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Effects of Indomethacin, Renal Denervation, 
and Propranolol on Plasma Renin Activity in 
Conscious Dogs with Chronic Thoracic Caval 
Constriction

STEPHEN F. ECHTENKAMP, JAMES O. DAVIS, JACK M. DEFORREST, BRIAN P. ROWE, 
RONALD H. FREEMAN, ANDREA A. SEYMOUR, AND JOHN R. DIETZ

SUMMARY The role of renal prostaglandins and the adrenergic nervous system in the control of 
renin release was studied in conscious dogs with thoracic caval constriction. Indomethacin reduced 
plasma renin activity (PRA) in intact animals with thoracic caval constriction by 43% but failed to 
change PRA after surgical renal denervation and during chronic propranolol administration; adre-
nergic blockade reduced the initial control level of PRA before indomethacin from 15 to 4 ng angiotensin 
1/ml per hr. Renal hemodynamic function was markedly reduced by indomethacin both before and 
after adrenergic blockade. These observations indicate that prostaglandins are involved in the control 
of renin release, but they appear to have a more important role in the control of renal arterial 
resistance. The adrenergic nervous system also plays a role in the hyperreninemia of caval constriction 
and, possibly, a greater role than the renal prostaglandins. In the first experimental design, surgical 
renal denervation and daily oral propranolol administration in dogs with caval constriction reduced 
PRA to normal in two of seven dogs and a natriuresis occurred. In four of the five remaining animals, 
PRA fell, but not to normal, and renal sodium excretion failed to increase. In a second experimental 
design, the kidneys were denervated and propranolol was given before the dogs 
were 
subjected to 
caval constriction and 
propranolol was continued for 5 days; PRA increased markedly, sodium 
retention occurred, and ascites formed. Under these circumstances, compensatory mechanisms secondary 
to caval constriction led to increased PRA in spite of adrenergic blockade. Circ Res 49: 492-500, 
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RENIN release mechanisms have been studied ex-
tensively in dogs with chronic thoracic caval con-
striction, a model for low output heart failure (Davis 
and Freeman, 1975). The decrease in cardiac output 
and, occasionally, in arterial pressure appears to 
activate both the vascular receptor in the renal 
afferent arteriole and the macula densa to increase 
renin release. The renal nerves are also important 
in mediating the increased renin secretion of tho-
racic caval constriction, since chronic bilateral renal 
denervation reduced plasma renin activity (PRA) 
by 50% in chronic conscious animals (Witty et al., 
1972). However, after this 50% reduction, PRA re-
mained elevated 8-fold, renal sodium retention was 
almost complete, and ascites formation continued 
unabated.

Recently, it has been proposed (Oates et al., 1979) 
that renin secretion is controlled by two major pathways which are mediated by (1) the renal pros-
taglandins and (2) the adrenergic nervous system. 
The present study was designed to examine the role 
of prostaglandins and of the adrenergic nervous 
system in the control of renin release in dogs with 
chronic thoracic caval constriction. The acute re-
sponse of PRA to indomethacin was studied in 
conscious animals. Subsequently, adrenergic ner-
vous effects on the kidney were eliminated by bi-
lateral renal denervation and propranolol adminis-
tration, and the acute renin response to indometh-
acin was observed again. Arterial pressure, renal
hemodynamic function, and electrolyte metabolism
were also studied to help define the action of indo-
methacin on renin release.

In studies of the chronic response to propranolol
in conscious dogs with renal denervation and caval
constriction, PRA returned to normal in two of
seven animals and fell substantially in others. Be-
cause of this striking response to adrenergic block-
ade, another series of dogs was studied in which
renal denervation was performed first and then
large doses of oral propranolol were given. After 3
days of propranolol, the thoracic inferior vena cava
was constricted to determine whether prior block-
ade of the adrenergic nervous system would prevent
a rise in PRA and prevent sodium retention with
ascites.

Methods

Female mongrel dogs (18–25 kg) were anesthe-
tized with sodium pentobarbital (30 mg/kg, iv) and
catheters were inserted into the femoral vessels and
exteriorized through an incision at the back of the
neck. A perineotomy was also performed to facil-
itate bladder catheterization. The thoracic inferior
vena cava was constricted under sterile conditions
to produce chronic sodium retention and ascites
formation. The dogs were trained to lie quietly on
a concave padded table. All experiments were done
on conscious resting animals. The animals were fed
a daily diet containing 35 mEq sodium, and the 24-
hour urinary excretion of sodium was determined.

When the kidneys were denervated, each kidney
was exposed retroperitoneally via a flank incision
and the renal nerves were removed surgically from
the renal vessels which were then painted with a
5% phenol solution. In previous studies (Gotshall et
al., 1973), this procedure reduced kidney norepi-
 nephrine content to near zero.

