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Plasma Angiotensin II and the Antihypertensive Action of Angiotensin-Converting Enzyme Inhibition

J. Nussberger, B. Waeber, and H. R. Brunner

The measurement of immunoreactive "angiotensin II" in plasma cannot provide an accurate reflection of the efficacy of angiotensin-converting enzyme (ACE) inhibition because different angiotensin fragments interfere in all radioimmunoassays available so far. More complex methods are necessary in order to measure specifically angiotensin-(1-8)octapeptide. With such methodology it can be shown that no tolerance develops to the angiotensin II-reducing effect of ACE inhibitors after prolonged administration. Marked reduction of angiotensin II levels can be shown even in patients with primary aldosteronism. At peak blockade, the level of plasma angiotensin II is still related to circulating active renin and angiotensin I. Accordingly, because ACE inhibitors raise circulating angiotensin I in a dose-dependent fashion, this should be taken into account when dosing ACE inhibitors. The hypothesis that tissue renin-angiotensin systems play an important independent role in determining vasomotor tone is very interesting. However, any discussion on whether tissue or plasma renin determines the pharmacological effect of ACE inhibitors should be based on the simultaneous measurement of true angiotensin II in tissue and plasma under steady-state conditions. Am J Hypertens 1989; 2:286–293

KEY WORDS: **Angiotensin II/angiotensin I ratio, dosing ACE inhibitors, primary aldosteronism, tissue renin angiotensin system.**

In the enzymatic cascade of the renin-angiotensin system, angiotensin II clearly is the main effector hormone whereas the enzymatic activity of renin represents the rate-limiting step in the generation of angiotensin II. Because it has been well recognized that the measurement of angiotensin II in plasma presents many problems, the measurement of plasma renin activity, ie, in vitro angiotensin I generation under standardized conditions, has become the substitute for the measurement of angiotensin II. All evidence available suggested that there is indeed a very good correlation between circulating angiotensin II and the measured plasma renin activity. The measurement of plasma renin activity has indeed turned out to be extremely useful to assess the degree of activation of the renin-angiotensin system under physiological and pathophysiological conditions.

This situation was completely changed when converting-enzyme inhibitors became available for experimental and clinical research.[1–4] These agents are designed to dissociate the generation of angiotensin II from renin activity. They markedly reduce angiotensin II generation while actually stimulating renin secretion. As a consequence, the measurement of plasma renin activity is no substitute any more for the measurement of angiotensin II. True, methods were developed to measure the plasma activity of angiotensin-converting enzyme (ACE). However, these again measure the in vitro activity under standardized conditions and the results do not necessarily parallel the in vivo activity. Fur-

From the Hypertension Division, University Hospital, Lausanne, Switzerland.

Address correspondence and reprint requests to Jürg Nussberger, MD, Division of Hypertension, C.H.U.V., 1011 Lausanne, Switzerland.

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thermore, it became evident that in the organism the bulk of the conversion of angiotensin I to angiotensin II is carried out by converting enzyme located on the vascular endothelial cells. Therefore, does converting-enzyme activity measured in plasma truly reflect global in vivo conversion? Inevitably, in order to directly assess the effect of ACE inhibitors, plasma angiotensin II rather than plasma ACE or renin activity has to be measured, and there is no real substitute for it. The need for this measurement is further emphasized by the development of a new generation of agents designed to inhibit the action of the enzyme renin itself.[5,6] These compounds also reduce the generation of angiotensin II whereas plasma ACE activity is not altered and renin secretion is actually enhanced.

The purpose of the following presentation is to discuss the fate of plasma angiotensin II during acute and long-term ACE inhibition, its relationship to circulating angiotensin I, and the problems encountered when measuring plasma angiotensin II. Because it is claimed with growing insistence that mainly tissue renin systems completely independent of plasma renin and angiotensin determine blood pressure, it seems more than ever imperative to study the fate of plasma angiotensin II carefully to establish a solid base from which to investigate tissue systems. Only based on a precise understanding of the behavior of plasma angiotensin II can true dissociations of tissue angiotensin II from plasma angiotensin II under steady-state conditions be identified, and this turns out to represent a formidable methodological task.

