Fibrinolytic/Hemostatic Variables in Arterial Hypertension: Response to Treatment With Irbesartan or Atenolol

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Essential hypertension is often accompanied by abnormalities of the coagulation/fibrinolytic system, predisposing to a procoagulant state. The aim of the present study was to compare the effects of atenolol (β₁-blocker agent) and irbesartan (angiotensin II type 1 receptor antagonist) on plasma levels of hemostatic/fibrinolytic and endothelial function markers in a cohort of previously untreated hypertensives. Fifty-four patients were randomly assigned to atenolol 25 to 150 mg (26 patients) or irbesartan 75 to 300 mg (28 patients). The plasma levels of plasminogen activator inhibitor-1 antigen, thrombomodulin, tissue factor pathway inhibitor antigen, fibrinogen, and factor XII were determined before and after 6 months of therapy. Age, gender distribution, body mass index, lipid profile, and baseline values of the measured markers were similar in both groups. Baseline values for systolic and diastolic blood pressure, as well as the reduction after treatment, were not significantly different between the two groups. Treatment with irbesartan was associated with a significant decrease in the levels of all the parameters. Similar findings were observed in the atenolol group, except for factor XII and tissue factor pathway inhibitor levels, which were not significantly decreased in this group. The reduction, however, of fibrinogen, plasminogen activator inhibitor-1, and thrombomodulin was significantly greater in the irbesartan than in the atenolol group. In conclusion, the results indicated that, despite an equally controlled blood pressure, 6-month therapy with irbesartan was associated with a more favorable modification of hemostatic/fibrinolytic status than atenolol.


KEY WORDS: Irbesartan, atenolol, hemostasis, endothelial dysfunction, hypertension.
ing that many of these markers are predictors of future vascular events, both ischemic heart disease and stroke.4

The aim of our study was to investigate the effect of 6-month treatment with either atenolol, the well known β₁-blocker agent, or irbesartan, a selective angiotensin II type 1 (AT₁) receptor antagonist, on plasma levels of a wide spectrum of hemostatic/fibrinolytic and endothelial function markers (PAI, fibrinogen, thrombomodulin, Factor XII [FXII], tissue factor pathway inhibitor), in a cohort of previously untreated hypertensive patients.

MATERIALS AND METHODS

This study was performed in 115 Greek patients who attended the Hypertension Clinic of our hospital. The study was approved by our institutional review committee and informed consent was obtained from each subject studied. Hypertension was diagnosed when the systolic BP was ≥ 140 mm Hg and/or the diastolic BP was ≥ 90 mm Hg on at least three separate occasions.5 BP was measured in the sitting position in a quiet room, using a mercury sphygmomanometer, after the patient had rested for at least 10 min. Systolic BP was recorded at the appearance of sounds (Korotkoff phase I) and the diastolic at their disappearance (Korotkoff phase V). All measurements were made by the same trained observer. No patient had ever received antihypertensive therapy. A detailed history was obtained and physical examination and electrocardiogram were conducted on each subject. Heart rate was measured from a standard electrocardiogram under the same conditions and calculated as the average of nine R-R intervals. Patients with coronary artery disease (CAD), secondary hypertension, renal failure, liver disease, or other serious illness were excluded from this study; smokers were defined as current smokers. Alcohol consumption was determined by a questionnaire that asked for information about the daily consumption of wine, liquor, and beer; alcohol intake was expressed in grams per day. Information concerning physical activity was obtained from questionnaires that have been previously described.6 Subjects were weighed (kg), and height (m) was measured wearing only light clothing without their shoes. The body mass index (BMI) was calculated as weight/height (kg/m²) (Table 1). The hypertensive patients entered a placebo run-in period of 2 weeks for assessment of their BP. Eight patients were withdrawn from the study after this period because they still did not meet the inclusion criteria. The remaining 107 were randomly assigned to either open-labeled irbesartan 75 mg (54 patients) or atenolol 25 mg (53 patients), once daily. Venous blood samples were collected without stasis after 10 min supine rest. Participants were instructed to avoid strenuous physical activity and not to smoke tobacco during the hour preceding this examination, which took place between 8 and 9 AM, to reduce interference by the diurnal variation of PAI-1. All subjects had fasted for at least 12 h. BP was checked every 2 weeks and the doses of the antihypertensive drugs were adjusted to attain a DBP < 90 mm Hg. Throughout the follow-up period no patient was allowed to take any other antihypertensive medication or other drugs that are known to interfere with measurement of the variables studied.