When dl-propranolol was given, the oral dose of
25 mg/kg per day was divided into three treatments
given at 8:00 a.m., 4:00 p.m., and 10:00 p.m. Blood
colors were taken at 8:00 a.m. before the morning
dose to determine the minimal level of serum pro-
pranolol. The average serum propranolol level at
this time (before 8:00 a.m.) was 741 ± 283 ng/ml (n
= 7), and at no time was the observed level of pro-
pranolol lower than the β-blocking dose of 45
ng/ml observed for this drug (Pettinger and Keeton,
1975).

For determination of PRA, blood samples were
collected in chilled tubes containing 0.1 ml 10%
EDTA. The radioimmunoassay technique of Sealey
et al. (1974) was used to measure angiotensin I. Se-
parate blood samples were collected with sodium
heparin as the anticoagulant for determination of
plasma electrolytes. Urinary prostaglandin E2 was
measured according to the method of Dray et al.
(1975). Urine was acidified to pH 3.0, extracted
twice with 3 volumes cyclohexane:ethylacetate 1:1,
and chromatographed on silicic acid columns. Re-
covers were calculated using [1H]PGE2 additions
the original sample. Antiserum to PGE2 was
obtained from Institute Pasteur, Paris. All values
were corrected for the measured recoveries.

Indomethacin was given intravenously as a 5 mg/
kg bolus. Indomethacin was prepared by dissolving
the compound in 5 ml ethyl alcohol. The solution
was then adjusted to pH 8.3 with phosphate buffer. In
a control study (DeForrest et al., 1980) with the
present experimental design, indomethacin dis-
solved in the same amount of ethanol failed to alter
arterial pressure, PRA, renal hemodynamic func-
tion, and renal electrolyte and water excretion in
normal conscious sodium-repleted dogs.

All blood pressure and heart rate measurements
were made with a Statham P23Db pressure trans-
ducer and recorded on a Hewlett-Packard 7702 B
recorder. Plasma and urine electrolytes, creatinine
(Cr), and p-aminohippurate (PAAH) were deter-
mined by standard analytical procedures. The se-
rum propranolol concentrations were assayed by
Ayerst Laboratories.

Experiment I. Acute Response to
Indomethacin in Conscious Dogs with
Thoracic Caval Constriction (n = 8)

Measurements were made of PRA, (Co), (CPAH),
arterial pressure, heart rate, urinary excretion of
sodium, potassium, and water and of plasma sodium
and potassium concentrations. After two 45 minute
control periods, an intravenous 5 mg/Kg bolus in-
jection of indomethacin was given and studies were
made during two 45-minute periods. The same dose
of indomethacin was given again and observations
were made for four additional 45-minute periods.

Experiment II. Chronic Effects of Renal
Denervation and Propranolol Administration
(n = 7)

Sodium balance studies were made for 3–4 days
before and for 4–6 days during propranolol admin-
istration in dogs with thoracic caval constriction
and bilateral renal denervation. Blood was obtained
for measurement of PRA almost daily before the
8:00 a.m. dose of propranolol. Inferior vena caval
pressure was measured frequently during this study;
a reference level of 6 cm from the surface of the
table was used.

Co and CPAH were measured in the postabsorp-
tive state before renal denervation and several days
later after renal denervation during propranolol
administration. Concurrent determinations of renal
sodium excretion, mean arterial pressure, and heart
rate were made.
Experiment III. Acute Response to Indomethacin in Dogs with Renal Denervation and Cava Constriction Receiving Propranolol (n = 7)

The experimental design and functions evaluated were the same as in experiment I. Propranolol was given orally for 4–6 days at 25 mg/kg per day before the acute experiment was performed.

Experiment IV. Chronic Effects of Thoracic Cava Constriction in Dogs with Renal Denervation Receiving Propranolol (n = 6)

The kidneys were denervated and the dogs allowed to recover from surgery for at least 5 days. After 4 days of control measurements, propranolol administration (25 mg/kg per day) was begun. After 3 days of propranolol, the dogs were again anesthetized and the thoracic inferior vena cava was constricted sufficiently to elevate inferior vena caval pressure and to produce sodium retention (less than 3 mEq Na excreted/day). Five days after cava constriction, propranolol administration was discontinued and the dogs were observed over a 4-day recovery period. Daily measurements were made of PRA, arterial pressure, heart rate, inferior vena cava constriction, propranolol administration was discontinued and the thoracic inferior vena cava was constricted sufficiently to elevate inferior vena caval pressure and to produce sodium retention (less than 3 mEq Na excreted/day). Five days after cava constriction, propranolol administration was discontinued and the dogs were observed over a 4-day recovery period. Daily measurements were made of PRA, arterial pressure, heart rate, inferior vena caval pressure, plasma sodium and potassium concentrations, and urinary sodium and potassium excretion.

Data are expressed as means ± SEM. Statistical significance of paired data was determined with the Student's t-test (Table 3). Analysis of variance was used to test the significance of differences between group means for all other experiments.

