# Thrombin activatable fibrinolysis inhibitor and other hemostatic parameters in patients with essential arterial hypertension

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**Abstract: Introduction.** Hypertension is associated with hemostatic abnormalities and endothelial dysfunction. thrombin activatable fibrinolysis inhibitor (TAFI) is a glycoprotein linking coagulation and fibrinolysis. **Objectives.** We evaluated TAFI concentrations in patients with essential hypertension in relation to blood pressure. Additionally, we studied TAFI activator, thrombin activity (thrombin-antithrombin complexes – TAT, prothrombin fragments F1+2), thrombomodulin (TM) – a marker of endothelial cell injury, degree of plasmin generation (plasmin-antiplasmin complexes [PAP]), other markers of endothelial cell injury – von Willebrand factor (vWF). **Patients and methods.** Seventy-two patients with essential hypertension (27 untreated,13 treated with enalapril (angiotensin-converting enzyme inhibitor [ACEI]), 32 with β-blocker, betaxolol). In every hypertensive patients ambulatory blood pressure measurements and echocardiography were performed. **Results.** All hypertensive patients did not differ with respect to age, creatinine, fibrinogen, D-dimers. In ACEI-treated patients a significantly higher TAFI concentration was observed when compared to β-blocker-treated patients. In β-blocker-treated patients both diastolic and systolic blood pressure were lower than in ACEI treated patients as well as ejection fraction, while serum triglycerides were higher. Diastolic blood pressure correlated significantly with TAFI concentrations in untreated patients ($r = 0.27$, $p < 0.05$), and in β-blocker-treated patients ($r = 0.25$, $p = 0.05$), TAFI activity was inversely associated with interventricular septal diameter ($r = -0.75$, $p < 0.01$) in patients treated with ACEI. **Conclusions.** Elevated TAFI concentrations and enhanced thrombin generation in hypertensive patients may contribute to atherosclerosis progression in this population. Differences in the studied parameters may be due to a small sample size, monotherapy and potential effects of antihypertensive drugs on glicemia, ejection fraction and triglycerides.

**Key words:** coaguation, endothelium, essential hypertension, fibrinolysis, TAFI

## INTRODUCTION

Hemostatic disturbances play a key role in atherosclerosis development. Hypertension, even in early stages, may cause blood vessel wall injury and activation of the coagulation system. According to the current data, the trigger of atherosclerosis process is functional and structural endothelial injury leading to its humoral and endocrine dysfunction. Endothelial damage factors stimulate platelets and the coagulation system as well, which, especially with coexisting impaired fibrynolytic activity, supports the formation of the marginal and intramural deposits of fibrin and the development of the atherosclerotic plaque. Atherosclerosis and its complications are responsible for several cardiovascular diseases which can lead to death in this population. A high risk of cardiovascular complications may occur as a result of endothelial cell dysfunction, platelet and coagulation system activation and reduced fibrynolytic activity. In spite of investigations performed since a long time, the pathogenesis of these abnormalities is still unclear.

Among potential hemostatic risk factors for hypertension and its complications development thrombin activatable fibrynolysis inhibitor (TAFI), determined by Bajzar et al. [1], ought to be considered. In normal circumstances, thrombin synthesis, generated by coagulation system activation, seems to be the physiologic activator of TAFI and its transformation to an activated form – TAFIa. This reaction is catalyzed

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by soluble and endothelium-bound thrombomodulin. The activated form of TAFI after fibrin complexes conjunction has the properties of carboxypeptydase and cuts lizyne rests from its C-end. This reaction inhibits the production of complexes containing plasma tissue activator, plasminogen and fibrin complexes. In consequence, increased plasmine production causes low fibrynolytic activity. Current studies more and more often show the essential role of TAFI in atherosclerosis development and/or discuss its complications [2]. Our previous studies demonstrated elevated TAFI levels in subjects with hypertension after kidney transplantation [3]. However, no study evaluating the activity and serum levels of TAFI in subjects with primary hypertension has been published so far.

The aim of this study was to evaluate the activity and serum level of TAFI and its physiologic activator – thrombin (indirectly – by prothrombin F1+2 fragments generation measurement, and thrombin activity – by thrombin-anti-thrombin complexes – TAT generation measurement), and the catalyst of activation – thrombomodulin – measurement, in subjects with hypertension. Fibrinolytic system activation was evaluated indirectly by plasmin-anti-plasmin (PAP) complexes serum level measurement.

Additionally, coagulation system activity was also evaluated on the basis of fibrinogen and D-dimer plasma levels measurements as indicators of the fibrynolytic system activity.

