ACE Inhibition and Bradykinin-Mediated Renal Vascular Responses

EDHF Involvement

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Angiotensin-converting enzyme (ACE) is known to catalyze the conversion of angiotensin I to angiotensin II and degrades bradykinin and other vasoactive peptides. The fact that ACE participates in the degradation of bradykinin has led to the postulate that the beneficial renal and cardiovascular actions of ACE inhibitors can be attributed to augmenting and prolonging the effects of bradykinin. These beneficial actions have been attributed to bradykinin stimulation of nitric oxide (NO) generation. The report by Matsuda et al in this issue of Hypertension provides initial evidence that the renal hemodynamic change in response to ACE inhibition and elevated bradykinin levels is also mediated by an endothelium-derived hyperpolarizing factor (EDHF). In addition, this renal vascular action of ACE inhibition provides greater hemodynamic and natriuretic effects in the presence of angiotensin type 1 receptor blockers (ARBs). Does this finding suggest that ACE inhibitors have yet another additional renal and cardiovascular beneficial effect not associated with ARBs? Thus, the debate regarding the renal and cardiovascular benefits of ACE inhibitors, ARBs, or combined therapy now includes the possible involvement of EDHF.

ACE Inhibition, Bradykinin, and Renal Vascular EDHF

In the current study, canine afferent and efferent arteriolar diameter responses of superficial and juxtamedullary nephrons were evaluated in vivo by intravital CCD camera videomicroscopy. As was demonstrated by this group in an earlier study, ARB treatment dilated afferent and efferent arterioles in the superficial and juxtamedullary regions. In the presence of the ARB, ACE inhibition resulted in a small dilation of the superficial efferent arteriole whereas it caused a much larger dilation of the juxtamedullary afferent and efferent arterioles. The renal vascular responses to ACE inhibition were dependent on activation of bradykinin receptors and the subsequent generation of NO. Nonetheless, a portion of the juxtamedullary afferent arteriolar dilator response to ACE inhibition was still evident in the presence of NO synthase blockade. Proadifen, a cytochrome P450 (CYP450) and calcium-activated potassium (K_{Ca}) channel blocker, eliminated this fraction of the juxtamedullary afferent arteriolar dilator response. These observations suggest that the afferent arterioles of the juxtamedullary region are unique in that they have a bradykinin-mediated EDHF dilatory component in response to ACE inhibition.

Why is this apparently unique EDHF regulation of afferent arterioles of the juxtamedullary region of importance to blood pressure control? An answer can be found if one considers the pressure natriuretic response. The importance of the pressure natriuresis response to control extracellular fluid volume has been recognized for decades. A hallmark of every experimental model of hypertension is a reduced renal excretory function. Likewise, a reduction in medullary blood flow results in a shift in the pressure natriuretic relationship and has been observed before the development of hypertension. Because arterioles of the juxtamedullary nephrons supply blood flow to the descending vasa recta, changes in the diameters of juxtamedullary arterioles will result in a change in medullary blood flow. For example, increases in medullary blood flow would be expected to increase renal medullary interstitial hydrostatic pressure and result in natriuresis. Consequently, increased juxtamedullary arteriolar diameters in response to ACE inhibition in ARB-treated kidneys would be expected to increase medullary blood flow and sodium excretion. In fact, a study by Fenoy et al reported that in ARB pretreated rats, ACE inhibition increased medullary but not cortical blood flow, and the increase in medullary blood flow was eliminated by bradykinin blockade. Bradykinin-mediated increases in sodium excretion have also been observed in response to ACE inhibition in ARB-pretreated animals. The findings of the current study are that EDHF and NO are involved in this bradykinin-mediated renal hemodynamic response. Therefore, ACE inhibition has renal hemodynamic actions that increase sodium excretion in addition to lowering angiotensin levels.

