ENDogenous prostaglandin E₂ appears to play an important role in cardiovascular homeostasis. When administered exogenously, it is a potent vasodilator, but the requirement for intravenous administration and its short duration of action have limited studies to its acute effects. A novel prostaglandin E₂ analogue, CL115347, can be administered transdermally on a long-term basis. The cardiovascular responses to the chronic administration of CL115347 were studied in a double-blind, placebo-controlled trial in 26 subjects with essential hypertension (16 given drug, 10 placebo) maintained on a 100-mEq sodium diet. Administration of CL115347 produced a fall in diastolic blood pressure of 7.8 ± 1.3 mm Hg, compared with a 2.3 ± 1.7 mm Hg fall in controls (p = 0.02), with no change in heart rate. The direct vascular effect of the drug was confirmed by attenuation of the vasoconstrictor response to angiotensin II infusion (13.4 ± 3.1 vs 21 ± 2 mm Hg at 3.0 ng/kg/min; p < 0.05). However, the chronic blood pressure effect of CL115347 was modest. Subjects receiving active drug showed significant compensatory increases in plasma renin, aldosterone, and norepinephrine levels accompanied by sodium retention and kaliuresis. In summary, chronic administration of this prostaglandin E₂ analogue resulted in a modest decrease in blood pressure and antagonism of angiotensin II-mediated vasoconstriction. However, its effects were largely offset by compensatory increases in vasoconstrictor hormones and sodium retention. (Hypertension 8: 489-496, 1986)

KEY WORDS • blood pressure • renin-angiotensin system • catecholamines • sodium retention

ARTERIAL blood pressure is dependent on several factors, including the balance between vasoconstrictor and vasodilator substances. It has been postulated that deficient production of vasodilator hormones such as endogenous prostaglandin E₂ (PGE₂) may underlie the pathogenesis of some patients with essential hypertension. Prostaglandin E₂ is produced locally in the kidney, where it increases renal blood flow and induces natriuresis, and in the vasculature, where it produces vasodilation and reduces the pressor response to angiotensin II (ANG II). In addition, PGE₂ inhibits norepinephrine (NE) release from peripheral nerve endings. Although PGE₂ is an effective hypotensive agent in humans, it must be given intravenously and has a brief duration of action. Thus, the chronic cardiovascular effects of PGE₂ in humans have not been studied previously.

