Effect of ACE Inhibitor on DOCA-Salt– and Aortic Coarctation–Induced Hypertension in Mice
Do Kinin B2 Receptors Play a Role?

Nour-Eddine Rhaleb, Hongmei Peng, Marcos E. Alfie, Edward G. Shesely, Oscar A. Carretero

Abstract—Kinins have been shown to play an important role in the cardioprotective effect of ACE inhibitors (ACEi) during heart failure and ischemia-reperfusion. However, it is controversial as to whether kinins oppose the hypertensinogenic effect of deoxycorticosterone acetate plus salt (DOCA-salt) or aortic coarctation and whether they mediate both chronic antihypertensive and cardiac antihypertrophic effects of ACEi in hypertension. Using normal 129/SvEvTac mice and mice lacking the bradykinin B2 receptor gene (B2-KO), we investigated whether (1) the hypertensinogenic effect of DOCA-salt or aortic coarctation is enhanced in B2-KO mice and (2) the chronic antihypertensive and antihypertrophic effects of an ACEi (ramipril, 4 mg \( \cdot \) kg\(^{-1} \cdot \) d\(^{-1} \)) are mediated by B2 receptors in aortic coarctation (6 weeks)– and DOCA-salt (4 weeks)–induced hypertension. Before surgery, there was no difference between 129/SvEvTac and B2-KO mice in terms of blood pressure and heart weight, suggesting that kinins are not essential to maintaining normal blood pressure. DOCA-salt (volume expansion) or aortic coarctation (renin-dependent) induced similar hypertension and left ventricular hypertrophy (LVH) in 129/SvEvTac and B2-KO mice, suggesting that kinins do not play an essential role in the development of DOCA-salt– or aortic coarctation–induced hypertension. We found that B2 receptors mediate only the early (1 week) but not the late phase (4 weeks) of the chronic hypotensive effect of ACEi in DOCA-salt hypertension. On the other hand, chronic ACE inhibition prevented the development of hypertension and LVH in both 129/SvEvTac and B2-KO mice given DOCA-salt or subjected to aortic coarctation, suggesting that kinins do not participate in the chronic antihypertensive and antihypertrophic effects of ACEi in these 2 models of hypertension. Thus, in mice, kinins acting via B2 receptors do not participate in (1) maintenance of normal basal blood pressure, (2) establishment and maintenance of hypertension induced by DOCA-salt or aortic coarctation, and (3) chronic antihypertensive and cardiac antihypertrophic effects of ACEi in DOCA-salt and aortic coarctation hypertension. (Hypertension. 1999;33[part II]:329-334.)

Key Words: receptors, bradykinin ■ angiotensin-converting enzyme inhibitors ■ deoxycorticosterone ■ coarctation, aortic ■ blood pressure ■ gene regulation

Kinins are endogenous vasodilators that act as autocrine/paracrine hormones by activating the release of endothelium-derived relaxing factors and prostaglandins.1,2 They act mainly via at least 2 distinct types of receptors, B1 and B2.3 Most of the known physiological effects of kinins are mediated by B2 receptors, which belong to a family of 7-transmembrane domains for hormone receptors linked to G proteins. Angiotensin-converting enzyme inhibitors (ACEi) act mainly by (1) abolishing the conversion of angiotensin (Ang) I to Ang II, a potent vasopressor agent, and (2) inhibiting the breakdown of bradykinin into inactive fragments.4,5 Locally produced kinins appear to play an important role in the protective effect of ACEi in myocardial infarction-induced cardiac dysfunction6 and preconditioning in a rat model of ischemia-reperfusion.7 These protective effects were absent when B2 receptors were inhibited with a kinin B2 receptor antagonist (icatibant or Hoe 140). Ischemia preconditioning was also absent in rats deficient in kininogen and mice with the bradykinin B2 receptor gene disrupted.7 B2 receptor antagonists have also been reported to completely prevent the antihypertensive and antihypertrophic effects of ACE inhibitors in rats subjected to aortic coarctation8; this finding was not confirmed in our laboratory.9 In addition, it has been shown that deoxycorticosterone (DOCA)-salt hypertension is associated with increased activity of the kallikrein-kinin system10,11 and suppression of the plasma renin-angiotensin system.12 In this regard, Majima et al13 found that DOCA-salt induced a faster rise in systolic pressure in kinin-deficient rats (Brown Norway Katholiek, BNK) than controls; moreover, BNK given a high-salt diet or chronic infusion of Ang II become hypertensive compared with controls.14,15 On the other hand, using a different

