Diminished Cardioprotective Response to Inhibition of Angiotensin-Converting Enzyme and Angiotensin II Type 1 Receptor in B₂ Kinin Receptor Gene Knockout Mice

Xiao-Ping Yang, Yun-He Liu, Dharmesh Mehta, Maria A. Cavasin, Edward Shesely, Jiang Xu, Fang Liu, Oscar A. Carretero

Abstract—Using B₂ kinin receptor gene knockout mice (B₂−/−), we tested the hypothesis that (l) lack of B₂ receptors may affect blood pressure and cardiac function and aggravate cardiac remodeling after myocardial infarction (MI), and (2) kinins partially mediate the cardiac beneficial effect of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II type 1 receptor antagonists (AT₁-ant), whereas lack of B₂ receptors may diminish this cardioprotective effect. Chronic heart failure (HF) was induced by MI, which was caused by coronary artery ligation in both B₂−/− and 129/SvEvTac mice (wild-type control, B₂+/+). An ACEi (ramipril, 2.5 mg/kg/d) or AT₁-ant (L-158809, 3 mg/kg/d) was given 1 week after MI and was continued for 12 weeks. Left ventricular (LV) ejection fraction, cardiac output (CO), diastolic LV dimension (LVDd), and LV mass were evaluated by echocardiography. Myocyte cross-sectional area and interstitial collagen fraction were studied histopathologically. We found that basal blood pressure and cardiac function were similar in B₂+/+ and B₂−/− mice. After MI, development of HF and remodeling were also similar between the 2 strains. The ACEi improved cardiac function and remodeling in both strains; however, its effects were attenuated in B₂−/− mice (respective values for B₂−/− versus B₂+/+: overall increase in ejection fraction, 64±10% versus 21±5% [P<0.01]; increase in CO, 69±17% versus 23±9% [P<0.01]; overall decrease in LVDd, −24±3% versus −7±4% [P<0.01]; and decrease in LV mass, −38±3% versus −6±6% [P<0.01]). The effect of ACEi or AT₁-ant on myocyte cross-sectional area was similar between strains; however, their effect on the interstitial collagen fraction was diminished in B₂−/− mice. We concluded that (1) lack of B₂ kinin receptors does not affect cardiac phenotype or function, either under normal physiological conditions or during the development of HF; and (2) kinins acting via the B₂ receptor play an important role in the cardioprotective effect of ACEi and AT₁-ant. (Circ Res. 2001;88:1072-1079.)

Key Words: angiotensin-converting enzyme inhibitors ■ AT₁ receptor antagonist ■ heart failure ■ B₂ kinin receptors ■ mice

Chronic heart failure (CHF) is characterized by left ventricular (LV) pump dysfunction, chamber dilatation, neurohormonal system activation, and exercise intolerance. The renin-angiotensin system (RAS) plays a central role in this process.1-4 Over the past decade, clinical and laboratory studies have provided evidence that interruption of the RAS achieved by angiotensin-converting enzyme inhibitors (ACEi) improves cardiac function, regresses LV remodeling, and prolongs survival in patients with CHF.4-8 However, it remains unclear whether the benefits of ACEi are entirely due to blockade of angiotensin II (Ang II) formation or partially derived from increased kinins, because ACE is also the major kininase that degrades kinins to inactive fragments.7,8 We and others have previously reported that ACEi attenuated the deterioration of LV function and remodeling in animals with CHF due to myocardial infarction (MI) and that this effect was either blocked by a B₂ kinin receptor antagonist (B₂-ant)9,10 or blunted in rats with kininogen deficiency due to spontaneous mutation of the kininogen gene,11 indicating that kinins play an important role in the cardioprotective mechanism of ACEi. However, it remains controversial whether kinins play an essential role in the cardioprotective mechanism of ACEi. It has recently been reported that disruption of the bradykinin B₂ receptor gene in mice (B₂−/− mice) increased BP, heart weight, and LV chamber dimen-
sion.12,13 However, we previously found that blockade of the B2 kinin receptor or genetic kinin deficiency neither altered BP nor aggravated cardiac remodeling and LV dysfunction, although it did partially block the cardioprotective effect of ACEi.9,11,14 We also showed that in B2−/− mice, BP and the severity of ischemia/reperfusion injury did not differ from their wild-type controls (B2+/+).15 However, it is not known whether the chronic maladaptive response to MI (such as LV hypertrophy, chamber dilatation, and dysfunction) is enhanced in B2−/− mice.

