Serial Evaluation of the Renin-Angiotensin-Aldosterone System in Caval Dogs

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SUMMARY The blood pressure (BP) response to a competitive inhibitor of angiotensin II (saralasin), was evaluated serially along with renal hemodynamics and sodium clearance in dogs with constriction of the thoracic inferior vena cava which were undergoing chronic sodium and water balance studies. Plasma renin activity (PRA), plasma and urinary aldosterone, and plasma volume were measured periodically. In 14 normal dogs under anesthesia, saralasin infusion, 6μg/kg per min, produced a transient agonistic pressor response. In 14 dogs after caval constriction, sodium balance became markedly positive, PRA and plasma and urine aldosterone increased, and sodium clearance decreased. Now saralasin infusion caused a decrease in BP. In five dogs, avid sodium retention persisted. In nine, after a variable period of time, sodium balance became less positive, PRA and plasma and urine aldosterone decreased, and sodium clearance increased. Saralasin infusion at this time again produced a transient agonistic pressor response. Renal hemodynamics remained stable throughout. Plasma volume increased following caval constriction. These data suggest that initially, following caval constriction, the renin-angiotensin-aldosterone system is responsible for BP maintenance. Following a period of salt and water retention and extracellular fluid volume expansion, sodium excretion increases, the renin-angiotensin-aldosterone system is suppressed, and BP becomes sodium-volume dependent. These dynamic physiological adjustments which lead to great variability in caval dogs may help to reconcile some of the conflicting findings reported for this model of salt and water retention, as well as for its clinical counterparts.

NUMEROUS physiological and pharmacological studies have been carried out in dogs with thoracic inferior vena cava constriction (TIVCC), a model of salt and water retention with ascites and edema (caval dogs). A review of the literature and observations in this laboratory reveal conflicting findings with regard to renal hemodynamics,1-10 site(s) of sodium retention,1-11 renal blood flow distribution,12-14 activity of the autonomic nervous system,9, 10, 15-18 and the renin-angiotensin-aldosterone (RAA) system19-24 in caval dogs. Analysis of the pertinent data suggests that the conflicting reports may be due to changing physiological characteristics of this model relating, at least in part, to salt and water retention and extracellular fluid volume expansion. Therefore, it seems essential to study the natural history of this animal model by serial evaluation of various physiological processes.

In the present experiments, the RAA system was evaluated serially in dogs following TIVCC by examining plasma renin activity (PRA), plasma and urine aldosterone and response to angiotensin II competitive inhibition, and correlating the findings with sodium balance, plasma volume, renal hemodynamics, and sodium clearance. The results demonstrate that initially, after TIVCC and during the stage of avid sodium retention, the RAA system is stimulated and blood pressure maintenance is renin (angiotensin) dependent. After a variable period of sodium retention and extracellular fluid volume expansion, urinary sodium excretion increases, the RAA system is much less active, and blood pressure maintenance becomes sodium-volume dependent.

Methods

Nineteen female mongrel dogs weighing 15-25 kg were studied. Seven dogs had an inflatable Silastic cuff inserted around the TIVC with constriction produced by inflation of the cuff 8-10 days after surgery. Since the Silastic cuff tends to leak, it was not possible to maintain TIVCC for long periods of time with this device. Therefore, in order to make prolonged observations, in 12 dogs TIVCC was performed according to the method of Davis and Howell,4 using a silk tie placed around the TIVC. The criterion for adequate constriction with both methods for the purposes of the present study was a decrease in mean arterial pressure (MAP) of 20 mm Hg.

Metabolic Studies

All dogs were placed in metabolic cages throughout the experiment. They were allowed free access to water and were given 400-500 g of a pellet dog chow containing sodium, 18 mEq/100 g, and potassium, 10 mEq/100 g. In most instances, the dogs ate 300 g or more per day. In an occasional dog, the intake was lower for short periods of time, particularly for a few days after surgery. Metabolic balance studies were carried out prior to TIVCC in five dogs and in all the dogs after caval constriction for periods...
varying from 14 to 90 days. Measurements were made to
determine the intake and urine output of water, sodium,
and potassium. Daily balances of sodium and water were
generally made 5-7 days a week. In a few dogs, daily
balance studies were carried out less frequently during
prolonged periods of stability. At periodic intervals prior
to and following TIVCC PRA, plasma and 24-hour urine
aldosterone, hematocrit, and plasma volume were deter-
mined in conscious animals.

