Relationship between left ventricular hypertrophy and remodeling of capillary network in hypertensive patients

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Abstract

Objective. To study relationship between left ventricular hypertrophy and peripheral capillary network remodeling in hypertensive patients with metabolic syndrome and without it. **Design and methods.** The study included 33 hypertensive patients (51,4 ± 11,0) with and without metabolic syndrome (n = 12 and n = 21, respectively). The control group included healthy volunteers without cardiovascular pathology (n = 41). Besides routine clinical and laboratory examination all participants underwent vital nail-fold capillaroscopy to define density of capillary network and an assessment of remodeling coefficient (calculated as the ratio of the mean diameters of venous to arterial portions of capillaries). The left ventricular mass and index mass were estimated by echocardiographic technique. **Results.** The study indicated change of capillary network: rarefaction and significant remodeling in hypertensive patients in comparison with healthy volunteers. Increased left ventricular index mass was predominant in hypertensive patients with metabolic syndrome (75 %) whereas it was found only in 27,3 % hypertensive patients without metabolic syndrome. **Conclusion.** There was a correlation between blood pressure level and capillary network remodeling and between blood pressure level and left ventricular hypertrophy. Left ventricular hypertrophy was more frequent in hypertensive subjects with metabolic syndrome, whereas capillary network remodeling was not associated with presence of metabolic syndrome.

Key words: capillary network remodeling, myocardial hypertrophy, hypertension, vital capillaroscopy, metabolic syndrome.

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Взаимосвязь между гипертрофией миокарда левого желудочка и ремоделированием микроциркуляторного русла у пациентов с артериальной гипертензией

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Резюме

Цель исследования. Определить взаимосвязь между гипертрофией миокарда левого желудочка и ремоделированием микроциркуляторного русла у больных артериальной гипертензией (АГ), в том числе у пациентов с сочетанием АГ и метаболического синдрома. **Материалы и методы.** В исследование включено 33 пациента (51,4 ± 11 лет) с АГ 1–2 степени, с метаболическим синдромом (n = 12) и без него (n = 21). Контрольную группу составили здоровые добровольцы без признаков сердечно-сосудистой патологии (n = 41). Испытуемым проводилось исследование параметров микроциркуляции ногтевого ложа руки с помощью цифрового капилляроскопа. Изучалась плотность капиллярного русла, рассчитывался коэффициент ремоделирования микрососудистого русла (Кво/ао) как отношение средних диаметров венозных отделов капилляров к артериальным отделам. Оценивалась степень гипертрофии левого желудочка. **Результаты.** У пациентов с АГ выявлено снижение плотности капиллярной сети и повышение коэффициента ремоделирования капиллярного русла по сравнению со здоровыми добровольцами. Гипертрофия левого желудочка более выражена у пациентов с сочетанием АГ и метаболического синдрома (в 75 %), тогда как у пациентов с АГ без метаболического синдрома гипертрофия левого желудочка выявлена лишь в 27,3 % случаев. Частота выявления ремоделирования капиллярного русла у пациентов с АГ не зависит от наличия или отсутствия метаболического синдрома. **Выводы.** Обнаружены тесные взаимосвязи между уровнем артериального давления и признаками ремоделирования капиллярного русла, а также между уровнем артериального давления и гипертрофией миокарда левого желудочка. Частота выявления гипертрофии миокарда левого желудочка оказалась существенно выше при сочетании АГ с метаболическим синдромом, тогда как признаки ремоделирования капиллярного русла не зависели от наличия или отсутствия метаболического синдрома.

Ключевые слова: цифровая капилляроскопия, ремоделирование капиллярного русла, гипертрофия миокарда левого желудочка, артериальная гипертензия, метаболический синдром.

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Introduction

Arterial hypertension (HTN) is a cardiovascular disease involving different organs and tissues. The first Russian echocardiographic study of left ventricular hypertrophy (LVH) in various HTN forms was published by Yurenev et al. in 1985. Nowadays echocardiography has become a "gold standard" examination in HTN, since it allows to measure myocardial mass and determine left ventricle geometry. According to the Framingham study and a meta-analysis, LVH verified by ultrasound is associated with an increased risk of cardiovascular complications.

