Effects of Acute ACE Inhibition on Pulsatile Renin and Aldosterone Secretion and Their Synchrony

Danilo Fliser, Johannes D. Veldhuis, Ralf Dikow, Heinrich Schmidt-Gayk, Eberhard Ritz

Abstract—Pulsatile (burstlike) secretion of renin and aldosterone is positively coupled with a short time lag of about 10 to 20 minutes. We investigated how acute interruption of the renin-angiotensin-aldosterone axis, ie, acute angiotensin-converting enzyme (ACE) inhibition, alters the pattern of renin and aldosterone secretion. Eight healthy men (mean age, 22±1 years) were studied while on standardized salt intake. They were allocated on 2 occasions in random order to injection of placebo or 1.25 mg of the ACE inhibitor enalaprilat. Blood samples were obtained every 10 minutes for 24 hours for measurement of plasma renin and aldosterone concentrations. The hormone concentration profiles were analyzed using a multiparameter deconvolution technique; basal (tonic) and pulsatile hormone secretion was assessed. The regularity of pulsatile hormone secretion was analyzed using approximate entropy (ApEn). Cross-correlation and cross-ApEn analysis of renin and aldosterone secretion were performed to assess synchrony. Acute ACE inhibition caused an immediate burst of renin release and, in addition, significantly (P<0.01) increased 24-hour pulsatile and total renin secretion. It did not affect basal (nonpulsatile) renin secretion. The amplitude of renin bursts and the mass of hormone secreted per burst were significantly (P<0.01) increased, whereas the burst frequency (ie, number of secretory events) was unchanged. ApEn analysis revealed significantly (P<0.05) more regular renin secretion after ACE inhibition. In contrast, neither basal nor pulsatile aldosterone secretion was affected by administration of enalaprilat. Cross-ApEn analysis documented not only a maintained pattern of reproducibility (ie, synchrony) but also greater conditional regularity between pulsatile renin and aldosterone secretions with acute ACE inhibition. However, the quantitative strength of hormone coupling (assessed by cross-correlation analysis) was markedly diminished by enalaprilat treatment. The present findings suggest that the renin-angiotensin-aldosterone axis may not be completely uncoupled by acute ACE inhibition or that pulsatile renin and aldosterone secretion is driven by a common signal generator that is unaffected by ACE inhibition. In addition, a background basal and pulsatile aldosterone secretion not regulated by the renin-angiotensin axis may exist. (Hypertension. 1998;32:929-934.)

Key Words: angiotensin-converting enzyme inhibitors ■ aldosterone ■ entropy ■ renin-angiotensin-aldosterone system ■ renin

Previous studies have shown that the rapid regulation of plasma renin activity and plasma aldosterone concentration is mediated via control of the hormone secretory rate rather than metabolic clearance rate.1,2 Furthermore, experimental studies have defined a pulsatile mode of renin and aldosterone secretion3-5 that is similar to the physiological output of pituitary and several other hormones. More recently, by using a deconvolution technique, ie, a computer-based algorithm for analysis of secretion underlying hormone time series, both a basal component (tonic, nonpulsatile) and a pulsatile component of renin and aldosterone secretion were identified in humans.6 Pulsatile secretion was responsible for about 50% to 60% of total renin and aldosterone release, and distinct aldosterone secretory events were coupled to the renin bursts with a short time lag of ~10 to 20 minutes.6 The physiological implications of pulsatile renin (and aldosterone) secretion are not well defined, but several interventions have been shown to enhance pulsatile renin and aldosterone secretion (eg, dietary salt restriction, sleep, meals, orthostasis).1-3

How biological regulation of the renin-angiotensin-aldosterone system (RAAS) is mediated via alterations in pulsatile renin secretion is not well understood. Furthermore, it has not been established whether (1) acute control of the overall activity of the RAAS is mediated preferentially by regulation of basal or pulsatile hormone secretion (or both) or (2) the pulsatile profiles of renin and aldosterone secretion are regulated in parallel, ie, whether synchrony is retained. Some of these questions can be answered by studying the effects of acute interruption of the short feedback loop of the RAAS via...
inhibition of angiotensin II production, ie, inhibition of the angiotensin-converting enzyme (ACE).

We therefore administered 1.25 mg of the ACE inhibitor enalapril enalaprilat by intravenous injection in a double-blind, randomized, placebo-controlled study in healthy volunteers on standardized salt intake. Blood was sampled frequently every 10 minutes for 24 hours for later measurements of plasma renin and aldosterone concentrations. Basal and pulsatile secretions of the 2 hormones and their interdependence were evaluated using deconvolution analysis and cross-correlation, and the orderliness and relative synchrony of renin and aldosterone secretion were quantified by approximate entropy.

