Captopril Compared with Other Antirenin System Agents in Hypertensive Patients: Its Triphasic Effects on Blood Pressure and Its Use to Identify and Treat the Renin Factor

JOHN H. LARAGH, M.D., DAVID B. CASE, M.D., STEVEN A. ATLAS, M.D., AND JEAN E. SEALEY, D.Sc.

SUMMARY Four different pharmacologic probes (propranolol, saralasin, teprotide, and captopril) have exposed and characterized the active participation of the renin system in sustaining the elevated blood pressure (BP) of most essential hypertension (i.e., the high and "normal" renin forms). Research indicates that renin measurements can be used to predict the effects of these drugs on BP, since control plasma renin activity levels correlate closely with reductions in pressure. Therefore, the renin assay provides a reliable estimate of angiotensin-mediated vasoconstriction, the normalcy of which is gauged by relating it to the urinary sodium excretion, an index of intake and balance. The effects of continued oral administration of captopril closely resemble those previously described with the intravenously administered nonapeptide-converting enzyme inhibitor, teprotide. Correlations between the induced antihypertensive effect and control plasma renin levels for 89 and 100 different patients receiving either teprotide or captopril alone were 0.82 and 0.89 respectively. The fact that captopril, like the other three antirenin-system drugs, was inactive in low renin states, including in primary aldosteronism and anephric patients, verifies the view that its main antihypertensive action is mediated via renin system blockade.

The BP response of untreated patients 90 minutes after an oral dose of captopril can be predictive of its long-term effectiveness. Of practical relevance is a transient rebound of BP observed in the first few days of continuous therapy, with pressures sometimes returning near control levels. This rebound usually subsides by 7 days. Captopril produces continued suppression of the renin system as evidenced by reduced plasma aldosterone levels. But the system retains a capacity to override drug blockade in response to physiologic stimuli. The great potency with specificity of captopril is expressed by its correction of hypertension with few side effects. The cumulative experience with this and earlier pharmacologic probes has opened the door to new approaches in diagnosis and therapy based on analysis of renin system behavior. It also points the way to new research to determine why the renin system so often participates in essential hypertension and to define other pressor factors that might operate when renin and sodium factors are absent or blocked.

KEY WORDS • captopril • renin angiotensin • vasoconstriction • teprotide • antirenin drug • aldosterone • beta blockade • hypertension • converting enzyme inhibitor

IN THIS REPORT we summarize our experience using the new antihypertensive agent, captopril, and compare its effects with those we have observed using other agents to block activity of the renin system. Our research is based on the concept that the renin system maintains and defends arterial BP while also regulating sodium and potassium balance. We reason that if, in fact, the renin system is a true control system for BP, it will be involved in all BP phenomena either by causing, participating in, or reacting to the arterial pressure level or to any intrusions placed upon it. In this context, identification of the extent of renin system contribution to the BP level is helpful for exposing both renin-system and nonrenin system mechanisms involved in the particular hypertension.

If one views the renin system as a long-term regulator of the BP level, then it follows that stimuli that tend to lower pressure will activate the system and vice versa. This has actually been shown to be the case. Numerous experiments indicate that threats to BP such as posture, phlebotomy, or sodium depletion turn on the system. If one views the renin system as a long-term regulator of the BP level, then it follows that stimuli that tend to lower pressure will activate the system and vice versa. This has actually been shown to be the case. Numerous experiments indicate that threats to BP such as posture, phlebotomy, or sodium depletion turn on the system. Accordingly, patients with high BP, "ceteris paribus," would be expected to "turn-off" renin secretion via a signal to the renal baroreceptor reflecting increased arterial pressure or volume. In this construction, low renin hypertensive patients are the only ones to behave physiologically by suppressing renin, whereas high renin and even "normal" renin...
patients in fact may be secreting too much renin in the face of high arterial pressure. This information supports our postulate that normal renin levels are in fact not "normal" in hypertensive patients because, as far as one can tell from various studies, the physiological response to a sustained elevation of pressure is to turn off renin secretion. If this reasoning is correct, a drug that blocks the renin system should have antihypertensive activity in patients with either "normal" or high values in direct proportion to the height of the renin level. So far, our studies using various antirenin agents support this reasoning.