However, LVH in hypertensive patients results from the increased peripheral vascular resistance. Moreover, a large number of neurohumoral and hormonal factors including renin-angiotensin-aldosterone system are involved in structural and functional microvascular and extracellular matrix remodeling in HTN. Thus, smooth muscle cells of arterioles progressively proliferate, collagen and fibronectin accumulates in vascular wall leading to the increased wall thickness/lumen ratio of the arterioles and to the reduced density of microvessel network.

A strong influence of HTN on the microvascular network structure and function is well-known and described in a number of scientific reviews. Vasoconstriction, microvascular network depletion, persistent stenosis of small peripheral arteries and arterioles are key characteristics of HTN.

In our earlier study, we showed the narrowing of arterial capillary diameter by nail-bed capillaroscopy in hypertensive patients and reported a remodeling coefficient (RC). It is calculated as a ration between the diameters of venous and arterial parts of capillaries. This kind of remodeling was detected at the early stages of HTN in patients with "high normal blood pressure." However, the relation between microvascular remodeling and LVH is unclear.

The aim of this study was to determine the association between LVH and peripheral capillary network remodeling in hypertensive patients, including those with metabolic syndrome.

Design and methods

The study included 74 subjects aged 30–70 years old. The group "HTN" included 33 patients with HTN 1–2 grade diagnosed in accordance with the European Society of Cardiology (2013) and the Russian Society of Hypertension guidelines. At the time of inclusion in the study patients of "HTN" group had been off regular drug therapy. The control group consisted of healthy volunteers (n = 41) with no apparent cardiovascular disease (Table 1). Patients with body mass index (BMI) more than 30 kg/m2 underwent additional examination to exclude metabolic syndrome (MS) in accordance with guidelines of the Russian Society of Hypertension.

The groups were comparable by age, sex and majority of biochemical parameters. Patients in «HTN» group were not different from the healthy ones in smoking status, though there were more smokers among HTN in combination with MS than in the subgroup with hypertension without MS. The patients of the «HTN + MS» subgroup were younger than subjects from the «HTN without MS» subgroup (47.4 ± 6.6 and 53.6 ± 6.0 years, respectively, p = 0.01). BMI was significantly higher in "AH + MS" subgroup compared to the «HTN without MS» subgroup (37.6 ± 4.7 vs. 26.0 ± 3.3 kg/m2, p < 0.0001).

Exclusion criteria in patients were the following: manifesting coronary heart disease, myocardial infarction, valvular heart disease with severe intercardiac hemodynamics disturbances, significant arrhythmias, heart failure, previous cerebral stroke, systemic diseases, diabetes mellitus, fever of any origin, pregnancy and lactation.

Routine clinical and diagnostic examination was performed in all subjects according to the Guidelines (2013). Investigation of microcirculation parameters was also performed. All participants signed an informed consent. Study protocol was approved by the Ethics Committee of the Scientific Clinical Centre» Russian Railways. **Electrocardiography (ECG)** ("Myokard", Russia) was carried out in order to detect significant arrhythmias, signs of myocardial ischemia, Q waves and LVH signs. LVH was assessed by Sokolov-Lyon index (SV1 + RV5 > 3.5 mV) or by modified Sokolov-Lyon index (the largest S wave + greatest R wave > 3.5 mV).

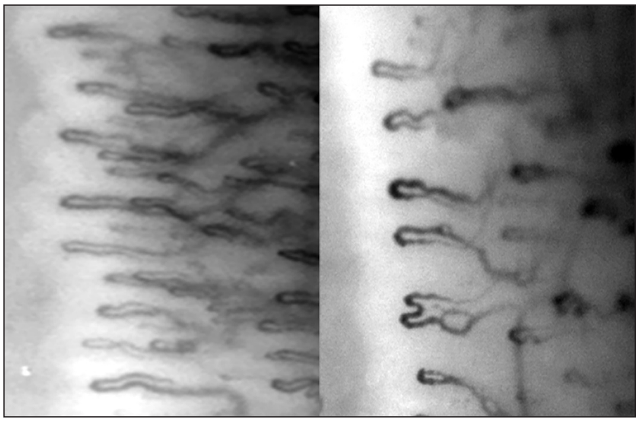
By **echocardiography (ECHO)** («Acuson» 128XP/10, Germany) global myocardial contractility, heart chambers size, intracardiac blood flow characteristics, and LVH were assessed. Left ventricular wall thickness below 12 mm was considered normal. Myocardial mass exceeding 170 g for women and 225 g for men was regarded as LVH sign. LV myocardial mass index (LVMI) was considered increased when it was higher than 115 g/m2 in males and 95 g/m2 in females. LVMI was calculated as a ratio of estimated myocardial mass to total body area.