CL115347 is the methyl ester of (±)-15-deoxy-16-hydroxy-16(α/β)-vinyl PGE₂ (Figure 1). In animal models of hypertension it has been shown to be 100 to 250 times more potent than PGE₂ as an antihypertensive, with a prolonged duration of action. It is active when administered orally, intravenously, or transdermally. The availability of this PGE₂ analogue enabled us to examine the cardiovascular, renal, and hormonal response to the chronic administration of PGE₂ to humans with essential hypertension.
overnight fast on the day before randomization and
ed subjects four times daily (0800, 1200, 1600, 2200).
These studies, except for radiography, were repeated
2 to 4 hours of ambulation in the morning following an
(PRA) was measured with the subjects supine and after
at least three times during each of three separate office
visits. None of the subjects had received any antihy-
pertensive agents or prostaglandin inhibitors for at
least 2 weeks before admission. Subjects with sec-
dary hypertension, diabetes mellitus, coronary artery
disease, or other cardiovascular diseases were ex-
cluded. The same double-blind protocol was followed
on an isocaloric diet containing 100 mEq sodium, 70
mEq potassium, and 400 mEq calcium and underwent
the results (greater than the upper limits of normal),
other than findings consistent with left ventricular hy-
pertrophy, were grounds for dismissal from the study.
Subjects and Methods
Twenty-six hypertensive subjects (23 men, 3 wom-
en), aged 18 to 60 years (mean, 38.8 ± 2.5 years),
were prospectively studied in three locations: Boston
(9 subjects), New Haven (7 subjects), and Miami (10
subjects). All had supine, sitting, and standing diastol-
ic blood pressures of 95 to 114 mm Hg determined at
least three times during each of three separate office
visits. None of the subjects had received any antihy-
pertensive agents or prostaglandin inhibitors for at
least 2 weeks before admission. Subjects with sec-
dary hypertension, diabetes mellitus, coronary artery
disease, or other cardiovascular diseases were ex-
cluded. The same double-blind protocol was followed
at all three institutions and was approved by the respec-
tive human subjects committees. All participants gave
informed consent.
On admission to the hospital, subjects were placed
on an isocaloric diet containing 100 mEq sodium, 70
mEq potassium, and 400 mEq calcium and underwent
complete histories and physical examinations. An ex-
tensive laboratory evaluation, including full chemistry
profile, complete blood count with differential, Wes-
tergren sedimentation rate, bleeding time, and urinaly-
sis, and electrocardiography and chest radiography
were also performed. Marked abnormalities in any of
the results (greater than the upper limits of normal),
other than findings consistent with left ventricular hy-
pertrophy, were grounds for dismissal from the study.
These studies, except for radiography, were repeated
at intervals throughout the admission.
Data Collection
Pulse rate and blood pressure were recorded in seat-
ed subjects four times daily (0800, 1200, 1600, 2200).
Daily weights were obtained. Plasma renin activity
(PRA) was measured with the subjects supine and after
2 to 4 hours of ambulation in the morning following an
overnight fast on the day before randomization and
while receiving the study drug. Electrolyte balance and
creatinine clearances were assessed daily after collect-
ion of the run-in period completed the study.
Additional studies were performed in Boston (9 sub-
jects: 5 given drug, 4 placebo) to assess any compen-
satory or secondary hormonal responses, changes in
renal hemodynamics, or pressor responsivity to drug
or placebo. Thus, at 0700 on the third day of the run-in
period, following an overnight fast, an intravenous
catheter was placed in an arm vein with the subject still
supine. At 0800, baseline blood samples were drawn
for measurement of PRA, aldosterone, cortisol, NE,
and epinephrine. The subjects were then ambulated
for 2 hours, after which blood samples again were drawn.
The subjects ate breakfast, returned to recumbency,
and had a second intravenous line placed in the contra-
lateral forearm. After a further 45 to 60 minutes, base-
line blood samples again were drawn for measurement
of PRA, aldosterone, NE, epinephrine, cortisol, sodi-
um, potassium, p-aminohippurate (PAH), and inulin.
Loading doses of PAH (8 mg/kg) and inulin (50
mg/kg) were administered, followed by continuous in-
fusion (PAH, 12 mg/min; inulin, 30 mg/min) through
an infusion pump (IMED, San Diego, CA, USA). After
60 minutes, the baseline blood sampling was repeated
and ANG II infusion (Hypertensin; Ciba Geigy, Summit,
NJ, USA) was begun at a rate of 0.3
ng/kg/min using a Harvard pump (Millis, MA, USA).
Blood pressure was recorded at 2-minute intervals
(Roche Arteriosonde, Nutley, NJ, USA). After 45
minutes, blood sampling was repeated and the ANG II
infusion rate was increased to 1.0 ng/kg/min. Blood
samples were again drawn after 45 minutes, and the
infusion rate was increased to 3.0 ng/kg/min. Follow-
ing the drawing of blood samples at this dosage, the
infusion was terminated and the intravenous catheters
removed. On the next day, subjects received NE infu-
sion, which was begun at a rate of 10 ng/kg/min and
increased to 30 ng/kg/min over 10 to 20 minutes.
Blood pressure was recorded at 2-minute intervals as
already described.
The same posture study and ANG II and NE infu-

FIGURE 1. Structural comparison of prostaglandin E2 and
CL 115347.
sions were repeated on the fifth and sixth day of drug (or placebo) administration.

**Laboratory Procedures**

All blood samples were collected on ice and spun immediately, and the plasma was separated and frozen until assay. Samples for PRA were drawn with ethylenediaminetetraacetic acid as the anticoagulant. Heparin was the anticoagulant in samples for aldosterone and cortisol. Aldosterone, cortisol, and PRA were measured with previously described radioimmunoassay methods. Plasma catecholamines were determined by the modified radioenzymatic method of Peuler and Johnson. Serum and urine sodium and potassium were measured by flame photometry using lithium as the internal standard. Plasma PAH was measured with a Technicon autoanalyzer (Tarrytown, NY, USA).

**Statistical Analysis**

Results are presented as group means ± standard error of the mean (SEM). Blood pressure results were assessed by analysis of variance with sources of variance extracted for investigator, treatment, and treatment by investigator. Hormonal responses were tested with the Wilcoxon rank-sum test. The null hypothesis was rejected when \( p \) achieved a value of 0.05 or less.