**Review of Research on the Renin System**

**Early Evidence that Renin-Angiotensin Excess can Cause or Maintain Human Hypertension**

To define the possible role of renin in human hypertension, we have pursued several different lines of research. After demonstrating the existence of the renin-aldosterone system and its major involvement in human malignant hypertension, we studied the effects of infusions of angiotensin II into normal human subjects and compared them with those of norepinephrine. We showed that, quite unlike norepinephrine, continuous infusion of angiotensin II for up to 11 days in relatively small amounts produced hypertension. The initial rise in BP produced by angiotensin actually became amplified in time by the sodium retention activated by aldosterone stimulation, an amplifying sequence that did not occur with norepinephrine infusions. Because of this, diminishingly small amounts of angiotensin were needed to sustain the hypertension. This research revealed that angiotensin II, unlike norepinephrine, might in fact be a final vector of chronic human hypertension, even when present in the blood in relatively small amounts.

**Proof of Renin Participation in Essential Hypertension**

A persuasive line of evidence that the renin system might be actively involved in essential hypertension emerged from a study by Bühler with our group in which we demonstrated that the beta-adrenergic blocking drug, propranolol, lowered BP in proportion to the height of the control renin level and also in proportion to the degree to which renin levels were reduced by the beta blocker. The study showed that not only was the beta-adrenergic receptor blocker, propranolol, most effective in lowering BP in high-renin human essential hypertension, but, conversely, in low-renin forms it usually had no effect or was even pressor. Since that study, many reports elsewhere have verified the renin-lowering action of beta-adrenergic blockers and its relationship to their effectiveness in high-renin and medium-renin forms of both essential and renovascular hypertension.

While this research strongly implicated renin suppression in the antihypertensive action of propranolol, it certainly did not establish it as the *only* mechanism by which beta-blockers might lower pressure. However, as of today, alternate theories invoked to explain the antihypertensive action of beta-blockers are not supported by either clinical observations or investigative data. For example, the theory that beta-blockers lower BP by lowering cardiac output must account for the inconsistency that, if cardiac output is lowered in all patients treated with beta-blockers, why does BP remain either unaltered, rise, or decrease greatly in some patients. This cardiac theory must then invoke some secondary mechanism, related to variable reactive changes in peripheral resistance consequent to the reduction in cardiac output. However, such postulated reactive changes in arteriolar tone would still have to be shown independent of changes in resistance produced by the induced reduction of angiotensin II levels.

Another alternate theory, that beta-blockers act on the central nervous system, has been proposed but has received little support, especially since some beta-blockers do not enter the central nervous system and since higher dosages of beta-blockers are more often pressor than depressor.

Some opposition to the renin-theory of propranolol's antihypertensive action also developed when some investigators could not demonstrate a renin-lowering effect using certain beta-blockers. The details of this controversy have been summarized elsewhere.

At least one such claim has been retracted, however, while it has become more generally appreciated that beta-blocking drugs as a species all exhibit a marked suppressing action on renin secretion. The failure to demonstrate renin suppression with a beta blocker in some cases was very likely due to the use of renin methods that inadvertently activated an inactive form of plasma renin (prorenin) that is not suppressed by beta-blockade therapy.

At the same time, more clinical and experimental evidence has accumulated, strengthening the view that the major antihypertensive action of beta-blockers is in fact mediated via renin suppression. This includes the lack of antihypertensive action or the pressor effect of beta-adrenergic blockers in low-renin states such as low-renin essential hypertension, in primary aldosteronism, and in anephric humans. Furthermore, a group of animal experiments show that propranolol and other beta blockers are, in fact, effective in lowering BP in relation to the height of the control renin level, and that they are quite ineffective in lowering BP or even pressor in hypertensive models where renin is low or is absent. Accordingly, propranolol is also ineffective in experimental angiotensin II infusion hypertension.

