Circadian Rhythm of Urinary Endothelin-1 Excretion in Mild Hypertensive Patients

Yeo-Shin Hwang, Tusty-Jiuan Hsieh, Yau-Jiunn Lee, and Juei-Hsiung Tsai

Endothelin-1 (ET-1) is a potent vasoconstrictive peptide with diverse physiologic actions and has been considered to be involved in the pathogenesis of hypertension. We sought to investigate the role of renal synthesis of ET-1 in the regulation of daily sodium homeostasis and the possible contribution of renal synthesized ET-1 in the pathogenesis of essential hypertension (EHT). Urinary ET-1–like immunoreactivity (ET-1-LI) was measured by a radioimmunoassay after extraction in 23 EHT patients without detectable target organ damage, and in 11 normotensive controls. All study subjects received a controlled diet during an 8-day study period. Urinary and blood samples were collected by four sampling periods/day from the 4th to 6th days, and on the 7th day, study subjects were given an intravenous infusion of 1250 mL normal saline over 2 h. In the basal state, the urinary sodium and ET-1-LI excretions showed diurnal patterns in both the normal and hypertensive groups, and urinary ET-1-LI excretion rate correlated well with urinary sodium excretion rate.

There were no differences found in plasma ET-1 levels, urinary ET-1-LI, and sodium excretion rates between the control and hypertensive groups. After saline infusion, ten hypertensive patients showed nonexaggerated natriuresis, and the 24-h urinary ET-1-LI excretion (47.0 ± 4.0 pmol/day), collected during the day of saline infusion, was significantly lower than that of the control group (86.3 ± 10.0 pmol/day) or the exaggeratedly natriuretic hypertensive patients (91.7 ± 8.4 pmol/day). Our results suggest that renal ET-1 may be responsible for the renal handling of sodium homeostasis, and alteration of renal ET-1 synthesis may be a contributory factor in the pathogenesis of essential hypertension and salt sensitivity.


KEY WORDS: Urinary endothelin-1 excretion, urinary sodium excretion, ambulatory blood pressure monitoring, circadian rhythm, exaggerated natriuresis.
ET-1 may act as a natriuretic factor and play some role in the handling of sodium excretion. Saito and colleagues have shown that urinary ET-1 excretion correlated well with urinary sodium excretion in patients with essential hypertension who received low-, normal-, and high-salt diets. However, no observations have been made concerning the diurnal pattern of urinary ET-1 excretion and the role of renal synthesized ET-1 in regulation of daily sodium homeostasis in normal subjects.

A number of studies have suggested that ET-1 participates in the physiologic regulation of systemic blood pressure (BP) and that alteration of ET production may contribute to the pathogenesis of essential hypertension (EHT). EHT is a syndrome of elevated blood pressure without a known definite etiology. Several proposals have been made to elucidate the possible mechanism of EHT, including increased sympathetic activity, alteration in renin-angiotensin-aldosterone activity, etc. Yet, until now no persuasive conclusions have been made to explain the pathophysiology of EHT. Recently, Hoffman et al reported that patients with EHT had lower urinary ET-1 excretion than control subjects, and suggest that impaired renal synthesized ET-1 may be one pathogenetic factor of EHT. However, Zoccali et al demonstrated that urinary ET-1 excretion was not altered in patients with EHT and was only elevated in hypertensive patients secondary to renoparenchymal diseases. Thus, the relationship between renal ET-1 synthesis and the pathogenesis of EHT is still controversial. However, some studies have shown that inner medullary ET-1 production is markedly reduced in spontaneously hypertensive rats, as compared with control normotensive Wistar-Kyoto rats. Medullary slices from hypertensive Dahl salt-sensitive rats release less ET-1 than those from Dahl salt-resistant rats. These results suggest that renal synthesis of ET-1 may be involved in the pathogenesis of hypertension. To clarify whether renal synthesized ET-1 contributes to the renal handling of sodium excretion and to investigate the possible role of renal ET-1 synthesis in the pathogenesis of EHT, the present study was designed to observe the relationship between urinary ET-1 and sodium excretions and to study the effect of isotonic saline infusion on urinary sodium and ET-1 excretions in patients with EHT.