Results

Experiment I. Acute Effects of Indomethacin

The response to indomethacin was studied in eight conscious dogs with thoracic cava constriction and ascites (Table 1). After two control periods, the initial 5 mg/kg bolus injection of indomethacin decreased PRA from an average control value of 15.0 to 10.5 ng angiotensin I/ml per hr (AI/ml per hr), a 30% decline (P < 0.05). The supplemental dose of indomethacin decreased PRA further to 8.5 ng AI/ml per hr, a 45% fall (P < 0.01). As the effects of indomethacin declined, PRA increased to 12.7 ng AI/ml per hr. A striking fall in renal hemodynamic function occurred. Cc decreased from an average value of 72.9 to 23.9 ml/min (64%) (P < 0.01) while CPAH fell from 151 to 70 ml/min (54%) (P < 0.01) at the peak of the responses. In two of the eight dogs, very marked falls in Cc and CPAH occurred. Cc fell from an average control value of 98 to 1 ml/min in one dog and from 56 to 2 ml/min in the other animal; as the effects of indomethacin declined, Cc returned to 54 and 7 ml/min, respectively, for the two animals. Similarly, CPAH fell from an average control value in one dog of 182 to 3 ml/min and from 98 to 6 ml/min in the other dog; during recovery from indomethacin, CPAH returned to 277 ml/min in the first dog and to 41 ml/min in the second.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Cc (ml/min)</th>
<th>Cc (ml/min)</th>
<th>FF</th>
<th>Uv (ml/min)</th>
<th>Ew (2E2/min)</th>
<th>Ew (2E2/min)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>PRA (ng AI/ml per hr)</th>
<th>Pn (mEq/liter)</th>
<th>Pk (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E0</td>
<td>37.4†</td>
<td>86†</td>
<td>0.47</td>
<td>0.21*</td>
<td>1.0*</td>
<td>9†</td>
<td>103</td>
<td>1.33*</td>
<td>102</td>
<td>106*</td>
<td>136.4</td>
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<td>±2.7</td>
<td>±18</td>
<td>±0.03</td>
<td>±0.04</td>
<td>±0.2</td>
<td>±2</td>
<td>±3</td>
<td>±0.42</td>
<td>±8</td>
<td>±2.0</td>
<td>±2.7</td>
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<tr>
<td>E2</td>
<td>32.4†</td>
<td>88*</td>
<td>0.46*</td>
<td>0.17†</td>
<td>1.2</td>
<td>7†</td>
<td>102</td>
<td>1.48*</td>
<td>106</td>
<td>103.3</td>
<td>137.4</td>
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<td>±9.2</td>
<td>±26</td>
<td>±0.03</td>
<td>±0.3</td>
<td>±3</td>
<td>±3</td>
<td>±0.45</td>
<td>±7</td>
<td>±1.4</td>
<td>±2.4</td>
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</table>

**Indomethacin (5 mg/kg iv bolus)**

<table>
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<tr>
<th></th>
<th>E0 (ml/min)</th>
<th>E0 (ml/min)</th>
<th>FF</th>
<th>Uv (ml/min)</th>
<th>Ew (2E2/min)</th>
<th>Ew (2E2/min)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>PRA (ng AI/ml per hr)</th>
<th>Pn (mEq/liter)</th>
<th>Pk (mEq/liter)</th>
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<tr>
<td>E0</td>
<td>25.9†</td>
<td>70†</td>
<td>0.33†</td>
<td>0.17†</td>
<td>1.0</td>
<td>5†</td>
<td>105</td>
<td>3.18*</td>
<td>101</td>
<td>85†</td>
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<tr>
<td>±8.2</td>
<td>±17</td>
<td>±0.03</td>
<td>±0.04</td>
<td>±0.2</td>
<td>±2</td>
<td>±4</td>
<td>±1.51</td>
<td>±8</td>
<td>±1.4</td>
<td>±2.3</td>
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<td>1.0†</td>
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<td>105</td>
<td>4.22*</td>
<td>98</td>
<td>89†</td>
<td>138.5</td>
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<td>±8.6</td>
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<td>±0.04</td>
<td>±0.2</td>
<td>±2</td>
<td>±5</td>
<td>±2.72</td>
<td>±9</td>
<td>±1.3</td>
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<td>E3</td>
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<td>95*</td>
<td>0.34†</td>
<td>0.29†</td>
<td>1.1</td>
<td>13†</td>
<td>103</td>
<td>1.34*</td>
<td>101</td>
<td>94.9†</td>
<td>138.7</td>
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<td>±10.5</td>
<td>±16</td>
<td>±0.06</td>
<td>±0.05</td>
<td>±0.2</td>
<td>±4</td>
<td>±4</td>
<td>±0.62</td>
<td>±10</td>
<td>±1.1</td>
<td>±2.8</td>
<td>±0.2</td>
</tr>
<tr>
<td>E4</td>
<td>48.5*</td>
<td>144</td>
<td>0.33†</td>
<td>0.43†</td>
<td>1.6</td>
<td>28</td>
<td>99</td>
<td>0.55</td>
<td>108</td>
<td>127</td>
<td>138.8</td>
</tr>
<tr>
<td>±10.6</td>
<td>±26</td>
<td>±0.04</td>
<td>±0.05</td>
<td>±0.3</td>
<td>±3</td>
<td>±0.14</td>
<td>±8</td>
<td>±2.1</td>
<td>±2.8</td>
<td>±0.2</td>
<td></td>
</tr>
</tbody>
</table>