Investigation of microcirculation (nail bed capillary blood flow assessment) was carried out with digital capillaroscope "Kapillyaroskan-1" ("New Energy Technologies", Russia). The study was conducted in a sitting position after 15–20 minutes of rest at constant room temperature (22–24 oC). On the day before examination subjects ought to refrain from smoking and drinking caffeinated beverages. The hand was placed on a special gently fixing bed of capillaroscope aligned the level of the patient's heart. Skin temperature was measured on eponychium area of 3rd or 4th fingers on the left hand before examination. The average skin temperature was similar in both groups (33.3 ± 1.4ºC and 33.9 ± 1.1ºC in control and HTN groups, respectively). Primary data were processed by special software programme.

Investigation of capillary network density was based on the visualization of finger nail bed cuticle panoramic images with 125-fold zoom (Fig. 1). The number of capillaries in the first line was estimated. The density of the capillary network was recognized to be low (1 score) when the number of estimated capillaries was 7 or less. Two scores were considered in case of 8–10 capillaries identified, and 3 scores were considered when the number of capillaries exceeded 11.

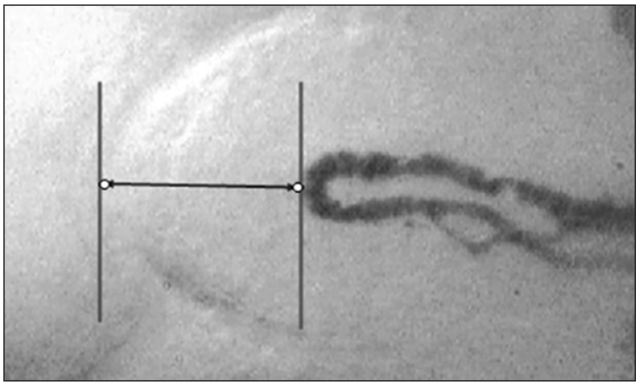
More detailed examination was performed at 450-time magnification. Quantitative measurements

Figure 1. Capillary network density



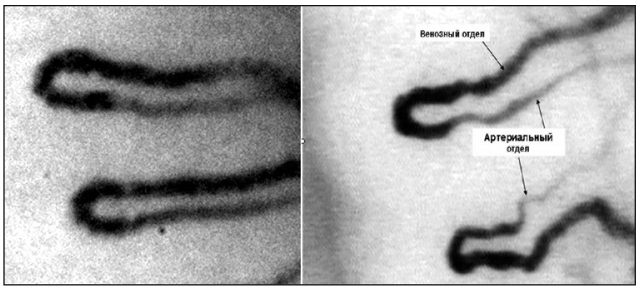
Note: On the left — capillaries of a healthy volunteer, capillary network density is normal (3 scores), on the right — capillaries of a hypertensive person, capillary network density is decreased (1 score).

Figure 2. The change of the linear dimension of the perivascular area



Note: Linear dimension of the perivascular area is the distance between the most prominent pat of capillary network at the transitional division to the most distant point of the perivascular area.

Figure 3. Singular capillary remodeling



Note: On the left — capillaries of the healthy volunteer (remodeling coefficient — 1.31), on the right — capillaries of a hypertensive patient (remodeling coefficient — 1.56).

of capillary diameters were performed in this study to determine values mentioned above. Diameter of the arterial initial part of capillary, middle part and at the border with transitional division were measured. Similar measurements of the venous capillary part at three points were performed. Perivascular area (PA) was measured as a linear dimension of its most remote point to the closest point in capillary transitional division (Fig. 2). Microvascular remodeling was assessed by remodeling coefficient (RC), estimated as the ration between capillary diameters in venous and arterial divisions (Fig. 3).