**Results**

All 26 subjects who were prospectively randomized completed the double-blind study. Subject characteristics are shown in Table 1. There were no significant differences in the groups with respect to sex, race, age, weight, or blood pressure on randomization. Four subjects were excluded before randomization during the run-in period for failure to maintain diastolic pressure greater than 90 mm Hg (2 subjects), marked abnormalities in blood test results on admission (1 subject), or accidental loss of blinding due to nursing error (1 subject).

Baseline blood pressures (final day of run-in period) were the same in drug-treated and placebo-treated groups (Figure 2; see Table 1). With treatment, the group receiving CL 115347 had a prompt decline in blood pressure. By the second day, the mean sitting systolic pressures for the drug-treated group had declined 7.7 ± 2.2 mm Hg as compared to their own predrug baseline values (\( p < 0.01 \)); sitting diastolic pressure decreased similarly by 8.2 ± 1.4 mm Hg (\( p < 0.01 \)). No significant change was seen in the placebo-treated group (see Figure 2). The blood pressure remained at approximately this level for the drug-treated group throughout the trial. After the second day, the between-group difference became smaller. For the 7 days of treatment, the subjects receiving CL 115347 exhibited an average fall in systolic pressure of 7.4 ± 1.7 mm Hg from predrug levels and 5.8 mm Hg when compared with that in placebo-treated controls (\( p = 0.1 \)), as well as an average fall in diastolic pressure of 7.8 ± 1.3 mm Hg from predrug baseline levels and 5.4 mm Hg when compared with that in placebo-treated controls (\( p = 0.02 \)). Of note, despite a CL 115347 dosage range of 1000 to 3000 \( \mu \)g, no dose-response relationship was seen. The magnitude of hypotensive effect was similar at all three centers. Heart rate was the same in treatment and control groups at baseline and did not change during the study (see Figure 2).

Supine and upright PRA levels are available for 22 subjects (10 given placebo, 12 drug). The remaining four subjects had incomplete data and were excluded from analysis. As can be seen in Figure 3, supine PRA
rose from baseline in response to CL 115347 treatment (from 1.77 ± 0.7 to 2.51 ± 0.7 ng angiotensin I/ml/min; p < 0.05), while subjects receiving placebo showed no significant change (from 1.42 ± 0.4 to 0.88 ± 0.26 ng angiotensin I/ml/min). In response to upright posture, there was a clear trend toward an increase in PRA in subjects receiving active drug, although the overall change was not significantly different from that seen in the placebo-treated group.

Plasma aldosterone levels followed the trend seen with PRA: a significant difference was noted in the supine plasma aldosterone levels in the subjects receiving CL 115347 as compared with that seen in placebo-treated subjects (Table 2). These changes could not be explained by adrenocorticotropic hormone–induced stimulation of aldosterone release because plasma cortisol levels were not different between groups or test periods (see Table 2). Supine epinephrine levels did not change (see Table 2), nor did the epinephrine response to posture (data not shown). As shown in Figure 4, however, plasma NE levels rose in the group receiving CL 115347. During the run-in period, supine NE levels in the drug-treated group exceeded those in the placebo-treated group (268 ± 123 vs 171 ± 32 pg/ml). The apparent difference was due entirely to one subject. By Day 5 of treatment, plasma NE levels were significantly different between drug-treated and placebo-treated groups (235 ± 15 vs 123 ± 22 pg/ml; p = 0.014). In response to upright posture, plasma NE levels were not significantly different from baseline (354 ± 28 vs 292 ± 34 pg/ml at 5 minutes; 268 ± 70 vs 274 ± 37 pg/ml at 2 hours). On Day 5, plasma NE levels in response to upright posture were significantly higher in the drug-treated group at 5 minutes (440 ± 103 vs 263 ± 36 pg/ml; p = 0.029) and at 2 hours (509 ± 105 vs 280 ± 35 pg/ml; p = 0.029).

Pressor responsiveness was assessed with infusions of ANG II. The blood pressure response to ANG II was

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**Table 2. Hormonal and Electrolyte Levels in Supine, Fasting Hypertensive Subjects Treated with Either Placebo or CL 115347**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Run-in (Day -2)</th>
<th>Study (Day +5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 4)</td>
<td>CL 115347 (n = 5)</td>
</tr>
<tr>
<td>PRA (ng ANG I/ml/min)</td>
<td>1.42 ± 0.4</td>
<td>1.77 ± 0.7</td>
</tr>
<tr>
<td>Aldosterone (ng/ml)</td>
<td>16.6 ± 2.7</td>
<td>16.0 ± 3.9</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>171.3 ± 32</td>
<td>267.7 ± 123</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>50.8 ± 20</td>
<td>46.7 ± 27</td>
</tr>
<tr>
<td>Cortisol (μg/dl)</td>
<td>10.0 ± 1.3</td>
<td>11.5 ± 1.6</td>
</tr>
<tr>
<td>Sodium (mEq/dl)</td>
<td>141.0 ± 1.7</td>
<td>139.2 ± 1.3</td>
</tr>
<tr>
<td>Potassium (mEq/dl)</td>
<td>4.3 ± 0.8</td>
<td>4.2 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SEM. All blood samples were drawn in supine, fasting subjects at 0800. Both groups received placebo during the run-in period.