Despite treatment with ACEi, some patients still experience worsening symptoms and deterioration of LV function, which may be related to incomplete inhibition of Ang II formation or continued activation of the RAS. Thus, it has been proposed that blockade of the RAS at the receptor level may provide an additional advantage over ACEi. However, our previous study in rats showed that an Ang II type 1 (AT1) receptor antagonist (AT1-ant) had a cardioprotective effect similar to that of ACEi, and that this effect was partially blocked by a B2-ant or Ang II type 2 (AT2) receptor antagonist (AT2-ant),9 indicating that (1) at least in this rat model of heart failure (HF), AT1-ant are not superior to ACEi; although it is not certain whether combined treatment with ACEi and AT1-ant would provide a better effect than either drug alone; and (2) activation of the AT2 receptor during AT1 inhibition might be partially responsible for the cardioprotective effect of AT1-ant either directly or via stimulation of kinins and/or NO and cGMP.16–18

To further test the hypothesis that kinins mediate the cardioprotective effect of ACEi and AT1-ant, we produced CHF in B2−/− and B2+/+ mice by ligating the left anterior descending coronary artery (LAD) and studied whether (1) lack of kinin B2 receptors aggravates cardiac remodeling and LV dysfunction, and (2) the cardioprotective effect of ACEi or AT1-ant is diminished or absent in B2−/− mice.

**Materials and Methods**

**Animals**

B2−/− mice were derived from a breeding pair of homozygous mice on a 129/SvEv genetic background19 and are currently being bred in our Mutant Mouse Facilities. Wild-type 129/SvEvTac mice (B2+/+) purchased from Taconic Farms (Germantown, NY) served as controls. Animals were housed in an air-conditioned room with a 12-hour light/dark cycle, received standard mouse chow, and drank tap water. The Henry Ford Hospital Care of Experimental Animals Committee approved the present study.

**Surgical Procedures**

Male mice aged 10 to 12 weeks were anesthetized with sodium pentobarbital (50 mg/kg IP), intubated, and ventilated with room air using a positive-pressure respirator. A left thoracotomy was performed via the fourth intercostal space, the heart was exposed, and the pericardium opened as described previously.20 The LAD was ligated with a 9-0 silk suture near its origin between the pulmonary outflow tract and the edge of the left atrium. MI was deemed successful when the anterior wall of the LV became cyanotic and the ECG showed obvious ST-segment elevation. The lungs were inflated by increasing positive end-expiratory pressure, and the thoracotomy site was closed. Sham-operated mice were subjected to the same procedure, except that the suture around the LAD was not tied. Animals were kept on a heating pad until they were awake.

**Measurement of BP and Cardiac Function**

**Systolic BP**

Systolic BP (SBP) was measured in conscious mice by use of a noninvasive computerized tail-cuff system (BP-2000, Visitech Systems) as described previously.21,22 Briefly, the mice were trained for 7 days by measuring SBP daily, after which SBP was recorded weekly. Three sets of 10 measurements were obtained during each recording; a set was accepted if the computer identified >6 successful readings out of 10 measurements.

**Echocardiography**

Cardiac geometry and function were evaluated with a Doppler echocardiographic system equipped with a 15-MHz linear transducer (Acuson c256) as described previously.21 All studies were performed on awake mice before MI and periodically thereafter. The following parameters were obtained: (1) LV chamber dimensions and wall thickness; (2) LV mass, which is equivalent to 1.055 [(IVSd+LVd+PWTd)(LVd)]−1, where 1.055 is the specific gravity of the myocardium, IVSd is interventricular septum thickness, LVd is diastolic LV dimension, and PWTd is diastolic posterior wall thickness (LV mass was normalized for body weight and expressed as mg/10 g); (3) ejection fraction (EF), which is equivalent to [(LVAd−LVAs)/LVAd]×100, where LVAd is LV diastolic area and LVAs is LV systolic area; and (4) cardiac output (CO), which is equivalent to SV×HR, with SV=CSA×VTI and CSA=[(AoD/2)]π, where SV is stroke volume, HR is heart rate, CSA is aortic cross-sectional area, VTI is the aortic flow velocity-time integral, and AoD is aortic diameter (CO was normalized for body weight and expressed as mL/min/10 g).

