Blood Pressure Control by the Renin-Angiotensin System in Normotensive Subjects
Assessment by Angiotensin Converting Enzyme and Renin Inhibition

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Background. The participation of the renin-angiotensin system in the control of blood pressure in normal, sodium-replete subjects is not clear. The use of a specific inhibitor of human renin should allow a better delineation of the importance of this system.

Methods and Results. Blood pressure responses were measured 1 hour after randomized, double-blind administration of the renin inhibitor Ro 42-5892 (600 mg p.o.) or the angiotensin converting enzyme inhibitor captopril (50 mg p.o.) in 20 healthy men on an ad libitum sodium diet. Effective inhibition of the renin-angiotensin system by either compound was indicated by increases of immunoreactive renin associated with an increase of angiotensin I production rate of 67.8±33.6% after captopril and a decrease of 79.5±16.4% after Ro 42-5892. Furthermore, Ro 42-5892 decreased plasma renin activity by 64%. Whereas intra-arterial diastolic (60±5.1 to 51.4±7.2 mm Hg, \( p < 0.01 \)) and mean arterial (77.7±6.0 to 71.4±8.5 mm Hg, \( p < 0.001 \)) pressures decreased after captopril, they remained unchanged after Ro 42-5892. Captopril, but not Ro 42-5892, increased forearm blood flow (2.4±0.8 versus 1.9±0.8 ml/min/100 ml, \( p < 0.01 \)) and significantly enhanced the increase of forearm blood flow to brachial artery infusions of bradykinin (0.15, 1.5, 5, 15, and 50 ng/min/100 ml; 5 minutes each) from 744±632% to 1,383±514% (\( p < 0.01 \)). Furthermore, repeat bradykinin infusions resulted in further decreases of blood pressure (from mean pressure of 71.4±8.5 to 63.2±7.6 mm Hg, \( p < 0.01 \)) only after captopril. Changes of blood pressure after captopril were unrelated to baseline plasma renin activity but correlated with captopril-induced enhancement of vasodilation to bradykinin (\( r = 0.68, \ p < 0.05 \)).

Conclusions. The lack of blood pressure effects of renin inhibition in contrast to angiotensin converting enzyme inhibition suggests that the renin-angiotensin system does not contribute significantly to blood pressure control in normotensive, sodium-replete subjects. The hypotensive activity of angiotensin converting enzyme inhibitors may result from additional hormonal effects, for example, inhibition of bradykinin degradation and/or subsequent increases of vasodilating prostaglandins or endothelium-derived relaxing factor(s). (Circulation 1992;85:1–8)

More than 50 years after the description of the renin-angiotensin-aldosterone (RAA) system,1–3 its precise role in the maintenance of blood pressure in normal humans and in primary hypertension is not completely elucidated. The view that the RAA system acts predominantly as a defense mechanism aimed at maintaining blood pressure during sodium and volume depletion4 was questioned by the demonstration of decreases of blood pressure after angiotensin converting enzyme inhibition by captopril in normal subjects maintained an educational grant from F. Hoffmann-LaRoche and Co., Basel, Switzerland.

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on a normal diet. However, angiotensin converting enzyme also cleaves other peptides, including vasodilating kinins. Accordingly, blockade of the enzyme also leads to reduced degradation of kinins, and there is evidence to suggest that accumulation of kinins or vasodilating prostaglandins may contribute to the blood pressure effects of angiotensin converting enzyme inhibitors in normotensive and hypertensive humans and animals. In addition, elevated kinin levels have been implicated in the pathogenesis of certain side effects of therapy with angiotensin converting enzyme inhibitors such as cough and angioneurotic edema. The advent of potent and specific inhibitors of renin has provided the opportunity to reexamine the question to what extent the RAA system participates in the maintenance of blood pressure in normal, sodium-replete humans. These compounds derived from the minimal sequence of angiotensinogen reacting with renin specifically inhibit renin as the rate-limiting enzyme in the cascade leading to formation of the vasoconstricting peptide angiotensin II. Because angiotensinogen is the only known natural substrate for renin, it appears that blockade of the enzyme should be better suited to investigate the physiological role of the RAA system in humans than angiotensin converting enzyme inhibition. Accordingly, we compared the effects of angiotensin converting enzyme inhibition by captopril with those of the orally active renin inhibitor Ro 42-5892 on resting blood pressure and bradykinin-induced vasodilation in normal volunteers.