**Saralasin Studies**

To correlate the effects of saralasin ([Sar^1, Ala^8]angio-
tensin II) on blood pressure with sodium clearance and
renal hemodynamics, this agent was infused during a
steady state water diuresis (protocol 1) or during a manitol
diuresis (protocol 2). In a third group, saralasin was
infused under hydro nephic, nondiuretic conditions (proto-
col 3).

**Protocol 1: Water Diuresis**

This protocol was used in eight experiments prior to
TIVCC and 11 experiments after TIVCC in nine dogs. All
food was withdrawn 16 hours before the experiment, but
water was permitted ad libitum. On the morning of the
experiment, an oral water load amounting to 5% of body
weight was administered via an orogastric tube. One hour
later, the dogs were anesthetized with sodium pentothal
(25 mg/kg, iv) and the level of anesthesia was maintained
with additional small doses intravenously, as needed. An
endotracheal tube then was inserted and ventilation was
regulated with a Bird respirator supplying 60% oxygen.
The urinary bladder was catheterized with a number 16
Foley catheter and double air washouts were used to
ensure complete emptying of the bladder. Blood samples
were obtained and blood pressure monitored through an
intracath secured in a femoral artery.

After initial blood and urine samples had been ob-
tained, priming doses of inulin and p-aminohippurate
(PAH) were administered followed by a sustaining solu-
tion of 0.45% NaCl containing sufficient inulin and PAH
to maintain adequate blood levels, infused at 0.5 ml/min
with a constant rate infusion pump. Water diuresis was
maintained by infusing 2.5% glucose at 0.5 ml/kg per min
initially and then adjusted to 2 ml/min above urine flow.
After an initial 60- to 90-minute equilibration period,
urine specimens were collected as described for the previous
experiment. After initial blood and urine specimens had been collected, priming doses of inulin and
PAH were administered followed by a sustaining infusion
of inulin and PAH administered at 0.5 ml/min in 0.9% saline to maintain adequate blood levels. Aqueous piret-
sin, sufficient to deliver 50 mU/kg per hour, also was
added to this infusion. Mannitol (10%) was administered
by a constant infusion pump at 2 ml/min. After an initial
60- to 90-minute equilibration period, blood and urine
specimens were collected as described for the previous
group.

In protocols 1 and 2, after a steady state of urine flow
was achieved (three 10-minute periods with less than 10% variation in urine flow), saralasin, 6 µg/kg per min, was
infused for 30 minutes. Clearance periods were continued
for a minimum of 30 minutes after stopping saralasin. In
all these experiments arterial blood pressure (BP) was
recorded continuously through the femoral artery catheter
by using a Statham transducer and Sanborn recorder.

Blood pressure measurements presented in the results
are during the steady state prior to saralasin, 15 minutes
after starting saralasin, and 20 minutes post-saralasin. In
most experiments, PRA was determined at the same time.

**Protocol 3: Hydropenia, Nondiuretic**

This protocol was used in seven experiments in four
dogs to eliminate any possible effect of the diuretic state
on the response to saralasin. In these experiments, the
dogs were prepared as in protocol 2, but on the morning
of the experiment the dogs were only lightly anesthetized
and a femoral artery catheter inserted. Blood samples
were obtained for PRA and blood pressure recorded
before, during, and after saralasin infusion as already
described.

Measurements of osmolality, sodium, potassium, inulin,
and PAH were performed as previously described. Plasma volume was determined by dye dilution technique
using Evans blue dye with blood samples drawn at 10
minutes. PRA was determined by radioimmunoassay with a
180I-Angiotensin I Immunoassay Kit (E.R. Squibb). Plasma
and urine aldosterone were determined by radioimmu-
noassay, with an Aldosterone-1H Assay Kit (Diagnostic
products). For these determinations, blood was collected
in iced tubes containing Na2-EDTA and immediately
centrifuged at +4°C. The supernatant fluid was pipetted
off and frozen at –20°C until determinations were carried
out. Samples of each 24-hour urine for aldosterone were
kept at 4°C. The results for PRA are expressed as ng/ml
per hour of angiotensin I generated. Clearances were
determined by standard methods. Statistical analyses were
performed using the Student t- and paired t-tests. All
results are expressed as mean ± se (standard error).

