Point of View

Angiotensin Converting Enzyme Inhibition and Its Impact on Cardiovascular Disease

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Manipulation of the renin-angiotensin system has evolved during the last few years from an obscure line of biochemical research and pathophysiologic experimentation into a new therapeutic approach, whose widespread clinical application is affecting the lives of large patient populations. Of particular interest in this respect is the emerging concept of the close relation between the renin-angiotensin system and heart disease. This article is not a pharmacologic review of angiotensin inhibitors but rather a brief historical overview of the subject as seen from the personal perspective of an investigator involved in the earliest stages of its evolution. This overview follows the steps leading from early observations to controlled studies that unraveled the role of this system in hypertension and its cardiovascular complications; it also speculates on the potential future impact of this work on the incidence of cardiovascular mortality in the hypertensive population.

The Problem

Several epidemiologic studies in the 1950s and 1960s, including the famous Framingham Heart Study, identified hypertension as one of the most important risk factors for cardiovascular disease. Moreover, large clinical trials such as the Veteran’s Administration study,1 showed beyond doubt that successful antihypertensive treatment could prevent or even reverse most hypertensive complications. Yet, it soon became apparent from that study, and confirmed by subsequent studies, such as the Hypertension Detection and Follow-up Program (HDFP)2 and the Multiple Risk Factor Intervention Trial (MRFIT),3 with the only exception being the European Working Party High Blood Pressure in the Elderly Trial (EWPH),4 that the high risk of coronary disease and heart attack remained unchanged even in optimally treated hypertensive patients. One possible explanation for this finding was that the common antihypertensive drugs (mostly thiazide diuretics) caused metabolic disturbances that in themselves became risk factors for coronary disease, thus offsetting the anticipated benefit from blood pressure lowering.5

At the same time, many researchers were investigating potential causes and mechanisms of high blood pressure. One prime suspect was the renin-angiotensin system, whose existence had been first suspected from the studies of Tigerstedt and Bergman6 near the turn of the century, and which had been extensively investigated 40 years later by Pickering and Prinzmell,7 Braun-Menendez et al,8 and Page and Helmer.9 This system was shown by the classic Goldblatt experiments in 1934 to be responsible for at least some types of hypertension. The problem was that in most animal models and in humans with essential hypertension, plasma renin activity was either similar to that of normal subjects or definitely suppressed. This prompted debate on its relevance in essential hypertension, the type encountered in over 95% of patients with hypertensive disease.

However, at least one hypertensive syndrome was very frequently associated with excessive levels of renin and with a high incidence of rapidly progressing cardiovascular complications: malignant phase hypertension, which seemed to offer the best model for exploring the link between the renin-angiotensin system (by the late 1960s being reliably measured by radioimmunoassay) and vascular pathology.10 In contrast to Pickering,11 who considered malignant hypertension to be mostly determined by the absolute height and speed of rise of blood pressure, earlier investigators had linked experimentally the vascular effects of renin to this syndrome.12,13 In keeping with this, our observations led us to believe that humoral factors, such as excessive stimulation of renin secretion and disorders of blood coagulation and rheology, were more important determinants of its severity.14

Vascular Effects of Endogenous or Exogenous Angiotensin

A series of clinicopathologic observations in patients with malignant hypertension disclosed that most of them died despite reversal of hypertension by the then standard treatment with high doses of furosemide and ganglionic blockers. All had striking eleva-

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tion of plasma renin and angiotensin II levels and widespread fibrinoid necrosis of renal arterioles.\textsuperscript{15}

Necrotic lesions could be reproduced in rabbits by exogenous infusion of angiotensin II in doses calculated to produce plasma levels in the range of those observed in patients with malignant hypertension or patients undergoing hemodialysis.\textsuperscript{16} After a continuous 3-day infusion of angiotensin II in these high quantities, the rabbits developed acute renal failure with the histologic characteristics of circulatory (i.e., ischemic) tubular necrosis. However, an interesting and unexpected by-product of these experiments was the discovery of widespread focal myocardial infarctions. This finding raised the possibility that in clinical situations an excessive rise in angiotensin II may cause similar lesions in the heart and thus lead to fatal myocardial ischemia.