**PRA** = plasma renin activity; **ANG I** = angiotensin I.

*p < 0.05, compared with values in placebo-treated group.
Figure 5. Effect of CL 115347 (n = 5) or placebo (n = 4) on the pressor response to angiotensin II infusion. Both groups received placebo during the run-in period. Asterisk indicates a significant difference (p < 0.05) between groups.

Although inulin clearances did not change between the run-in and study periods for either group (Table 4), sodium retention (as documented by 24-hour urinary sodium excretion) was noted in both groups (cumulative sodium balance by Day 7 was +95.7 ± 34 mEq for drug-treated group and +14.7 ± 57 mEq for the placebo-treated group). Sodium retention was accompanied by kaliuresis in drug-treated subjects (Figure 6). Systemic infusion of ANG II (up to 3 ng/kg/min) attenuated by CL 115347. As can be seen in Figure 5, at infusion rates of 0.3, 1.0, and 3.0 ng/kg/min, there were no differences between drug-treated and placebo-treated groups before randomization. During therapy, however, the subjects receiving CL 115347 became less responsive. This trend was first apparent at the 1.0 ng/kg/min dose (drug vs placebo treatment: 7.6 ± 1.9 vs 10.8 ± 0.9 mm Hg) and became significant at the maximum dose of 3.0 ng/kg/min (13.4 ± 3.1 vs 21 ± 2.0 mm Hg; p = 0.032). This CL 115347-induced attenuation in pressor response appeared to be specific for ANG II since it did not influence the pressor effect of NE infusion (Table 3).

Table 3. Maximal Pressor Response to Norepinephrine Infusion (30 ng/kg/min) in Hypertensive Subjects Receiving Either Placebo or CL 115347

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Placebo (n = 4)</th>
<th>CL 115347 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>Run-in</td>
<td>Study</td>
</tr>
<tr>
<td>+9 ± 3.5</td>
<td>+7.5 ± 0.5</td>
<td>+15.8 ± 6.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>+9 ± 2.7</td>
<td>+6.5 ± 1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM.

Table 4. Inulin and p-Aminohippurate Clearance During Angiotensin II Infusion (ml/min) in Hypertensive Subjects Receiving Either Placebo or CL 115347

<table>
<thead>
<tr>
<th>ANG II infusion (ng/kg/min)</th>
<th>Placebo (n = 4)</th>
<th>CL 115347 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inulin</td>
<td>Run-in</td>
<td>Study</td>
</tr>
<tr>
<td>Baseline</td>
<td>130 ± 13</td>
<td>119 ± 11</td>
</tr>
<tr>
<td>0.3</td>
<td>132 ± 13</td>
<td>123 ± 12</td>
</tr>
<tr>
<td>1.0</td>
<td>134 ± 11</td>
<td>126 ± 13</td>
</tr>
<tr>
<td>3.0</td>
<td>133 ± 11</td>
<td>124 ± 19</td>
</tr>
<tr>
<td>PAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>621 ± 50</td>
<td>652 ± 70</td>
</tr>
<tr>
<td>0.3</td>
<td>627 ± 62</td>
<td>625 ± 52</td>
</tr>
<tr>
<td>1.0</td>
<td>540 ± 36</td>
<td>592 ± 55</td>
</tr>
<tr>
<td>3.0</td>
<td>510 ± 30</td>
<td>543 ± 45</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ANG II = angiotensin II; PAH = p-aminohippurate.
did not influence inulin clearances in either group during either period (see Table 4).