The PAI-1 Ag and thrombomodulin were determined with an enzyme-linked immunosorbent assay (ELISA), (Diagnostica Stago, Asnieres, France). Plasma tissue factor pathway inhibitor (TFPI) antigen levels were assessed by a so-called “sandwich” ELISA method (Imubind Total TFPI, American Diagnostica Inc., Greenwich, CT). Fibrinogen levels were measured with the Clauss technique. FXII levels were determined by clotting assay. The value of the pooled plasma was taken as 100%. Serum cholesterol and triglyceride levels were determined by an enzymatic method and low-density lipoprotein (LDL) was calculated according to the Friedwald formula, because no subject had a triglyceride level > 400 mg/dL.

All the above parameters were measured before and after 6 months of treatment with atenolol or irbesartan.

Statistical Analysis Data are presented as mean ± 1 standard deviation. Comparisons of continuous variables were performed using two-factor analysis of variance for repeated measures using group (1 = irbesartan group, 2 = atenolol group) and treatment (1 = baseline, 2 = after treatment) as factors. Homogeneity of variables was tested with Hartbey’s Fmax test. Multiple comparisons were performed with the Scheffé procedure in cases with variance homogeneity and the Games-Howell procedure in cases with variance heterogeneity. A P value of ≤ .05 was regarded as statistically significant. The GB-STAT (Dynamic Microsystems, Inc., Silver Spring, MD) statistical package was used.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Irbesartan Group (n = 28)</th>
<th>Atenolol Group (n = 26)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 9</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/16</td>
<td>12/14</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3 ± 1.4</td>
<td>24.4 ± 1.1</td>
</tr>
<tr>
<td>Smokers</td>
<td>9 (32.1%)</td>
<td>8 (30.7%)</td>
</tr>
</tbody>
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Values are expressed as means ± SEM.
**RESULTS**

One hundred seven patients entered the active treatment period. During the follow-up period 10 patients (four in the irbesartan and six in the atenolol group) were withdrawn from the study because of side effects. Thirty-one patients (17 in the irbesartan and 14 in the atenolol group) were withdrawn because of insufficient BP reduction, and 12 patients (five in the irbesartan and seven in the atenolol group) were lost during the follow-up period. Finally, 54 patients (28 in the irbesartan and 26 in the atenolol group; age range, 40 to 65 years) completed the study protocol. During irbesartan therapy, the daily dose of the drug had to be increased to 150 mg in 17 cases and to 300 mg in seven cases. During atenolol treatment the daily dose had to be increased to 150 mg in 17 cases and to 300 mg in three cases.

**Demographic and Clinical Characteristics** Age (55 ± 9 v 57 ± 11 years), gender distribution (male/female: 12/16 v 12/14, P = NS), BMI (24.3 ± 1.4 v 24.4 ± 1.1 kg/m²) and number of smokers were not significantly different in the irbesartan and atenolol groups. No significant differences were observed with respect to physical activity or alcohol consumption between the two groups, before and after 6 months of therapy. Baseline values for systolic and diastolic blood pressure, as well as systolic and diastolic blood pressure reduction treatment, were similar in the irbesartan and atenolol groups. A significant reduction in heart rate compared to baseline values was observed in both groups, which, as expected, was more prominent in the atenolol group.

**Markers of Coagulation Activation and Endothelial Function** Baseline fibrinogen, plasminogen activator inhibitor-1 antigen, thrombomodulin, factor XII, and tissue factor pathway inhibitor antigen levels were similar in the two groups (Table 2). Treatment with irbesartan was associated with a significant decrease in the levels of all these parameters. Similar findings were observed in the atenolol group, except for FXII and TFPI levels, which were not significantly decreased in this group. However, the reduction of fibrinogen, plasminogen activator inhibitor-1, and thrombomodulin was greater in the irbesartan than in the atenolol group at follow-up.