Systolic (SBP) and diastolic (DBP) blood pressure (BP) and heart rate were measured twice by an automatic "Tonokard" device ("Current medical diagnostic technologies", Russia). The device enables three BP measurements in an automatic manner at a given time intervals in accordance with the guidelines of the European Society of Cardiology.

Statistical analysis

The groups were compared using Student's t-test. Multiple comparison correction was performed with FDR («False Discovery rate»), because Bonferroni correction commonly used for multiple comparisons was not applicable in case of more than 10 paired comparisons (there were more than 50 paired comparisons in our study). Normal distribution pattern of the assessed parameters was verified by Kolmogorov-Smirnov test. The dispersion homogeneity was evaluated by Leuven criteria. Non-parametric Mann-Whitbey test was used in case of non-normally distributed variables and non-homogenous dispersions. Percentages of categorical and nominal variables were analyzed by z-criterion with Yates correction. Relationship between the measured parameters were assessed by Pearson correlation coefficient and step-by-step regression analysis. Data are presented as M ± m, where M is mean value, m — standard deviation. Statistical analysis was performed by standard statistical software package.

Results and discussion

The results of comparison analysis are presented in Table 1. SBP and DBP mean values verify HTN 1st grade in patients from the "HTN" group (153.0 ± 12.0 and 92.8 ± 9.0 mmHg, respectively) and are significantly higher than in comparison “Healthy” group (110.1 ± 8.0 and 67.8 ± 7.0 mmHg, p << 0.0001). Heart rate was also significantly higher in “HTN” group compared to “Healthy” group (74.8 ± 12 and 66.5 ± 9 bpm, p < 0.01).

Significant difference in the capillary network density was found between “HTN” and “Healthy” groups: 2.2 ± 0.7 and 1.6 ± 0.6 points (p < 0.001). Normal capillary network density was found in 87.2 % in healthy volunteers group (3 scores — in 16 % volunteers, 2 scores — in 53.2 % volunteers), and 12.8 % volunteers in the “Healthy” group showed reduced capillary network density (1 point). The rate of normal capillary network density was significantly lower in the “HTN” group counting 55.3 % (3 scores — in 8.3 % participants, and 2 scores — in 47.2 %). Reduced capillary network density was found in 44.7 %.

Our results correspond to the data of other authors, who studied capillary network density in hypertensive patients. Its reduction is considered

Table 1

CHARACTERISTICS OF THE STUDIED GROUPS

	Group «Healthy» (n = 41)	Group «HTN» (n = 33)	p-value (in groups «Healthy» & «HTN»)	Group «HTN without MS (n = 21)	Group «HTN + MS» (n = 12)	p-value (in groups «HTN without MS» and «HTN + MS»
Age, years	51.4 ± 11.4	50.9 ± 7.0	0.81	53.6 ± 6.0	47.4 ± 6.6	0.01
Sex (m/f), %	54 %	55 %	0.94	53 %	58 %	0.77
HTN duration, years	–	7.0 ± 6.1	–	7.1 ± 6.6	6.8 ± 5.8	0.26
Smoking, %	19.5	29.7	0.05	14.2	38.4	**< 0.05**
BMI, kg/m^2	25.2 ± 2.8	31.5 ± 6.8	**< 0.001**	26.0 ± 3.3	37.6 ± 4.7	**<< 0.0001**
Cholesterol, mmol/l	5.3 ± 0.3	5.7 ± 1.0	0.68	5.5 ± 1.2	5.8 ± 0.8	0.58
Glucose, mmol/l	5.2 ± 0.3	5.6 ± 0.5	**< 0.05**	5.5 ± 0.5	5.7 ± 0.5	0.52
Microcirculation parameters, arterial blood pressure & heart rate						
TD, mcm	14.1 ± 2.7	15.4 ± 3.4	**< 0.05**	15.5 ± 3.3	15.1 ± 2.4	0.68
RC	1.31 ± 0.10	1.50 ± 0.15	**<< 0.0001**	1.50 ± 0.15	1.49 ± 0.19	0.95
PA, mcm	96.2 ± 12.6	107.7 ± 16.2	**< 0.01**	105.9 ± 17.1	112.7 ± 13.9	0.26
DN, points	2.2 ± 0.7	1.6 ± 0.6	**< 0.001**	1.5 ± 0.6	1.6 ± 0.6	0.58
SBP, mmHg	110.1 ± 7.9	153.0 ± 12.0	**<< 0.0001**	152.3 ± 13.1	155.6 ± 10.8	0.48
DBP, mmHg	67.8 ± 6.8	92.8 ± 9.1	**<< 0.0001**	90.8 ± 8.4	96.8 ± 11.4	0.09
HR, bpm	66.5 ± 8.7	74.8 ± 11.9	**< 0.01**	71.3 ± 11.1	78.7 ± 13.7	0.11
ECHO characteristics						
EF %	64.1 ± 2.4	61.5 ± 6.3	0.15	62.4 ± 6.5	61.0 ± 6.7	0.63
IVST, cm	1.05 ± 0.08	1.25 ± 0.15	**< 0.001**	1.14 ± 0.12	1.35 ± 0.17	**< 0.001**
LVPWT, cm	1.02 ± 0.01	1.21 ± 0.18	**< 0.001**	1.10 ± 0.11	1.30 ± 0.16	**< 0.001**
EDD, cm	5.1 ± 0.2	5.3 ± 0.5	0.12	5.1 ± 0.6	5.5 ± 0.4	0.16
MM, g	161.5 ± 26.2	266.8 ± 81.6	**< 0.0001**	213.5 ± 53.2	315.1 ± 80.4	**< 0.001**
LVMMI, g/m^2	86.4 ± 11.4	123.1 ± 31.7	**< 0.0001**	108.4 ± 26.8	138.1 ± 31.7	**< 0.05**
LA, cm	3.5 ± 0.5	3.8 ± 0.6	0.3	3.6 ± 0.3	3.9 ± 0.2	0.61

