Effect of Ganglion-Blocking Agents on Renin Release in Hypertensive Patients

By Yoshihiro Kaneko, M.D., Tadanao Takeda, M.D., Takao Ikeda, M.D., Hitoshi Tagawa, M.D., Masao Ishii, M.D., Yutaka Takabatake, M.D., and Hideo Ueda, M.D.

ABSTRACT

In 18 patients with benign essential hypertension, renin release during reduction of arterial pressure due to sodium nitroprusside infusion was measured before and after administration of ganglion-blocking agents (pentolinium or trimethaphan). In 12 patients, renin release induced by reduction in pressure was significantly reduced but not abolished by ganglion blockade. Simultaneously, ganglion blockade significantly reduced renal vascular resistance (RVR) and almost abolished a decrease in renal blood flow (RBF) due to hypotension. In 6 other patients in whom no significant renin release resulted from hypotension, ganglion blockade caused little changes in renin release, RVR or RBF. The results support the hypothesis that renal sympathetic nerve activity is a factor in variations in renin release in patients with essential hypertension.

Following ganglion blockade in the responsive patients, the significant reciprocal correlation between renal venous renin activity and sodium excretion rate shifted but still persisted, suggesting that the renin-releasing mechanism related to sodium excretion may be independent of innervation. On the other hand, the correlation between renin activity and the degree of reduction in pressure was insignificant after ganglion blockade. It is concluded that two intrarenal mechanisms, nerve-dependent and nerve-independent, are involved in renin release due to reduction in pressure.

Ganglion blockade also exerted an inhibitory effect on renin release due to hypotension in 4 normotensive subjects and 5 patients with renovascular hypertension.

ADDITIONAL KEY WORDS sympathetic nerve activity renal blood flow renal vascular resistance sodium excretion renal nerves essential hypertension renovascular hypertension

In a previous paper (1), we showed that variations in renin release in response to acute reduction of arterial pressure by sodium nitroprusside in patients with essential hypertension were associated with variations of changes in renal blood flow and in renal vascular resistance during reduction in pressure, and we suggested that renal sympathetic nerve activity may be a factor in the variations in renin release. To confirm the assumption, the present study examines the effect of ganglion-blocking agents on renin release during reduction of arterial pressure in patients with essential hypertension. The effect of ganglion-blocking agents was studied also in normotensive subjects and in patients with renovascular hypertension.

Methods

Studies were performed on 27 hospitalized normotensive and hypertensive patients. Normotensive subjects, 2 men and 2 women aged 19 to 32 years, showed no evidence of significant cardiovascular disease, and their arterial blood pressure ranged from 118/70 to 140/80 mm Hg on admission. Patients with benign essential hypertension, 11 men and 7 women aged 18 to 65 years, had neither a detectable cause of hypertension nor a syndrome of malignant hypertension.
after thorough examinations including pyelography and renal arteriography; their arterial pressure ranged from 160/90 to 228/144 mm Hg on admission. Patients with renovascular hypertension were 3 men and 2 women aged 15 to 54 years; their arterial pressure ranged from 180/90 to 210/140 mm Hg. The diagnosis of renovascular hypertension was established by demonstration of severe stenotic lesions of the renal artery by aortography and of an ischemic pattern in split renal function studies (Rapoport's test). Four patients had unilateral renal artery stenosis and one patient had severe stenosis on one side and slight stenosis on the other. In four patients, the diagnosis was confirmed later by relief of hypertension after surgical treatment; in one patient surgery is pending. None of the patients included in this study showed clinical evidence of heart or kidney failure.

The subjects had been on a normal diet containing from 130 to 200 mEq of sodium daily for at least 1 week, and had fasted for about 5 hours at the time of measurements performed in the supine position, usually between 2 and 5 o'clock in the afternoon. All medication, except for small amounts of sedatives, had been discontinued at least 1 week before the study. Renal and systemic venous blood for renin assay were collected simultaneously by the method previously described (1). In patients with renovascular hypertension, venous blood from the involved kidney was collected. In all of the patients with essential hypertension, urine samples were collected for approximately 10 minutes from the bladder by the method described previously (1), and renal blood flow (RBF) and sodium excretion rate were measured simultaneously with the measurement of renin activities in renal and systemic venous plasma. RBF was measured by the Fick principle using para-aminohippurate, and sodium by flame photometry. Brachial arterial blood pressure was measured by auscultation every 2 or 3 minutes, and mean arterial pressure (diastolic plus one-third of pulse pressure) was calculated.