The clinical counterparts to this were patients who died suddenly during hemodialysis for end-stage renal disease associated with hyperreninemia and malignant hypertension and who at autopsy were found to have widespread focal myocardial infarctions histologically indistinguishable from those seen in the rabbits.\textsuperscript{17} Further studies in such patients revealed the absence of either thrombotic or atheromatous lesions in the coronary vessels supplying the necrotic area, suggesting that the ischemia might have resulted from prolonged intense vasospasm.\textsuperscript{18} Moreover, two patients who had sustained repeat episodes of intradialysis nonfatal heart attacks and who were subsequently submitted to bilateral nephrectomy had no such episodes from then on. Based on these findings, as well as studies with nephrotic antibiotics,\textsuperscript{19} we suggested that hyperreninemia might have a deleterious effect on the microvasculature and that treating high blood pressure by short-term sodium and fluid depletion with diuretics in this setting may be undesirable, a view that at that time was hotly contested.\textsuperscript{20}

At the same time, other investigators using a different approach, that is, an epidemiologic survey of hypertensive patients classified by plasma renin level, also reached the conclusion that angiotensin may be a pathogenetic factor in vascular lesions.\textsuperscript{21} Although that study was subsequently criticized for its design and broad conclusions, it did point to a role of the stimulated renin-angiotensin system as either a cause of vascular damage or as a prognostic marker of cardiovascular complications.\textsuperscript{22}

The effect of sodium on renal content\textsuperscript{23} and thereby on glomerular filtration rate\textsuperscript{24} had been described earlier. Studies on microdissected individual glomeruli confirmed the presence of significantly greater quantities of renin in kidneys retrieved from salt-deprived than from salt-loaded animals.\textsuperscript{25} Subsequent studies in experimental animals with renovascular hypertension\textsuperscript{26,27} and in humans with essential hypertension\textsuperscript{28} showed the existence of a reciprocal relation between renin and sodium in blood pressure maintenance, whereby renin-dependent hypertension could be converted to sodium-dependent hypertension and vice versa, depending on the availability of salt. In other words, sodium depletion caused reactive hyperreninemia, and sodium-loading suppressed renin, whereas the level of blood pressure remained practically unchanged in many of these subjects. As sodium is abundant in the environment, it appears to play the predominant role in blood pressure maintenance in most hypertensive subjects. In fact, excessive retention of sodium could by itself push hypertension into the malignant phase (probably by mobilizing other vasopressor mechanisms) without the participation of angiotensin.\textsuperscript{29} However, in the absence of sodium, blood pressure appears to be maintained to a great extent through the vasoconstrictor action of angiotensin II. This was best shown by the hypertensive response to angiotensin blockade.

**Angiotensin II Blockade**

The advent of angiotensin inhibitors opened a new era in the research of this field. The first such compounds were synthetic polypeptide analogues of angiotensin II that acted as its competitive antagonists at the vascular receptor level.\textsuperscript{30,31} One of these analogues, Sar\textsuperscript{1}-Ala\textsuperscript{8} angiotensin II or saralasin,\textsuperscript{32} became available for experimental studies in humans\textsuperscript{33} and was used extensively in clinical research over the next several years. Although it never attained practical clinical usefulness as a diagnostic or therapeutic means, it did become an invaluable tool in the investigation of the role of the renin-angiotensin system in various conditions.

Our first opportunity to use this agent therapeutically was in a patient with malignant hypertension and pulmonary edema.\textsuperscript{34} Shortly after beginning the saralasin infusion, his blood pressure normalized, and the symptoms of congestive heart failure improved dramatically. That first infusion was given continuously during a 1-week period and, aided by three doses of furosemide, resulted in normotension with a cumulative negative sodium balance of 760 meq and with complete resolution of the signs and symptoms of heart failure.

