Study of Renovascular Hypertension in Rats.
IV. Renal Arterial Blood Velocity in One-Clip, Two-Kidney Hypertensive Rats

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In one-clip, two-kidney hypertensive models of rats, the renal arterial blood velocity was recorded using the bidirectional Doppler velocimeter before and at various times after clipping of the renal arteries.

In all the rats, immediately after placement of a clip, the blood velocity of the stenosed artery was lowered significantly.

Although the blood velocity remained low 2 weeks after clipping, it recovered to the pre-clip level at 6 and at 11 to 13 weeks after clipping. The plasma renin activity tended to decrease following the acute, high-renin stage of hypertension.

If it can be assumed that the blood velocity is one of the indexes representing blood flow, its return to the pre-clip normal level in the chronic stage of renovascular hypertension may signify recovery of blood flow to the clipped kidney leading to a reduction in renal renin synthesis and consequently a decrease in plasma renin activity.

(Key Words: Two kidney one-clip hypertension, Renal arterial blood velocity, Plasma renin activity.

INTRODUCTION

The role of the renin-angiotensin system in one-clip, two-kidney hypertensive rats seems to vary according to times following placement of a clip on the renal artery since the plasma renin concentration is reduced substantially in the chronic stage despite persistence of hypertension throughout the experimental period (5). However, angiotensin converting enzyme (ACE) inhibitors can bring about hypotensive response even at that stage, irrespective of the plasma renin level (4). Therefore, it is certain that angiotensin II is still a major contributing factor in maintaining hypertension at the chronic stage of this type of renovascular hypertension.

In the previous study, I demonstrated that the renal renin contents of chronically clipped kidneys were higher than those of the opposite, untouched kidneys during treatment with captopril started 30 days after clipping (2). Do alterations in blood flow of the stenotic renal artery still have an influence on renin contents of ipsilateral kidneys at the chronic stage when the plasma renin concentration is no longer elevated?

I conducted this study using the bidirectional Doppler velocimeter to measure renal arterial blood velocity as a parameter of blood flow in one-clip, two-kidney hypertensive rats.

METHODS

One-clip, two-kidney Goldblatt models were created in Wistar male rats aged 6 weeks by the same method as in the previous study (3). Renal arterial blood velocity was recorded using a bidirectional Doppler velocimeter, BVM 30 MODEL, Bach-Simposon Inc. before and after clipping of the renal artery. A 8MHz microprobe secured by a grasping forceps was placed on the renal artery, distal to the clip and slightly apart from the vascular wall with the

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intervention of Echogel (Fig. 1). The animals were returned to their cages and fed a standard rat diet. Blood pressure was measured by the tail-cuff method until reexploration. The hypertensive rats were divided into three groups. Group 1 underwent laparatomy after 2 weeks, group 2 after 6 weeks and group 3 after 11 to 13 weeks postoperatively. The clipped left renal artery was exposed, the microprobe was applied and blood velocity was recorded as initially. Then blood was sampled from the inferior vena cava for measurement of plasm renin. Angiotensin I generated in the rat plasma was quantitated by radioimmunoassay using Dinabott Renin RTA Kit II.

The wave-forms obtained by the bidirectional Doppler velocimeter were two- or three-phasic and they seemed to be influenced by the presence of reverse flow and the angle between the probe and the vascular wall. According to Johnston, the ratio of peak-to-peak velocity to mean velocity is constant regardless of the angle between microprobe and blood vessel (1). I adopted this method and calculated the ratio termed the peak-to-peak pulsatility index (Fig. 2). Statistical analysis was performed by the matched-pair t-test.

Fig. 1 Measurement of blood velocity of the stenotic renal artery with a bidirectional Doppler velocimeter using an 8 MHz microprobe.

Examples of Velocity Curve

Before Clip

Soon After

6 Weeks After

Calculation of Peak to Peak Pulsatility Index (Pl)

\[
Pl = \frac{\text{Peak to peak velocity}}{\text{Mean velocity}}
\]

Fig. 2 Blood velocity curve and peak-to-peak pulsatility index.
RESULTS

In group 3 rats that were reoperated in 11 to 13 weeks after clipping, the average peak-to-peak pulsatility index before clipping was 6.9 ± 2.2 and it was lowered significantly to 5.1 ± 1.7 immediately after clipping. However, on reexploration at the chronic stage of hypertension, the index had returned to the pre-clip level (Fig. 3). Two sham-operated rats underwent the same procedure, demonstrating no change in blood velocity before and after clipping (Fig. 3).

In group 2 at the time of clipping, the peak-to-peak pulsatility index was 7.9 ± 1.6 before and 4.6 ± 0.4 (p<0.005) just after clipping. In the later stage it was restored to the pre-clip level as in group 3 (Fig. 4).

