Renal Response to Propranolol Treatment in Hypertensive Humans

PETER W. DE LEEUW, M.D. AND WILLEM H. BIRKENHÄGER, M.D.

SUMMARY To investigate the relationship between sympathetic activity and blood flow in the kidney during propranolol treatment, 55 patients with uncomplicated essential hypertension were studied. Twenty-five of them had been treated with propranolol (average daily dose 240 mg) for about two weeks; the others served as untreated controls. In all patients renal arteriography was carried out, after which renal plasma flow (\(^{131}\)I-hippuran clearance), cortical blood flow (xenon-washout), and renal release of norepinephrine and renin were measured. In the propranolol group, renal plasma flow had also been determined before treatment. Cardiac output (dye-dilution) and creatinine clearance were measured both before as well as during therapy. In untreated hypertensives renal cortical blood flow was reduced to about 80% of what was predicted for the age level. On the basis of their changes in blood pressure, patients who were treated with propranolol were divided into responders (n = 15) and nonresponders (n = 10). Despite a similar fall in cardiac output in both subgroups, renal blood flow remained unchanged in responders, while it fell in nonresponders. In addition, renal norepinephrine release was significantly higher in nonresponders than in responders, while renin release in nonresponders was markedly suppressed. It may be concluded that sympathetic activity is an important determinant of renal (cortical) blood flow in essential hypertension. The effect of propranolol on the renal circulation depends, to some extent, on its unmasking of prevailing alpha-adrenergic tone. However, when blood pressure falls, an additional mechanism may be operative to cause renal vasodilation.

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KEY WORDS • renal blood flow • renin • norepinephrine • xenon washout

In normal humans, renal blood flow falls with age, especially after the fourth decade. The process responsible seems to be primarily vascular, a limitation of the cortical blood supply rather than a reduction in renal mass. It has also been demonstrated that renal cortical blood flow is reduced in patients with essential hypertension. The mechanism of this reduction is not known, but it has been suggested that increased sympathetic tone could play a role. However, while it is known that total renal blood flow decreases much faster with age in hypertensives than it does in normotensives, no such data are available for cortical flow. In previous studies, this possible effect of age has not been taken into account sufficiently.

Theoretically, beta-blocking drugs, by reducing cardiac output, could depress renal cortical flow even further. It is surprising that despite the wide-spread use of beta-blockers in the therapy of hypertension, no systematic studies have been carried out to assess their effect on the intrarenal circulation during chronic treatment. In this study we investigated the possible role of the sympathetic system in the reduction of renal cortical blood flow in essential hypertension, and assessed the effect of propranolol on the relationship between adrenergic activity and intrarenal flow patterns.

Methods

Patient Selection

Two groups of patients whose mean arterial pressure exceeded 110 mm Hg were studied. Group I consisted of 30 white patients (21 males, 9 females) with uncomplicated essential hypertension, aged 18 to 68 years (average, 42 years). They had been either untreated or had stopped taking antihypertensive drugs at least 3 weeks prior to the study. Arteriography was performed to exclude renal vascular or renal paren-
chymatous disease whenever this was suggested by clinical examination (such as the presence of an abdominal bruit) or by abnormal results on intravenous pyelography or renography.

Group 2 included 25 white patients (18 males, 7 females) with uncomplicated essential hypertension, who had been treated with propranolol (120 to 480 mg/day) for 2 weeks. Mean age in this group was 44 years (range, 27 to 67 years). Indications for arteriography were similar as for Group 1.

Measurements in a third group of 15 white normotensive subjects were taken as control data. Age in this group ranged from 16 to 72 years (average, 49 years), and renal arteriography in these subjects was performed to exclude space-occupying lesions. All patients had given their consent after full explanation of the procedure.

The inpatient evaluation included a complete history and physical examination, determination of blood electrolytes, urea and creatinine concentration, creatinine clearance, urinalysis, chest film, and electrocardiogram. Signs of overt cardiovascular or renal disease were not observed in either group. When other diseases such as diabetes mellitus, hyperlipidemia, etc., coexisted, patients were excluded from the study.

All subjects were admitted to a metabolic ward where sodium intake was standardized at 60 mmoles daily for at least 4 days prior to the investigation and checked by 24-hour urine collections. While the patients were still untreated, the following measurements were done: blood pressure, cardiac output (dye dilution), renal plasma flow (125I-hippuran) and creatinine clearance. Filtration fraction was calculated as the quotient of creatinine clearance and renal plasma flow. In patients from Group 2 these measurements were repeated after 2 weeks of treatment. The decision to treat patients with propranolol (Group 2) before the actual investigation was taken at random and not influenced by the age of the patient or level of blood pressure. The dose of propranolol was increased until blood pressure was satisfactorily controlled (MAP 110 mm Hg or less) or a total dose of 480 mg daily was reached.