Control samples of renal and systemic venous blood and urine were collected after at least 30 minutes of resting in the supine position. Thereafter, sodium nitroprusside dissolved in physiological saline was infused intravenously at a rate of 0 to 80 \( \mu \text{g} / \text{min} \), and mean arterial pressure was maintained at levels almost comparable to those in the hypotensive periods before ganglion-blocking agents were given. During the hypotensive periods after ganglion blockade, two more samplings of blood and urine were usually made. During these periods, the effect of ganglion-blocking agents was evident from markedly diminished or almost abolished cold pressor responses.

Renin activity of renal and systemic venous plasma was measured by the method described previously (2). The normal range of renal and systemic venous plasma for people on a normal diet, measured by this method in the supine position, was 8.1 ± 5.6 (2 SD) and 6.4 ± 4.6 ng angiotensin equivalent/ml plasma, respectively (2). A difference in renin activity between individual plasma samples was considered significant when it exceeded 36% and 5 ng/ml (2). The differences in the means were tested by Student's \( t \)-test.

**Results**

**EFFECTS OF GANGLION-BLOCKING AGENTS ON RENAL RELEASE DUE TO REDUCTION OF ARTERIAL PRESSURE IN PATIENTS WITH ESSENTIAL HYPERTENSION**

After control samplings were made, sodium nitroprusside was infused into 18 patients with essential hypertension to stimulate renin release. Reduction of average mean arterial pressure from 125 to 93 mm Hg caused significant increase of renin activity in renal venous plasma in 12 and no significant change in 6 of the 18 patients. As in the previous report (1), the patients were classified into two groups on the basis of renal responsiveness: 12 renin-responsive patients who showed significant increase in renin activity exceeding 36% and 5 ng/ml following reduction in pressure and 6 renin-unresponsive patients who showed no significant change in renin activity. In the responsive patients, there was also a significant increase in the renal-systemic difference in renin activity (\( \Delta \text{ARA} \), \( P < 0.001 \)) and in the products of \( \Delta \text{ARA} \) and RPF (\( P < 0.01 \)), calculated as an index of the amount of renin released from the kidney (2).
TABLE 1
Effects of Ganglion-Blocking Agents in Twelve Renin-Responsive Patients with Essential Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Before ganglion blockade (1)</th>
<th>After ganglion blockade (2)</th>
<th>Difference (1) vs (2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>169/103</td>
<td>123/81</td>
<td>115/82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>125 ± 6.3</td>
<td>95 ± 5.3</td>
<td>93 ± 5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRA (ng/ml)</td>
<td>16.2 ± 3.2</td>
<td>63.1 ± 10.0</td>
<td>34.7 ± 7.0</td>
<td>28.4 ± 7.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SRA (ng/ml)</td>
<td>12.8 ± 2.6</td>
<td>34.2 ± 7.5</td>
<td>26.3 ± 6.5</td>
<td>7.8 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>∆ RA (ng/ml)</td>
<td>3.3 ± 0.8</td>
<td>28.9 ± 5.8</td>
<td>8.3 ± 2.8</td>
<td>20.6 ± 5.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>∆ RA × RPF (µg/min)</td>
<td>1.90 ± 0.44</td>
<td>12.97 ± 3.74</td>
<td>4.85 ± 2.04</td>
<td>8.12 ± 3.51</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>1013 ± 84</td>
<td>730 ± 82</td>
<td>940 ± 65</td>
<td>210 ± 47</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>U Map (µEq/kg/min)</td>
<td>2.16 ± 0.25</td>
<td>1.35 ± 0.32</td>
<td>0.92 ± 0.22</td>
<td>0.43 ± 0.20</td>
<td>NS</td>
</tr>
<tr>
<td>RVR (mm Hg/ml/min)</td>
<td>0.139 ± 0.019</td>
<td>0.166 ± 0.035</td>
<td>0.107 ± 0.013</td>
<td>0.050 ± 0.029</td>
<td>NS</td>
</tr>
</tbody>
</table>

