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Editorial Comment

Angiotensin-Converting Enzyme Inhibitors: Are There Significant Clinical Differences?*

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The comparison of lisinopril with captopril in the treatment of heart failure by Giles and coworkers (1), published in this issue of the Journal, is a welcome first step toward the rational selection of an angiotensin-converting enzyme (ACE) inhibitor. In this study, lisinopril improved left ventricular ejection fraction and exercise capacity in subsets of patients in which captopril had no effect, and this is the first such comparison to show that clinical benefits occur more often with a specific ACE inhibitor. But, at our present level of understanding, we are ill prepared to comment on the mechanisms by which lisinopril effected these salutary results. The study underscores how little we know about the entire class of ACE inhibitors.

Mechanisms of beneficial effects of ACE inhibitors in heart failure. With the advent of these drugs for use in congestive heart failure came a rationale that initially appeared sound. The role of the renin-angiotensin system in the pathogenesis of heart failure had been well described (2,3). The acute hemodynamic response to oral ACE inhibitors, i.e., a reduction in right and left ventricular filling pressures and systemic vascular resistance with a concomitant increase in cardiac index, was shown to be directly related to plasma renin activity and attendant with reductions in plasma angiotensin II, aldosterone and plasma ACE activity (4–7). Most important, the clinical benefits of ACE inhibitors in the management of patients with heart failure have been unequivocally demonstrated in numerous controlled trials (6,8–10). The hypothesis that inhibition of circulating ACE activity in heart failure would diminish the deleterious effects of plasma angiotensin II and thereby provide symptomatic relief to patients had been proved. But this theory does little to explain why lisinopril may be more efficacious than captopril.

Other observations are also inconsistent with this simple hypothesis. There is little or no correlation between values for systemic vascular resistance in heart failure and plasma renin or norepinephrine (11). Neither the acute hemodynamic response nor the pretreatment plasma renin activity predicts the long-term clinical response to ACE inhibitors in patients with hypertension or heart failure (12–14). In animal vascular preparations, both captopril and enalaprilat can be shown to reduce mean arterial pressures for ≥24 h whereas ACE activity is inhibited for only approximately 6 h (15). Intracoronary infusion of enalaprilat produces both a selective vasodilation of the coronary arteries and a negative inotropic effect on left ventricular contractility in patients with dilated cardiomyopathy (16), in contrast to the effects seen with systemic administration of the ACE inhibitors (17). Finally, long-term consequences of ACE inhibition on exercise capacity and renal function in heart failure appear to be more dependent on complex alterations in regional vascular tone than on hemodynamic manipulations. Mancini et al. (18) showed that improvement in maximal oxygen uptake after 8 weeks of captopril therapy occurred only in those patients whose peak skeletal muscle blood flow also increased.

Several investigators have described the various effects of ACE inhibition on renal funciton (6,19,20). Over the short term, ACE inhibition leads to a pronounced decrease in renal plasma flow and glomerular filtration rate concomitant with a decrease in mean arterial pressure; the magnitude of the decrease correlates with baseline plasma renin and is paralleled by a reduction in sodium and water excretion. With long-term treatment, despite a similar decrease in mean arterial pressure, there is an increase in renal plasma flow, and baseline glomerular filtration rate, water and sodium excretion are maintained. Moreover, even those patients who develop elevations of serum urea and creatinine concentrations during therapy manifest meaningful clinical lessening of their symptoms of heart failure, discordant with their deteriorating renal profile. The underlying theme common to these observations is that ACE inhibitors seem to effect organ-specific physiologic adaptations in vascular tone or organ function that require time (or duration of long-term therapy) to be clinically apparent.