Clearance of PAH, a measure of renal plasma flow, showed a small, nonsignificant downward trend for subjects receiving CL 115347 after 5 days of therapy (from 618 ± 60 to 571 ± 40 ml/min; see Table 4). Infusion of ANG II resulted in a decline in PAH clearances during the run-in periods for both groups. During the study period, CL 115347 administration attenuated the ANG II–induced decline in PAH clearance, but this effect was not statistically significant. We examined the influence of CL 115347 on renal vascular resistance, which was estimated as (mean blood pressure/PAH clearance) × 80 (expressed as ×10³ dyn·sec·cm⁻²). There was no significant difference between groups at baseline. Treatment with CL 115347 did not significantly alter basal renal vascular resistance, which was 14.4 ± 2.4 and 14.4 ± 1.6 × 10³ dyn·sec·cm⁻² during the run-in and study periods, respectively, for the placebo-treated group and 14.4 ± 1.6 and 15.2 ± 1.6 × 10³ dyn·sec·cm⁻² during these periods for the drug-treated group. However, a decline in the renal vasoconstrictor response to ANG II infusion was observed (Table 5). During the 3.0-ng/kg/min ANG II infusion dose, the difference in renal vascular resistances between run-in and study periods in the drug-treated, but not the placebo-treated, group was significant (p < 0.01).

Minor side effects were common and related predominantly to local vasodilatation at the application site (Table 6). These side effects were considered mild by the subjects and did not lead to discontinuation of treatment. Three subjects reported myalgias, and one required a dosage reduction from 3000 to 100 µg/day. The drug was stopped for 12 hours, then restarted at a maximum dose of 2000 µg/day without recurrence of rash. A transient flulike syndrome with abdominal cramping and diarrhea developed in a subject receiving 3000 µg/day acquired a blotchy, macular rash. The drug was stopped for 12 hours, then restarted at a maximum dose of 2000 µg/day without recurrence of rash. A transient flulike syndrome with abdominal cramping and diarrhea developed in a subject receiving 3000 µg/day. The drug was stopped for 12 hours, then restarted at a maximum dose of 2000 µg/day. Other complications were reported in subjects receiving placebo. No other complications were reported in subjects receiving placebo.

### Discussion

The present study was designed to evaluate the cardiovascular, renal, and endocrine effects of chronic PGE₂ analogue administration in humans. To our knowledge, this is the first such study. Previous studies on the acute administration of PGE₂ to normotensive humans reported decreases in blood pressure of 10 to 34% that were accompanied by increases in heart rate of 20 to 40%. As shown in Figure 2, the effect of CL 115347 on diastolic blood pressure was modest but sustained. There was no change in heart rate. This response was not dose-dependent over the narrow range of dosages studied.

Our study demonstrates that chronic administration of PGE₂ analogue resulted in a modest blood pressure effect but stimulated a number of renal and hormonal responses that offset the vasodilator effects of the drug. As shown in Figure 3, PRA in the drug-treated group

### Table 5. Percentage Change in Renal Vascular Resistance (×10³ dyn·sec·cm⁻²) as Compared to Baseline During Angiotensin II Infusion in Hypertensive Subjects Receiving Either Placebo or CL 115347

<table>
<thead>
<tr>
<th>ANG II infusion (ng/kg/min)</th>
<th>Placebo (n = 4)</th>
<th>CL 115347 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-in</td>
<td>Study</td>
</tr>
<tr>
<td>0.3</td>
<td>+ 10.4 ± 5</td>
<td>+ 8.6 ± 1.4</td>
</tr>
<tr>
<td>1.0</td>
<td>+ 35.4 ± 13</td>
<td>+ 26.2 ± 1.9</td>
</tr>
<tr>
<td>3.0</td>
<td>+ 55.3 ± 18</td>
<td>+ 51.7 ± 4.5</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ANG II = angiotensin II.

*p < 0.01, compared with corresponding run-in period.

### Table 6. Adverse Effects in 26 Hypertensive Subjects Receiving Either Placebo or CL 115347

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Placebo (n = 16)</th>
<th>CL 115347 (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea, cramping</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Myalgias</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Induration*</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Localized flushing (hyperemia)*</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Generalized flushing</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Mood changes</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Burning skin</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*At application site.
rose 42%, as compared with that seen during the run-in period, and 285% in placebo-treated controls, as compared with that seen during the study period (p < 0.05). This increase in PRA could result from direct stimulation of renin release by the PGE₂ analogue or an indirect response to hypotension, or both. The relationship between the increase in PRA and PGE₂ activity has been supported by the observation that administration of the prostaglandin synthetase inhibitor indomethacin to sodium-depleted hypertensive humans blocked the rise in PRA.¹⁵ Whatever the mechanism, the increase in PRA was accompanied by maintenance of an elevated aldosterone level in the drug-treated group while the placebo-treated group experienced a concomitant fall (see Table 2).

