

Increased sensitivity to bradykinin among African Americans

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Background: Angioedema is a potentially life-threatening side effect of angiotensin-converting enzyme (ACE) inhibitors. Although the mechanism of angioedema is not certain, bradykinin has been implicated in its pathogenesis. Compared with Caucasians, African Americans are at an increased risk of ACE inhibitor-associated angioedema, independent of ACE inhibitor dose or concurrent medications. Because urinary kallikrein levels are decreased in African Americans with hypertension, we hypothesized that endogenous bradykinin levels may be decreased in African Americans and that they therefore may be more sensitive to ACE inhibitor-induced increases in bradykinin or to exogenous bradykinin.

Objective: To test this hypothesis, we measured the wheal response to intradermal injection of bradykinin in salt-replete hypertensive and normotensive African Americans and Caucasians.

Methods: Two doses of bradykinin, 1 μ g and 10 μ g, were administered on separate days in a randomized, double-blind fashion.

Results: Higher bradykinin dose (analysis of variance: $F = 38.33$, $p < 0.001$), African American race (analysis of variance: $F = 17.90$, $p < 0.001$), and hypertension (analysis of variance: $F = 4.37$, $p = 0.05$) were all associated with an increased wheal response to bradykinin.

Conclusion: These data provide additional support for racial differences in the kallikrein-kinin system and also implicate abnormalities of the tissue kallikrein-kinin system in essential hypertension. (*J Allergy Clin Immunol* 1996;98:283-7.)

Key words: Bradykinin, angioedema, race, ACE inhibitor, intradermal, wheal, hypertension, kininase II

Angioedema is a potentially life-threatening side effect of angiotensin-converting enzyme (ACE) inhibitors characterized by well-demarcated swelling of the lips, face, and oropharynx.¹ Although the mechanism of angioedema is not certain, bradykinin has been implicated in the pathogenesis of this side effect. ACE inhibitors block the breakdown of bradykinin, a potent vasodilator and mediator of capillary leakage.¹ Activation of the kinin-kallikrein system appears to play a role in hereditary forms of angioedema.² Plasma from patients with hereditary angioedema demonstrates kinin-like ac-

Abbreviations used

ACE: Angiotensin-converting enzyme
ANOVA: Analysis of variance

tivity.³ Dialysis membranes that cause anaphylactoid reactions resembling angioedema in patients taking ACE inhibitors activate the kinin-kallikrein system,⁴ and bradykinin receptor antagonists block these anaphylactoid reactions.⁵

African American patients taking ACE inhibitors are at increased risk of angioedema compared with Caucasian patients. This effect is independent of either ACE inhibitor dose or concurrent medications.⁶ Levy et al.⁷ have shown that African Americans with hypertension have lower urinary kallikrein levels than do Caucasians with hypertension. Taken together, these data suggest that endogenous bradykinin levels may be lower in African Americans than in Caucasians. If this is the

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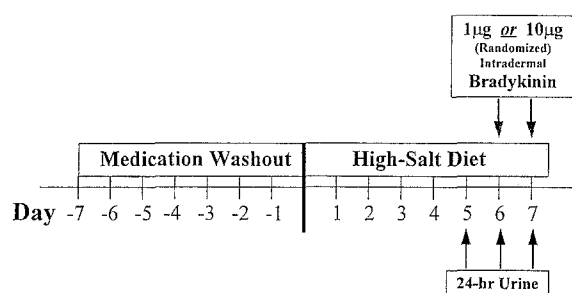


FIG. 1. Study protocol.

case, then African Americans may be more sensitive than Caucasians to ACE inhibitor-induced increases in bradykinin or to exogenous bradykinin. The purpose of this study was to test the hypothesis that African Americans are more sensitive to exogenous bradykinin than are Caucasians. To do this, we compared the wheal response to an intradermal injection of bradykinin in salt-replete normotensive and hypertensive African Americans and Caucasians. This wheal response to bradykinin may provide a model for the intradermal swelling seen in patients with angioedema.