Cc = creatinine clearance, Cc = PRA clearance, FF = filtration fraction, Uv = urine volume, Ew = excreted sodium, Ew = excreted potassium, MAP = mean arterial pressure, HR = heart rate, PRA = plasma renin activity, Pn = plasma sodium concentration, Pk = plasma potassium concentration.
animal. For the group of eight dogs, urine flow and renal potassium excretion fell strikingly while renal sodium excretion, which was very low during the control periods, decreased slightly and significantly during two of the six experimental periods (Table 1). Mean arterial pressure, heart rate, and plasma sodium and potassium concentrations were unchanged, but renal vascular resistance rose markedly to reach a 9.6-fold increase at the peak of the response (Table 1).

To evaluate the degree of prostaglandin synthetase inhibition, the urinary excretion of PGE$_2$ was measured in two additional dogs. The experimental design was the same as for the initial study with eight dogs. The two 5 mg/kg bolus injections produced an average reduction of 85% in PGE$_2$ excretion (Table 2); this response occurred in association with reductions in C$_{P AH}$ and PRA.

**Experiment II. Chronic Effects of Renal Denervation and Propranolol Administration**

Measurements were made almost daily in seven dogs with renal denervation and thoracic caval constriction for 3-4 days before and during 4-6 days of propranolol administration (Table 3); the values presented in the table are the averages for several days. PRA decreased from 19.1 and 7.2 ng Al/ml per hr to 0.6 and 0.8 ng Al/ml per hr, respectively, in two of the seven dogs (dogs 1 and 2, Table 3); these values were similar to the average normal value of 0.70 ± 0.17 ng Al/ml per hr for dogs studied under similar conditions in our laboratory (DeForrest et al., 1980). In the remaining five animals, PRA decreased significantly in four of the five dogs but not to normal. Renal sodium excretion increased significantly in the two dogs in which PRA

### Table 2 Effects of Indomethacin on Urinary PGE$_2$ Excretion

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>45</th>
<th>90</th>
<th>135</th>
<th>180</th>
<th>225</th>
<th>270</th>
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</thead>
<tbody>
<tr>
<td>Dog 1</td>
<td>1739</td>
<td>1677</td>
<td>978</td>
<td>331</td>
<td>222</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Dog 2</td>
<td>1485</td>
<td>1125</td>
<td>412</td>
<td>226</td>
<td>192</td>
<td>166</td>
<td></td>
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<tr>
<td>Urinary excretion of PGE$_2$ (pg/min)</td>
<td>Dog 1</td>
<td>14.9</td>
<td>15.1</td>
<td>12.2</td>
<td>12.8</td>
<td>11.9</td>
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<tr>
<td>Dog 2</td>
<td>270</td>
<td>270</td>
<td>270</td>
<td>270</td>
<td>270</td>
<td>270</td>
<td></td>
</tr>
</tbody>
</table>

| PRA (ng Al/ml per hr) | Dog 1 | 153 | 187 | 39 | 41 | 44 | 53 |
| C$_{P AH}$ (ml/min) | Dog 1 | 227 | 376 | 65 | 29 | 30 | 37 |