Percent
36.7 ± 12.3 < 0.005

Values are means ± se. BP = blood pressure; MAP = mean arterial pressure; RRA = renin activity of renal venous plasma; SRA = renin activity of systemic venous plasma; ∆ RA = renal-systemic difference of renin activity; RPF(B)F = renal plasma (blood) flow; RVR = renal vascular resistance; NS = not significant. See Methods for details.

during reduction in pressure (Table 1). In the unresponsive patients, reduction in arterial pressure to a comparable extent caused no significant increase in ∆RA and in ∆RA × RPF (Table 2).

After infusion of sodium nitroprusside was discontinued, pentolinium was given intravenously or infusion of trimethaphan was started. Following ganglion blockade, the infusion of sodium nitroprusside was repeated at a decreased rate to maintain mean arterial pressure at levels comparable to those in the hypotensive periods before ganglion blockade, and renin activity of renal and systemic venous plasma was remeasured. In the responsive patients, renal venous renin activity, ∆RA and ∆RA × RPF during reduction in pressure were significantly smaller after ganglion blockade than before blockade Table 1). No significant difference was noted in the effect on renin activity between pentolinium and trimethaphan. In some cases, reduction of arterial pressure was continued following termination of the infusion of trimethaphan by increasing the rate of infusion of sodium nitroprusside; renal venous renin activity increased.
to near the levels before ganglion blockade, more than 20 minutes after the termination of trimethaphan infusion. In other control observations, reduction of arterial pressure by sodium nitroprusside was maintained for about 90 minutes without giving ganglion-blocking agents, and renin activity was measured several times; no significant change occurred during the hypotensive periods. In the unresponsive patients, there was no significant difference between the values for renal venous renin activity, ΔRA and ΔRA × RPF during reduction in pressure before, and those after, ganglion blockade (Table 2).

**EFFECTS OF GANGLION-BLOCKING AGENTS ON RENAL BLOOD FLOW AND RENAL VASCULAR RESISTANCE**

During reduction in pressure before ganglion blockade, total renal vascular resistance (mean arterial pressure ÷ RBF) tended to increase, and RBF decreased significantly \( (P < 0.005) \) in the renin-responsive patients (Table 1), while renal vascular resistance tended to decrease and RBF was not significantly changed in the renin-unresponsive patients (Table 2); the results confirmed the former findings (1).

After ganglion blockade in the responsive patients, renal vascular resistance decreased markedly and there was no significant decrease in RBF during reduction in pressure; renal vascular resistance in percent was significantly \( (P < 0.025) \) smaller and RBF was significantly \( (P < 0.005) \) greater than those during reduction in pressure before ganglion blockade (Table 1). In the unresponsive patients, ganglion-blocking agents caused no significant change either in renal vascular resistance or in RBF (Table 2).

**EFFECTS OF GANGLION-BLOCKING AGENTS ON THE CORRELATIONS OF RENAL VENOUS RENIN ACTIVITY WITH SODIUM EXCRETION RATE AND WITH DEGREE OF REDUCTION IN PRESSURE**

Before ganglion blockade in the 12 renin-responsive patients, a significant reciprocal correlation was found between renal venous renin activity and sodium excretion rate measured simultaneously during 24 hypotensive periods, when compared both on the logarithmic scale \( (r = -0.54, P < 0.01, \text{Fig. 1}) \). After ganglion blockade, there was also a significant reciprocal correlation between renin activity and sodium excretion rate measured during 24 hypotensive periods in the same subjects \( (r = -0.59, P < 0.005) \) but the regression line shifted downwards, as shown in Figure 1. During the same hypotensive periods before ganglion blockade, there was a significant correlation between renal venous renin activity expressed in terms of logarithms and the degree of reduction in pressure expressed in terms of \( \Delta \text{MAP/MAP} \) \( (r = 0.53, P < 0.01) \), as observed in the previous report (1). The correlation, however, became less \( (r = 0.20) \) and insignificant after ganglion blockade.

