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Cutaneous microcirculation reactivity in patients with arterial hypertension, taking into account intake of anti-hypertensive drugs

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Abstract

Objective. The aim of the study was to assess the reactivity of the cutaneous microcirculation in patients with arterial hypertension (AH), taking into account the intake of anti-hypertensive drugs, using laser doppler flowometry (LDF) and the post-occlusive reactive hyperaemia (PORH) test.

Materials and method. The analysis included 44 patients with well-controlled AH, and 22 subjectively healthy volunteers aged 23 – 74 years, matched with the study group. During the study period, 22 patients in the study group were taking ACEI drugs, also in combination with other drug groups in terms of gender and age. 19 patients were taking other groups of drugs, including: ARB, beta-blockers, alpha-blockers, CCB, diuretics, also in combination, while 3 patients were not taking medication for AH; they were recommended non-pharmacological treatment. Blood biochemical tests, ambulatory blood pressure monitoring (ABPM) and PORH test using LDF were performed.

Results. The study showed that the PORH flow parameters were not differ statistically significantly between the study and control groups ($p > 0.05$). Statistically significant differences were shown in the PORH maximum level (ML) on the skin forearm between the study group not taking ACEI drugs and the control group. No statistically significant differences were shown between the study group taking ACEI and the control group.

Conclusions. The pathogenesis of AH is multifactorial and depends, *inter alia,* on disturbances at the level of microcirculation. Proper treatment, especially with the use of ACEI, can improve the microcirculation in AH patients.

Key words

arterial hypertension, microcirculation, laser dopper flowmetry, post occlusive reactive hyperaemia, angiotensin converting enzyme inhibitors

Abbreviations

ABPM – ambulatory blood pressure monitoring; **ACEI** – angiotensin converting enzyme inhibitors; **AH** – arterial hypertension; **BZ** – biological zero; **CCB** – calcium channel blockers; **CRP** – *C*-reactive protein; **eGFR** – estimated glomerular filtration rate; **HDL** – high density lipoproteins; **LDF** – laser dopper flowmetry; **LDL** – low density lipoproteins; **ML** – maximum level; **NO** – nitric oxide; **NT** – pro-BNP; **N** – terminal of the pro *B*-type natriuretic peptide; **PORH** – post-occlusive reactive hyperaemia; **RL** – resting level; **T0** – time of zero increase; **TG** – triglyceride; **TH** time to half decay; **TM** – time to maximum level; **TR** – time to recovery

INTRODUCTION

Arterial hypertension (AH) is a chronic disease of the circulatory system [1]. The pathophysiological mechanisms responsible for the development of AH are complex and overlap with the concomitant genetic predisposition [2]. AH is associated with changes in the microcirculation, both on a structural and functional basis. The vessel walls are remodeled and the vessel density is reduced, the main reason for which is believed to be increase in the level of oxidative stress [3]. The excessive secretion of endothelial vasoconstrictor substances, such as endothelin and angiotensin II, also lies in the pathogenesis of AH [4]. Thus, a key factor in understanding the pathogenesis of endothelial dysfunction in AH is the imbalance between vasodilating and constricting factors, which is mainly due to the reduced bioavailability of nitric oxide (NO) [5]. The LDF PORH test is based on the observation of a transient increase in skin blood flow after the end of a 3–5 minute vascular occlusion [6].

PORH assessment of the skin may be a sensitive indicator of endothelial damage. Microvascular disorders, including reduced NO-dependent vasodilation, structural changes in the vessels, and reduced perfusion, may both precede and affect the course of AH [7]. Studies conducted with the use of the LDF technique have shown a beneficial effect of drugs on changes in microcirculation through antioxidant and vasodilating effects [3]. Other studies indicate the reversibility of changes in microcirculation in the course of AH as a result of appropriate pharmacotherapy [8].

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MATERIALS AND METHOD

The study included 44 patients with well-controlled AH, aged 23 – 74 years, and 22 subjectively healthy volunteers matched in terms of gender and age to the study group. During the study period, 22 patients in the study group were taking ACEI drugs, also in combination with other drug groups, 19 patients were taking other groups of drugs, including: ARB, beta-blockers, alpha-blockers, CCB, diuretics, also in combination, while 3 patients were not taking medication for AH, and were recommended non-pharmacological treatment. In the study group, 7 people were treated for lipid disorders and were taking statins. Patients with diabetes mellitus, generalized atherosclerosis, infection, current neoplastic disease, G4 or G5 chronic renal failure, chronic heart failure and confirmed secondary hypertension, were not included in the study. Patients participating in the study were acquainted with the information regarding the research topic and provided their informed consent. The applied research methodology was approved by the Bioethics Committee at the Medical University of Lublin.