Methods

Subjects and Design

The protocol was approved by the ethics committee of the University of Heidelberg. Eight healthy, male, normotensive nonsmokers (mean age, 22±1 years; mean body mass index, 24.3±0.6 kg/m²), who were taking no medication and who gave written informed consent, were studied. Their family histories were negative for hypertension or metabolic diseases. At study entry, a physical examination, routine chemistry, and urinalysis were performed for all participants.

A double-blind, randomized, placebo-controlled study design was chosen. All subjects were allocated in random order to 2 interventions: (1) placebo injection, ie, 10 mL of a 0.9% NaCl solution (enalaprilat is the active form of the ACE inhibitor enalaprilat (Xanef Inject, MSD) dissolved in 10 mL of a 0.9% NaCl solution (enalaprilat is the active form of the prodrug enalapril). The interval between the interventions was at least 6PM, and room lights were turned off at 11 PM. Mean arterial blood withdrawn was replaced isovolumetrically by a slow infusion into aliquots, rapidly frozen, and stored at every 10 minutes for 24 hours in prechilled EDTA-containing tubes.

Assays

Active plasma renin concentrations were measured with an immuno- radiometric assay using a highly sensitive and specific monoclonal antibody for renin (Renin III Generation, E.R.I.A. Diagnostics Pasteur). The normal range of the assay for healthy subjects is 6 to 35 mU/L (supine position). The intra-assay and interassay coefficients of variation in healthy subjects are <5.2% and <7.4%, respectively. Plasma aldosterone concentrations were also measured with an immunoradiometric assay (normal range for supine position, 28 to 444 pmol/L) using a highly sensitive and specific monoclonal antibody (Aldosteron-Ria, DPC Biemann GmbH). The intra-assay and interassay coefficients of variation in healthy subjects are <6.5% and <8.1%, respectively.

Statistics

Data on renin and aldosterone secretion as estimated with deconvolution, cluster, ApEn, cross-ApEn, and cosinor analysis were compared using a Wilcoxon test for paired samples to assess differences between placebo and enalaprilat (ACE inhibitor) treatment (SPSS statistical package). The differences were considered statistically significant at a level of P<0.05. Data are shown as mean±SEM.
Results

Table 1 shows data on renin and aldosterone secretion as estimated by multiparameter deconvolution analysis. Enalaprilat significantly increased the amplitude of renin bursts and the mass per burst, whereas the frequency components of secretion (ie, number of bursts and interburst interval) were not affected. Furthermore, ACE inhibition significantly increased pulsatile (and total) renin secretion, but basal secretion remained unchanged. As a consequence, the relative proportion of pulsatile secretion was significantly higher than that of basal secretion in enalaprilat treatment. These changes in renin secretion were observed in each of the 8 subjects studied (Figure 1). A representative plot of the renin and aldosterone time-concentration profiles in 1 healthy volunteer with injection of placebo versus 1.25 mg enalaprilat is shown in Figure 2. The deconvolution-estimated renin secretory rate in the same volunteer is shown in Figure 3. Maximal peak renin pulse values were seen during nighttime and in the early morning hours (ie, sleep period); ACE inhibition markedly accentuated renin secretory bursts. A similar pattern of renin secretion was seen in the other volunteers as well. In contrast to the effects on renin secretion, acute ACE inhibition did not affect aldosterone secretion (Table 1).

Cluster analysis confirmed the deconvolution data. The number of renin secretory events (bursts) and the interburst interval were similar with placebo (13.4±1.7 bursts/24 hours and 102±11 minutes, respectively) and enalaprilat (12.0±0.9 bursts/24 hours and 107±9 minutes) administration, but the area and the amplitude of renin bursts increased significantly (P<0.01) with ACE inhibition (2893±1080 mU/L per minute and 35±10 mU/L) compared with placebo treatment (479±83 mU/L per minute and 10±2 mU/L). In contrast, there were no significant differences in the number of aldosterone bursts per 24 hours, the interburst interval (minutes), the burst area (pmol/L per minute), and the burst amplitude (pmol/L) with placebo (14.8±1.3, 96±7, 5900±896, and 111±11, respectively) or enalaprilat (13.8±0.7, 99±7, 6946±1540, and 122±19) treatment.