All primary measurements, such as LV wall thickness, dimensions, and CSA, were traced manually and digitized by goal-directed, diagnostically driven software installed within the echocardiograph. Three beats were averaged for each measurement.

**Histopathological Study**

**Heart Weight, Lung Wet Weight, and Infarct Size**

Mice were killed after 12 weeks of MI, and their hearts and lungs were weighed. The LV was sectioned transversely into 3 slices from apex to base, rapidly frozen in isopentane precooled in liquid nitrogen, and then stored at −70°C. For infarct size, 6-μm sections from each slice were stained with Gomori trichrome to identify fibrous tissue (infarction). Infarct size was calculated as the ratio of infarct length to the circumference of both endocardium and epicardium.24

**MCSA and ICF**

Sections (6-μm) were cut from each slice and double-stained with (1) rhodamine-labeled peanut agglutinin to delineate the myocyte cross-sectional area (MCSA) and interstitial space, and (2) rhodamine-labeled *Griffonia simplicifolia* lectin I to show the capillaries.9 Four radially oriented microscopic fields were selected from each section and photographed at a magnification of ×100. MCSA was measured by computer-based planimetry (Jandel). For the interstitial collagen fraction (ICF), the total surface area (microscop ic field), interstitial space (collagen plus capillaries), and area occupied by the capillaries alone were measured with computer-assisted videodensitometry and calculated as percent total surface area occupied by the interstitial space minus percent total surface area occupied by the capillaries. Average MCSA and ICF were calculated for each mouse.

**Experimental Protocols**

Protocol 1 involved comparing the cardiac phenotype between B2+/+ and B2−/− mice before and after MI and determining whether the development of cardiac dysfunction and LV remodeling was more severe or accelerated in B2−/− mice. Each strain was subjected to either coronary ligation (HF-vehicle) or sham MI and was followed up for 12 weeks.

Protocol 2 involved determining whether the effect of ACEi or AT1-ant was diminished or absent in B2−/− mice. One week after the
Body, Heart, Lung, and Liver Weight and Infarct Size in B$_2$^{-/-} and B$_2$^{+/+} Mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sham (n=13)</th>
<th>Vehicle (n=10)</th>
<th>ACEi (n=10)</th>
<th>AT$_1$-ant (n=8)</th>
<th>Sham (n=13)</th>
<th>Vehicle (n=16)</th>
<th>ACEi (n=13)</th>
<th>AT$_1$-ant (n=12)</th>
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<tr>
<td>BW, g</td>
<td>30.2±0.6</td>
<td>31.2±0.3</td>
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<td>Atria, mg</td>
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<td>21.1±1.3*</td>
<td>14.1±1.2‡</td>
<td>15.0±1.5‡</td>
<td>11.6±0.8</td>
<td>20.3±1.4*</td>
<td>16.8±1.4‡</td>
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<tr>
<td>RV, mg</td>
<td>25.9±0.7</td>
<td>34.9±2.7*</td>
<td>27.7±1.5‡</td>
<td>28.5±2.1‡</td>
<td>23.6±0.9</td>
<td>32.4±3.0*</td>
<td>27.0±1.1‡</td>
<td>30.0±1.6</td>
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<tr>
<td>LV, mg/10 g</td>
<td>34.0±0.7</td>
<td>51.8±4.0*</td>
<td>37.4±1.0‡</td>
<td>37.6±2.3‡</td>
<td>32.6±1.2</td>
<td>47.1±2.5*</td>
<td>37.2±1.3‡</td>
<td>38.9±1.7†</td>
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<td>Lungs, mg/10 g</td>
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<td>59.0±3.7*</td>
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<td>56.5±4.8</td>
<td>49.2±2.5</td>
<td>57.3±2.9*</td>
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<td>Liver, mg/10 g</td>
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<td>384±24†</td>
<td>404±13</td>
<td>393±19</td>
<td>367±23</td>
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<td>342±7</td>
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<td>IS, %</td>
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<td>39.8±3.7</td>
<td>34.4±2.8</td>
<td>36.1±1.7§</td>
<td>. . .</td>
<td>42.0±2.2</td>
<td>35.8±3.2</td>
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</table>

