Original Article

Vascular Permeability, Blood Pressure, and Organ Damage in Primary Hypertension

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Sub-clinical organ damage is a strong independent predictor of cardiovascular mortality in primary hypertension, and its changes over time parallel those in risk of cardiovascular events. A better understanding of the pathogenetic mechanisms underlying the development of target organ damage may help us devise more effective therapeutic strategies. We therefore investigated the relationship between the presence of organ damage and some of its potential determinants, such as blood pressure severity and early atherosclerotic abnormalities. Thirty-seven untreated, non-diabetic hypertensive patients were enrolled. Target organ damage was assessed by albuminuria and left ventricular mass index; systemic vascular permeability was evaluated by transcapillary escape rate of albumin (TERalb); and blood pressure was measured by 24-h ambulatory blood pressure monitoring. The albumin-to-creatinine ratio and left ventricular mass index were directly related to TERalb ($r=0.48$, $p=0.003$ and $r=0.39$, $p<0.020$, respectively) and 24-h systolic blood pressure values ($r=0.54$, $p<0.001$; $r=0.60$, $p<0.001$). The simultaneous occurrence of increased blood pressure load and TERalb was associated with higher left ventricular mass index values ($p=0.012$) and entailed an increased risk of having at least one sign of damage ($\chi^2=17.4$; $p<0.001$). Logistic regression analysis showed that the risk of presenting at least one sign of organ damage increased more than ten-fold when TERalb was above the median and more than five-fold with each 10 mmHg increase in 24-h systolic blood pressure. Blood pressure load and vascular permeability are potentially modifiable factors that are independently associated with the occurrence of sub-clinical signs of renal and cardiac damage in hypertensive patients. (*Hypertens Res* 2008; 31: 873–879)

***Key Words*: hypertension, vascular permeability, microalbuminuria, left ventricular hypertrophy, transcapillary escape rate of albumin**

Introduction

The presence of sub-clinical target organ damage (TOD), namely microalbuminuria and left ventricular hypertrophy (LVH), constitutes an increased risk for cardiovascular (CV) and renal complications in patients with primary hypertension (*1*). Indeed, both an increase in left ventricular mass and albuminuria have been shown to precede and predict the occurrence of CV events (*2–7*).

More recently, it has been demonstrated that the regression of TOD, achieved through pharmacological treatment of blood pressure (BP) as well as by correcting concomitant risk factors, is paralleled by a similar decrease in CV risk. Thus, in

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Table 1. Clinical Characteristics of the Study Patients ($n=37$)

Variables	All	Patients without TOD	Patients with TOD	*p*
n	37	20	17	
Sex, % males	73	80	65	n.s.
Age, years	51±9	50±10	52±8	n.s.
Smoking habits, %	24	15	35	n.s.
Duration of disease, months	72 (84)	42 (105)	86 (76)	0.043
BMI, kg/m^2	27±4	26±4	28±4	n.s.
Systolic BP, mmHg	156±11	153±12	159±10	n.s.
Diastolic BP, mmHg	96±9	94±11	98±6	n.s.
Mean BP, mmHg	116±8	114±9	118±6	n.s.
24 h systolic BP, mmHg	144±16	134±11	155±14	<0.001
24 h diastolic BP, mmHg	89±9	85±8	93±8	<0.010
24 h mean BP, mmHg	107±11	101±8	114±10	<0.001
Uric acid, μmol/dL	324±90	330±90	324±84	n.s.
Creatinine, μmol/dL	79±18	79±18	79±18	n.s.
Creatinine clearance, mL/s	0.84±0.22	0.84±0.19	0.85±0.26	n.s.
Triglycerides, mmol/L	1.06 (0.52)	1.09 (0.51)	1.00 (0.52)	n.s.
Cholesterol, mmol/L	5.34±1.16	5.49±1.24	5.10±1.08	n.s.
HDL-cholesterol, mmol/L	1.24 (0.34)	1.24 (0.47)	1.23 (0.38)	n.s.
LDL-cholesterol, mmol/L	3.52±0.85	3.60±0.96	3.37±0.73	n.s.
Hs-CRP, mg/L	1.9 (2.2)	1.2 (1.9)	2.2 (1.4)	0.032
Plasma active renin, pmol/L	0.037 (0.063)	0.026 (0.011)	0.064 (0.082)	n.s.
Plasma Aldosterone, pmol/L	249 (260)	249 (89)	271 (285)	n.s.
Urinary Aldosterone, nmol/24 h	47±25	41±8	50±28	n.s.
Urine sodium, mEq/24 h	139±41	149±40	137±43	n.s.
Urine potassium, mEq/24 h	59±19	67±26	57±17	n.s.
ACR, mg/mmol	0.5 (3.6)	0.3 (0.3)	3.6 (5.6)	<0.001
Microalbuminuria, %	27	0	59	0.024
LVMI, g/m^2	102 (5)	96 (10)	131 (37)	<0.001
LVH, %	33	0	71	<0.010
TERalb, %	6.8 (2.4)	6.3 (2.3)	7.6 (2.3)	0.021

