ORIGINAL RESEARCH

Hypertension and hemostatic/fibrinolytic balance disorders

Tabak O¹

Gelisgen R²

Uzun H²

Kalender B³

Balci H⁴

Curgunlu A⁵

Simsek G⁶

Karter Y⁵

¹ Department of Internal Medicine, Istanbul Education and Research Hospital, Istanbul, Turkey

² Department of Biochemistry, ⁴Central Research Laboratory, ⁵Department of Internal Medicine, ⁶Department of Physiology, Medical Faculty of Cerrahpasa, University of Istanbul, Istanbul, Turkey

³ Department of Internal Medicine, Medical Faculty, University of Kocaeli, Kocaeli, Turkey

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Abstract

Background: Hypertension is one of the principal risk factors for cardiovascular disease. We aimed to evaluate the impact of hypertension on fibrinolytic balance and endothelial function by measuring plasma levels of plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA), tPA/PAI-1 complex and fibrinogen.

Methods: Patients enrolled into the study were divided into four groups: 22 essential hypertensive (EH), 22 white coat hypertensive (WCH), 22 renovascular hypertensive (RH) and 22 normotensive control subjects. Plasma PAI-1, tPA, tPA/PAI-1 complex levels were measured by enzyme linked immunosorbent assays.

Results: There was no difference in the systolic and diastolic blood pressure measurements of the EH and RH groups. The four groups were comparable for age, gender, smoking habits and BMI. Patients with EH, RH and WCH had increased plasma levels of PAI-1, tPA, tPA/PAI-1 complex and fibrinogen compared with controls. No fibrinolytic parameter was associated with blood pressure in hypertensive subjects.

Conclusion: This prospective study showed that fibrinolytic markers such as PAI-1, tPA, tPA/PAI-1 complex are independently associated with the development of hypertension. This supports the hypothesis that disturbances in fibrinolysis precede a cardiovascular event. Therefore, hypertension may be associated with impaired fibrinolysis.

Despite evidence for the importance of reducing blood pressure (BP), hypertension continues to be one of the most frequent diseases in humans.¹ Hypertension is recognized as one of the principal risk factors for cardiovascular disease. Impaired fibrinolysis may be associated with hypertension.²

White coat hypertension (WCH), isolated clinic hypertension, is defined as the observation of blood pressure (BP) levels $\geq 140/90$ mmHg in several visits to the clinic, while 24-hr ambulatory blood pressure monitoring (ABPM) levels are $< 125/80$ mmHg.³ In-

patients with clinic hypertension, the prevalence of WCH varies from 15% to 35%.⁴

Renovascular hypertension is the most common cause of secondary hypertension. It accounts for about 3% or less of hypertensive patients. The etiology includes fibromuscular dysplasia and atherosclerosis of the renal artery. Renovascular hypertension is caused by stenosis of the main renal artery or one of its major branches.⁵

Plasminogen activators (PA) are serine proteases that convert inactive plasminogen into active plasmin, another serine protease. PAs exist in 2 forms, tissue-type PA (tPA) and urokinase-type PA (uPA). In humans, the gene for tPA is located on chromosome 8. tPA is primarily involved in fibrinolysis while uPA mediates tissue remodeling, tumour cell invasion and metastasis. Both tPA and uPA can be inhibited by 2 different serpin inhibitors, plasminogen activator inhibitor type 1 (PAI-1) and type 2 (PAI-2).⁶ All also promotes coagulation by inhibiting the fibrinolytic system by inducing PAI-1 in the vasculature.⁷ Circulating tPA derives exclusively from vascular endothelial cells, but PAI-1 is secreted from a variety of sources in different individuals, such as vascular smooth muscle cells or macrophages, monocytes, hepatocytes or adipocytes.⁸⁻¹⁰

Essential arterial hypertension often predisposes patients to a prothrombotic state and increased risk of vascular and organ complications. Genetic factors, renin-angiotensin system and disorders of lipid metabolism play a vital role in the regulation of hemostatic processes. Primary genetic factors involved are 4G/5G polymorphism of promoter region coding tissue plasminogen activator inhibitor-1 (PAI-1) and I/D polymorphism for angiotensin converting enzyme (ACE) gene.¹¹

We hypothesized that impaired fibrinolysis (tPA, PAI-1 and tPA/PAI-1 complex) was involved in sustained, white coat, renovascular hypertensives.

