Corcoran Lecture

Angiotensin-Converting Enzyme Inhibition and the Heart

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Research in the pathophysiology of hypertension and the development of antihypertensive treatments has evolved with long strides over the last decades. With every new therapeutic modality introduced in the field, the immediate objective has been the safe and effective lowering of blood pressure. Implicit is the expectation, established by the classic multicenter trials in the 1960s, that such lowering will prevent the complications of untreated hypertension. Yet most epidemiologic studies have shown a surprising lack of significant effect of antihypertensive therapy on the incidence of ischemic heart disease. This has led to the notion that such cardiac disease may not be simply a complication resulting from high blood pressure per se but rather a parallel product of some of the same pathophysiological alterations that characterize the hypertensive process. The logical upshot of this reasoning is that a successful therapy should address as many as possible of these alterations that constitute known coronary risk factors to protect the heart.

It is my belief that angiotensin-converting enzyme (ACE) inhibition is unique among antihypertensive modalities in offering the greatest potential for cardioprotection. Because of its dual action—inhibition of angiotensin II (Ang II) and potentiation of bradykinin—it benefits, directly or indirectly, a large number of risk factors influenced by either one or both of these vasoactive hormones. In addition to regulating systemic blood pressure levels and sodium handling, these hormones regulate preferentially the vascular tone of vital organs and especially that of the coronary vasculature; modulate the sympathoadrenal system with its vasoconstrictor, electrophysiological, and metabolic actions; affect the growth of cardiac myocytes and vascular smooth muscle cells, the generation of autocrine-paracrine factors by endothelial cells, the sensitivity to insulin, and the rate of glucose uptake; and alter overall cardiac function. In this brief review I will present experimental and clinical evidence in support of these statements, referring to the recent large multicenter trials that have demonstrated improved morbidity and mortality in patients with myocardial dysfunction and/or coronary disease treated with ACE inhibition. I will close with a tentative look in the future—the potential of genetic epidemiology to predict who might derive the greatest benefit from a possible preventative cardioprotective treatment with ACE inhibition.

Angiotensin II–Mediated Effects

The idea that excessive levels of circulating Ang II can cause myocardial infarcts originated from an early experiment in which exogenous infusion of Ang II produced widespread foci of myocardial necrosis in rabbits. Clinical observations in patients subjected to extreme stimulation of the renin-angiotensin system during hemodialysis revealed that these patients were prone to coronary death, which we attributed to intense coronary vasoconstriction because focal myocardial necrosis was described in areas with no detectable coronary obstructive lesions. These experiments were later replicated and amplified by other investigators, who found that endogenous or exogenous Ang II excess and attendant hyperaldosteronism can be cardiotoxic via several additional mechanisms, such as increased sarcolemmal permeability and death of cardiac myocytes or increased permeability and destruction of coronary microvascular endothelial cells, all of which eventually lead to the replacement of contractile myocardium by fibrotic tissue.

The preferential pressor action of Ang II on the coronary, renal, cerebral, and adrenal vasculatures was demonstrated in a series of experiments in dogs submitted to endogenous Ang II stimulation. Blockade of Ang II by either a competitive antagonist or an ACE inhibitor produced a redistribution of regional blood flows favoring those vascular trees most sensitive to Ang II–induced vasoconstriction. Indeed, under conditions of a stimulated renin-angiotensin system, Ang II blockade produced vasodilation in the heart, kidney, and brain at the expense of musculocutaneous tissue. The validity of these results was confirmed in humans, in whom coronary dilation in response to Ang II blockade was found to correlate with the level of plasma renin activity, regardless of oxygen demand, which meant that it could override the autoregulatory mechanisms of coronary perfusion. Subsequent clinical studies have corroborated the capacity of ACE inhibition to enhance the coronary blood flow, especially in the absence of fixed anatomic obstruction, and have demonstrated the antianginal effect of this treatment in patients with symptomatic coronary insufficiency.