METHODS

Study Subjects Eleven normotensive subjects and 26 patients with hypertension were included in this study. These normotensive subjects had no history of cardiac disease and had normal cardiac function, as assessed by ultrasonic cardiography (UCG), and none was receiving medical therapy. Hypertensive patients were enrolled after three separate clinic visits where use of a mercury sphygmomanometer had shown office diastolic BP to be > 95 mm Hg. Most of the hypertensive patients were untreated. Two hypertensive patients who were receiving antihypertensive agents were asked to discontinue treatment for 2 weeks before the study. The study protocol was approved by the Ethics Committee of the hospital, and all patients gave written informed consent.

Laboratory Examination Laboratory examinations included chest x-ray (posterior-anterior view), electrocardiography, M-mode, and two-dimensional UCG, as well as studies to exclude secondary or malignant hypertension, diabetes mellitus, renal disease, and hypop- or hyperthyroidism. All control subjects and hypertensive patients underwent blood biochemistry examinations including blood creatinine, cholesterol, triglyceride, creatinine clearance rate, fasting, and 2-h blood sugar after a meal. Concentrations of plasma and urinary sodium, potassium, and chloride were determined in an automatic analyzer (Nova 5, Nova Biochemical, Newton, MA). Serum and urine chemistries were determined by routine laboratory methods.

Noninvasive Ambulatory BP Monitoring Ambulatory BP monitoring (ABPM; Spacelabs, Model 90207, Redmond, WA) was performed for each subject studied on the second study day. This portable device uses a standard cuff, placed around the left upper arm and inflated at regular preset intervals (every 30 min between 6:00 AM and 6:00 PM and every hour between 6:00 PM and 6:00 AM). Systolic and diastolic BP were estimated using the oscillometric method. At the end of the 24-h monitoring period, collected BP and heart rates were unloaded from the memory into a microcomputer for further analysis. Recordings showing an inconsistent increase or decrease in systolic or diastolic BP of > 50 mm Hg without changes in heart rate, and a calculated pulse pressure of < 10 mm Hg, were excluded before analysis. Daytime BP was calculated as the average of the readings between 6:00 AM and 10:00 PM and nighttime BP as the average of the remaining readings. Hypertension was defined as sitting office BP > 140/90 mm Hg and mean 24-h ambulatory BP > 134/90 mm Hg by 24-h ABPM recording. Only stage 1 and II (JNC-V) hypertensive patients were enrolled in the study.

Study Protocol During the 8-day study period, all subjects were admitted to the Kaohsiung Medical College Hospital and had a control diet consisting of 2000 Kcal/day and 100 to 120 mmol/L of sodium. Meals were prepared by the kitchen of the hospital and served at 7:30 and 11:30 AM, and at 5:30 PM. The potassium, protein, carbohydrate, and fat content of the diets were kept constant. The daily amount of ~7 g NaCl was supplied in divided doses in each meal.
Compliance with the prescribed sodium diet was verified in each subject by daily urinary sodium determinations. Dietary water intake was ad libitum for the whole study period and was monitored every 12 h. The study subjects were awakened at 6:00 AM and went to sleep at 10 PM, and were allowed to carry out their normal daily activities. Urine samples were collected during four sampling periods/day (8:00 AM to noon, noon to 6:00 PM, 6:00 PM to 10:00 PM, and 10:00 PM to 8:00 AM) for 3 days (on the 4th to 6th study days). Blood samples were also collected at 8:00 AM, noon, 6:00 PM, and 10:00 PM. On the 7th study day, each subject was challenged with a 1250-mL isotonic saline infusion over a 2-h period. Blood and urine samples were also collected during the day of saline loading. Urine amounts were recorded and an aliquot of urine was stored at -20°C until analysis. Blood samples were collected into prechilled tubes containing aprotinin (500 KIU/mL, Sigma, St. Louis, MO) and ethylene diamine tetraacetic acid (EDTA, Sigma; 1 mg/mL). The plasma was immediately separated by centrifuge and stored at -80°C until assayed.

