The Effect of Regulation of High Blood Pressure on Plasma Endothelin-1 Levels in Blacks With Hypertension
Sitki Ergul, Adviye Ergul, John A. Hudson, David Puett, Bobbye M. Wieman, Marcus D. Durham, and David C. Parish

Plasma concentrations of immunoreactive endothelin-1 (irET-1) are significantly elevated in blacks with hypertension. In the present study, we investigated the effect of the regulation of high blood pressure on plasma irET-1 levels in black hypertensive individuals. After the initial blood samples were collected from 20 black patients with uncontrolled high blood pressure (Day 1), an intensive antihypertensive treatment was initiated, and the blood pressure and plasma irET-1 levels were monitored on days 2, 8, and 22. When the high blood pressure was brought under control with commonly used antihypertensive medications, plasma irET-1 concentrations dropped dramatically, suggesting that ET-1 concentrations rise as a consequence of high blood pressure in this study group. Am J Hypertens 1998;11:1381–1385 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Essential hypertension, endothelin-1, race, antihypertensive treatment, endothelin receptor antagonists.

Hypertension is associated with cardiovascular complications such as heart failure, myocardial infarction, and stroke.1 The prevalence of hypertension and its complications in the U.S. is higher in blacks than in whites, although the reasons for this difference are not well understood.2,3 In a previous study, we found that plasma immunoreactive levels of the potent vasoconstrictor endothelin-1 (irET-1) were significantly higher in a black hypertensive group than in white hypertensive and in white and black normotensive groups.4

Elevated levels of plasma endothelin-1 (ET-1) have been found in some studies of hypertension, atherosclerosis, asthma, acute renal failure, pulmonary hypertension, brain injury, cerebral vasospasm, and chronic heart failure.3 Blockage of endothelin receptors to inhibit the effects of ET-1 in disease states has become an area of research interest. Although results of clinical studies involving endothelin (ET) antagonists in human hypertension have not been reported, ET antagonists have been shown to be effective in animal models of hypertension.6

Our previous study demonstrated high endothelin levels in blacks with uncontrolled hypertension.4 This study was designed to assess the effect of rapid blood pressure control on plasma endothelin levels in this population.

SUBJECTS AND METHODS

Subjects This study was approved by the Medical Center of Central Georgia, Review Committee. Black
Subjects with uncontrolled hypertension were recruited from inpatient and outpatient units of the Medical Center of Central Georgia in Macon, Georgia. Uncontrolled hypertension was defined as a systolic pressure ≥ 160 mm Hg and a diastolic pressure ≥ 95 mm Hg. Blood pressure was measured using a mercury sphygmomanometer after 15 min resting in the supine position. Patients with serum creatinine > 2 mg/dL, pulmonary edema, cardiogenic shock, a myocardial infarction in the last 6 months, diabetes mellitus, congestive heart failure, a cerebrovascular accident in the last 6 months, acute asthma, or angina pectoris were excluded. Individuals with known hypertension who were receiving medical therapy were accepted if their hypertension was currently uncontrolled. As shown in Figure 1A, with the exception of two subjects, all patients presented with elevated irET-1 levels (range, 0.5 to 23.8 pmol/L), compared with normotensive groups in our previous study (1 to 5 pmol/L) and in healthy subjects reported in the literature (1 to 4 pmol/L). One patient, who presented with the highest plasma irET-1 level on Days 1 and 2, did not return for follow-up visits and was dropped from the study. As no blood was obtained, this patient could not be included in the analysis of data on days 8 and 22.

Surprisingly, one patient showed a gradual increase in plasma irET-1 levels despite antihypertensive treatment and blood pressure regulation.

The correlations between weight, age, and irET-1 levels in our previous study, both female and male black hypertensive subjects were included. As shown in Figure 1A, with the exception of two subjects, all patients presented with elevated irET-1 levels (range, 0.5 to 23.8 pmol/L), compared with normotensive groups in our previous study (1 to 5 pmol/L) and in healthy subjects reported in the literature (1 to 4 pmol/L). One patient, who presented with the highest plasma irET-1 level on Days 1 and 2, did not return for follow-up visits and was dropped from the study. As no blood was obtained, this patient could not be included in the analysis of data on days 8 and 22. Surprisingly, one patient showed a gradual increase in plasma irET-1 levels despite antihypertensive treatment and blood pressure regulation.

The irET-1 concentrations and mean arterial blood pressure (MAP) readings measured on days 1, 2, 8, and 22 (mean ± SD) are shown in Figure 1B. Analysis of the MAP and plasma irET-1 data indicated that these variables decreased significantly during the study. Analysis of variance of blood pressure change demonstrated F values 3.51 = 36.9, P < .001; changes in irET-1 were associated with F 3.51 = 52.4, P < .0001. As shown in Figure 1B, when elevated blood pressure was reduced, irET-1 levels exhibited a parallel decrease.