**Experience with Saralasin**

A second way for probing pharmacologically the participation of renin in essential hypertension became available with the development of the angiotensin II antagonist, saralasin. This compound has now been given to several thousand patients, and it is clear that saralasin's only significant biological actions are to competitively inhibit the engagement of angiotensin II to its natural receptors and to exert...
weak angiotensin II-like activity when these receptors are unoccupied. A conceptual problem with the saralasin experience has been the fact that it reduces BP in only some 15% or 20% of patients, whereas it is generally agreed that beta-adrenergic blockers are effective in about half of all essential hypertension. This discrepancy between the results with saralasin and those obtained with beta-adrenergic blockers initially cast doubt on the specificity of propranolol as an antirenin drug. Thus, if saralasin were entirely specific and sensitive, it perhaps could be taken to mean that renin really participates in only a minor fraction of essential hypertension, some 15% or 20%. Even this, of course, would still represent a substantial number of patients.

We have been able to reconcile this question. In studies of saralasin, we re-examined the issue of its specificity as a probe for angiotensin II participation. Results of these studies are summarized in figure 1, which show that the degree to which an intravenous infusion of saralasin lowers BP in patients with essential hypertension is, just like propranolol, proportional to the pretreatment plasma renin activity (PRA) value. These data further show that patients with a PRA level of about 4.5 ng/ml/hr or higher routinely exhibited a depressor response to the drug. Above 4.5 ng/ml/hr, the magnitude of reduction in diastolic blood pressure (DBP) was directly proportional to the height of the control renin value. Conversely, in patients whose control PRA values were equal to or less than 4.5 ng/ml/hr, saralasin became overtly pressor.

These data are best explained as reflecting the intrinsic partial agonism of the saralasin molecule. Thus, when the angiotensin vascular receptors are largely or completely unoccupied because of low endogenous plasma levels of angiotensin, saralasin moves into these vacant receptors and turns into a pressor agent. In fact, it is only when relatively large amounts of the endogenous hormone, angiotensin II, are present in the blood that saralasin is overtly depressor. Thus, saralasin, a weak pressor agent itself, displaces the stronger pressor agent, natural angiotensin II, from its receptors, and this lowers the BP. Similar results have been obtained by Streeten et al., Marks et al., and others; the intrinsic agonism of saralasin on the renal vasculature has also been described by Hollenberg et al.

![Figure 1. Relationship between the control plasma renin activity (PRA) and the average percent change in diastolic blood pressure (DBP) during saralasin infusion into hypertensive patients. (Reprinted from Case et al. by permission from the publisher, see ref. 18).](attachment:image-url)
What all of this means is that saralasin, because of its own weak angiotensin-like activity, grossly underestimates the true renin participation in hypertension. In fact, it is only overtly depressor or antihypertensive when the control PRA levels are relatively high. When angiotensin levels are low or absent, saralasin then fully expresses its own pressor potential. With medium levels of angiotensin, very little happens to BP because administration of large amounts of a weak pressor agent displaces smaller amounts of the more pressor angiotensin. This research provided a reasonable explanation for why propranolol testing implicated a renin factor in many more patients than saralasin.