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approach, Madeddu et al.\textsuperscript{16,17} reported that chronic blockade of B2 receptors with icatibant made rats hypertensive when given a high-salt diet or chronically infused with Ang II. Both Majimura and Madeddu concluded that kinins prevent the chronic hypertensinogenic effect of DOCA-salt, high salt or Ang II. However, neither of these findings was confirmed in our laboratory, for reasons that are unclear (Rhaleb et al., unpublished data, 1998). To further document the role of kinins in (1) the development and maintenance of hypertension and (2) the antihypertensive and antihypertrophic effect of chronic ACEi, we used mice with the bradykinin B2 receptor gene disrupted by gene targeting (B2-KO).\textsuperscript{18} We determined whether the absence of B2 kinin receptors (1) affects basal blood pressure (BP), (2) potentiates the hypertensinogenic effect of DOCA-salt (volume-dependent) or aortic coarctation (renin-dependent) in mice, and (3) whether the antihypertensive and antihypertrophic effects of chronic ACE inhibition are mediated by kinins acting via B2 receptors in DOCA-salt– or aortic coarctation–induced hypertension.

**Methods**

**Animals**

Nine- to 12-week-old male 129/SvEvTac and B2-KO mice weighing 23 to 26 g were used for these experiments. Homozygous B2-KO mice were provided by Fred Hess (Merck Laboratories); they were derived from breeding pairs generated by gene targeting. The B2-KO homozygous (−/−) breeding pairs were derived from an inbred strain on a 129Sv genetic background and routinely genotyped in our laboratory for the disrupted Bdkrb2 (B2 receptor) gene. 129/SvEvTac mice were purchased from Taconic Farms (Germantown, NY) and served as controls. Mice were housed in an air-conditioned room with a 12-hour light/dark cycle, received standard mouse chow (Rodent Laboratory Chow, Purina Mills) and drank tap water. This study was approved by the Henry Ford Hospital Care of Experimental Animals Committee.

**DOCA-Salt Hypertension**

A silicone rubber sheet containing DOCA (Sigma) at a silicone:DOCA ratio of 3:1 was implanted subcutaneously at a dose of 10 mg per 10 g in uninephrectomized mice. Mice receiving DOCA were given a solution of 1% NaCl and 0.2% KCl to drink. Systolic BP (SBP) was measured 3 times a week for 4 weeks. Animals were divided into 3 groups: (1) controls receiving tap water, (2) mice receiving DOCA-salt, and (3) mice receiving DOCA-salt + ramipril (4 mg·kg·s·d\(^{-1}\) in drinking water) (donated by Hoechst, Cincinnati, Ohio). Treatment started immediately after surgery and continued for 4 weeks.

**Aortic Coarctation-Induced Hypertension**

U-shaped silver clips with a luminal gap fixed at 0.203 mm were used. Mice were anesthetized with pentobarbital (80 mg/kg IP); the muscle layer was sutured and the skin incision closed. The sham operation included the entire aortic arch and the skin incision closed. The sham operation included the entire surgical procedure, except that the aorta was not clipped. Animals were divided into 3 groups: (1) sham, (2) mice receiving aortic coarctation, and (3) mice receiving aortic coarctation + ramipril (4 mg · kg·s·d\(^{-1}\) in drinking water). Treatment started immediately after surgery and continued for 6 weeks.