**EFFECT OF GANGLION-BLOCKING AGENTS IN NORMOTENSIVE SUBJECTS AND IN PATIENTS WITH RENOVASCULAR HYPERTENSION**

In four normotensive subjects and five...
GANGLION BLOCKADE AND RENIN RELEASE

TABLE 3
Effects of Ganglion-Blocking Agents in Four Normotensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>During reduction in pressure</th>
<th>Percent difference (1) vs (2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before ganglion blockade (1)</td>
<td>After ganglion blockade (2)</td>
<td></td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>135/73</td>
<td>109/52</td>
<td>106/54</td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>94 ± 2.9</td>
<td>71 ± 3.0</td>
<td>72 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>RRA (ng/ml)</td>
<td>9.5 ± 2.0</td>
<td>44.8 ± 13.9</td>
<td>19.0 ± 4.0</td>
<td>46.3 ± 17.1 NS</td>
</tr>
<tr>
<td>SRA (ng/ml)</td>
<td>7.8 ± 1.3</td>
<td>26.8 ± 10.5</td>
<td>14.5 ± 3.3</td>
<td>36.3 ± 15.6 NS</td>
</tr>
<tr>
<td>ΔRA (ng/ml)</td>
<td>1.6 ± 1.0</td>
<td>18.0 ± 6.7</td>
<td>4.5 ± 1.9</td>
<td>71.5 ± 18.4 &lt;0.05</td>
</tr>
</tbody>
</table>

Values are means ± se; abbreviations same as in Table 1. See Methods for details.

TABLE 4
Effects of Ganglion-Blocking Agents in Five Patients with Renovascular Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>During reduction in pressure</th>
<th>Percent difference (1) vs (2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before ganglion blockade (1)</td>
<td>After ganglion blockade (2)</td>
<td></td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>186/109</td>
<td>149/85</td>
<td>142/90</td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>134 ± 8.5</td>
<td>106 ± 5.4</td>
<td>107 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>RRA* (ng/ml)</td>
<td>28.8 ± 6.0</td>
<td>133 ± 41.3</td>
<td>52.4 ± 12.9</td>
<td>55.8 ± 5.8 &lt;0.001</td>
</tr>
<tr>
<td>SRA (ng/ml)</td>
<td>20.6 ± 4.4</td>
<td>55.8 ± 14.2</td>
<td>30.8 ± 5.2</td>
<td>39.0 ± 7.8 &lt;0.01</td>
</tr>
<tr>
<td>ΔRA (ng/ml)</td>
<td>8.2 ± 2.0</td>
<td>77.2 ± 28.1</td>
<td>21.6 ± 7.9</td>
<td>67.6 ± 5.5 &lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± se; abbreviations same as in Table 1. See Methods for details.

*Renin activity of venous plasma from the involved kidney.

patients with renovascular hypertension, renin activity of renal venous plasma and the renal-systemic difference of renin activity during reduction of arterial pressure before, were compared with those after, ganglion blockade. In normotensive subjects, renal venous renin activity and ΔRA were smaller after ganglion blockade than before; the difference in renal venous renin activity was not significant, but in ΔRA it was significant (P < 0.05) when compared in percent (Table 3). In patients with renovascular hypertension, the values for renal venous renin activity and ΔRA for the involved kidney after ganglion blockade were significantly (P < 0.001) smaller than those before ganglion blockade when compared in percent (Table 4).

Discussion

When values before were compared with those after ganglion blockade in the renin-responsive patients with essential hypertension, renin release during reduction in arterial pressure due to the infusion of sodium nitroprusside, estimated by ΔRA × RPF, was significantly smaller after ganglion blockade. Although the dose of sodium nitroprusside infused was less after ganglion blockade than before blockade (Table 1), the results seem to indicate that ganglion blockade caused a significant decrease in renin release induced by reduction in pressure, since it has been shown that renin release during reduction in pressure by sodium nitroprusside is not dependent on the dose of sodium nitroprusside infused but is dependent on the degree of reduction in pressure (1), and the degree of reduction in pressure before and after ganglion blockade was almost comparable (Table 1). In the renin-responsive patients, ganglion blockade also caused a significant decrease in renal vascular resistance and almost abolished the decrease in RBF induced by reduction in pressure. The findings appear to give evidence to the former assumption (1) that an increase in renin release and a decrease in RBF induced by reduction in pressure in renin-responsive patients are associated with activa-