Experience with Teprotide

Further pursuit and clarification of the problem of renin involvement in hypertensive diseases became possible with the availability of pharmacological probes that do not have any agonism of their own and act instead to block the actual formation of angiotensin II by another mechanism, inhibition of the angiotensin I converting enzyme. Our first application of this approach involved intravenous administration of the nonapeptide SQ 20,881, or teprotide.24, 25

Figure 2 shows the effects of intravenous converting enzyme inhibitor SQ 20,881 on BP. This research involving 89 patients with essential and other forms of human hypertension is much the largest single experience with this agent in human hypertension. Administration of the nonapeptide intravenously lowered BP in those hypertensive patients whose PRA levels were above 1 ng/ml/hr. Furthermore, the extent of the BP lowering was found to be directly proportional to the height of the control renin level. Even with renin values below 1 ng/ml/hr, we sometimes observed small decreases in DBP of around 5 mm Hg. This may simply express the natural BP fluctuations that occur, or it could be a small effect of acute converting enzyme blockade, apart from the angiotensin blockade, that might involve the transient release of bradykinin. This remains for future research.

Whatever this slight background effect may be, the important implications of this study are twofold: 1) it confirms the major active participation of the renin system in maintaining the hypertensive state in about 70% of all patients with essential hypertension (those with either high or normal renin values) and the lack of its participation in about 30% (those who have low-renin values); and 2) it confirms that plasma renin measurements per se really do mean something, i.e., renin levels are an accurate biochemical estimate of the degree to which angiotensin II participates in BP maintenance. Thus, a properly performed plasma renin measurement is a means to estimate the amount of renin-mediated active vasoconstriction. Note that there is some variation in pressure responses around each renin level (fig. 2), which perhaps describes the biological variations between different individuals. Future research might also show this variation to be due to a change in sensitivity to angiotensin, however, perhaps from altered vascular receptor behavior, perhaps influenced by the state of sodium balance.

The nonapeptide experience, taken together with the previous research with propranolol and saralasin, collectively provide the evidence for active renin-system participation in most human essential hypertension and, therefore too, the basis for pursuing the possibility of blocking the renin system pharmacologically in longer-term or chronic situations. This could represent an exciting new approach to the everyday treatment of hypertension. Theoretically, too, renin blockade, without attendant autonomic nervous system blockade, might lead to an approach freer of side effects than with previous agents and one that could tell us more about renin participation in long-term BP regulation in various forms of hypertension.

Experience with Captopril

The development of captopril as the first orally active agent for continuous blockade of angiotensin II formation is an important achievement in biochemistry and pharmacology. Our detailed findings on its metabolic effects in 26 hypertensive patients have been reported.26 Figure 3 is a plot of new data involving 100 patients treated continuously for up to 18 months with captopril alone. It demonstrates the close correlation between the height of the control PRA values and the antihypertensive action of captopril as measured 90
minutes after the first oral dose. The correlation coefficient of 0.89 expresses the extremely close relationship between the control PRA value and the acute antihypertensive action of captopril in these 100 patients. The similarity between the correlations observed with oral captopril and our previous research using teprotide (fig. 2) is evident.

Figure 4 describes what happens to plasma aldosterone at the same 90-minute point in time after a 10 mg dose of captopril. Plasma aldosterone values dropped from a control of about 24 to 12 ng/ml, a highly significant reduction of 50%. This is evidence for blockade of angiotensin II, since angiotensin II is known to exhibit a major tonic influence on aldosterone secretion rate. The concurrently induced compensatory rise in PRA for this group of 26 patients is also shown. This reactive rise in renin secretion may be explained as a reaction to both a baroreceptor-mediated response to the fall in pressure and by blockade of the suppressing action of the direct feedback loop of angiotensin II on renin release.

Triphasic Course of the Antihypertensive Action of Oral Captopril

Figure 5 presents a new analysis of what we have found to be a common pattern in the evolution of the antihypertensive response to the oral converting enzyme inhibitor, captopril. This patient, a 59-year-old man with high-renin essential hypertension, exhibited a prompt and dramatic drop in mean arterial pressure 90 minutes after the first oral dose of captopril. In the next several hours the patient's BP appeared to escape from the original antihypertensive action with a rise in pressure that persisted over the next 6 days, even though the dose of captopril was increased to a high value of 600 mg/day. During this period, no other drugs were used, and his diet was maintained at a level of 100 mEq of sodium per day. Finally, beginning on Day 6 and following through on Day 7, BP fell back to the low value induced in the first 90 minutes, and the patient has remained in good control over the long-term for over a year.