The relationship between hypertension, endothelial cells damage (von Willebrand factor and thrombomodulin plasma levels measurements) and plasma hemostase activity, in comparison to the clinical status of patients and the anti-hypertonic therapy they were undergoing, was analyzed as well.

## PATIENTS AND METHODS

The study involved 72 patients with primary hypertension. No anti-hypertonic therapy was used in 27 from among them, 13 patients were treated with angiotensin converting enzyme inhibitors (ACEI) (enalapril in a dose of 10 mg, twice a day), 32 patients received β–blocker (betaksol 10 mg, once a day). The history of hypertension in all studied groups was similar and ranged about 12 months. Exclusion criteria included: diabetes, liver dysfunction, active inflammatory process, past or recent malignancy, heart failure causing hypertension, ischemic heart disease, cigarette or pipe smoking.

All investigations were performed using commercial immunoenzymatic kits.

Measurement of TAFI serum levels was conducted using the VisuLize™ TAFI AntigenKit, Affinity Biological Inc., Canada. TAFI plasma activity was measured by the chromogenic method using the ACTICHROME® Plasma TAFI Activity Kit, Amerian Diagnostica, USA.

Serum F1+2 levels were measured by the immunoenzymatic method (ELISA) using the kit Enzygnost® F1+2 micro, Dade-Behring, Germany. Serum TAT levels was measured by the immunoenzymatic method (ELISA) applying the kit Enzygnost® TAT micro, Dade-Behring, Germany. Serum level PAP complexes in studied samples were measured employing the ELISA Kit – Enzygnost® PAP micro, Dade Behring, Germany. Thrombomodulin serum levels were measured using the ELISA, IMUBIND®, Thrombomodulin ELISA Kit, American Diagnostica, USA. Von Willebrand factor activity was evaluated with the use of the IMMUBID® vWF activity ELISA, American Diagnostica, USA.

Other study parameters like: blood cells evaluation, electrolites, creatynine, bilirubine, albumine, total proteins, asparte aminotransferase, alanine animotransferase, prothrombin time, international normalized ratio, glucose, lipid levels were measured by standard laboratory methods.

Plasma D-dimer levels were measured using the Olympus analyzer, Diagnostica GmbH (Hamburg, Germany), in the central hospital laboratory.

Each patient underwent the echocardiography, the 24-hour Holter blood pressure monitoring in an outpatient clinic, and eye fundus examination (in all studied patients *angiopathia hypertonica retinae I/II* was diagnosed).

The data were presented as mean values with standard deviations, and statistical analysis was conducted using the STATISTICA 6.0 PL computer program for Windows.

To evaluate statistically significant relationships between study parameters, nonparametric tests for not normally distributed variables, or parametric tests for normally distributed parameters, were used. The correlation between variables was evaluated by Pearson's or Spearman's methods. The significance level was set at $p < 0.05$.

## RESULTS

In subjects with hypertension, TAFI activity, plasma levels of TAT, PAP, F1+2, and thrombomodulin were significantly higher compared to the control group (Tab. 1).

In the studied patients who received enalapril, serum TAFI and vWF levels were higher than in the control group and the patients who received betaksolol.

No statistically significant differences concerning age, creatynin, fibrinogen and D-dimer plasma levels between the three studied groups were observed (Tab. 2). In the group receiving betaksolol, serum triglycerides levels were significantly higher than in the other groups, and the ejection fractions were similar.

The values of diastolic blood pressure significantly correlated with TAFI serum levels ($r = 0.27$, $p < 0.05$), both in subjects receiving betaksolol and those who did not receive any medication ($r = 0.25$, $p < 0.05$). A positive correlation between PAP serum levels and thrombomodulin activity was observed in the group receiving ACEI ($r = 0.94$, $p < 0.01$), but TAFI activity significantly correlated with the interventricular septum size ($r = 0.75$, $p < 0.01$) in patients treated with enalapril.