The mean ApEn value for pulsatile renin secretion was significantly lower (P<0.05) after enalaprilat administration (1.46±0.05) compared with placebo (1.64±0.04), ie, ACE inhibition induced a more regular or orderly pattern of renin secretion. In contrast, it did not affect the regularity of pulsatile aldosterone secretion (mean ApEn value, 1.71±0.02 with placebo versus 1.72±0.02 with enalaprilat treatment). Cross-ApEn analysis documented highly significant synchrony between pulsatile renin and aldosterone secretion with placebo treatment, ie, the mean observed cross-ApEn value (1.34±0.11) was significantly (P<0.01) lower than the mean random cross-ApEn value (2.15±0.04), resulting in a mean cross-ApEn ratio greater than 1 (1.70±0.15). Synchrony of pulsatile renin and aldosterone secretion patterns persisted even during enalaprilat treatment (mean observed cross-ApEn value, 1.09±0.06; mean random cross-ApEn value, 2.15±0.04).

Table 1. Basal and Pulsatile Renin and Aldosterone Secretion After Injection of Placebo or 1.25 mg Enalaprilat in 8 Healthy Men as Estimated by Deconvolution Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Enalaprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal secretory rate, mU/L</td>
<td>3.9±0.6</td>
<td>3.9±0.7</td>
</tr>
<tr>
<td>Burst frequency, bursts per 24 h</td>
<td>16.3±0.9</td>
<td>16.1±0.9</td>
</tr>
<tr>
<td>Interburst interval, min</td>
<td>87.8±4.0</td>
<td>88.9±5.3</td>
</tr>
<tr>
<td>Hormone mass per burst, mU/L</td>
<td>442±21</td>
<td>483±23</td>
</tr>
<tr>
<td>Amplitude, mU/L per min</td>
<td>9.6±1.3</td>
<td>9.5±1.3</td>
</tr>
<tr>
<td>Time-averaged concentration, mU/L</td>
<td>231±6.4</td>
<td>243±9.4</td>
</tr>
<tr>
<td>Total secretion, mU/L per 24 h</td>
<td>12968±1132</td>
<td>13101±949</td>
</tr>
<tr>
<td>Basal secretion, %</td>
<td>49</td>
<td>73*</td>
</tr>
<tr>
<td>Pulsatile secretion, %</td>
<td>51</td>
<td>27*</td>
</tr>
<tr>
<td>Pulsatile secretion, mU/L</td>
<td>230±42</td>
<td>251±53</td>
</tr>
<tr>
<td>Basal secretion, mU/L per 24 h</td>
<td>222±29</td>
<td>674±173*</td>
</tr>
<tr>
<td>Pulsatile secretion, mU/L</td>
<td>1018</td>
<td>13101±949</td>
</tr>
<tr>
<td>Aldosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal secretory rate, pmol/L</td>
<td>819</td>
<td>5675</td>
</tr>
<tr>
<td>Burst frequency, bursts per 24 h</td>
<td>1018</td>
<td>1132</td>
</tr>
<tr>
<td>Interburst interval, min</td>
<td>13.4±1.7</td>
<td>96±7</td>
</tr>
<tr>
<td>Hormone mass per burst, pmol/L</td>
<td>5900±896</td>
<td>5900±896</td>
</tr>
<tr>
<td>Amplitude, pmol/L per min</td>
<td>111±11</td>
<td>111±11</td>
</tr>
<tr>
<td>Time-averaged concentration, pmol/L</td>
<td>7426±744</td>
<td>7426±744</td>
</tr>
<tr>
<td>Total secretion, pmol/L per 24 h</td>
<td>5900±896</td>
<td>5900±896</td>
</tr>
<tr>
<td>Basal secretion, %</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Pulsatile secretion, %</td>
<td>57</td>
<td>57</td>
</tr>
</tbody>
</table>

*P<0.01, comparison between placebo and enalaprilat.
The mean observed cross-ApEn value was lower with enalaprilat than with placebo treatment in 7 of the 8 volunteers examined ($P$, 0.07), ie, ACE inhibition tended to induce greater pattern synchrony between pulsatile renin and aldosterone secretion. In the cross-correlation analysis of plasma renin concentration versus aldosterone secretory rate, median cross-correlation coefficients were highly significant ($P<0.01$) with placebo treatment at all lag times tested (ie, $-50$, $-40$, $-30$, $-20$, $-10$, $0$, $+10$, $+20$, $+30$, $+40$, and $+50$ minutes). The strongest cross-correlation between renin and aldosterone secretions was observed with a lag time of $+20$ minute. In contrast, there was no significant cross-correlation at all tested lag times after enalaprilat treatment.

Table 2 shows the cosinor analysis of renin and aldosterone secretion. Both plasma renin and aldosterone concentrations showed significant 24-hour rhythms. Administration of enalaprilat significantly increased the differences (amplitudes) between the zeniths and nadirs of this nyctohemeral renin rhythm and, in addition, altered their timing (ie, time of maximal value or acrophase). The amplitude of aldosterone secretion was not significantly altered, but the timing was shifted similarly as for renin.