Methods

The protocol was approved by the Istanbul University, Cerrahpasa Medicine Faculty Ethics Committee and was carried out according to the requirements of the Declaration of Helsinki. All patients were fully informed of the study procedures before they gave their consent.

Study population

The study was performed in Turkish patients who attended to the hypertension clinic of Istanbul University, Cerrahpasa Medicine Faculty. Three groups of hypertensive and one control group of normotensive patients were included. Twenty two essential hypertensive subjects (EH) (M/F: 4/18) aged 51.6 ± 10 yr, 22 white coat hypertensive (WCH) subjects (M/F: 4/18) aged 51.4 ± 10 yr, 22 renovascular hypertensive (RH) subjects (M/F: 7/15) aged 55.5 ± 12 yr and 22 normotensive control subjects (M/F: 4/18) aged 49.6 ± 8 yr.

Subjects in the sustained hypertensive group were referred directly from general practitioners to obtain a thorough evaluation before the start of medical therapy. Subjects with diastolic blood pressure >90 mmHg were referred to our outpatient clinic and patients whose ambulatory daytime diastolic pressure >85 mmHg were enrolled in EH group, and cases with clinical diastolic pressure >90 and ambulatory daytime arterial pressure $< 135/85$ mmHg in the WCH group. Renovascular hypertension was determined by arteriography. Healthy subjects in the same age range as the hypertensive groups were selected as controls. Most subjects in the same age range entered the database by random selection of employees in the hospital. The normotensive group consisted of subjects with diastolic pressure < 90 mmHg measured by a nurse in the clinic.

Subjects with other risk factors for atherosclerosis (LDL >130 mg, diabetes mellitus, BMI >27 , smoking), and subjects having signs or symptoms of atherosclerotic vascular disease and other endocrine diseases or

alcoholism were excluded as were patients using drugs that may affect blood pressure and lipid metabolism, and antioxidant substances. Vascular disease, malignancy and connective tissue diseases were not evident on thorough evaluation.

Blood pressure measurements

Measurements of brachial artery pressures in the patients referred to our outpatient clinic because of high blood pressure (diastolic pressure >90 mmHg) were obtained with a mercury sphygmomanometer, which was standardized in accordance with the approval of American and British Hypertension Society and World Health Organization. Measurements were obtained with the subject in the sitting position after resting for 20–30 min.¹² Korotkoff phase I was used to determine the systolic pressure and phase V for diastolic pressure. Measurements were performed on three different days within 5 days. The average of three measurements was taken as the mean systolic and diastolic pressures. Ambulatory 24-h arterial blood pressure recording was performed in patients whose diastolic pressure was > 90 mmHg in the out-

patient department, with an instrument (A and D Engineering, TM-2421), approved and suggested by the European Society of Hypertension.¹³ Measurements were performed, as suggested by the British Society of Hypertension, on the left arm.¹⁴ According to ambulatory BP measurement, patients were classified into white coat or sustained hypertension groups. WCH was defined as clinical hypertension and daytime ambulatory blood pressure < 135/85 mmHg. Patients with daytime ambulatory diastolic blood pressure > 85 mmHg were included in the hypertensive group (Table 1).

Sample collection and measurements

Venous blood samples were drawn into chilled polypropylene tubes dry and containing onetenth volume of 0.1 M sodium citrate without venous stasis after 12 hr overnight fasting. After centrifugation at 2500 x g for 5 min, plasma was removed and, for erythrocyte lysate preparation, erythrocytes were washed 3 times in 5 ml. saline, hemolyzed by diluting fourfold with water and plasma was stored at –80°C, until bio-

TABLE 1. Demographic characteristics, ambulatory blood pressures and biochemical parameters.