Data are mean±SD or percentage except for duration of disease, triglycerides, HDL-cholesterol, Hs-CRP, plasma active renin, aldosterone, ACR and LVMI, expressed as median (interquartile range). TOD, target organ damage; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; ACR, albumin-to-creatinine ratio; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; TERalb, transcapillary escape rate of albumin.

the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, regression of LVH was accompanied by a decrease in CV events (*8*). The same study showed that a reduction of albuminuria over time was related to similar changes in left ventricular mass (LVM) and greater CV protection (*9*).

The pathogenetic mechanisms underlying both the development and regression of TOD are likely to be multifactorial, with BP load playing a large, but not exclusive role. Other factors, such as atherosclerotic changes, subclinical inflammation, and genetic susceptibility are thought to contribute to the development of LVH and microalbuminuria. The systemic transcapillary escape rate, an expression of vascular permeability, has been shown to be an early marker of atherosclerotic changes and of organ damage (*10*).

With this in mind, we investigated the relationship between the occurrence of target organ damage and some of its potential determinants, such as the severity of hypertension and vascular permeability.

Methods

Subjects and Protocols

Between January 2000 and June 2002, all patients with primary hypertension attending the outpatient clinic of our institution were asked to participate in this study, which was part of a larger trial (MAGIC: Microalbuminuria: A Genoa Investigation on Complications). Details of the study have already been published (*11*). Among these patients, 37 (27 males and 10 females) agreed to participate. The study protocol was approved by the Ethical Committee of our Department, and

Table 2. Multiple Regression Linear Analysis of ACR and LVMI

Independent variables	Coefficient	SEM	Standard coefficient	*t*-value	*p*-value
Multiple regression linear analysis of ACR*					
Duration of disease, month	0.051	0.082	0.094	0.621	0.538
TERalb, %	7.276	3.422	0.326	2.127	0.042
24 h mean BP, mmHg	1.318	0.614	0.342	2.147	0.039
Multiple regression linear analysis of LVMI†					
BMI, kg/m^2	0.007	0.020	0.046	0.351	0.728
TERalb, %	0.098	0.045	0.281	2.168	0.038
24 h systolic BP, mmHg	0.038	0.009	0.945	4.263	<0.001
24 h diastolic BP, mmHg	−0.048	0.015	−0.656	−3.183	0.003

*Regression degrees of freedom=3, $F=5.064$, $p<0.006$, adjusted $r^2=0.26$. †Regression degrees of freedom=4, $F=9.617$, $p<0.0001$, adjusted $r^2=0.50$. ACR, albumin-to-creatinine ratio; TERalb, transcapillary escape rate of albumin; BP, blood pressure; LVMI, left ventricular mass index; BMI, body mass index.

written informed consent was obtained from each subject. Patients underwent a complete physical examination and routine biochemical blood and urine analyses. Twenty-four hour urine samples were obtained from each subject on the day prior to the study to assess dietary sodium intake and measure kaliuria and aldosteronuria. All patients were on a free, salt-unrestricted diet at the time of the study. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula (*12*). Creatinine clearance was estimated by the Cockcroft-Gault formula (*13*). Hypertension was defined as an average office BP ≥140/90 mmHg on at least three different occasions. Office BP was assessed by three consecutive readings and the average was recorded. Each patient also underwent 24-h ambulatory blood pressure recording (ABPM; Spacelabs 90207) (dabl®Educational Trust web-site: http://www.dableducational.org/). Non-dominant arm readings were taken with an appropriate-sized cuff and the device was set to obtain blood pressure readings every 15 min during the day time (7 AM to 11 PM) and every 30 min during the night-time (11 PM to 7 AM). The monitorings were taken into consideration only if valid readings made up no less than 80% of the expected readings. Body mass index (BMI) was calculated using the formula: BMI=weight (in kg)/height (in m) squared. Family history for hypertension and cardiovascular disease, the amount of physical activity, smoking habits, and alcohol consumption were assessed by means of a standardized questionnaire. Plasma active renin was measured by radioimmunoassay (Sanofi Diagnostic Pasteur, Milano, Italy). Plasma and urine aldosterone were measured by radioimmunoassay (Sorin Biomedica, Saluggia, Italy). The intra- and inter-assay variability for RAAS parameters was below 5% in our laboratory. High sensitivity C-reactive protein (Hs-CRP) was measured by a turbidimetric immunoassay (Beckman Coulter Inc., Fullerton, USA).

