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Original article

Structural and functional state of various zones of skin microcirculation in men with isolated diastolic hypertension

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Abstract: The *objective* of our study was to assess the structural and functional characteristics of various skin microcirculation zones in men with newly diagnosed isolated diastolic hypertension (IDH).
Material and Methods — Our study sample included 275 men (aged 30 to 60 years) subjected to the comprehensive medical examination, which included blood tests, videocapillaroscopy (VCS) on the left ring finger, laser Doppler flowmetry (LDF) in the skin of the middle finger tip and forearm at rest, functional tests and photoplethysmography (PPG) on the left forefinger, determination of flow-mediated vasodilation of the brachial artery, echocardiography, ultrasound imaging of extracranial and femoral arteries, and also 24-hour ambulatory blood pressure monitoring (ABPM). According to the ABPM data, an isolated increase in diastolic blood pressure (BP) was noted in 83 subjects who formed the IDH group. The control group (CG) consisted of 90 men with normal BP.
Results — VCS and LDF revealed no significant differences between the groups at the scale of capillaries and precapillary arterioles. According to PPG, IDH subjects had significantly higher values of reflection index vs. the CG (35.6% vs. 30.4%, p=0.0013) and lower values of ejection duration (310.5 ms and 319.5 ms, p=0.0159), respectively.
Conclusion — The greatest contribution to peripheral vascular resistance in men with IDH most likely comes from large muscle arterioles, in which neurogenic regulation of vascular tone prevails.

Keywords: isolated diastolic hypertension, microcirculation, photoplethysmography, peripheral vascular resistance, smooth muscle cells.

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Introduction

Isolated diastolic hypertension (IDH) prevails among people of working age. According to the NHANES III study, IDH with diastolic blood pressure (DBP) exceeding 90 mm Hg occurs in 46.9% of untreated patients with hypertension (HTN) under 50 years of age [1]. The incidence of IDH has increased significantly after the American College of Cardiology and the American Heart Association had followed new clinical guidelines for the treatment of HTN in 2017 [2, 3], which lowered the threshold values for DBP to 80 mm Hg [4]. The peak of IDH prevalence occurs in the age range of 30-49 years and is more common in men [5]. Another feature of IDH is its asymptomatic state, which leads to fewer people knowing about the presence of the disease. According to the NHANES III study, 46.8% of patients with IDH, 58.4% of patients with isolated systolic HTN and 67.2% of patients with systolic-diastolic HTN are aware of the presence of this pathology. In another large study (China PEACE Million Persons Project), awareness of the IDH presence was characteristic for only 10.3% of patients [6].

The question of whether IDH is the initial form of HTN development or rather an independent phenotype of the pathology has not yet been resolved. The Framingham study showed that new-onset IDH develops predominantly in patients with normal blood pressure (BP), in whom the risk ratio for progression to systolic-diastolic HTN over 10 years is 23 compared with relatively healthy individuals [7]. The HARVEST study among young adults found that patients diagnosed with IDH were more likely to develop persistent HTN after seven years of follow-up compared with normotensive individuals [8]. The literature has identified associations with the development of myocardial infarction and cardiovascular disease (CVD) mortality when assessing the association of IDH with cardiovascular risk [9–11]. In another study, patients with untreated IDH had a high incidence of cerebral hemorrhage and overall CVD over a ten-year follow-up period, the mean age of the patients was 48 years, and 80% of the patients were men [3].

Currently, there is no specialized protocol for drug treatment of IDH that goes beyond the treatment of HTN in general. In young patients with IDH, it is undoubtedly important to control regular

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BP and eliminate modifiable risk factors due to the high risk of progression of IDH to any form of systolic HTN and its association with the risk of developing CVD. A number of studies have found a close relationship between IDH and overweight and obesity (especially central obesity) associated with other components of metabolic processes in young people [5, 6, 12]. However, in other studies, the prevalence of overweight or obesity in young patients with IDH was low [13, 14]. The issue of the hemodynamic phenotype of IDH, which is key for the personalized selection of antihypertensive therapy, has not yet been resolved.

One of the pathophysiological mechanisms for the development of HTN, along with an increase in blood viscosity, is an increase in cardiac output and/or total peripheral vascular resistance (TPVR) [15], most of which is formed at the level of microvasculature and depends on the tone and diameter of the lumen of microvessels [16], which is due to their structural and functional state [17]. Patients with isolated systolic HTN are thought to have increased arterial stiffness and/or high cardiac output, and patients with IDH generally have high TPVR [18], but these patterns are not observed in all patients [18, 19, 13].

The results of our previous comprehensive noninvasive study of various zones of skin microcirculation in working age men with newly diagnosed HTN demonstrated a higher pulse-wave velocity (PWV), vascular stiffness and smooth muscle cell (SMC) tone of terminal arteries and distributing arterioles vs. men with normal BP [20]. However, in this study, the analyzed group was represented by both systolic-diastolic HTN and IDH, which does not allow answering the question about the presence of changes in the functional state of these vascular links in men with IDH. Moreover, in the available scientific literature it was not possible to find publications on noninvasive studies of various zones of skin microcirculation in IDH.

Taking into account the above, the main goal of our study was to conduct a comprehensive simultaneous research of the structural and functional state of various zones of the skin microcirculation in men of working age with newly diagnosed IDH.

Material and Methods

The analyzed group was formed as part of a prospective study of the male population of a modern European metropolis, *Continuum of Cardiovascular Diseases*. The study was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee (No. 01-01/19 of February 12, 2019). All participants signed written consent to participate in the study.

The study included 275 male participants aged 30 to 60 years (mean age 43.8±7.9 years) who considered themselves healthy, had no health complaints, and did not take medications on a regular basis.

