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ORIGINAL ARTICLE

Determinants of the structure of resistance-sized arteries in hypertensive patients

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Abstract

Objective. It has been previously demonstrated that structural alterations of subcutaneous small resistance arteries of hypertensive patients, as indicated by an increased media to lumen (M/L) ratio, is the most potent predictor of cardiovascular events. The aim of the present study was to identify possible determinants of small resistance artery structure that may be evaluated with non-invasive approaches. *Materials and methods.* One hundred and ninety-nine subjects (normotensives, essential hypertensives and patients with secondary hypertension) were included in the present study. All subjects were submitted to a biopsy of subcutaneous fat from the gluteal or the anterior abdominal region. Small resistance arteries were dissected and mounted on an isometric myograph, and M/L ratio was measured. All patients underwent standard biochemical tests, clinic blood pressure measurement, standard echocardiography and 24-h ambulatory blood pressure measurement. Glomerular filtration rate (GFR) was calculated according to MDRD study formula and Cockroft's formula. *Results.* Significant correlation was found between M/L ratio and, respectively: GFR calculated both with MDRD study formula and Cockroft–Gault formula, creatinine serum, blood urea nitrogen, glycaemia, circulating sodium, clinical pulse pressure, stroke volume to pulse pressure ratio, clinical systolic, diastolic and mean arterial pressure, daytime pulse pressure. However, in a multivariate regression analysis, only serum creatinine remained in the model, and proved to be an independent predictor of small artery structure. *Conclusions.* Indices of renal function and, probably, of large artery distensibility may be related to small arteries remodelling in hypertension.

Key Words: *Blood pressure, determinants, media to lumen ratio, microcirculation, predictors, small arteries structure*

Introduction

Small resistance arteries remodelling may be involved in the development and/or maintenance of elevated blood pressure values; in addition, it may exert a relevant role in the onset of target organ damage (1–6). Some evidence suggests that an increased tunica media thickness/lumen diameter (M/L) ratio may have a relevant prognostic significance both in high and moderate-risk hypertensive patients (7–10). However, the evaluation of microvascular structure is not an easy task, and reliable data may be obtained only with relatively invasive techniques, in particular using *in vitro ex vivo* micromyographic approaches (1–3,7). Small vessels are dissected free from the surrounding adipose tissue obtained by biopsies of the subcutaneous fat, usually taken from the gluteal region (1,3,7). The invasiveness of this approach limits the application of such determination to wide populations of patients. Therefore, possible identification of markers of small resistance artery structure that might be evaluated by non-invasive approaches might provide a relevant contribution in this field.

A significant correlation between M/L ratio and systolic, diastolic and mean blood pressure has been observed (11,12). The relation between microvascular structure and pulse pressure (a rough index of

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large artery distensibility) is still controversial, since both positive (13,14) and negative (12,15) data are reported.

Also, left ventricular mass has shown a correlation with small arteries structure (16,17), especially in patients with activation of the renin–angiotensin system (18). Recently it has been found out that subcutaneous small artery structure is related to morning rise of blood pressure as well (19). However, as previously mentioned, a possible limitation of these studies is related to the relatively small number of patients studied.

It was postulated that alterations in the large artery distensibility may be influenced by microvascular structural alterations through the impact of reflected waves. In fact, microvascular structure is not only the site of vascular resistance but also the origin of most of the wave reflections generating increased central systolic blood pressure, with relevant consequence in large artery compliance (20,21).

Finally, it was also postulated that microvascular alterations in the renal glomeruli may be the most important determinants of the progressive decline of renal function that may be observed in long-standing hypertension (22).

Therefore, aim of the present study was to identify a group of possible determinants of small resistance artery structure (e.g. indices of renal function, of large artery distensibility or haemodynamic variables), obtained with non-invasive approaches in a relatively large sample of hypertensive patients and normotensive controls.

Patients and methods

One hundred and ninety-nine subjects, submitted to an evaluation of subcutaneous small resistance artery structure in the last decade in our Laboratory of Vascular Biology, were included in the present study. They were 26 normotensive subjects (NT), 103 patients with essential hypertension (EH), 16 with pheochromocytoma (PHEO), 21 with primary aldosteronism (PA), 12 with renovascular hypertension (RVH) and 21 normotensive patients with non-insulin-dependent diabetes mellitus (NIDDM). Their age ranged from 20 to 81 years. The presence of hypertension was established according to International Society of Hypertension/World Health Organization Guidelines (23). The presence of NIDDM was established according to the Guidelines of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (24). The diagnosis of secondary forms of hypertension was made on the basis of an indication for renal artery revascularization or adrenal tumour resection, after proper investigations by imaging techniques and humoral assessments.