**Results**

**Balance Studies**

In the five dogs started on balance studies for 5-7 days
prior to TIVCC, there was essentially a zero sodium
balance with virtually all of the sodium intake recovered
in the urine and no change in weight.

Of the 19 dogs in which TIVCC was carried out, 14
eventually developed ascites. In these 14 dogs, avid
sodium retention became evident immediately after
TIVCC and sodium excretion was less than 2% of intake. In five dogs (nos. 308, 310, 315, 327, 328), avid sodium retention persisted for 18 to 45 days, with the dogs expiring in this state of sodium balance. At the time of death, three dogs had gained 6.4 ± 0.5 kg and two dogs lost weight. All had ascites. In nine of the dogs, avid sodium retention persisted for 5 to 38 days with a mean of 22 ± 4 days, after which time sodium balance became much less positive. Of these nine dogs, eight had gained 3.9 ± 1.1 kg up to the time sodium balance changed, and one dog lost weight.

After the variable period of very avid sodium retention, urine sodium excretion increased in these nine dogs, primarily due to an increase in urine sodium concentration. In most, sodium balance remained positive, but in a few dogs, sodium balance became negative for short periods of time (1-3 days) interspersed with days of positive balance. Weight tended to level off or increase at a slower rate, except those dogs that went into periods of negative balance in which weight decreased during these periods. This second phase lasted throughout the remaining period of observation (30-60 days) in seven of the dogs. In two dogs (nos. 330 and 334), the stage of less avid sodium retention was followed by a return to avid sodium retention. In one of these dogs (no. 330), sodium excretion again increased following the second period of avid retention.

After TIVCC, urine volume did not change significantly from the control state although most of the dogs gained weight; this could be accounted for by increased water intake. This pattern was evident during both of the stages described above.

**Effects of Saralasin on MAP and PRA**

Since the effects of saralasin on MAP and PRA were independent of the state of hydration or the method of diuresis, the results obtained under the three experimental protocols are described together. Table 1 summarizes these findings. In 14 normal dogs, control MAP was 153 ± 5 mm Hg and PRA was 0.9 ± 0.2 ng/ml per hour. Saralasin administration led to a pressor (or agonist) effect only, with MAP reaching a peak of 175 ± 6 mm Hg (P < 0.001) in 2-3 minutes. Thereafter MAP returned toward control levels and, at the time of discontinuation of the drug, was 161 ± 5 mm Hg (P < 0.001 compared to control values). The post-saralasin MAP was 158 ± 5 mm Hg.

In caval dogs, two types of blood pressure response to saralasin infusion were seen. In type 1 response, MAP decreased and reached a nadir at 10-15 minutes. The depressor response was noted in 16 experiments carried out in 10 caval dogs. This depressor effect lasted for the duration of drug infusion. In this group, control MAP was 119 ± 4 mm Hg, significantly less than normal dogs (P < 0.001), and decreased to a mean of 96 ± 5 mm Hg (P < 0.001) after saralasin. PRA prior to saralasin administration was 18.7 ± 4.2 ng/ml per hour (P < 0.001 compared to normal dogs) and increased to 71.4 ± 15.9 ng/ml per hour (P < 0.001 compared to control). Twenty minutes after discontinuation of saralasin, MAP was 123 ± 5 mm Hg, not significantly different from control, and PRA had decreased, but remained somewhat higher than control, 36.2 ± 6.6 ng/ml per hour (P < 0.05). In 14 of these 16 experiments there was a small, initial transitory pressor effect of saralasin which peaked in 2-3 minutes. In these dogs, control MAP was 121 ± 4 and increased to 129 ± 4 mm Hg (P < 0.001). The pressor effect was not obtained in the dog with the highest control PRA and in one dog in which the PRA was not determined. In general, the magnitude of the initial transient pressor effect was inversely related to the control PRA (Fig. 1).