---

**Table 3 Chronic Effects of Renal Denervation and Propranolol Administration in Dogs with Thoracic Caval Constriction**

<table>
<thead>
<tr>
<th>PRA (ng Al/ml per hr)</th>
<th>C</th>
<th>RD + P*</th>
<th>Renal Na excretion (mEq/day)</th>
<th>C</th>
<th>RD + P</th>
<th>Inferior vena caval pressure (mm Hg)</th>
<th>C</th>
<th>RD + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog 1</td>
<td>19.1</td>
<td>n = 4</td>
<td>4.0</td>
<td>17.6</td>
<td>188</td>
<td>&gt;0.1</td>
<td>215</td>
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<tr>
<td>$P$</td>
<td>&lt;0.005</td>
<td>n = 4</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>Dog 2</td>
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<td>288</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$</td>
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<td>n = 4</td>
<td>1.3</td>
<td>26.5</td>
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<tr>
<td>Dog 3</td>
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<td>&gt;0.2</td>
<td>221</td>
<td>&gt;0.05</td>
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<tr>
<td>$P$</td>
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<td>n = 3</td>
<td>0.6</td>
<td>&gt;0.2</td>
<td>221</td>
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<tr>
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<tr>
<td>$P$</td>
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<td>n = 4</td>
<td>0.9</td>
<td>1.6</td>
<td>210</td>
<td>&gt;0.1</td>
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<td>&gt;0.05</td>
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<td>&lt;0.025</td>
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<tr>
<td>$P$</td>
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<td>n = 3</td>
<td>1.5</td>
<td>&gt;0.05</td>
<td>184</td>
<td>&lt;0.025</td>
<td>171</td>
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<tr>
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<td>n = 3</td>
<td>2.8</td>
<td>&gt;0.2</td>
<td>233</td>
<td>&gt;0.2</td>
<td>223</td>
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</tr>
<tr>
<td>$P$</td>
<td>&lt;0.05</td>
<td>n = 3</td>
<td>2.8</td>
<td>&gt;0.2</td>
<td>233</td>
<td>&gt;0.2</td>
<td>223</td>
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<tr>
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<td>&gt;0.2</td>
<td>220</td>
<td>&gt;0.1</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.05</td>
<td>n = 4</td>
<td>3.0</td>
<td>&gt;0.2</td>
<td>220</td>
<td>&gt;0.1</td>
<td>233</td>
<td></td>
</tr>
</tbody>
</table>

* C and RD + P represent control measurements and studies during renal denervation and propranolol administration; n = number of days in the control and experimental periods.
Table 4  Measurements in the Postabsorptive State before and during Propranolol Administration in Dogs with Thoracic Caval Constriction and Renal Denervation

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>C*</th>
<th>RD+P*</th>
<th>C</th>
<th>RD+P</th>
<th>C</th>
<th>RD+P</th>
<th>C</th>
<th>RD+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl (ml/min)</td>
<td>CCl (ml/min)</td>
<td>Renal Na excretion (µEq/min)</td>
<td>Mean arterial pressure (mm Hg)</td>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>51.4</td>
<td>78.4</td>
<td>120</td>
<td>212</td>
<td>0.5</td>
<td>46</td>
<td>105</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>99.1</td>
<td>85.3</td>
<td>189</td>
<td>226</td>
<td>0.9</td>
<td>23</td>
<td>91</td>
<td>101</td>
</tr>
<tr>
<td>3</td>
<td>70.5</td>
<td>55.6</td>
<td>219</td>
<td>156</td>
<td>2.3</td>
<td>1.7</td>
<td>120</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>61.0</td>
<td>51.4</td>
<td>175</td>
<td>114</td>
<td>1.2</td>
<td>10.0</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>61.0</td>
<td>45.1</td>
<td>175</td>
<td>114</td>
<td>0.8</td>
<td>13.2</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>68.4</td>
<td>53.6</td>
<td>184</td>
<td>98</td>
<td>1.9</td>
<td>2.3</td>
<td>103</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>105.7</td>
<td>72.3</td>
<td>280</td>
<td>268</td>
<td>2.8</td>
<td>1.4</td>
<td>109</td>
<td>94</td>
</tr>
</tbody>
</table>

Mean ± SEM | 74.3 ± 7.05 | 63.7 ± 7.64 | 188 ± 19.4 | 175 ± 23.4 | ±0.3 | ±6.1 | ±4 | ±2 | ±8 | ±7

P values | >0.1 | >0.5 | >0.05 | >0.05 | <0.005

* C and RD+P represent control periods and periods with renal denervation plus propranolol.

returned to normal, but was unchanged (P > 0.05) in the other five animals. Inferior vena caval pressure was unchanged during the propranolol administration in five of the six dogs studied; in the remaining dog, a slight decline occurred.

Measurements of renal hemodynamic function were made in the postabsorptive state before and during propranolol administration in dogs with caval constriction and renal denervation. The associated changes in renal sodium excretion, arterial pressure, and heart rate are recorded in Table 4. The values presented for kidney function represent the averages for two or three renal clearance periods. Creatinine clearance and C\textsubscript{PAH} were not consistently changed by adrenergic blockade. Renal sodium excretion increased in four of the seven animals, but the average increase for the group from 1.5 to 19.9 was not significant (P > 0.05). The most striking change was the decrease in heart rate from 131 to 98 beats/min (P < 0.005). Arterial pressure was not significantly changed.