Radioimmunoassays The plasma and urinary ET-1–like immunoreactivities (ET-1-LI) were determined by a specific ET-1 radioimmunoassay (RIA; Peninsula Laboratories, Inc. Belmont, CA) after extraction, as previously reported.27 Briefly, the plasma (5 mL) or urine (4 mL) was applied to a Sep-Pak C18 cartridge (Waters Associates, Milford, MA) and eluted with 5 mL 60% acetonitrile in 0.1% trifluoroacetic acid. The eluate was lyophilized and reconstituted for RIA. The antibody used for ET-1 cross-reacted with ET-1 (100%), big ET-1 (17%), ET-2 (7%), and ET-3 (7%), and the antibody used for ET-1 cross-reacted with ET-1 (100%), big ET-1 (17%), ET-2 (7%), and ET-3 (7%), and did not react with angiotensin II, vasoactive intestinal peptide, or α-ANP.1–28 The recovery rate of plasma ET-1, extracted through the Sep-Pak C18 column by adding radiolabeled ET-1 to the media, was 61.2% ± 1.2%. The sensitivity of the ET-1 RIA was 0.4 pg/tube, and the 50% intercept was 20 pg/tube. The intra- and interassay coefficients of variations were 9.7% and 10.5%, respectively, over a range of concentrations between 0.1 and 64 pg/tube. Plasma renin activity was also determined by a RIA (Du Pont Company, Billerica, MA).

Statistics Results are expressed as mean ± SD. All data were compared by Student’s t test or analysis of variance (ANOVA) to test for differences among the groups when appropriate. If differences were found by ANOVA, the Scheffé’s F test was used for comparison between individual groups. Linear regression analysis was used to assess the influence on the dependent variable of one independent variable. Differences were considered significant at P < .05.

RESULTS

Clinical Characteristics The total of 37 subjects who completed the study included 26 hypertensive patients (office BP > 140/90 mm Hg and mean 24-h ambulatory BP > 134/90 mm Hg) and 11 normotensive subjects (office BP < 140/90 mm Hg and mean ambulatory BP < 134/90 mm Hg) as a control group. Three hypertensive patients were excluded because two of them had renal function impairment (serum creatinine > 2 mg/dL) and one of them had severe hypertension (mean SBP > 110 mm Hg). Table 1 shows the clinical characteristics of the subjects studied. The male/female ratios, mean ages, creatinine clearance rates, and serum levels of fasting blood sugar, creatinine, cholesterol, and triglycerides were similar between the control subjects and hypertensive patients.

Ambulatory BP Monitoring The mean 24-h ABPM in 11 normotensive subjects was 126 ± 8/79 ± 6 mm Hg, and the mean day and nighttime BP were 131 ± 3/84 ± 2 and 116 ± 4/72 ± 3 mm Hg, respectively. The consecutive hourly systolic and diastolic BP are shown in Figure 1. The circadian variation showed a peak BP at 10:00 AM and nadir at midnight. The standard deviation of BP in the control group was 11 ± 3/8 ± 3 mm Hg. The mean 24-h ambulatory BP in 23 hypertensive patients was 141 ± 7/91 ± 5 mm Hg, and the mean day and nighttime BP were 145 ± 3/93 ± 2 and 139 ± 4/86 ± 3 mm Hg, respectively. The standard deviation of BP in the hypertensive group (13 ± 3/11 ± 3 mm Hg) was similar to those of the control group. The consecutive hourly SBP and DBP patterns, as shown in Figure 1, were similar to those in the normotensive group. The circadian rhythm showed a peak at 11:00 AM and a nadir at 1:00 AM. This result suggested that the circadian rhythm is preserved in hypertensive patients.

Urinary Sodium and ET-1-LI Excretion Rates The mean daily urinary sodium (UNa) and ET-1-LI excretion rates collected at four intervals/day on the 4th to 6th admission days (−3 to −1 days) are shown in Figures 2A, B. The highest UNa excretion rate appeared during 8:00 AM to noon and the lowest during 10:00 PM to 8:00 AM in both the control and hypertensive groups. The mean UNa excretion rate during the midnight period (10:00 PM to 8:00 AM) was only half that of the early morning period (8:00 AM to noon). The urinary ET-1-LI excretion rate was parallel to the UNa excretion in both control and hypertensive subjects. Furthermore, urinary ET-1-LI excretion was significantly correlated with the UNa excretion rate (r = 0.33, P < .001, Fig. 3A) when values from all subjects studied were pooled together. Figure 2 and Table 1 also show that the daily urinary sodium and ET-1
excretion of hypertensive patients, either in divided fractions or total daily amount, were not statistically different from those of the control subjects.