All hypertensive patients were untreated or had been treated previously for less than 6 months with different classes of hypertensive drugs. There was no difference in the relative proportion of different drug classis among the subgroups. Treatment was withdrawn at least 3 weeks before the procedure.

The protocol of the study was approved by the Ethics Committee of our institution (Medical School, University of Brescia), and informed consent was obtained from each participant. The procedures followed were in accordance with institutional guidelines.

Venous blood samples were taken with the participants in the supine position, after a washout period of at least 2 weeks, for standard haematology and serum biochemistry tests (including triglycerides, cholesterol and assessment of renal function).

In each patient a standard echocardiography evaluation was performed. Left ventricular internal dimensions, left ventricular posterior wall and interventricular septum thicknesses were measured according to the recommendations of the American Society of Echocardiography and the Penn convention (25). Left ventricular mass (LVM) and left ventricular mass indexed for the body surface area (LVMI) or the height at the 2.7 power (LVMh) were calculated.

Left ventricular hypertrophy was considered present if the LVMI exceeded 125 g/m^2 in both sexes.

Stroke volume (SV), pulse pressure (PP), stroke volume/pulse pressure ratio both as absolute value (SV/PP) and percentage of predicted value (SV/PP%) were calculated. For further technical details, see reference (21).

All subjects underwent a 24-h non-invasive blood pressure monitoring (ABPM) (Spacelab 90207/90217, Spacelab Medical, Issaquah, WA, USA). Systolic, diastolic and mean blood pressure as well as pulse pressure were measured during 24-h, daytime and night-time.

Details about timing of application, intervals between measurements and data processing may be found elsewhere (26).

Micromyography

All subjects were then submitted to a biopsy of subcutaneous fat from the gluteal or the anterior abdominal region. The biopsy of the abdominal subcutaneous fat was taken during a surgical procedure (usually cholecystectomy in normotensives and essential hypertensives and adrenalectomy

or vascular surgical intervention on the renal arteries in patients with secondary hypertension), whereas in the remaining patients, a standard skin biopsy from the gluteal region (3 cm long, 0.5 cm wide, 1.5 cm deep) was performed (27,28).

Small arteries (100–300 μm average diameter in relaxed conditions, 2 mm long) were dissected from the subcutaneous fat and mounted as a ring preparation on an isometric myograph (410 A, Danish Myo Technology, Aarhus, Denmark), by threading onto two stainless steel wires (40 μm in diameter). The total wall thickness, tunica media thickness, internal diameter and M/L ratio were then measured. The M/L ratio of small arteries was previously demonstrated to be the best indicator of small resistance artery structure, since it is independent of the vessels' dimensions (29).

Details about the micromyographic technique of evaluation of small artery morphology were reported previously (30–32).

Statistical analysis

Linear regression analysis was applied to all variables, considering M/L ratio as a dependent variable.

The following independent variables were considered: age, gender, presence of hypertension, smoking habits, body mass index (BMI), heart rate (HR), LVM, LVMI, LVMh, SV, PP, SV/PP, SV/PP%, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), 24-h, day-time and nigh-time SBP, DBP and MBP, serum creatinine, sodium, potassium, chloride, triglycerides, total cholesterol, uric acid, blood urea nitrogen (BUN), glomerular filtration rate (GFR) calculated respectively with MDRD formula (33) and Cockroft–Gault formula (34), M/L ratio and other parameters as indexes of microvascular structure (media cross-sectional area, MCSA; internal diameter and wall thickness). A multivariate analysis was then performed, with M/L ratio as dependent variable, and all the previously mentioned variables as possible independent predictors.

A value <0.05 was considered statistically significant. All analyses were carried out with SPSS 13.0 software.

Results

Demographic data of all study population are shown in Table I. Table II shows demographic data of the six different groups of patients. As reported in Table III, statistically significant correlations were observed between M/L ratio and, respectively, GFR calculated using MDRD study formula ($r=-0.25$, $p=0.002$) and Cockroft–Gault formula ($r=-0.18$, $p=0.049$); serum creatinine ($r=0.29$, $p<0.001$), BUN ($r=0.27$, $p=0.003$), glycaemia ($r=0.18$, $p=0.024$), circulating sodium ($r=0.23$, $p=0.013$), PP ($r=0.23$, $p=0.001$), PP/SV ($r=0.21$, $p=0.019$) (Figure 1), SBP ($r=0.29$, $p<0.001$), DBP ($r=0.22$, $p=0.002$) and MBP ($r=0.27$, $p<0.001$) and ABPM daytime pulse pressure ($r=0.21$, $p=0.003$).