To better define the hemodynamic changes produced by this treatment, we chose as the next patient with congestive heart failure suitable for such studies, a 55-year-old man with known severe high renin hypertension, who was scheduled to undergo a diagnostic cardiac catheterization.\textsuperscript{35} In the course of his diagnostic procedure, we administered the saralasin infusion and documented the increase in cardiac output and the fall in heart rate, peripheral and pulmonary vascular resistance, arterial pressure, pulmonary wedge pressure, and left ventricular end-diastolic pressure. These changes resulted in a striking improvement in left ventricular stroke work index associated with a decrease in myocardial oxygen consumption. Surprisingly, despite the diminished blood pressure and heart rate product, there was an increase in coronary blood flow in the face of a concurrent major fall in systemic pressure. This was in contrast to observations with other common vasodilators, where the fall in systemic pressure leads to
diminished coronary blood flow,\textsuperscript{36} which can actually aggravate cardiac ischemia when coupled with some reflex tachycardia. All of these parameters returned to baseline at the end of the 30 minutes of infusion.

To further pursue this intriguing observation, we devised a series of animal experiments to study the effect of angiotensin on coronary flow and other regional blood flows. These experiments revealed that the vasodilation produced by angiotensin blockade differed physiologically from that induced by other pharmacologic vasodilators in that it was selective, affecting mostly the vasculature of tissues sensitive to the vasoconstrictor effect of angiotensin II.\textsuperscript{37–39} Thus, we observed a redistribution of regional blood flows, with significant increases in the fraction of output going to vital organs (such as kidney, heart, and brain), the vasculature of which is sensitive to angiotensin, at the expense of the less-sensitive musculoskeletal tissues. Other investigators found that angiotensin blockade was accompanied by a suppression of aldosterone production by the adrenal cortex.\textsuperscript{40} These findings meant that even in the face of falling arterial blood pressure, the perfusion of vital organs could be augmented and maintained; moreover, the secondary hyperaldosteronism that resulted in the salt and fluid retention characteristic of other vasodilators was abolished by angiotensin blockade. The main obstacle to more widespread use of this therapeutic approach was the fact that saralasin had to be administered by constant intravenous drip.

**Angiotensin Converting Enzyme Inhibition**

Another approach to angiotensin inhibition became possible when a Brazilian researcher discovered that the venom of a local snake contained polypeptides that could block the enzyme converting the precursor angiotensin I to biologically active angiotensin II.\textsuperscript{41} These agents, termed "angiotensin converting enzyme (ACE) inhibitors," were shown to decrease blood pressure in animals with renovascular hypertension of the high renin type.\textsuperscript{42,43} One of these agents, the nonapeptide teprotide, was eventually synthesized by biochemists of the Squibb Research Institute\textsuperscript{44} and made available for use in humans.\textsuperscript{45} It was subsequently used extensively for experimental and human studies, and it led to an explosion of research activity in this field.

The systemic hemodynamic and biochemical effects of ACE inhibition were found to be qualitatively similar to those produced by saralasin, though more pronounced: decrease of systemic and pulmonary vascular resistance with fall in blood pressure without reflex tachycardia or orthostatic hypotension, suppression of aldosterone with a tendency to natriuresis and slight retention of potassium, preferential vasodilation of "angiotensin-sensitive" organs with increase in renal, cardiac, and cerebral blood flow,\textsuperscript{39,46} and reversal of congestive heart failure.\textsuperscript{47} The fact that these effects were more pronounced with teprotide than with saralasin could be attributed either to the kinin-potentiating effect of ACE inhibition or to a weak agonistic property of saralasin that might have partially offset its antagonistic effect against angiotensin II.

An early study\textsuperscript{48} reported that the levels of circulating bradykinin were elevated after ACE inhibition with teprotide; however, subsequent studies by the same research team,\textsuperscript{49} as well as by others,\textsuperscript{50} failed to confirm this with captopril. Because of the methodologic difficulties, as well as the debate regarding the importance of circulating as opposed to tissue-bound bradykinin, the matter remained controversial until much later, when the use of bradykinin antibodies\textsuperscript{51} and specific competitive antagonists\textsuperscript{52} demonstrated the contribution of this vasodilatory hormone to the blood pressure–lowering effect of ACE inhibitors.