The triphasic nature of this antihypertensive action is of interest both theoretically and practically. From a theoretical standpoint, its mechanism of action is not fully explained since it is clearly not due to delayed suppression of aldosterone. Aldosterone excretion was reduced immediately (fig. 5), and any natriuresis consequent to aldosterone suppression would have not begun to exert its antihypertensive benefit until several days of treatment. This rebound is apparently also not due to ineffective blockade of the renin system since aldosterone suppression remains constant from the second day of therapy on. Therefore, it seems likely that the interim opposition to the antihypertensive action of captopril might be due to a transient defense of the preexisting BP by the buffer nervous system.

Based on these clinical observations, Case and his associates studied 26 patients by dividing them into two groups of 13 each: those whose MAP was reduced.
Course of blood pressure response in a 59 year-old man with high-renin essential hypertension. Mean arterial pressure (MAP) fell significantly after the first dose but returned toward control levels during the first 5-6 days before reaching a stable level representative of the long-term blood pressure. This occurred despite an increase in captopril dosage to 600 mg/day and a decline in urine aldosterone excretion to 20% of the pretreatment level. The aldosterone suppression was maintained for 30 days.

Absence of Captopril Effectiveness in Patients with Little or No Active Plasma Renin

Finally, to evaluate further the specificity of captopril as an antirenin-antihypertensive drug and at the same time to gain more information about renin participation in BP support, we examined the action of this agent in patients with primary aldosteronism.
used as a model for low-renin hypertension and we also evaluated the acute effects of the drug in anephric people. Recent studies show that captopril does not lower BP in anephric patients (unpublished observations). Since we previously reported that teprotide is similarly ineffective in anephric patients, the experience with both of these converting enzyme inhibitors suggests that their antihypertensive action depends upon the presence of the kidneys and presumably, too, the renal renin system.

This impression is further supported by studies in seven patients with primary aldosteronism in whom, on eight occasions, the antihypertensive action of captopril was small to negligible. Since we had previously studied other such patients with teprotide and obtained similar results, it is fair to conclude that both of these converting enzyme blockers show little or no depressor activity in two different states associated with little or no PRA. Altogether, the data provide strong evidence for the view that the major antihypertensive action of both teprotide and captopril is mediated by a blockade of PRA. This evidence is in keeping with previously described direct correlations between the antihypertensive action of both teprotide and captopril and the control renin values. As convincing as these relationships seem to be, the data do not rule out the possibility that a very small component of the antihypertensive effect of captopril might be related to the induction of transient bradykininemia. If this effect occurs at all, however, our data suggest that it is subordinate to the major action of angiotensin blockade.

Animal Studies also Describing Similarities Between Beta-Blockade and Converting Enzyme Blockade

Animal experiments from Chiu and Sommer and also from Young and Diepstra working at the University of Mississippi have provided new data indicating that beta-blockers and converting enzyme blockers operate through a common mechanism. In the research by Chiu and Sommer, extremely similar effects of propranolol and captopril were described in spontaneously hypertensive rats. The antihypertensive effects of both were closely related to the PRA levels, and neither type of drug was antihypertensive if a prior nephrectomy had been performed.

In the research of Young and Diepstra, one group of dogs made hypertensive by angiotensin II infusions had undetectable renin levels and showed no BP fall in response to either propanolol or captopril administration. In contrast, in a second group made hypertensive by renal artery constriction and exhibiting high renin levels, extremely similar BP reductions were produced either by captopril or propranolol. The authors concluded that renin suppression was the main factor responsible for the BP fall induced by either drug.