The day before the study, participants were instructed to avoid vigorous physical activity, alcohol consumption, and night shift work. Six and two hours before the onset of the study, energy drinks (tea, coffee, etc.) and smoking were excluded, respectively. Starting from 9 a.m., the following studies were carried out: 1) a complex of medical examination, anthropometry (body weight, height, waist circumference (WC), hip circumference (HC), calculation of body mass index (BMI) according to the Quetelet Index), anamnesis collection, three office BP measurements; 2) Videocapillaroscopy (VCS) on the ring finger of the left hand; 3) Laser Doppler flowmetry (LDF) on the left middle finger and forearm; 4) Photoplethysmography (PPG) on the index finger of the left hand; 5) collection of venous blood for laboratory research; 6) echocardiography; 7) Ultrasound imaging of the main arterial vessels (extracranial and femoral arteries); 8) 24-hour ambulatory blood pressure monitoring (ABPM). The above studies were carried out in a temperature-controlled laboratory (air temperature of 23±1 °C, humidity of 40-60%).

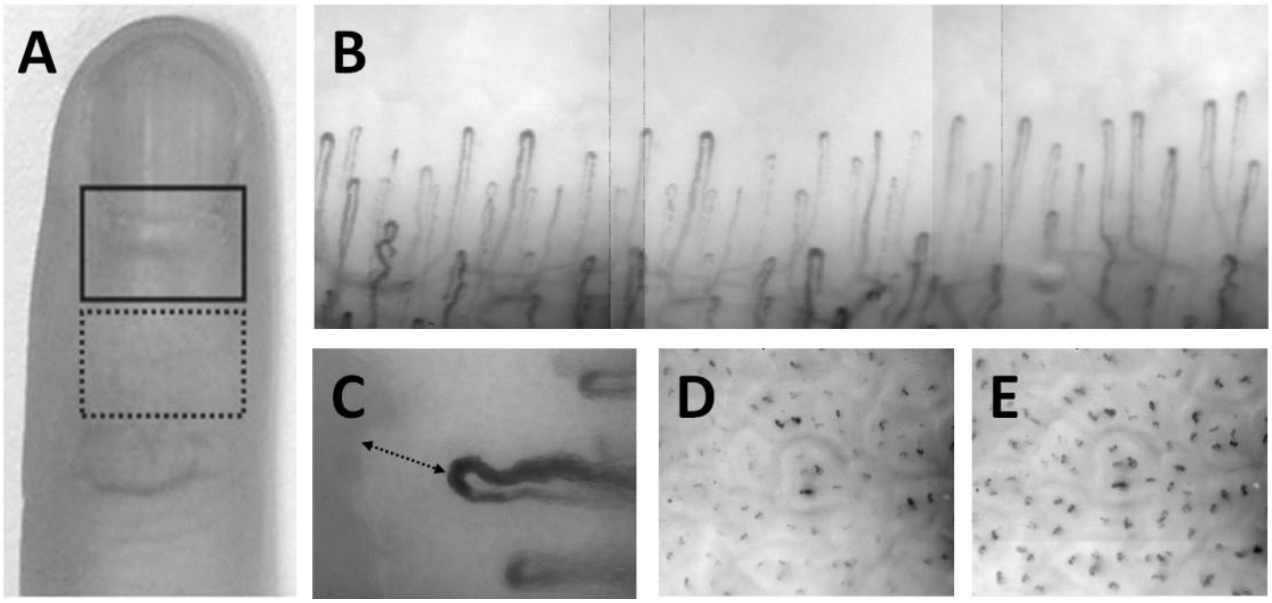

Figure 1. Videocapillaroscopy (VCS). A, zones of assessed capillary system. B, panoramic image of the nailfold capillary system (formed from three frames). C, measurement of pericapillary zone size. D, capillaries functioning at rest. E, maximum number of capillaries.

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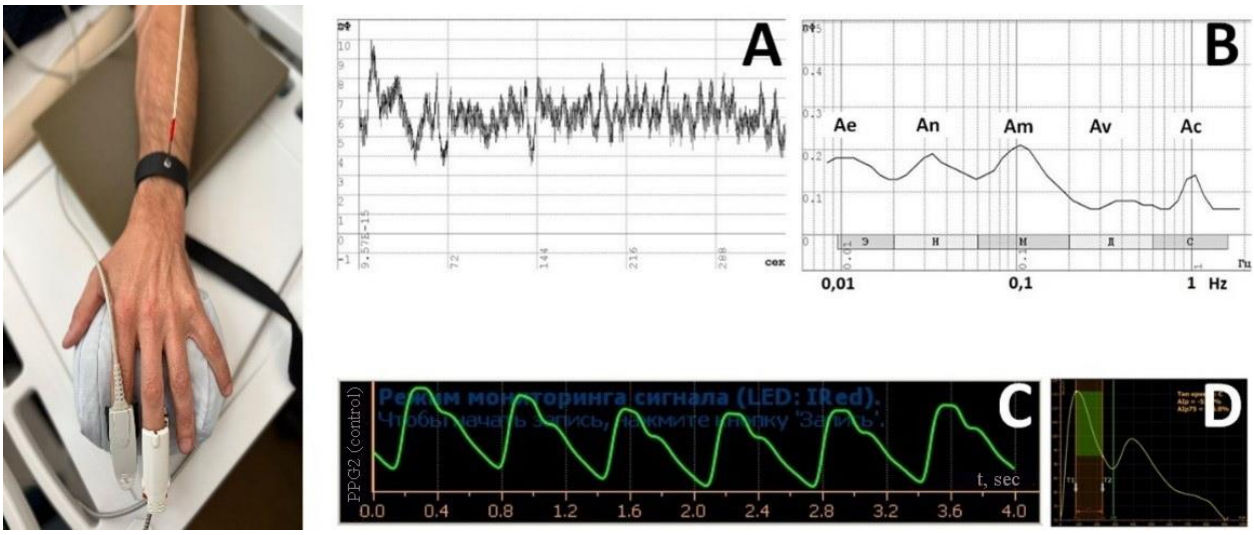

Figure 2. Laser Doppler flowmetry (LDF) on the middle finger and forearm and photoplethysmography (PPG) on the index finger. A, LDF-gram of basal perfusion. B, amplitude-frequency wavelet analysis of skin perfusion fluctuations in basal perfusion (logarithmic scale). C, photoplethysmography recording. D, pulse wave contour analysis.