Table I. Demographic data and structural parameters in the study population.

Parameter	
Age (years)	57 ± 12
Sex (M/F)	112M, 87F
SBP (mmHg)	149 ± 21
DBP (mmHg)	90 ± 13
PP (mmHg)	59 ± 14
BMI	27 ± 6
Serum glucose (mg/dl)	123 ± 50
Diabetes (%)	38%
Smokers (%)	38%
Serum cholesterol (mg/dl)	211 ± 48
Hypercholesterolemia (%)	56%
Creatinine (mg/dl)	1.05 ± 0.34
GFR (MDRD formula - ml/min)	72 ± 20
GFR (Cockroft formula - ml/min)	87 ± 27
Left ventricular mass (g)	215 ± 74
LVMI (g/m^2)	117 ± 39
LVMh (g/h$^{2.7}$)	53 ± 18
Left ventricular hypertrophy (%)	37%
Small resistance arteries:	
Media thickness (μm)	22.08 ± 5.26
Wall thickness (μm)	41.31 ± 8.85
Internal diameter (μm)	255.62 ± 93.68
Media cross-sectional area (μm^2)	19,887 ± 10245
M/L ratio	0.098 ± 0.07

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; GFR, glomerular filtration rate; LVMI, left ventricular mass indexed for the body surface area; LVMh, left ventricular mass indexed for the height at the 2.7 power; M/L, media to lumen ratio.

After applying a multivariate regression analysis, only serum creatinine was an independent predictor of small arteries structure ($r=0.29$, $p<0.001$) (Figure 2).

We included also, as possible independent predictor of M/L, the classification in different subgroups (*normotensives, essential hypertensives, primary aldosteronism, renovascular hypertension, phaeochromocytoma, normotensive diabetic patients*). The concerned variable did not enter the model. Therefore, our results are not influenced by differences in subgroups.

RVH patients ($n=12$) showed a significantly more elevated serum creatinine, compared with the mean of whole group (RVH 1.66 ± 0.82 vs. all subjects

Table II. Demographic data and structural parameters in the different groups of the study population.