IMMUNOREACTIVE "ANGIOTENSIN II" DURING ACE INHIBITION: RELATIONSHIP TO RENIN AND ANGIOTENSIN I

In 1981, once the efficacy of the converting-enzyme inhibitor enalapril had been established in normal volunteers,[7] this same compound was administered to 19 hypertensive patients.[8] When evaluating the data obtained from the measurement of imunoreactive "angiotensin II" (ir-ANG II) and of plasma renin activity, a very interesting and at that time surprising relationship was observed. As one would have expected, before the administration of enalapril, plasma ir-ANG II levels of the nine patients in whom they were measured correlated very well with the corresponding plasma renin activity. These results are illustrated in panel A of Figure 1. In all four panels, this initial ir-ANG II to plasma renin activity relationship is depicted as a solid line. Also shown in all panels are two parallel dotted lines that represent the relationship (regression line ± 1 SD from regression) that was observed previously in normal volunteers four and ten hours after administration of 10 mg of enalapril or lisinopril.[7] Results obtained four hours after administration of 10 or 20 mg of enalapril are illustrated in panel B. They fall within the range determined in the normal volunteers. Interestingly, even at peak ACE inhibition, there is still a clear and statistically significant correlation between plasma ir-ANG II and plasma renin activity, though the slope of this correlation is considerably shifted compared to that observed before the administration of enalapril (slope of dotted versus slope of solid line). In panel C, data obtained 12 to 16 hours after 10 or 20 mg of enalapril are depicted. Plasma ir-ANG II levels tended to increase in some of the patients (values above the dotted lines), suggesting a tendency for the blockade to wear off. In panel D, plasma ir-ANG II 24 hours after enalapril have returned to baseline. However, the normal relationship determined before blockade is still not reached, because the return to baseline of ir-ANG II levels has occurred in the face of a still markedly elevated plasma renin activity. Already several years back, these data suggested that even during peak ACE inhibition, ir-ANG II levels are still under the influence of the concomitant plasma renin activity and thus angiotensin I. Two important conclusions from these observations could be drawn: first, converting-enzyme inhibition was not complete, even at peak effect, and second, therefore the concomitant renin and angiotensin I levels prevailing during ACE inhibition might be of greater importance than generally appreciated.

In a more recent study, using a new ACE inhibitor, trandolapril (Roussel Uclaf, Paris, France), similar observations were made (unpublished data). This compound was administered to groups of normal volunteers at three dose levels, ie, 0.5, 2, or 8 mg po qd for ten days. On day 1 and day 10, the various components of the renin-angiotensin system were determined in the plasma before and 2, 4, and 6 hours post-drug. As well on day 1 as on day 10, the measurement of plasma ACE activity clearly reflected the dose of drug administered, because a clearly dose-dependent ACE inhibition was observed. That this measurement reflected global ACE inhibition was confirmed by the ratio of plasma ir-ANG II / angiotensin I that was equally reduced in dose-dependent fashion. However, on day 1, but even more so on day 10, the increasing doses of the ACE inhibitor induced a marked rise in angiotensin I levels that again was clearly dose-dependent. Thus, the progressive ACE blockade obtained with increasing doses of the ACE inhibitor induced dose-dependent increases in plasma angiotensin I. Plasma ir-ANG II levels were significantly reduced with the 0.5 mg dose, but more so on day 10 than on day 1. In contrast, with the 8 mg dose ir-ANG II levels were also reduced, but they tended to be higher on day 10 than on day 1. As a consequence, plasma levels of ir-ANG II on day 10 at peak effect of the drug were actually the same with the 0.5 mg as with the 8 mg dose. Thus, the concomitant angiotensin I levels again seemed to determine the plasma ir-ANG II levels. Raising the dose of the ACE inhibitor did not produce any