Experimental Procedures

Studies were carried out in the morning after an overnight fast and complete bed rest for about 12 hours. One hour before the investigation, 10 mg diazepam (Valium, Roche) was given by intramuscular injection.

Percutaneous aortic and selective renal artery catheterization with Elecath-cope catheters was carried out by the method of Seldinger. After completion of the angiographic studies, the right kidney was catheterized for 18Xe-washout studies. Patients were admitted to this part of the study only when no obvious abnormalities were found on the arteriogram. In the hypertensive patients (Group 1 and 2), the right renal vein was also catheterized. A small amount (less than 2 ml) of contrast material was injected through the catheters to ensure proper position. To allow for dissolution of the hemodynamic and endocrine effects of the contrast agent, we waited for at least 30 minutes before the next stage of the investigation. Subsequently 1 mCi of 18Xe, dissolved in 2 ml of isotonic saline, was injected into the renal artery in 5 seconds. The disappearance of 18Xe from the kidney was monitored during 20 minutes by external counting with sodium iodide crystals placed in a cylindrical collimator and positioned above the kidney. The number of counts was recorded every 2 seconds by a pulse height analyzer (window setting, 70–100 keV) and punched on tape. Altogether, 600 data points were obtained.

The time-activity curve was transformed by computer to a curve of 200 points. The latter was composed from the first 100 data points of the original curve and the average of each following block of five. When recirculation of the tracer was suspected, curves were rejected for analysis. Subsequent analysis of the washout data was based on a three-compartmental model, but since the physiological meaning of the second and third component were uncertain, data will be presented here only for the fast-flow compartment (C1). Weighted arithmetic mean blood flow (MBF) was calculated as described by Ladefoged, and flow rates were corrected for hematocrit. In the hypertensives, total renal blood flow (TRBF) was determined as well by constant infusion of 125I-hippuran. Renal plasma flow (RPF) was calculated from the clearance and extraction of 125I-hippuran and total renal blood flow from the formula TRBF = RPF/liter – Ht, where Ht is the arterial hematocrit. Extraction of hippuran (ER) was calculated from its concentration in blood samples, drawn simultaneously from the renal artery and vein. Absolute cortical blood flow (CBF) was calculated as %C1 × TRBF, where %C1 is the fractional distribution of blood flow over the first compartment as derived from the xenon-washout curve. Infrarenal pressure was measured through the arterial catheter via a Statham transducer.

Before and after the assessment of intrarenal hemodynamics, blood samples were drawn simultaneously from the renal artery and vein for determination of renin (total and active) and norepinephrine. To avoid erroneous conclusions due to withdrawal of adrenal venous blood, all samples were also analyzed for their content of aldosterone and cortisol.

In patients from Group 2, total renal blood flow as well as peripheral venous concentration of renin and norepinephrine had been assessed also before treatment.

Analytical Methods

Total renin concentration was assayed by the method of Skinner as described before. This involves an acidification step to pH 3.3, which activates inactive renin. The amount of active renin was determined according to Skinner et al. after acidification to pH 4.5. Inactive renin was taken as the difference between total and active renin. Norepinephrine was measured radioenzymatically, as previously de-
TABLE 1. Characteristics of Patients in Groups 1 and 2 Before Treatment

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>122 ± 5</td>
<td>122 ± 7</td>
<td>ns</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index (liter/min/m²)</td>
<td>2.5 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>ns</td>
</tr>
<tr>
<td>Total renal blood flow</td>
<td>813 ± 43</td>
<td>834 ± 50</td>
<td>ns</td>
</tr>
<tr>
<td>(ml/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>131 ± 8</td>
<td>127 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>(ml/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>24 ± 0.7</td>
<td>24 ± 0.7</td>
<td>ns</td>
</tr>
<tr>
<td>Total renin concentration (μU/ml)*</td>
<td>170 ± 25</td>
<td>179 ± 28</td>
<td>ns</td>
</tr>
<tr>
<td>Active renin concentration (μU/ml)*</td>
<td>35 ± 8</td>
<td>38 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>Norepinephrine concentration (ng/ml)*</td>
<td>0.28 ± 0.10</td>
<td>0.30 ± 0.11</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Measured in peripheral venous blood.