METHODS

Men and women, aged 18 to 65 years, were eligible for study. Four groups of subjects were studied: normotensive African Americans, normotensive Caucasians, hypertensive African Americans, and hypertensive Caucasians. Subjects were considered to have hypertension if they had an untreated diastolic blood pressure of 90 mm Hg or greater on three occasions. Subjects with significant comorbid disease or secondary hypertension were excluded by history and physical examination and laboratory testing, including renal arteriogram if appropriate. All subjects gave written informed consent, and the study was approved by the Institutional Review Board of Vanderbilt University.

Fig. 1 shows the randomized, double-blind study design. All medications were discontinued for at least 1 week before initiation of a high-salt diet. Subjects remained on a 200 mEq sodium, 100 mEq potassium, 2500 ml water per day caffeine-free diet for an additional 7 days. To measure dietary compliance and ensure sodium balance, 24-hour urinary sodium collections were performed on diet days 5, 6, and 7. On diet days 6 and 7, subjects were randomly assigned to receive, in double-blind fashion, either a 1 µg or 10 µg (mixed in 0.1 ml of normal saline solution) intradermal bradykinin injection in the volar forearm. Wheal response (in square millimeters) was assessed by the same investigator at 15 minutes after injection. Only two doses of bradykinin were administered to limit the number of days patients with hypertension were ingesting a high-salt diet while not receiving antihypertensive medications. The doses of

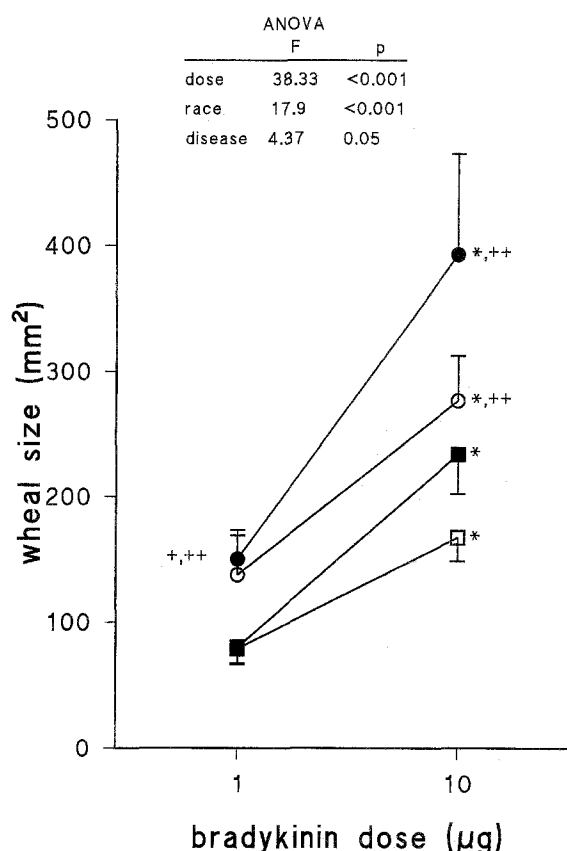


FIG. 2. Mean wheal sizes $\pm$ SEM for the 1 µg and 10 µg doses measured at 15 minutes in hypertensive (filled circles) and normotensive (open circles) African Americans and hypertensive (filled squares) and normotensive (open squares) Caucasians. * $p < 0.001$ versus 1 µg dose in same group. † $p < 0.03$ versus Caucasian patients with hypertension. †† $p < 0.03$ versus Caucasian normotensive subjects.

bradykinin were chosen to be at the low and high ends of the dose-response curve on the basis of previously published data.⁸⁻¹³ In the first subject studied, doses were repeated in a blinded fashion on a separate day, and the wheal response to a given dose of bradykinin was found to be reproducible.

