Urinary Kallikrein Activity, Renal Hemodynamics, and Electrolyte Handling during Chronic Beta Blockade with Propranolol in Hypertension

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SUMMARY Propranolol has been reported to diminish renal perfusion and impair sodium excretion, but the relationship of these phenomena has not been well characterized during chronic propranolol administration in hypertensive man, nor has the potential involvement of the renal kallikrein-kinin system been explored. Fifteen essential hypertensive white men were treated with both placebo and oral propranolol for 1 month each, with dosage titrated for blood pressure control. Propranolol normalized mean arterial pressure (from 112.6 ± 1.9 to 94.0 ± 2.8 mmHg, p < 0.01) with associated decrements in glomerular filtration (GFR) by 12% (p < 0.02), renal plasma flow (RPF) by 15% (p < 0.02), and renal blood flow (RBF) by 16% (p < 0.01), while filtration fraction was unchanged. Neither blood urea nitrogen nor serum creatinine were affected. Propranolol also diminished urinary kallikrein excretion (from 9.0 ± 2.7 down to 4.8 ± 1.3 esterase units/24 hrs, p < 0.04). Comparison to a group of 10 controls showed a progressive decrease in RBF from normotensive man, to hypertensive man, to propranolol-treated hypertensive man, with a parallel progressive fall in kallikrein excretion in the same three groups. Change in RBF on propranolol correlated inversely with pretreatment RBF (r = —0.91, p < 0.01) and pretreatment urinary catecholamine excretion (r = —0.64, p < 0.01), directly with pretreatment RVR (r = —0.85, p < 0.01) and inversely with change in RVR (r = —0.86, p < 0.01). This suggests that: 1) there was a failure of renal perfusion autoregulation; 2) a decrement in RBF was most likely to occur in patients with a relatively "normal" renal vascular tree; and 3) unopposed alpha mediated vasoconstriction was a likely mediator of the RBF fall. Change in RBF did not correlate with change in kallikrein excretion (r = —0.16), while change in kallikrein excretion correlated best with pretreatment kallikrein excretion (r = —0.87, p < 0.01), although not with change in plasma aldosterone concentration or urinary sodium/potassium ratio. Urinary sodium excretion was unimpaired on propranolol (160 ± 21 vs 173 ± 12 mEq/24 hrs, p > 0.1), even in the face of a diminished glomerular filtration rate, and was sustained by an increase in the fractional excretion of sodium (from 0.75 ± 0.09 to 0.96 ± 0.06%, p < 0.05). This is perhaps related to diminished mineralocorticoid activity as reflected by decreased plasma aldosterone concentration (from 68.4 ± 9.6 to 61.4 ± 16.1 pg/ml, p < 0.02), increased urinary sodium/potassium ratio (from 2.41 ± 0.33 to 3.12 ± 0.30, p < 0.01), and correlation between fractional sodium excretion increment with urinary sodium/potassium ratio increment (r = 0.82, p < 0.01). Preservation of sodium homeostasis was also indicated by constancy in body weight, plasma volume, and blood volume. Kallikrein changes did not correlate with changes in renal sodium handling. (Hypertension 4: 742-749, 1982)

KEY WORDS: hypertension, propranolol, renal blood flow, kallikrein, fractional sodium excretion, plasma volume, dopamine-β-hydroxylase

ALTHOUGH propranolol is widely used in the treatment of hypertension, its effects upon renal perfusion remain in debate. Some studies have recorded unchanged renal function after the drug, while others noted a diminution in both glomerular filtration rate and renal perfusion.