EDHF involvement in the afferent arteriole of the juxtamedullary region was assessed by the administration of proadifen. The identity of the EDHF in the current study is still in question because proadifen is a CYP450 and K_{Ca} channel blocker. It has been clearly established that vascular smooth muscle cell K_{Ca} channel activation participates in the response to EDHF and is a criteria for a dilator to be a candidate EDHF. Epoxyeicosatrienoic acids (EETs) are the leading candidates as an EDHF in the renal vasculature, as well as many other organ beds. EETs dilate afferent arterioles.
arterioles and activate renal microvascular smooth muscle cell K<sub>Ca</sub> channels. Additionally, the selective CYP450 epoxyeicosa-5(Z)-enoic acid (14,15-EEZE). Nevertheless, dilation was also inhibited by the EET antagonist 14,15-epoxyeicosa-5(Z)-enoic acid (14,15-EEZE). Nevertheless, there is evidence that EETs may also influence bradykinin-mediated regulation of efferent arterioles. In a recent report by Ren et al., data are presented that EETs produced by the glomerulus are involved in the rabbit efferent arteriolar response to bradykinin. In another study, the involvement of a CYP450 metabolite in the bradykinin response of rat juxtamedullary efferent arterioles was evident even though pradifen eliminated the EDHF response in these arterioles. Although the current study did not provide a thorough evaluation of the EDHF involved in the bradykinin dilution of the canine juxtamedullary efferent arterioles, the preponderance of the data would suggest that a CYP450 epoxyeicosa-5(Z)-enoic acid is likely the involved EDHF.

**Bradykinin, NO, EDHF, and End-Organ Damage**

A major cause of mortality is the progression of organ damage associated with cardiovascular diseases, and endothelial dysfunction has been touted as a major indicator for poor cardiovascular prognosis in humans. ACE inhibitors appear to exert beneficial cardiovascular effects that are unrelated to blood pressure control. In agreement with this concept, the Trial on Reversing Endothelial Dysfunction (TREND) study demonstrated that 6 months of quinapril treatment in normotensive patients with coronary artery disease improved endothelial function without affecting blood pressure. All the same, there is still a lot of controversy as to whether ACE inhibitors do have cardiovascular-protective effects independent of lowering blood pressure. Additionally, the idea that potentiation of kinins by ACE inhibitors and the subsequent cardiovascular protective actions of NO and EDHF has been around for ~10 years. EET and NO have favorable properties that would protect the vasculature and organs during cardiovascular diseases, and these properties go beyond their effects on blood pressure. The vascular protective actions of NO beyond its dilatory properties have been extensively studied; however, the multiple vascular actions of EETs are just beginning to be explored. Initial studies have discovered that EETs have profibrinolytic and antiinflammatory actions. Accordingly, the ACE inhibitor increase in kinins and the resultant cardiovascular protective effects could be caused by increased NO and EET generation.

**ACE Inhibition, ARBs, or Combined Therapy?**

One of the implications of the study by Matsuda et al is that ACE inhibition may have advantageous renal hemodynamic actions in the presence of ARBs. Although the current study evaluated acute ACE inhibition, the renal and cardiovascular benefits of combined ARB and ACE inhibition are being evaluated as a therapy for end-organ damage associated with diabetes, hypertension, and other cardiovascular diseases. Initial clinical studies have found that despite identical reductions in blood pressure, proteinuria reduction with combination ACE inhibition and ARB treatment in patients with nephropathy was more effective than either agent alone. Cardiac-protective actions of ACE inhibition have also been attributed to the increased generation of kinins. However, in bradykinin B2 receptor knockout mice, the beneficial actions of ACE inhibition, as well as ARBs, to alter cardiac remodeling after myocardial infarction appear to be kinin-mediated. The improvement of EDHF-mediated responses in the spontaneously hypertensive rat are similar between combined ACE inhibition and ARB treatment and ACE inhibition or ARB intervention alone. Does ACE inhibition provide additional beneficial renal and cardiovascular actions? Obviously, the debate concerning combined ARB and ACE inhibition treatment will continue as more basic science and clinical data are gathered. In any case, combined ARB and ACE inhibition is safe and well tolerated by patients and demonstrates potential as a treatment for nephropathy.

**Conclusion**

This report by Matsuda et al provides evidence of renal hemodynamic effects of ACE inhibition that are independent of decreased kidney angiotensin levels. The vascular response was primarily in the juxtamedullary nephrons, and the bradykinin-mediated generation of NO and EDHF increased afferent arteriolar diameters. Although at first glance the clinical implications may not be apparent, this study provides another piece of evidence that the ACE inhibition connection to bradykinin is involved in sodium excretion and could have vascular protective properties that depend on NO and EDHF generation. Although the vascular actions of NO have been extensively studied, the multiple renal and cardiovascular-protective actions of the EETs are just beginning to be vigorously explored.

**References**


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