To assess the transcapillary escape rate of albumin (TERalb), free ^{125}I was eluted by passing the injection solution through a Sephadex G-25-M column (Column PD-10; Pharmacia, Uppsala, Sweden). ^{125}I-Labeled human serum albumin (6 to 8 μCi, SARI-125 A-2; SORIN Biomedica, Saluggia, Italy) was injected as a bolus after a 30-min rest in the supine position and blood was withdrawn from the contralateral arm at 5, 10, 15, 20, 25, 30, 40, 50, 55 and 60 min after the injection. The slope of the linear regression of radioactivity over time was used to calculate TERalb, expressed as the percentage decay of radioactivity per hour (%/h). As for TERalb, unpublished data from our laboratory indicate an intra-individual variability of 2.5% ($n=6$). TERalb measurements were accepted only if the coefficient of correlation between the time points for blood collection and the corresponding values of a specific radioactivity exceeded 0.90.

Target Organ Damage

Albuminuria

The presence of microalbuminuria was evaluated in each patient by measuring the albumin-to-creatinine ratio (ACR) in three nonconsecutive first morning urine samples. Urine albumin concentration was measured by a commercially available radioimmunoassay kit (Immunotech; Pantec, Torino, Italy), and the intra- and inter-assay variability of the method in our laboratory were 4.5% and 6.1%, respectively. Microalbuminuria was defined as ACR≥2.5 mg/mmol in men and ACR≥3.5 mg/mmol in women (*1*).

Echocardiography

All echocardiographic studies were performed using an Acuson Sequoia C-256 ultrasound machine (Acuson, Mountain View, USA). The overall, monodimensional left ventricular measurements and the bidimensional (apical four and two chamber) views were obtained according to the recommendations of the American Society of Echocardiography (*14*). All tracings were obtained and read by a single observer blinded to the clinical characteristics of the patients under observation. The presence of LVH was defined as left ventricular

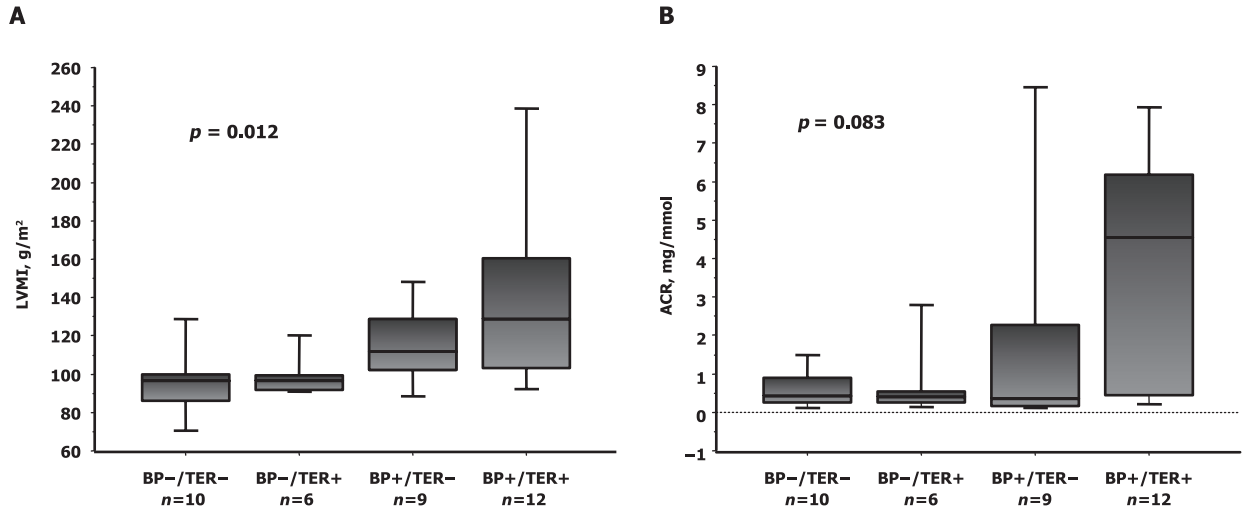

Fig. 1. *Association between cardiac (A) and renal (B) damage and the degree of hypertension and systemic vascular permeability in hypertensive patients. To provide more adequate information about data distribution, the results are presented as Box-and-Whisker plots. The central box includes the middle 50% of the data; the horizontal line inside the box represents the median. Vertical lines (whiskers) extend from each end of the box and cover the distance between the 10th and 90th percentiles. Patients were classified by 24 h BP and TERalb median values; TER−/+, systemic vascular permeability below/above or equal to the median; BP−/+, 24 h systolic and/or diastolic blood pressure below/above or equal to the median.*

