SUMMARY The acute effects of small doses of intravenous propranolol on renin release and on circulatory dynamics were studied in normal man at the time of renal arteriography in 12 persons with essential hypertension. All of the subjects had a normal peripheral renin response to chronic sodium depletion and all had normal renal function. Seven subjects received a 10-mEq sodium diet for at least 4 days prior to study and five received a 200-mEq sodium diet. At the time of arteriography, arterial blood pressure, pulse rate, cardiac output, renal blood flow, and arterial and renal venous renin activity were measured before and 6-20 minutes after the intravenous administration of propranolol (9-18 μg/kg). Average renin secretion rate in the salt-depleted subjects fell from 367 ± 80 (SEM) U/ml per 100 g/min to 122 ± 51 U/ml per 100 g/min (P < 0.03), and renal plasma flow fell from 189 to 155 ml/min per 100 g (P = 0.018). We also found that in the salt-loaded subjects, renal plasma flow fell from 213 to 184 ml/min per 100 g (P = 0.025), whereas renin secretion did not change significantly. Furthermore we found that mean arterial pressure and cardiac index did not change significantly in either group. We conclude that propranolol rapidly blocks renin release despite circulatory changes which ordinarily constitute a stimulus for renin secretion, i.e., renal vasoconstriction and reduced renal blood flow.

PROPRANOLOL exerts several pharmacological effects including production of β-adrenergic receptor blockade and local anesthesia and a quinidine-like action of cell membranes. This agent now is used widely in the management of patients with cardiac arrhythmias or angina pectoris, and is being used increasingly to treat patients with hypertension. The mechanism responsible for the hypotensive effect of propranolol is not clear. Possible explanations include: reduction of cardiac output, central nervous system effect, and decreased renin release. It has been suggested that propranolol is most effective in renin-dependent forms of hypertension. Although oral administration of propranolol has been shown to reduce peripheral plasma renin activity (PRA) in human subjects after a variety of challenges, the relationship of reduced renin release to propranolol-induced hemodynamic changes has not been investigated in man and is the subject of this report.

Methods

Twelve subjects with essential hypertension participated in the study. In all, diastolic blood pressure was elevated to levels above 110 mm Hg on at least two separate outpatient visits prior to admission. Eight of the 12 had not received prior antihypertensive therapy, two had received therapy with thiazide diuretic agents, one had been treated with hydrochlorothiazide, methyldopa, and hydralazine, and one with spironolactone, methyldopa, and guanethidine. All medications were discontinued at least 2 weeks prior to study. The study protocol was approved by the Human Experimentation Committee of the Peter Bent Brigham Hospital. All of the subjects were informed of the experimental nature of the protocol and gave their written consent. The subjects (seven female and five male) ranged in age from 19 to 42 years; nine were white. All were judged to be free of complicating illness after undergoing a clinical evaluation consisting of a complete history and physical examination; routine urinalysis; urine culture; hematocrit; white blood cell and differential counts; measurement of serum creatinine, glucose, sodium potassium, chloride, bicarbonate, calcium, phosphorus, uric acid, cholesterol, and triglycerides; serum protein by electrophoresis; antinuclear antibodies; 24-hour endogenous creatinine clearance; urinary excretion of vanillylmandelic acid (VMA); total metanephrines, 17-hydroxysteroids, 17-ketosteroids; and rapid sequence intravenous pyelograms. The subjects were admitted to a metabolic ward and given a constant diet containing a daily intake of 2,500 calories, 2,500 ml of fluid, 100 mEq of potassium, and either 10 or 200 mEq of sodium for at least 4 days before study. Twenty-four-hour sodium excretion was measured daily to access metabolic balance. Peripheral PRA was measured after 3 hours of ambulation when each subject had reached metabolic balance on a 10-mEq sodium diet, and all 12 subjects were found to have peripheral PRA levels within our laboratory’s range of normal relative to the sodium intake. Seven of the subjects underwent hemodynamic study while receiving a 10-mEq sodium diet and 5 were studied while receiving a 200-mEq sodium diet. All subjects were found to be in metabolic balance at the time of hemodynamic study.