Parameter	1: Normotensives	2: Essential hypertensives	3: Pheochromocytoma	4: Primary aldosteronism	5: Renovascular hypertension	6: Diabetic normotensives
Age (years)	59±14	59±12	51±13	53±12	58±13	59±7
Sex (M/F)	15M, 11F	61M, 42F	8M, 8F	11M, 10F	9M, 3F	12M, 9F
SBP (mmHg)	$129\pm14^{2,3,4,5}$	$154\pm17^{1,3,6}$	$141\pm17^{1,2,4,5}$	$155\pm20^{1,3,6}$	$163\pm16^{1,3,6}$	$133\pm10^{2,4,5}$
DBP (mmHg)	$77\pm7^{2,3,4,5}$	$93\pm13^{1,3,6}$	$85\pm13^{1,2,4,5}$	$94\pm14^{1,3,6}$	$100\pm11^{1,3,6}$	$80\pm3^{2,4,5}$
PP (mmHg)	$52\pm12^{2,4,5}$	61 ± 12^{1}	56±13	61 ± 14^{1}	63 ± 12^{1}	54±11
BMI	20 ± 9^{2}	$28\pm5^{1,5}$	21 ± 8^{4}	27 ± 4^{3}	24 ± 4^{2}	26±8
Glycaemia (mg/dl)	$100\pm24^{3,4,6}$	$130\pm51^{3,4,5,6}$	$86\pm13^{1,2,4,6}$	$96\pm15^{1,2,3,6}$	$96\pm44^{2,6}$	$172\pm50^{1,2,3,4,5}$
Diabetes (%)	0%	30%	6%	27%	8%	100%
Smokers (%)	37%	11%	27%	20%	8%	42%
Serum cholesterol (mg/dl)	205±56	216±48	208±36	209±55	192±40	211±48
Hypercholesterolemia (%)	50%	38%	60%	80%	33%	62%
Creatinine (mg/dl)	1.03 ± 0.23^{4}	$1.09\pm0.31^{3,5,6}$	$0.91\pm0.19^{2,5}$	$1.16\pm0.75^{1,6}$	$1.66\pm0.82^{2,3,6}$	$0.96\pm0.15^{2,4,5}$
GFR (MDRD; ml/min)	74 ± 16^{4}	$69\pm18^{3,6}$	$84\pm18^{2,5}$	$73\pm23^{1,6}$	$54\pm26^{3,6}$	$77\pm14^{2,4,5}$
GFR (Cockroft; ml/min)	86±31	89 ± 25^{5}	88 ± 19^{5}	93 ± 36^{5}	$61\pm31^{2,3,4,6}$	91 ± 17^{5}
Left ventricular mass (g)	$169\pm38^{2,4,5,6}$	$234\pm59^{3,1}$	$179\pm42^{2,4,5}$	$230\pm81^{1,3,6}$	$282\pm97^{1,3,6}$	$161\pm44^{1,4,5}$
LVMI (g/m^2)	$92\pm17^{2,4,5,6}$	$123\pm30^{3,1}$	$104\pm21^{2,5}$	$123\pm36^{1,6}$	$153\pm40^{1,3,6}$	$87\pm21^{1,4,5}$
LVMh ($g/h^{2.7}$)	$40\pm10^{2,4,5,6}$	$57\pm14^{3,1}$	$47\pm12^{2,5}$	57 ± 17^{1}	$67\pm19^{1,3,6}$	$41\pm10^{1,4,5}$
Small resistance arteries:						
Media thickness (μm)	$18.75\pm4.76^{2,4,6}$	$23.28\pm4.96^{1,3}$	$20.43\pm3.85^{2,6}$	20.27 ± 6.54^{1}	23.10±4.31	$23.10\pm3.57^{1,3}$
Wall thickness (μm)	$35.40\pm8.13^{4,6}$	42.93±9.00	38.58±7.96	38.09 ± 10.76^{1}	39.34±5.12	42.71 ± 5.58^{1}
Internal diameter (μm)	$280.62\pm74.55^{3,4}$	249.06±83.97	225.99 ± 48.01^{1}	252.94 ± 72.43^{1}	215.87±82.06	258.65±57.48
Media cross-sectional area (μm^2)	18,088±7812	$20,575\pm9374^{3}$	$16,150\pm5626^{2}$	18,224±9620	17,208±9227	20,627±5769
M/L ratio	$0.070\pm0.019^{2,3,4,6}$	$0.100\pm0.024^{1,4}$	0.092 ± 0.018^{1}	$0.083\pm0.025^{1,2,5}$	0.117 ± 0.050^{4}	0.095 ± 0.019^{1}

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; GFR, glomerular filtration rate; LVMI, left ventricular mass indexed for the body surface area; LVMh, left ventricular mass indexed for the height at the 2.7 power; M/L, media to lumen ratio. Superscript numbers refer to groups for which the values are significantly different ($p<0.05$).

Table III. Correlations between media to lumen ratio of subcutaneous small arteries ratio and different parameters from the study population.

	R	*p*
All study population		
GFR with MDRD study formula	−0.25	0.002
GFR with Cockroft–Gault formula	−0.18	0.049
Serum creatinine	0.29	<0.001
BUN	0.27	0.003
Clinical systolic blood pressure	0.29	<0.001
Clinical diastolic blood pressure	0.22	0.002
Clinical mean blood pressure	0.27	<0.001
Clinical pulse pressure	0.23	0.001
ABPM daytime pulse pressure	0.21	0.003
PP/SV	0,21	0.019
Circulating sodium	0.23	0.013
Serum glucose	0.18	0.024
Population after exclusion of renovascular hypertensives		
Serum creatinine	0.20	0.027
BUN	0.21	0.045
Clinical systolic blood pressure	0.30	0.001
Clinical mean blood pressure	0.25	0.009
Clinical pulse pressure	0,26	0.016
24-h systolic blood pressure	0.23	0.001
24-h diastolic blood pressure	0.21	0.04
PP/SV	0.20	0.049

GFR, glomerular filtration rate; BUN, blood urea nitrogen; ABPM, ambulatory blood pressure monitoring; PP/SV, pulse pressure/stroke volume ratio.