Positive correlations between the studied parameters observed in all groups were as follow:

**Table 1. Evaluated parameters of hemostasis in patients with hypertension (mean value ±SD-standard deviation)**

| | Non-treated | ACEI | β-blocker |
|---|---|---|---|
| TAFI activity (μg/ml) | 1.24 ±0.90 | 1.33 ±0.87 | 1.07 ±0.71 |
| TAFI antigen (μg/ml) | 3.23 ±0.58$^{+}$ | 3.58 ±0.41** | 2.58 ±1.40 |
| PAP (ng/ml) | 750.52 ±1102.67 | 547.31 ±420.44* | 550.97 ±1152.93 |
| vWF (%) | 80.72 ±19.57 | 92.55 ±16.74 | 78.77 ±19.72 |
| TM (ng/ml) | 5.04 ±5.60 | 5.82 ±5.82 | 5.74 ±4.49 |
| F1+2 (nmol/l) | 2.28 ±3.00$^{\#}$ | 1.68 ±0.97* | 2.17 ±2.70 |
| TAT (μg/l) | 15.63 ±28.57 | 18.20 ±18.89 | 19.29 ±28.82 |
| Fibrynogen (mg/dl) | 330.0 ±65.7 | 333.2 ±39.3 | 318.5 ±60.9 |
| D-dimer (mg/dl) | 303.07 ±65.66 | 324.83 ±171.15 | 320.20 ±175.05 |

ACEI vs. β-blocker. * $p<0.01$, ** $p<0.001$

Non-treated vs. ACEI. $^{\#}$ $p<0.001$

Non-treated vs. β-blocker. $^{+}$ $p<0.001$

Abbreviations: ACEI – angiotensine conversion enzyme inhibitors, PAP – plasmin-anti-plasmin complex, TAFI – thrombin activatable fibronolysis inhibitor, TAT – thrombin-anti-thrombin complex, TM – thrombomodulin, vWF – von Willebrand factor

1) TAFI antigen serum levels and systolic blood pressure ($r = 0.27$, $p < 0.05$), trigliceryde serum levels ($r = 0.35$, $p < 0.01$), vWF ($r = 0.33$, $p < 0.05$); vWF and creatynine serum levels ($r = 0.35$, $p < 0.01$), systolic blood pressure ($r = 0.27$, $p < 005$), LDL ($r = 0.27$, $p < 0.05$)
2) PAP serum level complexes and creatynine serum levels ($r = 0.35$, $p < 0.01$), IVS ($r = 0.48$, $p < 0.001$), thrombomodulin serum levels and hemoglobin concentration ($r = 0.27$, $p < 0.05$), fibrynogen serum levels ($r = 0.38$, $p < 0.01$), total protein concentration($r = 0.32$, $p < 0.05$)
3) TAT serum complexes and serum levels of F1+2 fragments of prothrombine ($r = 0.80$, $p < 0.001$), left ventricular size ($r = 0.27$, $p < 0.05$), hematocrite levels ($r = 0.33$, $p < 0.05$).

## DISCUSSION

Results of the study demonstrated that in patients with untreated essential hypertension, hypercoagulable state, increased TAFI serum levels with normal PAP serum level complexes and increased thrombomodulin serum levels as indicators of endothelium dysfunction, occurred. In hypertonic patients treated with ACEI, or untreated, coagulation and fibrynolytic system activation was observed more frequently compared with those who received β-blockers. β-blockers anti-hypertonic therapy, in turn, results in the lower values of both systolic and diastolic blood pressure and metabolic disturbances, i.e. elevated triglycerides serum levels, comparing with subjects treated with ACEI or untreated.

Increased von Willebrand factor levels were noted in vascular inflammation, in patients with peripheral artery disease with coronary heart disease or cerebral events, and in patients with hypertension [4-7].

The recent results of the ASCOT studies [8,9] showed that the increased vWF serum level is an independent risk factor for hypertonic-bind organ damage, e.g. microalbuminuria as an indicator of kidney damage, or left ventricular failure, which was confirmed by previous investigations [5,10].

In our own studies, we observed normal vWF serum activity, but the vWF serum level was not measured, because this parameter was evaluated in our earlier investigations [11-13].

Markis et al. [14] observed the increased soluble thrombomodulin plasma level as a marker for essential hypertion-dependent endothelial dysfunction, with multiple organ damage, and similar but not severe abnormalities in patients with hypertension without complications.

In all studied groups no statistically significant differences in thrombomodulin plasma levels were found. It is possible that in these patients high thrombin generation (elevated prothrombin F1+2 fragments serum level) can overcome the inhibiting effect of thrombomodulin on the process of TAFI activation. In the studied groups, both treated and untreated with enalapril, significantly higher TAFI plasma levels with comparable values of TAFI serum activity compared with patients treated with betaksolol, were observed. Both in patients with ischemic heart failure confirmed by the coronary angiography and unstable [15], higher TAFI plasma levels were noted [16]. A potential role of TAFI activity as an ischemic heart disease risk factor was demonstrated in a 5-year prospective study PRIME [15]; all participating in this study patients with high TAFI plasma levels developed ischemic heart disease during 5 years [17]. So far no data about the anti-hypertensive therapy influence on TAFI activity and plasma level, have been published; in our own study we excluded patients with ischemic heart disease.