**Methods**

**Subjects**

Twenty healthy, normotensive (casual sitting blood pressure less than 140/90 mm Hg) caucasian men aged 21 to 29 years (mean 24.8 years) participated in the study. The study protocol was approved by the Hospital Ethical Committee on the use of human subjects in clinical investigations, and written informed consent was obtained from all subjects.

**Forearm Blood Flow Measurements**

Forearm blood flow was measured bilaterally by venous occlusion plethysmography. A mercury-in-Silastic strain gauge was placed at the upper third of the forearm, which rested comfortably on a support slightly above the level of the heart. The strain gauge was coupled to an electronically calibrated plethysmograph (EC3, Hokanson, Watassah, Wash.). Venous occlusion was achieved by a blood pressure cuff applied proximal to the elbow and inflated to 40 mm Hg by a rapid cuff inflator (EC10, Hokanson). The hand was excluded from the circulation by a pediatric blood pressure cuff placed around the wrist and inflated to 50 mm Hg above systolic pressure 1 minute before and during the forearm blood flow measurements to eliminate the unpredictable influence of arteriovenous shunts in the hand. Experiments were done on the left (experimental) forearm, while blood flow measurements on the right (control) arm served as continuous control. Determinations of forearm blood flow were made by analyzing four to six consecutive recordings with a digitizing board and a suitably programmed computer. The mean value was taken for statistical evaluation. Forearm vascular resistance was calculated as mean arterial pressure divided by forearm blood flow and is expressed as arbitrary units. The ECG was monitored throughout the study.

**Hormone Determinations**

Blood for renin determinations was drawn into prechilled tubes containing EDTA, immediately placed on ice, centrifuged at 4°C, and frozen at −70°C until assay. All samples from each subject were analyzed in duplicate in the same assay to avoid interassay variability. For the determination of plasma renin activity, the trapping methodology of Poulsen and Jørgensen as modified by Nussberger et al was used. Immunoreactive renin was measured with an immunoradiometric assay (Diagnostics Pasteur, Marnes-La-Coquette, France) according to the method of Menard et al. The monoclonal antibody used does not cross-react with inactive prorenin but cross-reacts fully with active renin even when inhibited. Ro 42-5892 interferes slightly in this assay, but interference was less than 10% at 10 nM, a plasma concentration 10 times higher than the IC50 measured in the plasma assay. Angiotensin I production rate was calculated as the ratio of (plasma renin activity control/1 hour) and (plasma immunoreactive renin control/1 hour) and is expressed as percentage change from the control value.

**Drugs**

The forearm volume of each subject was measured by water displacement according to the Archimedes principle, and drug doses were adjusted accordingly. All solutions were freshly prepared before each study. The nonapeptide bradykinin (Sigma Chemical, St. Louis, Mo.) was diluted in Physiogel (gelatin solution, 4%; molecular weight, 22,000; Swiss Red Cross, Bern, Switzerland) to avoid binding to syringes or tubing. For each subject, six identical-appearing capsules were provided. According to a randomization list, subjects received either one capsule of 50 mg captopril and five capsules filled with cornstarch or six capsules of 100 mg Ro 42-5892. Ro 42-5892 is a transition-state renin inhibitor with the structure (S)-α-L-[(tert-butylsulfonyl)-methyl]hydrocinnamido]-N-[(1S,2R,3S)-1-(cyclohexyl-methyl)-3-cyclopropyl-2,3-dihydropropyl]imidazole-4-propionamide (molecular weight, 631), which inhibits purified human renin at pH 7.4 with an IC50 of 0.7×10−9 M. Studies in normal volunteers have shown that lactose capsules used in this present study have a higher bioavailability and result in decreased variability of Ro 42-5892 plasma concentrations compared with...
the previously used\(^{19,21}\) drinking solution (C. Klein-bloesem, unpublished observation).