**BP and Tissue Weight**

SBP and heart rate (HR) were determined using a validated noninvasive computerized tail-cuff system (BP-2000, Visitech Systems).\textsuperscript{19} Mice were trained for 1 week and measurements recorded every 2 days thereafter for 4 weeks. Each session included 2 sets of 10 measurements; to include each set of measurements for an individual mouse, the computer had to identify a BP successfully in at least 6 of the 10 trials within the set. We averaged the data for 3 days per week, then expressed them as 1 SBP and 1 HR per week for each mouse. At the end of the study, direct mean arterial pressure (MAP) and HR were measured via the femoral artery for mice given DOCA-salt or the common carotid artery for mice with aortic coarctation. After anesthesia, a modified polyethylene catheter (PE-10 fused to PE-50; Clay-Adams) was passed into the aorta via either the femoral or carotid artery and subcutaneously brought to the back of the neck. Mice were allowed to recover from anesthesia for 24 hours and then placed in a customized plastic restrainer (Falcon 50-mL tubes, Fisher). Arterial cannulas were connected to BP transducers and monitored on a 4-channel recorder (Brush 440, Gould). BP was recorded continuously in restrained and awake mice in a quiet environment for 30 minutes at 30-sec intervals. After determining BP, mice were anesthetized with 50 mg/kg pentobarbital sodium; the heart was excised, cleaned of blood with saline, and gently blotted to dryness, and left ventricular weight including the septum (LVW), right ventricular (RVW), atrial (AW), and kidney weight (KW) were determined and normalized to 10 g body wt.

**Determination of Plasma Renin Concentration in DOCA Groups**

Before and 4 weeks after starting DOCA, blood (30 μL) was collected in a preheparinized pipette from ether-anesthetized mice by puncturing the retro-orbital plexus. Plasma renin concentration (PRC) was determined using a method previously described by Harding et al.\textsuperscript{20} Briefly, plasma (2 μL) was incubated in medium containing a peptidase inhibitor cocktail (3% PMSF in methanol and 3.8% EDTA, pH 6.5) and 250 ng sheep angiotensinogen (expressed in terms of capacity to release Ang I) at 37°C for 30 minutes in a final volume of 200 μL. To terminate the reaction, samples were boiled for 15 minutes and centrifuged at 1680g for 10 minutes and the supernatants were removed. Generated Ang I was measured by a radioimmunoassay using previously published methods,\textsuperscript{21} and the results were expressed as ng Ang I per mL of plasma per hour. Experiments designed to test the validity of this assay have demonstrated that <1% of the substrate is consumed under these conditions and have shown linearity of product generated with time. Nephrectomized sheep angiotensinogen was used as a substrate, since it is known that mouse renin can release Ang I from this heterologous substrate.\textsuperscript{22}

**Statistics**

All data were expressed as mean±SEM. For DOCA-salt hypertension, ANOVA with an interaction effect and Student’s 2-sample *t* test were used to evaluate differences between 129/SvEvTac and B2-KO mice. Paired *t* tests were performed to look at the early hypertensive effect of ACEi. An adjusted α level of 0.01 was used to determine statistical significance due to multiple comparisons. For aortic coarctation-induced hypertension, all data were analyzed using ANOVA. Groups were compared with the control using Dunnett’s test; this adjusts the *P* value from multiple testing while using a pooled estimate of variance. In this case, the familywise *P* value for testing was 0.05.

**Results**

**DOCA-Salt Hypertension**

Basal systolic pressure (SBP) was 109±2 mm Hg (n=20) in 129/SvEvTac mice and 113±3 mm Hg (n=18) in B2-KO mice. SBP tended to be higher in B2-KO mice, but the difference was not significant (Figure 1). Four weeks after treatment with DOCA-salt, SBP was significantly higher in 129/SvEvTac mice given DOCA-salt (139±3 mm Hg; n=27) than controls (123±3; n=19) (*P*<0.001); similarly, SBP was
significantly higher in DOCA-salt–treated B₂-KO mice (144 ± 2 mm Hg; n = 27) than controls (117 ± 5; n = 15) (P < 0.001) (Figure 1). SBP tended to be greater in B₂-KO mice given DOCA-salt compared with 129/SvEvTac; at week 4, SBP increased by 27 mm Hg in B₂-KO mice and 16 mm Hg in 129/SvEvTac, but the difference was not significant (P = 0.07). However, at the end of the study, MAP was similar in both DOCA-salt–treated 129/SvEvTac [153 ± 6 mm Hg; (n = 14)] and B₂-KO mice [150 ± 4 mm Hg; (n = 13)], and was higher than the respective controls [125 ± 6 (n = 11) and 124 ± 4 mm Hg (n = 12); P < 0.005] (Table 1).