The wheal area was outlined and defined to be the average of three measurements with the Jandel Scientific Graphic Digitizer (model 2210; Jandel Scientific Corp., San Rafael, Calif.) and Sigma-Scan (Version 3.90, Jandel Scientific Corp.). Data are presented as the means $\pm$ SEM for a given race, disease, and bradykinin dose. The effects of bradykinin dose, race, and disease on wheal size were compared by using repeated-measures analysis of variance (ANOVA) in which the within-subjects factor was bradykinin dose and the between-subjects factors were race and disease state (hypertension vs normotensive). Post hoc comparisons were made by using paired or unpaired t tests, as appropriate. Reported p values are from the t tests

TABLE I. Subject characteristics

	Caucasian		African American	
	HTN	NT	HTN	NT
Age (yr)	41.3 ± 5.0	32.5 ± 3.1	47.2 ± 7.0	35.7 ± 6.2
Gender (M/F)	3/3	3/3	4/1	3/3
MAP (mm Hg)	108.5 ± 2.5*	85.6 ± 3.9	108.1 ± 4.3†	90.4 ± 3.7
Urinary Na ⁺ (mEq/L/day)	138.8 ± 21.5	162.6 ± 16.9	168.3 ± 21.1	145.5 ± 15
Weight (lb)	217.7 ± 30.1	152.8 ± 12.4	186.2 ± 10.2	170.3 ± 12

Means ± SEM are shown.

HTN, Hypertensive; NT, normotensive; MAP, mean arterial pressure.

* $p < 0.001$ versus Caucasian normotensive subjects.

† $p < 0.02$ versus African American normotensive subjects.

unless indicated ANOVA; p values less than 0.05 were considered significant.

RESULTS

Table I displays subject characteristics. Twenty-three men and women were studied. The hypertensive African American group had four men and one woman; otherwise, each group had three men and three women. The mean arterial blood pressure was significantly higher in the subjects with hypertension than in the normotensive subjects (109 vs 86 mm Hg, $p < 0.001$ in Caucasian and 108 vs 90 mm Hg, $p < 0.02$ in African American groups). There were no other significant differences in age, gender, weight, or the average of three measurements of 24-hour urinary sodium excretion among the subjects. A family history of hypertension was present in 90% of the subjects with hypertension and 50% of the normotensive subjects.

Intradermal injection of both 1 μ g and 10 μ g doses of bradykinin resulted in a measurable wheal, which peaked in size at 15 minutes. A flare response was observed in one fourth of the subjects and generally persisted for about 5 to 7 minutes after injection.

Fig. 2 shows the mean wheal sizes by race (African American, Caucasian), disease (hypertensive, normotensive), and dose (1 μ g, 10 μ g). Bradykinin dose was significantly associated with wheal size (ANOVA, $F = 38.33$, $p < 0.001$). As determined by paired t test, higher dose was associated with increased mean wheal size ($p < 0.001$) in all four groups. At the lower dose, African American subjects with hypertension had significantly larger mean wheal size than Caucasians, either those with hypertension ($p < 0.03$) or Caucasian normotensive subjects ($p < 0.02$). At the higher dose, mean wheal sizes of African American normotensive subjects were significantly larger than those of Caucasian normotensive subjects

($p < 0.03$). African Americans had, on average, 70% larger wheal sizes than did the Caucasian group. The subjects with hypertension had 48% larger wheal sizes than the normotensive subjects. Wheal sizes were not significantly different between male and female subjects.

DISCUSSION

This is the first study to demonstrate increased sensitivity to exogenous bradykinin in African Americans compared with Caucasians and in patients with hypertension compared with normotensive subjects.