In the light of these findings, it now appears that all four pharmacologic probes, beta-adrenergic blockers, saralasin, the nonapeptide teprotide, and captopril, exert their main antihypertensive actions by blocking the renin-angiotensin-aldosterone system. The effectiveness of all four agents is directly related to the control PRA level, and all are ineffective or pressor (i.e., saralasin, beta-blockers) in states where renin is low or absent. The broader effectiveness of converting enzyme blockade (about 70% of essential hypertension) is probably related to its more complete blockade of the system since beta-blockers, for example, do not block the macula densa-perceived sodium depletion signal for renin release. While saralasin underestimates the renin factor because of its own agonism that is increasingly a factor when angiotensin receptors are vacant. Use of these agents will help us define and treat the renin factor and therefore perhaps expose other pressor factors for further study. The issue of why renin so often participates also becomes a defined challenge for research.

Discussion

Studies in human subjects using four different types of pharmacological probes: the beta-adrenergic receptor blocker propranolol, the angiotensin antagonist saralasin, the nonapeptide converting enzyme inhibitor teprotide, and the orally active converting enzyme inhibitor captopril, have exposed and defined the broad participation of the renin system in human essential hypertension.

Propranolol produces significant antihypertensive effects in about half of patients with essential hypertension. This activity is closely related to the height of the control PRA value. By contrast, saralasin, given as an acute intravenous infusion, reduces pressure in only about 15% or 20%. The failure of saralasin to exhibit a broader antihypertensive action in essential hypertension appears to be due to its partial agonism, making it pressor or neutral in low and normal renin patients respectively. Studies with an intravenous nonapeptide inhibitor of the converting enzyme SQ 20,881 and then with its orally active analog, captopril, have both produced antihypertensive responses in about 70% of patients with essential hypertension.

Since all four agents, acting in three different ways to suppress the activity of the renin-aldosterone system, produce parallel responses which in each case are directly related to the height of the control renin level, the sum of these observations can be taken as pharmacological proof of the active participation of the renin system in maintaining the hypertension of most patients with essential hypertension (i.e., those with either high or medium renin levels). In fact, this parallelism of response patterns among the four drugs is apparent despite the extraneous influence of other factors such as the agonism of saralasin, the cardiac depressant actions of beta blockers, and the potential kinin accumulation of captopril.

This research leads logically to other critical questions: Why does the renin system participate in the hypertension of normal- and high-renin patients? Why does the renin system fail to turn itself off in the normal- or high-renin patients as it does in patients with low-renin essential hypertension? We need to ex-
explore further the mechanisms that control renin secretion and their relevance to low-, medium-, and high-renin hypertensive conditions.

Meanwhile, the evidence already enables real gains from the increased specificity of antirenin therapy. Thus, patients whose BP is controlled with captopril are, in general, uniquely free of side effects and appear to have a more ideal physiological correction in which peripheral resistance is reduced and the flow to vital organs, in particular the kidneys and heart, is maintained or increased. Correction with fewer side effects in itself suggests greater specificity for the therapy and implies that inappropriate participation of the renin system was responsible in the first place for maintenance of the hypertension.

In contrast, whenever BP has been controlled by older agents, sympatholytic drugs, for example, a new set of unwanted side effects almost invariably accompanies the correction, possibly suggesting that inappropriate participation of the sympathetic nervous system was responsible in the first place for maintenance of the hypertension.

Now that active participation of the renin system is recognized as a broad and measurable factor in the maintenance of human hypertensive disease, determining its absence or the degree of its presence not only has considerable diagnostic value, but also opens the door for planned therapy directed at the precise correction, possibly suggesting that inappropriate participation of the sympathetic nervous system is, in fact, not a factor in causing the hypertension.

References

Captopril compared with other antirenin system agents in hypertensive patients: its triphasic effects on blood pressure and its use to identify and treat the renin factor.
J H Laragh, D B Case, S A Atlas and J E Sealey

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