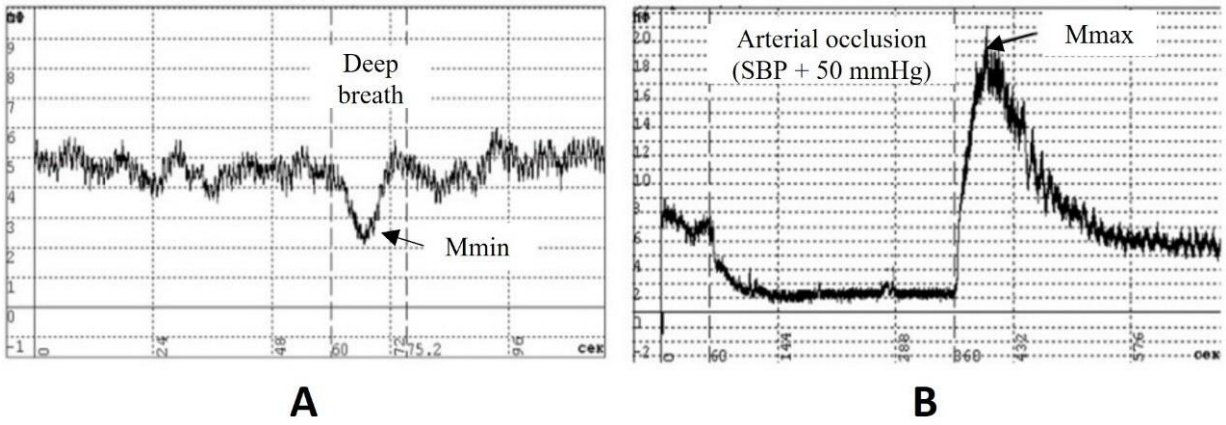

Figure 3. Functional tests in Laser Doppler flowmetry. A, holding breath test; B, flow-mediated dilation test with 5-minute arterial occlusion.

Table 1. Clinical characteristics of studied groups

Parameter	*Control group (n=90)*	*IDH group (n=83)*	*p*
Age (years)	43.5 [38; 49]	45 [39; 50]	0.6410
Height (cm)	179.5 [175; 183]	179 [175; 183]	0.9848
Body weight (kg)	81.9 [74.05; 92.88]	86 [77.65; 98.75]	0.2260
BMI (kg/m^2)	26.07 [23.04; 28.32]	26.46 [24.73; 29.57]	0.1974
WC (cm)	93 [87; 100]	97 [92; 104]	0.0184
HC (cm)	104 [99; 107.75]	104 [99; 110]	0.6954
Smoking, n (%)	19 (21.1)	21 (25.3)	0.1842
Office BP and HR			
SBP (mm Hg)	120 [110; 130]	120 [115; 130]	0.4449
DBP (mm Hg)	80 [70; 80]	80 [80; 90]	0.0045
HR (bpm)	63 [56; 68]	64 [59.25; 68]	0.7236

IDH, isolated diastolic hypertension; BMI (kg/m^2), body mass index; WC (cm), waist circumference; HC (cm), hip circumference; BP, blood pressure; SBP (mm Hg), systolic blood pressure; DBP (mm Hg), diastolic blood pressure; HR (bpm), heart rate.

Exclusion criteria were: stages 3-5 of chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2); liver disease (>3-fold increase in transaminase levels); signs of familial hypercholesterolemia (in particular, LDL-C >4.9 mmol/L, total cholesterol >8 mmol/L); left ventricular hypertrophy with myocardial mass index >115 g/m^2; heart valve diseases (stenosis, moderate and severe regurgitation); reduction in ejection fraction (EF) <50%; atherosclerotic lesions of extracranial or femoral arteries >25%.

Assessment of microcirculation

Videocapillaroscopy. Digital VCS is a noninvasive method for studying the structural and functional state of the capillary system in the skin based on high-speed digital video recording of papillary capillaries of the dermis [21]. We used a computer capillaroscope Capillaroskan-1 (New Energy Technologies LLC, Russia). When using the VCS method, participants were in a sitting position. The participant's nail bed area and the dorsal surface of the nail phalanx of the left ring finger were used (*Figure* 1A). Three sections of the nail bed were sequentially recorded for further panoramic imaging (*Figure* 1B). The values of the following parameters were identified: PZ (the size of the pericapillary zone as shown in *Figure* 1C), FCD (the functional density of capillaries as seen in *Figure* 1D), SCD (the structural density of capillaries as presented in *Figure* 1E), and the FCD/SCD ratio (calculated according to a previously described method [22]).

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Table 2. Results of echocardiography and ultrasound imaging of major arteries in studied groups