Biochemical Analysis. For laboratory tests, blood was collected from fasting subjects from the cephalic vein. The tests were performed in the Laboratory Diagnostics Department of the Independent Public Clinical Hospital No. 1 in Lublin. Peripheral blood counts were performed, including haemoglobin level (g / dl) norm for men: 14–18 g /dl, women 12–16 g / dl, WBC (10^9/L) norm 4–10 10^9/L, PLT (10^9/L) norm 130–400 10^9/L, full lipid profile, including total cholesterol (mg / dl) norm 115–190 mg / dl, HDL (mg/dl) norm> 40 mg / dl, LDL (mg / dl) norm < 115 mg / dl, TG (mg/dl) norm <150 mg / dl, and other biochemical tests, such as NT pro-BNP (pg / ml) norm 0–225 pg / ml, creatinine (mg/dl) norm 0.7- 1.2 mg / dl, eGFR (ml / min / 1.73m2) m2, fasting glucose (mg / dl) norm 70–99 mg / dl and CRP (mg/l) norm <5 mg / l.

ABPM. Assessment of the diurnal blood pressure profile was performed using the Microlife WatchBP O3 AFIB Holter device placed on the arm, from which a higher value of systolic blood pressure was obtained, measured directly before insertion using the Korotkov method. The device had been programmed to measure every 20 min during the day and every 30 min during the night. The day was divided arbitrarily, assuming the period 07.00 – 23.00 per day and 23.00 -07.00 per night. After reading the data, parameters important for clinical management, such as mean systolic and diastolic blood pressure in the 24h cycle (mmHg), were assessed using the Microlife WatchBP Analyzer O3 Polish software supplied with the equipment. The test was considered normal if more than 70% of the day and night readings were successful.

PORH. In the laser-Doppler part, a 2-channel device for examining microcirculation haemodynamics moorVMS-LDF (MOOR Instruments, Axminster, Devon, UK) was used to assess the resting measurement and PORH examination. Patients were advised to avoid caffeine, high salt food, alcohol, vigorous exercise, smoking and e-cigarettes for 24 hours prior to testing. The test was carried out in a quiet room with a constant temperature of around 22 °C from 14:00–18:00. The acclimatization time for the patient was 30 min in the supine position. Measurement was performed in a supine position, indicating relaxation and normal breathing, with the right upper limb at the level of the heart. The number 1 laser Doppler (FLUX 1) receiving probes were placed on the skin 10 cm below the elbow flexion on the anterior surface of the right forearm in the midline, and the number 2 (FLUX 2) probe on the right thumbstick. The equipment and the PORH test protocol were calibrated in accordance with the manufacturer's instructions and recommendations (Tab. 1). The following PORH parameters were calculated: resting level (RL), biological zero (BZ), maximum level (ML), time of zero increase (T0), time to recovery (TR), time to maximum level (TM), time to half decay (TM), ML/RL. Table 1 shows an exemplary own result from the research protocol.

Table 1. PORH test protocol

Test parameter [units]	Value
Resting flow time [s]	20
Occlusion time [s]	180
Cuff pressure [mmHg]	30 mmHg above systolic blood pressure, measured directly before the test
Flow after occlusion [s]	360

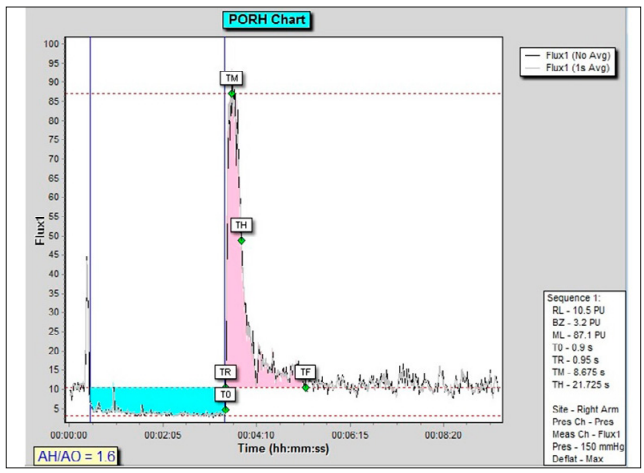

Figure 1. Sample own result from the PORH protocol

Statistical Analysis. The obtained results were analyzed statistically. The values of the analyzed measurable parameters were presented by means of the mean value, median and standard deviation, and for non-measurable ones – by the number and percentage. For measurable features, the normal distribution of the analyzed parameters was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare 2 independent groups. The Kruskal-Wallis test was used to compare the age of the groups. A significance level of $p < 0.05$ was adopted, indicating the existence of statistically significant differences or relationships. The database and statistical research were carried out on the basis of the STATISTICA 13.0 computer software (StatSoft, Kraków, Poland).