Type 2 response was noted in 15 experiments on nine caval dogs and was characterized by only a pressor response as in normal dogs. MAP increased within 1 minute and peaked at 2 to 3 minutes. Thereafter, MAP tended to return toward control levels, remaining above control in 12 of the 15 dogs at the time of discontinuation of saralasin. The control MAP was 14 ± 4 mm Hg (P < 0.001 compared to type 1 caval dogs, but not statistically different from normal dogs) and increased to a peak of

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**Table 1 Effects of Saralasin on Mean Arterial Pressure and Plasma Renin Activity in Normal and Caval Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Plasma renin activity (ng/ml per hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-saralasin</td>
<td>Saralasin</td>
</tr>
<tr>
<td>Normal dogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14 dogs, 14 experiments)</td>
<td>153 ± 5 (14)</td>
<td>175 ± 6 (14)</td>
</tr>
<tr>
<td>P value*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Caval dogs, type 1 response</td>
<td>119 ± 4 (16)</td>
<td>96 ± 5 (16)</td>
</tr>
<tr>
<td>P value*</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caval dogs, type 2 response</td>
<td>141 ± 4 (15)</td>
<td>161 ± 4 (15)</td>
</tr>
<tr>
<td>P value*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Significance of the differences between groups, P value

<table>
<thead>
<tr>
<th></th>
<th>Normal—type 1 caval</th>
<th>Type 1—type 2 caval</th>
<th>Normal—type 2 caval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± se; numbers in parentheses = number of observations; NS = not significant.

* P value compared to pre-saralasin.
161 ± 4 mm Hg \( (P < 0.001) \). At the time of discontinuation of the drug, MAP was still significantly elevated above control, 147 ± 3 mm Hg \( (P < 0.01) \) and, 20 minutes after discontinuing the drug, MAP was 145 ± 3 mm Hg. Control PRA was 1.1 ± 0.2 ng/ml per hour \( (P < 0.001 \) compared to type 1 dogs, but not statistically different from normal dogs) and did not change appreciably during saralasin administration or following discontinuation of the drug.

Table 2 lists all the experiments on normal and caval dogs according to the types of response to saralasin and the experimental conditions under which saralasin was administered. Of the nine caval dogs which were also studied prior to caval constriction, four had serial studies with both types of response demonstrated one or more times. In the other five dogs, either the type 1 or type 2 response was obtained one or more times. Five dogs were studied only after TIVCC and had either a type 1 or type 2 response except for dog no. 325 which had both types of response in serial studies. Five normal dogs did not become caval after TIVCC.

Figure 2 depicts all the individual blood pressure responses in normal dogs studied either during water or mannitol diuresis. In all instances MAP increased.

Figure 3 shows data for all the individual experiments on caval dogs with type 1 response studied during mannitol diuresis, water diuresis, or under hydropenic, nondiuretic conditions. Note that the lowest level of pre-saralasin PRA in these dogs was 2.7 ng/ml per hour.

Figure 4 shows data for all the individual experiments on caval dogs with type 2 response studied during mannitol diuresis, water diuresis, or under hydropenic, nondiuretic conditions. Note that the highest pre-saralasin PRA in these studies was 2.5 ng/ml per hour, which was lower times. In the other five dogs, either the type 1 or type 2 response was obtained one or more times. Five dogs were studied only after TIVCC and had either a type 1 or type 2 response except for dog no. 325 which had both types of response in serial studies. Five normal dogs did not become caval after TIVCC.

Figure 2 Effects of saralasin on mean arterial blood pressure (MAP) in normal dogs.