Because of the importance of the renal circulation in hypertension, we studied 15 essential hyperten-
Materials and Methods

Patients

Patients were 15 white male essential hypertensives who had mean arterial pressures (MAP) (defined as diastolic blood pressure plus 1/3 pulse pressure) greater than 105 mm Hg, as outpatients. Their mean age was 52.1 ± 2.3 years, with a range of 36 to 67 years. Before the study, they were screened for secondary causes of hypertension with determinations of blood urea nitrogen (BUN) concentration and the serum concentration of sodium, potassium, chloride, and bicarbonate; hemogram; electrocardiogram; chest roentgenogram; intravenous urogram; and 24-hour urinary excretion of sodium, potassium, chloride, and bicarbonate; hemogram; electrocardiogram; chest roentgenogram; intravenous urogram; and 24-hour urinary collection for excretion of catecholamines, metanephrines, vanillylmandelic acid, and 17 hydroxycorticosteroids. After this screening, all subjects were found to be essential hypertensives. In addition, all patients with demonstrable target organ damage from hypertension (specifically, stroke, congestive heart failure, myocardial infarction, or renal insufficiency) were excluded.

To establish a normal range for renal blood flow and urinary kallikrein excretion, we also studied 10 healthy normotensive males on an unrestricted sodium diet; that is, the group was matched for race, sex, age, and dietary sodium intake. Each subject gave his informed, written consent, and the Human Subjects Committee of the University of California, San Diego, approved the protocol.

Procedures

In random order patients were given oral placebo for 1 month or oral propranolol for 1 month, at a dose individually titrated for blood pressure control (MAP < 105 mm Hg). The dose range was 80 to 320 mg/day, with median dose of 160 mg/day, and a mean ± SEM of 168.0 ± 19.6 mg/day. No other medications were taken, and the diet was unrestricted in fluid and salt.

At the end of each 1 month period, patients were admitted to the Special Diagnostic and Treatment Unit of the San Diego Veterans Administration Medical Center for a 2 day protocol evaluation. During the admission, as well as during outpatient status, the diet was unrestricted in fluid, sodium (> 100 mEq/day), and potassium (> 50 mEq/day).

Blood pressure was obtained in the supine position on admission, with a standard sphygmomanometer, and the MAP was calculated as noted above. The diastolic blood pressure was taken as the phase V Korotkoff sound (disappearance). On the first admission day, urine was collected over 24 hours for measurement of kallikrein activity and the excretion of free catecholamines, volume, creatinine, sodium, potassium, and chloride. During collection, the urine was kept refrigerated at 4° C, and at the end of 24 hours, the volume was measured and an aliquot frozen at —80° C for later analysis.

On the morning of Day 2, blood was obtained for determination of BUN, serum creatinine, serum electrolytes, hemogram, total serum protein, supine plasma renin activity (SPRA), and upright plasma renin activity (UPRA), supine plasma aldosterone concentration, and supine and upright plasma dopamine-β-hydroxylase (DBH) activity.

Plasma volume and whole blood volume were determined utilizing both 51Cr-tagged autologous erythrocytes and 125I-albumin. The isotopes were injected intravenously and blood and plasma samples were obtained for counting at 10 and 20 minutes in the Volemotron apparatus.

Detailed renal hemodynamic studies were undertaken in the 15 patients. Glomerular filtration rate (GFR) was measured by the clearance of endogenous creatinine (Ccr). Renal plasma flow (RPF) was measured in the supine position from 7:00 am to 11:00 am, using the method of constant infusion of paraaminohippurate (PAH) without urine collection to determine the clearance of PAH (Cpafr). This method has proved reliable in our previous studies of renal blood flow in normotensive and hypertensive man.

The 10 normotensive white males underwent a hospitalization as described above, except that they were studied only once and received neither placebo nor propranolol. We report here these patients’ renal blood flows and urinary kallikrein activities in order to establish comparative norms for these parameters in white normotensive males on an unrestricted sodium diet; that is, the group was matched for race, sex, age, and dietary sodium intake.

Chemical Assays

Blood for renin and aldosterone determination was drawn into chilled EDTA tubes which were kept on ice until the samples could be centrifuged and the plasma frozen at —30° C. Plasma renin activity was determined by radioimmunossay, with results in nanograms of angiotensin I generated per ml plasma per hour (ng A/ml/hr). Plasma aldosterone concentration was determined by radioimmunossay, with results expressed as picograms per ml plasma (pg/ml).