Parameter	*Control group (n=90)*	*IDH group (n=83)*	*p*
Echocardiography			
LA (cm)	3.5 [3.3; 3.7]	3.6 [3.4; 3.88]	0.1376
LA volume (mL)	49.5 [43.25; 57]	53 [45.25; 60]	0.3928
LAVI (mL/m^2)	24.45 [22; 28]	26.45 [23; 29]	0.4881
LVIDd (cm)	5 [4.8; 5.2]	5 [4.71; 5.2]	0.9762
LVIDs (cm)	2.7 [2.5; 2.9]	2.7 [2.5; 3.1]	0.5759
LVEDV (mL)	108 [98; 121]	113 [99.75; 127]	0.3675
LVESV (mL)	37 [33; 42]	39.5 [35.75; 44.25]	0.5904
SV (mL)	73 [59; 81]	76 [65; 83.25]	0.3834
CO (L/min)	4.5 [4.1; 5.06]	4.84 [4.46; 5.62]	0.2028
LVEF (%)	64 [63; 66]	64.5 [63.25; 66]	0.7919
IVSd (cm)	1 [0.9; 1.1]	1 [1; 1.1]	0.2191
LVPWd (cm)	0.9 [0.9; 1]	0.9 [0.9; 1]	0.1903
LVM (g)	156 [131.5; 178.75]	170 [153; 193]	0.0127
LVMI (g/m^2)	78 [67; 86.75]	84 [73.25; 92]	0.0185
RA volume (mL)	44 [38; 54]	48 [39; 53]	0.5343
RAVI (mL/m^2)	22 [19; 27.1]	23.1 [20; 26]	0.8787
RVOT (cm)	2.7 [2.6; 3]	2.9 [2.7; 3]	0.1238
sPAP (mm Hg)	23 [20; 25]	23 [20; 25]	0.9731
E/A	1.4 [1.2; 1.5]	1.2 [0.9; 1.4]	0.0292
e`(cm/sec)	11 [10; 13]	10 [8; 11]	0.0093
Ultrasound imaging of major arteries			
IMT CCA (mm)	0.6 [0.5; 0.7]	0.6 [0.5; 0.65]	0.9046
IMT CFA (mm)	0.6 [0.5; 0.75]	0.65 [0.5; 0.7]	0.9763
FMD (%)	8.8 [5.82; 11.08]	8.1 [5; 12]	0.1005

IDH, isolated diastolic hypertension; LA (cm), left atrial anterior-posterior linear measurement; LAVI (mL/m^2), left atrial volume index; LVIDd (cm), left ventricular internal diameter at end-diastole; LVIDs (cm), left ventricular internal diameter at end-systole; LVEDV (mL), left ventricular end-diastole volume (biplane); LVESV (mL), left ventricular end-systole volume (biplane); SV (mL), stroke volume; CO (L/min), cardiac output; LVEF (%), left ventricular ejection fraction (biplane); IVSd (cm), interventricular septal thickness at end-diastole; LVPWd (cm), left ventricular posterior wall thickness at end-diastole; LVM (g), left ventricular mass; LVMI (g/m^2), left ventricular mass index; RA volume (mL), right atrial volume; RAVI (mL/m^2), right atrial volume index; RVOT (cm), right ventricular outflow tract proximal diameter; sPAP (mm Hg), systolic pulmonary artery pressure; E/A, early to late diastolic transmitral flow velocity; e´, diastolic peak velocity of mitral valve annulus; IMT (mm), intima-media thickness; CCA, common carotid artery; CFA, common femoral artery; FMD (%), flow-mediated vasodilation.

Table 3. ABPM results

Parameter		*Control group (n=90)*	*IDH group (n=83)*	*p*
Day	SBP (mm Hg)	118.5 [114; 124]	126 [123; 130]	0.0003
	DBP (mm Hg)	77 [74; 79.75]	85 [82; 88]	<0.0001
	HR (bpm)	75 [69.25; 81]	76 [70; 83.5]	0.4277
Night	SBP (mm Hg)	102.5 [98; 107]	108 [105; 113]	<0.0001
	DBP (mm Hg)	65 [61; 67]	71 [68; 74]	<0.0001
	HR (bpm)	60 [56; 67]	63 [57; 68]	0.5149
24 hours	SBP (mm Hg)	114.5 [111; 119]	122 [119; 125]	0.0002
	DBP (mm Hg)	74 [72; 76]	81 [80; 84]	<0.0001
	HR (bpm)	71.5 [67; 78]	73 [67.5; 79]	0.4214
Morning BP increase (mm Hg)		20 [14; 28]	17 [10; 23]	0.354
Nocturnal SBP decrease (%)		13.5 [9; 17]	12 [10; 16]	0.9213
Nocturnal DBP decrease (%)		16 [13; 20.25]	17 [10.5; 19.5]	0.9102

IDH, isolated diastolic hypertension; ABPM, 24-hour ambulatory blood pressure monitoring; SBP (mm Hg), systolic blood pressure; DBP (mm Hg), diastolic blood pressure; HR (bpm), heart rate.

Laser Doppler flowmetry. Using LDF, skin microcirculation was assessed in the supine position with the head end of the couch raised by 30°, after a 15-minute adaptation. Laser analyzer LAKK-02 (Scientific Production Enterprise LAZMA, Russia) was employed in the near-infrared region (800 nm). The sensor was located in the area of the nail phalanx of the middle finger of the left hand and the dorsal surface of the skin of the left forearm (*Figure* 2).

Basal tissue perfusion (BTP) was recorded at rest for 10 minutes. The original LDF-gram (*Figure* 2A) was subjected to amplitude-frequency analysis using the wavelet transform (*Figure* 2B). The BTP analysis included the level of perfusion (M), tissue blood flow variability (σ) and time-averaged amplitude of vasomotor regulatory mechanisms based on maximum values (Ai) in the following frequency ranges: endothelial (Ae) – 0.0095-0.0200 Hz, neurogenic (An) – 0.021-0.052 Hz, myogenic (Am) – 0.052-0.145 Hz, venular (Av) – 0.145-0.600 Hz, and cardiac (Ac) – 0.6-2.0 Hz [23, 24]. The values of M, σ and Ai are presented in arbitrary blood perfusion units (BPU). In addition to the absolute values of vasomotor amplitudes, the functional contribution of each regulatory mechanism to total tissue perfusion was assessed using the formula: Ai/M×100%, where Ai is the vasomotor amplitude of the regulatory mechanism, M is the mean level of tissue perfusion. This parameter (Ai/M) allows indirectly assessing the perfusion (metabolic) efficiency of each regulatory mechanism at the level of precapillary arterioles [25]. We also assessed the vasomotor efficiency of each regulatory mechanism using the formula: Ai/3σ×100%, where Ai is the amplitude of the vasomotor activity of the regulatory mechanism, σ is the variability of tissue blood flow. This parameter (Ai/3σ) allows assessing the functional contribution of each regulatory mechanism to the modulation of microvascular blood flow [26].