Note: BMI — body mass index; TD — capillary transitional division ; RC — remodeling coefficient; PA — perivascular area; DN — density of capillary network; SBP — systolic blood pressure; DBP — diastolic blood pressure; EF % — left ventricular ejection fraction; IVST — interventricular septum thickness; LVPWT — left ventricular posterior wall thickness; EDD — left ventricular end-diastolic dimension; LVM – left ventricular mass; LVMMI — left ventricular myocardial mass index; LA — anteroposterior left atrial dimension; «HTN without MS» — group of hypertensive patients without metabolic syndrome; «HTN + MS» — the group of patients with arterial hypertension and metabolic syndrome. Values “p” are listed for statistically significant differences adjusted for multiple comparisons.

Table 2

CAPILLARY DIAMETERS VALUES REPORTED BY VARIOUS AUTHORS BASED ON THE CAPILLAROSCOPY

	Capillary size in healthy volunteers (our data)	Capillary size in healthy volunteers (Mahler F. et al.)	Capillary size in healthy volunteers (Brülisauer M., Bollinger A.)
Number of healthy volunteers	41	33	12
Arterial division, mcm	8.9 ± 2.6	10.8 ± 3.0	12.3 ± 2.9
Transitional division, mcm	14.1 ± 2.7	–	18.5 ± 5.4
Venular division, mcm	11.5 ± 3.3	12.1 ± 2.7	13.5 ± 3.5

one of the features of microvascular impairment. There are two hypothesis explaining possible reasons of capillary network density reduction: “hemodynamic” and “genetic”. “Hemodynamic” theory suggests that elevated BP leads to the decrease in number of perfused capillaries, followed by a decrease in the number of capillaries per unit area. Followers of “genetic” theory argue that a capillary network depletion precedes HTN development. Signs of decreased capillary network density were found in healthy subjects with anamnesis compromised by HTN. We did not find any difference in capillary network density between “HTN without MS” and “HTN + MS” subgroups (Table 1).

The diameter of dermal capillaries in the nail bed increased starting from the arteriole and reaching the greatest values at the transition division. It was already shown by a number of authors and confirmed by our study.

Mean values of capillary diameters in “Healthy” group were the following: about 8.9 ± 2.6 mcm in arterial division, 14.1 ± 2.7 mcm in transition division, and 11.5 ± 3.3 mcm in venous division (Table 2). Our findings are similar to those reported by Mahler F. et al (1982). They estimated the size of capillaries in 33 healthy volunteers. Brülisauer M. and A. Bollinger (1991) obtained data from 12 healthy participants. This might explain the diversion of the results.

