Reflex control of renin release in essential hypertension

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Summary

1. The reflex control of renin release was studied in subjects with essential hypertension by comparing the effects of a variable-pressure neck chamber and head-up tilting.

2. Increase in carotid sinus transmural pressure (obtained by reducing tissue pressure outside the carotid sinus by 34 ± 3 mmHg) decreased mean arterial pressure by 16 ± 2 mmHg, but did not reduce significantly the renal venous–arterial difference in plasma renin activity. Likewise decrease in carotid sinus transmural pressure (obtained by increasing tissue pressure outside the carotid sinus by 39 ± 2 mmHg) increased mean arterial pressure by 14 ± 3 mmHg, but caused only a very slight increase in the renal venous–arterial difference in plasma renin activity.

3. Passive tilting reduced mean arterial pressure by 9 ± 1 mmHg. In this circumstance the renal venous–arterial difference in plasma renin activity increased significantly and markedly.

4. It is concluded that in essential hypertension the carotid sinus baroreceptors, though active in blood pressure control, do not exert a major influence on renin release. In these patients reflex increase of renin during tilting is apparently mediated through other receptors than those in the carotid sinuses.

Key words: carotid baroreceptors, head-up tilting, low-pressure receptors, plasma renin activity, variable-pressure neck chamber.

Introduction

In recent years there has been a growing body of evidence from animal experiments as to the importance of neural factors in control of renin secretion (see Davis & Freeman, 1976). It has also been found that this neural influence on renin secretion is under reflex modulation, though some disagreement still exists as to the relative importance of the receptors in the low- and high-pressure areas (Bunag, Page & McCubbin, 1966; Hodge, Lowe & Vane, 1966; Hodge, Lowe, Ng & Vane, 1969; Schmid, 1972; Brennan, Henninger, Jochim & Malvin, 1974; Mancia, Romero & Shepherd, 1975; Schrier, Reid, Berl & Earley, 1975; Zehr, Hasbargen & Kurtz, 1976).

In contrast with the extensive information available in animals, information on the neural control of renin release in man is limited to responses to the upright position and injection of frusemide, which are both largely reduced by \( \beta \)-adrenoreceptor blockers (Michelakis & McAllister, 1972; Leonetti, Mayer, Morganti, Terzoli, Zanchetti, Morselli, Di Salle & Chidsey, 1975). Nothing is known on reflex control of renin in man. This lack of information includes subjects with essential hypertension, despite the fact that neural autonomic influences on one side, and renin derangements on the other, are still being regarded as possible causative or maintaining factors (Laragh, Baer, Brunner, Buhler, Sealey & Vaughan, 1972; Zanchetti & Bartorelli, 1977; Zanchetti, Stella, Leonetti, Morganti & Terzoli, 1976).

We performed the present study in subjects with essential hypertension to gain information on the reflex control of renin release exerted by the
carotid sinus baroreceptors, and on the possible difference with the control exerted from the low-pressure receptor area. To this aim, the response to selective increase and decrease in carotid sinus transmural pressure, obtained by using a neck-chamber device, were compared with the responses induced by a more diffuse stimulus, such as passive head-up tilting.

Methods

The subjects of the present study were 11 hospital in-patients (six male, five female), age range 28–56 years, in all of whom diastolic blood pressure was greater than 100 and less than 120 mmHg. Patients were included in the study if (a) catheterization of renal arteries and veins was required as diagnostic procedure, to investigate the possible existence of unilateral renal disease, (b) a diagnosis of essential hypertension was reached, (c) no renal or cardiac failure was present, (d) no symptoms of coronary, cerebral or other vascular insufficiency had ever occurred, (e) no major diseases other than the hypertension were diagnosed and (f) there had been no treatment with cardiovascular drugs during the preceding 3 weeks. The protocol has been approved by the Ethical Committee of our Institution, and all patients gave free consent to the procedure after having had the nature and the purpose of the investigation explained to them.

To increase and decrease the stimulus to the carotid sinus baroreceptors we employed the neck-chamber method described in a previous study (Ludbrook, Mancia, Ferrari & Zanchetti, 1977). In principle the method allows prompt and sustained application of negative and positive pneumatic pressures to the neck, with linear transmission of respectively 64% and 86% of the pressures to the tissues outside the carotid sinuses. Application of these pressures can therefore increase and decrease carotid sinus transmural pressure with resulting increase and decrease in the baroreceptor activity.