After recording the BTP, a holding breath test (BT) was performed, during which the subjects took a forced deep breath through the mouth, held their breath at the height of inspiration for 15 seconds, and then voluntarily exhaled. The minimum level of perfusion (Mmin) and the time of its development (T) were determined. The degree of vasoconstriction (reduced perfusion) (↓ΔM) was assessed using the following formula: ↓ΔM=(M–Mmin)/M×100%, where M is the level of tissue perfusion in BTP and Mmin is the minimum level of perfusion in BT (*Figure* 3A).

After BT, a flow-mediated dilation test with 5-minute arterial occlusion (AO) was performed. The BP tonometer cuff located on the left shoulder was pressurized for 5 minutes at 50 mm Hg above the baseline systolic blood pressure (SBP). After cuff decompression, post-occlusion reactive hyperemia (Mmax) and the time of its development (T) were determined. The maximum increase in perfusion (↑ΔM) was assessed using the formula: ↑ΔM=Mmax/M×100%, where M is the level of tissue perfusion during BTP and Mmax is the level of post-occlusion reactive hyperemia (*Figure* 3B).

Photoplethysmography. PPG was performed simultaneously with LDF. The radiation sources that we used were the Angioscan-01 computer appliance (Angioscan, Russia) with two near-infrared wavelengths (680 nm and 870 nm), allowing photons to pass through the entire thickness of the nail phalanx and capture larger arterioles. The optical sensor was installed on the nail phalanx of the index finger of the left hand (*Figure* 2). Pulse wave contour analysis (*Figure* 2D) assessed the following parameters over time span of 10 minutes: 1) pulse rate (PR, bpm); 2) augmentation index in % normalized for a heart rate (HR) of 75 beats per minute

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(AIx75, bpm); 3) blood oxygen saturation (SpO_2, %); 4) stiffness index (SI, m/s) reflecting the mean pulse-wave velocity (m/s) through large elastic vessels; 5) reflection index (RI, %) assessing the contribution (%) of the reflected component to the pulse wave and characterizing the tone of small muscular arteries and arterioles; 6) ejection duration (ED, ms).

Complete blood count and biochemical tests. Complete blood count was performed on MEK-8222 K automated hematology analyzer (Nihon Kohden, Japan). Levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), C-reactive protein (CRP) and glucose were determined in serum using Architect c8000 clinical chemistry analyzer (Abbott, USA). Fibrinogen levels were assed using ACL Elite coagulation analyzer (Instrumentation Laboratory, USA); low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation; very low-density lipoprotein cholesterol (VLDL-C) was calculated using the formula: VLDL-C=TG/2.18.

Echocardiography and ultrasound imaging of major blood vessels. Echocardiography in M- and B-mode and ultrasound imaging of the main arteries (including determination of flow-mediated vasodilation (FMD) of the brachial artery via the Celermajer method) was performed using a Philips iE33 XMATRIX ultrasound system (Netherlands).

Table 4. Results of laboratory tests

Parameter	*Control group (n=90)*	*IDH group (n=83)*	*p*
RBC (10^{12}/L)	4.99 [4.76; 5.22]	4.99 [4.76; 5.20]	0.9390
Hemoglobin (g/L)	150 [144.25; 157]	155 [148; 161]	0.0831
Hematocrit (%)	43.55 [42.3; 45.48]	44.7 [43.1; 46.2]	0.0850
MCV (µm)	87.85 [85.82; 90.18]	90.3 [87.8; 92.1]	0.0046
MCH (pg)	30.3 [29.6; 31]	31 [30.1; 32.15]	0.0014
WBC (10^9/L)	6.25 [5.3; 7.2]	6.1 [5.4; 6.7]	0.6699
Platelet count (10^9/L)	216 [188; 247]	216 [189.5; 238.5]	0.8951
Total cholesterol (mmol/L)	5.3 [4.8; 6.1]	5.4 [4.85; 6.05]	0.9999
HDL-C (mmol/L)	1.32 [1.12; 1.64]	1.29 [1.12; 1.47]	0.3576
LDL-C (mmol/L)	3.47 [2.91; 4.10]	3.41 [2.94; 4.12]	0.9946
VLDL-C (mmol/L)	0.47 [0.35; 0.68]	0.56 [0.39; 0.86]	0.1448
TG (mmol/L)	1.03 [0.77; 1.48]	1.21 [0.83; 1.86]	0.1803
Total protein (g/L)	73 [71; 76]	73 [69; 77]	0.7126
Albumin (g/L)	46 [45; 48]	46 [44; 47]	0.4760
Uric acid (mg/dL)	5.8 [5.03; 6.57]	6.2 [5.7; 7.05]	0.0147
Creatinine (µmol/L)	83 [74; 91]	82 [75.5; 91]	0.9876
Glucose (mmol/L)	5.7 [5.4; 6]	5.7 [5.25; 6.22]	0.6743
ALT (IU/L)	21.5 [16; 32]	26 [20; 32.5]	0.1326
AST (IU/L)	20 [17; 23]	21 [18; 25]	0.3903
CRP (mg/L)	0.9 [0.47; 1.65]	1.13 [0.57; 2.4]	0.23
Fibrinogen (g/L)	3.4 [3; 3.7]	3.4 [3.1; 3.8]	0.9309

IDH, isolated diastolic hypertension; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; WBC, white blood cells; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; TG, triglycerides; ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein.