The drug-treated subjects showed significant sodium retention and kaliuresis compared with placebo-treated controls, as compared with that seen during the study period. Although some sodium retention also occurred in the placebo-treated group, the drug-treated group demonstrated a significant increase (see Table 2), consistent with the modest initial sodium retention in the placebo-treated group is interesting. Our interpretation is that the subjects were not in complete sodium balance at the completion of the run-in period. By Day 3, however, balance was achieved in the placebo-treated group, as evidenced by steady state urinary sodium excretion and concomitant falls in PRA and aldosterone in these subjects. Despite additional sodium retention, the drug-treated group maintained elevated PRA and aldosterone levels.

This increased activity of the renin-angiotensin system seen in the CL 115347-treated subjects occurred despite sodium retention and represents an effect of chronic drug administration. Since no change was seen in plasma cortisol or serum potassium levels in either group (see Table 2), increased adrenocorticotropic hormone levels or hyperkalemia cannot explain the aldosterone responses.

Plasma NE levels (both supine and in response to upright posture) also were significantly elevated by administration of CL 115347 (see Figure 4). This finding is somewhat surprising in view of data that PGE₂ depresses catecholamine release from adrenal gland and peripheral nerve endings of normal animals in response to stimulation, although it has no effect on the spontaneously hypertensive rat.⁶ We interpret this response to be the result of indirect or direct stimulation of NE release by CL 115347, but we cannot exclude an effect of CL 115347 on NE clearance.

To observe the direct vascular effects of CL 115347, we performed graded ANG II infusions in nine subjects (5 given drug, 4 placebo). Previous acute studies on PGE₂ and PGE₃ have demonstrated that these substances blunted the hypertensive response to ANG II.¹⁻³ As shown in Figure 5, a reduction in the pressor response to ANG II, readily apparent at the highest dose, was seen in the group receiving active drug for 5 days (p < 0.05). Interestingly, CL 115347 did not influence the pressor response to exogenous noradrenaline, suggesting a somewhat specific effect on ANG II–mediated vasoconstriction. Inulin and PAH clearances also were performed during ANG II infusion, as shown in Table 4. Administration of CL 115347 appeared to attenuate the fall in renal plasma flow (as measured by PAH) in response to ANG II. Inulin clearance, representing glomerular filtration rate, did not change in either group. Thus, CL 115347 reduced vascular responsiveness to infused ANG II in the peripheral circulation, including the renal vasculature.

As stated earlier, previous studies have demonstrated that PGE₂ infusion can result in tachycardia. This response has been attributed to a direct chronotropic effect⁶⁻¹³ or, alternatively, considered a baroreceptor reflex response to hypotension.¹¹⁻¹⁴ Our subjects did not manifest tachycardia at any time during this study. Animal studies with CL 115347 revealed only modest
increases in heart rate (5–10%) and showed no direct positive chronotropic effects. We interpret these findings to indicate that unlike PGE₂, CL 115347 has no direct cardiac effects and produced insufficient hypotension in our subjects to stimulate a tachycardiac response.

Transdermal application was chosen for use in this study because this route has been shown to yield greater potency and duration of action than intravenous or oral administration in animal models. Side effects in our subjects were those that would be expected from a PGE₂ analogue: they were primarily related to local vasodilatation at the site of drug application (e.g., flushing, induration, erythema). In general, the drug was well tolerated with adequate subject acceptance.

This report includes prospective data from three centers. The protocols were prospectively designed and were the same with respect to duration, days on drug or placebo, diet, and collection of vital signs. Differences included the collection of additional data in Boston with respect to hormones, urinary electrolytes, and assessment of vascular responses to ANG II. The drug dosage differed over a narrow range, but the blood pressure responses were remarkably similar at all centers.

In conclusion, chronic administration of CL 115347, the first PGE₂ analogue available for long-term study in humans, produced a modest reduction in blood pressure. We postulate that this response is limited by compensatory increases in vasopressor hormonal systems and renal sodium retention. Because it produced several of the same compensatory responses seen with other direct vasodilators, CL 115347 does not appear to be useful as an agent for monotherapy of hypertension. However, its effectiveness in combination with other agents, such as β-blockers and diuretics, merits further study, as does its use in other disease states, such as congestive heart failure or peripheral vascular disease.

**Acknowledgment**

We thank Dr. Norman Hollenberg for his generous assistance in determining PAH and inulin clearances in our patient samples.

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