RESULTS

66 patients were included in the study, 66.67% (n = 44) of whom were being treated for AH (study group) and 33.33%

(n = 22) of healthy patients (control group). Both in the study group and in the control group, women (59.09%) and men (40.91%) constituted the same percentage. The mean age in the study group was 54.02 years, while in the control group – 53.09 years. In the study group, the patients were most often overweight (38.64%) or obese (36.36%), while in the control group the majority of people had a normal BMI (54.44%). Most often, patients suffering from hypertension had been treated for more than 5 years (43.18%).

In the part concerning the statistical analysis of blood chemistry, in most parameters, no significant differences were found between the groups (p> 0.05). Both selected blood count parameters, including haemoglobin, WBC and PLT, and other biochemical results, including glucose, creatinine, eGFR, NT-proBNP, and CRP did not differ statistically between the study and control groups. However, in the analysis of the lipid profile, statistically significant differences were found in the level of total cholesterol (p = 0.0002) and LDL (p = 0.001); the differences in the level of HDL were statistically insignificant. Higher values of total cholesterol and LDL cholesterol were observed in the study group (Tab. 2).

Moreover, in the part concerning ABPM, significant statistical differences nwere shown in the values of systolic and diastolic pressure between the study and control group (p = 0.005). The pressure values were higher in the study group (Tab. 3).

There were also no significant differences in the blood pressure values in the study group between the respondents receiving ACEI drugs and those not using drugs (p> 0.05) (Tabl. 4).

In the main part of the study on LDF PORH, the statistical analysis performed did not show any significant differences between AH and healthy patients in terms of PORH parameters, including flow parameters (RL, BZ, ML, ML / RL) and time parameters (T0, TR, TM TH), (p> 0.05). There were no statistically significant differences between the probe placed on the skin of the forearm (FLUX 1) and the thumb pad (FLUX 2) (Table 5). The distribution of the statistical feature of selected PORH parameters, including ML and TM in the study and control group is presented in the box-plot chart (Fig. 2).

Statistical analysis showed significant differences in the assessment of ML FLUX 1 between the study and control