Table 5. VCS data

Parameter	*Control group (n=90)*	*IDH group (n=83)*	*p*
PZ (µm)	115.5 [97.3; 133]	115 [101; 126]	0.7414
FCD (n/mm^2)	81 [73.25; 94.5]	82 [71; 98]	0.9998
SCD (n/mm^2)	105 [93.25; 121.75]	112 [97; 128]	0.4270
FCD/SCD	0.77 [0.68; 0.84]	0.73 [0.68; 0.81]	0.5906

IDH, isolated diastolic hypertension; PZ, the size of the pericapillary zone; VCS, videocapillaroscopy; pericapillary zone (µm); FCD, functional capillary density; SCD, structural capillary density.

ABPM. ABPM was performed using the BpLab system (Pyotr Telegin LLC, Russia) after all stages of the examination (beginning of observation from 12 a.m. to 1 p.m.). The BP cuff was placed on the left shoulder. The interval for measuring BP was 20 minutes during active daytime and 40 minutes at night.

Statistics. Statistical processing of collected data was performed using the STATISTICA 10.0 software (StatSoft Inc., USA). The Shapiro-Wilk test was used to assess the type of distribution. The obtained data were presented as medians and interquartile ranges (Me [Q25; Q75]). The Mann-Whitney test was employed to determine differences between groups. Differences were considered significant at $p<0.05$. The nonparametric Spearman method was used to assess correlations between various parameters. Correlations were considered statistically significant at $p<0.05$.

Results

According to ABPM data, 175 men (67.3%) were newly diagnosed with HTN in accordance with the ESC Guidelines for the Management of Arterial Hypertension [27]. At the same time, an isolated increase in DBP was noted in 83 study subjects included in the IDH group. The control group (CG) comprised 90 men with normal BP levels.

The main clinical characteristics of the analyzed groups are presented in *Table* 1. Our data show that with comparable height and BMI, men with IDH had a significantly higher WC.

The results of ultrasound imaging of the heart and main arteries are presented in *Table* 2. According to ultrasound imaging of the main arteries, no significant differences between the groups were revealed either in structure or in FMD. The presence of atherosclerotic lesions in the brachiocephalic arteries with a maximum stenosis of up to 25% was detected in 7 men in the CG vs. 6 men in the IDH group, respectively ($p>0.05$). All echocardiographic parameters in both groups were within the reference values. However, men with IDH had higher left ventricular (LV) mass, LV mass index (LVMI) and lower LV diastolic function relative to those in the CG.

ABPM data are presented in *Table* 3. Our data demonstrated that in patients with IDH, DBP levels were slightly higher than normal values, regardless of the time of day.

The results of laboratory tests are presented in *Table* 4. All analyzed indicators were within the reference values, with the exception of a slight increase in TC and LDL-C in both groups but without significant differences between the groups. At the same time, men with IDH had significantly higher values of MCV, MCH and UA relative to CG.

The results of assessing the capillary blood circulation of the skin in the ring finger zone are presented in *Table* 5. Collected data demonstrate the absence of significant differences between the groups for all analyzed indicators.

The results of LDF on the middle finger (*Table* 6) did not reveal significant differences between the groups in the functional characteristics of skin microcirculation for all analyzed indicators. The results of functional tests also revealed no significant differences between the groups in vasoconstriction and dilator reserve of precapillary arterioles in the skin of the finger.

The results of LDF on the forearm (*Table* 7) also did not establish significant differences between the groups in the functional characteristics of skin microcirculation for all analyzed

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indicators. The results of functional tests also detected no significant differences between the groups in vasoconstriction and dilator reserve of precapillary arterioles of the skin of the forearm.

The PPG results are presented in *Table 8*. The obtained data revealed significantly higher values of SMC tone (RI) of small muscular arteries and distributing arterioles, as well as shorter ED with comparable PR in men with IDH vs. the CG.

Table 6. Laser Doppler flowmetry of the finger

Parameters		*Control group (n=90)*	*IDH group (n=83)*	*p*
M (PU)		18.56 [15.83; 19.88]	19.51 [15.5; 20.96]	0.3798
σ (PU)		1.97 [1.34; 2.51]	1.81 [1.34; 2.48]	0.8945
Endothelial	Ae (PU)	0.96 [0.52; 1.25]	0.84 [0.49; 1.3]	0.9760
	Ae/M (%)	5.12 [3.05; 7.37]	4.68 [2.67; 7.86]	0.9241
	Ae/3σ (%)	15.1 [11.87; 18.09]	15.54 [12.2; 18.92]	0.9189
Neurogenic	An (PU)	0.88 [0.56; 1.23]	0.86 [0.56; 1.17]	0.9932
	An/M (%)	4.84 [3.06; 7.31]	5.05 [3.06; 7.46]	0.9952
	An/3σ (%)	14.61 [12.25; 17.19]	15.94 [12.07; 19.07]	0.3807
Myogenic	Am (PU)	0.57 [0.39; 0.84]	0.58 [0.42; 0.74]	0.9390
	Am/M (%)	3.51 [2.24; 4.6]	3.1 [2.04; 4.63]	0.8083
	Am/3σ (%)	10.49 [7.88; 12.6]	10.9 [8.49; 13.51]	0.8309
Venular	Ab (PU)	0.2 [0.16; 0.28]	0.19 [0.16; 0.26]	0.7549
	Ab/M (%)	1.22 [0.93; 1.67]	1.16 [0.87; 1.53]	0.6266
	Ab/3σ (%)	3.74 [2.95; 5.26]	3.5 [2.74; 5.19]	0.8465
Cardiac	Ac (PU)	0.87 [0.65; 1.08]	0.8 [0.57; 1.16]	0.8680
	Ac/M (%)	4.89 [3.56; 7.29]	4.35 [3.07; 7.2]	0.6982
	Ac/3σ (%)	16.02 [11.04; 21.33]	15.57 [11.87; 21.7]	0.9930
Functional tests				
BTP	Mmin. (PU)	8.8 [7.29; 11.36]	9.22 [6.98; 12.68]	0.9252
	T (sec)	8 [7; 9]	8 [7; 9]	0.9574
	↓ΔM (%)	47 [36; 56]	45.5 [34.25; 59]	0.9835
AO	Mmax. (PU)	21.26 [18.23; 22.99]	21.27 [18.98; 23.28]	0.7949
	T (sec)	26 [21; 42]	27.5 [21; 52.75]	0.8797
	↑ΔM (%)	115 [109; 130]	113 [107.5; 127]	0.5919

IDH, isolated diastolic hypertension; BPU, blood perfusion units; BTP, basal tissue perfusion; AO, arterial occlusion.