**Study Protocol**

All studies were performed in the morning with the subjects recumbent and resting comfortably after a light breakfast. All subjects had been asked to refrain from smoking and caffeinated beverages for 8 hours before the study; none was taking medication, and all were on their regular diet, which contains approximately 130–150 mmol Na per day, as shown in previous studies from a similar student and hospital personnel population.\(^{27}\) The studies were performed in a quiet, air-conditioned room at an ambient temperature of 20–22°C and lasted for approximately 5 hours. Under local anesthesia (lidocaine 1%), an 18-gauge catheter (Abbocath-T, Abbott, Sligo, Ireland) was inserted into the left brachial artery for regional drug infusion and recording of arterial pressure by a Statham P23 Pb pressure transducer. A second catheter was inserted into a cubital vein for withdrawal of blood for hormone determinations except in three subjects, in whom blood was drawn via the arterial line. The subjects were allowed to rest for 30 minutes after completion of instrumentation; then basal forearm blood flow, intra-arterial blood pressure, and heart rate were recorded, and blood was drawn for renin measurements. Next, bradykinin (0.15, 1.5, 5, 15, and 50 ng/min/100 ml forearm tissue; 5 minutes each) was infused into the brachial artery; forearm blood flow was measured in the last minute of each infusion. Blood pressure and heart rate were recorded immediately after completion of each bradykinin infusion. After completion of the bradykinin infusions, subjects received either 50 mg captopril or Ro 42-5892 p.o. One hour after drug administration, blood pressure, forearm blood flow, and heart rate were measured, and blood was drawn for hormone determinations. Then, bradykinin infusions were repeated in an identical manner, and forearm blood flow, blood pressure, and heart rate were recorded accordingly. Bradykinin infusions were generally well tolerated, but a feeling of warmth associated with a forearm flush was reported by most subjects. The highest dose of bradykinin was omitted in one subject (randomized to captopril) because of discomfort in the infused arm with the second highest dose.

**Statistical Analysis**

Results are expressed as mean±SD. One-factor analysis of variance (ANOVA) was used to test for differences attributable to the different drugs. Responses to bradykinin infusions and the influence of captopril and Ro 42-5892, respectively, were analyzed with a two-way profile analysis of repeated measures. The unpaired Student’s *t* test and linear regression analysis were used as appropriate. A two-tailed probability value of *p*<0.05 was considered to indicate a significant difference. All calculations were performed with the STATVIEW II (Abacus Inc., Berkeley, Calif.) statistical program.

**Results**

**Hemodynamic and Hormonal Findings at Rest**

The hemodynamic and hormonal findings are summarized in Table 1. Both drugs significantly increased immunoreactive renin. Plasma renin activity decreased after renin inhibition by 64% on average (range –15 to –92%). As expected from their mode of interference with the renin-angiotensin system, angiotensin I production rate increased after captopril by 67.8% and decreased after renin inhibition by 79.5%. Captopril significantly decreased diastolic (–8.6±5.2 mm Hg) and mean (–6.3±3.8 mm Hg) arterial pressures. Resting forearm blood flow increased 28.1±33%, and forearm vascular resistance

**Table 1. Hemodynamic and Hormonal Findings in Captopril- and Ro 42-5892–Treated Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Captopril (n=10)</th>
<th>Ro 42-5892 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>1 Hour after drug</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>60.4±8.6</td>
<td>67.8±8.8*</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>113±9.0</td>
<td>111.8±12.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>60±5.1</td>
<td>51.4±7.2†</td>
</tr>
<tr>
<td>Mean</td>
<td>77.7±6.0</td>
<td>71.4±8.5†</td>
</tr>
<tr>
<td>Forearm blood flow  (ml/min/100 ml)</td>
<td>1.9±0.8</td>
<td>2.4±0.8†</td>
</tr>
<tr>
<td>Plasma renin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoreactive (pg/ml)</td>
<td>19.4±12.4</td>
<td>68.7±54.4†</td>
</tr>
<tr>
<td>Activity (ng Al/ml/hr)</td>
<td>1.63±1.22</td>
<td>6.10±4.24†</td>
</tr>
<tr>
<td>Al production rate (%)</td>
<td>100</td>
<td>167.8±33.6</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Al, angiotensin I.
*\(^{*}\)p<0.05.
†\(^{†}\)p<0.01 vs. control.
FIGURE 1. Plots of forearm blood flow measurements in response to graded brachial artery infusions of bradykinin. Measurements were performed before (control) and 1 hour after administration of 600 mg p.o. of the renin inhibitor Ro 42-5892 (left panel) or of 50 mg captopril p.o. (right panel) in 10 normal subjects each. Only captopril significantly enhanced the forearm vasodilator to bradykinin. Values are mean±SD. **, p<0.001.