Experiment III. Acute Response to Indomethacin in Dogs with Renal Denervation and Caval Constriction Receiving Propranolol (n = 7)

PRA appeared to decline slightly but the change was not significant (Table 5). The most striking change was in renal hemodynamic function; C\textsubscript{Cl} decreased by 51% (P < 0.01) and C\textsubscript{PAH} fell by 58%

Table 5  Effects of Indomethacin in Conscious Dogs with Chronic Thoracic Caval Constriction (n=7) (Renal Denervated and Propranolol Treated)

<table>
<thead>
<tr>
<th>C\textsubscript{Cl} (ml/min)</th>
<th>C\textsubscript{PAH} (ml/min)</th>
<th>FF</th>
<th>U\textsubscript{Cl} (µEq/min)</th>
<th>E\textsubscript{Cl} (µEq/min)</th>
<th>MAP (mm Hg)</th>
<th>HVR [mm Hg (ml/min)]</th>
<th>HR (beats/min)</th>
<th>P\textsubscript{A} (mg A/l liter)</th>
<th>P\textsubscript{E} (mg A/l liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>63.6</td>
<td>167.1</td>
<td>0.30</td>
<td>0.30</td>
<td>11.0</td>
<td>36.8</td>
<td>94</td>
<td>0.44</td>
<td>19.4</td>
</tr>
<tr>
<td>±5.6</td>
<td>±21.1</td>
<td>±0.03</td>
<td>±0.04</td>
<td>±4.8</td>
<td>±10.7</td>
<td>±3</td>
<td>±10.05</td>
<td>±2</td>
<td>±1.6</td>
</tr>
<tr>
<td>C2</td>
<td>64.0</td>
<td>183.5</td>
<td>0.38</td>
<td>0.41</td>
<td>16.8</td>
<td>22.1</td>
<td>93</td>
<td>0.34</td>
<td>2.5</td>
</tr>
<tr>
<td>±5.8</td>
<td>±27.5</td>
<td>±0.04</td>
<td>±0.04</td>
<td>±7.7</td>
<td>±4.5</td>
<td>±2</td>
<td>±0.09</td>
<td>±7</td>
<td>±1.7</td>
</tr>
</tbody>
</table>

Indomethacin (5 mg/kg i.v. bolus)

| E1 | 47.2 | 119.7 | 0.42 | 0.35 | 19.4 | 87 | 91 | 0.85 | 0.05 | ±1.6 | ±0.18 |
| | ±28.3 | ±25.9 | ±0.03 | ±0.16 | ±12.2 | ±12.1 | ±3 | ±0.27 | ±6 | ±0.8 | ±1.6 | ±0.18 |
| E2 | 39.5 | 88.7 | 0.50 | 0.25 | 6.2 | 6.9 | 88 | 0.93 | 90 | ±2.8 | ±2.2 | ±0.18 |
| | ±28.3 | ±29.8 | ±0.05 | ±0.07 | ±3.0 | ±2.1 | ±2 | ±1.86 | ±6 | ±0.6 | ±2.2 | ±0.18 |

Indomethacin (5 mg/kg i.v. bolus)

| E3 | 31.5 | 73.7 | 0.43 | 0.19 | 2.4 | 56 | 90 | 14.13 | 88 | ±3.7 | ±13.5 | ±0.06 |
| | ±8.1 | ±18.8 | ±0.02 | ±0.04 | ±0.7 | ±1.1 | ±2 | ±13.02 | ±3 | ±0.9 | ±2.3 | ±0.22 |
| E4 | 34.9 | 88.2 | 0.40 | 0.24 | 1.8 | 84 | 85 | 6.7 | 90 | ±3.5 | ±142.7 | ±3.77 |
| | ±8.7 | ±22.6 | ±0.03 | ±0.06 | ±0.3 | ±2.9 | ±2 | ±15.90 | ±3 | ±1.5 | ±19.0 | ±0.24 |
| E5 | 34.8 | 81.9 | 0.42 | 0.19 | 2.5 | 8.4 | 87 | 11.86 | 92 | ±3.7 | ±143.5 | ±3.82 |
| | ±8.6 | ±20.4 | ±0.04 | ±0.06 | ±0.9 | ±2.9 | ±2 | ±11.19 | ±6 | ±1.2 | ±16.6 | ±0.27 |
| E6 | 43.3 | 117.2 | 0.39 | 0.29 | 2.7 | 13.6* | 85 | 5.30 | 91 | 5.4 | 143.4 | 3.79 |
| | ±9.8 | ±28.7 | ±0.05 | ±0.06 | ±1.1 | ±3.6 | ±2 | ±4.73 | ±5 | ±2.2 | ±1.5 | ±0.31 |

Abbreviations described in Table 1.

* P < 0.05 from C\textsubscript{Cl} + C\textsubscript{PAH}.
† P < 0.01 from C\textsubscript{Cl} + C\textsubscript{PAH}.
After renal denervation

During propranolol administration (25 mg/kg per day)

During propranolol and after thoracic caval constriction

During propranolol discontinued with thoracic caval constriction

Abbreviations same as Table 1; IVCP represents inferior vena caval pressure.