Table 7. Laser Doppler flowmetry of the forearm

Parameters		*Control group (n=90)*	*IDH group (n=83)*	*p*
M (PU)		3.34 [2.71; 4.11]	3.5 [3; 4.35]	0.2978
σ (PU)		0.41 [0.31; 0.55]	0.42 [0.31; 0.53]	0.9427
Endothelial	Ae (PU)	0.13 [0.1; 0.21]	0.17 [0.11; 0.22]	0.6179
	Ae/M (%)	3.68 [2.73; 7.04]	4.52 [2.56; 6.05]	0.9696
	Ae/3σ (%)	11.36 [8.57; 14.29]	12.4 [8.93; 15.33]	0.4812
Neurogenic	An (PU)	0.15 [0.11; 0.24]	0.16 [0.12; 0.23]	0.9691
	An/M (%)	4.63 [3.08; 7.31]	4.52 [2.81; 6.41]	0.5629
	An/3σ (%)	12.9 [10; 16]	12.78 [9.8; 16.67]	0.9966
Myogenic	Am (PU)	0.13 [0.1; 0.18]	0.13 [0.1; 0.18]	0.9996
	Am/M (%)	3.92 [2.68; 6.44]	3.68 [2.36; 4.78]	0.5417
	Am/3σ (%)	10.57 [8.33; 13.33]	10.26 [8.33; 13.54]	0.9999
Venular	Ab (PU)	0.07 [0.05; 0.09]	0.07 [0.05; 0.11]	0.9714
	Ab/M (%)	2.1 [1.62; 3.02]	1.83 [1.43; 3.18]	0.3852
	Ab/3σ (%)	5.95 [4.07; 8.57]	5.38 [4.44; 8.81]	0.9499
Cardiac	Ac (PU)	0.26 [0.18; 0.33]	0.23 [0.17; 0.34]	0.6533
	Ac/M (%)	7.78 [5.81; 12.12]	6.25 [4.36; 10]	0.1680
	Ac/3σ (%)	21.37 [15.87; 25.56]	20.69 [14.67; 25.83]	0.7450
Functional tests				
BTP	Mmin. (PU)	2.2 [1.59; 2.8]	2.02 [1.57; 2.72]	0.9833
	T (sec)	8 [6; 9]	8 [7; 9]	0.7616
	↓ΔM (%)	38 [21.5; 50]	40 [27; 52]	0.7199
AO	Mmax. (PU)	9.08 [7.76; 10.6]	8.86 [7.63; 10.5]	0.9396
	T (sec)	15 [11; 20]	14 [12; 19]	0.9630
	↑ΔM (%)	262 [221; 330]	251 [213; 284]	0.1221

IDH, isolated diastolic hypertension; BPU, blood perfusion units; BTP, basal tissue perfusion; AO, arterial occlusion.

Table 8. PPG data

Parameter	*Control group (n=90)*	*IDH group (n=83)*	*p*
PR (bpm)	62 [56; 69]	64 [58; 69.75]	0.6916
AIx75 (%)	-4.1 [-13.8; 5.2]	1.75 [-8.38; 8.88]	0.0733
SpO_2 (%)	95.8 [94.5; 96.7]	95.3 [93.9; 96.4]	0.3166
SI (m/sec)	7.4 [7.1; 7.8]	7.6 [7.02; 8]	0.5211
RI (%)	30.4 [26; 37.1]	35.6 [29.82; 45.8]	0.0013
ED (ms)	319.5 [310; 332.25]	310.5 [299; 320]	0.0159

PPG, photoplethysmography; PR, pulse rate; AIx75, estimated value of augmentation index in % normalized for a heart rate of 75 bpm; SpO_2, blood oxygen saturation; RI (%), reflection index; SI (m/s), stiffness index; ED (ms), ejection duration.

Discussion

For the first time, a comprehensive simultaneous study of various zones of the skin microcirculation in men of working age with newly diagnosed IDH was carried out using three noninvasive procedures complementing each other (VCS, LDF and PPG). Interest in studying the state of microcirculation in this category of patients is due to the fact that the pathogenetic mechanism for the development of IDH could be represented by an increase in TPVR [15], which is formed at the level of resisting microvessels and depends mainly on the tone and diameter of the lumen of microvessels [28-30].

The study of capillary blood circulation was carried out using VCS. The results summarized in *Table 5* revealed no differences in the structural and functional state of the capillary bed of the skin between the groups, which implies no decrease in the density of the capillary network, exchange surface area and no hidden fluid retention in the interstitial space of the skin in men with IDH. In a previous study, we obtained similar results: in men of working age, at the onset of HTN, no changes in the capillary bed of the skin occurred [20]. Comparing current data with the results of previous studies, we assumed that as BP further increases and pathology progresses, rarefaction of the capillary bed may develop in patients with systolic-diastolic HTN [31-33]. Further prospective studies are needed to confirm this hypothesis.