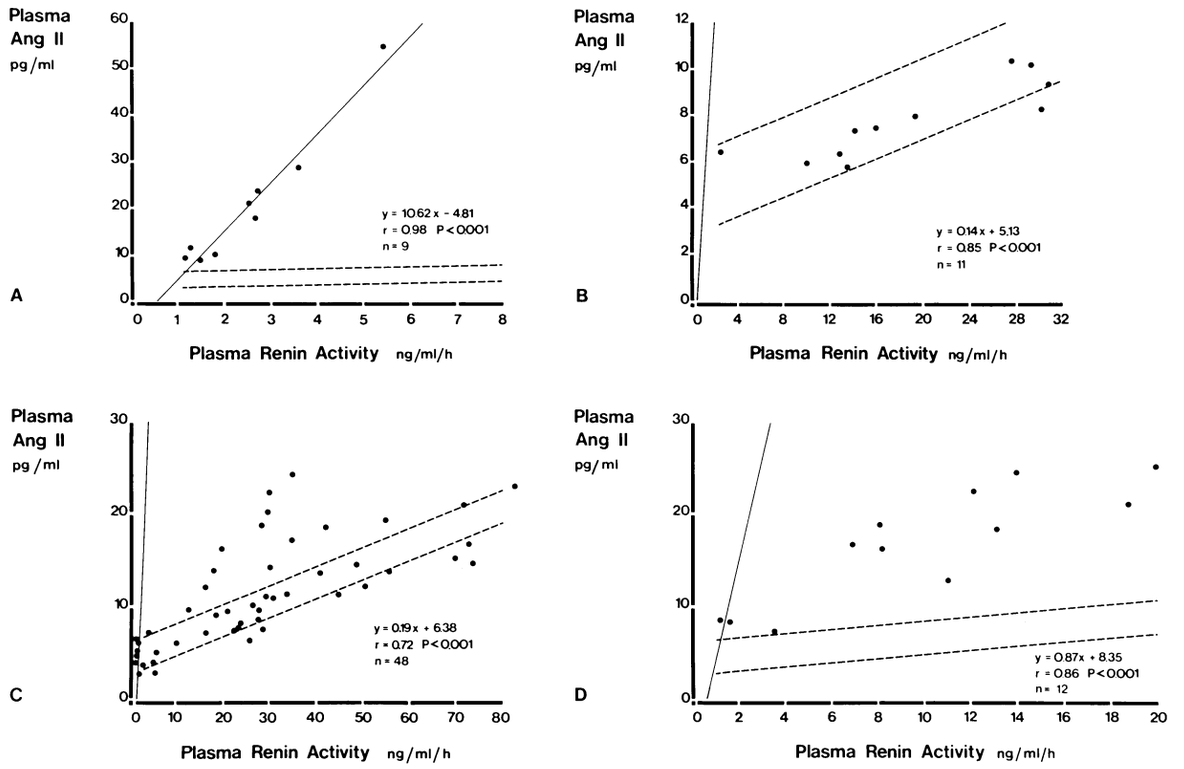

FIGURE 1. *Relationship between immunoreactive angiotensin II and renin activity in plasma of hypertensive patients before converting-enzyme inhibition (panel A) and 4 hours (panel B), 12 to 16 hours (panel C), and 24 hours (panel D) after enalapril intake (10 or 20 mg). In all panels, the regression of panel A is represented by the solid line. The ANG II/PRA-relationship of normal volunteers during peak ACE inhibition (4 and 10 hours after 10 mg enalapril) is represented by the area between the dotted lines (regression ± 1 SD). Recovering from ACE inhibition, ir-ANG II reaches pretreatment levels when PRA is still markedly increased. Reproduced from Biollaz et al with permission.*[8]

additional gain, even though it did enhance the degree of ACE inhibition, because this was offset by the compensatory rise in renin secretion and consequently angiotensin I levels.

These observations lead to several comments. Assuming that ACE inhibitors reduce blood pressure by reducing plasma angiotensin II, what is the optimal dose of an ACE inhibitor? In our mind, it has always been doubtful that for any ACE inhibitor increasing the dose that provides biochemical maximal ACE-inhibition once a day results in a net therapeutic gain. For the first time, our observation suggesting that increasing doses do not produce lower and lower plasma angiotensin II levels may provide an explanation for the lack of therapeutic benefit derived from dose increases. Furthermore, these observations also let the simultaneous administration of an ACE inhibitor with a β-adrenoceptor blocking agent appear in a new light. It is generally thought that the association of a β-blocker with an ACE inhibitor is not very useful, but unquestionably in some individual patients a net additive antihypertensive effect can be obtained by associating these two types of compounds. Is it possible that this association is particularly beneficial in those patients who raise their plasma renin activity and angiotensin I levels more than the average hypertensive patient?

As interesting as these results may appear, they were obtained measuring ir-ANG II. The specificity of these angiotensin II to angiotensin I relationships still remained to be established, and therefore better methodology to measure true angiotensin II was clearly needed.

PLASMA ANGIOTENSIN II VERSUS BLOOD PRESSURE

Already in the late 1970s when captopril was still used at excessive doses, a clear dissociation in time between ACE inhibition and blood pressure reduction was observed.[9] Thus, in patients treated for several weeks with captopril, 12 hours after the last dose of 200 mg, no ACE inhibition could be demonstrated any more, whereas blood pressure was still reduced.