	NT (n=22)	WCH (n=22)	EH (n=22)	RH (n=22)
Age (Yr)	49.48±8.43	51.41±10.16	51.50±9.98	55.45±11.46
Sex (M/F)	10/12	10/12	10/12	9/13
SBP (mmHg)	119.67±10.92 b*,c ^Δ ,d ^Δ	129.77±7.20 a*,c ^Δ ,d ^Δ	167.09±9.94 a ^Δ ,b ^Δ ,d ^Δ	151.77±17.81 a ^Δ ,b ^Δ ,c ^Δ
DBP (mmHg)	77.24±6.91 b*,c ^Δ ,d ^Δ	86.32±5.20 a*,d*	91.27±8.61 a*	94.36±15.04 a ^Δ ,b*
Total cholesterol (mg/dl)	181.29±30.53	193.36±26.87	188.68±37.64	189.64±36.63
HDL-cholesterol (mg/dl)	49.62±9.81 d [#]	49.55±9.39 d [#]	45.59±12.43	38.68± 8.44 a [#] ,b [#]
LDL-cholesterol (mg/dl)	117.62±30.86	123.77±19.75	120.72±43.55	119.91±31.42
Triglyceride (mg/dl)	106.62±50.17	133.27± 90.80	137.59±70.73	123.82±52.10
Potassium (mEq/L)	4.17±0.35	4.17±0.58	4.10±0.48	4.97±0.67

NT: Normotensive Group; WCH: White Coat Hypertensive Group; EH: Essential Hypertensive group; RH: Renovascular Hypertensive Group; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

a - statistically different from controls

b - statistically different from WCH

c - statistically different from EH

d - statistically different from RH

* - $P<0.05$, # - $P<0.01$, Δ - $P<0.001$

TABLE 2. Plasma plasminogen activator system components of the study groups.

	NT (n=22)	WCH (n=22)	EH (n=22)	RH (n=22)
PAI-1 (ng/ml)	6.11±1.93 c*,d ^Δ	7.91±2.55	10.26 ± 6.09 a*	10.98±3.68 a ^Δ
tPA (pg/mL)	5.38±2.06 c*,d*	6.44±3.09	8.38 ± 4.96 a*	8.23±3.26 a*
tPA/PAI-1 (mg/l)	3.82±2.15 c [#] ,d [#]	4.96±2.16	6.23 ± 2.28 a [#]	6.14±2.53 a [#]
Fibrinogen (mg/dL)	314.96±47.49 b ^Δ , c ^Δ , a ^Δ	499.35±114.14 a ^Δ	552.52±177.44 a ^Δ	563.59±147.84 a ^Δ

NT: Normotensive Group; WCH: White Coat Hypertensive group; EH: Essential Hypertensive Group; RH: Renovascular Hypertensive Group.

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c - statistically different from EH

d - statistically different from RH

* - $P<0.05$, # - $P<0.01$, Δ - $P<0.001$

chemical analysis. All parameters were analyzed in all samples together in a single batch, after we had finished our protocol (control and patient samples were analysed in the same batch).

Plasma PAI-1, tPA, tPA/PAI-1 complex levels were measured by a quantitative sandwich enzyme immunoassay technique, using commercial assay kits, according to manufacturer's instructions (Assaypro, Brooklyn, USA). Absorbance values were read in an ELISA plate reader and the concentration of samples was automatically calculated by software. Samples were run in duplicate, and the 2 measurements were averaged for statistical analysis.

Fibrinogen (by the Clauss method) was measured using the Dade Behring BCS analyzer.

Plasma lipid levels were determined on the Olympus AU 800 analyzer by enzymatic methods using commercial kits (Roche Diagnostics, GmbH, Mannheim).

Statistical analysis

For each variable, values were expressed as mean $\pm$ SEM. Differences among groups were evaluated using Kruskal-Wallis analysis and multiple comparisons among groups were performed with Mann-Whitney U test. Correlation analysis was tested using Pearson's

correlation. Differences were considered statistically significant when $P<0.05$. Data were analyzed by statistical software (SPSS for Windows 11.5; SPSS, Chicago, IL).

Results

Basic characteristics and clinical and ambulatory blood pressure values of the groups were given in Table 1. There were no differences in age, sex or BMI among groups. Glucose, total cholesterol, LDL cholesterol and triglycerides levels were not different among groups. HDL cholesterol was lower in the RH group than in the WCH and NT ($P<0.01$) groups; but there was no difference in EH and other groups. Systolic blood pressure values were different among groups. There were difference in NT ($P<0.001$) groups while diastolic blood pressure values were not different among RH, WCH and EH groups. Diastolic blood pressures were different NT ($P<0.001$), WCH ($P<0.05$) and RH groups.