1.05 ± 0.34; $p=0.043$ between groups). Therefore, we repeated our analysis after removal of RVH patients. In a multivariate regression analysis, independent predictors of M/L ratio were: clinic systolic blood pressure ($r=0.30$, $p<0.001$), clinic mean blood pressure ($r=0.25$, $p=0.009$), clinic pulse pressure ($r=0.26$, $p=0.016$), 24-h systolic blood pressure ($r=0.23$, $p=0.001$), 24-h diastolic blood pressure ($r=0.21$, $p=0.04$), PP/SV ($r=0.20$, $p=0.049$), BUN ($r=0.21$, $p=0.045$) and serum creatinine ($r=0.20$, $p=0.027$).

Discussion

Our analysis confirms, in a large number of subjects and patients, that small artery structure is related to a subset of parameters that can be easily and non-invasively evaluated, like clinic and 24-h blood pressure. These data are in agreement with previous findings (11–15). In the present study, we did not find a significant correlation between cardiac mass and M/L ratio. Although some degree of correlation was previously observed in this regard (11,18), the time course of alterations in the heart and in the microcirculation is probably different, as previously pointed out (15,35). In addition, closer correlations between cardiac and microvascular structure may be observed when a pronounced activation of the renin–angiotensin–aldosterone system is present, such as in patients with renovascular hypertension or primary aldosteronism (18,36).

Renal alterations (including glomerular function, sodium handling, renin incretion, etc.) may play a key role in the development of hypertension (37). Studies performed in animal models of genetic hypertension have shown a progressive impairment of renal function in parallel with the development of hypertension (38); structural and functional alterations of renal afferent arterioles (39) have been detected in spontaneously hypertensive rats (SHR), with consequent increase of vascular resistances

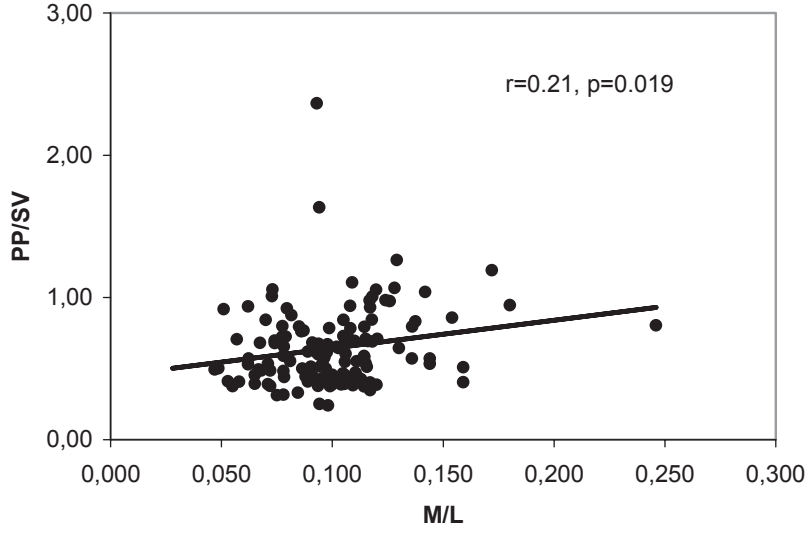

Figure 1. Correlation between pulse pressure/stroke volume (PP/SV) ratio and media to lumen ratio of subcutaneous small resistance arteries (M/L).

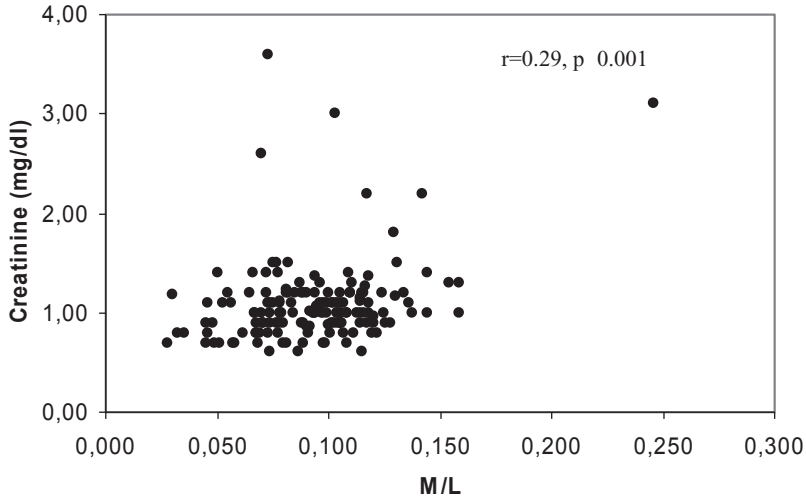

Figure 2. Correlation between serum creatinine and media to lumen ratio of subcutaneous small resistance arteries (M/L).

