

Original Paper

# Intrarenal Vascular Resistance is Associated With a Prothrombotic State in Hypertensive Patients

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## Key Words

Hypertensive nephroangiosclerosis • Renal ultrasound • Fibrinogen • D-dimer • Prothrombotic state

## Abstract

**Background/Aims:** Hypertensive nephroangiosclerosis is associated with progressive increase of intrarenal vascular resistance. In addition to blood pressure, other factors can contribute to hypertensive renal damage including a prothrombotic state. We investigated the relationship between hemostatic markers and intrarenal vascular resistance in hypertension. **Methods:** In 115 untreated, nondiabetic, hypertensive subjects free of cardiovascular complications and advanced renal function impairment, we measured 24-hour creatinine clearance (GFR) and urinary albumin excretion (UAE), fasting plasma glucose, HOMA-index, and plasma levels of fibrinogen, D-dimer, prothrombin fragment 1+2, plasminogen activator inhibitor-1, homocysteine, and lipoprotein(a). In all patients, measurement of intrarenal resistance was obtained by renal Doppler ultrasound with calculation of the renal resistance index (RI). **Results:** Patients in the highest tertile of RI were older and had greater body mass index, pulse pressure, fibrinogen, and D-dimer levels and lower GFR than patients in the lowest RI tertile. RI was directly correlated with age, pulse pressure, HOMA-index, UAE, D-dimer, and inversely with GFR. On multivariate analysis, RRI was independently associated with age, GFR, and plasma D-dimer. **Conclusions:** A prothrombotic state is associated with increased intrarenal vascular resistance in nondiabetic hypertensive patients and might contribute to the early stages of hypertensive renal disease.

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## Introduction

Hypertensive nephroangiosclerosis is a common cause of end-stage renal failure and is associated with an increased risk of cardiovascular events [1]. This condition is characterized by narrowing of preglomerular arteries that is due to intimal thickening and hyalinosis of the vascular wall and is associated with progressive increase of intrarenal vascular resistance [2]. The structural changes of preglomerular vessels can cause glomerular ischemia thereby leading to progressive decline of glomerular filtration. In addition to high blood pressure, other conditions might concur to facilitate progression of intrarenal vascular damage including aging, race, male sex, smoking, plasma lipids and uric acid levels, proteinuria, and insulin resistance [3-5]. The extent of intrarenal vascular damage can be reliably assessed noninvasively by use of renal duplex Doppler ultrasound with measurement of the intrarenal resistance index (RI) [6, 7].

Additional cardiovascular risk factors beyond those traditionally identified in epidemiologic studies are possibly involved in the occurrence of hypertensive complications and are commonly referred to as “emergent” [8]. Among these emergent risk factors, a prothrombotic state has been repeatedly called into play [9]. In hypertension, an activated hemostatic system has been reported in association with cardiovascular events [10], functional changes of the left ventricle [11], thickening of the carotid artery intima-media [12], and impaired renal function [13]. We hypothesized that a prothrombotic state might contribute to the hypertension-related intrarenal vascular damage. Therefore, this study was designed to investigate the relationship of intrarenal RI with hemostasis markers in nondiabetic hypertensive patients free of cardiovascular complications.

## Patients and Methods

### *Patients*

One-hundred-fifteen patients with grade 1-2 essential hypertension who were consecutively referred to the Hypertension Clinic of our University were included in a cross-sectional study. The patients seen at our clinic are white, include individuals with all grades of hypertension who live in northeast Italy, and are representative of hypertensive patients in this geographical area [14]. Blood pressure was measured with an automated device (Omron M6, OMRON Healthcare Co., Kyoto, Japan) after each subject had been supine for 15 min and the average of 3 readings was recorded. Diagnosis of hypertension was established in all patients according to current guidelines [15].