Blood for plasma dopamine-β-hydroxylase determination was drawn into chilled heparin tubes and kept on ice until the samples were centrifuged and the plasma frozen at —30° C until assay. Enzymatic activity was determined spectrophotometrically, with results expressed as international units (IU)/liter of plasma (IU/liter), where an IU is 1 μmole of octopamine formed from tyramine per minute at 37° C.

Urinary free catecholamines were determined by the trihydroxyindole fluorimetric method, while urinary...
vanillylmandelic acid was assayed by the spectrophotometric method.

Urinary kallikrein activity was measured by enzymatic hydrolysis of radiolabelled p-tosyl arginine methylester (TAME)$^{22,23}$ under our conditions for assay, pH 8.5 and 37°C,$^{16,24}$ using a purified human urinary kallikrein internal standard to correct for recovery,$^{24}$ with results expressed as esterase units/24 hrs (EU/24 hrs), where an esterase unit is defined as the amount of enzyme that hydrolyzes 1 µmole TAME/minute at pH 8.5 and 37°C. Urinary TAME esterolytic activity correlates with kallikrein bioactivity ($r = 0.95$ for esterase activity versus rat blood pressure reduction) in our laboratory.$^{24}$

Calculations

Filtration fraction was calculated as the quotient of $C_u/C_{PAH}$ (i.e., GFR/RPF). Renal blood flow (RBF, in ml/min) was obtained by the formula $RBF = (RPF/1-venous hematocrit)$. Total renal vascular resistance (RVR, in dyne·sec/cm$^5$) was computed$^{16,25}$ as the quotient of MAP/RBF. Fractional sodium excretion was calculated, over 24 hours, as the sodium excreted divided by that filtered at the glomerulus.$^{26}$

Statistics

Results are expressed as the mean value plus or minus the standard error of the mean. Paired $t$ tests determined the significance of differences between subjects on placebo and propranolol, while unpaired $t$ tests assessed the difference between normal controls and hypertensive patients on either placebo or propranolol. Correlations were performed by linear least squares regression analysis. Significance was taken to be a $p$ value of 0.05 or less.$^{27}$

Results

The hypertensives had a fall in blood pressure on propranolol ($p < 0.01$) into the normotensive range (table 1), with an associated fall in heart rate ($p < 0.01$), but no change in weight, plasma volume, or whole blood volume (all $p > 0.1$). Blood urea nitrogen and serum creatinine were unchanged on propranolol, as were serum sodium, potassium, chloride, total protein, and hematocrit (all $p > 0.1$).

Assessment of renal hemodynamics, however, revealed that propranolol treatment produced significant decrements in GFR, RPF, and RBF (all $p < 0.05$, table 2), without associated changes in filtration fraction or total renovascular resistance (all $p > 0.1$). The magnitude of the decline in GFR was 12.1%, while that of renal plasma flow was 14.5%, and that of renal blood flow, 15.8%.

When renal perfusion in the hypertensive group was compared to that in the normotensive control group (table 3), renal blood flow was diminished by 21% in the hypertensives vs normotensives (1096 ± 84 vs 1386 ± 117 ml/min, $p < 0.05$), and this diminution was compounded by propranolol (to 923 ± 38 ml/min, $p < 0.01$ vs placebo, $p < 0.01$ vs normotensives).

Analysis of some biochemical correlates of renal function is shown in table 4. Urinary kallikrein excretion fell by 47% during propranolol treatment (from 9.0 ± 2.7 to 4.8 ± 1.3 EU/24 hrs, $p < 0.04$). Reference to the normotensive control group (table 3, fig. 1) shows that urinary kallikrein excretion was diminished by 55% in the hypertensives vs normotensives (20.0 ± 3.8 vs 9.0 ± 2.7 EU/24 hrs, $p < 0.03$), and this diminution, too, was enhanced by propranolol (down to 4.8 ± 1.3 EU/24 hrs, $p < 0.04$ vs placebo, $p < 0.01$ vs normotensives).

