Hypertension and heart failure are marked by activation of both the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. These forms of neurohumoral activation, in turn, have deleterious effects on the heart, kidney, and other target organs, worsening the prognosis in these disease states. Pharmacological agents that interrupt the RAAS are useful in both improving hemodynamics and preventing morbidity and mortality in such patients. In particular, treatment with ACE inhibitors has been shown to improve survival in patients with advanced heart failure and after myocardial infarction. It is hypothesized that ACE inhibitors exert beneficial effects by inhibiting both circulating and cardiac tissue ACE, thus attenuating unfavorable remodeling of the left ventricle (LV), reducing afterload, and improving the balance between thrombotic and thrombolytic factors. It remains unclear whether the dominant mechanism of action of ACE inhibitors in the setting of LV dysfunction relates to their global hemodynamic effects (which result in improved loading conditions), to reduced production of angiotensin (Ang) II with subsequent diminished Ang II type 1 (AT1) receptor activation, or to alteration of other neurohumoral systems, such as the kallikrein-kinin system.

See p 2359

Importantly, in addition to generating Ang II from Ang I, ACE catalyzes the degradation of bradykinin (BK) to inactive metabolites. Studies of recombinant full-length ACE have shown that the apparent \( K_m \) of ACE for BK is substantially lower than for Ang I, which indicates more favorable kinetics for hydrolysis of BK than for conversion of Ang I to Ang II. Furthermore, site-directed mutagenesis demonstrated that the \( K_m \) for BK was lower than that for Ang I at both active sites of ACE, suggesting that at physiological concentrations, BK could be a preferential substrate over Ang I at both active sites of ACE. The biological effects of BK and other kinins are mediated by stimulation of specific receptors, classified as BK\(_1\) and BK\(_2\), both of which have been cloned and extensively characterized. BK receptors are expressed mainly in pathological conditions such as tissue injury and are thought to mediate the inflammatory and pain-producing effects of kinins; BK\(_2\) receptors mediate most of the known cardiovascular effects of kinins. In the vasculature, BK-mediated activation of endothelial BK\(_2\) receptors stimulates endogenous nitric oxide synthase (NOS), thus increasing NO and counteracting the effects of Ang II by inhibiting contraction and growth of smooth muscle cells. Both BK\(_1\) receptors and NOS activity have been detected in cardiac myocytes, and an intact kallikrein/kinin system has been found in the heart. Kinins are detectable in the effluent of isolated perfused hearts and are increased by ACE inhibitors, as well as by ischemia, which demonstrates that the cardiac kallikrein/kinin system can be regulated.

Studies in a mouse strain with targeted disruption of the BK\(_1\) receptor gene have given important new insights into the role of the kallikrein/kinin system in the pathogenesis of hypertension and heart failure. Mice lacking a functional BK\(_2\) gene (BK\(_2\), both of which have been cloned and extensively characterized. BK receptors are expressed mainly in pathological conditions such as tissue injury and are thought to mediate the inflammatory and pain-producing effects of kinins; BK\(_2\) receptors mediate most of the known cardiovascular effects of kinins. In the vasculature, BK-mediated activation of endothelial BK\(_2\) receptors stimulates endogenous nitric oxide synthase (NOS), thus increasing NO and counteracting the effects of Ang II by inhibiting contraction and growth of smooth muscle cells. Both BK\(_1\) receptors and NOS activity have been detected in cardiac myocytes, and an intact kallikrein/kinin system has been found in the heart. Kinins are detectable in the effluent of isolated perfused hearts and are increased by ACE inhibitors, as well as by ischemia, which demonstrates that the cardiac kallikrein/kinin system can be regulated.

Studies in a mouse strain with targeted disruption of the BK\(_2\) receptor gene have given important new insights into the role of the kallikrein/kinin system in the pathogenesis of hypertension and heart failure. Mice lacking a functional BK\(_2\) gene (BK\(_2\), both of which have been cloned and extensively characterized. BK receptors are expressed mainly in pathological conditions such as tissue injury and are thought to mediate the inflammatory and pain-producing effects of kinins; BK\(_2\) receptors mediate most of the known cardiovascular effects of kinins. In the vasculature, BK-mediated activation of endothelial BK\(_2\) receptors stimulates endogenous nitric oxide synthase (NOS), thus increasing NO and counteracting the effects of Ang II by inhibiting contraction and growth of smooth muscle cells. Both BK\(_1\) receptors and NOS activity have been detected in cardiac myocytes, and an intact kallikrein/kinin system has been found in the heart. Kinins are detectable in the effluent of isolated perfused hearts and are increased by ACE inhibitors, as well as by ischemia, which demonstrates that the cardiac kallikrein/kinin system can be regulated.