Ang II exerts a number of direct effects on the heart via activation of the angiotensin type 1 receptor, a G protein–linked receptor identified on cardiac myocytes that activates protein kinase C through formation of diacylglycerol and hydrolysis of phosphatidylinositol. The positive
inotropic, mitogenic, and arrhythmogenic actions of Ang II are now well documented. Withdrawal of the direct inotropic action of Ang II is by far outweighed by the hemodynamic improvement (reduced afterload, enhanced coronary blood flow) and its metabolic consequences (diminished myocardial oxygen demand) during treatment of congestive heart failure by Ang II antagonists or ACE inhibitors. Reversal of left ventricular hypertrophy, an independent coronary risk factor in its own right, has been documented with various ACE inhibitors. It is attributed in part to normalization of previously increased left ventricular wall tension and in part to withdrawal of Ang II–induced stimulation of cardiac myocyte growth. The normalization of left ventricular mass and isomyosin patterns by ACE inhibition is associated with maintenance of adaptive changes in creatine kinase isoenzymes that lead to better use of energy-rich phosphates. This effect, along with the bradykinin-mediated improvement of glucose utilization (see below), is particularly important under conditions of relative myocardial ischemia or hypoxia, in which chronic energy starvation leads to gradual deterioration and cell death. The arrhythmogenic action of Ang II is believed to be mediated via activation of protein kinase C. The antiarrhythmic influence of ACE inhibition is well established, although it is probably attributable to both inhibition of Ang II and potentiation of bradykinin.

Acute myocardial infarction (MI) is accompanied by activation of the three major neuroendocrine vasoconstrictor systems—the renin-angiotensin, the sympatoadrenal, and the arginine-vasopressin—as well as local tissue hormones such as bradykinin. Some experimental studies reported that ACE inhibition in the immediate post-MI period could reduce both infarct size and myocardial damage. However, our own experiments failed to demonstrate a reduction of infarct size, and a subsequent large clinical trial indicated that ACE inhibition given intravenously immediately after MI was not beneficial. Speculative explanations for these findings include the possibility that Ang II induces protein synthesis and cell proliferation, thereby enhancing the early healing process after MI. On the contrary, when ACE inhibition is instituted at a later post-MI stage, it can prevent or retard the progression of myocardial remodeling, i.e., distension of certain areas and hypertrophy of others, to the advanced stages of dilated cardiomyopathy and chronic heart failure. This effect is presumably attributable to the favorable hemodynamic consequences of Ang II inhibition and bradykinin potentiation (preload and afterload reductions, improved coronary perfusion) as well as to withdrawal of the direct Ang II effects on myocardial tissue, as mentioned earlier.

Interaction between the renin-angiotensin and sympathetic nervous systems is evident at several levels and is maintained via a complex positive feedback mechanism. In addition to vasoconstriction, sympathetic activation has a number of well-recognized effects via its "trrophic" (on myocytes and vascular smooth muscle cells), arrhythmogenic, and thrombogenic properties as well as its metabolic actions (myocardial oxygen demand changes, electrolyte alterations). The role of sympathetic overactivity as an independent coronary risk factor has been extensively reviewed elsewhere. ACE inhibition is associated with diminished sympathetic tone and suppression of circulating catecholamines, presumably via interruption of the positive feedback loop. Furthermore, the permissive action of Ang II enhances tissue responses to sympathetic stimulation, whereas its withdrawal during ACE inhibition attenuates the release of norepinephrine and the vascular or myocardial tissue response to the stimulus. Bradykinin-Mediated Effects

Although generally less appreciated, the potentiation of bradykinin is as important a contributor to the hemodynamic and metabolic consequences of ACE inhibition as Ang II. Early measurements of circulating bradykinin levels during ACE inhibition generated contradictory results, probably because bradykinin is an autacoid acting mostly locally before its rapid inactivation by kininas. The use of specific antibodies against bradykinin produced the first incontrovertible evidence for its participation in the blood pressure-lowering effect of ACE inhibitors. Recent progress in the field was spurred by the development of a variety of bradykinin analogues with antagonistic properties and the elucidation of the pharmacology of the bradykinin receptors. These studies indicated that the Br, type is the receptor mediating most clinically relevant physiological and pharmacologic actions of bradykinin. These actions depend on mobilization of the arachidonic acid cascade and generation of prostaglandins and nitric oxide. Using a bradykinin antagonist, we demonstrated in an experimental model of renovascular hypertension that approximately 30% of the hypotensive action of ACE inhibition was due to bradykinin. These findings have been confirmed and amplified by other investigators in short-term and long-term experiments. Other in vivo studies have explored the interdependence of the vasodepressor effects of bradykinin with prostaglandins and nitric oxide. These studies revealed that in general the same vascular trees that are most sensitive to the vasoconstrictor effect of Ang II (mainly coronary and renal) are also the ones most sensitive to the vasodilator action of bradykinin, prostaglandins, and nitric oxide—the predominant endothelium-derived relaxation factor. Nevertheless, under conditions of a stimulated renin-angiotensin system, the withdrawal of Ang II appears to be the predominant mechanism of ACE inhibition on hemodynamics, because the regional effects of ACE inhibition and Ang II blockade with losartan were similar even in vascular trees known to have differential sensitivity to Ang II versus bradykinin (such as the cerebral vasculature).