decreased 23.1±22.9% (both p<0.01). Heart rate increased by 7.4±6.3 beats per minute (p<0.01). In contrast, Ro 42-5892 did not cause systematic hemodynamic changes. The decrease of blood pressure after captopril was unrelated to baseline plasma renin activity but correlated significantly with concomitant changes of forearm blood flow (r=0.64, p<0.05).

Response to Bradykinin

Forearm blood flow responses to brachial artery infusions of ascending doses of bradykinin and the influence of captopril and Ro 42-5892 are depicted in Figure 1. During control conditions, blood pressure and heart rate were unchanged during bradykinin infusions, whereas forearm blood flow increased dose dependently from 1.9±0.8 to 14.3±7.8 (744%) in subjects randomized to captopril and, similarly, from 2.0±0.5 to 17.6±7.7 ml/min/100 ml (798%) in subjects randomized to Ro 42-5892. The vasodilator response to repeat bradykinin infusions was significantly enhanced by captopril, which increased the maximal response of forearm blood flow to 1383% (from 2.4±0.8 to 34.1±8.7 ml/min/100 ml). In contrast, Ro 42-5892 did not alter the forearm vasodilator response to bradykinin, which increased maximally by 853% from 2.2±1.1 to 23.0±12.3 ml/min/100 ml (p<0.001 for difference between captopril- and Ro 42-5892-induced changes; two-factor repeated-measures ANOVA). Captopril-induced changes of blood pressure were significantly correlated with the enhancement of the forearm vasodilator response to the highest bradykinin dose (Figure 2). Furthermore, blood pressure did not change during bradykinin infusions after Ro 42-5892, but captopril decreased diastolic blood pressure from 51.4±7.2 to 47.7±6.9 mm Hg (p<0.01) and, as shown in Figure 3, mean blood pressure from 71.4±8.5 to 63.2±6.7 mm Hg (p<0.01), while heart rate increased further from 67.8±8.8 to 87.8±9.4 beats per minute (p<0.01).

Discussion

The interpretation of data based on angiotensin converting enzyme inhibitors is complicated by their additional properties related to interference with the degradation of bradykinin and kinin-induced release of vasodilating prostaglandins and endothelium-derived relaxing factor (EDRF). The present work emphasizes these properties, because in sodium-replete normal volunteers the angiotensin converting enzyme inhibitor captopril, but not the specific renin inhibitor Ro 42-5892, caused peripheral vasodilation and decreases in diastolic and mean blood pressures. Therefore, our results provide evidence that 1) the renin-angiotensin system is not a major regulator of blood pressure in salt-replete normotensive subjects and that 2) the mechanisms whereby angiotensin converting enzyme inhibitors lower blood pressure entail more than reduction of circulating angiotensin II levels.

