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

DANIEL T. O’CONNOR, M.D. AND RICHARD A. PRESTON, M.D.

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 with 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-
sives before and after 1 month of propranolol therapy, assessing renal perfusion, renal electrolyte handling, and several potential mediators of propranolol effects on the kidney, including intravascular volume, the renal kallikrein-kinin system, the renin-angiotensin-aldosterone system, and the sympathetic nervous system.

**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 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 adult white male normotensive volunteers on no medication, matched to the hypertensives for sex (male), race (white), age (mean 46.8 ± 2.4 years, p > 0.1 vs the hypertensives), and dietary sodium intake (unrestricted, > 100 mEq/24 hrs).

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-B-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 Volemetron 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 (C_PAH). 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 radioimmunoassay, with results in nanograms of angiotensin I generated per ml plasma per hour (ng A/ml/hr). Plasma aldosterone concentration was determined by radioimmunoassay, with results expressed as picograms per ml plasma (pg/ml).

Blood for plasma dopamine-B-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.21

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,18,24 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 C7/C7,FH (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/cm⁵) was computed16,25 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).
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>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>112.6 ± 1.9</td>
<td>76.8</td>
<td>6151</td>
<td>3045</td>
<td>90.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Propranolol</td>
<td>94.0 ± 2.8</td>
<td>63.4</td>
<td>5903</td>
<td>3358</td>
<td>89.5</td>
<td>&gt; 0.1 (NS)</td>
</tr>
</tbody>
</table>

Table 2. Renal Hemodynamic Parameters

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Race</th>
<th>Age (yrs)</th>
<th>BSA (m²)</th>
<th>MAP (mm Hg)</th>
<th>USE (mEq/24 hrs)</th>
<th>RBF (ml/min)</th>
<th>UKE (EU/24 hrs)</th>
<th>Sex, Race</th>
<th>Age (yrs)</th>
<th>BSA (m²)</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</td>
<td>M, white</td>
<td>white</td>
<td>46.8</td>
<td>2.04</td>
<td>82.7</td>
<td>166</td>
<td>1386</td>
<td>20.0</td>
<td>M, white</td>
<td>52.1</td>
<td>2.09</td>
<td>122.6</td>
<td>160</td>
<td>1096</td>
<td>9.0</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>M, white</td>
<td>white</td>
<td>52.1</td>
<td>2.09</td>
<td>122.6</td>
<td>160</td>
<td>1096</td>
<td>9.0</td>
<td>M, white</td>
<td>52.1</td>
<td>2.09</td>
<td>122.6</td>
<td>160</td>
<td>1096</td>
<td>9.0</td>
</tr>
<tr>
<td>on placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.02</td>
<td>&lt; 0.02</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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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/m²/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>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9.0 ± 2.7</td>
<td>0.83 ± 0.24</td>
<td>1.44 ± 0.36</td>
<td>68.4 ± 9.6</td>
<td>40.0 ± 5.3</td>
<td>36.9 ± 5.6</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4.8 ± 1.3</td>
<td>0.53 ± 0.22</td>
<td>0.53 ± 0.17</td>
<td>61.4 ± 16.1</td>
<td>40.3 ± 5.8</td>
<td>37.4 ± 3.9</td>
<td>&gt; 0.1 (NS)</td>
</tr>
</tbody>
</table>

UKE = urinary kallikrein excretion; PRA = plasma renin activity; PAC = plasma aldosterone concentration; DBH = dopamine-β-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>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1612 ± 147</td>
<td>1605 ± 104</td>
<td>160</td>
<td>69</td>
<td>131</td>
<td>0.75</td>
<td>2.41</td>
<td>&gt; 0.1 (NS)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1869 ± 177</td>
<td>1540 ± 102</td>
<td>173</td>
<td>58</td>
<td>155</td>
<td>0.96</td>
<td>3.12</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

UKE = urinary kallikrein excretion; PRA = plasma renin activity; PAC = plasma aldosterone concentration; DBH = dopamine-β-hydroxylase; CAT = catecholamine; VMA = vanillylmandelic acid.
Figure 2. Change in fractional sodium excretion as a function of change in urinary sodium/potassium ratio, going from placebo to propranolol. Each point is an individual subject. The two parameters increased in parallel ($r = 0.82$, $p < 0.01$).