- MAP = mean arterial pressure
- IVCP = inferior vena caval pressure
- HR = heart rate
- PRA = plasma renin activity
- EA = excretion of sodium
- PKI = potassium excretion

<table>
<thead>
<tr>
<th>Days</th>
<th>MAP</th>
<th>IVCP</th>
<th>HR</th>
<th>PRA</th>
<th>EA</th>
<th>PKI</th>
<th>EA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>beats/min</td>
<td>(ng AL/ml per hr)</td>
<td>(mEq/day)</td>
<td>(mEq/liter)</td>
<td>(mEq/day)</td>
</tr>
<tr>
<td>1</td>
<td>99±3</td>
<td>88±3</td>
<td>96±3</td>
<td>1.0±0.9</td>
<td>37±5</td>
<td>18±2</td>
<td>139±1</td>
</tr>
<tr>
<td>2</td>
<td>93±2</td>
<td>84±3</td>
<td>79±4</td>
<td>0.9±0.4</td>
<td>31±4</td>
<td>19±1</td>
<td>138±2</td>
</tr>
<tr>
<td>3</td>
<td>96±3</td>
<td>80±4</td>
<td>82±7</td>
<td>1.1±0.5</td>
<td>33±2</td>
<td>18±1</td>
<td>139±1</td>
</tr>
<tr>
<td>4</td>
<td>94±2</td>
<td>91±3</td>
<td>82±7</td>
<td>1.3±0.4</td>
<td>34±3</td>
<td>22±2</td>
<td>141±1</td>
</tr>
</tbody>
</table>

(P < 0.01). Renal potassium excretion and urine flow decreased but sodium excretion failed to show a significant change. There were no detectable changes in plasma sodium and potassium concentrations. Arterial pressure was significantly decreased during the last three experimental periods, but heart rate was unchanged. Renal vascular resistance appeared to increase from an average control value of 0.39 to as high as 14.13 mm Hg (ml/min/100 g) but the change was not significant because of the wide variation among animals.

Experiment IV. Chronic Effects of Thoracic Caval Constriction in Dogs with Renal Denervation Receiving Propranolol

In this study, the effects of prior renal denervation and propranolol treatment on the response to caval constriction were observed (Table 6). After 4 days of control measurements in dogs with renal denervation, propranolol failed to produce a change in PRA; sodium excretion appeared to increase on the first day of propranolol administration but the change was not significant. However, a significant fall in renal sodium excretion occurred on days 2 and 3 of propranolol treatment. Constriction of the thoracic inferior vena cava at the beginning of day 8 and during propranolol administration produced a striking increase in PRA, a marked reduction in renal sodium excretion, and ascites accumulation. After 5 days of caval constriction, propranolol was discontinued. The high levels of PRA, the sodium retention, and ascites formation were maintained.

Inferior vena caval pressure was unchanged when propranolol was given to dogs with renal denervation but increased from an average of 88 mm water during propranolol treatment to 185-215 mm water following caval constriction (P < 0.01). Discontinuation of propranolol did not significantly alter the high level of venous pressure. Arterial pressure was 95-99 mm Hg during the first 4 control days before propranolol and decreased slightly only on the first day after caval constriction (P < 0.01 for comparison with days 1-4). Heart rate did not change significantly until after propranolol was discontinued, at which time a significant increase occurred. Urinary potassium excretion was increased (P < 0.05) on days 1 and 4 after caval constriction, compared with the first 4 days and the 3-day propranolol control period and was increased slightly on the last day of propranolol compared with days 1-4. Hyponatremia occurred (P < 0.05) during the first 3 days of caval constriction compared with control days 1-4, and a slight hyperkalemia resulted during the periods of propranolol (P < 0.05), propranolol plus caval constriction (P < 0.01), and during the recovery period (P < 0.05).

Discussion

In dogs with chronic thoracic caval constriction, the increased activity of the renin-angiotensin-aldosterone system and the changes in salt and water metabolism are almost identical to the findings in low cardiac output failure in humans (Davis, 1965). Consequently, this experimental model has been used extensively to investigate the mechanisms regulating renin release in low output heart failure. It should be pointed out, however, that there is no myocardial element of failure; indeed, the pulmonary circulatory bed is underdistended and pressure is low. Thoracic caval constriction results in a decrease in cardiac output, a marked fall in renal hemodynamic function, increased filtration fraction, increased renin and aldosterone secretion, and
marked sodium retention with edema and ascites formation (Davis, 1965).

The present study was undertaken to evaluate the relative roles of the prostaglandins and the adrenergic nervous system in the hyperreninemia of low output heart failure. A secondary objective was to determine the role of the renal prostaglandins in the maintenance of renal blood flow (RBF) and glomerular filtration rate (GFR) in heart failure.