Regulation of Blood Pressure by Angiotensin II in Normotensive Subjects

The renin inhibitor used in the present study is a renin substrate analogue with a high affinity for human renin, little or no affinity for other aspartyl
proteases, and virtually no effect on angiotensin converting enzyme in vitro.20 The present study confirms in vivo that it does not interfere with angiotensin converting enzyme, because vascular responses to bradykinin were unchanged but plasma renin activity and angiotensin I production rate decreased significantly. In agreement with the known regulatory mechanisms governing renin release, immunoreactive renin, determined by a monoclonal antibody technique, increased after Ro 42-5892 as a result of interruption of negative feedback control of plasma renin by reduced angiotensin II levels.32 Although biochemical evidence, therefore, suggests significant blockade of the renin-angiotensin system, blood pressure remained unchanged. This observation is in agreement with other studies investigating the effects of renin inhibitors in salt-replete normotensive subjects. Thus, neither CGP 38560A33,34 nor enalkiren35 decreased blood pressure in normotensive subjects despite evidence of almost total inhibition of plasma renin activity in all studies. In contrast, when the renin-angiotensin system was activated by dietary sodium restriction or administration of diuretics, blood pressure decreased in nonhuman primates20,36–39 and other animals.40,41 These studies and our results are compatible with the contention that the renin-angiotensin system acts as a defense mechanism in normal humans during states of sodium or volume depletion but is of little importance for the maintenance of blood pressure in sodium-replete normal humans.4 Interestingly, renin inhibition was effective in lowering blood pressure in patients with essential hypertension both on a normal diet19,42 and, more pronouncedly, after stimulation of the renin-angiotensin system by 1 week of thiazide treatment.42 Furthermore, blood pressure decreased after renin inhibition in a model of ovine heart failure characterized by high renin levels.43 While the difference in the response to renin inhibition between normal volunteers and patients with hypertension points toward the importance of the renin-angiotensin system in hypertensive patients, the results also suggest that renin inhibition may be a better tool to delineate more precisely the role of this system in the pathophysiology of hypertension as compared with angiotensin converting enzyme inhibition. Ultimately, this approach may lead to a better understanding of the physiology and pathophysiology of this system in both normal and diseased subjects and to more rational therapy.

Two important aspects need to be discussed in this context. It appears possible that acute administration of renin inhibitors suppresses only circulating renin activity but leaves the vascular renin-angiotensin system intact. Theoretically, more prolonged therapy or different renin inhibitors of smaller molecular size and better access to the vascular renin-angiotensin system might yield different results. However, oral Ro 42-5892 rapidly lowered blood pressure in patients with hypertension,19 indicating that hemodynamic effects can be seen within the time frame chosen for our experiments irrespective of the disputable site of action.

Suppression of plasma renin activity varied between subjects and was not complete. Theoretically, this might also contribute to the observed difference. However, blood pressure did not decrease in six subjects in whom plasma renin activity decreased by more than 60% (mean, 79%). This finding and the lack of blood pressure effects of other renin inhibitors, which suppressed plasma renin activity to almost undetectable levels when given intravenously,33–35 make this an unlikely explanation for our findings. The small degree of renin inhibition in some subjects might also be taken as evidence that the bioavailability of Ro 42-5892 may be variable. Ours was not a pharmacokinetic study, so we cannot comment on this aspect. However, immunoreactive renin was increased in all subjects, suggesting blockade of the renin-angiotensin system even in those subjects with low degrees of renin inhibition at the time of measurement. A dissociation between short-lasting renin inhibition and long-lasting elevations of immunoreactive renin has been noted before.33

Our results also show that renin inhibition did not influence bradykinin metabolism. Reduced bradykinin degradation may be involved in the pathogenesis of angiotensin converting enzyme inhibitor–induced cough13 and angioneurotic edema.14 Although a kinin-induced increase of prostaglandins rather than increased kinin levels per se may lead to a sensitization of the cough reflex,15 it might nevertheless be anticipated that these unwanted effects would not be present during therapy with renin inhibitors.

Blood Pressure Effects of Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme inhibition with captopril increased forearm blood flow and reduced blood pressure along with the expected blockade of the renin-angiotensin system, as evidenced by increased immunoreactive renin, plasma renin activity, and, therefore, markedly increased angiotensin I production rate. Because renin inhibition did not change blood pressure, it appears likely that effects unrelated to the renin-angiotensin system accounted for the fall in blood pressure. Captopril-induced changes of blood pressure were caused by peripheral vasodilation, as documented by the relation between increases in forearm blood flow and decreases of mean arterial pressure. Heart rate increased significantly in our subjects, probably resulting from baroreflex-mediated sympathetic stimulation. This finding differs from hypertensive subjects8–10 or patients with heart failure,47 in whom heart rate either does not change or may actually decrease. Although this difference is not readily explained, it may reflect differences in baroreflex function, which presumably was normal in our young, normotensive subjects compared with the depressed function usually observed in patients with hypertension48 or heart fail-
ure. Furthermore, this was an acute study, and heart rate responses might differ during long-term therapy.