Plasma renin activity was unchanged in the supine position ($p > 0.1$) but declined in the upright position on propranolol, from 1.44 ± 0.36 to 0.53 ± 0.17 ng Al/ml/hr ($p < 0.05$, table 4). Plasma aldosterone concentration was diminished by propranolol (from 68.4 ± 9.6 to 61.4 ± 16.1 pg/ml, $p < 0.02$).

All biochemical indices of sympathetic nervous system activity were unchanged by propranolol (all $p > 0.1$, table 4).

Urinary excretion of volume, creatinine, and electrolytes is considered in table 5. The excretion of volume and creatinine was unchanged from placebo to propranolol phase ($p > 0.1$), as was the total 24-hour excretion of sodium, potassium, and chloride (all $p > 0.1$, NS), in spite of the diminution of GFR (table 2). However, the fractional excretion of sodium rose on propranolol (from 0.75 ± 0.09 to 0.96 ± 0.06%, $p < 0.05$), while the urinary sodium/potassium ratio also increased on propranolol (from 2.41 ± 0.33 up to 3.12 ± 0.30, $p < 0.01$). Change in fractional sodium excretion did not correlate with change in plasma aldosterone concentration ($r = -0.05$) but did correlate with change in urinary sodium/potassium ratio ($r = 0.82, p < 0.01$, fig. 2).

Figure 1. Urinary-kallikrein excretion. Urinary kallikrein activity excreted per 24 hours shows a progressive decline from the normotensive group to the placebo-treated hypertensive group ($p < 0.03$), to the propranolol-treated hypertensive group ($p < 0.04$). Bars represent mean values ± SEM.
### Table 1. Systemic Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Whole blood volume (ml)</th>
<th>Plasma volume (ml)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>112.6 ± 1.9</td>
<td>76.8 ± 4.1</td>
<td>6151 ± 387</td>
<td>3045 ± 144</td>
<td>90.1 ± 3.5</td>
</tr>
<tr>
<td>Propranolol</td>
<td>94.0 ± 2.8</td>
<td>63.4 ± 1.9</td>
<td>5903 ± 313</td>
<td>3358 ± 104</td>
<td>89.5 ± 3.5</td>
</tr>
<tr>
<td><em>p</em> value</td>
<td>&lt; 0.01</td>
<td>&gt; 0.1 (NS)</td>
<td>= 0.07 (NS)</td>
<td>&gt; 0.1 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Renal Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>$C_{cr}$ (ml/min)</th>
<th>$C_{\text{PAH}}$ (ml/min)</th>
<th>Filtration fraction</th>
<th>RBF (ml/min)</th>
<th>RVR (dyne sec/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>103.7 ± 5.9</td>
<td>601 ± 41</td>
<td>0.18</td>
<td>1096</td>
<td>7509</td>
</tr>
<tr>
<td>Propranolol</td>
<td>91.2 ± 5.4</td>
<td>514 ± 19</td>
<td>0.18</td>
<td>923</td>
<td>7988</td>
</tr>
<tr>
<td><em>p</em> value</td>
<td>&lt; 0.02</td>
<td>&gt; 0.1 (NS)</td>
<td>&lt; 0.01</td>
<td>&gt; 0.1 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

$C_{cr}$ = creatinine clearance; $C_{\text{PAH}}$ = clearance of paraaminohippurate; RBF = renal blood flow; RVR = renal vascular resistance.