During the first 3 weeks, the ACEi ramipril (4 mg · kg⁻¹ · d⁻¹) prevented hypertension in DOCA-salt B₂-KO but only partially in 129/SvEvTac mice (Figure 2). However, at 4 weeks SBP was significantly lower in both strains given DOCA-salt plus ACEi than DOCA-salt alone but similar to controls (P < 0.001) (Figure 2). In addition, an early hypotensive effect of ACEi was observed at 1 week in 129/SvEvTac (from 112 ± 2 to 96 ± 5 mm Hg; P < 0.005) but was absent in B₂-KO mice (114 ± 2 versus 113 ± 4 mm Hg). At the end of the study, ACEi significantly prevented hypertension in DOCA-salt–treated 129/SvEvTac mice with a MAP of 126 ± 4 mm Hg (n = 14) and B₂-KOs with 126 ± 5 mm Hg (n = 8); these values were not different from controls but were significantly lower than those measured in mice given DOCA-salt alone (P < 0.005) (Table 1). Heart rate was similar in all groups. There was no significant difference between 129/SvEvTac and B₂-KO mice in terms of AW, LVW, RVW, or KW either under control conditions or during DOCA-salt administration; LVW was significantly higher in DOCA-salt

![Figure 1](image1.png) Time-dependent increase in tail-cuff SBP in uninephrectomized male 129/SvEvTac and B₂-KO mice given DOCA plus 1% NaCl and 0.2% KCl (DOCA-salt). Basal SBP was similar in both strains. At week 4, DOCA-salt induced similar increased SBP in both strains. SBP increased slightly faster in B₂-KO mice than in 129/SvEvTac, but the difference was not significant. *P < 0.05 and **P < 0.005 versus baseline.

![Figure 2](image2.png) Effect of ACEi (ramipril, 4 mg · kg⁻¹ · d⁻¹) on DOCA-salt hypertension in 129/SvEvTac (upper panel) and B₂-KO mice (lower panel) given DOCA-salt. At week 1, the acute hypotensive effect of ACEi was absent in B₂-KO mice. At week 4, SBP was significantly lower in both strains given DOCA-salt plus ACEi than DOCA-salt alone. *P < 0.05 and **P < 0.005 versus DOCA-salt + ACEi.

### TABLE 1. Effect of ACEi on Body Weight, AW, RVW, and Total Heart Weight in 129/SvEvTac and B₂-KO Mice Given DOCA-Salt

<table>
<thead>
<tr>
<th></th>
<th>129/SvEvTac</th>
<th></th>
<th>B₂-KO</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DOCA-Salt</td>
<td>DOCA-Salt+ACEi</td>
<td>Control</td>
</tr>
<tr>
<td>BW, g</td>
<td>27.8 ± 0.7</td>
<td>26.9 ± 2.6</td>
<td>29.4 ± 0.7</td>
<td>25.9 ± 0.4</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>125 ± 6</td>
<td>153 ± 8*</td>
<td>126 ± 4</td>
<td>124 ± 4</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>556 ± 34</td>
<td>620 ± 27</td>
<td>646 ± 26</td>
<td>550 ± 36</td>
</tr>
<tr>
<td>AW, mg/10 g BW</td>
<td>2.5 ± 0.2</td>
<td>3.4 ± 0.3*</td>
<td>2.4 ± 0.2</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>RVW, mg/10 g BW</td>
<td>7.9 ± 0.4</td>
<td>9.0 ± 0.3</td>
<td>8.5 ± 0.5</td>
<td>7.6 ± 0.2</td>
</tr>
<tr>
<td>LW, mg/10 g BW</td>
<td>34.5 ± 0.8</td>
<td>44.1 ± 2.0*</td>
<td>35.3 ± 1.2</td>
<td>36.4 ± 1.2</td>
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<tr>
<td>THW, mg/10 g BW</td>
<td>44.9 ± 0.9</td>
<td>56.5 ± 2.2*</td>
<td>46.2 ± 1.7</td>
<td>46.3 ± 4.5</td>
</tr>
<tr>
<td>KW, mg/10 g BW</td>
<td>91.9 ± 2.5</td>
<td>117.1 ± 3.5*</td>
<td>113.1 ± 3.5</td>
<td>101.0 ± 2.9</td>
</tr>
</tbody>
</table>

BW indicates body weight; THW, total heart weight.