The renin-angiotensin system in various organs and tissues. Further investigations into the mechanisms of ACE inhibition in hypertension have afforded us some insight into the role of the renin-angiotensin system in various tissues (Table 1). Researchers have identified components of the renin-angiotensin cascade in blood vessel walls, kidney, heart, adrenal gland and brain. Angiotensin II, whether systemically derived or tissue specific, has been shown to have locally mediated functions. This growing list includes en-

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Table 1. Diversity of Tissue Renin-Angiotensin Systems and Their Possible Functions

Tissue	Functions
Kidney	Renal blood flow, glomerular filtration rate and hemodynamics, sodium reabsorption
Blood vessel	Vascular tone, vascular hypertrophy
Heart	Myocardial metabolism, hypertrophy, contractility
Adrenal	Aldosterone secretion, catecholamine release
Brain	Thirst, behavior, blood pressure, vasopressin and catecholamine release
Pituitary	ACTH, gonadotropin hormone, prolactin release

ACTH = adrenocorticotropin. Adapted from Dzau (21), with permission.

hancement of norepinephrine release from noradrenergic nerve endings, stimulation of vasopressin, development of vascular or myocardial hypertrophy, influence on myocardial metabolism during ischemia and, in the brain, stimulation of water drinking behavior. Likewise, ACE inhibition of tissue angiotensin will result in local alterations of each organ. For example, in spontaneously hypertensive rats, inhibition of ACE activity in the aorta was better correlated with the magnitude and duration of the hypotensive action of several ACE inhibitors than with serum enzyme activity (22). In the same animal model, infusion of captopril into the cerebral ventricle for several weeks led to a marked attenuation of the development of hypertension in contrast to the negligible effect of long-term systemic therapy (23). Finally, inhibition of the angiotensin-converting enzyme is responsible for the stimulation of bradykinin and the formation of prostaglandin, with their own attendant local or systemic effects.

Differences among the ACE inhibitors. The evidence suggests, therefore, that ACE inhibition at the level of the vascular endothelium and the individual organ response is the more relevant to the observed clinical effects of long-term therapy. Indeed, the data have prompted Dzau (24) to formulate an attractive hypothesis. He argues that the renin-angiotensin system should be viewed as two compartments, one in circulation and the other in local tissues. The principal function of the circulating renin-angiotensin system is to provide short-term cardiorenal homeostasis whereas tonic control of vascular resistance and local tissue function is modulated by the intrinsic tissue system. Thus, many of the confusing actions of long-term ACE inhibitor therapy observed in patients with heart failure, alluded to previously, can be explained by the assumption that the primary site of drug action occurs at the local tissue level. Furthermore, it is one plausible way to explain the findings of Giles et al. (1). One can speculate that important distinctions between the increasing number of ACE inhibitors will primarily be a function of their individual tissue penetration, metabolism, subsequent local ACE inhibition, stimulation of bradykinin and prostaglandin and antagonism of the diverse angiotensin effects at that site. For instance, differences among the ACE inhibitors on brain ACE activity will be partly dependent on the lipid solubility of a given metabolite and the ability of a drug to cross the blood-brain barrier (25).

The tantalizing evidence provided by Giles et al. (1) and other investigators (26) suggests that there are real differences between ACE inhibitors. However, the conceptual framework for understanding the mechanisms responsible for these differences is fragile at best. Unfortunately, until more research is accomplished, the choice of an ACE inhibitor for the patient with heart failure rests more on whimsy than on wisdom.