Values are mean±SE. BW indicates body weight; RV, right ventricular weight corrected for body weight; LV, LV weight corrected for body weight; and IS, infarct size.

*P<0.01 and †P<0.05 vs sham within strains; ‡P<0.05 and §P<0.01 vs vehicle within strains; and §P<0.05 vs AT$_1$-ant between strains.

Results

Mortality
The mortality rate was similar between the 2 strains. Early mortality (within 24 hours after surgery) was 15.8% in B$_2$^{+/+} mice and 13.5% in B$_2^{-/-}$ mice. During the first week of MI, 40% of the B$_2^{+/+}$ mice and 23% of the B$_2^{-/-}$ mice died, mostly from cardiac rupture. During weeks 2 to 12, only 1 B$_2^{+/+}$ mouse and 2 B$_2^{-/-}$ mice died. None of the B$_2^{+/+}$ or B$_2^{-/-}$ mice that underwent the sham procedure died during or after the operation.

Body, Heart, Lung, and Liver Weight and Infarct Size
There was no significant difference in any of these parameters between sham-ligated groups (Table). In the HF-vehicle groups, heart and lung weight increased similarly in both strains. ACEi or AT$_1$-ant reduced heart weight to a similar extent in both strains but had no effect on lung weight. Liver weight was increased only in B$_2^{+/+}$ mice, and drug treatment had no effect on it.
was significantly attenuated in B₂⁻/⁻ mice compared with B₂⁺/+. The bar graphs in Figures 4 and 5 show the average percent increase in EF and CO and decrease in LVDd and LV mass from 2 to 12 weeks of treatment between the 2 strains.

The overall increase in EF after ACEi was 64±10% in B₂⁺/+ and 21±5% in B₂⁻/⁻ (P<0.01), and the increase in CO was 69±17% in B₁⁺/+ and 23±9% in B₂⁻/⁻ (P<0.01). The overall reduction in LVDd was −24±3% in B₁⁺/+ versus −7±2% in B₂⁻/⁻ (P<0.01), and the reduction in LV mass was −38±3% in B₂⁺/+ and −6±6% in B₂⁻/⁻ (P<0.01). AT₁-ant had a beneficial cardiac effect similar to ACEi; this effect was also diminished in B₂⁻/⁻ mice. The overall increase in EF with AT₁-ant was 46±10% in B₁⁺/+ and 25±9% in B₂⁻/⁻ (P<0.01), and the increase in CO was 44±14% in B₂⁺/+ and 15±5% in B₂⁻/⁻ (P<0.01). The overall reduction in LVDd was −14±4% in B₁⁺/+ and −6±3% in B₂⁻/⁻ (P<0.01), and the reduction in LV mass was −33±4% in B₂⁺/+ and −16±7% in B₂⁻/⁻ (P<0.01) (Figures 4 and 5). Although the ACEi appeared to have a better protective effect, the difference between ACEi and AT₁-ant did not reach statistical significance.

**Myocyte Size and ICF**

MCSCA and ICF were similar in sham-operated B₁⁺/+ and B₂⁻/⁻ mice and increased similarly after MI in both strains (Figures 6 and 7). ACEi and AT₁-ant significantly decreased MCSCA in both the B₁⁺/+ and B₂⁻/⁻ groups, and no statistical difference between strains was detected (Figure 7, top). However, the effect of ACEi and AT₁-ant on ICF was observed only in B₂⁺/+ mice and was absent in B₂⁻/⁻ (Figure 7, bottom).