After saline infusion, the collected 1-day UNa and urinary ET-1-Ll excretion rates showed no significant differences between the control group (227.1 ± 26.4 mmol/day and 86.3 ± 10.0 pmol/day, respectively) and the hypertensive patients (239.5 ± 16.0 mmol/day and 73.8 ± 8.8 pmol/day, respectively). The urinary ET-1-Ll excretion rates after saline infusion were significantly increased, compared with the basal state in both the control (39.7 ± 9.9 pmol/day) and hypertensive (34.5 ± 9.0 pmol/day) groups. When urinary sodium excretion was observed during four periods/day, the highest UNa and urinary ET-1-Ll excretions were observed between 6:00 and 10:00 pm and the lowest between 10:00 pm and 8:00 am (Figure 2C, D) in the control group. Only 20.8 ± 3.3% of the infused sodium was excreted within the first 4 h in the control group, whereas sodium excretion during the first 4 h in the hypertensive patients showed two different patterns. Thirteen patients showed exaggerated natriuretic responses, which was defined as the excretion of more than 30% of loaded salt (the upper limit of the normal group) during the initial 4 h of infusion (mean urinary sodium excretion during the first 4 h = 44.4 ± 4.4% of infused saline). The remaining 10 hypertensive patients showed similar urinary sodium excretion rates (mean urinary sodium excretion during the first 4 h = 16.7 ± 2.3% of infused saline). The 24-h urinary ET-1-Ll excretion rates collected during the day of saline infusion were significantly lower in nonexaggerated hypertensive patients (47.0 ± 4.0 pmol/day, P < .05), compared with those of the control group (86.3 ± 10.0 pmol/day) and exaggerated natriuretic hypertensive patients (91.7 ± 8.4 pmol/day). As shown in Figure 3B, the urinary ET-1-Ll excretion rate was significantly correlated with the UNa excretion.

### Table 1. Clinical Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal Controls (n = 11)</th>
<th>Hypertensive Patients (n = 23)</th>
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<tbody>
<tr>
<td>Male/female</td>
<td>7/4</td>
<td>13/10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.2 ± 12.1</td>
<td>48.0 ± 10.3</td>
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<tr>
<td>24-h Ambulatory BP</td>
<td></td>
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<tr>
<td>Mean 24-h (mm Hg)</td>
<td>126 ± 8/79 ± 6</td>
<td>141 ± 7*/91 ± 5*</td>
</tr>
<tr>
<td>Daytime BP (mm Hg)</td>
<td>131 ± 3/84 ± 2</td>
<td>145 ± 3*/93 ± 2*</td>
</tr>
<tr>
<td>Nighttime BP (mm Hg)</td>
<td>116 ± 4/72 ± 3</td>
<td>139 ± 4*/86 ± 3*</td>
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<tr>
<td>CCr (mL/sec)</td>
<td>1.77 ± 0.46</td>
<td>1.72 ± 0.37</td>
</tr>
<tr>
<td>Fasting sugar (mmol/L)</td>
<td>5.3 ± 0.6</td>
<td>5.2 ± 0.6</td>
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<tr>
<td>Serum creatinine (µmol/L)</td>
<td>76 ± 12</td>
<td>88 ± 21</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.62 ± 0.74</td>
<td>4.97 ± 0.81</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.40 ± 0.54</td>
<td>1.53 ± 0.72</td>
</tr>
<tr>
<td>Plasma renin activity (ng/L/sec)</td>
<td>0.51 ± 0.20</td>
<td>0.39 ± 0.29</td>
</tr>
<tr>
<td>Plasma ET-1 (pmol/L)</td>
<td>1.12 ± 0.32</td>
<td>0.80 ± 0.36</td>
</tr>
<tr>
<td>Urinary ET-1 excretion† (pmol/day)</td>
<td>39.7 ± 9.9</td>
<td>34.5 ± 9.0</td>
</tr>
<tr>
<td>Urinary sodium excretion† (mmol/day)</td>
<td>104.1 ± 28.5</td>
<td>105.1 ± 29.1</td>
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</table>

* Data were expressed as mean ± SD.

† The values of urinary ET-1 and sodium excretions were the means of data from three continuous daily collections.