Studies in a mouse strain with targeted disruption of the BK\(_2\) receptor gene have given important new insights into the role of the kallikrein/kinin system in the pathogenesis of hypertension and heart failure. Mice lacking a functional BK\(_2\) gene (BK\(_2\), both of which have been cloned and extensively characterized. BK receptors are expressed mainly in pathological conditions such as tissue injury and are thought to mediate the inflammatory and pain-producing effects of kinins; BK\(_2\) receptors mediate most of the known cardiovascular effects of kinins. In the vasculature, BK-mediated activation of endothelial BK\(_2\) receptors stimulates endogenous nitric oxide synthase (NOS), thus increasing NO and counteracting the effects of Ang II by inhibiting contraction and growth of smooth muscle cells. Both BK\(_1\) receptors and NOS activity have been detected in cardiac myocytes, and an intact kallikrein/kinin system has been found in the heart. Kinins are detectable in the effluent of isolated perfused hearts and are increased by ACE inhibitors, as well as by ischemia, which demonstrates that the cardiac kallikrein/kinin system can be regulated.
The concept that BK may play an important role in cardiovascular function and in the pathogenesis of cardiovascular disease in humans gained further credence from the observation that chronic ACE inhibitor treatment increases circulating and/or tissue kinin levels\(^2\) but does not produce sustained inhibition of Ang II.\(^1,2\) The beneficial effects of ACE inhibitor therapy are maintained in the face of normal plasma and tissue Ang II levels. Continued Ang II production during ACE inhibitor therapy occurs in the normal heart and blood vessels because of alternative Ang II–forming pathways, particularly serine protease chymase, that bypass ACE.

Evidence obtained from both animal models and humans suggests that the benefits of ACE inhibitor therapy may be mediated by kinins. In patients with hypertension, the coadministration of the selective BK\(_2\) receptor antagonist icatibant significantly attenuated the acute hypertensive effect of captopril.\(^3\) This effect was observed in both black and white hypertensive subjects, as well as in normotensive volunteers. Work in isolated ejecting guinea pig hearts also demonstrated BK-induced enhancement of LV relaxation that was attributable to the paracrine release of NO.\(^4\) Similarly, captopril increased and that BK, acting through BK\(_1\) receptors, produced coronary vasodilation and improved LV relaxation and ventricular performance. Furthermore, concomitant treatment with BK\(_1\) receptor antagonists has been shown to reverse ACE inhibitor–induced attenuation of LV hypertrophy in dog\(^6\) and rat\(^7\) models of myocardial infarction and pressure overload hypertrophy. However, Weber and coworkers have questioned the proposed protective effects of BK at the myocardial structural level. In rat models of chronic exogenous Ang II infusion\(^8\) and myocardial infarction,\(^9\) administration of icatibant prevented perivascular fibrosis, which suggests that pharmacological interference with BK receptor binding or prostaglandin synthesis is associated with reduced fibrillar collagen formation. These findings suggest that in the setting of chronic Ang II excess, BK may have a deleterious effect on myocardial structure that is mediated by the BK\(_2\) receptor.

BK is also upregulated in acutely ischemic myocardium, and its effects may offset the increases in myocardial oxygen demand imposed by enhanced local production of catecholamines and Ang II. It has been hypothesized that further enhancement in BK production in the setting of ACE inhibitor therapy may protect the ischemic myocardium by these mechanisms. In support of this hypothesis, Yang and coworkers\(^10\) demonstrated that the cardioprotective effect of preconditioning was abolished in BK\(_1\) knockout mice, as well as in mice deficient in high-molecular-weight kininogen.

However, there is controversy regarding the protective effect of BK in myocardial ischemia. Seyedi and coworkers\(^11\) demonstrated an active kallikrein/kinin system in a preparation of sympathetic nerve endings from the guinea pig heart that produced norepinephrine exocytosis when BK synthesis was increased or when its breakdown was retarded by ACE inhibitor treatment. This observation is consistent with the finding of diminished norepinephrine release from isolated atria of BK\(_1\)r\(^+/−\) mice.\(^12\) Taken together, these findings raise the possibility of a differential effect of BK accumulation in the cardiac interstitium, where it interacts directly with nerve terminals and fibroblasts and may have a deleterious effect by promoting norepinephrine release and perivascular/myocardial fibrosis, versus at the luminal surface of the vasculature,

Furthermore, studies in isolated canine coronary arteries\(^13\) have shown that Ang-(1–7) acts as a local mediator of kinin-induced vasodilation by releasing NO and inhibiting ACE. Recent data have demonstrated that the hypotensive effect of ACE inhibitor treatment in the spontaneously hypertensive rat was mediated by Ang-(1–7) via stimulation of a non-AT\(_1\)/AT\(_2\) angiotensin subtype receptor.\(^14\) Thus, it has been hypothesized that Ang-(1–7) is synergistic with BK either because it has an agonist effect on a novel non-AT\(_1\)/AT\(_2\) angiotensin subtype receptor, because it is an alternative ligand for the BK\(_1\) receptor, or because it inhibits the enzymatic inactivation of BK.