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-B-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, plasma electrolyte excretion, plasma renin activity, or plasma aldosterone concentration).

Likewise, to investigate change in kallikrein excretion from placebo to propranolol, the change was correlated inversely with change in urinary sodium/potassium ratio ($r = -0.91$, $p < 0.01$; fig. 2) and directly with change in renal blood flow ($r = 0.85$, $p < 0.01$).

![Figure 3. Change in renal blood flow on propranolol, as a function of initial renal blood flow on placebo. Each point is an individual subject. Higher initial renal blood flow predicts a greater fall in renal blood flow on propranolol ($r = -0.91$, $p < 0.01$).](image)

![Figure 4. Change in renal blood flow on propranolol, as a function of initial renal vascular resistance on placebo. Each point is an individual subject. Lower initial renal vascular resistance predicts a greater fall in renal blood flow on propranolol ($r = 0.85$, $p < 0.01$).](image)

Table 6. Change in Renal Blood Flow 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 renal blood flow</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.30</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>-0.04</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>-0.91*</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>0.85*</td>
</tr>
<tr>
<td>Whole blood volume</td>
<td>0.37</td>
</tr>
<tr>
<td>Urinary sodium excretion</td>
<td>0.05</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>-0.38</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>-0.15</td>
</tr>
<tr>
<td>Urinary kallikrein excretion</td>
<td>-0.16</td>
</tr>
<tr>
<td>Urinary catecholamine excretion</td>
<td>-0.64*</td>
</tr>
<tr>
<td>Covariants with change in renal blood flow</td>
<td></td>
</tr>
<tr>
<td>Propranolol daily dose</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.2</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>-0.26</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>-0.86*</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>-0.06</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>0.28</td>
</tr>
<tr>
<td>Urinary kallikrein excretion</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

* $p < 0.01$ for correlation coefficient. In each case, the dependent variable in the correlation is change in renal blood flow.
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. We suggest the fall in renal blood flow (cardiac output) decline. What is the mechanism for the fall in renal blood flow? Prior studies have suggested several explanations, including: impaired renal perfusion autoregulation, unopposed alpha vasoconstriction in the renal bed after beta blockade, 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.5, 10, 31

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

### Table 7

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>( r )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of change in kallikrein excretion</td>
<td>( r )</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>( r )</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 vas-
cular 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
endogenous 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 ac-
Table 4). Preservation of sodium homeostasis and ex-
cretion via an increase in fractional sodium excretion
is the increase in the fractional sodium excretion, or
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 con-
centration, 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.

Acknowledgments
We appreciate the collaboration of Richard A. Stone, M.D., the
biochemical expertise of Ronald P. Frigon, Ph.D., the technical
assistance of Justine Cervenka, the secretarial support of Marta
Zekan-Czoka, and the help of the nursing staff on the Special
Diagnostic and Treatment Unit of the San Diego Veterans Admin-
istration Medical Center.

References
1. Weber MA, Drayer JM: Renal effects of beta-adrenoeceptor
2. Pnchard BNC, Gillam PMS: Treatment of hypertension with
3. Lydion H, Kusus T, Daniel W, Schierl W, Ackenneil M,
Kempter H, Lohmoller G, Niklas M, Walter I: Propranolol
therapy in essential hypertension. Am Heart J 83: 589, 1972
4. Thompson FD, Joekes AM: Beta blockade in the presence of
5. Ibsen H, Sederberg-Olsen P: Changes in glomerular filtration
rate during longterm treatment with propranolol in patients
7. Warren DJ, Swinson CP, Wright D: Deterioration in renal
function after beta blockade in patients with chronic renal
8. Schimpgether VJ. Decot M, Hallauer W, Willman H: B-recep-
toren und renale hemodynamik es menschen. Arzneim Forsch
16: 847, 1966
9. Krauss KH, Schalekamp MADO, Kosters G, Zaal GA, Birk-
enhager WH: Effects of chronic beta adrenoeergic blockade on
systemic and renal hemodynamic responses to hyperosmotic

Downloaded from http://hyper.ahajournals.org/ by guest on July 12, 2017
Urinary kallikrein activity, renal hemodynamics, and electrolyte handling during chronic beta blockade with propranolol in hypertension.

D T O'Connor and R A Preston

Hypertension. 1982;4:742-749
doi: 10.1161/01.HYP.4.5.742

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/4/5/742.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/