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tion of renal sympathetic nerve activity caused reflexly by reduction in pressure. In the renin-unresponsive patients with essential hypertension, ganglion blockade had little effect on renin release, renal vascular resistance or RBF, suggesting that renal sympathetic nerve activity had already been diminished before ganglion-blocking agents were given. The findings confirm the assumption (1) that the suppressed renin release in patients with essential hypertension is associated with reduced renal sympathetic nerve activity. These results support the hypothesis that renal sympathetic nerve activity is a factor in the variations in renin release in patients with essential hypertension.

The inhibitory effect of ganglion blockade on renin release induced by reduction in arterial pressure was observed also in normotensive subjects and patients with renovascular hypertension. The results are in accord with the observations of Bunag and associates (3), who found in dogs that ganglion blockade prevented renin release induced by hemorrhage, and those of Božović and Casterfors (4), who found in rats that ganglion blocking prevented an increase of plasma renin activity during exercise. The results are also consistent with the observations in dogs that local anesthesia of the renal nerves (3, 5) or renal denervation (6-9) inhibited or slowed renin release due to hemorrhage (3, 5), salt depletion (7-9) or reduction in renal perfusion pressure (6), and with those in man that adrenergic receptor-blocking agents inhibited a rise in plasma renin activity due to upright posture or administration of diazoxide, ethacrynic acid or theophylline (10). It seems evident that the renal sympathetic nervous supply is importantly connected with the renin releasing mechanism of the kidney.

On the other hand, there have been recent reports demonstrating that patients with transplanted, denervated kidneys can manifest significant increase in plasma renin activity in response to upright posture (11, 12) or sodium deprivation (12, 13). The increase in plasma renin activity may be due, in part, to the activity of regenerating adrenergic nerve fibers in the transplanted kidney (9, 14). However, in the present study, renin activities in both systemic and renal venous plasma during reduction in pressure were significantly higher even after ganglion blockade than in the control period in the renin-responsive patients with essential hypertension (Table 1; \( P < 0.01 \) and \( P < 0.005 \), respectively) and in normotensive subjects (Table 3; \( P < 0.05 \) and \( P < 0.025 \), respectively). The results suggest that blockade of the nervous supply to the kidney cannot completely abolish renin release. A similar conclusion was drawn previously by Brubacher and Vander (8) from observations in dogs deprived of sodium.

The significant reciprocal correlation between renal venous renin activity and sodium excretion rate observed during reduction in pressure before ganglion blockade in the responsive patients with essential hypertension is consistent with other observations during reduction of renal perfusion pressure in dogs (15) and with those during sodium depletion in humans (16, 17). The present study demonstrates further that the significant correlation persists also after ganglion blockade, suggesting that the renin-releasing mechanism of the kidney related to sodium excretion is independent of innervation. The findings that renin release during reduction in pressure was significantly reduced but was not abolished by ganglion blockade and that the correlation between renal venous renin activity and the degree of reduction in pressure became insignificant indicate that two intrarenal mechanisms, nerve-dependent and nerve-independent, are involved in renin release induced by reduction in pressure; the proportion of nerve-dependent and nerve-independent renin release may be roughly presumable from Figure 1. It appears possible that nerve-independent renin release occurs by stimuli from the macula densa (18, 19), while nerve-dependent release occurs by stimuli from the stretch receptors (20, 21) located in the afferent arterioles or directly from the juxtaglomerular cells (22). The hypothesis is compatible with recent reports that the sympathetic nerve fibers are not seen in
association with tubules (23) or in close relation to the macula densa (24, 25), while they are richly distributed to the juxtaglomerular arterioles (23, 24, 26).

References
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MASAO ISHII, YUTAKA TAKABATAKE and HIDEO UEDA

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