An ongoing argument in the literature is whether the capacity of ACE inhibitors to potentiate nitrates is a sulfhydryl-dependent effect or a bradykinin-mediated effect, in which case it should be inherent in ACE inhibition. The latter appears to be more plausible because non-sulfhydryl-containing ACE inhibitors have also demonstrated such effect. The vascular-protective capacity of nitric oxide is attributed not only to its vasodilator action but also to its antiinflammatory, antiproliferative, and antiplatelet properties, which probably contribute to the effects of ACE inhibition on vascular smooth muscle. The same is probably true for the antiatherogenic action of ACE inhibitors, which some investigators originally attributed to the antioximeter
The effects of bradykinin on the coronary vasculature and myocardial tissue suggest that the cardioprotective potential of ACE inhibition is to a large extent due to enhancement of the local actions of bradykinin. In a recent experimental study in swine, we compared the effects of ACE inhibition with captopril, Ang II inhibition with losartan, and bradykinin inhibition with an antagonist synthesized in our laboratory on coronary blood flow: Captopril increased the coronary blood flow of various myocardial regions by 30% to 40%; subsequent injection of losartan produced no further significant changes in overall myocardial perfusion, although it did produce alterations in regional perfusion, with shunting of flow from endocardial to epicardial areas. Infusion of the bradykinin antagonist as a next step produced a decline in regional flows between 15% and 25%, more pronounced in the subendocardial areas. The results indicate that a significant proportion of the overall increase in flow is attributable to local bradykinin potentiation and that the influence of bradykinin is more pronounced in the subendocardial regions. It is notable that these regions are most vulnerable to the nontransmural MIs.

Likewise, ACE inhibition has been shown to prevent or minimize myocardial damage (“stunning” and malignant ventricular arrhythmias) during the reperfusion phase after an acute MI. Part of this benefit appears to be due to the local action of bradykinin, because bradykinin infusion per se can mimic the effect of ACE inhibition and diminish the levels of biochemical markers of tissue damage, such as creatine phosphokinase in the effluent, whereas infusion of a bradykinin antagonist can abolish to a large extent the benefits of ACE inhibition, ie, electrophysiological stability and cell integrity.

In addition to the coronary dilating and antiarrhythmic influences, bradykinin probably protects the ischemic myocardium also via its metabolic action, ie, the enhanced glucose uptake by myocytes. Indeed, a major metabolic advantage of ACE inhibition is that, unlike other antihypertensive agents, which tend to accentuate the insulin resistance common in hypertensive patients, treatment with ACE inhibitors tends to improve insulin sensitivity. To investigate whether this effect is attributable to bradykinin, we conducted an experimental study using a euglycemic clamp in normal animals, because after infusion of a B1 bradykinin antagonist the calculated insulin sensitivity index was significantly reduced. The data suggest that improvement of insulin-dependent glucose transport and utilization during ACE inhibition is mediated via potentiation of bradykinin.

Multicenter Clinical Trials

Proof that the evidence from basic research, animal experimentation, and human studies cited up to this point is clinically relevant comes from clinical follow-up studies assessing the evolution of hemodynamic parameters in small groups of post-MI patients and from the large randomized multicenter trials of the past 10 years, such as the CONSENSUS, SAVE, SOLVD, and V-HeFT II trials.