Remodeling coefficient (RC) was higher in “HTN” group than in “Healthy” group: 1.50 ± 0.2 and 1.31 ± 0.1, respectively ($p << 0.001$). There was a positive correlation between RC and BP

Table 3

CORRELATIONS BETWEEN MICROCIRCULATION PARAMETERS IN THE GROUPS “HEALTHY” AND “HTN”

	PA	RC	DN	BMI	EF%	SBP	DBP	HR	IVWT	LVPWT	LVMM	LVMMI
PA	1.0	0.31	–0.19	0.29	–0.05	0.44	**0.55**	0.08	0.42	0.34	0.42	0.40
RC	0.27	1.0	–0.05	0.32	0.21	**0.64**	**0.68**	**0.53**	**0.53**	**0.53**	0.34	0.26
DN	–0.19	–0.05	1.0	–0.46	0.15	–0.39	–0.39	0.24	**–0.55**	–0.42	–0.50	–0.40
BMI	0.29	0.27	–0.46	1.0	–0.15	**0.64**	**0.58**	–0.15	**0.86**	**0.82**	**0.86**	**0.82**
EF%	–0.05	0.21	0.15	–0.15	1.0	–0.25	0.04	–0.20	–0.08	–0.26	–0.35	–0.40
SBP	0.44	**0.64**	–0.39	**0.64**	–0.25	1.0	**0.89**	0.23	**0.83**	**0.83**	**0.76**	**0.72**
DBP	**0.55**	**0.69**	–0.39	**0.58**	0.04	**0.89**	1.0	0.19	**0.72**	**0.66**	**0.62**	**0.57**
HR	0.08	**0.53**	0.24	–0.15	–0.20	0.23	0.19	1.0	0.05	0.14	0.01	0.03
IVST	0.42	**0.53**	**–0.55**	**0.84**	–0.08	**0.83**	**0.72**	0.05	1.0	**0.95**	**0.91**	**0.86**
LVPWT	0.34	**0.53**	–0.42	**0.82**	–0.08	**0.83**	**0.66**	0.14	**0.95**	1.0	**0.95**	**0.2**
LVMM	0.42	0.34	–0.50	**0.86**	–0.35	**0.76**	**0.62**	0.01	**0.91**	**0.95**	1.0	**0.98**
LVMMI	0.40	0.26	–0.40	**0.82**	–0.40	**0.72**	**0.57**	0.03	**0.86**	**0.92**	**0.98**	1.0

Note: PA — perivascular area; RC — remodeling coefficient; DN — density of capillary network; BMI — body mass index; EF % — left ventricular ejection fraction; SBP — systolic blood pressure; DBP — diastolic blood pressure; IVWT — interventricular wall thickness; LVPWT — left ventricular posterior wall thickness; LVMM — left ventricular myocardial mass; LVMMI — left ventricular myocardial mass index. Correlation coefficients with $p < 0.05$ are marked out by bold type.

Table 4

RELATIONSHIP BETWEEN REMODELING COEFFICIENT, LEFT VENTRICULAR MYOCARDIAL MASS INDEX AND MICROCIRCULATION PARAMETERS, ECHOCARDIOGRAPHY PARAMETERS IN "HEALTHY" AND "HTN" GROUPS (REGRESSION ANALYSIS RESULTS)