Similarly to the previous investigations concerning subclinical activation of the coagulation system and impaired fibrin-

**Table 2. Clinical and laboratory parameters of studied groups (mean value ±standard deviation)**

| | | Non-treated | ACEI | β-blocker | p |
|---|---|---|---|---|---|
| Age (years) | | 37.2 ±13.4 | 44.7 ±15.0 | 38.1 ±13.7 | NS |
| The lowest systolic blood pressure (mmHg) | | 120.0 ±5.9 | 110.0 ±11.5 | 107.3 ±14.6 | NS |
| The lowest diastolic blood pressure (mmHg) | | 80.6 ±13.3 | 67.7 ±9.3 | 70.8 ±13.6 | NS |
| The highest systolic blood pressure (mmHg) | | 165.8 ±14.0 | 160.0 ±35.9 | 148.3 ±21.4 | *###+ |
| The highest diastolic blood pressure (mmHg) | | 103.0 ±9.6 | 100.8 ±15.0 | 95.9 ±14.4 | + |
| ESR (after 1 hour) | | 6 ±5.0 | 13.1 ±11.7 | 7.6 ±5.1 | *# |
| WBC (thousand/μl) | | 5.9 ±1.6 | 6.4 ±1.9 | 6.7 ±1.2 | NS |
| RBC (million/μl) | | 5.0 ±0.5 | 4.7 ±0.5 | 4.9 ±0.5 | NS |
| Haemoglobin (g/l) | | 15.1 ±1.4 | 14.5 ±1.4 | 14.5 ±1.6 | NS |
| Haematocrit (%) | | 43.3 ±4.9 | 43.5 ±4.0 | 42.7 ±4.6 | NS |
| Platelets (thousand/μg) | | 227 ±58.5 | 235 ±41.8 | 235.9 ±59.0 | NS |
| PT (s) | | 12.2 ±1.0 | 12.2 ±1.4 | 11.7 ±0.8 | NS |
| INR | | 1.1 ±0.2 | 1.1 ±0.1 | 1.0 ±0.1 | *+++ |
| Total proteine (g/dl) | | 7.4 ±0.5 | 7.1 ±0.6 | 7.3 ±0.5 | NS |
| Albumine (g/dl) | | 4.6 ±0.3 | 4.4 ±0.6 | 4.6 ±0.4 | *#### |
| Bilirubine (mg/dl) | | 0.8 ±0.3 | 0.9 ±0.5 | 0.7 ±0.3 | *# |
| Urea (mg/dl) | | 34.5 ±11.4 | 35.8 ±6.2 | 30.9 ±9.0 | NS |
| Creatynine (mg/dl) | | 0.9 ±0.1 | 0.9 ±0.1 | 0.9 ±0.2 | NS |
| Glucose (mg/dl) | | 90.4 ±7.7 | 95.9 ±7.9 | 94.0 ±12.3 | + |
| Cholesterol total (mg/dl) | | 192.8 ±45.4 | 203.8 ±40.4 | 195.2 ±33.8 | NS |
| LDL-cholesterol (mg/dl) | | 114.8 ±37.0 | 126.8 ±34.3 | 1 21.1 ±25.8 | NS |
| HDL-cholesterol (mg/dl) | | 54.6 ±14.1 | 52.0 ±13.2 | 53.7 ±14.9 | NS |
| Triglycerides (mg/dl) | | 125.7 ±68.2 | 121.7 ±52.8 | 162.7 ±123.4 | *+ |
| AST (U/l) | | 24.6 ±11.1 | 23.1 ±8.1 | 21.8 ± 5.5 | + |
| ALT (U/l) | | 26.6 ±17.9 | 24.5 ±17.6 | 25.9 ±15.7 | NS |
| Sodium (mmol/l) | | 139.8 ±3.1 | 139.6 ±2.6 | 135.1 ±25.4 | **+++ |
| Potassium (mmol/l) | | 4.5 ±0.3 | 4.5 ±0.4 | 4.4 ±0.4 | NS |
| Calcium (mmol/l) | | 2.56 ±0.6 | 2.4 ±0.1 | 2.4 ±0.2 | ##++ |
| Echocardiography: | Left ventricle (mm) | 46.9 ±5.9 | 48.3 ±3.6 | 45.8 ±5.0 | NS |
| | Left atrium (mm) | 36.3 ±4.5 | 38.8 ±3.1 | 36.4 ±4.1 | NS |
| | Right ventricle (mm) | 26.7 ±3.6 | 26.8 ±3.3 | 25.1 ±2.6 | NS |
| | Interventricular septum (mm) | 11.7 ±5.1 | 10.5 ±3.7 | 11.4 ±2.9 | + |
| | Left ventricle back wall (mm) | 10.0 ±1.4 | 10.9 ±1.6 | 10.3 ±1.1 | NS |
| | Ejection fraction (%) | 62.3 ±3.8 | 60.0 ±8.4 | 59.3 ±10.7 | #+++ |