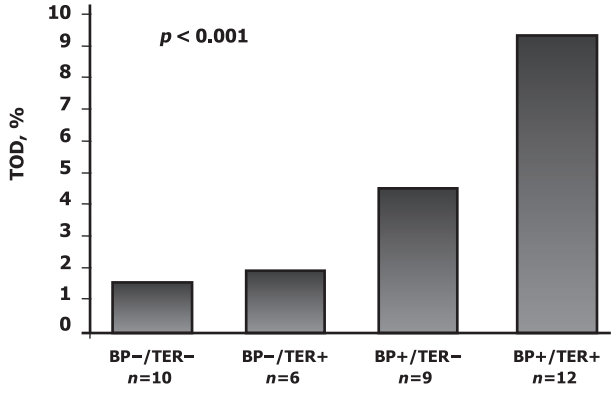

Fig. 2. *Prevalence of target organ damage on the basis of blood pressure load and vascular permeability in hypertensive patients. p for trend* <0.001, $\chi^2=17.4$. *TOD, target organ damage; TER−/+, systemic vascular permeability below/above or equal to the median; BP−/+, 24 h systolic and/or diastolic blood pressure below/above or equal to the median.*

mass index (LVMI)≥125 g/m^2 in males and ≥110 g/m^2 in females (*15*).

Statistical Analysis

Data are expressed as the means±SD, with the exception of skewed variables (*i.e.*, duration of disease, triglycerides, high-density lipoprotein [HDL]-cholesterol, Hs-CRP, plasma active renin and aldosterone, ACR, and LVMI), which are expressed as the median and interquartile range. Logarithmically transformed values of skewed variables were used for the statistical analysis. The degree of association between variables was assessed using Pearson's correlation coefficient (r). Comparisons between groups were made by analysis of variance. Comparisons of proportions among groups were made using the χ^2 test. Relative risk and 95% confidence intervals were calculated by exponentiation of logistic regression coefficients. The detectable alternative was calculated for all data to determine whether the sample size was sufficient to avoid type 2 error by setting the power at 80%, and whether it was sufficient to avoid type I error by setting α at 5% (*16*). Statistical analyses were performed using Statview for Windows (version 5.0.1; SAS Institute Inc., Cary, USA). Values of $p<0.05$ were considered statistically significant.

Results

The main clinical characteristics of our study patients (27 men, 10 women) are reported in Table 1. The overall prevalences of microalbuminuria and LVH were 27% and 33%, respectively. Patients with TOD (namely, microalbuminuria or LVH) showed longer duration and greater severity of hypertension as compared to those without TOD. Moreover, they had higher values of Hs-CRP, although our sample size was not powered to detect a difference in this parameter. There were no significant differences between the two groups with regards to all the other variables we examined, except for TERalb, which was significantly higher in patients with

Table 3. Multiple Logistic Regression Analysis

Independent variables	Relative risk	95% confindece interval	*p* value
TERalb (being >6.95%)	10.33	1.05–101.84	0.045
24 h systolic BP (per 10 mmHg increase)	5.81	1.59–20.10	0.008

Dependent variable: presence of at least one sign of organ damage. Also in the model: known duration of hypertension and high sensitivity C-reactive protein not significantly related to the presence of target organ damage; $r^2=0.56$. TERalb, transcapillary escape rate of albumin; BP, blood pressure.

microalbuminuria or LVH than it was in patients without signs of organ damage, thus indicating an abnormal increase in vascular permeability (Table 1).

Univariate analysis showed that the degree of organ damage, namely ACR and LVMI, was directly related to TERalb ($r=0.43$, $p<0.009$ and $r=0.35$, $p=0.035$, respectively), 24-h systolic BP values ($r=0.60$, $p<0.001$; $r=0.61$, $p<0.001$), and 24-h mean BP values ($r=0.44$, $p=0.006$; $r=0.48$, $p=0.003$). Multiple regression analysis revealed that vascular permeability and BP load independently influenced variations in ACR ($r^2=0.50$, $p<0.001$) and LVMI ($r^2=0.26$, $p<0.010$) (Table 2).