**Discussion**

We found that basal SBP and cardiac function as well as morphological and histological parameters were no different in B₂⁻/⁻ mice compared with B₂⁺/+. Development and severity of cardiac dysfunction after MI were also similar in B₂⁻/⁻ and B₂⁺/+ mice, suggesting that kinins acting on the B₂ receptor may not play an essential role in the regulation of BP and cardiac function, either under normal physiological conditions or during the development of HF. Inhibition of ACE or blockade of the AT₁ receptor improved cardiac function and remodeling, as evidenced by increased EF and reduced LV chamber dimension, mass, and interstitial collagen deposition; these effects were attenuated in B₂⁻/⁻ mice, indicating that kinins are at least partially responsible for the therapeutic effect of ACEi and AT₁-ant in HF.

Kinins are vasodilator polypeptides released from low- and high-molecular-weight kininogens by plasma and tissue kallikreins and hydrolyzed mainly by ACE (also called kininase II). The biological action of kinins is mediated by activation of at least 2 known subtypes of G-protein–coupled receptors, B₁ and B₂. The B₁ receptor is only weakly expressed under physiological conditions but is strongly induced under pathological conditions, such as inflammation or tissue injury, and is sensitive to des-Arg⁹-bradykinin, a metabolite of bradykinin. B₂ receptors, which are constitutively expressed in most tissues, are sensitive to bradykinin and kallidin and are responsible for most known effects of bradykinin. Although the role of endogenous kinins in the regulation of BP and cardiac hemodynamic homeostasis as well as in the pathophysiology of HF has been studied extensively, the data remain controversial. Emanueli et al reported that disruption
of the B2 receptor led to high BP, LV dilatation, and functional impairment, suggesting that kinins are essential for functional and structural preservation of the heart. However, we found that BP, cardiac performance, and histology in kininogen-deficient rats or B2−/− mice are no different from their wild-type controls.11,14,29 In the present study, we further demonstrated that lack of B2 kinin receptors neither alters BP or cardiac phenotype nor aggravates cardiac remodeling after MI, indicating that either (1) kinins may not play an important role in regulation of BP and function, or (2) there is a compensatory mechanism whereby metabolites of bradykinin act on the B1 receptor to assume some of its vasoactive properties. Tschöpe et al30 recently showed that both B1 and B2 receptors are upregulated after MI, indicating that either (1) kinins may not play an important role in regulation of BP and function, or (2) there is a compensatory mechanism whereby metabolites of bradykinin act on the B1 receptor to assume some of its vasoactive properties. Furthermore, Duka et al32 recently reported that the B1 receptor is upregulated in B2−/− mice and that these mice had a hypotensive response to a selective B1 agonist and a hypertensive response to a selective B1 receptor antagonist, indicating a compensatory function of the B1 receptor in maintaining hemodynamic homeostasis when the B2 receptor is absent.

Despite the fact that the hemodynamic and cardiac phenotypes are similar in B2−/− and control mice, we found that B2−/− mice had a diminished response to ACEi and AT1-ant. This agrees with our previous findings that ACEi and AT1-ant improved LV function and structural remodeling in Lewis inbred rats and that these effects were partially blocked by a kinin receptor antagonist,9 suggesting that the cardioprotective effects of ACEi are not solely attributable to inhibition of Ang II formation. In fact, ACE not only converts angiotensin I to Ang II but also degrades kinins to inactive fragments.

Figure 4. Effect of ACEi and AT1-ant on EF and CO in B2−/− mice and B2+/+ mice with HF induced by CL before ligation (basal) and after ligation (1 to 12 weeks). Veh indicates treatment with vehicle. *P<0.01 vs HF-vehicle for both ACEi and AT1-ant. Bar graphs show average per cent increase from 2 to 12 weeks of treatment.