ACEI vs. β-blocker. * $p < 0.05$; ** $p < 0.001$
Non-treated vs. ACEI. # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$
Non-treated vs. β-blocker. + $p < 0.05$; ++ $p < 0.01$; +++ $p < 0.001$
Abbreviations: ALT – alanine transferase, AST – asparagine transferase, ESR – erythrocyte sedimentation rate, HDL – high-density lipoprotein, INR – international normalized ratio, LDL – low-density lipoprotein, NS – not significant, PT – prothrombin time, RBC – red blood cells, WBC – white blood cells

olysis in hypertensive subjects [4,11], in the present study, significantly higher thrombin generation, detected by F1+2 prothrombin fragments, and the TAT complex serum level, were observed. Kłoczko et al. [12] showed that even in early stages of hypertension, without multiple organ damage, the activation of coagulation system occurred. Investigators observed no

correlations between TAT and F1+2 plasma levels and diastolic and systolic blood pressure. Similar findings were obtained in our study. A slightly different results are presented in the study by Sechi et al. [11]. These investigators, like Trifletti et al. [18], observed a positive correlation between F1+2 serum levels and systolic blood pressure in patients with hypertension-dependent multiple organ damage. This demonstrated a positive correlation between F1+2 high serum levels and diastolic blood pressure in patients treated with ACEI, and TAT activity with systolic and diastolic blood pressure in patients treated with β-blockers. The causes of various positive correlations between the studied parameters are unclear. Population differences in the studied patients might be the reason for that. In the three studied groups: untreated or ACEI or β-blockers treated patients, PAP serum levels were significantly higher in comparison to the control group (stored in methodology). The higher PAP serum level as an indicator of increased fibrynolytic activity coexisting with increased activity of the coagulation system (high F1+2 and TAT complexes serum levels) in hypertonic subjects may protect them from acute coronary events. Moreover, high D-dimer levels (compared to the reference values) in the studied group confirm the hypothesis about the excessive activation of the coagulation system and formation of large amounts of fibrin deposits. Increased PAP activity as a marker for high plasmine generation and its proteolytic activity towards fibrin, is the reaction of hemostasis which aims at maintaining a balance in the system. Jastrzębska et al. [19] observed hypercoagulable state in hypertension, possibly caused by tissue plasminogen activator and converting enzyme gene polymorphism which affects fibrinolysis modification. It must be emphasized that a positive correlation between PAP and TM in patients treated with ACEI was observed. From the obtained results, it might be concluded that PAP and TM serum levels increase due to hypertension development and enhanced coagulation system activity. Although increased PAP and TM plasma levels are indicators of pathologic processes in blood vessels, they prevent patients from thromboembolic events and their severe complications (thrombomodulin activity prevents from TAFI and impaired fibrinolytic activity, PAP serum complexes are indicators of fibrinolytic activity).

The fact that the present study was of prospective and not comparative character caused some inconvenience to investigators. However, it ought to be emphasized that this study involved homogenous groups of patients as concerns age, hypertension history and therapy. All studied subjects underwent deep eyes examination and *angiopathia hypertonica retinae I/II* was diagnosed; echocardiography examination excluded myocardial contractility abnormalities, myocardial hypertrophy or valvular heart diseases. The homogeneity of the studied groups was confirmed by the 24-hour Holter monitoring of blood pressure. Patients with secondary hypertension were excluded from the study and each studied group received the same anti-hypertensive treatment. The discrepancies in the obtained findings may be caused by differences in glucose serum levels (despite the exclusion of diabetic subjects from the study), or differences in blood pressure measurements between patients treated with ACEI and β-blockers.

The results of the study obtained from patients treated with ACEI and β-blockers were compared with the results obtained from untreated patients, who served as a control group. No healthy volunteers were included into the study because the aim of this investigation was to perform a comparative analysis of clinical symptoms and laboratory tests in treated and untreated hypertensive patients.

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