When two 5 mg/kg bolus injections of indomethacin were given to dogs with caval constriction, PRA decreased from 15.0 to 8.5 ng angiotensin I/ml per hr, a 43% fall; this occurred during an 85% decrease in the urinary excretion of PGE2. This result confirms earlier reports of marked reductions of PGE2 in renal venous blood (Terragno et al., 1977) and in urine (Zambraski and Dunn, 1979) in response to doses of indomethacin similar to or less than used here. It should be emphasized that the present studies were done in conscious dogs. Normal conscious dogs studied under conditions similar to those of the present study (DeForrest et al., 1980) failed to show a change in PRA in response to indomethacin. The possibility that indomethacin inhibited an adrenergically mediated component of renin release should be considered. This seems unlikely, since recent studies in conscious dogs and rats (Seymour et al., 1980) and in isolated rat glomeruli (Beierwaltes et al., 1980) provided convincing evidence that a full renin response to β-agonists occurred during indomethacin administration. Collectively, these findings indicate that prostaglandins contribute to the increased PRA in dogs with caval constriction. However, the relatively small decrease in PRA (43%) with this large dose of indomethacin indicates that other factors are important in the control of renin release.

Blockade of the adrenergic nervous system with bilateral renal denervation and large doses of propranolol produced a striking decrease in PRA in dogs with caval constriction. In two of seven animals, PRA returned to normal and sodium excretion increased markedly; in four of the other five dogs, PRA fell but not to normal and sodium excretion was not increased significantly. It seems likely that the primary change here was adrenergic blockade, with a resultant fall in PRA and plasma aldosterone concentrations; it is suggested that the increase in renal sodium excretion occurred in response to the return in renin and aldosterone in plasma to normal. There was no evidence that propranolol produced an indirect effect in such a way as to block the primary mechanism producing a high PRA; inferior vena caval pressure was unchanged in five of the six dogs, and the postabsorptive values for CCl and CPAR were unaltered by propranolol. The high values for serum propranolol and the marked decrease in heart rate indicate that β adrenergic blockade was complete or nearly complete; in the five dogs of Table 3 in which PRA did not fall to normal, the average fall in heart rate was 31 beats/min. It seems likely, therefore, that the changes in PRA resulted from surgical removal of the renal nerves and pharmacological blockade of the β-adrenergic receptor which controls renin release.

The variability of the renin responses to blockade of the adrenergic nervous system in dogs with caval constriction (Table 3) might reflect differences in the initial level of adrenergic activity. There is no evidence for variability of adrenergic blockade, since the fall in heart rate with propranolol was consistent and marked. In view of the multifaceted control of PRA in dogs with caval constriction, the variation in nonadrenergic control mechanisms might also have contributed to the different levels of PRA achieved after adrenergic blockade.

When this group of seven dogs with adrenergic blockade (renal denervation and propranolol administration) was given indomethacin (Table 5), the initial control level of PRA was 4.0 ng angiotensin I/ml per hr compared with 15.0 ng angiotensin I/ml per hr observed before adrenergic blockade (Table 1), and PRA failed to decrease significantly in response to indomethacin. The present observations suggest, therefore, that the adrenergic nervous system plays a role and possibly a more important role than prostaglandins in the increased PRA in this model of experimental heart failure. These results are in striking contrast to the failure of adrenergic blockade to produce a detectable fall in PRA in sodium-depleted dogs (DeForrest et al., 1980) and to the marked decrease in PRA which occurred during prostaglandin synthesis inhibition in sodium-depleted dogs with adrenergic blockade (DeForrest et al., 1980).

In a previous report, Hanson et al. (1976) found that thoracic caval constriction produced a high PRA, sodium retention, and ascites in every animal that was receiving the large oral dose of propranolol given here. Because of this earlier finding, it was decided to study another series of animals (experiment IV and Table 6) in which dogs with renal denervation receiving propranolol were subjected to caval constriction. All of the six dogs studied showed a striking increase in PRA, marked sodium retention, and ascites formation in spite of adrenergic blockade. It appears, therefore, that other mechanisms are yet available to increase PRA and produce the syndrome of salt and water metabolism following caval constriction after sympathetic nervous mechanisms have been blocked. It is suggested that the fundamental mechanism available to increase renin release after blockade of the renal prostaglandins and the adrenergic nervous system is the renal vascular receptor in the renal afferent arteriole. The initial suggestion of Data et al. (1978) that prostaglandins mediate the renin release produced by the renal vascular receptor mechanism.
The present experiments demonstrate that prostaglandins help sustain the elevated PRA in dogs with caval constriction and verify that the adrenergic nervous system is also an important mechanism for increasing renin release in this model of heart failure. On the basis of the present findings and of earlier work (Witty et al., 1972), it is suggested that the renal vascular receptor mechanism is responsible for the increased PRA when the prostaglandins and adrenergic nervous system are inhibited. The macula densa also appears to be involved in the intact animal with caval constriction because the filtered load of sodium is markedly decreased (Davis et al., 1965). Finally, the results with indomethacin demonstrate an important role for the renal prostaglandins in the maintenance of renal blood flow in this model of heart failure.

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Effects of indomethacin, renal denervation, and propranolol on plasma renin activity in conscious dogs with chronic thoracic caval constriction.
S F Echtenkamp, J O Davis, J M DeForrest, B P Rowe, R H Freeman, A A Seymour and J R Dietz

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