In contrast, group 1 rats reexplored 2 weeks after clipping gave a peak-to-peak pulsatility index which remained as low as the value at the time of clipping (Fig. 5).

In all three groups, the mean arterial blood pressure was in the range of hypertension and the plasma renin activities showed a tendency to decrease after the acute, high-renin stage of hypertension (Table 1).

The blood velocity of the renal artery to the opposite, unclipped kidney and of the aorta were measured inconstantly at the time of reexploration, but these data were not taken into consideration in this study.

\[
\begin{array}{ccc}
\text{Peak to Peak Pulsatility Index} & 10 & 5 \\
6.9 \pm 2.2 & 5.1 \pm 1.7 & 6.4 \pm 1.9 \\
(\text{P}<0.025) & (\text{N.S.}) & \\
\end{array}
\]

\(x---\times\) Sham Operation

\(\text{CLIP}\)

\(\text{Before} \quad \text{Soon} \quad 11-13 \text{ Weeks} \quad \text{After} \quad \text{After}\)

Fig. 3 Renal Arterial Blood Velocity in One-clip, Two-kidney Hypertensive Rats in Chronic Stage (Group 3)
Fig. 4 Renal Arterial Blood Velocity in One-clip, Two-kidney Hypertensive Rats in Intermediate Stage (Group 2)

Fig. 5 Renal Arterial Blood Velocity in One-clip, Two-kidney Hypertensive Rats in Acute Stage (Group 1)
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Table 1 Parameters of Renal Arterial Blood Velocity (Peak to Peak Pulsatility Indices) and Plasma Renin Contents at Various Times

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Before Clipping</th>
<th>Soon After Clipping</th>
<th>At the stated time</th>
<th>PRA (ng/ml/hr)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute (2 Weeks)</td>
<td>10.5 ± 3.15</td>
<td>8.6 ± 2.7 (p &lt; 0.05)</td>
<td>6.8 ± 2.6 (p &lt; 0.05)</td>
<td>24.5 ± 6.0</td>
<td>169 ± 38</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate (6 Weeks)</td>
<td>7.9 ± 1.6</td>
<td>4.6 ± 0.4 (p &lt; 0.005)</td>
<td>6.2 ± 1.2 (N.S.)</td>
<td>9.35 ± 1.9</td>
<td>165 ± 30</td>
</tr>
<tr>
<td>3</td>
<td>Chronic (11-13 Weeks)</td>
<td>6.9 ± 2.2</td>
<td>5.1 ± 1.7 (p &lt; 0.025)</td>
<td>6.4 ± 1.9 (N.S.)</td>
<td>10.8 ± 5.7</td>
<td>179 ± 32</td>
</tr>
</tbody>
</table>

DISCUSSION

It is known that in the one-clip, two-kidney Goldblatt model, the renin content is increased in the kidney with the stenosed artery and decreased in the opposite kidney because of decreased renal blood to the damaged kidney (7). In the rat experimental model, however, study of renal blood flow is limited because the renal artery is too small to be searched with even the smallest probe of the electromagnetic flowmeter. Therefore it is practically impossible to measure renal blood flow directly in rats. C. Risoe et al. calculated blood flow of various human arteries by measuring blood velocity with a bidirectional ultrasonic Doppler flowmeter, using the equation, \( \pi r^2 \times \text{mean blood velocity} \), where \( r \) was the assumed diameter of the given vessel (6). On the basis of these data and those of Johnston (1), I examined velocity instead of flow under the assumption that the diameter of the clipped renal artery should be constant throughout the experiment.

In this study, decrease in blood velocity to the kidney immediately after clipping was a common finding in all three groups. This may mean a decrease in blood flow to the clipped kidney. Renal ischemia should last for at least up to two weeks since in group 1 rats the blood velocity remained in the same diminished state as at the time of clipping. The plasma renin activity of this group was fully stimulated and the highest among the three groups. This can be attributed to the ischemia induced by clipping of the renal artery (Table 1).

On the other hand, in groups 2 and 3, 6 and 11 to 13 weeks after clipping, respectively, the blood velocity to clipped kidneys had returned to the pre-clip level. The plasma renin activity was also decreased significantly, whereas the arterial blood pressure remained in the hypertensive range (Table 1). As previously mentioned, if it is assumed that the return of the blood velocity index to the pre-clip level represents recovery of blood flow to the clipped kidneys, decrease in the plasma renin activity in the two groups can be explained by cessation of over-production of renin in the kidneys with stenosed arteries. This hypothesis is relevant to the findings of my previous study in which I demonstrated that differences in the renal renin content between clipped and unclipped kidneys was insignificant (p < 0.2) in chronically hypertensive rats (2).

It may be concluded that the reason why the rats in groups 2 and 3 were hypertensive despite possible reduction in renin synthesis in clipped kidneys was the presence of extrarenal renin production independent of alterations in blood flow of the stenotic renal artery.

REFERENCES