### FIGURE 1. Consecutive hourly SBP and DBP profiles. The circadian variation showed a peak BP at 10:00 AM and nadir at midnight in the control group and a peak at 11:00 AM and nadir at 1:00 AM in the hypertensive group. The standard deviations of BP in the hypertensive group were similar to those in the control group. These results suggest that the circadian rhythm is preserved in hypertensive patients. H/T sys, systolic blood pressures of hypertensive patients; H/T dia, diastolic blood pressures of hypertensive patients; NC sys, systolic blood pressures of normal controls; NC dia, diastolic blood pressures of normal controls.
FIGURE 2. Urinary sodium (A) and ET-1 like immunoreactivity (ET-1-LI) excretion rates (B) during a control experiment. The mean daily urinary sodium (UNa) and ET-1-LI excretion rates on the 4th to 6th admission days (−3 to −1 days) collected by four periods/day were shown. The highest UNa and urinary ET-1-LI excretion rates appeared during 8:00 to 12:00 AM and the lowest during 10:00 PM to 8:00 AM in both the control (□) and hypertensive (■) groups. The mean UNa and ET-1-LI excretion rates during the midnight period (10:00 PM to 8:00 AM) was only half that of the early morning period (8:00 AM to noon). The urinary ET-1 excretion rate was parallel to the pattern of the UNa excretion rate in both control and hypertensive subjects. There was no statistical difference in the urinary sodium and ET-1-LI excretion rates between the control subjects and hypertensive patients. Urinary sodium (C) and ET-1-LI excretion rates (D) were determined during the day of saline infusion. The highest UNa and urinary ET-1-LI excretion rates were observed between 6:00 and 10:00 PM and the lowest between 10:00 PM and 8:00 AM in the control group (□). Thirteen hypertensive patients (□) showed an exaggerated natriuretic response during the initial 4 h of saline infusion, and the other 10 hypertensive patients (■) showed a urinary sodium excretion rate similar to that of the control subjects.
rate during the day of saline infusion (r = 0.588, P < .001) when values from all subjects studied were pooled together. No significant correlation between the plasma ET-1 or plasma renin activity (PRA) and urinary sodium excretion was found (results not shown).

Plasma Levels of Renin Activity and ET-1 The basal plasma levels of plasma renin activity and ET-1 were not significantly different between the control and hypertensive groups (Table 1). Both the plasma renin activity and ET-1 levels were significantly suppressed after saline infusion (Figure 4). When the hypertensive patients were further divided into two groups according to the urinary sodium excretion in response to intravenous saline infusion, the plasma level of renin activity in patients with exaggerated natriuresis was significantly lower than that of the nonexaggeratedly natriuretic hypertensive patients and control subjects (Figure 4), whereas the plasma ET-1 levels of the two hypertensive subgroups were not significantly different (results not shown).

DISCUSSION

The present study has demonstrated that by making use of 24-h ABPM recordings, the circadian patterns of mild to moderate hypertensive patients without target organ damage show the same rhythms as those of normotensive subjects, with a nocturnal fall in blood pressure. The urinary sodium excretion showed a rhythm similar to blood pressure and the urinary ET-1 excretion rate paralleled the urinary sodium excretion rate in both control and hypertensive subjects in the basal state. After saline infusion, urinary ET-1 excretion increased and correlated well with urinary sodium excretion. To our knowledge, this is the first demonstration of the existence of circadian urinary ET-1 excretion and increased urinary ET-1 excretion in response to saline loading in normotensive subjects and in hypertensive patients. Our results indicate that urinary ET-1 may be a physiologic regulator of sodium homeostasis during daily living conditions.

After acute intravenous saline challenge, a subgroup (56.5%, 13/23) of hypertensives showed exaggerated natriuresis during the first 4-h collection period. Exaggerated natriuresis is a well-known biologic phenomenon in patients with essential hypertension.28 The mechanism for exaggerated natriuresis is still not well understood. A suppressed plasma renin-angiotensin-aldosterone system,29,30 an abnormality in
sodium-lithium countertransport,\textsuperscript{31} a decreased cate-
cholamine responsiveness,\textsuperscript{32} and an enhanced natri-
uretic response to an increased plasma ANP\textsuperscript{33} have all
been suggested as possible mechanisms of this phe-
nomenon. The present study demonstrates that en-
hanced urinary excretion of ET-1-LI may be another
contributing factor to the exaggerated natriuresis in
patients with EHT. This result further supports the
idea that renal synthesized ET-1 is responsible for
regulation of sodium balance.