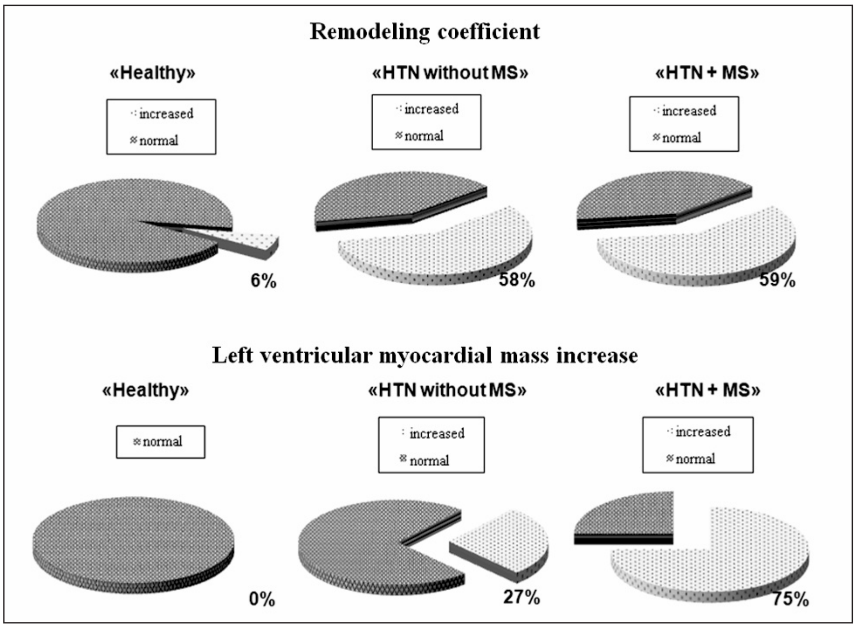
	RC	LVMMI
PA	0.21	–0.07
AD	**–0.37**	0.16
TD	–0.10	–0.03
VD	0.05	**0.26**
RC	–	0.16
BMI	**0.29**	**0.61**
SBP	**0.50**	**0.68**
DBP	**0.25**	**0.54**
HR	**0.36**	–0.06
LVMI	0.18	–
EF	0.04	**–0.49**

Note: RC — remodeling coefficient; LVMMI — left ventricular myocardial mass index; PA — perivascular area; AD — capillary arterial division mean diameter; TD — capillary transitional division mean diameter; VD — capillary venous division mean diameter; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; LVMMI — left ventricular myocardial mass index; EF %, — left ventricular ejection fraction. Correlation coefficients with $p < 0.05$ are marked out by bold type.

(r-value for SBP was 0.64, and for DBP — 0.69, $p < 0.05$) (Table 3). These data were also confirmed by regression analysis that showed a highly significant relationship between RC and both SBP and DBP. Apparently, the diameters of capillary arterial divisions depend on upstream arterioles lumen. The changes of the latter one affect the capillaries. Sympathoadrenal system activation characteristic for HTN might be one of the possible causes of the mentioned changes. Heart rate acceleration and its strong association with RC (shown by correlation analysis, r = 0,53, and by regression analysis, r = 0,31) indirectly confirm this suggestion. Regression analysis also demonstrated a negative correlation between RC and median diameter of capillary arterial divisions (Table 4).

Statistical analysis showed correlation between RC and BMI. Despite younger age, patients with

Figure 4. The frequency of the decreased capillary network density, increased remodeling coefficient and left ventricular myocardial mass



HTN + MS had similar microvascular alterations as patients from the subgroup "HTN without MS": RC was 1.49 ± 0.2 and 1.5 ± 0.15 ($p > 0.05$). Thus, we might suggest that remodeling of capillary bed in patients with a combination of HTN and MS is more likely to occur earlier than in hypertensive patients without MS.

Echocardiography demonstrated significant differences between hypertensive patients and healthy volunteers (Table 1). Lower severity of LVH (LVMMI = 123 ± 32 g/m2) was found in "HTN" group. LVMMI values did not exceed normal range in "Healthy" group (86 ± 11 g/m2, $p \ll 0.0001$). Regression and correlation analyses demonstrated strong relationship between LVH, BP and BMI that corresponds to data reported by other authors.

Figure 4 shows the incidence of LVH in hypertensive patients indicating its dependence on the presence of MS. At the same time, the rate of increased remodeling coefficient is equal in both subgroups of hypertensive patients. It is increased in 58 % hypertensive patients without MS, while LVH was detected only in 27 % cases in the same group.

Conclusions

Hypertensive patients showed significant alteration of capillary network in comparison with healthy volunteers (a capillary network density decrease and an increased remodeling coefficient were found).

Close relationship between BP levels and parameters of capillary bed remodeling was found along with the well-known association between BP and LVH.

Frequency of LVH is significantly higher in co-existent HTN and MS; at the same time, the rate of capillary bed remodeling in hypertensive patients is independent from the presence of MS.

Conflict of interest

Authors declare no conflicts of interest.

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