<table>
<thead>
<tr>
<th>Table 2 Outline of Protocols Followed for Saralasin Study in Normal and Caval Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caval dogs</strong></td>
</tr>
<tr>
<td><strong>Dog no.</strong></td>
</tr>
<tr>
<td><strong>Normal dogs</strong></td>
</tr>
<tr>
<td><strong>Type 1 response</strong></td>
</tr>
<tr>
<td><strong>Type 2 response</strong></td>
</tr>
<tr>
<td>316</td>
</tr>
<tr>
<td>334</td>
</tr>
<tr>
<td>320</td>
</tr>
<tr>
<td>330</td>
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<tr>
<td>315</td>
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<tr>
<td>327</td>
</tr>
<tr>
<td>328</td>
</tr>
<tr>
<td>325</td>
</tr>
<tr>
<td>319*</td>
</tr>
<tr>
<td>321*</td>
</tr>
<tr>
<td>300</td>
</tr>
<tr>
<td>277</td>
</tr>
<tr>
<td>308</td>
</tr>
<tr>
<td>310</td>
</tr>
<tr>
<td>318*</td>
</tr>
<tr>
<td>322*</td>
</tr>
<tr>
<td>326*</td>
</tr>
<tr>
<td>313*</td>
</tr>
</tbody>
</table>

W = saralasin administered during protocol 1 (water diuresis); M = saralasin administered during protocol 2 (mannitol diuresis); H = saralasin administered during protocol 3 (hydropenia, nondiuretic condition). Numbers in parentheses = number of experiments.

* Dogs with silastic cuff around the thoracic inferior vena cava.
FIGURE 3  Effects of saralasin on MAP and PRA in caval dogs with type 1 response.

than the lowest level obtained in caval dogs with type 1 response. Also, note the rather large pressor response noted in some of these dogs.

In all the caval dogs demonstrating type 1 response, sodium retention was virtually complete during the 24-hour period prior to saralasin infusion. In caval dogs with a type 2 response, sodium retention was less avid and occasionally absent, with the dogs (as a group) retaining 65 ± 41% of sodium intake 24 hours prior to the saralasin infusion. The relationship between the response to saralasin and the state of sodium balance was applicable even in the two dogs in which there was a recurrent period of avid sodium retention following the period of less positive sodium balance. During these periods of recurrent avid sodium retention (98% or greater), PRA increased again and saralasin decreased BP. Figures 5 and 6 show these relationships for these two dogs (nos. 330 and 334).

Blood Composition, Plasma Volume, and Urine Aldosterone

Table 3 summarizes the data on hematocrit, plasma volume, PRA, and plasma aldosterone obtained prior to induction of anesthesia for saralasin studies in normal and caval dogs. In addition, urinary aldosterone excretion is shown for the 24-hour period immediately prior to the clearance experiment. The caval dogs are divided into two groups depending on the response to saralasin. The im-

FIGURE 4  Effects of saralasin on MAP and PRA in caval dogs with type 2 response.
experiments on type 1 caval dogs, and seven experiments on type 2 caval dogs. There was no significant difference in glomerular filtration rate (GFR), PAH clearance (CPAH), or filtration fraction (FF) among the groups. Absolute values for sodium and potassium excretion were significantly lower in type 1 caval compared to normal dogs but not statistically lower than in type 2 caval dogs. Fractional sodium excretion was also lower in type 1 caval dogs compared to normal and type 2 caval dogs, but did not reach statistical significance.

Protocol 2: Mannitol Diuresis

Table 5 summarizes the clearance data obtained under mannitol diuresis in six normal dogs, six caval dogs with type 1 response to saralasin, and four caval dogs with type 2 response to saralasin. There was no statistically signifi-

<table>
<thead>
<tr>
<th></th>
<th>Hematocrit (%)</th>
<th>Plasma volume (ml)</th>
<th>Plasma renin activity (ng/ml per hr)</th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Urine aldosterone (ng/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>46 ± 1</td>
<td>1139 ± 54</td>
<td>1.2 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>41 ± 21</td>
</tr>
<tr>
<td></td>
<td>(14)</td>
<td>(10)</td>
<td>(14)</td>
<td>(14)</td>
<td>(14)</td>
</tr>
<tr>
<td>Type 1 caval</td>
<td>42 ± 2</td>
<td>1459 ± 136</td>
<td>29.2 ± 3.6</td>
<td>83.5 ± 15.1</td>
<td>3368 ± 682</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(6)</td>
<td>(14)</td>
<td>(14)</td>
<td>(12)</td>
</tr>
<tr>
<td>Type 2 caval</td>
<td>38 ± 2</td>
<td>1406 ± 59</td>
<td>3.2 ± 1.0</td>
<td>9.5 ± 2.2</td>
<td>424 ± 174</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(8)</td>
<td>(9)</td>
<td>(9)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