The fact that ACE inhibition produced preferential vasodilation in “sensitive” organs raised the interesting possibility that ischemic disorders of such organs could be selectively reversed without the problems of generalized vasodilation. This was first shown experimentally in the cerebral circulation, of which the microvessels had been shown to contain large amounts of reninlike enzyme.\textsuperscript{53} Acute or delayed cerebral vasospasm is one of the most dangerous complications of subarachnoid hemorrhage. We reproduced experimentally this condition in dogs and showed that systemic ACE inhibition could reverse the vasospasm and restore cerebral blood flow in previously ischemic areas, without much change in systemic blood pressure.\textsuperscript{54,55} The clinical benefit of this preferential effect of ACE inhibition on the cerebral vasculature became apparent much later in patients with congestive heart failure, in whom ACE inhibitors caused a marked fall of an already low blood pressure, with no change or even with an increase in cerebral blood flow, which enables these patients to tolerate the very low systemic pressure needed to boost their myocardial performance.\textsuperscript{56,57}

Nevertheless, the effect of chronic inhibition of angiotensin II on the cerebral circulation recently became a matter of further debate. The controversy arose from the Medical Research Council (MRC) trial,\textsuperscript{58} which showed that patients with mild hypertension controlled with a thiazide appeared to be better protected against stroke than did patients with hypertension controlled with propranolol. Based on this, one group of investigators\textsuperscript{59} hypothesized that because diuretics increase renin-angiotensin levels and \(\beta\)-blockers suppress them, angiotensin-mediated constriction may exert some protective effect on the cerebral vasculature against hemorrhagic stroke. Many investigators were quick to point out the flaws in this kind of reasoning.\textsuperscript{60} First, the overwhelming majority of strokes are ischemic, not hemorrhagic (the MRC trial did not actually specify type of stroke). Second, the unopposed \(\alpha\)-adrenergic activity during \(\beta\)-blockade would constrict the cerebral resistance vessels in the face of lowered systemic pressure, which would be a far more likely explanation for the observed increased frequency of strokes (presumably ischemic) in patients with hypertension controlled by
a β-blocker. Despite the tendency of cerebral flow to remain constant by autoregulation, there is evidence in the literature suggesting that ACE inhibition tends to shift the lower limits of this phenomenon downward, thus improving the brain’s tolerance to hypotension, whereas β-blockade has the opposite effect. Accordingly, inhibition of the production of angiotensin II would be expected to enhance the preventative effect of blood pressure lowering against ischemic stroke. Moreover, chronic antihypertensive treatment is believed to cause readaptation of structural hypertensive vascular changes and to blunt excessive vasodilation, thus conferring some protection against hemorrhagic stroke. Therefore, the hypothesis that elevated angiotensin II is necessary to protect against stroke seems untenable.

With regard to the cardiac effects of ACE inhibition, however, there is general agreement. As anticipated from the experimental studies in dogs mentioned earlier, ACE inhibition was also found to cause a similar fractional redistribution of cardiac output in humans. In a series of such studies conducted during diagnostic cardiac catheterizations, we were able to show the increase in coronary blood flow in selected patients (i.e., those with elevated renin levels) and the universal increase in renal blood flow, with practically unchanged regional flows to the liver and skeletal muscles. The increase in renal flow resulted frequently in improvement of the previously diminished renal excretory capacity.

But one of the most important applications of experimental knowledge to human therapeutics came with the first use of ACE inhibition in the treatment of congestive heart failure. These early studies, soon confirmed by others, showed the advantages of treating rationally a functional disorder by attacking one of the factors contributing to the pathophysiology of that disorder. By reversing the angiotensin-dependent elevation of vascular resistance characteristic of decompensated heart failure, one could induce systemic and regional hemodynamic amelioration associated with beneficial metabolic alterations: decrease in afterload, increase in cardiac output, improved perfusion of vital organs, reversal of myocardial ischemia with decreased oxygen consumption, and prevention of secondary hyperaldosteronism causing salt and fluid retention. Subsequently, numerous studies from many centers used teprotide to further explore and define the role of angiotensin in various target organs, and especially in intrarenal hemodynamics, cardiodynamics, cerebral circulation, and adrenal function.