Patients younger of 18 years and older than 80 years and pregnant women were excluded, together with patients with diabetes, secondary hypertension, body mass index (BMI) of more than 35 kg/m<sup>2</sup>, 24-hour creatinine clearance (GFR) of less than 30 ml/min/1.73 m<sup>2</sup>, use of drugs that could interfere with the hemostatic system, and history of acute illness, stroke, transitory ischemic attack, ischemic heart, cardiac valve, or other types of heart and peripheral artery disease. Diabetes was excluded by measurement of fasting blood glucose, glycosylated hemoglobin, and standard oral glucose test [16]. Secondary forms of hypertension were excluded after extensive clinical and laboratory investigations that included duplicate measurements of GFR, plasma active renin and aldosterone, urinary cortisol and catecholamines, and renal ultrasound examination [17]. Renal angio MRI/CT-scan and additional functional tests were performed when appropriate [18]. Cardiovascular complications were identified for exclusion by analysis of medical records, physical examination, ECG, echocardiography, and ultrasound examination of aorta, carotid, iliac, and femoral arteries. Additional evaluations included exercise testing, myocardial scintigraphy, and angiography and were done when indicated [14].

Sixty-two (54%) of 115 patients had never been treated with antihypertensive drugs. The remaining 53 patients (46%) were treated with calcium-channel blockers (33%), angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (18%), beta-blockers (13%), diuretics (11%), and alpha-blockers (5%). In all patients, antihypertensive drugs were washed-out for a minimum of 2 weeks before the study. All patients were closely monitored during the wash-out period and in those with blood pressure persistently higher than 180/110 mm Hg alpha-blockers and/or calcium-channel blockers were given. No patients were treated with lipid-lowering, anticoagulant, or anti-platelet drugs. Before evaluation, patients ate a standard diet to keep a sodium intake of 100-150 mmol/day that was checked with measurement

of sodium excretion in 24-hour urine collections. Patients were defined as smokers if they had smoked for at least 5 years and up to 1 year before the study and smoking habit was quantified by the average number of cigarettes/day. Alcohol intake was estimated by a questionnaire [19] as grams/day. The study was performed in accordance with the principles of the Declaration of Helsinki and received approval from the local Institutional Review Board. Informed consent was obtained from all patients.

#### *Renal function studies and renal imaging*

Renal function studies included assessment of GFR by duplicate collections of 24-hour creatinine clearance and 24-hour urinary albumin excretion (UAE). Ultrasound examination by a duplex Doppler apparatus was performed after a 12 hour fasting, as described previously [20]. All measurements were obtained by experienced operators and tracings were examined by an experienced reader who was blinded to any clinical information of the patients. Doppler scans were performed using a 3.5 MHz convex phased-array probe and color Doppler mapping in order to identify the renal arteries. Measurements were collected with patients in lateral decubitus position through the flank, using the liver as an acoustic window whenever possible. The Doppler angle was always lower than 60° and as close as possible to 0°; specific care was taken not to compress the kidney. Peak systolic velocity [Vmax (cm/sec)] and end diastolic velocity [Vmin (cm/sec)] were obtained for the calculation of RI (Vmax-Vmin/Vmax) [6]. This parameter was calculated from Doppler measurements obtained by placing the sample volume at the level of the color signals visualized on the interlobar arteries, along the edge of medullary pyramids. The average of 4 to 6 homogeneous measurements from the upper, middle, and lower third of both kidneys was considered. The intraobserver and interobserver coefficient of variability for IR were 6.6% and 8.3%, respectively.

#### *Laboratory measurements*

A sample of venous blood was obtained from each patient in the sitting position in the morning after an overnight fast and without venous stasis. Blood was collected into silicone-treated glass tubes and plasma was separated and frozen at -80 °C until assayed. Plasma fibrinogen, D-dimer, prothrombin fragment 1+2 (F1+2), and plasminogen-activator inhibitor-1 (PAI-1) were determined as reported previously [14, 18]. Briefly, plasma fibrinogen was measured by a functional assay in an automatic coagulometer autoanalyzer (intra-assay and inter-assay coefficient of variation: 5.1 and 6.8%, respectively); fibrin D-dimer was measured immunoenzymatically (intra-assay and inter-assay coefficient of variation: 5.3 and 7.1%, respectively); F1+2 plasma levels were evaluated by ELISA (intra-assay and inter-assay coefficient of variation: 5.5 and 11.2%, respectively); PAI-1 was assayed by enzyme immunoassay (intra-assay and inter-assay coefficient of variation: 4.6 and 6.8%, respectively). Plasma homocysteine was determined by a nephelometric method (intra-assay and inter-assay coefficient of variation: 7.0 and 8.2%, respectively) [21] and plasma concentration of lipoprotein(a) by the Macra® Lp(a) enzyme linked immunosorbent assay kit (intra-assay and inter-assay coefficient of variation: from 2 to 7% and from 6 to 9%, respectively) [18]. All measurements were done in duplicate.