The same phenomenon has also been observed with enalapril. If it is administered once a day, it clearly controls blood pressure throughout 24 hours. However, this continuous blood pressure control occurs despite a re-

turn to baseline of plasma ir-ANG II before the subsequent administration of enalapril.[8,10]

Based on this dissociation between ACE inhibition and reduction of angiotensin II levels on the one hand and blood pressure decrease on the other, it has been claimed that ACE inhibitors do reduce blood pressure by an angiotensin II independent mechanism, for instance via accumulation of bradykinin[11] or an increase in vasodilating prostaglandins.[12] An alternative explanation has been that ACE inhibitors reduce blood pressure by inhibiting the conversion of angiotensin I to angiotensin II in the vascular wall rather than in plasma, because ACE inhibition may last longer in tissues.[13–15] Whereas this represents a fascinating concept, it would still have to be explained why the reappearing angiotensin II in plasma cannot reach the vascular angiotensin II receptor, when it is known that angiotensin I and II diffuse easily from the plasma into the tissues and vice versa. Most important however, when appreciating this dissociation one must keep in mind the behavior of many of the other antihypertensive drugs. Thus, it is well known that there exists no clear relationship between the plasma half-life of any antihypertensive drug and the duration of its antihypertensive action. A phenomenon that has been recognized a long time ago is the dissociation between the plasma levels after discontinuation of an antihypertensive drug and the increase in blood pressure. Often it takes weeks and months after discontinuation of the drug before blood pressure starts to rise or reaches the hypertensive levels known to exist before initiation of treatment. Accordingly, the dissociation between the half-life of ACE inhibitors and the antihypertensive effect is a phenomenon that is not specific for these drugs.

DOES TOLERANCE DEVELOP TO LONG-TERM ACE INHIBITION?

During the first study of enalapril in hypertensive patients, we noticed that plasma ir-ANG II levels of the eight patients treated for six months tended to return to baseline levels after initial marked suppression.[16] This of course raised the question, whether tachyphylaxis developed to the enzyme inhibitory effect of enalapril. However, plasma ir-ANG II levels had been measured 12 hours after the last dosing and not at peak effect. Furthermore, five out of the eight patients also took a diuretic in order to normalize their blood pressure.

In order to clarify this issue of tachyphylaxis, six hypertensive patients continuously treated with enalapril for an average of two years were brought to the outpatient department on the morning before taking their daily dose of the ACE inhibitor.[17] The goal was to do a carefully timed study of the components of the renin-angiotensin system after taking the usual morning dose. Plasma renin and ACE activity as well as blood angiotensin I and plasma ir-ANG II were measured before and 2, 4, and 6 hours after medication. Clearly, even after two years of uninterrupted treatment with enalapril, plasma ir-ANG II levels fell by approximately 50% after taking the converting-enzyme inhibitor. Figure 2 illustrates the relationship between plasma ir-ANG II and blood angiotensin I levels before and 2, 4, and 6 hours post-drug. Not only did plasma ir-ANG II exhibit a substantial fall after enalapril administration, but also blood angiotensin I levels increased markedly, thus reflecting the characteristic behavior of the renin-angiotensin system following ACE inhibition.

These data demonstrate quite clearly that the enzyme-inhibiting effect of enalapril does not wear off after an average treatment period of two years and most probably not thereafter. The ACE inhibitor, even with long-term administration, reduces the generation of ir-ANG II. This however does not preclude a rise in blood pressure, or even a return of blood pressure to the initial hypertensive levels. For instance, any sodium retention due to a change in renal function, in diet, or a reduction in concomitant diuretic therapy can result in what might appear as tachyphylaxis. This of course is not a true tachyphylaxis, because the weakening of the antihypertensive effect is not related to a reduced pharmacological action of the ACE inhibitor, but rather to a change in other unrelated factors contributing to blood pressure regulation.

Figure 2 demonstrates one other fact that corresponds with the results obtained by all the other investigators measuring plasma ir-ANG II: even at peak effect of any ACE inhibitor, plasma ir-ANG II never is reduced to zero. Similarly, even after total nephrectomy of animals, substantial amounts of ir-ANG II keep circulating in the plasma.[18] It seemed important to investigate whether this truly represented angiotensin II or whether these remaining levels of immunoreactive "angiotensin II" were due to some measuring artifact. Therefore the quantitation of plasma angiotensin II needed to be improved.