(40,41) and activation of the renin–angiotensin–aldosterone system (38,42); angiotensin II seems to be involved in renal fibrosis (43) and in the observed reduction of glomeruli number (44). In addition, it was demonstrated that alterations in afferent arterioles may predict subsequent development of hypertension in animal models (45). Experiments conducted in primates have confirmed these findings (45). In humans, hypertensive patients show structural alteration of glomeruli (46) and renal vascular resistance is increased in normotensive offspring of hypertensive parents (47). We observed a correlation between M/L ratio of subcutaneous small arteries and indices of renal function; in fact, serum creatinine was the most potent predictor of vascular structure in our population.

After removing from our analysis patients with renovascular hypertension ($n=12$), creatinine was no longer the most powerful independent predictor; however, it remained, together with BUN, among the predictors of small resistance arteries structural remodelling.

Another stimulating finding of our study was the relation between M/L ratio and indirect measures of arterial compliance, namely PP and SV/PP (48). Two major events characterize the blood pressure curve. First, at each discontinuity of the arterial wall, the ''incident'' pressure wave may be reflected. Second, the sum of the incident (coming from the heart) and the ''reflected'' (returning towards the heart) waves determine the shape of the blood curve at each site of the arterial tree. With age, this shape is more and more influenced by the timing and amplitude of the reflected wave, which returns toward the heart at the same pulse wave velocity as the incident wave (20,21). Pressure waves are reflected at every discontinuity of the arterial wall, but reflections predominate at the sites of arteriolar bifurcations, where the geometry and stiffness of vessel wall material determine the reflection angle and, therefore, the value of its coefficient (20,21). Herein, the major factors to consider are not only the distensibility and the diameter of each arteriolar branch of the bifurcation, but also their exact location. With age, the reflection sites are closer to vital organs, such as the heart, brain and kidney, and even wave reflections may contribute particularly to organ damage (20,21). Wave reflections may occur at any vascular site where vasomotor tone and pulsatility are still present. They disappear almost completely at precapillary and capillary levels (diameter: <150 μm), that is, when blood perfusion becomes almost completely steady (20,21). It is therefore possible that complex relationships are present between macrovascular structure and mechanical properties and microvascular structure, and reciprocal influence may be postulated. These interrelationships between alterations in the macro and microcirculation and mechanisms possibly involved represent an extremely interesting topic, which deserve further and thorough investigation, also considering its relevant clinic impact, especially in terms of possible prevention or regression of the concerned alterations. An important possibility in the future is that regression of structural vascular changes should become a necessity, particularly at microcirculation level, in order to prevent the occurrence of cardiovascular events. There is a strong need of a study aimed at evaluating possible relationships between indicators of small resistance artery structure and of large artery distensibility (e.g. pulse wave velocity, augmentation index, etc.) both

in basal condition and under antihypertensive drug treatment.

In our study, GFR was calculated indirectly, using Cockroft–Gault formula and MDRD formula. It is possible that, in the evaluation of renal function, a direct evaluation of serum creatinine, might be slightly more reliable that an indirect evaluation of GFR, although both formulas used for calculation of GFR were previously validated and extensively applied. It should, however, be considered that correlation coefficients between M/L and serum creatinine or GFR were of similar magnitudes, and, being GFR and creatinine auto-correlated, only one parameter could enter the model.

Previous antihypertensive treatment might have theoretically influenced small vessels' morphology. However, the duration of previous therapy in our patients was relatively short (few months) and drugs used were similar in the different groups. It was previously demonstrated that small artery structure might be improved by some (but not all) antihypertensive drugs only after 1 year or more of effective treatment (49).

In conclusion, our data suggest that indices of renal function and, probably, of large artery distensibility may be related to microvascular structure.

However, correlation observed, although statistically significant was not close, and may explain only a modest portion the variability of the dependent variable. Therefore, other non-invasive techniques, aimed at directly evaluation of microvascular structure, are needed. Some of these techniques, such as intravital microscopy, acoustic microscopy or confocal microscopy, are presently under clinical evaluation. In addition, the identification of possible relationships between microvascular structure and indices of large artery distensibility represents an interesting and stimulating issue, which deserve further specific investigations.

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