The patients included in these trials had a wide spectrum of cardiac disease, ranging from asymptomatic left ventricular dysfunction to New York Heart Association class IV congestive heart failure, as well as a number of concurrent problems, including cardiac hypertrophy, coronary artery disease of various degrees, and arrhythmias. The therapeutic efficacy of ACE inhibitors was assessed in terms of symptomatic relief, improvement of functional class, prolongation of exercise capacity, diminished arrhythmias, decreased incidence of subsequent coronary events, and generally longer survival with an improved quality of life and fewer hospitalizations. Not surprisingly, the largest gains were observed in the most severely affected patients who had the poorest initial prognosis. To cite a few numbers comparing placebo with ACE inhibition: in patients with severe class IV congestive heart failure, at 6 months the mortality was decreased by 40% in the post-MI patients of the SAVE trial, the overall mortality decreased by 19%, the cardiovascular mortality by 21%, and the development of severe heart failure by 37%; in the SOLVD trial, which comprised patients with asymptomatic myocardial dysfunction as well as patients with clinically significant heart failure, the overall mortality decreased by 13%, cardiovascular death by 16%, and hospitalizations or deaths from worsening of heart failure by 24%; and the incidence of MI dropped by 20% to 25% in both the SOLVD and SAVE trials.

Likewise, in the V-HeFT II trial, which compared two vasodilator treatments (with no placebo arm), the patients receiving enalapril had a significant reduction in mortality, especially from sudden and unexpected death (although functional status and exercise tolerance did improve more with the hydralazine-nitrate combination).

Epidemiologic Evidence

The possibility that circulating high renin-angiotensin levels in hypertension may be a causative factor or a marker of increased propensity for coronary heart disease was first proposed by Laragh’s group in 1972 (Brunner et al) in a retrospective survey. It was corroborated by a recent prospective follow-up study of hypertensive patients from the same laboratory. This view is far from being universally accepted and is still under hot debate. One of the challengers actually published a retrospective study showing that patients with ischemic heart disease had lower, not higher, levels of plasma renin activity than those without coronary disease, evidently dismissing the fact that the former group must have been under the standard medication for this condition. Recently, this group reported another prospective survey on normotensive men, in which they found no association between plasma renin activity and myocardial infarcts over the next 13 to 19 years. Interestingly, however, in the subgroup of this population whose blood pressures were in the highest third of the distribution (with systolic pressures higher than 148 mm Hg), the authors conceded that “there may have been an association between plasma renin activity and later events.” Taken together, these data suggest that high circulating renin-angiotensin levels could be a
coronary risk factor for hypertensive but not normoten-
vensive individuals.

One aspect that had not been considered until re-
cently is that circulating levels of ACE per se could also be
an independent coronary risk factor, or at least a marker
of higher-than-average risk. A series of studies by a European
team in the last few years suggested that genetic factors are
important in determining plasma concentrations of ACE\footnote{106} and that subjects homozygous for a delec-
tion polymorphism of the ACE gene are characterized by the highest circulating ACE levels.\footnote{103}

Over the past year they observed that this DD genotype
was significantly more frequent in patients who had
sustained a myocardial infarct and that the association
between high levels of ACE and coronary events was
strongest especially in people who would otherwise
be classified as “low risk” according to the usual clinical
criteria. Based on these findings, they proposed that the
dele tion polymorphism of the ACE gene and conse-
cut elevated circulating ACE levels may be an inde-
pendent hereditary coronary risk factor.\footnote{105}

These studies, of course, need to be verified by other
investigators and still do not permit conclusions as to
possible mechanisms by which the ACE, which is not
believed to be the rate-limiting enzyme for the production
of Ang II, might play a causative role in MI or indeed
be classified as “low risk” according to the usual clinical
criteria. Based on these findings, they proposed that the
dele tion polymorphism of the ACE gene and conse-
cut elevated circulating ACE levels may be an inde-
pendent hereditary coronary risk factor.\footnote{105}

When we used an ACE inhibitor in hypertensive
patients for the first time,\footnote{106} we thought we were simply
contemplating a future in which genetic typing might iden-
tify healthy subjects who could hope to derive cardiopro-
tection from preventative ACE inhibition.

We thought we might simply continue a future in which
genetic typing might identify healthy subjects who could hope to derive cardioprotex-
tion from preventative ACE inhibition.

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