Haemodynamic measurements

We measured pulsatile aortic blood pressure by a catheter percutaneously introduced through the right femoral artery and a strain-gauge transducer positioned at the level of the right atrium. Mean arterial pressure was obtained by integration of the pulsatile signal over periods of 10 s, and heart rate by a cardiotachometer triggered by the R wave of an electrocardiogram. The pressure within the neck chamber was also measured by a strain-gauge transducer via a connecting rigid polyethylene tube. The measurements were displayed on a Grass Polygraph.

Plasma renin activity

We measured plasma renin activity by radioimmunoassay for angiotensin I, according to the method described by Haber, Koerner, Page, Kliman & Purnode (1969), with modifications mentioned in a previous study of our group (Richardson, Stella, Leonetti, Bartorelli & Zanchetti, 1974). We withdrew blood samples (5 ml) for plasma renin activity measurements from a renal vein reached through a catheter introduced percutaneously via a femoral vein, and from the aorta by a percutaneously introduced left femoral artery catheter (1 mm o.d.). Small amounts of contrast material (Angio-conray, 60%) were injected at the beginning and at the end of the study through the renal vein catheter to check that its position had not changed, and that the blood samples had thus always been withdrawn from the renal vein. The total amount of blood withdrawn in each patient was 60–90 ml; this blood was replaced by an equal amount of isotonic sodium chloride solution.

Protocol

One to two days before the study each patient was brought to the laboratory, fitted with the neck chamber, and familiarized with the procedure.

During the study the patient was supine on the radiological table. Pressure in the neck chamber was twice increased, and twice decreased, all changes being greater than 40 mmHg. These pressure changes were maintained for 5 min. After the completion of the study with the neck chamber five patients were also subjected to two trials of head-up passive tilting to 80° for 5 min. Intervals of 10 min were allowed between the end of each trial (either carotid sinus manipulation or tilting) and the beginning of the subsequent one. For each trial, blood samples were withdrawn immediately before and during minute 5 of the trial (in six patients also during minute 2).

Analysis of results

We expressed the increased and decreased stimuli to the carotid sinus baroreceptors as
changes in tissue pressure outside the carotid sinuses, the magnitude of which were derived from the applied pressure changes in the neck chamber, after correction for the imperfect pressure transmission through the neck tissues (see above).

We analysed the effects of the stimuli by comparing measurements during application of neck pressures and during tilting with control measurements taken immediately before the beginning of these two manoeuvres. Blood pressure and heart rate values were calculated as the average of 30 s readings at the time of the corresponding withdrawal of blood samples. We also calculated the difference between plasma renin activity in the renal vein and the aorta, and used it as an index of renin secretion from the kidney. Results obtained in each subject were averaged and the mean (±SEM) for the groups was calculated. Statistical comparison was performed by paired t-test, taking \( P < 0.05 \) as the level of significance.

**Results**

**Changes in carotid sinus transmural pressure (11 patients)**

Decreasing carotid sinus transmural pressure for 5 min (Table 1) was accompanied by a significant increase in mean arterial pressure and heart rate. Arterial plasma renin activity did not change significantly during this manoeuvre; plasma renin activity in the renal vein showed a significant but very slight increase, as did the calculated difference between the venous and the arterial values.

Increasing carotid sinus transmural pressure for 5 min (Table 2) was accompanied by a significant decrease in mean arterial pressure with no significant change in heart rate. No significant changes were observed in the plasma renin activity of the aorta and the renal vein blood, or in the renal venous–arterial difference.

In six of 11 patients changes in arterial blood pressure and heart rate, as well as in plasma renin activity, were substantially similar at minutes 2 and 5 of reduced and increased carotid sinus transmural pressure (Fig. 1).

**Tilting (five patients)**

Passive head-up tilting for 5 min (Table 3) was accompanied by a significant though moderate decrease in mean arterial pressure, and by a significant tachycardia. Arterial plasma renin activity did not change significantly with this manoeuvre and the renin activity from renal plasma (and the renal venous–arterial difference) increased significantly and markedly. A comparison in the same five patients of the effects of tilting and application of positive neck pressure is shown in Fig. 2. It is clear that the former manoeuvre increased the renal venous–arterial difference in plasma renin activity to a significantly greater extent \( (P < 0.05) \) than the latter.