**Lipid Profile** Baseline values for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were similar in the irbesartan and atenolol groups. Treatment with irbesartan was associated with a mild decrease in total cholesterol (P = .066) and LDL cholesterol, a mild increase in HDL cholesterol, and no change in the triglyceride levels. Besides a mild decrease in the LDL cholesterol, no significant changes in the other blood lipids were observed after treatment with atenolol. However, the levels of the blood lipids at follow-up were not significantly different in the two groups.

**DISCUSSION**

Blood pressure lowering with both drugs was achieved with an acceptable safety and tolerability. However, given a comparable satisfactory effect on BP, irbesartan was shown to induce a more favorable effect than atenolol with respect to a number of fi-
brinolytic, hemostatic, and endothelial dysfunction markers. To our knowledge, this is the first report investigating a potential influence of AT1 receptor antagonism on plasma levels of thrombomodulin, TFPI, or FXII. Several studies have shown that EH is associated with increased PAI-1 plasma levels, indicating decreased fibrinolytic capacity. In our study BP control with both drugs was followed by a decrease in PAI-1 plasma levels, which was more pronounced in the irbesartan group. Previous studies have shown that administration of atenolol or other β-selective blockers had no effect on PAI-1 plasma levels. Irbesartan administration was proved more efficacious in improving fibrinolytic function. There is abundant evidence about the interaction of the renin-angiotensin-system (RAS) with the fibrinolytic system. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II, which has been shown in studies with cell cultures, and humans as well, to exert a selective, dose-dependent increase in levels of PAI-1. Thus, it could be expected that antihypertensive drugs acting within the RAS should exert effects also within the fibrinolytic system. However, this has not been confirmed in clinical studies with ACE inhibitors, which have shown conflicting results regarding the effect of ACE inhibition on fibrinolysis. With respect to AT1 receptor antagonists, in a study by Seljeflot et al, a 4-week treatment with losartan had no effect on PAI-1 plasma levels. This can be explained by the findings of Kerins et al, who showed that Ang II-induced PAI-1 increase does not appear to be mediated by type 1 or type 2 angiotensin receptors, but it occurs via the AT4 receptor, an endothelial receptor specific for the hexapeptide angiotensin IV. However, it must be taken into account that PAI-1 plasma levels are subject to multifactorial regulation and can be influenced by a variety of stimuli. Thus, it can be suggested that in the setting of our study, long-term treatment (6 months) has induced, apart from BP regulation, a regression in endothelial dysfunction, which has indirectly resulted in the downregulation of PAI-1 expression. This hypothesis is supported by the influence on the other variables that were also studied.

Thrombomodulin (TM) is a protein cofactor expressed on endothelial cells of most blood vessels. Thrombin-bound TM activates protein C, which inhibits thrombin generation by degrading factors Va and VIIIa. TM has also been proposed as a marker of endothelial cell damage and increased plasma levels have been noted in atherosclerosis and diabetes. Treatment with both drugs was followed by a decrease in TM plasma levels in our study, which however, was significantly greater in the irbesartan group. In a previous study by Trifiletti et al, 12 months of treatment with the ACE inhibitor cilazapril was not followed by a significant effect on TM plasma levels. Although the precise mechanisms of TM regulation are not yet clear, it can be suggested that an attenuation in EH-mediated damage has consequently resulted in a decrease of endothelial release of this marker. Previous reports have shown that hypertensive patients with equally well controlled blood pressure but treated with β-blocker agents did not exhibit any improvement in the altered structure of small arteries or endothelium-dependent relaxation, compared to those observed with ACE inhibitors or angiotensin receptor antagonists.