*P < 0.05, †P < 0.005 vs control; ‡P < 0.005 vs 129/SvEvTac.
mice versus their respective controls in 129/SvEvTac [44.1±2 mg per 10 g (n=22) versus 34.5±1.2 (n=16)] and B2-KO mice [43.6±1.3 mg per 10 g (n=28) versus 36.4±1.2 (n=16); P<0.001] (Table 1). DOCA-salt hypertension was also associated with significantly increased AW and RVW compared with the respective controls, reaching similar values in both 129/SvEvTac and B2-KO mice (Table 1). ACE inhibition resulted in reduced AW and LVW in 129/SvEvTac and B2-KO, becoming similar to the respective controls (Table 1). Unexpectedly, chronic DOCA-salt only attenuated but did not suppress plasma renin concentration (PRC) in 129/SvEvTac [from 1323±489 to 297±72 ng · mL⁻¹ · h⁻¹ Ang I (n=8 to 10); P=0.055] and B2-KO mice [from 620±78 to 369±83 ng · mL⁻¹ · h⁻¹ Ang I (n=9); P<0.05] (Figure 3). There was no difference between 129/SvEvTac and B2-KO mice either before or after DOCA-salt treatment.

**Aortic Coarctation-Induced Hypertension**

Aortic coarctation for 6 weeks induced hypertension in both 129/SvEvTac and B2-KO mice. MAP increased to a similar extent in both strains, becoming higher than the sham group [167±4 (n=8) versus 138±3 mm Hg (n=9); P<0.05] for 129/SvEvTac mice and [169±8 (n=7) versus 131±4 mm Hg (n=8); P<0.05] for B2-KO mice, while heart rate was the same in all 3 groups (Table 2). Aortic coarctation-induced hypertension was associated with greater LVW compared with the respective controls in both 129/SvEvTac mice [42.5±1.0 mg per 10 g BW (n=31) versus 34.3±0.5 (n=29); P<0.001] and B2-KO mice [48.0±4.1 mg per 10 g (n=13) versus 34.1±1.1 (n=13); P<0.005] (Table 2). Although the difference did not reach significance, we found that hypertensive B2-KO mice had greater LVW than 129/SvEvTac mice (P=0.21). Chronic treatment with ACEi prevented hypertension similarly in both 129/SvEvTac and B2-KO, leading to MAP values of 131±12 (n=7) and 123±11 (n=8) mm Hg, respectively (P<0.05). ACEi also prevented left ventricular hypertrophy, leading to a LVW of 33.3±1 mg per 10 g (n=10) for 129/SvEvTac mice given DOCA-salt and ACEi and 30.2±1.2 mg per 10 g (n=11) for B2-KO (P<0.05). No significant changes were observed for body weight, AW, or RVW due to hypertension in either strain.

**Discussion**

These results indicate that basal BP and LVW are no different in wild-type mice (129/SvEvTac) versus mice lacking B2 receptors (B2-KO), confirming the findings of Alfie et al but not those of Madeddu et al. Madeddu et al found that B2-KO mice had higher BP and greater LVW compared with 129 Sv/J mice. While we could not explain these conflicting results, we may attribute the differences to the genetic background of the controls. Indeed, we chose 129/SvEvTac mice as our controls because they are genetically closer to 129Sv/J than is the case for 129Sv/J. We based our decision on a recent study examining simple sequence-linked polymorphisms among various mouse 129 substrains. This study showed that there were fewer differences between 129/SvEvTac and either of the 2-129 substrains (ES cell line AB 2.1 from J129/Sv and J129/SvEv) previously used by Borkowski et al comprising the B2-KO mouse genetic background than is the case for 129Sv/J.

The systematic observation of higher MAP values compared with SBP could result from 2 possibilities: (1) mice were trained for 1 week before SBP was measured and thereafter every 2 days for 4 weeks, whereas MAP was measured only 24 hours after the mouse recovered from

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**Table 2. Effect of ACEi on Blood Pressure, BW, AW, RVW, and THW in 129/SvEvTac and B2-KO Mice Subjected to Aortic Coarctation**

<table>
<thead>
<tr>
<th></th>
<th>129/SvEvTac</th>
<th>B2-KO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Aortic Coarctation</td>
</tr>
<tr>
<td>BW, g</td>
<td>26.9±0.5</td>
<td>27.2±0.5</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>138±3</td>
<td>167±4*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>580±46</td>
<td>585±39</td>
</tr>
<tr>
<td>AW, mg/10 g BW</td>
<td>3.1±0.2</td>
<td>3.3±0.2</td>
</tr>
<tr>
<td>RVW, mg/10 g BW</td>
<td>8.4±0.2</td>
<td>9.1±0.2</td>
</tr>
<tr>
<td>LWV, mg/10 g BW</td>
<td>34.3±0.5</td>
<td>42.5±1.0*</td>
</tr>
<tr>
<td>THW, mg/10 g BW</td>
<td>45.8±0.6</td>
<td>54.9±1.2*</td>
</tr>
</tbody>
</table>

Abbreviations as in text and Table 1.