Captopril significantly enhanced the forearm vasodilator response to brachial artery infusions of bradykinin in our subjects. Although blockade of bradykinin degradation by angiotensin converting enzyme inhibition is expected, it was interesting to observe that the captopril-induced enhancement of the vasodilator response to bradykinin was related to the decrease of blood pressure. This finding and the lack of a relation between baseline plasma renin activity and blood pressure effects of captopril suggest that the hypotensive response to angiotensin converting enzyme inhibition may be related to an interference with the degradation of bradykinin. The powerful vasodilator activity of the bradykinin system is supported by the observation that low concentrations of this peptide had no effect on blood pressure before captopril administration but significantly and markedly lowered blood pressure after captopril.

Interference with degradation of bradykinin has long been suspected to play a role in the vasodilator activity of angiotensin converting enzyme inhibitors. Plasma bradykinin levels and urinary kinin excretion were elevated in hypertensive patients, and captopril increased plasma bradykinin levels in patients with congestive heart failure. Bradykinin infusion restored the vasodilator action of teprotide in nephrectomized rats, and administration of captopril during renin inhibition in sodium-depleted dogs resulted in an additional decrease of blood pressure, probably explained by an effect of captopril unrelated to reduced angiotensin II levels. Most convincingly, infusion of a bradykinin antagonist partially prevented the antihypertensive effect of enalaprilat in rat models of hypertension, suggesting that at least part of the blood pressure-lowering effect of angiotensin converting enzyme inhibition is mediated by inhibition of the degradation of kinins. Whether this effect results from an increase in tissue kinins acting as autacoids in the regulation of vascular tone or from bradykinin-mediated release of vasodilating prostaglandins is less clear. However, there is considerable support for a role of prostaglandins in the vascular response to angiotensin converting enzyme inhibitors. Teprotide increased plasma prostaglandin E concentrations in hypertensive patients, and captopril-induced decreases of blood pressure in normal men correlated with increases of 13,14-dihydro-15-keto prostaglandin E2. Furthermore, the acute hypotensive effect of captopril was attenuated after inhibition of cyclooxygenase in normotensive and hypertensive subjects, and the peripheral vasodilator effect of captopril was blunted in patients with congestive heart failure after pretreatment with indomethacin along with a complete blockade of captopril-induced increases of prostaglandin E2 and 6-keto-prostaglandin F1α. Therefore, both local effects of vascular bradykinin accumulation and systemic increases of vasodilating prostaglandins may be involved in the hemodynamic effects of angiotensin converting enzyme inhibition. Bradykinin also mediates release of EDRF, and tonic release of EDRF contributes significantly to the control of arteriolar tone in humans, and stimulation of EDRF release results in marked vasodilation both in normotensive and, less pronouncedly, in hypertensive subjects. There are no data in humans investigating the effects of angiotensin converting enzyme inhibition on the control of arteriolar tone by EDRF, but cilazapril, for example, normalized impaired EDRF-mediated vasodilation in spontaneously hypertensive rats. However, it is not clear whether or to what extent this powerful vasodilator system contributes to the antihypertensive effects of angiotensin converting enzyme inhibitors in humans. Finally, it must be reemphasized that this was an acute study performed in salt-replete normotensive subjects. Accordingly, the magnitude of non-angiotensin II–mediated effects of angiotensin converting enzyme inhibitors may be less during long-term therapy, in sodium depletion, or in disease states.

Conclusions

Our results suggest that the renin-angiotensin system does not contribute significantly to the maintenance of blood pressure in normotensive, sodium-replete subjects and that the hypotensive activity of angiotensin converting enzyme inhibitors, at least in normotensive subjects, may be a result of additional hormonal effects. Use of specific renin inhibitors may be a more appropriate tool than angiotensin converting enzyme inhibitors to study the renin-angiotensin system in humans. This approach may have considerable impact on the design of future studies to assess this system both in normal subjects and in patients with such diseases as primary hypertension or congestive heart failure.

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References


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