References

1. Giles TD, Katz R, Sullivan JM, et al. Short- and long-acting angiotensin-converting enzyme inhibitors: a randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. J Am Coll Cardiol 1989;13:1240–7.
2. Laragh JH. Hormones in the pathogenesis of congestive heart failure: vasopressin, aldosterone, and angiotensin II. Circulation 1962;25:1015–23.
3. Curtiss C, Cohn JN, Vrobel T, Franciosa JA. Role of the renin-angiotensin system in the systemic vasoconstriction of chronic congestive heart failure. Circulation 1978;58:763–70.
4. Ader R, Chatterjee K, Ports T, Brundage B, Hiramatsu B, Parmley W. Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by an oral-angiotensin-converting enzyme inhibitor. Circulation 1980;61:931–7.
5. Cody RJ, Covit A, Schaer G, Williams G. Captopril pharmacokinetics and the acute hemodynamic and hormonal response in patients with severe congestive heart failure. Am Heart J 1982;104:1180–3.
6. Cleland JGF, Dargie HJ, Ball SG, et al. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. Br Heart J 1985;54:305–12.
7. Dickstein K, Aarsland T, Woie L, et al. Acute hemodynamic and hormonal effects of lisinopril (MK-521) in congestive heart failure. Am Heart J 1986;112:121–9.
8. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in congestive heart failure. J Am Coll Cardiol 1983;2:755–63.
9. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
10. The Captopril-Digoxin Multicenter Research Group. Comparative effects of captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
11. Levine TB, Francis GS, Goldsmith SR, Simon A, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relationship to hemodynamic abnormalities in congestive heart failure. Am J Cardiol 1982;49:1659–66.
12. Massie BM, Kramer BL, Topic N. Lack of relationship between the short-term hemodynamic effects of captopril and subsequent clinical responses. Circulation 1984;69:1135–41.
13. Creager MA, Faxon DP, Halperin JL, et al. Determinants of clinical response and survival in patients with congestive heart failure treated with captopril. Am Heart J 1982;104:1147–53.
14. Vlasses PH, Conner DP, Rotmensch HH, et al. Double-blind comparison of captopril and enalapril in mild to moderate hypertension. J Am Coll Cardiol 1986;7:651–60.

15. Lindsey CJ, Bendhack LM, Paiva ACM. Effects of teprotide, captopril and enlaprilat on arterial wall kininase and angiotensin converting activity. J Hypertension 1987;5(suppl 2):571–6.

16. Foult JM, Tavolaro O, Antony I, Nitenberg A. Direct myocardial and coronary effects of enalaprilat in patients with dilated cardiomyopathy: assessment by a bilateral intracoronary infusion technique. Circulation 1988;77:337–44.

17. Rouleau JL, Chatterjee K, Benge W, Parmley WW, Hiramatsu B. Alterations in left ventricular function and coronary hemodynamics with captopril, hydralazine and prazosin in chronic ischemic heart failure: a comparative study. Circulation 1982;65:671–6.

18. Mancini DM, Davis L, Wexler JP, Chadwick B, LeJemtel TH. Dependence of enhanced maximal exercise performance on increased peak skeletal muscle perfusion during long-term captopril therapy in heart failure. J Am Coll Cardiol 1987;10:845–50.

19. Majais SK, Fouad FM, Textor SC, et al. Transient renal dysfunction during initial inhibition of converting enzyme in congestive heart failure. Br Heart J 1984;52:63–71.

20. Packer M, Lee WH, Medina N, Yushak M, Kessler PD. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. Ann Intern Med 1987;106:346–54.

21. Dzau VJ. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. Circulation 1988;77(suppl I):I-4–I-13.

22. Cohen ML, Kurz KD. Angiotensin converting enzyme inhibition in tissues from spontaneously hypertensive rats after treatment with captopril or MK-421. J Pharmacol Exp Ther 1982;220:63–9.

23. Okuno T, Nagahama S, Lindheimer MD, Oparil S. Attenuation of the development of spontaneous hypertension in rats by chronic central administration of captopril. Hypertension 1983;5:653–9.

24. Dzau VJ. Significance of vascular renin-angiotensin pathway. Hypertension 1986;8:553–9.

25. Unger T, Badoer E, Ganten D, Lang RE, Rettig R. Brain angiotensin: pathways and pharmacology. Circulation 1988;77(suppl I):I-40–I-54.

26. Packer M, Lee WH, Yushak M, Medina N. Comparison of captopril and enalapril in patients with severe chronic heart failure. N Engl J Med 1986;315:I-40–I-54.