#### *Statistical analysis*

Values are expressed as mean ± standard deviation for normally distributed variables, with median and interquartile range used for variables with skewed distributions. Normality of distribution was assessed with the Kolmogorov-Smirnov test, and variables with skewed distribution were analyzed after logarithmic transformation. The Student's t test was used for comparison between two independent groups and analysis of variance for comparison among more than two groups with Bonferroni correction. The Pearson  $\chi^2$  test was used to compare categorical variables. Relationships between continuously distributed variables were examined by linear regression analysis and the correlation was expressed by the Pearson's correlation coefficient. Multivariate linear regression analysis was performed to identify which variables were independently associated with RI. Two-tailed probability value of less than 5% was considered to indicate statistical significance. All data analyses were performed using Stata 9.2 (StataCorp LP, TX, USA).

## **Results**

One-hundred-fifteen hypertensive patients (age 46±13 years; 63 men, 52 women; 62 treatment-naïve) were enrolled. Clinical characteristics of the study patients are summarized in Table 1, where patients are also grouped according to tertiles of renal RI. Patients in the

**Table 1.** Clinical characteristics of hypertensive patients who were grouped according to tertiles of intrarenal resistance index (RI)

Characteristics	All patients (n=115)	Tertile I (n=39)	Tertile II (n=39)	Tertile III (n=37)	P
Age, years	46±13	43±13	44±9	53±15	<0.001
Males, n (%)	63 (55)	26 (65)	21 (55)	16 (43)	0.159
Body mass index, kg/m <sup>2</sup>	28.0±5.1	27.5±3.9	26.7±4.4	29.8±6.4	0.026
Waist circumference, cm	94±14	95±10	92±15	96±16	0.443
Heart rate, bpm	72±12	72±11	74±13	69±11	0.280
Systolic blood pressure, mm Hg	153±17	152±18	153±16	156±16	0.516
Diastolic blood pressure, mm Hg	97±10	98±11	97±9	96±10	0.212
Pulse pressure, mm Hg	57±15	54±15	53±14	63±15	0.005
Duration of hypertension, years	5±6	4±6	5±5	6±7	0.571
Smokers, n (%)	27 (23)	7 (17)	13 (34)	7 (19)	0.160
Alcohol intake, g/d	10±23	7±18	17±32	6±14	0.097
Antihypertensive treatment, n (%)	53 (46)	15 (37)	18 (47)	20 (54)	0.340
Calcium-channel blockers, n (%)	38 (33)	12 (30)	13 (34)	13 (35)	0.876
ACEi / ARB, n (%)	21 (18)	6 (15)	7 (18)	8 (22)	0.754
Beta-blockers, n (%)	15 (13)	4 (10)	5 (13)	6 (16)	0.721
Diuretics, n (%)	13 (11)	3 (8)	3 (8)	7 (19)	0.051
Alpha-blockers, n (%)	6 (5)	2 (5)	2 (5)	2 (5)	0.997

Values are expressed as mean ± SD. Comparisons were done by analysis of variance. Pearson's chi-square test was used to compare frequency distributions. ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers.

highest tertile of RI were significantly older, had greater BMI and pulse pressure, but no significant difference in sex distribution, duration of hypertension, smoking habits, daily alcohol consumption, and frequency of use of different classes of antihypertensive drugs.

As shown in Table 2 and as expected, increasing intrarenal RI was associated with progressive decline in GFR, whereas no association was observed with UAE, mostly because microalbuminuria (UAE >30 mg/d) was detected in only 19 (16%) of 115 patients and overt proteinuria (UAE>300 mg/d) in only 6 (5%). Plasma glucose, lipids and uric acid levels, and HOMA-index were comparable across RI tertiles. Both C-reactive protein and lipoprotein(a) had a nonsignificant trend to increase with increasing RI, but plasma homocysteine did not change. Plasma fibrinogen and D-dimer levels increased progressively with increasing RI (Figure 1), whereas F1+2 and PAI-1 were comparable in patients with different RI.