The study group was divided on the basis of median 24-h BP values (*i.e.*, systolic BP 144 mmHg; diastolic BP 89 mmHg) and TERalb (*i.e.*, 6.95%). The sub-division into four groups was as follows: BP−/TER−, BP−/TER+, BP+/TER−, BP+/TER+, where BP−/+ indicates patients with 24-h systolic and/or diastolic blood pressure below/above or equal to the median, and TER−/+ indicates patients with systemic vascular permeability below/above or equal to the median. Based on this classification, LVMI increased across all categories (Fig. 1A, $p=0.012$). The correlation between the severity of BP and TERalb and ACR values, even in the presence of a positive linear trend, did not reach statistical significance (Fig. 1B). Moreover, the prevalence of TOD increased significantly across all categories (Fig. 2, $\chi^2=17.4$; $p<0.001$). Interestingly, there were no significant differences in BP levels within the BP− categories or within BP+ categories.

Patients with TERalb above the median showed a ten-fold greater risk of developing microalbuminuria and/or LVH, regardless of the severity of hypertension. Furthermore, each 10 mmHg increase in 24-h BP values was associated with a more than five-fold risk of having at least one TOD, regardless of TERalb values (Table 3).

Discussion

Our data demonstrate that in addition to BP load, vascular permeability is also associated with the occurrence of subclinical cardio-renal damage in primary hypertension (Table 1, Fig. 1). Furthermore, we found that the simultaneous occurrence of increased BP load and TERalb constitutes a greater risk of having TOD (Fig. 2).

The impact of BP values on the presence of cardio-renal damage has been consistently demonstrated, especially by using 24-h ambulatory BP monitoring. It has clearly been shown that both the degree of BP load as well as abnormalities in circadian BP profiles are associated with LVH and increased urinary albumin excretion (UAE) (*17–19*). Accordingly, a recent report by Cuspidi *et al*. indicates that long-term, strict 24-h BP control is able to reverse hypertension-induced structural and functional alterations at the cardiac and renal level (*20*). These observations are in keeping with the linear and independent correlation between BP levels and the severity of organ damage, namely LVH and microalbuminuria, that we observed in our study (Tables 2 and 3, Figs. 1 and 2).

Nevertheless, there is also evidence that the development of sub-clinical TOD arises from a mosaic of mechanisms and is not merely a reflection of BP load in hypertensive patients. In the Framingham Study, systolic BP levels accounted for less than 8% of the variations in LVH over 30 years follow-up (*21*), and other authors showed that LVH and increased albuminuria are not attributable to pressure overload alone (*22*, *23*). Although our study could not definitively establish a causal relationship between the observed findings because of its cross-sectional design, it does support the view that hypertensive TOD is a multifactorial process resulting from an interaction between hemodynamic factors and endothelial activation (*24*).

Indeed, we observed that the higher the degree of UAE and LVMI, the greater the transvascular escape of albumin (see Results and Figs. 1 and 2). Moreover, we found no correlation between BP components and TERalb values (data not shown). Thus, our data support the hypothesis that increased vascular permeability, an early marker of atherosclerotic changes, may contribute *per se* to the development of organ damage (*25*). Our results are in agreement with some previous studies that showed associations between albuminuria and TERalb in diabetic patients (*26*, *27*). Other studies, however, did not show a significant, positive relationship between TERalb and signs of organ damage (*9*, *28*).

Several other factors may have an impact on the development of TOD (*29–31*). Our study, however, does not confirm that RAAS activity increases in association with microalbuminuria and LVH, at least at the systemic level (Table 1). Similarly, while dyslipidemia has been implicated in the pathogenesis of LVH (*32*), we did not observe any significant differences in lipid profiles among our patients with and with-

out TOD. While our hypertensive patients with cardiorenal damage showed signs of inflammation (Table 1), these findings must be considered somewhat tentative, since our sample size was not powered to detect a difference in this parameter.

Due to the cross-sectional design of our study and the relatively low number of patients, our findings should be taken as "hypothesis generating." However, they may have useful, clinical implications and could provide a rationale for the choice of treatment in hypertensive patients. Indeed, some antihypertensive drugs have been shown to modify vascular permeability irrespective of their BP-lowering effects.

In summary, our data suggest that the occurrence of microalbuminuria and LVH in hypertensives may not be solely due to increased hemodynamic load, but likely reflects a more complex, multifactorial process which includes increased vascular permeability and therefore atherosclerotic changes. Further studies to clarify the pathogenetic mechanisms underlying the development and/or the regression of TOD might prove useful for the development of more effective therapeutic strategies.

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