### Table 3. Normotensive Control Group — Comparison with the Hypertensive Subjects on Placebo

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex, Race</th>
<th>Age (yrs)</th>
<th>BSA ($m^2$)</th>
<th>MAP (mm Hg)</th>
<th>USE (mEq/24 hrs)</th>
<th>RBF (ml/min)</th>
<th>UKE (EU/24 hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive (n = 10)</td>
<td>M, white</td>
<td>46.8 ± 2.4</td>
<td>2.04 ± 0.06</td>
<td>82.7 ± 2.4</td>
<td>166 ± 117</td>
<td>1386</td>
<td>20.0</td>
</tr>
<tr>
<td>Hypertensive (n = 15)</td>
<td>M, white</td>
<td>52.1 ± 2.7</td>
<td>2.09 ± 0.04</td>
<td>112.6 ± 1.9</td>
<td>160 ± 84</td>
<td>1096</td>
<td>9.0</td>
</tr>
<tr>
<td>on placebo (n = 15)</td>
<td>—</td>
<td>&gt; 0.1 (NS)</td>
<td>&gt; 0.1 (NS)</td>
<td>&lt; 0.01</td>
<td>&gt; 0.1 (NS)</td>
<td>&lt; 0.05</td>
<td>&lt; 0.03</td>
</tr>
</tbody>
</table>

BSA = body surface area; MAP = mean arterial pressure; USE = urinary sodium excretion; RBF = renal blood flow; UKE = urinary kallikrein excretion; EU = esterase units; M = male.

### Table 4. Biochemical Determinants of Renal Function

<table>
<thead>
<tr>
<th>Drug</th>
<th>UKE (EU/24 hrs)</th>
<th>PRA (ng/A/ml/hr)</th>
<th>PAC (pg/ml)</th>
<th>Plasma DBH activity (U/liter)</th>
<th>Urinary CAT excretion (µg/24 hrs)</th>
<th>Urinary VMA excretion (mg/24 hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9.0 ± 0.83</td>
<td>1.44 ± 0.14</td>
<td>40.0 ± 6.9</td>
<td>36.9 ± 4.1</td>
<td>208 ± 5.2</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4.8 ± 0.53</td>
<td>0.53 ± 0.05</td>
<td>40.3 ± 3.7</td>
<td>37.4 ± 3.9</td>
<td>167 ± 5.9</td>
<td>5.9 ± 0.6</td>
</tr>
<tr>
<td><em>p</em> value</td>
<td>&gt; 0.04</td>
<td>&lt; 0.05</td>
<td>&lt; 0.02</td>
<td>&gt; 0.1 (NS)</td>
<td>&gt; 0.1 (NS)</td>
<td>&gt; 0.1 (NS)</td>
</tr>
</tbody>
</table>

UKE = urinary kallikrein excretion; PRA = plasma renin activity; PAC = plasma aldosterone concentration; DBH = dopamine-ß-hydroxylase; CAT = catecholamine; VMA = vanillylmandelic acid.

### Table 5. Urinary Excretion of Volume, Creatinine, and Electrolytes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Urinary volume (ml/24 hrs)</th>
<th>Urinary creatinine (mg/24 hrs)</th>
<th>Urinary sodium (mEq/24 hrs)</th>
<th>Urinary potassium (mEq/24 hrs)</th>
<th>Urinary chloride (mEq/24 hrs)</th>
<th>Fractional excretion of sodium (%)</th>
<th>Sodium/potassium ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1612 ± 147</td>
<td>1605 ± 102</td>
<td>160 ± 21</td>
<td>69 ± 5</td>
<td>131 ± 4</td>
<td>0.75 ± 0.09</td>
<td>2.41 ± 0.33</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1869 ± 177</td>
<td>1540 ± 102</td>
<td>173 ± 12</td>
<td>68 ± 4</td>
<td>152 ± 4</td>
<td>0.96 ± 0.06</td>
<td>3.12 ± 0.30</td>
</tr>
<tr>
<td><em>p</em> value</td>
<td>&gt; 0.1 (NS)</td>
<td>&gt; 0.1 (NS)</td>
<td>&gt; 0.1 (NS)</td>
<td>= 0.09 (NS)</td>
<td>&gt; 0.1 (NS)</td>
<td>&lt; 0.05 (NS)</td>
<td>&lt; 0.01 (NS)</td>
</tr>
</tbody>
</table>
To investigate change in renal blood flow from placebo to propranolol, the change was correlated (table 6) with several pretreatment variables (predictors of change) and change in several other variables (covariants). Change in renal blood flow correlated inversely with pretreatment renal blood flow ($r = -0.91$, $p < 0.01$; fig. 3) and pretreatment urinary catecholamine excretion ($r = -0.64$, $p < 0.01$), directly with pretreatment renal vascular resistance ($r = 0.85$, $p < 0.01$; fig. 4), and inversely with change in renal vascular resistance ($r = -0.86$, $p < 0.01$; fig. 5). Change in renal blood flow did not correlate with several other pretreatment parameters (age, MAP, heart rate, GFR, plasma volume, whole blood volume, urinary electrolyte excretion, plasma renin activity, plasma aldosterone concentration, urinary kallikrein activity, or plasma dopamine-β-hydroxylase activity). In addition, pretreatment urinary catecholamine excretion correlated directly with pretreatment renal blood flow ($r = 0.73$, $p < 0.01$) and inversely with pretreatment renal vascular resistance ($r = -0.64$, $p < 0.01$). Change in renal blood flow did not correlate with change in kallikrein excretion ($r = -0.16$; table 6) or change in several other parameters (propranolol dose, MAP, heart rate, GFR, urinary electrolyte excretion, plasma renin activity, or plasma aldosterone concentration).