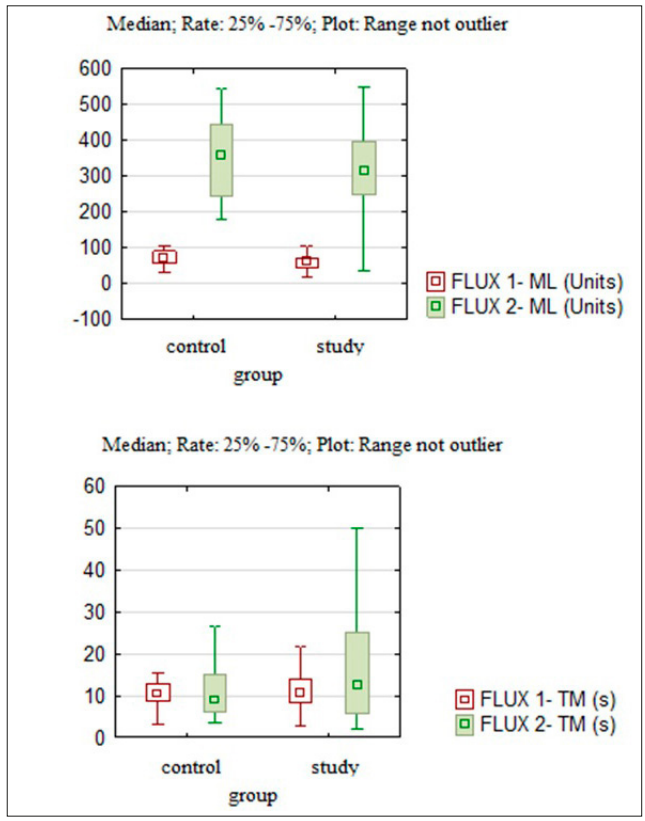

Figure 2. Values of selected PORH parameters in groups

Table 2. Results of individual parameters in the studied groups

Parameters	Study group (n=44)			Control group (n=22)			Statistical analysis	
	Mean	Median	SD	Mean	Median	SD	Z	p
Haemoglobin (g/dl)	13.58	13.80	1.41	13.42	13.20	1.35	0.89	0.37
WBC (10^9/L)	6.52	6.22	1.64	6.70	6.81	1.74	-0.80	0.43
PLT (10^9/L)	252.52	250.5	66.03	247.91	231.00	70.28	0.67	0.51
Fasting glucose (mg/dl)	94.81	94.65	10.30	92.80	93.60	6.89	0.75	0.45
Total cholesterol (mg/dl)	202.90	204.8	48.32	158.84	150.6	31.08	3.67	**0.0002***
HDL (mg/dl)	50.28	49.75	15.53	48.52	49.20	14.53	0.41	0.68
LDL (mg/dl)	140.27	143.0	45.79	102.18	98.00	26.34	3.35	**0.001***
TG(mg/dl)	142.55	105.5	115.3	102.05	89.50	45.84	1.52	0.13
CRP (mg/dl)	3.12	1.45	4.01	5.53	1.65	6.54	-0.96	0.34
Creatinine (mg/dl)	0.86	0.80	0.22	0.84	0.87	0.26	0.37	0.71
eGFR (ml/min/1.73m^2)	88.63	84.77	21.05	92.84	93.79	17.92	-1.01	0.31
NT-proBNP (pg/ml)	85.89	49.00	111.4	60.14	49.00	45.89	0.66	0.51

Table 3. Blood pressure values in the studied groups

Blood pressure	Study group (n=44)			Control group (n=22)			Statistical analysis	
	Mean	Me	SD	Mean	Me	SD	Z	p
Systolic	121.48	120.00	14.32	110.18	110.00	10.86	-2.81	**0.005***
Diastolic	72.45	71.50	8.97	65.59	66.50	6.68	-2.84	**0.005***

Table 4. Blood pressure values in the study group, taking into account the intake of anti-hypertensive drugs from the ACEI group

Blood pressure	Study group with ACEI drugs (n=22)			Study group without ACEI drugs (n=22)			Statistical analysis	
	Mean	Me	SD	Mean	Me	SD	Z	p
Systolic	123.18	121.00	15.84	119.77	117.50	12.75	0.61	0.54
Diastolic	73.50	73.00	9.30	71.41	70.50	8.72	0.88	0.38

Table 5. Values of PORH parameters in groups

Parameters		Study group (n=44)			Control group (n=22)			Statistical analysis	
		Mean	Median	SD	Mean	Median	SD	Z	p
ML	FLUX 1	63.88	60.40	26.98	73.59	70.00	25.52	1.65	0.10
	FLUX 2	314.25	316.20	111.32	356.29	356.85	115.23	1.15	0.25
ML /RL	FLUX 1	4.38	3.90	2.27	4.37	4.30	1.96	0.28	0.78
	FLUX 2	2.56	1.91	2.23	3.08	2.03	2.42	0.65	0.52
TM	FLUX 1	11.74	10.76	6.58	10.91	10.50	3.84	-0.07	0.94
	FLUX 2	16.82	12.65	13.19	11.15	8.89	6.89	-1.26	0.21
RL	FLUX 1	16.89	15.75	7.69	19.75	16.85	10.87	0.94	0.35
	FLUX 2	171.82	181.40	90.85	186.94	205.25	120.00	0.59	0.55
BZ	FLUX 1	4.23	4.10	1.21	4.69	4.65	1.24	1.41	0.16
	FLUX 2	4.54	3.85	2.89	5.14	3.45	3.78	-0.36	0.72
T0	FLUX 1	0.47	0.43	0.33	0.48	0.46	0.38	-0.18	0.85
	FLUX 2	0.51	0.49	0.38	0.56	0.56	0.33	0.92	0.36
TR	FLUX 1	1.29	1.18	0.65	1.20	1.16	0.43	-0.14	0.89
	FLUX 2	1.65	1.28	1.52	1.40	1.33	0.40	0.39	0.70
TH	FLUX 1	23.83	20.75	10.00	22.47	21.83	8.36	-0.09	0.93
	FLUX 2	36.11	25.03	31.76	31.17	22.73	19.97	-0.10	0.92

Table 6. Values of selected PORH parameters in the study and control group in patients not taking ACEI drugs