In this study, the wheal response to an intradermal injection of bradykinin was used to measure sensitivity to bradykinin. Bradykinin has been shown to cause a measurable and reproducible wheal when injected intradermally into the forearm of either normotensive subjects or patients with hypertension.⁸⁻²³ In some studies, a flare response has been reported as well.^{10, 11, 16-23} This model has been used to demonstrate that ACE inhibitors potentiate the effects of bradykinin in human beings.* One of the limitations of this model is that the measurement of wheal size can be subjective; because the investigator could not be blinded to the race of the subject, this may have introduced bias into the study. In an attempt to minimize bias we administered two doses of bradykinin in a randomized, double-blind fashion. The dramatic relationship between dose and wheal size suggests that this strategy was valid. In addition, the wheal sizes measured in the Caucasian subjects in this study are similar to wheal sizes measured in response to similar doses of bradykinin in previously published studies.⁸⁻²²

Studies with B₁- and B₂-selective agonists suggest that the wheal response to bradykinin is

*References 8, 9, 11-13, 18, and 22.

mediated through the B₂ receptor.¹⁷ Although the exact mechanism of the wheal response is not known, this response does not appear to involve either prostaglandins^{11, 12, 23} or histamine.^{10, 22, 23} Thus nonsteroidal antiinflammatory drugs do not alter the wheal response to bradykinin,^{11, 12, 23} although Ferner et al.¹³ did show that sulindac reduced the dose-dependent increase in skin thickness in response to bradykinin in patients taking ACE inhibitors. The wheal response to bradykinin is not blocked by the histamine antagonists terfenadine, chlorpheniramine, and cimetidine.^{10, 22, 23} Studies with capsaicin suggest that tachykinins, such as substance P, may mediate the flare response to bradykinin²⁴; however, capsaicin has been shown both to inhibit²⁴ and have no effect²⁵ on the wheal response to bradykinin.

The mechanism that underlies the increase in wheal response to bradykinin in African American subjects is also not known. One possible explanation is that African Americans have decreased tissue levels of bradykinin.²⁶ In support of this hypothesis, Levy et al.⁷ have shown that urinary kallikrein excretion is decreased in salt-deplete hypertensive African Americans compared with hypertensive Caucasians. Because of difficulties in obtaining reliable, reproducible bradykinin levels, urinary kallikrein has been used to infer the activity of the kinin system. Margoilius²⁷ and others have shown that urinary kallikrein is lower in African American children than in Caucasian children and that urinary kallikrein correlates inversely with blood pressure. Further, ACE is largely responsible for degradation of bradykinin, and baseline ACE levels are noted to be higher in African Americans with hypertension compared with Caucasians with hypertension.²⁸ Because bradykinin levels have been shown to regulate B₂ receptors²⁹ and because decreased kallikrein excretion has been associated with increased bradykinin receptor density in a hypertensive animal model,³⁰ decreased tissue bradykinin levels in African Americans then could lead to receptor upregulation and increased sensitivity to exogenous bradykinin. Because ACE inhibitors block degradation of bradykinin, a similar mechanism could underlie the increased susceptibility of angioedema in African Americans.

In this study the wheal response to bradykinin tended to be greater in subjects with hypertension than in normotensive subjects, although this finding was of borderline significance (ANOVA, $F = 4.37$, $p = 0.05$). Again, decreased activity of the kallikrein-kinin system in essential hypertension could account for this increased sensitivity to bradykinin. Elliot and Nuzum³¹ first reported reduced urinary excretion of

kallikrein in patients with hypertension in 1934. Reduced renal or urinary kallikrein levels have been implicated in several animals models of hypertension.³² A gene for high urinary kallikrein appears to protect against hypertension in several large Utah pedigrees.³³ Administration of porcine pancreatic kallikrein lowers blood pressure in patients with hypertension.³⁴ On the other hand, intrinsic differences in the bradykinin receptor could account for the increased wheal response to bradykinin observed in African Americans and, possibly, patients with hypertension.

This study is the first to examine responses to intradermal bradykinin with specific regard to race and hypertension and provides support for racial differences in the kinin system. Further characterization of these differences may allow delineation of the role of bradykinin in the development of essential hypertension and ACE inhibitor-associated angioedema, as well as the identification of susceptible individuals.

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