Likewise, to investigate change in kallikrein excretion from placebo to propranolol, the change was cor-
related (table 7) with several pretreatment variables (predictors of change) and change in several other variables (co-variants). Change in kallikrein excretion correlated inversely with pretreatment kallikrein excretion \((r = -0.87, p < 0.01; \text{fig. 6})\), but there were no other significant predictors or covariants identified (age, propranolol dose, MAP, heart rate, GFR, RBF, RVR, plasma volume, whole blood volume, urinary electrolyte excretion, plasma renin activity, plasma aldosterone concentration, or plasma dopamine-B-hydroxylase activity).

**Discussion**

Propranolol lowered blood pressure in these hypertensive subjects without any appreciable change in the usual serum indices of renal function (BUN and creatinine), but declines in GFR (12%), RPF (15%), and RBF (16%) were noted, in accordance with previous observations.° They suggested several explanations, including: impaired renal perfusion autoregulation, a direct alpha agonist effect of propranolol in renal vessels, and a renal blood flow decline in parallel with a systemic blood flow (cardiac output) decline.

Our data suggest a failure of renal perfusion autoregulation, since the renal perfusion decrement correlated with a renal resistance increment (fig. 5); the normal response of the kidney to reduced perfusion pressure is a decrease in RVR.° The renal perfusion decrement in

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**Table 7.** Change in Urinary Kallikrein Excretion on Propranolol: Correlation Coefficients for Predictors and Covariants

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>(r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of change in kallikrein excretion</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.07</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.35</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>0.18</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>-0.14</td>
</tr>
<tr>
<td>Whole blood volume</td>
<td>0.28</td>
</tr>
<tr>
<td>Urinary sodium excretion</td>
<td>0.51</td>
</tr>
<tr>
<td>Urinary potassium excretion</td>
<td>0.16</td>
</tr>
<tr>
<td>Urinary sodium/potassium</td>
<td>0.48</td>
</tr>
<tr>
<td>Fractional sodium excretion</td>
<td>-0.52</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>-0.02</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>-0.11</td>
</tr>
<tr>
<td>Urinary kallikrein excretion</td>
<td>-0.87*</td>
</tr>
<tr>
<td>Covariants with change in kallikrein excretion</td>
<td></td>
</tr>
<tr>
<td>Propranolol daily dose</td>
<td>-0.44</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.06</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>0.20</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>-0.16</td>
</tr>
<tr>
<td>Urinary sodium/potassium</td>
<td>-0.38</td>
</tr>
<tr>
<td>Fractional sodium excretion</td>
<td>-0.39</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.09</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*\(p < 0.01\) for correlation coefficient. In each case, the dependent variable in the correlation is change in urinary kallikrein excretion.
our subjects was heterogenous, occurring most promi-
nently in those with a relatively ‘‘normal’’ renal vascular
tree, i.e., those with the highest RBFs and lowest
RVRs (figs. 3 and 4); those with evidence of the most
nephrosclerosis (low RBF, high RVR) had little if any
decline in RBF on propranolol. Perhaps those with
nephrosclerosis had a relatively inelastic renal bed,
impervious to further vasoconstriction. In addition, the
inverse correlation of RBF decrement with basal uri-
cary catecholamine excretion, coupled with the direct
correlation between basal catecholamine excretion and
basal renal blood flow, suggests that the fall in renal
perfusion is greatest in those subjects with the highest
endogenious sympathetic tone; one might expect a
greater degree of unopposed alpha mediated renal
vasoconstriction after beta blockade in such subjects,
even without change in endogenous sympathetic activ-
ty. This heterogeneity of renal blood flow response
may help explain conflicting results in other studies of
beta blocker effects on renal function,1 and may ex-
plain the especially pronounced effects of propranolol
upon renal perfusion in normotensive, healthy
subjects.6

