1 vs. 3	2 vs. 3
VFB _E	0.98 ± 3.85	0.97 ± 0.43	0.98 ± 0.35	0.98	0.89	0.91
VFB _M	0.82 ± 0.37	0.92 ± 0.43	0.96 ± 0.32	0.36	0.14	0.42
ABPI	0.57 ± 0.24	0.53 ± 0.23	0.59 ± 0.15	0.01	0.78	0.02
FMD	3.88 ± 1.92	4.27 ± 2.14	4.41 ± 1.88	0.61	0.29	0.65
NMD	14.19 ± 3.98	14.84 ± 3.67	14.25 ± 3.41	0.55	0.98	0.61

VFB_E — vasomotion in the endothelial frequency band; VFB_M — vasomotion in the myogenic frequency band; ABPI — ankle brachial pressure index; FMD — flow mediated dilatation; NMD — nitroglycerin-mediated dilatation

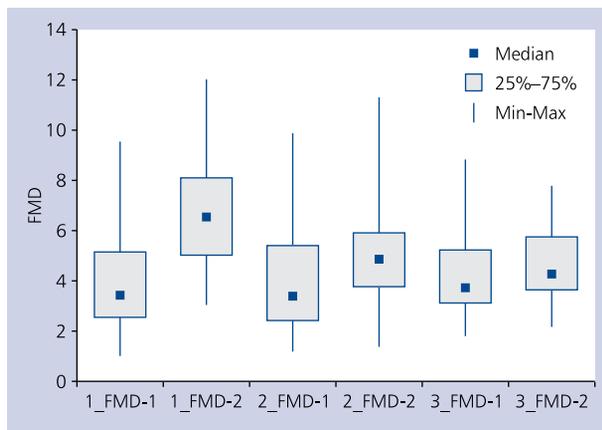
Table 3. Analysed parameters at the completion of the study (second measurement — Day 90 of the follow-up)

	Study group			P		
	1	2	3	1 vs. 2	1 vs. 3	2 vs. 3
VFB _E	1.02 ± 0.37	1.07 ± 0.38	0.96 ± 0.33	0.23	0.01	0.04
VFB _M	1.0 ± 0.38	1.67 ± 0.85	1.11 ± 0.42	0.01	0.34	0.04
ABPI	0.75 ± 0.1	0.75 ± 0.15	0.61 ± 0.18	0.90	< 0.01	< 0.01
FMD	6.69 ± 2.23	4.8 ± 2.26	4.54 ± 1.67	0.01	0.01	0.83
NMD	14.85 ± 4.55	14.91 ± 4.62	14.07 ± 3.68	0.85	0.99	0.72

Abbreviations as in Table 2

Table 4. Statistical significance of changes in analysed parameters from baseline to the completion of the study in each patient group

	Study group		
	1	2	3
Vasomotion in the endothelial frequency band	0.299	0.002	0.751
Vasomotion in the myogenic frequency band	0.007	< 0.001	0.035
Ankle brachial pressure index	0.049	0.002	0.198
Flow mediated dilatation	< 0.001	0.049	0.478
Nitroglycerin-mediated dilatation	0.116	0.975	0.765

**Figure 1.** Baseline (1) and ultimate (2) flow-mediated dilatation (FMD) values in each study group (1, 2, 3). The values were expressed as mean and a range of standard deviation

baseline vs. 4.54 ± 1.67 ultimately, $p = 0.478$). The postoperative FMD value in Group 1 was significantly higher than in the remaining groups (Tables 2–4, Fig. 1).

The NMD values were comparable across the groups. The postoperative assessment did not show significant changes compared to baseline ($p > 0.116$) (Tables 2–4).

The preoperative vasomotion values in the respective frequency bands were comparable between the groups. The postoperative changes affected the endothelial and myogenic frequency bands only. The findings included a significant vasomotion increase in the endothelial fre-

quency band in Group 2 (from 0.97 ± 0.43 to 1.67 ± 0.85 ; $p = 0.002$) and a significant vasomotion increase in the myogenic frequency band in all three groups (Group 1 from 0.82 ± 0.37 to 1.0 ± 0.38 , $p = 0.007$; Group 2 from 0.92 ± 0.43 to 1.67 ± 0.85 , $p < 0.001$; and Group 3 from 0.96 ± 0.32 to 1.11 ± 0.42 , $p = 0.035$) (Tables 2–4).