Only two patients were diagnosed with hypertension at the beginning of this study; the remaining subjects were receiving antihypertensive treatment, but their blood pressure was uncontrolled. The duration of hypertension was known with certainty in only 11 subjects. The average length of time patients had been diagnosed with hypertension was 10.5 years and ranged from < 1 year to 27 years. There was no significant correlation between the duration of hypertension and ET-1 levels on Day 1.

The correlations between weight, age, and irET-1

<table>
<thead>
<tr>
<th>TABLE 1. CHARACTERISTICS OF STUDY SUBJECTS</th>
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<tbody>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>No. of patients with known hypertension</td>
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<tr>
<td>History</td>
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<tr>
<td>Age (yr, mean ± SD)</td>
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<tr>
<td>Weight (kg, mean ± SD)</td>
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<tr>
<td>MAP (mm Hg, mean ± SD)</td>
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<td>SBP (mm Hg, mean ± SD)</td>
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<td>DBP (mm Hg, mean ± SD)</td>
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MAP, mean arterial blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.
levels on Day 1 were also analyzed and were not significant. Moreover, as found in our previous study, no significant correlation was observed between the irET-1 levels and the severity of hypertension.

Antihypertensive medications employed in this study were Ca\textsuperscript{2+} channel blockers, ACE inhibitors, and diuretics. If one medication was not sufficient to regulate blood pressure, patients were given a combination regimen. The number of patients who continued receiving any one regimen was not sufficient for statistical analysis. Although there appears to be no substantial difference among the different treatment plans used (data not shown), this issue has to be addressed in a larger study group.

**FIGURE 1.** Distribution of plasma irET-1 in black hypertensive individuals at days 1, 2, 8, and 22 (A) and changes in plasma irET-1 levels and mean arterial blood pressure (MAP, mm Hg) over a 22-day period in black hypertensive patients receiving different antihypertensive regimens, as described in the text (B). The number of patients included at days 1 and 2 is 20 and at days 8 and 22 is 19. * and † indicate that the changes in irET-1 levels and MAP, respectively, compared with Day 1 were statistically significant (P < .001, by repeated measures ANOVA).
DISCUSSION

This report shows that rapid regulation of high blood pressure with conventional antihypertensive drugs lowers the elevated plasma irET-1 levels in black individuals with hypertension. There was no significant correlation between irET-1 and age, weight, or gender in our study group. Although plasma irET-1 concentrations were substantially elevated in most patients with high blood pressure, this elevation did not show any significant correlation with the severity of hypertension.

Whether ET-1 is involved in the etiology of hypertension is still unknown. Several groups have reported that plasma irET-1 levels are not elevated in patients with mild to moderate essential hypertension. However, in some studies, including ours, patients with essential hypertension were found to have higher plasma ET-1 levels than control subjects. We also demonstrated, for the first time, that black hypertensive patients have significantly higher levels of irET-1 than white hypertensives and white or black normotensives, suggesting that ET-1 may be one of the factors in racial differences in the development of hypertension or its complications.

Few studies have assessed racial variations in ET-1 levels. Evans et al reported that irET-1 levels were significantly increased in healthy black men compared with white men, but not in black versus white women. Although normotensive controls were not included in the present study, we previously found no difference in plasma irET-1 levels among white and black female and male individuals with normal blood pressure. Recently, an association between birthplace and mortality from cardiovascular causes among blacks has been reported. The difference in our findings from those reported by others might be related to this interesting observation. Future studies of ET-1 in racially balanced study groups from different areas are required to determine whether ET-1 plays a role in the development of cardiovascular and renal complications of hypertension in black Americans.

In addition to the higher prevalence and severity of hypertension, as well as its complications, in the black population, it has also been reported that blacks are more resistant to antihypertensive treatment and that they respond to Ca++ channel blockers better than ACE inhibitors. In this study, we also observed that when patients were switched to Ca++ channel blockers because their blood pressure was uncontrolled with ACE inhibitors, blood pressure was more easily controlled. Our finding that irET-1 levels decrease upon reduction of high blood pressure in blacks supports the notion that vascular constriction plays a major role in raising the blood pressure in blacks, and also suggests that ET-1 may be involved in mediating the vasoconstriction. Because all the antihypertensive regimens employed in this study lowered the MAP and there was a parallel decrease in irET-1 levels, it is not possible to reach a conclusion about the mechanism by which control of high blood pressure lowered plasma irET-1 levels. The change might be due to a direct effect of these agents on ET-1 production or it may reflect an indirect result of the lowering of blood pressure. In the same context, we cannot distinguish to what extent the reduction in irET-1 levels reflects a lowering of blood pressure versus a reduction in the salt-dependent component of blood pressure.

In conclusion, we found that elevated plasma irET-1 levels in blacks with hypertension normalize when the high blood pressure is controlled using conventional antihypertensive therapy. Future studies with endothelin receptor antagonists are needed to assess whether ET-1 is involved in the pathogenesis of hypertension. In addition, long-term follow-up studies are required to investigate whether ET-1 plays a role in the development of cardiovascular and renal complications of hypertension in black Americans.

REFERENCES