Figure 5. Effect of ACEi and AT1-ant on LVDd and LV mass in B2−/− mice and B2+/+ mice with HF induced by CL before ligation (basal) and after ligation (1 to 12 weeks). *P<0.01 vs HF-vehicle for both ACEi and AT1-ant. Bar graphs show average per cent decrease from 2 to 12 weeks of treatment.
angiotensin I. Thus, inhibition of kinin degradation, which in turn results in increased endogenous kinins, is also largely responsible for the cardioprotection seen with ACEi. The precise mechanism by which kinins protect the heart is not yet well defined. It is known that kinins are potent stimuli for the release of endothelial NO and prostaglandins. Recently, Emanueli et al showed that local delivery of the human tissue kallikrein gene accelerated ischemia-induced hindlimb angiogenesis and preserved energy utilization of ischemic muscle and that this effect was blocked by the inhibition of cyclooxygenase or NO synthase, indicating a prostaglandin- and/or NO-mediated mechanism. It has also been shown that kinins inhibit collagen gene expression and collagen production via stimulation of arachidonic acid metabolites, particularly prostaglandin I2. In addition, kinins and NO may be involved in myocardial energy metabolism. Zhang et al recently showed that incubation of coronary microvessels or myocardial slices with ACEi or kininogen significantly increased NO production and decreased myocardial oxygen consumption, both of which were blocked by a B2 kinin receptor antagonist. They also showed that bradykinin stimulated the release of NO from the mouse myocardium and that this effect is absent in B2−/− mice. Using NO synthase (NOS) inhibitors or endothelial NOS knockout mice, Tada et al recently reported that NO participates in the regulation of myocardial glucose, lactate, and fatty acid metabolism. Perfuusing the ischemic heart with bradykinin increases the production of myocardial high-energy phosphates as well as glycogen content, along with a reduction in lactate dehydrogenase and creatinine kinase activity. Taken together, these data suggest that kinins or NO may reduce oxygen consumption and facilitate energy utilization, thereby contributing significantly to the cardioprotective action of ACEi.

Two major Ang II receptor subtypes, AT1 and AT2, have been identified. Most known biological actions of Ang II have been attributed to the AT1 receptor, whereas the role of the AT2 receptor remains controversial. Recent evidence suggests that AT2 activation may antagonize the vasopressor, hypertrophic, and fibrogenic effects of AT1. Tsutsumi et al showed that in aortas from mice with overexpression of the AT2 receptor, Ang II caused a significant increase in kininogenase activity and cGMP production, which was further enhanced by an AT1-ant but blocked by an AT2-ant, kinin antagonist, or NOS inhibitor, suggesting that AT2 activation stimulates kinin release, which further promotes NO/cGMP production in a paracrine manner and thus potentiates vasodilatation and regional blood flow regulation. We previously reported that in a rat model of CHF induced by MI, AT1-ant had a cardioprotective effect similar to ACEi and that part of the effect of AT1-ant, such as reducing LV systolic and diastolic volume, was blocked by an AT2-ant or a B2 kinin antagonist. In the present study, using B2−/− mice as a model, we further confirmed the role of kinins in the cardioprotective effect of AT1-ant. It is possible that blockade of AT1 increases the level of Ang II, which in turn activates AT2. Activation of AT2 may stimulate the release of NO either directly or via kinins, leading to cardioprotection. We have recently demonstrated that the cardioprotective effect of ACEi or AT1-ant

![Image](http://circres.ahajournals.org/)

**Figure 6.** Representative slides showing MCSA and interstitial collagen deposition (green staining) in B2−/− and B2+/+ mice with either sham coronary ligation (sham) or HF.

**Figure 7.** Effect of ACEi and AT1-ant on MCSA (top) and ICF (bottom) in B2−/− and B2+/+ mice with sham coronary ligation (sham) or HF.
was diminished in endothelial NOS knockout mice with CHF induced by MI (Y.-H. Liu, J. Xu, X.-P. Yang, F. Yang, E.G. Shesely, O.A. Carretero, unpublished data, 2001), which may provide further evidence that endothelium-derived NO plays an important role in the beneficial cardiac effect of ACEi and AT1-ant.

In summary, we have demonstrated that (1) kinins acting via the B2 receptor do not seem to play an essential role in cardiac hemodynamics, morphology, and function either under normal physiological conditions or during the development of HF, insomuch as none of these parameters differed between B2−/− and B2+/+ mice, and (2) inhibition of ACE or blockade of the AT1 receptor improves cardiac function and regresses remodeling in HF, and this therapeutic effect is partially mediated by kinins, since it was attenuated in B2−/− mice.

Acknowledgments

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References


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