### The Outcome

All this wealth of knowledge was put into practical application as soon as the first orally active ACE inhibitor, captopril, became available for clinical use in hypertension and heart failure. This agent, ingeniously designed and synthesized by the same team of biochemists who had synthesized teprotide, made possible the widespread therapeutic use of this new approach for treating conditions that benefitted from ACE inhibition in previous animal and clinical experiments. Soon, a second generation of ACE inhibitors was synthesized that did not contain a sulfhydryl group, the moiety incriminated for some adverse effects of captopril. These agents act by competitive displacement of the substrate from binding sites of the enzyme but do not have the chelating effect exerted by the sulfhydryl group of captopril on the zinc atom of the ACE. After the first such “second generation” ACE inhibitor, enalapril, was successfully released, it was followed by numerous other similar compounds (lisinopril, ramipril, cilazapril, quinapril, perindopril, etc.).

This new approach for the treatment of hypertension was shown to control a wide spectrum of hypertensive diseases, not only those characterized by high renin levels, but most characterized by normal renin and many by low renin levels as well. The pharmacologic characteristics of ACE inhibition, including the absence of side effects common to most other antihypertensive drugs (i.e., drowsiness, loss of mental acuity, fatigue, and impotence), permitted good blood pressure control without adversely affecting the subject’s psychosocial performance and quality of life and therefore led to better patient acceptance. Its lack of metabolic disturbances such as seen with diuretics or β-adrenergic blockers (i.e., alterations in lipid profile, glucose metabolism, and electrolytes) was perceived as another advantage; when used in combination with a thiazide, which increases its effectiveness so that over 85% of hypertensive patients respond to it, ACE inhibition could even reverse part the metabolic side effects of the diuretic.

Captopril and enalapril have been used extensively in the treatment of all types of hypertension. Not surprisingly, in the last few years, the advantages of ACE inhibitors have made them increasingly popular as drugs of first choice for unselected hypertensive patients of all age groups, including the elderly who were thought in the past to be less responsive to this treatment. At present, the main obstacle to their being widely adopted as the first line of treatment in hypertension is probably the high cost of these drugs in the marketplace. This is not to say that ACE inhibitors are free of undesirable effects. Their adverse effects have been well documented and include “class effects,” that is, those attributed to their mechanism of action, such as functional renal insufficiency, cough, and angioedema, as well as allergic or idiosyncratic reactions particular to each compound, such as rashes and blood dyscrasias, that require monitoring, dose adjustments, and sometimes discontinuation of the treatment.

ACE inhibition has also emerged as the treatment of preference for chronic congestive heart failure (with or without coexisting hypertension). A number of studies from large multicenter trials using captopril, enalapril, or lisinopril in heart failure have documented that ACE inhibition can reverse symptoms and signs of congestive cardiac failure and
maintain its effectiveness on long-term therapy, with improved hemodynamic parameters, thus leading to amelioration by one or two functional classes of the New York Heart Association and without the tachyphylaxis or the salt and fluid retention of secondary hyperaldosteronism caused by conventional vasodilators. ACE inhibition was also shown to work more advantageously for the heart’s economy than did inotropic agents or other vasodilators; by decreasing the arterial pressure without reflex tachycardia, ACE inhibition decreases the blood pressure and heart rate product. Thus, myocardial work is diminished and so is myocardial oxygen consumption, which improves the exercise capacity.\textsuperscript{88} This is true even in patients with coronary insufficiency whose anginal threshold was found in preliminary studies to be significantly elevated by ACE inhibition.\textsuperscript{89} Several comparative studies have established the apparent superiority of ACE inhibitors over other vasodilators in congestive heart failure.\textsuperscript{90–92}

Moreover, a recently completed trial\textsuperscript{95} revealed that long-term ACE inhibition in patients with severe congestive heart failure (class IV) not only improved the signs and symptoms of their condition and their quality of life, but, unlike most other vasodilators, ACE inhibition also decreased the rate of mortality. The only other long-term treatment shown to improve survival in patients with congestive cardiac failure is the combination of hydralazine and isosorbid dinitrate used in the Veterans Administration Heart Failure Trial (V-HeFT).\textsuperscript{96} A second V-HeFT is now planned to compare this combination with the ACE inhibitor enalapril. This trial should determine whether the prolonged survival is due simply to unloading the heart or whether the neurohumoral alterations of long-term ACE inhibition confer an additional advantage.