The effect of 6-month antihypertensive treatment on TFPI plasma levels was also investigated. TFPI is an endogenous inhibitor of tissue factor, regulating the extrinsic pathway of blood coagulation. Recently, biologically active TFPI has been identified within human atherosclerotic plaque, indicating an involvement in the atherosclerotic process. Moreover, enhanced TFPI plasma activity has been associated with subclinical cardiovascular disease, suggesting that it may closely reflect endothelial dysfunction. In our study the therapeutic BP-lowering effect was paralleled by a reduction of TFPI levels, which was significant only in the irbesartan group. Interestingly, in a recent work Ang II has been shown to increase TF mRNA expression, without affecting that of TFPI, on an endothelial cell culture model and this effect was attenuated by an AT1 receptor antagonist. These data may provide a source of discrepancy with our study, as no direct effect on TFPI levels could be expected. Although the precise mechanisms are not yet clear, it can be suggested that an improvement in vascular condition has resulted in a normalization of an upregulated clotting system rather than an unfavorable reduction of a natural anticoagulant.

The influence of the antihypertensive therapy with either irbesartan or atenolol on FXII levels was also examined. FXII (Hageman factor) is a serine protease, which is also involved in the pathway leading to fibrinolysis. In addition, increased FXII levels have been recently associated with the extent of coronary atherosclerosis. In our study we demonstrated a decrease in FXII activity after 6 months of antihypertensive treatment, which was again significant only in the patients to whom irbesartan was administered. The mechanisms operating in the regulation of this novel factor within cardiovascular pathophysiology are not completely understood. However, it is worth noting that recent data have shown significant correlations with some features of the insulin resistance syndrome, as well as with established CAD risk factors and it has been suggested that it may serve as a potentially useful marker of atherosclerotic vascular damage. Hence, recently a new pressor protein (NPP) has been described, which not only exerts an obvious BP-raising effect, but also has an interesting
structural and functional relationship with activated β
FXII. 33 It is not clear whether the FXII activity attenua-
tion that was observed is an independent phenomen-
on or results from its association with other variables
that have been influenced by therapy. However, these
data provide evidence for a connection between coag-
ulation and BP mechanisms in a new way, the signif-
ificance of which to the pathophysiology of essential
hypertension remains to be further investigated.

The possible impact of therapy with irbesartan or
atenolol on fibrinogen plasma levels was under con-
sideration. Most of the studies on hypertensive sub-
jects have shown an elevated fibrinogen level com-
pared with normotensive controls. 34–36 Fibrinogen has
also been shown to be a predictor of subsequent
events, ie, coronary heart disease and stroke. 37,38 In
our study a statistically significant decrease in fibrino-
gen levels was observed after 6 months of treatment,
which was more pronounced in the irbesartan than in
the atenolol group. Previous studies examining the
influence of therapeutic intervention on fibrinogen
plasma levels have shown conflicting results. 39–41 It
has not yet been determined whether the decrease in
fibrinogen levels, whenever observed, is related di-
rectly to BP reduction or is associated with coexisting
properties of the drugs used. It has been suggested
that it may result from hemodilution caused by vaso-
dilating agents or by a decrease in red cell rigidity. 41
No significant influence on the metabolic profile of our
study group that might interfere with fibrinogen val-
ues was observed. Further research is required to es-

It must be noted that because all patients were
previously untreated, no stimulation of the RAS in-
duced by therapies such as diuretics could be expected
to interfere with the measurement of the measured
variables. In addition, the effect of both therapies on
these parameters cannot be attributed to the decline of
BP per se, as baseline BP values, as well as the reduc-
tion in BP after treatment, were similar in both groups.

In our study the novel AT1 receptor antagonist irbe-
sartan was shown to induce a more favorable effect
than atenolol, with respect to a wide range of fibrino-
lytic/hemostatic and endothelial damage markers,
despite an equally controlled BP. Beyond their BP-lowe-
ring potential, antihypertensive agents may exert a
variety of nonhemodynamic effects, such as inducing
changes in metabolic profile, endothelial function, and
fibrinolytic-hemostatic pathways. However, large-
scale intervention trials are required to determine
whether this apparently beneficial effect will result in
reduced morbidity and mortality in hypertensive pa-
tients, as has already been established for β-blockers.

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