The subjects were studied after an overnight fast. Diazepam (5–10 mg, im) was given 1 hour before the study. Percutaneous selective renal arterial and venous catheterization was performed under local anesthesia with fluoroscopic monitoring. The arterial catheter was used to monitor blood pressure, renal blood flow, and arterial and renal venous renin activity.
pressure and heart rate, to inject xenon, and for arterial blood sampling. A venous catheter was used to draw blood from the renal veins and for the injection of indocyanine green.

Blood pressure was measured with a Statham P23Dc pressure transducer and recorded on an Electronics for Medicine recorder simultaneously with the electrocardiogram and instantaneous pulse rate. Mean blood pressure was calculated as the sum of diastolic pressure and 1/3 of the pulse pressure. Cardiac output was measured by the indicator-dilution technique using indocyanine green dye, with injection into the inferior vena cava at the level of the diaphragm and sampling from the abdominal aorta. Renal and systemic vascular resistances were calculated from the Frank formula: Resistance (dyne cm⁻⁵ sec) = mean pressure (mm Hg) × 1,330/cardiac output (ml/sec). Renal blood flow (ml/sec per 100 g) was used to estimate renal vascular resistance. Mean renal blood flow was measured from the initial slope of ¹³³Xe disappearance with external probe counting determined graphically with a hematocrit-corrected partition coefficient. Curves reanalyzed on a coded basis showed a coefficient of variation of 7%.

The subjects were studied no sooner than 30 minutes after renal arteriography at a time when they were comfortable and blood pressure and pulse rate were stable. At this time arterial and renal venous blood samples were obtained for the measurement of PRA. Cardiac output, blood pressure, and heart rate were recorded and renal blood flow was measured. The subjects then received propranolol, 9–18 µg/kg, iv, over 1 minute. Ten minutes later (range, 5–20 minutes) measurements were repeated.

PRA was measured by a modification of the method of Boucher et al. and Blaufox et al. Renin secretory rates were calculated as the product of renal plasma flow and venoarterial renin difference.

Statistical probability was evaluated with the paired data t-test or by standard regression formulas.

**Results**

**PLASMA RENIN ACTIVITY**

Renal vein renin activity fell significantly from 781 ± 98 (SEM) ng/ml per 3 hours to 626 ± 78 ng/ml per 3 hours (20%) promptly after propranolol was administered intravenously to subjects receiving a 10-mEq sodium diet (P < 0.005). Arterial PRA did not fall significantly (595 ± 113 vs 513 ± 90 ng/ml per 3 hours). Resting PRA was 50% lower in subjects receiving a 200-mEq sodium diet and did not change significantly in either arterial or renal venous blood when propranolol was administered (Fig. 1).

Nine measurements of renin secretion rates before and after propranolol were made in five subjects on a 10-mEq sodium diet (Table 1). Blood samples were drawn from the aorta and from the right and left renal veins before and after propranolol in four of the subjects. Renin secretion fell significantly to 37% of control values (P < 0.03). That the magnitude of the reduction (x) related closely to the control renin secretion rate (y), is apparent from Figure 2 (y = −0.99x + 123; r = −0.86; f = ±19.6; P < 0.01). Thus it appears the greater the stimulus that sodium restriction provided, the larger was the reduction induced by propranolol. Four unilateral measurements were made in four subjects on a 200-mEq sodium diet and did not show a consistent change in renin secretion after propranolol; in two subjects, values did not change, in one they decreased, and in one they increased. The last subject became very anxious during the study.

**RENAL PLASMA FLOW**

Renal plasma flow fell significantly after propranolol was given to subjects on a diet containing either 10 mEq (P <

**Table 1** Effect of Propranolol on Renin Secretion Rates in Subjects Receiving a 10-mEq Sodium Diet

<table>
<thead>
<tr>
<th>Patient</th>
<th>Kidney</th>
<th>Control (U/ml per min/100g)</th>
<th>Propranolol (U/ml per min/100g)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Right</td>
<td>75</td>
<td>0</td>
<td>−100</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>Right</td>
<td>231</td>
<td>2</td>
<td>−99</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>325</td>
<td>16</td>
<td>−95</td>
</tr>
<tr>
<td>C</td>
<td>Right</td>
<td>771</td>
<td>33</td>
<td>−96</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>736</td>
<td>61</td>
<td>−92</td>
</tr>
<tr>
<td>D</td>
<td>Right</td>
<td>341</td>
<td>147</td>
<td>−57</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>139</td>
<td>73</td>
<td>−48</td>
</tr>
<tr>
<td>E</td>
<td>Right</td>
<td>329</td>
<td>376</td>
<td>+14</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>361</td>
<td>389</td>
<td>+8</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td>367 ± 80</td>
<td>122 ± 51*</td>
<td>−63</td>
</tr>
</tbody>
</table>