*P<0.005 vs control.
anesthesia; therefore mice would be under less stress during SBP measurements; and (2) SBP was measured in mice placed on a continuously heated plate (38°C), which may cause dilatation and decreased BP, while MAP was measured in mice placed in a restrainer at room temperature.

DOCA-salt or aortic coarctation induced hypertension and increased LVW in a similar manner in 129/SvEvTac and B2-KO mice, suggesting that kinins do not play a role in the establishment and maintenance of high BP and left ventricular hypertrophy in these hypertension models. This finding is not compatible with results of Majima et al.13 and Madeddu et al.,16 who found an exaggerated BP response to DOCA-salt in kinin-deficient rats (BNK) or normal rats that were chronically treated with a B2 receptor antagonist.

Surprisingly, PRC was only partially reduced in 129/SvEvTac and B2-KO mice when given DOCA-salt compared with their respective baselines. The remaining PRC in DOCA-salt mice could be due to the existence of 2 genes expressing renin in 129/SvEvTac and B2-KO mice, namely Ren-1, which expresses renin in the juxtaglomerular apparatus of the kidney, and Ren-2, which expresses renin mainly in the convoluted tubular cells of the submaxillary gland and at very low levels in the kidney.26,27 However, it is unclear how the expression of renin from Ren-2 would be affected by DOCA-salt in 129/SvEvTac and B2-KO mice. Conversely, PRC was suppressed by approximately 90% in mice with 1 renin gene (Ren-1, Balb/c) given DOCA-salt;28; this is in accord with the 82% PRC suppression and undetectable plasma renin activity observed in rats (1 renin gene) given DOCA-salt.29,30 Nevertheless, the remaining high PRC may explain why ACE prevented hypertension and LVW in DOCA-salt mice of both strains, suggesting that the renin-angiotensin system may still be functional during DOCA-salt administration; other mechanisms may also account for the chronic effect of ACEi, such as peptides that are also catabolized by ACE, including substance P,31 vasoactive intestinal peptide, met-enkephalin,32 and acetyl-Ser-Asp-Lys-Pro-COOH (AcSDKP).33

Moreover, we found that B2 receptors mediate only the early but not the late phase of the chronic hypertensive effect of ACEi. This finding is compatible with previous results showing that administration of the ACEi ramipril over 1 week34 or captopril over 60 minutes35 gradually lowered BP in DOCA-salt hypertensive rats and that this effect was completely prevented by a concomitant B2 kinin receptor antagonist (icatibant).

Our study also showed that chronic ACEi in mice subjected to aortic coarctation completely blunted hypertension and increased LVW in both 129/SvEvTac and B2-KO strains, suggesting that kinins do not mediate the chronic antihypertensive and antihypertrophic effect of ACEi in this model of hypertension. This last finding confirmed our previous results in rats, showing that a B2 receptor antagonist (icatibant) did not block the chronic antihypertensive and antihypertrophic effects of ACEi in aortic coarctation-induced hypertension.9 In contrast, Lim and Schöllkens8 reported that icatibant completely blunted the antihypertensive and antihypertrophic effects of ACEi. We cannot explain these discrepancies.

Nevertheless, our study suggests that chronic decreased BP and LVW induced by ACEi are unlikely to be due to rising circulating and tissue kinin concentrations but could be attributed to blockade of the conversion of angiotensin I to II, as has been demonstrated in other models, such as the spontaneous hypertension16 and 2K-1C hypertension models.37

In conclusion, we have shown that in mice kinins acting via B2 receptors (1) do not participate in the maintenance of normal basal BP, (2) are not involved in the development of either DOCA-salt or aortic coarctation hypertension, and (3) are not essential for the chronic antihypertensive and cardiac antihypertrophic effect of ACEi in DOCA-salt and aortic coarctation hypertension.

Acknowledgments
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