DISCUSSION

Regardless of the improved quality of life and increased number of saved limbs, one of the main treatment goals in peripheral artery occlusive disease (PAOD) is to reduce the risk of cardiovascular complications, which are caused by systemic vascular endothelial dysfunction. Decreased FMD values were shown in patients with angina pectoris, arterial hypertension, idiopathic pulmonary hypertension, chronic venous insufficiency, and lower extremity ischaemia due to atherosclerosis, as well as in patients with infections caused by *Salmonella spp.* [4, 10, 11]

Earlier studies showed that the risk of cardiovascular complications can be reduced with revascularisation, which restores normal vascular endothelial function. Both the increased preoperative FMD values and the wider range of postoperative FMD increments are associated with a significantly reduced incidence of serious cardio-cerebral vascular events including patient mortality [12].

Our results show that three-week treadmill training in patients with PAOD leads only to local improvement in microcirculation, which is reflected by the increased vasomotion in the myogenic frequency band with unchanged FMD value.

The six-month treadmill training additionally affected vasomotion in the endothelial frequency band. However, FMD values still remained unchanged in this case [13]. It was like this despite the subjective patient-reported improvement including increased pain-free walking time and distance [14].

The unchanged FMD value after treadmill training in patients with PAOD may seem strange at first, especially because in healthy individuals the FMD value increased as early as after a seven-day intensive workout [3]. Anvar et al. [15] observed a similar improvement, but its onset was after a six-month workout regimen. The human body adapts to regular exercise by means of the increased endothelial nitric oxide synthesis, and regular exercise improves vascular function regardless of modification of other risk factors [16].

Physical exercise that activates large muscle groups, increases blood pressure, and heart rate, has been shown to modify vascular function by means of, for example, wall shear stress [17]. Different endothelial response to treadmill training in patients with PAOD and healthy individuals can be due to the variable wall shear stress in these two groups. Evaluating healthy cyclists, Birk et al. [17] showed that physical exercise when intensive and long enough, increases wall shear stress in upper extremity vessels as a result of increased blood flow velocity in these vessels. Maximum FMD value increase was observed after two weeks of intensive workout. At the same time, conducting a similar study in subjects with cuffs placed on their arms to reduce blood inflow to the upper extremity during exercise, Birk et al. [17] observed unchanged FMD values throughout the entire follow-up period. The effect of haemodynamically significant vasoconstriction can be comparable.

This experiment appears to provide an explanation to the beneficial effect of surgical treatment on the systemic improvement in vascular endothelial function. It seems that the FMD increase in these patients is primarily associated with the improved haemodynamic parameters of peripheral blood flow after revascularisation rather than with changes in smooth muscle sensitivity or vascular wall remodelling. The unchanged NMD despite significantly increased FMD value appears to support this hypothesis [18].

The observed lesions may be attributed to the resolution of the preoperative inflammation affecting vascular endothelium as a result of revascularisation. It is initiated by inflammatory mediators released by the vascular endothelial cells and hypoxic skeletal muscle cells in patients with intermittent claudication or symptoms of critical ischaemia. Additionally, the decreased FMD value in patients with elevated serum C-reactive protein and fibrinogen or decreased ABPI appears to support the hypothesis of inflammatory component in mediating the systemic vascular endothelial function [19].

Disruption of blood flow below atherosclerotic lesions is thought to be one of the key factors to affect the preoperative

FMD decrease. With the low oscillatory shear stress, the genes stimulating deposit formation take over, and vascular endothelium switches to proatherogenic phenotype. The expression of factors involved in the atherogenesis process is intensified, among other monocyte chemoattractant protein-1, vascular cell adhesion protein 1, intercellular adhesion molecule 1, interferon-gamma, tumour necrosis factor alpha, endothelin 1, and angiotensin II [20]. When formed, atherosclerotic plaque enters the vicious circle maintaining turbulent blood flow while a severed boundary layer and circular motion directly behind the plaque contribute to its increase in size distally [21, 22].