PAI-1 antigen levels were different ($P<0.01$) in EH and RH groups from NT group. On the other hand, there was no difference among WCH, EH and RH groups in PAI-1 antigen levels. Similarly, there was no difference between WCH and NT groups in PAI-1 antigen levels. tPA and tPA/PAI-1 levels in EH

and RH groups were different ($P < 0.05$) from NT and WCH groups while there was no difference between NT and WCH groups. There was no difference in fibrinogen levels among EH, RH and WCH groups while differences ($P < 0.001$) were determined between these and the NT group.

Discussion

A new assay has been developed that solely detects tPA in complex with PAI-1. This tPA/PAI-1 complex assay has been proposed as a new marker of the fibrinolytic system.¹⁵ Our results indicated increased PAI-1 antigen, t-PA and t-PA/PAI-1 levels in EH, RH and WCH. Our study confirms that hypertension is independently associated with elevated levels of this parameter. Coagulation (fibrinogen, factor VII, von Willebrand factor) and fibrinolytic (t-PA, PAI-1) factors play an important role in the development of cardiovascular diseases besides hypertension, smoking cigarette, diabetes mellitus and obesity. There is a relationship between elevated levels of fibrinogen, vWF, t-PA and angina pectoris: low fibrinogen is associated with a low risk of cardiovascular disease despite high cholesterol.¹⁶

Fibrinogen, a major component of the coagulation system, acts like an independent and effective risk factor for cardiovascular diseases in postmenopausal women.¹⁷ Activity of factor VII is defined as a critical risk factor for cardiac death.¹⁸ Plasma fibrinogen was increased in EH, RH and WCH groups compared with normotensives. Elevated fibrinogen levels have not been consistently associated with hypertension. Whether an elevated fibrinogen level is a risk factor for, or a consequence of, hypertension remains unclear. Although Sechi et al.¹⁹ did not observe differences in fibrinogen between hypertensive patients and normotensive controls, their study demonstrated a strong and independent association between fibrinogen and the presence and severity of hypertension-related damage in different target organs. Similar evidence was presented by Lip et al.²⁰ who showed that

TABLE 3. Summary

What is known

- Essential hypertension is associated with abnormalities in haemostatic/fibrinolytic balance
- Endothelial function, indicated by alterations in plasma levels of fibrinogen, PAI-1, tPA and thrombomodulin.

What is now

- Fibrinolytic markers such as PAI-1, tPA, tPA/PAI-1 complex are independently associated with the development of hypertension.
- Renovascular hypertension is also associated with impaired fibrinolysis.

fibrinogen was related to left ventricular mass in hypertensive patients. These data suggest a pathogenic role of fibrinogen in the development of target-organ damage (TOD) in hypertensive patients that could be related to the atherogenic and thrombotic actions of this protein. It is unlikely that the association between plasma fibrinogen and TOD in these patients is due to chance, because the strength of the association, the dose-response relationship, and the independent association demonstrated by multivariate analysis suggest causality and reduce the likelihood of confounding variables. Because fibrinogen is an acute phase reactant, it is also possible that vascular lesions with inflammatory components could be responsible for the association between fibrinogen and TOD. Against this possibility is the observation of comparable values of erythrocyte sedimentation rate and reactive C-protein in hypertensive patients with different degrees of TOD.²¹

Fibrinogen acts like a triggering factor for myocardial infarction in those who have coronary artery diseases. Likewise, Wiman et al.²¹ found high plasma levels of fibrinogen, vWF, t-PA, PAI-1 and t-PA/PAI-1 complex in recurrent myocardial infarction compared with controls. Plasma concentration of vWF is an important risk determinant for recurrent MI.²¹ There is major impairment of endothelium function in the prethrombotic state. Levels of vWF and factor VIII show the function of endothelium. Our findings and data from the literature indicate that coagulation is highly likely in hypertensive patients²² and has a

negative impact on morbidity and mortality. Evaluation of coagulation parameters of risk groups may determine treatment strategies.