The functional state of the pre- and postcapillary zones of the microcirculation was studied by the LDF method using amplitude-frequency wavelet analysis of microvascular blood flow oscillations in two zones: in the skin of the fingertip, where, due to the abundance of superficially located arteriovenous anastomoses, the microvascular blood flow is predominantly shunting, and in the skin of the forearm, where arteriovenous anastomoses are located deeper than the probing zone with LDF, which determines the predominantly nutritional nature of the recorded microvascular blood flow. The results of LDF demonstrated the absence of changes in the level and variability of tissue blood flow, the tone of precapillary arterioles and postcapillary venules, the efficiency of perfusion and vasomotor activity of the main mechanisms of modulation of microvascular blood flow in men with IDH in the studied zones of skin. Functional tests were employed to assess the adaptive capabilities of microvessels. The vasoconstriction activity of precapillary arterioles was studied during BT, when activation of the sympathetic nervous system at the level of neuromuscular synapses causes short-term constriction of arterioles and a decrease in tissue perfusion [34]. The dilator reserve of microvessels was studied during a test with a 5-minute AO, in which an increase in tissue blood flow is aimed at restoring tissue homeostasis after a short-term episode of ischemia. The results of functional tests demonstrated the absence of an

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increase in vasoconstrictor activity and a decrease in the dilator reserve of microvessels in the studied zones of the skin in men with IDH.

Therefore, the LDF results indicate the absence of changes in the functional state and adaptive capabilities of the pre- and postcapillary segments of the microcirculation in the skin of the fingertips and forearm in men with IDH.

The lack of differences in the functional state of the precapillary circulation may be due to several causes. The first one is related to the LDF method; it has a number of limitations [35]. The second cause is probably due to the fact that the object of the study was precapillary arterioles, in which humoral regulation of vascular tone prevails, and in men with IDH. Regulatory mechanisms ensure adequate blood delivery to the capillary system to maintain the required level of transcapillary fluid exchange (compensation).

Of particular interest in this context are the results of laboratory blood tests (*Table* 3), which demonstrated higher MCV and MCH values in men with IDH vs. men with normotensive BP. These changes can be identified as a compensatory reaction of the body aimed at increasing the oxygen transport function of red blood cells in order to maintain tissue homeostasis against the background of the development of disturbances in the mechanisms of gas exchange at the level of the microvascular endothelium in the absence of changes in the structural and functional state of capillary, pre- and postcapillary blood circulation in men with IDH. The levels of hemoglobin and hematocrit against this background tend to increase, but do not exhibit statistically significant differences.

Another interesting observation is the higher level of UA in the IDH group compared to the GC, since some data from epidemiological and clinical studies demonstrated an association of increased UA levels with the development of HTN [36, 37]. The results of an experimental study showed the ability of UA to enhance oxidative stress and the expression of angiotensin II in vascular endothelial cells, which contributes to the development of endothelial dysfunction, vasoconstriction, proliferation of SMC [38], and leads to the formation of HTN. During the study, in men with IDH, no significant correlation of UA with the level of DBP and microcirculatory parameters was revealed. This may be due to a slight increase in UA and the absence of a significant contribution to the increase in DBP and increased tone of the SMC in the terminal muscular arteries and distributing arterioles in this category of patients.

In addition to the oxygen transport function of the blood and an increase in UA levels, metabolic disorders in patients with IDH are also evidenced by a statistically significant increase in WC (*Table* 1), which implies the predominance of central obesity in this group of patients and is fully consistent with data previously obtained by other researchers [5, 6, 12].

Using the transmission PPG method, we studied the functional state of large distributing arterioles located deeper relative to the skin surface (up to 150 μm), in which the neurogenic mechanism of regulation of vascular tone dominates. PPG results demonstrated higher tone of terminal muscular arteries and distributing arterioles (RI) in men with IDH (*Table* 8). This may be a consequence of functional changes in the SMC with increased activity of the sympathetic adrenergic nervous system, of increased sensitivity to circulating tissue and systemic vasoconstrictor agents (angiotensin II, norepinephrine, etc.), and of the eutrophic remodeling of the SMC in these microvessels. All of these are the most vulnerable specific changes in microvessels in patients with HTN [39]. An increase in the SMC tone of the terminal muscular arteries and distributing arterioles may be one of the main mechanisms of increased TPVR in the proximal microcirculation, leading to the development of IDH. This can be confirmed by the identified correlations between RI and 24-hour ($r=0.25$; $p<0.05$) and daytime ($r=0.27$; $p<0.05$) DBP levels. However, further research is needed to clarify the cause-and-effect relationship between an increase in DBP and an increase in the tone of the SMC in the terminal muscular arteries and distributing arterioles.

PPG results also demonstrated shorter systole duration (ED) in men with IDH vs. the CG at comparable HR values, which could be explained by different reasons. An increase in the SMC tone of the terminal muscular arteries and distributing arterioles leads to an increase in TPVR and DBP. As a result, the reflected pulse wave reaches the aortic valve leaflets faster, which leads to earlier closure and a reduction in the duration of systole. This can be confirmed by the identified correlations between ED and values of 24-hour ($r=-0.28$; $p<0.05$) and daytime DBP ($r=-0.27$; $p<0.05$). Due to earlier closure of the aortic valve, left ventricular end-diastole pressure increases, which is reflected in the observed decrease in LV diastolic function (E/A, e`) with a simultaneous increase in left ventricular mass in men with IDH.

Conclusion

Our comprehensive noninvasive cross-sectional study of the cardiovascular system in men of working age with IDH allowed us to draw the following conclusions:

1. Capillary rarefaction, a decrease in the exchange surface area, as well as signs of latent fluid retention in the interstitial space of the skin were not observed;

2. No changes in tone, increased vasoconstriction, decreased dilator reserve of precapillary arterioles, or decreased skin perfusion were detected;

3. An increase in TPVR in IDH may be associated with an increase in the tone of small muscular arteries and distributing arterioles, in which neurogenic (sympathetic) regulation of tone dominates.

Study limitations

We did not evaluate circulating vasoactive substances, the concentration and sensitivity of microcirculatory elements to which may be altered in men in the early stages of HTN. This requires further study.

Conflict of interest

The authors declare that they have no conflicts of interest.

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