Significance of the differences, P value

Normal—type 1 caval NS <0.05 <0.001 <0.001 <0.001
Type 1—type 2 caval NS NS <0.001 <0.001 <0.02
Normal—type 2 caval <0.01 <0.01 <0.05 <0.001 <0.01

Values are means ± se. Numbers in parentheses = number of observations; NS = not significant.
cant difference in GFR, C_{PAH}, FF, or potassium excretion. The tendency for GFR and C_{PAH} to be higher and FF to be lower in type 1 caval compared to normal dogs was partially related to the very low C_{PAH} in dog no. 313 and high C_{PAH} in dog no. 310, neither of which had serial studies (Table 2). Values for absolute and fractional sodium excretion were significantly lower in caval dogs with type 1 response (P < 0.01) compared either to normal dogs or type 2 caval dogs. There was no significant difference in absolute or fractional sodium excretion between normal and type 2 caval dogs.

**Discussion**

In dogs that developed ascites and edema following TIVCC, two types of BP response to angiotensin II blockade with saralasin were observed. In type 1 response, saralasin produced a significant fall in BP and a rise in PRA. The caval dogs with this response had low BP, high control PRA and plasma aldosterone, elevated 24-hour urinary aldosterone, and avid sodium retention as indicated by metabolic balance and clearance studies. Following progressive sodium retention, most of the caval dogs attained a new steady state in which BP returned to pre-caval levels, PRA, plasma aldosterone, and urinary aldosterone decreased significantly, sodium retention became less avid, and saralasin infusion no longer caused a fall in BP (type 2 response). In two caval dogs, after they had demonstrated a type 2 response, avid sodium retention returned and saralasin infusion again produced a type 1 response. Some caval dogs never showed a type 2 response because avid sodium retention persisted and PRA remained elevated until the dog expired. These data provide evidence for physiological heterogeneity in caval dogs in that sodium balance, BP, and the activity of the RAA system changed in the post-TIVCC period, probably as a physiological adjustment related to extracellular fluid volume expansion.

It is unlikely that anesthesia played any role in the pattern of the RAA system and response to saralasin in the present experiments, since the overall pattern was similar in awake animals. Moreover, similar observations of serial changes in the RAA system were obtained by Watkins et al.²⁴ in awake caval dogs. The lower PRA levels seen in each group of animals and the absence of a

### Table 5

**Renal Hemodynamics and Electrolyte Excretion in Experiments Performed under Protocol 2 (Mannitol Diuresis)**

<table>
<thead>
<tr>
<th>V (ml/min)</th>
<th>U_{Na}V (µEq/min)</th>
<th>U_{K}V (µEq/min)</th>
<th>C_{Na}/GFR (x 100)</th>
<th>GFR (ml/min)</th>
<th>C_{PAH} (ml/min)</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (6 dogs, 6 experiments)</td>
<td>2.7 ±0.4</td>
<td>201 ±61</td>
<td>52 ±10</td>
<td>2.98 ±0.78</td>
<td>50 ±7</td>
<td>123 ±18</td>
</tr>
<tr>
<td>Type 1 caval (6 dogs, 7 experiments)</td>
<td>1.9 ±0.2</td>
<td>4 ±1</td>
<td>62 ±12</td>
<td>0.06 ±0.02</td>
<td>59 ±10</td>
<td>168 ±22</td>
</tr>
<tr>
<td>Type 2 caval (4 dogs, 6 experiments)</td>
<td>2.5 ±0.4</td>
<td>179 ±50</td>
<td>63 ±12</td>
<td>2.92 ±0.89</td>
<td>45 ±3</td>
<td>130 ±8</td>
</tr>
</tbody>
</table>