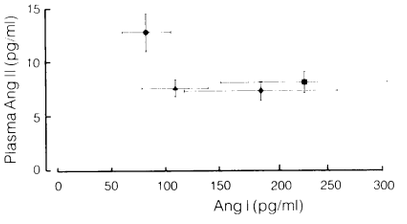

FIGURE 2. *Relationship between plasma immunoreactive angiotensin II and blood angiotensin I before (●) and 2 hours (▲), 4 hours (◆), and 6 hours (■) after the daily dose of enalapril (10 to 40 mg) in six hypertensive patients. Significant fall in ir-ANG II together with substantial increase in angiotensin I levels indicate absence of tachyphylaxis to chronic treatment. Reproduced from Brunner et al with permission.*[17]

MEASUREMENT OF TRUE ANGIOTENSIN-(1-8)OCTAPEPTIDE

Circulating in plasma is not only the octapeptide angiotensin II, but also the precursor decapeptide angiotensin I, its C-terminal nonapeptide, and breakdown fragments consisting of 7, 6, 5, and less amino-acids. Angiotensin I differs from angiotensin II only by the two amino-acids at the C-terminal. On the other hand, the breakdown products of angiotensin II have their sequence reduced starting from the N-terminal. As a consequence, in order to measure specifically angiotensin II by radioimmunoassay alone, antibodies would be needed that identify simultaneously the N- and the C-terminal.[19] So far, antisera of such properties have not become available in sufficient quantity, and the antisera in use are mostly selective for the C-terminal of angiotensin II. Accordingly, they differentiate quite readily angiotensin II from angiotensin I but exhibit a considerable cross-reactivity with the smaller fragments. When using such antisera, it is necessary in order to improve the specificity of the assay to separate the different angiotensins before radioimmunoassay. This separation can be achieved by high performance liquid chromatography (HPLC). Detection limits of conventional HPLC procedures are several orders of magnitude higher than the attomoles to be quantitated in plasma angiotensin II measurement during ACE inhibition. By combining the almost absolute specificity of HPLC with the extreme sensitivity of a radioimmunoassay, it has become possible to measure specifically angiotensin-(1-8)octapeptide with a limit of detection of 0.1 fmol/mL and an overall recovery rate of 80% and more.[20] Moreover, this methodology enables the quantitation of the various metabolites of angiotensin II in plasma. It actually turned out that one reason for ir-ANG II in plasma not to fall to zero after acute converting-enzyme inhibition is the presence of cross-reacting angiotensin fragments in plasma.[21]

Even after these improvements, an important problem persisted that finally could be solved. Conventional inhibitor cocktails containing EDTA and other peptidase inhibitors do not stop renin activity immediately after blood sampling.[21] In order to avoid angiotensin generation in vitro, Waite[22] had introduced several years ago the method of whole blood precipitation immediately after blood drawing in order to measure circulating angiotensin I. The same problem prevails when measuring plasma angiotensin II, because particularly after ACE inhibition substantial amounts of renin are present in plasma that continue to produce enormous amounts of angiotensin I in the test tube. These tend to generate in vitro ir-ANG II, albeit at a reduced rate due to the presence of EDTA and the specific ACE inhibitor. It has been shown in vivo and in vitro that angiotensin II can be generated during potent ACE inhibition. Adding a synthetic renin inhibitor to the sampling tube prevents in vitro generation of angiotensin I and II and thus further improves the measurement of circulating angiotensin II.[23] At the same time, whole blood precipitation for the measurement of angiotensin I has become obsolete.

With this markedly improved though somewhat tedious methodology, the investigation of the precise role of angiotensin II in blood pressure regulation particularly before and during ACE inhibition has become feasible and reproducible. Knowing all the pitfalls possible with the measurement of plasma angiotensin II, it is not surprising that this measurement has not led so far to the unraveling of its role in blood pressure homeostasis. Whatever the errors committed in the past, today it seems inappropriate to attempt the characterization of ACE inhibition and of the role of angiotensin II using any second best methodology or even relying solely on the measurement of immunoreactive "angiotensin II."