Univariate correlation analysis indicated that intrarenal RI was significantly and directly related to age ( $r=0.413$ ,  $P<0.001$ ), systolic blood pressure ( $r=0.188$ ,  $P=0.044$ ), pulse pressure ( $r=0.376$ ,  $P<0.001$ ), HOMA-index ( $r=0.219$ ,  $P=0.024$ ), UAE ( $r=0.195$ ,  $P=0.038$ ) and log D-dimer ( $r=0.313$ ,  $P=0.001$ ; Figure 2), and inversely related to GFR ( $r=-0.326$ ,  $P<0.001$ ). D-dimer levels were significantly higher in women than in men ( $P=0.024$ ) and log transformed values were directly correlated with age ( $r=0.305$ ,  $P=0.002$ ), UAE ( $r=0.256$ ,  $P=0.006$ ) and log fibrinogen levels ( $r=0.256$ ,  $P=0.006$ ). Multivariate regression analysis was performed including variables that were correlated with RI on univariate analysis, with the addition of sex, BMI, and log fibrinogen as independent variables. This analysis showed that intrarenal RI was independently associated with pulse pressure, GFR, and log D-dimer values (Table 3).

## Discussion

In addition to the level of blood pressure, many factors facilitate progression of intrarenal arteriolar damage in hypertensive patients. This type of arteriolar damage is a hallmark of the hypertensive kidney and can be investigated noninvasively by measurement of intrarenal RI [6, 7]. We have investigated the role of the hemostatic system in a large group of nondiabetic, hypertensive patients free of cardiovascular complications and advanced renal failure. In these patients, we have found that both plasma fibrinogen and

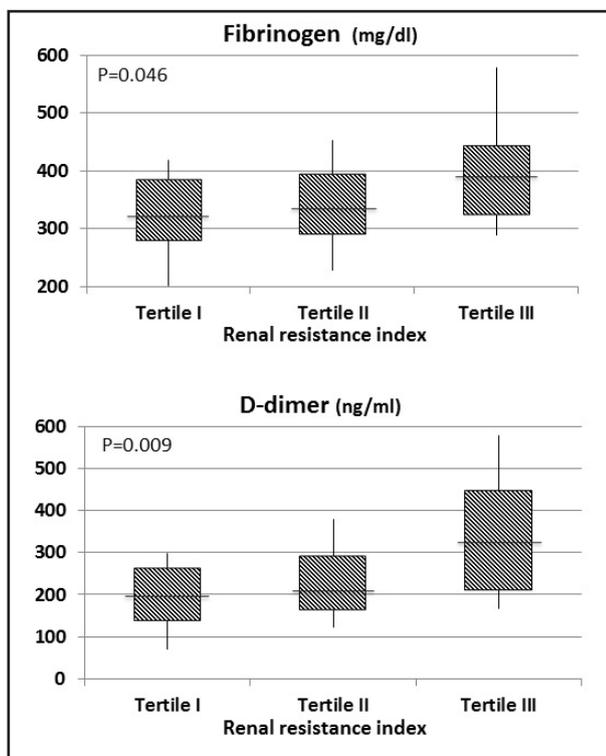
**Table 2.** General biochemistries, hemostatic, and renal function variables of hypertensive patients who were grouped according to tertiles of intrarenal resistance index (RI)

