The renal, forearm, and hormonal responses to standing in the presence and absence of propranolol

GEORGE L. BAKRIS, M.D.,* DAVID M. WILSON, M.D., AND JOHN C. BURNETT, JR., M.D.

ABSTRACT Nine normal volunteers underwent assessment of renal, forearm, and hormonal responses to orthostasis (quiet standing) in the presence and absence of 1 week of oral propranolol (160 mg/day). This was done to test the hypothesis that physiologic decrements in renal function (glomerular filtration rate, effective renal plasma flow, and absolute urinary sodium excretion) are attenuated by propranolol during quiet standing. The present studies, however, demonstrate that propranolol exaggerates the physiologic decrement in glomerular filtration rate, effective renal plasma flow, and absolute sodium excretion during orthostasis. Forearm and renal vascular resistances were also accentuated in the presence of propranolol during quiet standing. These responses were associated with significant increases in plasma norepinephrine. We conclude that long-term administration of propranolol accentuates the physiologic decrement in renal hemodynamic and excretory function as well as in the forearm hemodynamic response to orthostasis in normal subjects.


Inasmuch as propranolol has been reported to alter the sensitivity of cardiovascular reflexes both over the short and long term,7,8 the present study was designed to examine the renal hemodynamic and excretory response to orthostasis in the presence and absence of long-term propranolol.

Methods

Nine normotensive subjects (eight men and one woman) with a mean age of 26 ± 3 years were studied in the Clinical Nephrology Unit of the Mayo Clinic after informed consent was obtained from each. All subjects underwent a preliminary screening that included taking of a history, physical examination, chest x-ray, and electrocardiographic examination. Subjects were placed on a 140 meq/day sodium diet beginning 7 days before the protocol and continued on this diet for the duration of the study. A 24 hr urinary sodium specimen was collected the day before each period of timed renal and neurohumoral measurements to ensure compliance with the diet.

Patients were placed in the supine position for 1 hr of equilibration. During the first 15 min, percutaneous venous butterfly catheters were placed for infusion and blood sampling. Twenty minute timed measurements were obtained in subjects in both the supine and upright positions. The supine measurements were obtained beginning 1 hr after equilibration in subjects in the recumbent position. They were then placed in the upright position (quiet standing) for two 20 min periods so that upright measurements could be obtained. Renal measurements included those of glomerular filtration rate, effective renal plasma flow, renal vascular resistance, and absolute urinary sodium excretion. Hemodynamic measurements obtained in subjects in the supine and upright positions included forearm blood flow and vascular resistance, arterial pressure, and heart rate. Neuroendocrine measurements include plasma norepinephrine and plas-
Glomerular filtration rate was calculated from the clearance of inulin, effective renal plasma flow (ERPF) was determined from the clearance of para-aminohippurate, and renal blood flow was calculated with the equation ERPF/(1 - hematocrit).

The presence and absence of propranolol was based on previous studies performed in subjects in the supine position. Arterial hematocrit was measured in heparinized glass capillary tubes in each period. Renal vascular resistance was derived from the ratio arterial pressure/renal blood flow. Plasma and urine samples were analyzed for inulin by the anthrone method, for para-aminohippurate by the method of Harvey and Brothers, and for sodium with the Beckman ion-selective analyzer.

Forearm blood flow was measured by venous occlusive plethysmography as previously described. The strain gauge was placed 5 cm below the antecubital fossa of the right arm. The pressure of the venous occlusion was 40 mm Hg. Circulation to the right hand was arrested by inflating a cuff around the wrist to 180 mm Hg during determination of forearm blood flow. Forearm vascular resistance was calculated by dividing arterial pressure by forearm blood flow. Arterial pressure was measured in the left arm by sphygmomanometry and heart rate was determined by measurement of the apical pulse.

Plasma norepinephrine and renin activity were measured by appropriate radioimmunoassays.

Values are expressed as the mean ± SE. Values obtained before and during quiet standing and before and during administration of propranolol were compared by paired t tests and Dunnett’s t test for simultaneous multiple comparisons. A statistically significant difference was considered to be present when p < .05.

Results

Renal hemodynamics and excretory responses. The renal and excretory reflex responses to the stress of orthostasis in the presence and absence of propranolol are summarized in table 1.