Results

Data on blood pressure, hemodynamics, and hormones for both groups are summarized in table 1. When still untreated, patients from Group 2 did not differ significantly from those of Group 1. Treatment with propranolol induced a significant fall in blood pressure (p < 0.01), which was associated with a decrease in cardiac output and total renal blood flow (p < 0.05), renal vascular resistance (0.05 < p < 0.10), and peripheral venous levels of active as well as inactive renin (p < 0.05). Total renin also fell, but norepinephrine was not significantly altered. When patients from Group 2 were divided according to their response to propranolol treatment, different patterns emerged (fig. 1 and table 2). In responders (patients whose MAP fell by at least 5 mm and reached 110 mm Hg or less) renal blood flow remained unchanged, while renal vascular resistance fell (p < 0.01). In contrast, in nonresponders (patients whose blood pressure either remained unchanged or fell to levels still above 110 mm Hg) renal blood flow fell (p < 0.05), while renal vascular resistance rose (p < 0.05). During treatment, the latter variable was significantly higher in nonresponders than in responders (p < 0.01). When responders (n = 15) were compared to nonresponders (n = 10), the latter were found to be significantly older (50 ± 4 years vs 40 ± 3 years, p < 0.01) and to have slightly lower renin levels (0.05 < p < 0.10) before

TABLE 2. Comparison of Data from Responders and Nonresponders to Propranolol Before and During Treatment

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Before</td>
</tr>
<tr>
<td>Age</td>
<td>treatment</td>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>120 ± 6</td>
<td>95 ± 5</td>
<td>126 ± 8</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index (liter/min/m²)</td>
<td>2.4 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Total renal blood flow</td>
<td>847 ± 48</td>
<td>820 ± 45</td>
<td>825 ± 50</td>
</tr>
<tr>
<td>(ml/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>130 ± 7</td>
<td>110 ± 6</td>
<td>120 ± 8</td>
</tr>
<tr>
<td>(ml/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>24 ± 0.7</td>
<td>20 ± 0.7</td>
<td>24 ± 0.7</td>
</tr>
<tr>
<td>Total renin concentration (μU/ml)*</td>
<td>185 ± 28</td>
<td>160 ± 30</td>
<td>170 ± 30</td>
</tr>
<tr>
<td>Active renin concentration (μU/ml)*</td>
<td>37 ± 11</td>
<td>28 ± 10</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Norepinephrine concentration (ng/ml)*</td>
<td>0.31 ± 0.10</td>
<td>0.29 ± 0.08</td>
<td>0.28 ± 0.10</td>
</tr>
</tbody>
</table>

*Measured in peripheral venous blood.
MAP  
mmHg

130
120
110
100
90
80
70
60

RBF  
ml/min/173m²

900
800
700
600

RVR  
dyn sec cm⁻¹/173m²

16000
12000
8000
4000

RESPONDERS

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NON-RESPONDERS

FIGURE 1. Changes in mean arterial pressure (MAP), renal blood flow (RBF), and renal vascular resistance (RVR) in responders and nonresponders during treatment with propranolol.

FIGURE 2. Average levels of cortical flow rates (absolute and as a percentage of predicted) in untreated hypertensives and in patients treated with propranolol (*p < 0.005).

In untreated hypertensives, secretion of both active and inactive renin occurred. In the propranolol-treated group, renin secretion was reduced, but again a difference was observed between responders and nonresponders. Compared to patients from Group 1, responders to propranolol had only modestly depressed renin secretion, while in nonresponders secretion had nearly fallen to zero. Parallel differences were observed for active and inactive renin, and this trend was to some degree reflected in peripheral venous levels of the hormone (fig. 3).
For norepinephrine, a different pattern was observed. Renal secretion of this substance was higher in Group 2 than in Group 1. However, in responders to propranolol, renal norepinephrine production was slightly lower than in untreated subjects (0.05 < \( p < 0.10 \)), but in nonresponders was unequivocally higher (\( p < 0.01 \)). This pattern could not be predicted from peripheral venous norepinephrine levels since these were similar in responders and nonresponders. Moreover, these levels were not different from those observed in the untreated hypertensives (fig. 4).

Both in Group 1 and Group 2 an inverse relationship was found between circulating norepinephrine and absolute cortical blood flow (\( r = -0.78; p < 0.01 \) in both groups).

Discussion

Previous studies on the renal effects of propranolol invariably showed a decrease in renal blood flow, although this was not always statistically significant.\(^{27-30} \) None of these studies, however, is comparable to the present one and none mentioned differences between responders and nonresponders.