Previous reports have indicated that urinary ET-1
derives mainly from the nephron, in particular, from
the inner medullary collecting duct.\textsuperscript{5} Evidence sup-
porting this conception is based on the finding that
only negligible amounts of labeled ET-1 infused into
the systemic circulation of normal rats could be recov-
ered in the urine.\textsuperscript{34,35} ET-1 synthesized in the tubular
epithelial cells may act in an autocrine or paracrine
manner to affect sodium and water reabsorption.\textsuperscript{8,20}
Although there are two components (vascular and
tubular) of renal ET-1 synthesis with quite different
actions,\textsuperscript{36} research has given evidence that decreased
renal tubular ET-1 synthesis potentially leads to en-
hanced salt and water retention and is involved in the
pathogenesis of hypertension.\textsuperscript{15} More evidence for
decreased renal tubule ET-1 production in hypertension
comes from studies in which inner medullary ET-1
content and synthesis was shown to be greatly re-
duced in hypertensive SHR,\textsuperscript{20} and also from studies of
heterozygous mice with a defective ET-1 gene that are
hypertensive.\textsuperscript{37}

Urinary ET-1 excretion in a subgroup of hyperten-
sive patients with nonexaggerated natriuresis in re-
sponse to intravenous saline infusion was markedly
decreased, compared with the exaggeratedly natri-
uretic hypertensive patients and control subjects. This
result suggests that decreased renal synthesis of ET-1
may be one of the contributing factors of hypertension
and salt sensitivity. Previous reports have shown that
alteration of renal ET-1 synthesis is involved in the
pathogenesis of hypertension.\textsuperscript{18,20–22,37} In view of
these facts, we propose that the nonexaggerated natri-
uretic hypertensive patients may be genetically defec-
tive in renal tubular ET-1 production and that renal
deficiency of the peptide causes sodium and water
retention and salt sensitivity, thereby leading to the
development of hypertension. Recently, Stevens and
Brown demonstrated that ET-1 gene polymorphism is
associated with essential hypertension.\textsuperscript{38} Whether
ET-1 gene polymorphism is related to the renal ET-1
synthesis needs to be clarified by further experiments.

A number of studies have demonstrated that plasma ET-1
levels increased in patients with cardio-
vascular and renal diseases, whereas plasma ET-1
concentrations have not been shown to correlate with
systemic, diastolic, or mean arterial blood pressure.\textsuperscript{39,40}
Instead, plasma ET-1 levels may reflect endothelial cell
injury.\textsuperscript{39,40} That the plasma level of ET-1 in hyperten-
sive patients in the present study was not different
from that of the control group is in accordance with
the hypothesis that plasma ET-1 may not be associated
with the pathogenesis of hypertension, but may reflect
the involvement of cardiovascular injury. Previous
reports have indicated that EHT patients with low
plasma renin activity were associated with an exag-
ggerated natriuretic response to intravenous saline in-
fusion.\textsuperscript{29,30} Our patients with exaggerated natriuresis
also showed suppressed plasma renin activity, com-
pared with that of nonexaggerated EHT patients and
control subjects. The relationship between plasma re-
nin activity and renal ET-1 synthesis was not investi-
gated in the present study. ET-1 has been shown to
inhibit renin secretion in vitro,\textsuperscript{41} whereas ET-1 has
been found to play no relevant regulatory role in renin
secretion and renin gene expression in vivo.\textsuperscript{42}

It is easier to label hypertensive patients as having
an exaggerated or nonexaggerated natriuretic re-
sponse to the saline loading than to differentiate salt-
sensitive and salt-resistant hypertension. We believe
that subgrouping hypertensive patients according to
the natriuretic pattern in response to acute salt loading
may be beneficial in understanding the mechanism of
essential hypertension and may provide some guid-
ance to the pharmacologic intervention in the disease.
In conclusion, the present study has demonstrated
that there exists a circadian urinary ET-1-LI excretion
rhythm as well as a significant correlation between
UNa and urinary ET-1-LI excretions. A subgroup of
hypertensive patients with nonexaggerated natriure-
sis in response to salt loading also showed blunted
urinary ET-1-LI excretion. Our results suggest that
renal ET-1 synthesis may be responsible for renal han-
dling of sodium homeostasis and that alterations of
renal ET-1 synthesis may be a contributing factor in
the pathogenesis of essential hypertension and salt
sensitivity.

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