Revascularisation procedures offer blood flow normalisation in previously ischaemic limb segments. Laminar blood flow restoration characterised by an axially symmetrical profile and increased velocity activates atheroprotective genes and increases the expression of atheroprotective molecules, among other tissue plasminogen activator, prostaglandin I₂, transforming growth factor-beta, nitric oxide, and manganese superoxide dismutase. Normal blood flow exerts antioxidant, anti-inflammatory, anti-proliferative, and antiplatelet effects on vascular endothelium [4, 5, 21, 23].

Other authors also support the improved vascular endothelial function. However, they anticipate such improvement after at least six months following revascularisation [1]. It is thought that the presence and scope of change in FMD values in patients after successful coronary angioplasty and stent implantation procedures reflects both the systemic improvement of vascular endothelial function and mechanical removal of pre-existing occlusion [4]. FMD measurement proved to be helpful in identification of patients at particular risk of recurrent occlusion, who require more frequent follow-up examinations [4, 5, 7].

As far as peripheral arteries are concerned, FMD values increased by 30–50% at four weeks following femoral angioplasty [8]. Another study was conducted in patients with femoropopliteal occlusion receiving medical and endovascular treatment. In the medical treatment group, FMD, ABPI, and white blood cell count remained unchanged over the four-week treatment duration. At the same time, the surgical patients encountered a significant increase of FMD and ABPI at four weeks postoperatively. The C-reactive protein and fibrinogen levels remained unchanged in both groups [24].

CONCLUSIONS

Treadmill training in patients with severe PAOD increases pain-free walking distance but it does not affect the systemic vascular endothelial function. In order to reduce the risk of cardiovascular complications by means of improving the systemic vascular endothelial function, these patients should be referred for surgery earlier. This management may increase the systemic benefits of treadmill training if continued.

Conflict of interest: none declared

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Zmiany rozszerzalności naczyń zależnej od śródbłonna u pacjentów z niedrożnością udowo-podkolanową leczonych zachowawczo i zabiegowo

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Streszczenie

Wstęp: Chociaż potwierdzono korzystny wpływ rewaskularyzacji na zmniejszenie miejscowych klinicznych objawów niedokrwienia, to nadal niejednoznaczny pozostaje jej wpływ na ogólnoustrojową funkcję śródbłonna naczyniowego.

Cel: Celem badania było określenie zmian zależnej od śródbłonna wazodylatacji indukowanej przepływem (FMD) u pacjentów leczonych zachowawczo i zabiegowo z powodu jednostronnej niedrożności udowo-podkolanowej.

Metody: Do badania włączono 79 pacjentów w objawami miażdżycowego niedokrwienia kończyn leczonych wewnątrz-naczyniowo, pomostowaniem udowo-podkolanowym lub zachowawczo (21-dniowy kontrolowany trening marszowy). Przed leczeniem i po upływie 90 dni oznaczono wskaźnik kostka–ramię (ABPI), parametry przepływu w mikrokrążeniu skórnym na stopach oraz FMD na tętnicach ramiennych.

Wyniki: U pacjentów leczonych zabiegowo znamienne zwiększyły się wartości ABPI, gęstości mocy pasma mięśniowego *flowmotion* oraz FMD. U chorych po pomostowaniu dodatkowo wzrosła gęstość mocy pasma śródbłonkowego *flowmotion*. U osób leczonych zachowawczo zwiększyła się tylko gęstość mocy pasma mięśniowego, przy niezmienionej wartości FMD.

Wnioski: Wydaje się, że zmniejszenie ryzyka wystąpienia powikłań sercowo-naczyniowych u pacjentów z zaawansowanym miażdżycowym niedokrwieniem kończyn dolnych, w następstwie ogólnoustrojowej poprawy funkcji śródbłonna naczyniowego, jest możliwe poprzez wdrożenie leczenia zabiegowego. Ograniczenie się wyłącznie do stosowania treningu marszowego, poza wydłużeniem dystansu przejścia bezbólowego, nie poprawia ogólnoustrojowej funkcji śródbłonna.

Słowa kluczowe: rozszerzalność naczyń zależna od śródbłonna, zaburzenia funkcji śródbłonna, miażdżycowe niedokrwienie kończyn dolnych, trening marszowy, *flowmotion*

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