TRUE ANGIOTENSIN II DURING ACE INHIBITION

In a pilot study, when ramipril (Hoechst AG, Frankfurt, Germany) was administered to normotensive volunteers, it reduced ir-ANG II by only 46%.[20] In contrast, true angiotensin II or angiotensin-(1-8)octapeptide fell from 5.2 ± 1.2 fmol/mL to undetectable levels (<0.4 fmol/mL). Thus, for the first time, it could be demonstrated that at least with acute initial administration of an ACE inhibitor, plasma angiotensin II was virtually reduced to zero, as we would have expected based on theoretical considerations.

A similar experiment was carried out, during which not only immunoreactive and true angiotensin II were measured but also plasma-converting enzyme and renin activity as well as blood angiotensin I and plasma aldosterone levels.[20] The behavior of these different components was followed over a period of 24 hours (Figure 3). One hour after the administration of ramipril, plasma ACE activity was reduced by more than 90%, plasma angiotensin-(1-8)octapeptide had fallen from 3.8 ± 1.0 to undetectable levels, whereas immunoreactive "angiotensin II" had only decreased by 44%. At this time, plasma renin activity and blood angiotensin I levels had hardly changed. By four hours post-drug, plasma angiotensin-(1-8) octapeptide was again detectable and it reached by eight hours 1.5 fmol/mL when plasma renin activity and angiotensin I levels had increased at least five-fold. These results again strongly suggest, but this time based on the measurement of true angiotensin II in plasma containing EDTA and phenanthroline, that this hormone is still under the influence of circulating renin, even at the peak effect of an ACE inhibitor. Preliminary data of similar experiments but with renin-inhibitor in the blood sampling tubes lead to the same conclusion and therefore indicate that we are dealing with an in vivo phenomenon rather than with an in vitro artifact.[23]

Plasma angiotensin II and ACE activity were also

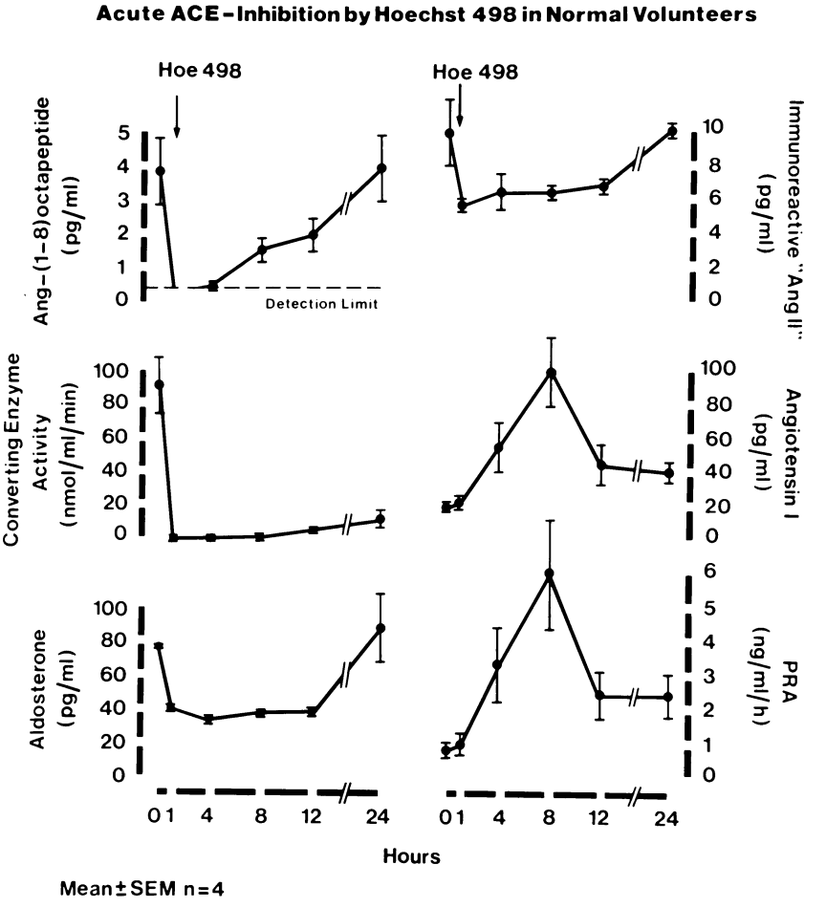

FIGURE 3. *Response of the renin-angiotensin-aldosterone system to short-term converting-enzyme inhibition with a single oral dose of ramipril (10 or 20 mg) in four normal volunteers. ANG-(1-8)octapeptide virtually disappeared from plasma whereas levels of immunoreactive "angiotensin II" decreased by only 44%. Reproduced from Nussberger et al with permission.*[20]

