**Inhibiting Tissue Angiotensin-Converting Enzyme**

**A Pound of Flesh Without the Blood?**

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“...This bond doth give thee here no jot of blood. The words expressly are ‘a pound of flesh.’” Portia, in Shakespeare’s *The Merchant of Venice*

Angiotensin-converting enzyme catalyzes the formation of angiotensin II (Ang II) from Ang I but also degrades bradykinin (BK). Ang II, acting through the AT₁ receptor, is a potent vasoconstrictor, stimulates norepinephrine release from sympathetic nerve terminals in the heart, and causes hypertrophy of cardiac myocytes. BK, via activation of the BK₁ receptor, stimulates the release of NO and prostaglandins and may counteract Ang II–mediated effects. ACE inhibition may exert beneficial effects both by interrupting Ang II–mediated AT₁ receptor signal transduction and by augmenting BK₁ receptor activation. Because of the proven survival benefit from ACE-inhibitor therapy in patients with heart failure, great attention has been given to understanding the structure and function of ACE and to the design of optimally effective ACE inhibitors. In this issue of *Circulation*, Hornig and colleagues¹ compare the effects of 2 such ACE inhibitors, enalaprilat and quinaprilat, on the peripheral circulation in patients with heart failure. To understand the implications of their work, a discussion of the ACE molecule itself, the chemical structure of ACE inhibitors, and their interaction with ACE is required. The major issue to be examined is the proposed dichotomy between high- and low-affinity tissue ACE inhibitors.

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In somatic tissues, ACE is a glycoprotein of ~140 kDa; in testicular cells, it is synthesized from the same gene but at an alternative transcription start site that results in a protein of 100 kDa.² The somatic form of ACE has 2 homologous domains (the amino, or N-terminal, and carboxy, or C-terminal, sites) that are both catalytically active and that both require the presence of Zn²⁺ for activity.³ Testicular ACE contains only the C-terminal active site, whereas an ileal low-affinity tissue ACE inhibitors.

Enalaprilat and quinaprilat are derived from human plasma ACE at a concentration 2 orders of magnitude lower than that of enalaprilat; however, the differences in EC₅₀ of 351A and quinaprilat for lung and cardiac ACE appeared to be far more modest.⁵ The equilibrium dissociation constants (Kᵢ) of Ro 31-8472 (a derivative of cilazaprilat), 351A, and quinaprilat for displacement of ¹²⁵I-351A from the cell membrane is a regulated process.⁵ Mice genetically engineered to express only the N-terminal domain of ACE have no tissue-bound ACE and are hypotensive; this finding supports the concept that tissue-bound ACE is more important than circulating ACE in the metabolism of Ang I and BK. However, this particular model does not distinguish between the importance of the C-terminal active site and the carboxy tail that anchors the enzyme in the cell membrane.⁶

Both enalaprilat and quinaprilat contain a phenylpropyl moiety in place of the sulfhydryl group present in captopril. The carboxy oxygen atom of the ketomethyl group in enalaprilat and quinaprilat coordinates with the Zn²⁺ ion at the active site, whereas the phenyl group in both inhibitors interacts with a hydrophobic site. The distinctive tetrahydroisoquinolone moiety of quinaprilat is predicted to increase interaction at a second hydrophobic site. This additional interaction biochemically defines the “high-affinity” ACE inhibitors.

Hornig et al⁴ found that the ACE inhibitor quinaprilat infused directly into the brachial artery increased flow-dependent (primarily endothelium-dependent) dilation (FDD) of the radial artery in patients with heart failure. In contrast, enalaprilat had no effect on this parameter. The component of FDD mediated by NO was doubled by quinaprilat. This finding suggests that the mechanism of action of quinaprilat was to increase the local concentration of BK and thereby stimulate the release of NO.

The authors propose that the different effects of quinaprilat compared with enalaprilat arise because quinaprilat has a high affinity to tissue ACE compared with enalaprilat. What is actually meant by this proposed dichotomy? Does it refer to tissue-bound versus circulating ACE, or is it meant to apply generally to somatic ACE whether circulating or tissue-bound? Are we being asked to take a pound of flesh and not spill any blood?

It has been reported that quinaprilat displaced 50% of ¹²⁵I-labeled 351A (the tyrosyl derivative of enalaprilat) from human plasma ACE at a concentration 2 orders of magnitude lower than that of enalaprilat; however, the differences in EC₅₀ of 351A and quinaprilat for lung and cardiac ACE appeared to be far more modest.⁷ The equilibrium dissociation constants (Kᵢ) of Ro 31-8472 (a derivative of cilazaprilat), 351A, and quinaprilat for displacement of ¹²⁵I-351A from lung ACE were 32±7, 15±3, and 6±1 pmol/L, respectively.⁸ Assuming particular assay conditions, the Kᵢ is directly related to the EC₅₀; therefore, these latter data do not describe

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In failing human heart, endothelial dysfunction and changes in cardiac myocytes are closely intertwined. ACE protein expression is increased in the failing human heart, and this increase may occur as the result of ACE gene expression in both endothelial cells and cardiac myocytes. Thus, the pertinent question may not be simply whether one is effectively inhibiting endothelial ACE but also whether effective inhibition of cardiac myocyte ACE has been achieved. Similarly, the inducible form of NOS (iNOS) is increased in cardiac myocytes from failing human hearts relative to ecNOS. Although an increase in endothelial cell production of NO appears to be desirable, it does not necessarily follow that an increase in NO production mediated by iNOS in cardiac or vascular myocytes will have a beneficial or protective effect on these cells. The important role of the endothelium in modulating cardiac myocyte structure and function was recently demonstrated by Ritchie et al., who found that BK prevented Ang II–induced hypertrophy of cardiac myocytes in the presence of endothelial cells; however, in the absence of endothelial cells, BK had a hypertrophic effect. Whether this differential effect of BK was related to the specific cell type in which NO production occurred or whether BK signal transduction in myocytes actually stimulated NO production was not determined. The effects of BK in this system were blocked by the BK1 receptor–selective agonist HOE140. Nevertheless, one is tempted to speculate that BK effects on cardiac myocytes in failing human heart could be brought about by activation of BK1 subtype receptor expression, which, like iNOS expression, is turned on by cytokines. Signaling through the BK1 receptor may oppose effects mediated by the BK2 receptor. It is likely that the antihypertrophic effect of BK in the presence of endothelial cells was mediated by ecNOS. This supposition is supported by the recent report that ecNOS-deficient mice develop paradoxical hyperplasia of the carotid wall after vessel ligation. In the context of relatively long-term NO inhibition, ACE-inhibitor administration has been shown to prevent coronary vascular remodeling and myocardial hypertrophy. But, as a final counterpoint, captopril may also be effective in preventing such changes without affecting NOS activity.

The acute effects of quinaprilat found in this study predict long-term changes in vascular remodeling. From a mechanistic viewpoint, studies designed to test this prediction not only in the peripheral circulation but also in the intact failing human heart would be of interest. With regard to therapeutics, it is premature to recommend the use of quinapril over enalapril in the treatment of patients with heart failure, and as the authors observe, further studies are needed.


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