A combination of improved myocardial perfusion, diminished myocardial sympathetic tone, reversal of hypokalemia (spontaneous or diuretic-induced), and, in the long run, reversal of left ventricular hypertrophy, may account for the significant decrease in cardiac arrhythmias in some studies observed after long-term treatment with ACE inhibitors.\textsuperscript{97,98} As for long-term cardioprotection in patients with coronary artery disease, recent experimental and clinical studies\textsuperscript{99,100} show that ACE inhibition, when started soon after a transmural anterior myocardial infarction with evidence of systolic dysfunction, could attenuate the progression of left ventricular enlargement, which otherwise usually leads to dilated cardiomyopathy. The prolonged survival in these patients can probably be attributed theoretically to the pharmacodynamics of ACE inhibition. A multicenter trial modeled after these preliminary studies is now in progress, the Survival and Ventricular Enlargement (SAVE) study, to determine whether ACE inhibition starting right after a myocardial infarction can indeed prevent dilated cardiomyopathy.

Despite the philosophical argument that interference with one of nature’s homeostatic mechanisms might in the long run have some detrimental effect,\textsuperscript{101} experience during the past 15 years does not support such fears. The three main physiologic functions of the renin-angiotensin-aldosterone system are maintenance of arterial blood pressure, maintenance of glomerular filtration, and retention of salt. The last function is probably not as necessary in today’s society where salt is available in excess\textsuperscript{102} as it must have been in primitive populations. As for the other two functions, in most cases, they can be adequately maintained by compensatory changes in other hormonal systems.\textsuperscript{103} Only rarely do patients become unable to tolerate suppression of angiotensin II, and those who do were probably overzealously treated with multiple other drugs (especially loop diuretics) or have a renal filtration that depends mostly on the vasoconstriction of the efferent arteriole because of proximal anatomic obstruction.

The Future

Today, a large number of drugs are available to the practitioner, all of which have been shown to be safe and effective in lowering high blood pressure by various mechanisms. However, as stated in the beginning, the high risk of coronary disease is the only hypertensive complication found to be unaffected in the past by optimal blood pressure control with conventional antihypertensive agents. Would long-term ACE inhibition also decrease the morbidity and mortality from coronary disease and sudden cardiac death associated with hypertension? The answer to this is not available yet. However, one may intuitively expect it to be affirmative because of the beneficial effect of ACE inhibition on the heart’s economy and because coronary insufficiency and complex cardiac arrhythmias are enhanced by the metabolic disorders caused or aggravated by other common antihypertensive drugs. \(\beta\)-Adrenoceptor blockers were shown to confer secondary protection from reinfarction when given to patients after myocardial infarction\textsuperscript{104,105}; however, in most studies, \(\beta\)-blockers failed to show the anticipated primary cardioprotective effect in hypertensive patients\textsuperscript{58,106} with the exception of metoprolol in the MAPHY trial.\textsuperscript{107} Also, the hormonal consequences associated with long-term ACE inhibition, that is, the suppression of angiotensin II, the decrease of tissue catecholamine levels and turnover,\textsuperscript{108} and possibly potentiation of bradycardia in\textsuperscript{51,52} may themselves exert a beneficial effect on the coronary vasculature and the myocardium. Large multicenter controlled trials would be required to show such an effect, since historical controls would be impossible to use because of other concurrent changes in life style (e.g., cessation of smoking and low fat diet) being vigorously promoted in recent years. Nevertheless, the evidence suggests that ACE inhibition has already contributed to better treatment of patients with hypertension and congestive cardiac failure, and it seems justified to speculate that the more widespread use of ACE inhibition will
accentuate further the trend to diminished cardiovascular mortality observed during the past decade.

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