Parameters		Study group without ACEI drugs (n=22)			Control group (n=22)			Statistical analysis	
		Mean	Median	SD	Mean	Median	SD	Z	p
ML	FLUX 1	57.51	53.45	20.78	73.59	70.00	25.52	2.01	0.04*
	FLUX 2	286.83	274.35	111.13	356.29	356.85	115.23	1.63	0.10
ML /RL	FLUX 1	4.58	4.43	2.19	4.37	4.30	1.96	-0.16	0.87
	FLUX 2	2.95	2.18	2.54	3.08	2.03	2.42	-0.27	0.79
TM	FLUX 1	12.44	10.75	7.81	10.91	10.50	3.84	-0.32	0.75
	FLUX 2	18.71	17.00	13.12	11.15	8.89	6.89	-1.96	0.05*

Table 7. Values of selected PORH parameters in the study and control groups in patients receiving ACEI drugs

Parameters		Study group with ACEI drugs (n=22)			Control group (n=22)			Statistical analysis	
		Mean	Median	SD	Mean	Median	SD	Z	p
ML	FLUX 1	70.26	61.50	31.20	73.59	70.00	25.52	-0.82	0.41
	FLUX 2	341.67	340.70	107.00	356.29	356.85	115.23	-0.34	0.73
ML /RL	FLUX 1	4.17	3.61	2.38	4.37	4.30	1.96	-0.66	0.51
	FLUX 2	2.18	1.66	1.84	3.08	2.03	2.42	-1.40	0.16
TM	FLUX 1	11.04	10.76	5.17	10.91	10.50	3.84	-0.18	0.86
	FLUX 2	14.93	9.59	13.29	11.15	8.89	6.89	0.20	0.84

group in patients who did not take ACEI drugs (p = 0.04), and at the limit of significance in assessment of the TM FLUX 2 parameter (p = 0.05), while in the assessment of other parameters, no significant differences were found (p> 0.05) (Tab. 6).

Comparing the group of patients taking ACEI with the group of healthy subjects, no statistically significant differences were found in the assessment of individual PORH parameters (p> 0.05) (Table 7).

DISCUSSION

Changes in the course of AH may occur both in the macro- and micro-circulation. The arteries are stiffened, among other things, especially in the elderly [9]. The first changes in normal micro-circulation can be found in approximately 93% of patients with primary hypertension, long before the appearance of clinical organ dysfunction. Micro-circulation disorders in AH are systemic in nature and are a hallmark of distant complications of AH. Currently, there is substantial evidence that microvascular changes occur very early and may play a role in their pathogenesis and progression [10]. In this context, it is impossible to ignore the modern methods of endothelial and micro-circulation assessment, such as LDF, which have a recognized clinical value [11]. The LDF method has some limitations resulting from the sensitivity of the results to various external measurement conditions, individual and local variability of blood flow in micro-circulation; therefore, measurements should be standardized through the use of so-called provocation tests, most often causing local tissue hyperaemia [12].

It should be noted that the PORH mechanism has not been sufficiently explained [13]. The results of the LDF PORH study are influenced by numerous factors, including NO release, endothelium dependent hyperpolarization [14], and shear stress [15]. According to Yvonne-Tee et al., ML and TM are the most reproducible parameters of the PORH method [16], and according to Zegar-Parodi, more reproducible results are obtained on the fingertips than on the forearm [11].

The current study did not show any statistically significant differences in PORH parameters between the study group and the control group ($p > 0.05$). The results could have been influenced by the insufficiently large group of patients participating in the study, as well as the fairly optimal treatment of patients with hypertension, and the beneficial effect of drugs used by patients on the PORH test result. On the other hand, statistically significant differences between the study group and the control group were found in the average values of systolic and diastolic pressure during the day, which were higher in the study group. Average blood pressure during the day is a risk factor for cardiovascular complications [17]; however, according to the ESC / ESH guidelines, the mean pressure values during the day should fall within the range <130/80 mmHg [1], thus, both groups (study and control) had normal results. Considering the above, it can be concluded that AH patients were well controlled. In order to evaluate the effect of antihypertensive drugs on PORH, an analysis correlation was performed, which showed statistically significant differences between the non-ACEI study group and the control group in the range of ML FLUX 1 ($p = 0.04$), while in the study group receiving ACEI and the group no statistically significant differences were found ($p > 0.05$). PORH test results, in the opinion of the authors of the current study, may be related to the beneficial effects of ACEI on vascular endothelial function and improvement of myogenic response.

According to Farkas et al., the longer the duration of antihypertensive treatment, the longer it takes for the recovery of abnormalities in patients with hypertension, such as increased blood pressure, remodeling of the vascular walls or impaired vasodilation [18].