Glomerular filtration rate decreased in both control (118 ± 4 to 102 ± 5 ml/min, p < .05) and propranolol (112 ± 3 to 82 ± 6 ml/min, p < .05) periods with orthostasis, with the greatest decrease occurring in the presence of propranolol (−16 ± 5 control vs −30 ± 4 Δml/min after propranolol, p < .05) (figure 1). Effective renal plasma flow decreased with quiet standing during control (590 ± 21 to 481 ± 22 ml/min, p < .05) and propranolol (528 ± 30 to 354 ± 28 ml/min, p < .05) periods, with the greatest decrement occurring in the presence of propranolol (−108 ± 14 control vs −174 ± 18 Δml/min after propranolol, p < .05) (figure 1). Renal vascular resistance increased with orthostasis during both control (0.07 ± 0.01 to 0.10 ± 0.02 mm Hg/ml/min, p < .05) and propranolol (0.08 ± 0.01 to 0.13 ± 0.02 mm Hg/ml/min, p < .05) periods. There was a greater increase in renal vascular resistance during the propranolol period than during the control period (0.026 ± 0.009 control vs 0.055 ± 0.013 Δmm Hg/ml/min after propranolol, p < .05) (figure 2).

Urinary sodium excretion diminished in both control (266 ± 13 to 140 ± 12 μeq/min, p < .05) and propranolol (227 ± 13 to 69 ± 15 μeq/min, p < .05) periods during quiet standing. This decrement was greatest in the presence of propranolol (−126 ± 5 control vs −158 ± 7 Δμeq/min after propranolol, p < .05) (figure 3).

Hemodynamic response. The systemic hemodynamic responses to quiet standing in the presence and absence of propranolol are summarized in table 2.

Mean arterial pressure increased during both control (86 ± 2 to 93 ± 3 mm Hg, p < .05) and propranolol

![FIGURE 1. Decreases (% change) in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) during orthostasis before and after propranolol.](http://circ.ahajournals.org/doi/10.1161/01.CIR.92.6.126)

TABLE 1

The renal hemodynamic and excretory response to the reflex stress of orthostasis in the presence and absence of propranolol

<table>
<thead>
<tr>
<th></th>
<th>Control (Supine)</th>
<th>Control (Upright)</th>
<th>Propranolol (Supine)</th>
<th>Propranolol (Upright)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>118 ± 4</td>
<td>102 ± 5</td>
<td>112 ± 3</td>
<td>82 ± 6</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>590 ± 21</td>
<td>481 ± 22</td>
<td>528 ± 30</td>
<td>354 ± 28</td>
</tr>
<tr>
<td>RVR (mm Hg/ml/min)</td>
<td>0.07 ± 0.01</td>
<td>0.10 ± 0.02</td>
<td>0.08 ± 0.01</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>U_{14}V (meq/min)</td>
<td>266 ± 13</td>
<td>140 ± 12</td>
<td>227 ± 13</td>
<td>69 ± 15</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; ERPF = effective renal plasma flow; RVR = renal vascular resistance; U_{14}V = absolute urinary sodium excretion.

*p < .05 different from supine; **p < .05 different from control.
(83 ± 2 to 88 ± 2 mm Hg, p < .05) periods with orthostasis. Although baseline arterial pressures did not differ between these groups (86 ± 2 control vs 83 ± 2 mm Hg after propranolol), supine heart rate was lower in the propranolol as compared with during the control period (60 ± 3 vs 48 ± 2 beats/min, p < .05). Heart rate increased during both control (60 ± 3 to 74 ± 3 beats/min, p < .05) and propranolol (48 ± 2 to 56 ± 3 beats/min, p < .05) periods with orthostasis. The heart rate response, however, was blunted in the propranolol period during the reflex stress of orthostasis (14 ± 2 control vs 7 ± 2 Δbeats/min after propranolol, p < .05). Forearm vascular resistance increased in both control (36 ± 5 to 54 ± 7, p < .05) and propranolol (43 ± 6 to 118 ± 11, p < .05) periods, with a greater increase in forearm vascular resistance occurring in the propranolol period (18 ± 3 control vs 75 ± 10 ΔU after propranolol, p < .05) with quiet standing (figure 2). Forearm blood flow decreased during both control (2.8 ± 0.4 to 1.9 ± 0.3 ml·min⁻¹·100 ml⁻¹, p < .05) and propranolol (2.2 ± 0.2 to 0.8 ± 0.1 ml·min⁻¹·100 ml⁻¹, p < .05) periods. This decrement was greater during the propranolol period (0.9 ± 0.3 control vs 1.4 ± 0.1 Δml·min⁻¹·100 ml⁻¹ after propranolol, p < .05) with orthostasis.