Variable	All patients (n=115)	Tertile I (n=39)	Tertile II (n=39)	Tertile III (n=37)	P
<i>General biochemistries</i>					
Glucose, mg/dl	90±14	90±15	90±12	90±17	0.982
HOMA-index	1.60 [0.85-2.77]	1.17 [0.77-2.63]	1.84 [1.26-2.85]	1.58 [0.97-2.66]	0.331
Triglycerides, mg/dl	113±61	116±64	115±65	108±54	0.822
Total cholesterol, mg/dl	199±42	196±45	200±45	201±38	0.900
HDL-cholesterol, mg/dl	57±19	54±14	59±19	59±22	0.171
LDL-cholesterol, mg/dl	119±39	121±39	115±43	120±35	0.739
Uric acid, mg/dl	5.2±1.2	5.3±1.2	5.2±0.8	4.9±1.4	0.429
C-reactive protein, mg/l	1.52 [0.82-2.83]	1.16 [0.73-2.52]	1.25 [0.75-2.74]	1.82 [1.00-3.08]	0.093
Lipoprotein(a), mg/dl	13.2 [5.8-25.2]	12.7 [3.3-23.9]	14.1 [7.0-26.8]	14.7 [10.3-24.5]	0.074
Homocysteine, μMol/l	12.5 [10.2-15.1]	12.6 [10.4-15.8]	12.5 [9.6-14.1]	12.0 [10.3-15.6]	0.406
<i>Hemostatic variables</i>					
Fibrinogen, mg/dl	348 [308-419]	335 [281-385]	341 [290-395]	389 [325-445]	0.046
D-dimer, ng/ml	230 [151-339]	196 [140-263]	208 [163-293]	321 [210-450]	0.009
F1+2, pmol/l	159 [130-228]	167 [138-231]	138 [118-189]	162 [137-232]	0.614
PAI-1, ng/ml	7.6 [4.4-14.7]	7.0 [4.2-10.3]	9.0 [4.4-19.8]	7.6 [5.2-15.1]	0.423
<i>Renal function</i>					
Creatinine, mg/dl	0.95±0.25	0.94±0.18	0.95±0.25	0.95±0.32	0.989
GFR, ml/min/1.73 m <sup>2</sup>	101±28	110±26	101±31	90±23 <sup>  </sup>	0.008
UAE, mg/day	91 [69-121]	93 [64-116]	78 [56-130]	100 [76-119]	0.194
Resistance index	0.60±0.05	0.55±0.03	0.60±0.01	0.66±0.04	<0.001

Values are expressed as mean ± SD. Median and interquartile range in square brackets are shown for variables with skewed distribution. Comparisons were done by analysis of variance. Pearson's chi-square test was used to compare frequency distributions. HOMA, homeostatic model assessment; F1+2, prothrombin fragment 1+2; PAI-1, plasminogen activator inhibitor-1; GFR, 24-hour creatinine clearance; UAE, 24-hour urinary albumin excretion.

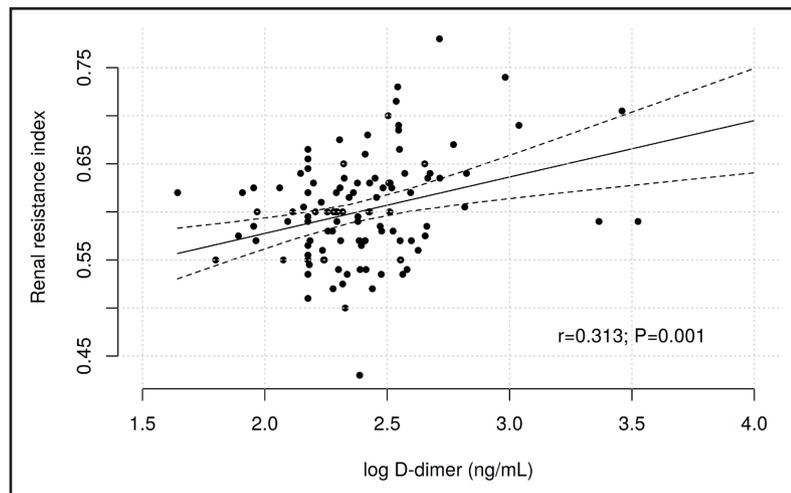
D-dimer levels increase significantly with increasing renal RI. Moreover, fibrin D-dimer is associated with intrarenal RI independently of age, sex, blood pressure, renal function, and insulin sensitivity, suggesting that a prothrombotic state might contribute to the increased resistance of intrarenal vessels.

Fibrin D-dimer is the major breakdown fragment of fibrin and a reliable marker of an existing thrombophilia [22]. Measurement of D-dimer, in fact, provides an estimation of the overall state of activation of the coagulation system. Prospective studies have demonstrated that D-dimer levels are independently associated with the risk of stroke [23], myocardial infarction [24], and peripheral artery disease [25]. Fibrinogen is also a major independent risk factor for cerebrovascular, coronary artery, and peripheral artery disease [26, 27]. A combined increase of fibrinogen and D-dimer levels therefore indicates the existence of a prothrombotic state that might have a role in the development and progression of vascular damage. This role seems to



**Fig. 1.** Box and whiskers plot of plasma fibrinogen (top panel) and D-dimer (bottom panel) levels in hypertensive patients who were grouped according to tertiles of renal resistance index.