measured in nine patients treated for at least eight months with enalapril.[20] Blood samples were drawn on EDTA/phenanthroline in the morning before and two hours after the administration of enalapril. Plasma-converting enzyme activity fell from 17 ± 5.4 to 0.9 ± 0.3 nmol/mL/h. At the same time, plasma immunoreactive "angiotensin II" fell by a mere 17%, whereas plasma angiotensin-(1-8)octa peptide decreased from 2.7 ± 0.9 to 0.9 ± 0.3 fmol/mL ($P < .05$). These results confirmed once more that, probably due to renin stimulation, angiotensin-(1-8)octapeptide remains present in plasma of patients treated for a prolonged period of time with ACE inhibitors. They also underlined the fact that there exists no tachyphylaxis to the converting-enzyme inhibitory effect of enalapril and to blockade of angiotensin II generation in plasma, despite some claims to the contrary.

One feature of ACE inhibitors has been used repeatedly as evidence in favor of an angiotensin II independent antihypertensive effect of these agents. Not only patients with elevated plasma renin activity, but also many with what appear to be "normal" or even low renin levels respond to monotherapy by an ACE inhibitor with a decrease in blood pressure. The argument is actually based on two lines of thought: a low plasma renin activity cannot have any effect on vascular tone and, if angiotensin II levels are already low, they cannot fall further during ACE inhibition. The contribution of angiotensin II to blood pressure regulation is a complex question involving changes in receptor availability and affinity and interactions with many other pressor and depressor systems, and therefore, it cannot be tested easily. On the other hand, it seemed appropriate to investigate whether an ACE inhibitor can reduce circulating angiotensin II in patients who have extremely low levels to start with, ie, in patients with documented primary aldosteronism.

EFFECT OF ACE INHIBITION ON ANGIOTENSIN II OF PATIENTS WITH PRIMARY ALDOSTERONISM

Figure 4 illustrates the effect of converting-enzyme inhibition on the components of the renin-angiotensin system of three patients with primary aldosteronism. The shaded areas represent the normal range of the variables measured (mean ± 2 SD in supine normal volunteers), the lower end of the logarithmic scale represents the detection limit, and the heavy lines illustrate the mean value of the three patients. The patients came to the outpatient facility one hour before starting the study

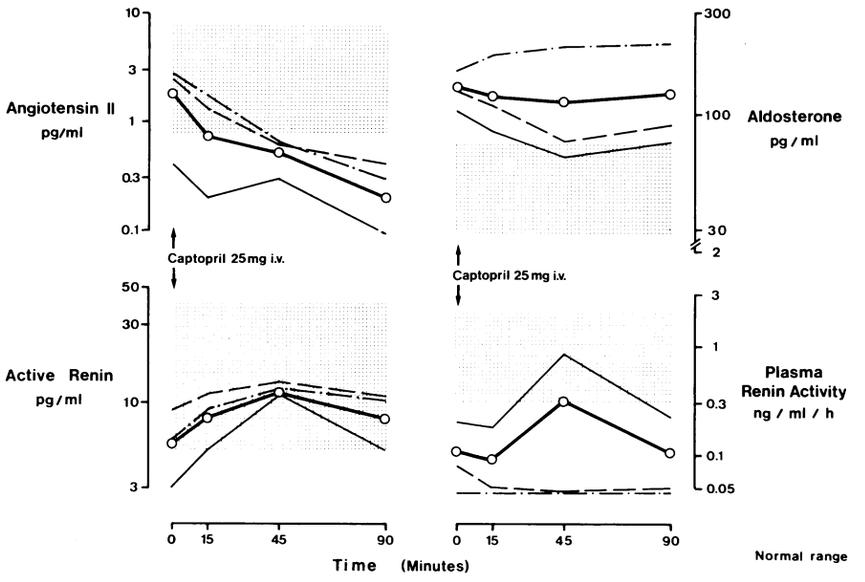

FIGURE 4. *Response of the plasma renin-angiotensin-aldosterone system to acute converting-enzyme inhibition in three patients with primary aldosteronism. The heavy line represents the mean values. Shaded areas represent the normal range (mean ± 2 SD) obtained in 15 supine healthy subjects. The lower end of the logarithmic scales indicates the detection limit of our methods. Low initial angiotensin-(1-8)octapeptide concentrations further decrease after captopril, whereas aldosterone levels remain abnormally high and renin values extremely low.*

and they were installed comfortably in a supine position. After blood sampling to establish predrug baseline captopril was given as a bolus intravenous injection at a dose of 25 mg. Low plasma renin activity and abnormally high plasma aldosterone levels predrug confirmed the diagnosis of primary aldosteronism. Following the administration of captopril, plasma angiotensin II that was low to begin with at 1.80 ± 0.70 fmol/mL (mean ± SEM) fell markedly to 0.17 ± 0.09 fmol/mL 90 minutes after captopril injection.