**Hormonal response.** The hormonal responses to orthostasis in the presence and absence of propranolol are summarized in table 3. Plasma norepinephrine levels increased both during control (260 ± 34 to 517 ± 63 pg/ml, p < .05) and propranolol (290 ± 37 to 591 ± 61 pg/ml, p < .05) periods with orthostasis. The magnitude of increases in plasma norepinephrine did not differ in the presence or absence of propranolol. Supine plasma renin activity was decreased in the presence of propranolol (0.8 ± 0.1 control vs 0.4 ± 0.1 ng/ml after propranolol, p < .05). An increase in plasma renin activity was observed during the control period (0.8 ± 0.1 to 1.7 ± 0.3 ng/ml, p < .05), and there was no significant increase in the presence of propranolol.

**Discussion**

The present studies demonstrate that quiet standing is characterized by a maintenance of arterial pressure and tachycardia in association with a decrease in glomerular filtration rate, renal plasma flow, and urinary sodium excretion. Vascular resistance within both the renal and forearm circulation increases. These cardio-renal adjustments to orthostasis are associated with

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**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Propranolol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>86 ± 2</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>60 ± 3</td>
<td>74 ± 3</td>
</tr>
<tr>
<td>FVR (U)</td>
<td>36 ± 5</td>
<td>54 ± 7</td>
</tr>
<tr>
<td>FBF (ml·min⁻¹·100 ml⁻¹)</td>
<td>2.8 ± 0.4</td>
<td>1.9 ± 0.3</td>
</tr>
</tbody>
</table>

FVR = forearm vascular resistance; FBF = forearm blood flow; MAP = mean arterial pressure.

*p < .05 different from supine; *p < .05 different from control.

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increases in plasma norepinephrine and renin activity. These studies further demonstrate that the renal hemodynamic and excretory as well as the forearm vascular response to orthostasis are accentuated in the presence of \(\beta\)-adrenoreceptor blockade.

The exaggerated decreased in glomerular filtration rate, renal blood flow, and sodium excretion in the presence of propranolol during orthostasis may provide insight into the mechanism of orthostatic-mediated decreases in renal hemodynamic and excretory function. During orthostasis in the presence of propranolol, \(\alpha\)-adrenoreceptor activity would be relatively unopposed in association with increased levels of norepinephrine. This unopposed \(\alpha\)-adrenoreceptor activity would result in an exaggerated \(\beta\)-mediated decrease in renal hemodynamics. The subsequent decline in glomerular filtration rate and subsequent filtered load of sodium would yield a decrease in sodium excretion. Enhanced \(\alpha\)-adrenoreceptor activity has also been shown to contribute to increased tubular reabsorption of sodium. Since plasma renin activity did not increase during orthostasis in the propranolol period, the exaggerated decrease in renal hemodynamic and excretory function in response to orthostasis cannot be attributed to the renin-angiotensin system. Results of our study are in contrast to the previous investigations of Ferguson et al.,\(^7\) who studied the short-term vascular actions of propranolol during lower body negative pressure, but are consistent with those of Larsen and Pedersen\(^8\) and Pedersen,\(^9\) who investigated the long-term actions of propranolol on renal hemodynamics during exercise, and of Davies et al.,\(^15\) who investigated the effects of short-term propranolol on the endocrine response to orthostasis. Our findings are most consistent with the interpretation that, in the presence of propranolol therapy, the integrated renal, endocrine, and vascular responses to quiet standing are exaggerated and reflect the unopposed activity of the adrenergic nervous system. Thus, this study provides data in humans that are consistent with an important relationship between the adrenergic nervous system and the tubular reabsorption of sodium.\(^{16, 17}\)

The present study was also designed to simultaneously compare the responsiveness of the renal to the forearm circulation in an integrated reflex maneuver of true orthostasis in man in the presence and absence of \(\beta\)-adrenoreceptor blockade. The present studies document similar directional changes in the renal and forearm circulation during quiet standing and suggest that the reflex control of both vascular beds is altered by propranolol.

In summary, our study demonstrates that reflex control of renal and forearm circulations is by similar pathways with comparable sensitivities. This study further demonstrates that in the presence of propranolol, the renal hemodynamic and excretory response to the complex reflex stimulation of true orthostasis is exaggerated and may be mediated by activation of the adrenergic nervous system.

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| TABLE 3 | The hormonal responses to the reflex stress of orthostasis in the presence and absence of propranolol |
|------------------|------------------|------------------|------------------|
|                  | Control          | Propranolol       |                  |
|                  | Supine           | Upright           | Supine           | Upright           |
| PNE (pg/ml)      | 260 ± 34         | 517 ± 63\(^a\)   | 290 ± 37         | 591 ± 61\(^a\)    |
| PRA (ng/min)     | 0.8 ± 0.1        | 1.7 ± 0.3\(^a\)  | 0.4 ± 0.1\(^b\)  | 0.6 ± 0.1\(^b\)   |

\(^a\) - \(p < .05\) different from supine; \(^b\) - \(p > .05\) different from control.
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