**Fig. 2.** Relationship between log D-dimer and intrarenal resistance index in 115 hypertensive patients.



**Table 3.** Multivariate regression analysis with renal resistance index (RI) as the dependent variable

Variable	$\beta$	P
Age	0.195	0.052
Sex	-0.154	0.065
Body mass index	0.012	0.908
Pulse pressure	0.192	0.037
GFR	-0.297	0.001
UAE	0.089	0.296
Log HOMA-index	0.108	0.293
Log Fibrinogen	-0.042	0.640
Log D-dimer	0.218	0.017

GFR, 24-hour creatinine clearance; UAE, 24-hour urinary albumin excretion; HOMA, homeostatic model assessment.

have specific relevance in patients with hypertension [8] in whom it was reported that elevated levels of fibrin D-dimer and fibrinogen are associated with activation of the renin-angiotensin system [14] and increased cardiovascular morbidity [9, 10]. In hypertension, a prothrombotic state was also associated with evidence of subclinical organ damage, including left ventricular diastolic dysfunction [11] and carotid intima-media thickening [12]. The present study is the first to report the association of a prothrombotic state with increased intrarenal vascular resistance suggesting its possible contribution to the early stages of hypertensive renal damage.

The technique of renal duplex Doppler ultrasonography has been used to evaluate renal blood flow in disease states such as main renal artery stenosis and other diseases involving the intrarenal vascular compartment, such as diabetes [28], primary aldosteronism [20], and essential hypertension [6, 7, 29]. Distal velocimetric indices obtained with this technique reliably assess intrarenal hemodynamics [6, 30]. How much different intrarenal vascular beds contribute to increased RI in hypertension is not known, although it is likely that the velocimetric indices better explore the preglomerular hemodynamics. Consistent with previous studies [7] this study reports a highly significant inverse relationship between renal RI and GFR, whereas no association of RI with urinary albumin losses was observed. This might be explained by the very low prevalence of microalbuminuria (16%) and overt proteinuria (5%) observed in our hypertensive patients most likely due to exclusion of patients with advanced impairment of renal function.

It must be noticed also that increased levels of D-dimer and fibrinogen were reported in hypertensive patients with early impairment of renal function [13]. This might suggest the possibility that the association between increased intrarenal RI and prothrombotic factors might be just the consequence of the inverse relationship of RI with GFR. However, this should not be the case because in our multivariate regression model the relationship of D-dimer with RI remained significant even after correction for GFR supporting the possibility of a direct contribution of the prothrombotic state to intrarenal arterial damage.

Limitations of this study should be highlighted. First, the cross-sectional design does not permit to establish evidence of a causal relationship between the prothrombotic state and increased intrarenal resistance, although the strength and independence of association would suggest so. Second, inclusion in the study of a significant proportion of patients who were not treatment-naïve might have introduced, despite a relatively long wash-out of antihypertensive drugs, a possible confounder affecting both hemostatic markers and

intrarenal resistance. Relevant to this point is that no significant differences in frequency of use and different classes of antihypertensive drugs were observed in patients with different intrarenal resistance index (Table 1). The strengths of this study include its size and the ability to control for major determinants of intrarenal vascular resistance after exclusion of patients with potential confounders including diabetes and advanced impairment of renal function.

## Conclusion

This study demonstrates that activation of the hemostatic system is independently associated with higher intrarenal renal resistance in nondiabetic hypertensive patients free of cardiovascular complications and advanced impairment of renal function. This suggests that a prothrombotic state might play a role in the early stages of hypertensive renal disease. These findings might have clinical relevance inasmuch as measurement of hemostatic markers could be useful for identification of hypertensive patients who have developed or will likely develop hypertensive renal damage. Appropriately designed studies will be needed to test the possible benefits of pharmacological interventions on the hemostatic system for renal outcomes of hypertensive patients.

## Disclosure Statement

The authors have no conflict of interest to disclose.

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