* P = 0.03 in comparison with control values. Dashes = not measured.
Control Propranolol change Significance Control Propranolol change Significance

Mean arterial pressure (mm Hg) 127 ± 7 127 ± 9 0 NS 99 ± 5 100 ± 5 +1 NS
Heart rate (beats/min) 79 ± 4 75 ± 4 −5 NS 77 ± 5 69 ± 3 −11 P = 0.03
Cardiac index (liters/min per m²) 3.06 ± 0.7 2.77 ± 0.6 −9 NS 3.24 ± 0.4 2.66 ± 0.2 −18 NS
Peripheral vascular resistance (dyne cm⁻² sec) 2501 ± 425 2723 ± 503 +9 NS 1220 ± 128 1482 ± 125 +21 P < 0.025
Renal plasma flow (ml/min per 100 g) 189 ± 26 155 ± 23 −18 P < 0.025 213 ± 26 184 ± 24 −14 P < 0.025
Renal vascular resistance, [(dyne cm⁻² sec)/100 g] × 10⁶ 301 ± 28 361 ± 26 +19 NS 236 ± 55 280 ± 68 +19 P < 0.05

Results are expressed as mean ± SEM. NS = not significant.
the dog in which Carriere*1 found that infusion of small
doses of propranolol directly into the renal artery resulted in a
significant reduction of renal blood flow without systemic
hemodynamic changes. As this effect could be blocked by
phenoxycbenzamine, Carriere suggested that propranolol had a
direct effect on intrarenal $\beta$-adrenergic receptors.

Despite the fall in renal blood flow, which ordinarily
constitutes a potent stimulus for renin secretion,13 we found
that propranolol significantly decreased both renal vein
renin activity and renin secretion rates in salt-depleted
human subjects. A consistent effect on renin release was not
seen in the small number of measurements made in salt-
loaded subjects whose renin secretion rates were relatively
low before the administration of propranolol; this may have
made detection of further small changes beyond the sensitivity
of our methods. As an effect of propranolol on renin
secretion was seen in salt-depleted subjects, this study supports
the concept that renin release in response to sodium
deposition is modulated by $\beta$-adrenergic receptors. The
observation that renal vein renin activity after $\beta$-adrenergic
blockade in salt-depleted subjects was higher than levels in
subjects on a high salt diet without $\beta$-adrenergic blockade
suggests that the increase in renin activity after salt deple-
tion does not depend entirely upon the sympathetic nervous
system.

Since it has been demonstrated that the optical isomer of
propranolol which has a local anesthetic effect without
$\beta$-receptor blocking activity does not reduce renin secretion in
the isolated perfused rat kidney,23 it is reasonable to
come to the conclusion that the results of the present study, in which
extremely low doses of propranolol were used, were due to a
$\beta$-blocking effect. Although the addition of excess pro-
pranolol to in vitro systems of renin assay has not been found to have an effect on measured renin activity,4,6,21 the possibility that propranolol reduces measured renal vein renin activity by stimulating the release of a renin inhibitor, or by preventing the release of an activator, has not been assessed. Similarly, the effect of prior diazepam administra-
tion on the observations reported herein has not been examined.