The PORH study of the skin by Siega-Dobrescu et al. showed a significantly reduced parameter of the percentage increase in flow after occlusion in patients after discontinuation of drugs for AH. The authors suggest that the impaired PORH response in the study after discontinuation of antihypertensive therapy may result from the development of endothelial dysfunction and vascular remodeling, which may contribute to an increase in blood pressure in patients after drug discontinuation. In patients who used antihypertensive drugs, no differences in skin flow were found [19].

Moreover, a study by Rossi et al. showed that newly-diagnosed, untreated patients with AH had a significantly reduced percentage increase in post-occlusion flow relative to the control group. The authors associate the normalization of skin PORH in patients with hypertension who were re-tested after antihypertensive treatment, mainly with the normalization of skin vasoreactivity, as a result of restoration of myogenic function as a consequence of reduced occlusion shear stress [8].

The studies by Higashi et al. show that the maximal flow after occlusion was significantly higher in the group treated with ACEI than in the groups treated with CCB, beta-blockers, diuretics or untreated. The authors suggest that this is related to the level of bradykinin, which binds to B2 receptors on the endothelial surface, releasing NO. Additionally, the authors showed that in patients treated with ACEI, despite improvement, the hyperaemic reaction was worse than in healthy people, which may suggest that antihypertensive therapy with only one group of drugs may not restore full endothelial function to the level of healthy people [20]. Thus, it seems that other drugs have a beneficial effect on endothelial function only in mechanisms independent of bradykinin [21].

More recent studies, for example Korolev et al., show decrease in the perfusion efficiency of the endothelial and myogenic mechanisms of tissue perfusion modulation in men of working age with newly-diagnosed AH [22]. Moreover, Gkaliagkousi et al. have shown that skin microvascular function was significantly impaired in patients with primary aldosteronism, compared to patients with essential AH with similar blood pressure profile [23].

The results of the presented research are therefore partially consistent with the previous observations of researchers, despite the differences in the characteristics of the studied groups as well as the methods and objectives of the research. In the opinion of the authors', the cumulative positive effect of using drugs from different groups, also in combination, could have influenced the results of the study, although it is not known what results would be obtained if most patients used only one preparation. In the presented study group, 22 patients took ACEI, which may have a particularly significant effect on improving PORH, but more research is needed on this topic.

Limitations of the study. One of the limitations of the current study was the use of statins by 7 patients with lipid disorders, which, according to some authors, improve endothelial function due to increased secretion of endothelial prostaglandins [24]; however, the study by Tousoulis et al. showed that atorvastatin did not change the maximum hyperaemic flow in PORH [25]. Moreover, the fact that 3 patients were treated non-pharmacologically (lifestyle modification) which, however, as indicated by a study by Gerage et al., may also have a beneficial effect on PORH parameters, which the authors associate with lower

endothelial inflammation, improved oxidative-antioxidant balance and a higher level of NO bioavailability [26].

CONCLUSIONS

To sum-up, due to the small amount of research, the topic of micro-circulation assessment in patients with hypertension requires further investigation. In theopinion of the authors, the need to assess the endothelial status and micro-circulation in patients with hypertension seems unquestionable. It is worth remembering here about the multitude of factors influencing the PORH measurement result, both dependent on the homeostasis of the organism, such as metabolic factors [7] and medications taken [19], as well as external factors or individual characteristics [12]. Further research should focus on the study and evaluation of factors influencing the micro-circulation status and function of the endothelium, and how to prevent and monitor disturbances in its function. The choice of test methods is also important, for the presnted study it was decided to use LDF PORH. Although this is a promising and non-invasive method, more research is required on the mechanisms involved in the reaction, evaluation of factors influencing the outcome of the parameters studied, and the clinical usefulness of LDF PORH. It seems that LDF PORH can be used in primary and secondary prevention in AH. In primary prevention, to detect changes in the micro-circulation before AH develops, and in secondary prevention to modification treatment in AH patients with diagnosed changes in microcirculation, which can prevent organ complications. In the authors' opinion, ACEI have a particularly significant effect on improving PORH. This is consistent with the observation by Guerrero-García et al., who consider that ACEI can improve vasodilation by inhibiting the conversion of angiotensin I to II,and increasing the level of NO, inhibiting kinase II, which is responsible for the degradation of bradykinin. Bradykinin influences vasodilation through NO, prostacyclin and EDH [27].

Conflict of interest

The authors have no conflicts of interest to disclose.

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