These results clearly demonstrate that even in patients with the lowest possible angiotensin II levels to start with, ACE inhibition still substantially reduces circulating angiotensin II. It is therefore certainly inappropriate to assume that ACE inhibitors cannot reduce plasma angiotension II in patients with low renin hypertension. Indeed, blood pressure of these patients with primary hyperaldosteronism did not fall substantially after the administration of captopril. However, response or nonresponse of blood pressure to substantial angiotensin II reduction has nothing to do with the inhibitory efficacy of the drug per se but rather with the set-point of the pressure-response curve to prevailing angiotensin II levels that is known to be highly variable from one patient to the other and also within a given patient depending on many variables.

PLASMA ANGIOTENSIN II DURING RENIN INHIBITION

The goal of renin inhibition being the same as that of ACE inhibition, ie, reduction of angiotensin II generation, the measurement of plasma angiotensin II can be used just the same way to assess the efficacy and potency of renin inhibitors. This has been done recently, administering two renin inhibitors, CGP 38560A (Ciba-Geigy, Basel, Switzerland) and A-64662 (Abbott Laboratories, Abbott Park, Illinois) to normal volunteers by either 30 minute IV infusion or bolus IV infusion.[24,25] Both compounds reduced plasma angiotensin-(1-8)octapeptide in a dose-dependent fashion to very low levels, comparable to those observed during ACE inhibition. Thus, the measurement of plasma angiotensin II makes it possible not only to evaluate the efficacy of any new renin inhibitor but also to compare it to that of ACE inhibitors.

CONCLUSIONS

Because angiotensin II appears to be the only vasoactive component of the renin-angiotensin system, any assessment of drugs designed to inhibit this system and thereby to reduce vasomotor tone, should be based on the accurate measurement of the octapeptide angiotensin II. The quantitation of this hormone in plasma has presented considerable difficulties but at the present, precise methods are available to determine angiotensin II in plasma with a high degree of specificity and sensitivity. Using this approach, it can be clearly demonstrated that ACE inhibitors reduce circulating angiotensin II and that no tolerance develops with prolonged use of this drug. Expressed differently, even though there exists some dissociation in time between the antihypertensive effect and the angiotensin II-reducing action of ACE inhibitors, there is little evidence that ACE inhibitors ever lower blood pressure without reducing plasma angiotensin II levels at least for a short period during the day. It could also be shown that even during peak blockade angiotensin II levels are probably still under the influence of circulating active renin. Accordingly, ACE inhibitors should be used in a way that provides maximal angiotensin II reduction in the face of minimal increase in active renin. There seems to be little benefit in increasing excessively the dose of ACE inhibitors,

because circulating angiotensin II levels may not be further reduced. On the other hand, even in patients with very low plasma angiotensin II, such as patients with primary aldosteronism, plasma angiotensin II can still be shown to be markedly reduced by ACE inhibition. Accordingly, there is little doubt today that acute as well as long-term administration of an ACE inhibitor at adequate doses markedly reduces angiotensin II in plasma. Whether this fall in circulating angiotensin II induces any change in blood pressure depends on the interaction of several independent variables prevailing in a given patient that determine the set-point of the pressure-response to angiotensin II.

In these clinical studies, angiotensin II has only been measured in plasma. The determination of angiotensin II in tissue will present even greater methodological difficulties and will probably be of little practical use in clinical medicine. For the time being, the studies discussed certainly cannot provide the answer to whether a local tissue renin-angiotensin system rather than the components circulating in plasma are the main determinant of blood pressure homeostasis. The results presented do however demonstrate how much more can still be learned by measuring the octapeptide angiotensin II in plasma. The prospect, that tissue rather than plasma angiotensin II may determine vascular tone is certainly of great interest. However, much more work will have to be done before this hypothesis can be confirmed or refuted.

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