**Discussion**

It is apparent from our observations that the increase and the reduction in the inhibitory influence exerted by the carotid sinus baroreceptors were accompanied by respectively no decrease and by a significant but only very small rise in the plasma renin activity of a systemic artery and a renal vein. However, before reaching the conclusion that no or minimal reflex inhibition is exerted by the carotid baroreceptor reflex on renin

### Table 1. Effects of decreasing carotid transmural pressure (increasing neck tissue pressure) on haemodynamic and plasma renin activity values in the 11 hypertensive subjects

Results are shown as mean values ± SEM. Values were measured immediately before (control) and during minute 5 of the decrease in carotid sinus transmural pressure. The reduction in carotid transmural pressure was obtained by increasing neck tissue pressure by 39 ± 2 mmHg. NS: Not significant.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Decreased carotid transmural pressure</th>
<th>Change</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>134 ± 5</td>
<td>149 ± 4</td>
<td>+15 ± 3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79 ± 3</td>
<td>87 ± 4</td>
<td>+8 ± 2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma renin activity (pmol h⁻¹ ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aorta</td>
<td>0.29 ± 0.07</td>
<td>0.32 ± 0.08</td>
<td>+0.03 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>renal vein</td>
<td>0.39 ± 0.09</td>
<td>0.47 ± 0.10</td>
<td>+0.08 ± 0.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>renal venous–arterial difference</td>
<td>0.10 ± 0.03</td>
<td>0.15 ± 0.06</td>
<td>+0.05 ± 0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
TABLE 2. Effects of increasing carotid transmural pressure (decreasing neck tissue pressure) on haemodynamic and plasma renin activity values in the 11 hypertensive subjects of Table 1

Results are shown as mean values ± SEM. Values were measured immediately before (control) and during minute 5 of the increase in carotid sinus transmural pressure. The increase in carotid transmural pressure was obtained by reducing neck tissue pressure by 34 ± 3 mmHg. NS: Not significant.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Increased carotid transmural pressure</th>
<th>Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>135 ± 5</td>
<td>119 ± 6</td>
<td>-16 ± 2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80 ± 3</td>
<td>78 ± 4</td>
<td>-2 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (pmol h⁻¹ ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aorta</td>
<td>0.30 ± 0.07</td>
<td>0.34 ± 0.10</td>
<td>+0.04 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>renal vein</td>
<td>0.42 ± 0.12</td>
<td>0.44 ± 0.15</td>
<td>+0.02 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>renal venous-arterial difference</td>
<td>0.12 ± 0.05</td>
<td>0.10 ± 0.05</td>
<td>-0.02 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

TABLE 3. Effects of passive head-up tilting (80°) on haemodynamic and plasma renin activity values in five hypertensive subjects

Results are shown as mean values ± SEM. Values were measured immediately before (control) and during minute 5 of tilting. NS: Not significant.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Tilting</th>
<th>Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>142 ± 5</td>
<td>133 ± 4.5</td>
<td>-9 ± 1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 4</td>
<td>87 ± 4</td>
<td>+15 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma renin activity (pmol h⁻¹ ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aorta</td>
<td>0.26 ± 0.10</td>
<td>0.28 ± 0.11</td>
<td>+0.02 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>renal vein</td>
<td>0.30 ± 0.12</td>
<td>0.60 ± 0.23</td>
<td>+0.30 ± 0.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>renal venous-arterial difference</td>
<td>0.04 ± 0.03</td>
<td>0.32 ± 0.13</td>
<td>+0.28 ± 0.11</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

FIG. 1. Effects of decrease (continuous lines) and increase (broken lines) in carotid sinus transmural pressure (obtained by increasing and decreasing neck tissue pressure by 42 ± 2 and 35 ± 5 mmHg respectively) on the renal venous-arterial difference plasma renin activity (PRA). Results are shown as mean values ± SEM from six patients. C, 2 and 5 indicate respectively control values and values measured during minutes 2 and 5 of the change in carotid sinus transmural pressure.

secretion, a number of other possible interpretations of our findings must be discussed.