The mean 24-hour urinary sodium and potassium excretion of our subjects was comparable before the 2 study days, ie, $98 \pm 6$ and $58 \pm 6$ mmol with placebo injection and $104 \pm 9$ and $61 \pm 5$ mmol with injection of enalaprilat. Mean blood potassium concentrations decreased with time from baseline during both treatments (from $4.0 \pm 0.1$ to $3.7 \pm 0.1$ mmol/L), but we observed no significant differences in blood potassium concentrations between placebo and enalaprilat treatment. MAP was unchanged after placebo injection but decreased markedly after injection of enalaprilat, with the maximal change from preinjection levels being $8.6 \pm 0.3$ mm Hg.
ies.24,25 A “pacemaker” located within the glomerulosa cells possibility already has been suggested by some past stud-

which is not regulated by the renin-angiotensin axis; this observation may point to the existence of a “background” basal and pulsatile aldosterone secretion, analogous to what is found for insulin secretion from the pancreatic β-cell.26 Alternative explanations could be incomplete ACE inhibition and/or direct control of background basal and pulsatile aldosterone secretion by ACTH or potassium ions.24 However, in agreement with previous observations,23 we found no significant changes of blood potassium concentration after acute ACE inhibition. Nevertheless, in (patho)physiological conditions with increased renin secretion and angiotensin II production (eg, heart failure), aldosterone secretion can be readily increased above the background level. Our finding of unchanged aldosterone secretion despite a significant decrease of blood pressure after injection of enalaprilat confirms the well-known fact that aldosterone plays no major role in acute blood pressure control.

Third, we confirmed an accentuation of renin and aldosterone secretion during the sleep period.16 The mechanisms underlying this phenomenon are not clear, but an association with nonrapid eye movement has been reported.3 A complementary explanation may be the decrease in blood pressure during nighttime. ACE inhibition markedly enhanced nocturnal renin oscillations, but we cannot readily discriminate between the effects of ACE inhibition and blood pressure decrease after enalaprilat injection. By analysis of 24-hour hormonal rhythmicity (ie, cosinor analysis), we confirmed a strong tendency for late nighttime (early morning) increases in renin and aldosterone secretion concurrently in the placebo treatment session. As expected, with the morning dose of enalaprilat, the acrophase for renin secretion shifted substantially during ACE inhibition. Unexpectedly, this shift occurred also with aldosterone secretion. The observation suggests that ACE inhibition did not eliminate coupling between renin and aldosterone completely, or that the ACE inhibitor acts also on central neuronal rhythmicity systems in the central nervous system, where circadian rhythms are believed to originate.

An unexpected finding of the present study was the observation that acute ACE inhibition rendered renin pulsatility more regular (ie, more synchronous), as documented by a decrease in ApEn value. In contrast, it did not influence the regularity of aldosterone secretion. In most biological systems that are controlled by a feedback loop, ie, most of the coupled multihormononal axes in the human body, greater regularity corresponds to greater component and subsystem autonomy. Vice versa, hormone secretion pathology usually corresponds to greater secretion irregularity.17,18 Furthermore, interventions with the potential of interrupting such hormonal axes usually cause an increase in randomness of hormonal secretion, ie, an increase of ApEn value, the opposite of what we have observed with ACE inhibition. The physiological significance of this effect remains uncertain, since the control of synchronous generation of renin secretory bursts by the cells of the macula densa is less well studied, as are the mechanisms that might serve to couple both kidneys with respect to the timing of renin bursts. Although these questions can be answered only in experimental studies, the pulsatile secretion of renin may serve as a regulatory mechanism (via angiotensin II as the effector hormone) through which the end-organ receptor number (up/downregulation) and/or receptor affinity is adjusted, eg, as proposed for pulsatile insulin secretion.28 Evidence for the latter comes from studies in

**TABLE 2. Cosinor Analysis of Renin and Aldosterone Secretion After Injection of Placebo and 1.25 mg Enalaprilat in 8 Healthy Men**

<table>
<thead>
<tr>
<th>Cosinor Analysis</th>
<th>Placebo</th>
<th>Enalaprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average, mU/L per min</td>
<td>29±5</td>
<td>75±27*</td>
</tr>
<tr>
<td>Amplitude, mU/L per min</td>
<td>10±2</td>
<td>36±18*</td>
</tr>
<tr>
<td>Acrophase, min†</td>
<td>287±45</td>
<td>826±106*</td>
</tr>
<tr>
<td><strong>Aldosterone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average, pmol/L per min</td>
<td>231±19</td>
<td>243±28</td>
</tr>
<tr>
<td>Amplitude, pmol/L per min</td>
<td>95±21</td>
<td>128±32</td>
</tr>
<tr>
<td>Acrophase, min†</td>
<td>178±40</td>
<td>753±190*</td>
</tr>
</tbody>
</table>

*Cosinor average indicates average hormone concentration during 24-h observation period; cosinor amplitude, difference between maximal and minimal hormone concentration during 24-h observation period; cosinor acrophase, time point of highest hormone concentrations (ie, secretion maximum) during 24-h observation period.