Since reductions in renal blood flow (and glomerular filtration rate) are common with agents that reduce cardiac output,\(^{31} \) the renal response to propranolol has usually been attributed to the effects of this drug. However, from the literature there are no data to unequivocally support such a statement. On the other hand, there are several arguments that speak against it. First of all, the relationship between changes in cardiac output and changes in renal perfusion seems to be rather small,\(^{32} \) indicating that a reduced renal blood flow cannot be due to a decrease of cardiac output alone. Second, not all beta-blocking drugs seem to suppress renal perfusion.\(^{33-35} \) Third, experiments in both man\(^{36} \) and dog\(^{37} \) have shown that intrarenal infusion of propranolol in doses too low to have a systemic effect could reduce renal blood flow. Whether this is due to unmasking of alpha-adrenergic tone by blockade of vascular beta-receptors or to a direct effect on vascular alpha-receptors has not been established.

The results of our present study suggest that the renal effects of propranolol, when given to hyper-
tensive man for at least 2 weeks, are closely related to the effect on blood pressure. In patients who responded to the drug with a fall in mean arterial pressure to 110 mm Hg or less, renal blood flow remained unchanged despite a fall in cardiac output. These data indicate that vasodilatation had occurred in the renal bed. On the other hand, in patients in whom blood pressure did not fall to acceptable levels, renal blood flow was reduced due to a marked increase in renal vascular resistance. Nevertheless, in these patients cardiac output had fallen to the same degree as in those in whom renal blood flow remained constant. When the results on cortical blood flow were considered, this pattern appears to be even better demonstrable. Whereas in untreated hypertension, cortical flow rates appeared to be reduced to about 80% of normal, complete normalization of cortical perfusion was found in propranolol responders. On the other hand, cortical blood flow was even further suppressed in the nonresponders.

Since assessment of the intrarenal circulation by means of the xenon-washout technique requires arterial catheterization, this investigation could be performed only once in each patient. Therefore, it cannot be completely excluded that the observed differences in cortical blood flow between responders and nonresponders were already present before treatment. However, this seems unlikely in view of the similarities in total renal blood flow, measured by hipuran clearance, before treatment and the changes that occurred upon treatment. It is also unlikely that a different level of beta-blockade was achieved in both groups, since cardiac output fell to the same extent in both groups. Thus, we are left with the conclusion that propranolol can induce two types of renal responses, the more favorable of which is normalization of cortical flow rates. The question then is: What determines the type of response to occur? When, in our study, responders were compared to nonresponders, nonresponders were found to be 10 years older on the average. It is well known that in older normotensive subjects renal cortical blood flow is reduced and that a blunted response to vasodilators is found in them. These data suggest that fixed organic vascular lesions exist intrarenally. It is conceivable that such lesions were present also in our group of nonresponders thus preventing the renal blood flow from increasing. Even if this mechanism may be operative, it still does not explain why vasocostriction occurred. Therefore, a functional component has to be considered.

A likely candidate would be the renin-angiotensin system, but our studies seem to refute this possibility, since peripheral levels of renin and, more important, renin secretion were far more depressed in patients who did not respond to propranolol than in those who did. On the other hand, we found that norepinephrine release by the kidney was markedly enhanced in the nonresponders. If norepinephrine secretion by the kidney can be taken as an index of sympathetic traffic to that organ, then it may be inferred that the renal vascular response to propranolol depends on the intensity of alpha-adrenergic tone. A possible explanation, then, for our findings could be that patients with essential hypertension are heterogeneous with respect to their degree of renal sympathetic tone. If, before treatment, the nonresponders in Group 2 had greater sympathetic tone, the unmasking of the alpha-effect by propranolol would be more evident in this group of patients. The slightly higher filtration fraction in these patients during treatment may be taken in support of this idea. Such a mechanism, however, could by itself hardly explain the findings in the responders. Even if there was no alpha-adrenergic tone in these patients before treatment, propranolol would not be expected to cause a vasodilatory response, unless one assumes an additional mechanism, for instance autoregulation operating in response to the drop in pressure.

An alternative explanation for the findings would be that the differences in renal sympathetic activity during treatment were secondary to changes in overall neurogenic function induced by propranolol. Since renal blood flow and filtration in both groups were comparable at the start of treatment, it may very well be that reduced alpha-adrenergic activity plays a role in the renal vasodilatation of responders. Our data, however, do not permit a definitive conclusion on this point.

In summary, our study demonstrates that in untreated essential hypertension, renal cortical blood flow is reduced by about 20%. This is probably related to enhanced alpha-adrenergic tone. Treatment with propranolol seems to normalize cortical perfusion, concomitant with the fall in blood pressure. In nonresponders, neurogenic vasoconstriction is maintained and perhaps even enhanced, leading to a fall in renal perfusion. Careful monitoring of kidney function seems mandatory in patients who poorly respond to propranolol. It is also important to note that peripheral venous levels of norepinephrine in no way reflected sympathetic activity in the kidney.

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