First, in this study we could only measure the difference in plasma renin activity from a renal vein and the arterial circulation, whereas a precise calculation of renin release would also require measurements of renal blood flow. Although observations on animals cannot always be safely extrapolated to man, it should be mentioned that studies on several animal species have shown that changes in carotid sinus baroreceptor activity do not affect, or very slightly affect, renal blood flow (Mancia, Shepherd & Donald, 1975; Kirchheim, 1976). In any case, if any blood flow changes occur in man, a decrease in carotid transmural pressure could only be expected to decrease renal blood flow, and in this case the small increase in the renal venous-arterial difference in renin we have obser-
Fig. 2. Effects of head-up passive tilting (broken lines) and application of positive pressures in the neck chamber (continuous lines) in five patients: mean arterial pressure; heart rate; plasma renin activity (PRA); \(v-a\), venous–arterial difference. Results are shown as mean values ±SEM. C: Values during control; S: values during minute 5 of tilting or positive neck pressure.

ved would mean an even smaller increase in renin release. Likewise, an augmented renal blood flow during an increase in carotid transmural pressure would make a decrease in renin release even smaller than the minimal and non-significant decrease in the renal venous–arterial difference we have measured.

Secondly, the 5 min reflex changes in sympathetic activity caused by the carotid sinus baroreceptors might have been too short to induce alterations in renin secretion. This possibility can be ruled out because renin secretion was substantially altered by 5 min of passive tilting, and this stimulus is known to act largely through the renal nerves (Zanchetti et al., 1976; Stella & Zanchetti, 1977).

Thirdly, an increase in renin release due to reduction in carotid baroreceptor inhibition might have been buffered by the simultaneous reflex increase in blood pressure, and vice versa. It must be mentioned, however, that the reflex changes in blood pressure were small in our patients, that a number of animal studies have shown that sympathetic stimulation can markedly increase renin release even if accompanied by large rises in arterial pressure, and vice versa that blood pressure falls greater than those occurring in our study cannot counteract the suppression of renin secretion induced by reduction in sympathetic renal nerve activity (Zehr & Feigl, 1973). Thus, though this factor cannot be excluded, its importance is likely to be minor.

The last possibility is related to the fact that the basal renin secretion rate of our patients ranged from normal to low values. This might have prevented at least in part a baroreceptor-induced decrease in renin secretion, but certainly did not prevent a baroreceptor-induced increase, as the capability of renin secretion to rise in response to the appropriate neural stimulus was demonstrated by the effects of passive tilting. However, we should take our data as indicative of those essential hypertensive subjects in whom basal secretion rate of renin is low or normal, without extrapolation to the hypertensive subjects in whom this basal value is high. As this latter group represents a small minority of uncomplicated essential hypertensive subjects (Zanchetti et al., 1976) our data probably describe the most common pattern of response.

In conclusion, our findings indicate that in subjects with essential hypertension of mild to moderate degree, the carotid baroreceptor reflex is not involved in the control of renin release, though it is still active as a controlling mechanism for arterial pressure. This conclusion would apply to that large group of hypertensive patients with normal renin secretion rates. It is also possible that our data apply to normotensive people, but of course evidence on this point was not obtained for ethical reasons.

We must comment further upon the rapid and marked increase in renin secretion induced by passive tilting. We see two possibilities to explain this finding. First, tilting might have caused a large increase in renin secretion because of a reduction in carotid sinus transmural pressure much greater than that caused by application of positive pressure to the neck. However, the tilting-induced reduction in carotid transmural pressure was approximately 30 mmHg (21 mmHg because at 80° tilting the vertical distance between the carotid sinuses and the right atrium is of the order of 27 cm, plus 9 mmHg because of the reduction in mean arterial pressure). This is only slightly greater than the 24 mmHg reduction in carotid transmural pressure obtained in the same subjects with positive neck pressure (36 mmHg increase in neck tissue pressure).
pressure minus the resulting 12 mmHg reflex increase in mean arterial pressure). It seems unlikely that this small difference might account for the marked difference in renin release obtained with the two stimuli.

The second and more likely explanation is that in hypertensive humans reflexes other than those from the carotid sinuses are involved in control of renin secretion. As to the origin of these reflexes, a number of experimental data favour the cardio-pulmonary receptors connected with the vagi; indeed, (i) activity of these receptors is markedly reduced by the reduction in central blood volume caused by tilting, (ii) stretch receptors located at this site have been shown in animals to exert a powerful tonic and phasic inhibition of renin secretion (Mancia et al., 1975; Zehr & Feigl, 1973; Zanchetti, Dampney, Ludbrook, Mancia & Stella, 1976; Mancia, Lorenz & Shepherd, 1976), and, finally (iii), Dampney, Stella & Zanchetti (1977) have shown in the cat that most of the increment in renin release induced by tilting is prevented by bilateral vagotomy. Thus the reflex control of renin secretion would be fundamentally analogous in animals and man, as in both the cardiopulmonary receptors and not the carotid sinus baroreceptors would play a major role.

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References