Why did kallikrein diminish after propranolol? Poten-
tial mechanisms include diminished mineralocorti-
coid activity23 and a direct linkage of a renal beta recep-
tor to kallikrein excretion.35 Mineralocorticoid activity
was diminished, but change in plasma aldosterone
concentration or urinary sodium/potassium ratio did
not correlate with the kallikrein decrement; nor was the
kallikrein fall dose dependent, weighing against direct
beta blockade as the explanation (table 7). In fact, the
only significant predictor of a marked fall in kallikrein
excretion was a relatively high pretreatment kallikrein
excretion (fig. 6).

While there was a progressive decrease in both RBF
and kallikrein excretion in the groups normals→hypertensives on placebo→hypertensives on propranolol
tables 2-4; fig. 1), there was no significant correlation
(r = -0.16) between RBF decrement and kallikrein
decrement after propranolol, casting some doubt on
kallikrein decrement as a mechanism for RBF decre-
ment. Indeed, some would suggest that diminished
kallikrein excretion could be secondary to the decline
in RBF.34

Some studies suggest that propranolol is anti-
natriuretic.9,31,35 We found no change in plasma vol-
ume, blood volume, weight, or overall sodium excre-
tion on propranolol, however, consistent with other
studies where plasma volume has not been expanded by
longterm use of the drug.36-38 Sodium excretion
remained unimpaired even in the face of diminished
GFR; the quantitative expression for this phenomenon
is the increase in the fractional sodium excretion, or
that fraction of filtered sodium which is excreted, from
0.75% ± 0.09% up to 0.96% ± 0.06% (p < 0.05,
table 4). Preservation of sodium homeostasis and ex-
cretion via an increase in fractional sodium excretion
as GFR declines, is reminiscent of the usual adaptive
renal response to nephron loss.43 Correlation of frac-
tional sodium excretion enhancement with the increase
in urinary sodium/potassium ratio (r = 0.82, fig. 2),
coupled with decreased plasma aldosterone concentra-
tion, suggests that diminished mineralocorticoid activity
lead to enhanced excretion of filtered sodium.

Was there a role for renal kallikrein in this change in
renal sodium handling? Some studies suggest that the
renal kallikrein-kinin system is natriuretic41-42 while
others suggest that it is antinatriuretic in action.43
We found an increase in fractional sodium excretion (that
is, a natriuretic effect) in association with a decrease in
kallikrein excretion on propranolol, suggesting, per-
haps, that kallikrein was antinatriuretic in this setting.
However, change in kallikrein excretion did not corre-
late with either change in fractional sodium excretion
or change in urinary sodium/potassium ratio (table 7),
weighing against a prominent kallikrein mediation of
the electrolyte changes noted.

In summary, hypertensives given propranolol had a
decrease in GFR, RPF, RBF, plasma aldosterone
concentration, and urinary kallikrein excretion. Decre-
ment in kallikrein excretion did not correlate with RBF
fall. Sodium homeostasis was maintained by an en-
hanced fractional sodium excretion, best explained by
diminished mineralocorticoid activity with an increase
in the urinary sodium/potassium ratio. No correlation
was found between kallikrein change and electrolyte
excretion changes.

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