In studies on humans propranolol has been found to block
the rise in PRA caused by upright posture or diuretics.5,11 lower blood pressure in proportion to its effect on PRA in persons with various forms of hypertension,1 to lower PRA without an effect on blood pressure in persons with renovas-
cular hypertension,4 and to lower blood pressure without significantly affecting PRA in patients with essential hyper-
tension receiving long-term diuretic therapy.25 As a result of studies showing increased PRA following salt depletion in
patients on long-term propranolol therapy, Bravo et al.24 have postulated that propranolol blocks renin release with-
out effecting renin synthesis. All of these studies in man have
depended on the measurement of an equilibrium peripheral
PRA. Although the present study showed that propranalol
caused significant changes in renin secretion rates, renal
vascular resistance, and renal blood flow at a time when
measurement of peripheral arterial renin activity and sys-
temic arterial blood pressure did not show significant
changes, it should be emphasized that our observations were

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Gestational Changes in Pulmonary Vascular Responses in Fetal Lambs in Utero

ALAN B. LEWIS, M.D., MICHAEL A. HEYMANN, M.D., AND ABRAHAM M. RUDOLPH, M.D.

SUMMARY Pulmonary arterial (PA) blood flow patterns, changes in pulmonary blood flow, and pulmonary vascular responses to graded hypoxemia and intravenous acetylcholine (ACh) were studied in 15 fetal lambs in utero 3-12 days after surgical implantation of an electromagnetic flow transducer and PA catheter. Phasic PA flow in the fetus was forward only during the first third of systole, almost zero during midsystole, and backward during late systole and early diastole. In contrast, neonatal lambs showed forward PA flow throughout systole. The constriction of the fetal pulmonary vasculature in response to progressive hypoxemia varied with gestational age. At 103 days there was no significant drop in PA flow and only a small increase in pulmonary vascular resistance (Rp) with hypoxemia. The greatest increase in Rp was seen in fetuses after 121 days of gestation. This response was unaffected by α- and β-sympathetic and parasympathetic blockade. Similarly, the pulmonary vascular response to ACh injected into the fetal jugular vein depended on gestational age. Little or no increase in pulmonary flow was noted in the youngest fetus, whereas ACh produced a marked increase in pulmonary flow in fetuses over 120 days of gestation. These data suggest that the mechanisms by which hypoxemia constricts and ACh relaxes the pulmonary vascular smooth muscle are not fully developed in fetal lambs at 100 days of gestation and furthermore, that these mechanisms progressively develop during the last third of gestation.

THE PULMONARY CIRCULATION of the fetus has been shown to be more responsive to hypoxemia and to vasoactive agents than is that of the adult. However, previous observations on these responses were made on fetal lambs exteriorized from the uterus, usually with the ewe under general anesthesia. Since these procedures alter the distribution of blood flow in the fetus and may modify responses of the pulmonary circulation, pulmonary vascular responses of the undisturbed fetus in utero could not be defined. Furthermore, in previous studies little attempt was made to delineate the effects of graded hypoxemia, nor was there a detailed consideration of possible gestational differences in pulmonary vascular responses.

We designed a preparation to study changes in pulmonary blood flow and pulmonary vascular responses of fetal lambs in utero. After recovery from surgery, pulmonary blood flow was monitored continuously with an electromagnetic flow transducer, and pulmonary arterial pressures were measured. Constriction of the pulmonary vascular bed by graded hypoxemia and dilation of the pulmonary vascular bed by the infusion of acetylcholine (ACh) were studied during advancing gestation. The role of the sympathetic nervous system in the hypoxic response was assessed.

Methods

Twenty-six time-dated pregnant sheep with gestational periods ranging from 0.66 to 0.93 (100-140 days) were studied. Low spinal analgesia was produced with 2-3 ml of 1% tetracaine hydrochloride. The abdomen was opened in the midline, a small incision was made in the uterine wall to expose a fetal hindlimb, and polyvinyl catheters were inserted into a hindlimb artery and vein. Through a separate incision catheters were inserted into the fetal carotid artery and jugular vein and, through a purse-string suture, the trachea. A thoracotomy then was performed in the 3rd or 4th left intercostal space, the pericardium was opened, and the main pulmonary trunk was isolated.

In the fetal lamb the right ventricle ejects into the pulmonary trunk, which continues into the ductus arteriosus. The blood vessels to the lung arise as a common main pulmonary artery segment which divides into the left and right branch pulmonary arteries (Fig. 1). The main pulmonary artery is of variable length; in nine fetuses a precalibrated electromagnetic flow transducer was placed around it...
beta-adrenergic blockade in essential hypertension: reduced renin release despite renal vasoconstriction.

J M Sullivan, D F Adams and N K Hollenberg

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