It has been proposed that both the RAAS and the kallikrein/kinin system are activated in pathophysiological states and that BK protects against the adverse effects of Ang II in these situations. For example, in a canine model of pacing tachycardia-induced heart failure, Cheng and coworkers\(^15\) demonstrated that circulating BK levels were significantly increased and that BK, acting through BK\(_1\) receptors, produced coronary vasodilation and improved LV relaxation and ventricular performance. Furthermore, concomitant treatment with BK\(_1\) receptor antagonists has been shown to reverse ACE inhibitor–induced attenuation of LV hypertrophy in dog\(^16\) and rat\(^17\) models of myocardial infarction and pressure overload hypertrophy. However, Weber and coworkers have questioned the proposed protective effects of BK at the myocardial structural level. In rat models of chronic exogenous Ang II infusion\(^18\) and myocardial infarction,\(^19\) administration of icatibant prevented perivascular fibrosis, which suggests that pharmacological interference with BK receptor binding or prostaglandin synthesis is associated with reduced fibrillar collagen formation. These findings suggest that in the setting of chronic Ang II excess, BK may have a deleterious effect on myocardial structure that is mediated by the BK\(_2\) receptor.

Another interaction between the RAAS and the kallikrein/kinin system at the level of ACE, there is mounting evidence for a direct relationship between Ang peptides and BK levels in vivo. Siragy et al\(^20\) reported that during low sodium intake, BK levels were increased in the interstitial fluid space of the dog kidney and that this effect was mediated by activation of the RAAS via a non-AT\(_1\) receptor pathway. Subsequent studies\(^21\) in the rat in vivo demonstrated that during low sodium intake, Ang II infused into the renal artery stimulated renal interstitial cGMP and that this effect was blocked by the AT\(_2\) receptor antagonist PD 123319 and the NOS inhibitor L-NNAME. These data suggest that activation of the RAAS during sodium depletion increases BK and NO production through stimulation of the AT\(_2\) receptor by Ang II. The authors postulated that the increase in renal BK levels during sodium depletion offsets or modulates the vasoconstriction induced by stimulation of the RAAS.

This pathway of Ang II formation from Ang II to Ang-(1–7) is formed from Ang I and Ang II by peptidases other than ACE, and ACE inhibition is associated with elevations of Ang-(1–7), because blockade of ACE activity diverts the pathway of Ang II formation from Ang II to Ang-(1–7).

Evidence obtained from both animal models and humans suggests that the benefits of ACE inhibitor therapy may be mediated by kinins. In patients with hypertension, the coadministration of the selective BK\(_2\) receptor antagonist icatibant significantly attenuated the acute hypertensive effect of captopril.\(^3\) This effect was observed in both black and white hypertensive subjects, as well as in normotensive volunteers. Work in isolated ejecting guinea pig hearts also demonstrated BK-induced enhancement of LV relaxation that was attributable to the paracrine release of NO.\(^4\) Similarly, captopril increased and that BK, acting through BK\(_1\) receptors, produced coronary vasodilation and improved LV relaxation and ventricular performance. Furthermore, concomitant treatment with BK\(_1\) receptor antagonists has been shown to reverse ACE inhibitor–induced attenuation of LV hypertrophy in dog\(^6\) and rat\(^7\) models of myocardial infarction and pressure overload hypertrophy. However, Weber and coworkers have questioned the proposed protective effects of BK at the myocardial structural level. In rat models of chronic exogenous Ang II infusion\(^8\) and myocardial infarction,\(^9\) administration of icatibant prevented perivascular fibrosis, which suggests that pharmacological interference with BK receptor binding or prostaglandin synthesis is associated with reduced fibrillar collagen formation. These findings suggest that in the setting of chronic Ang II excess, BK may have a deleterious effect on myocardial structure that is mediated by the BK\(_2\) receptor.

BK is also upregulated in acutely ischemic myocardium, and its effects may offset the increases in myocardial oxygen demand imposed by enhanced local production of catecholamines and Ang II. It has been hypothesized that further enhancement in BK production in the setting of ACE inhibitor therapy may protect the ischemic myocardium by these mechanisms. In support of this hypothesis, Yang and coworkers\(^10\) demonstrated that the cardioprotective effect of preconditioning was abolished in BK\(_1\) knockout mice, as well as in mice deficient in high-molecular-weight kininogen.

However, there is controversy regarding the protective effect of BK in myocardial ischemia. Seyedi and coworkers\(^11\) demonstrated an active kallikrein/kinin system in a preparation of sympathetic nerve endings from the guinea pig heart that produced norepinephrine exocytosis when BK synthesis was increased or when its breakdown was retarded by ACE inhibitor treatment. This observation is consistent with the finding of diminished norepinephrine release from isolated atria of BK\(_1\)r\(^+/−\) mice.\(^12\) Taken together, these findings raise the possibility of a differential effect of BK accumulation in the cardiac interstitium, where it interacts directly with nerve terminals and fibroblasts and may have a deleterious effect by promoting norepinephrine release and perivascular/myocardial fibrosis, versus at the luminal surface of the vasculature,
where it interacts with endothelial cells and may have a beneficial effect by promoting NO synthesis. Further study is needed to test this intriguing hypothesis.

References


Key Words: Editorials ■ bradykinin ■ angiotensin ■ myocardium ■ heart failure ■ hypertension
Bradykinin in the Heart: Friend Or Foe?
Louis J. Dell'Italia and Suzanne Oparil

Circulation. 1999;100:2305-2307
doi: 10.1161/01.CIR.100.23.2305

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/100/23/2305