†Minutes before 9 AM.

Discussion

The present study demonstrates that interrupting the short feedback loop of the RAAS via acute ACE inhibition modulates the pulsatile secretion of specific components of the RAAS in a distinct fashion. The injection of 1.25 mg enalaprilat elicited a significant increase in pulsatile renin secretion and, as a consequence, in total renin secretion, whereas basal renin secretion remained unaffected by this intervention. In contrast, aldosterone secretion, whether basal or pulsatile, was not influenced by acute ACE inhibition. We emphasize that both deconvolution and cluster analysis yielded similar results.

With respect to these findings, several comments seem appropriate. First, in contrast to what is known for several other hormones (eg, gonadotropin axis), where both amplitude and frequency control of secretion is recognized,25 renin secretory burst frequency was not affected by acute ACE inhibition. This is similar to what has been documented previously with modulation of salt intake.3 The latter intervention was also shown to affect both basal and pulsatile renin secretion, whereas acute ACE inhibition significantly increased only pulsatile renin secretion, leaving basal secretion unchanged. We cannot exclude the possibility that chronic ACE inhibition could also have an impact on basal renin secretion, however. Hemodynamic and humoral adaptations to changes of salt intake take several days in contrast to the almost immediate increase in pulsatile renin secretion after ACE inhibition.

Second, ACE inhibition acutely uncoupled renin and aldosterone secretion. This observation may point to the existence of a “background” basal and pulsatile aldosterone secretion, which is not regulated by the renin-angiotensin axis; this possibility already has been suggested by some past studies.24,25 A “pacemaker” located within the glomerulosa cells of the adrenal cortex could be responsible for this background aldosterone secretion, analogous to what is found for insulin secretion from the pancreatic β-cell.26 Alternative explanations could be incomplete ACE inhibition and/or direct control of background basal and pulsatile aldosterone secretion by ACTH or potassium ions.24 However, in agreement with previous observations,23 we found no significant changes of blood potassium concentration after acute ACE inhibition. Nevertheless, in (patho)physiological conditions with increased renin secretion and angiotensin II production (eg, heart failure), aldosterone secretion can be readily increased above the background level. Our finding of unchanged aldosterone secretion despite a significant decrease of blood pressure after injection of enalaprilat confirms the well-known fact that aldosterone plays no major role in acute blood pressure control.

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patients with type 2 diabetes mellitus and their relatives, in whom an irregular insulin secretion pattern is found.\textsuperscript{28,29} Loss of the physiological mode of hormone secretion has been also shown in patients with Cushing’s disease.\textsuperscript{30} Similar changes of renin secretion in pathophysiological conditions with stimulated RAAS have not been investigated to date, however.

We identified strongly positive cross-correlations between plasma renin concentration and calculated aldosterone secretory rates with placebo treatment. This is consistent with the view that changes in plasma renin concentration would be mirrored directly within an appropriate time lag in increases in aldosterone secretory rate. In contrast, during enalaprilat treatment we found marked disruption of this quantitative relationship, with complete loss of positive cross-correlations over a broad lag window of $-50$ to $+50$ minutes. This indicates severe quantitative damping of the coupling between renin and aldosterone. Of considerable interest, the cross-ApEn value showed greater conditional regularity between the 2 series during acute ACE inhibition. This initially unexpected finding could be interpreted to indicate some breakthrough signaling by renin in an incompletely inhibited axis. Indeed, it is reported that during chronic ACE inhibitor treatment, aldosterone levels increase to pretreatment levels even above after some time, despite ongoing inhibition of intravascular angiotensin II production (“aldosterone escape”).\textsuperscript{31} An alternative explanation would be that both renin and aldosterone secretion respond to a common signal generator that is unaffected by ACE blockade. Consequently, the most general inference from these synchrony analyses is that pattern reproducibility is maintained between renin and aldosterone secretion, but the quantitative strength of feedforward drive is remarkably attenuated.

Acknowledgment

We thank Paula Azimi for assistance in the analysis of renin and aldosterone secretion.

References

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