Plasminogen activator inhibitor-1 (PAI-1) is a marker of impaired fibrinolysis and atherothrombosis.²³ Increased levels of PAI-1 cause impaired fibrinolysis that may lead to vascular disease especially in subjects with metabolic syndrome and/or type 2 diabetes.²⁴ According to The National Cholesterol Education Program (NCEP) criteria,²⁵ the definition of metabolic syndrome consists of at least three of the five components (central obesity, hypertension, hypertriglycerides, low HDL-C, IFG).²⁵ PAI-1 levels were higher in individuals with coronary artery disease.²⁶ Furthermore, in a study of young adults, central obesity was correlated with high blood pressure and levels of insulin and PAI-1 while being negatively correlated with HDL-C.²⁷ Hypertriglyceridemia is suggested to stimulate abdominal adipocytes to excrete PAI-1 into blood.^{28,29}

PAI-1 levels are elevated in established hypertension.³⁰ Two studies reported differences between PAI-1 levels in WCH and NT groups.³¹ Likewise, Penesova et al.³² reported that basal PAI-1 levels were higher in hypertensive than normotensive groups. Their study also showed that a young hypertensive group, diagnosed early, had higher baseline levels of norepinephrine, insulin and PAI-1. In patients suffering from cardiovascular events, impaired fibrinolysis is a poor prognostic factor.³³ Elevated PAI-1 activity is a major independent predictor of coronary microvascular dysfunction.³⁴ However, agents previously used to treat hypertension, such as diuretics and β -blockers, have adverse effects on lipid, carbohydrate metabolism, and fibrinolysis, perhaps counteracting the beneficial antihypertensive effect.² The activity of the renin-angiotensin-aldosterone axis can influence endothelial function and endogenous fibrinolysis.

In humans, plasma PAI-1 antigen concentrations correlate with serum aldosterone concentrations in salt-depleted normal controls, hypertensive subjects, and individuals with primary hyperaldosteronism.³⁵⁻³⁷

Makris et al.²³ showed that subjects with white coat hypertension have increased plasma levels of PAI, tPA, fibrinogen, and thrombomodulin compared to normotensives, indicating a procoagulant tendency and endothelial damage. Binding of angiotensin II to endothelial cells results in many functional abnormalities of these cells, including dose-dependent PAI-1 release. Endothelial dysfunction anticipates both cardiac and renal hypertensive complications.³⁸ Sechi et al.³⁹ showed that plasma fibrinogen and PAI-1 levels were greater among hypertensive patients with clinical or instrumental evidence of organ damage than in patients without organ damage. Additional variables that were associated with presence of organ damage were age, blood pressure level, duration of hypertension, smoking status, and lower HDL cholesterol levels. Essential hypertension is associated with a prothrombotic state. Fibrinogen, d-dimer, and PAI-1 are independent risk factors for major cardiovascular events in the general population and hypertensive subjects.⁴⁰

Poli et al. showed that PAI-1 antigen levels remained associated with increasing blood pressure after adjustment for known confounders, including hypertriglyceridemia and diabetes.⁴¹ Therefore, although PAI-1 activity is strongly correlated with hyperinsulinemia and triglycerides, it appears that PAI-1 antigen levels are independently associated with hypertension. Our findings confirm the results of Poli et al.⁴¹ The mechanism whereby increasing blood pressure may result in impaired fibrinolysis is unclear, but it may be related to the increase in shear stress or endothelial dysfunction.

Our study is limited by the low number of subjects. Fibrinolytic markers were found to be higher in hypertensive patients than in controls. Previous studies did not involve a renovascular hypertensive group, giving our study additional value. Mogielnicki et al.⁴² showed that angiotensin II enhances thrombosis in renovascular hypertensive rats due to the increased synthesis of PAI-1. Our results support the concept that impaired fibrinolysis plays an important role in

white coat hypertension.⁴³ Therefore, WCH may not be a completely innocent trait, indicating the cardiovascular risk in white coat hypertensives.

Hypertension is a major risk factor for cardiovascular disease. Increased plasma levels of t-PA or PAI-1 cause impairment of the fibrinolytic system. We observed an independent relationship between fibrinolytic markers and development of hypertension. Thus, our data supports the hypothesis that disturbances in fibrinolysis precede a cardiovascular event. Therefore, hypertension may be associated with impaired fibrinolysis. Further studies are needed to assess the increased cardiovascular risk conferred by high fibrinolytic markers in hypertension.

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Correspondence to:

Hafize Uzun, Assoc. Prof. PhD
Istanbul University, Cerrahpasa Medicine Faculty, Department of Biochemistry
34303 Cerrahpasa- Istanbul / Turkey
e-mail: huzun59@hotmail.com