**Significance of the differences, P value**

| Normal—type 1 caval | NS | <0.01 | NS | <0.01 | NS | NS | NS |
| Type 1—type 2 caval | NS | <0.01 | NS | <0.01 | NS | NS | NS |
| Normal—type 2 caval | NS | NS | NS | NS | NS | NS | NS |

For explanations see Table 4, footnotes.
difference in PRA in type 2 caval dogs compared to normal dogs during the acute study may be related to anesthesia, but probably are better attributed to other experimental factors (such as mannitol loading). Since Johnson and Malvin\textsuperscript{20} have demonstrated that PRA is increased during pentobarbital anesthesia. In any event, it seems highly unlikely that the small decrease in PRA in type 2 caval dogs during the acute study compared to awake determinations accounted for the different response to saralasin.

To characterize more precisely the renal handling of sodium, particularly at the time of saralasin infusion, renal clearances were obtained. As a corollary to the findings in the sodium balance studies, the clearance data further document the difference in renal handling of sodium between type 1 and type 2 caval dogs. Avid sodium retention in type 1 caval dogs was particularly striking during mannitol infusion in that sodium reabsorption in these dogs was virtually complete despite a significant diuresis. In view of possible alteration of the RAA system by mannitol infusion, diuresis also was induced with hypotonic glucose, because isotonic glucose infusion has been shown to have no effect on the RAA system over a period of 6 hours.\textsuperscript{27} Significant sodium retention was again seen in type 1 caval as compared to normal dogs. The inability to demonstrate a statistical difference in sodium excretion during water diuresis between type 1 and type 2 caval dogs was most likely due to the fact that sodium excretion usually is not increased during hypotonic glucose diuresis and, therefore, a difference in sodium excretion may not be evident in salt-retaining animals.\textsuperscript{28}

Acute TIVCC produces marked systemic hemodynamic changes.\textsuperscript{2, 6, 10, 14, 18} These circulatory alterations initiate compensatory responses including a rise in PRA and, by inference, angiotensin II. This elevation in angiotensin II is important for the maintenance of arterial pressure in caval dogs initially when sodium retention is avid, as indicated by a decrease in blood pressure when saralasin is infused. This also has been reported by Johnson and Davis.\textsuperscript{21, 22} Davis\textsuperscript{28} proposed that, following TIVCC, sodium and water accumulate inefficaciously in the ascitic space without closing the feedback loop for sodium retention and enhanced renin secretion. The findings in the caval dogs with persistent type 1 response support this concept. However, it is evident that a caval dog with type 1 response may eventually compensate through salt and water retention and extracellular fluid volume expansion. Sodium and water retention will become less avid and arterial blood pressure will increase, even though PRA decreases or even returns to the control level. Infusion of saralasin at this point does not produce a fall in arterial pressure and, by inference, blood pressure is no longer renin dependent.

The rise in sodium excretion associated with falling PRA, plasma aldosterone, and urinary aldosterone excretion in many of the caval dogs is reminiscent of the early study by Davis and Ball\textsuperscript{29} on the effects of a body cast on urinary aldosterone and sodium excretion in this model. Application of a plastic body cast to a caval dog resulted in an increased intra-abdominal pressure, cessation of fluid filtration into the peritoneal cavity, decreased aldosterone secretion, and natriuresis. In those dogs which converted from type 1 to type 2 response, it is conceivable that increased intra-abdominal pressure retarded fluid entry into the peritoneal cavity and, with continuing sodium retention, the intravascular compartment was expanded. At this point, sodium excretion would increase, which might lead to a return to an "ineffective extracellular fluid volume" and secondary sodium retention as observed in two dogs. Alternatively, but less likely, scar formation around the TIVC tie might lead to progressive constriction and recurrent avid sodium retention.

Watkins et al.\textsuperscript{24} carried out experiments similar to those described in this report using converting enzyme inhibitor instead of a competitive inhibitor of angiotensin II and using awake dogs with TIVCC and pulmonary artery constriction. They concluded that there was a sequence of events in which blood pressure was initially renin dependent and then became volume dependent after a period of salt and water retention. The present experiments confirm their findings and strengthen their basic hypothesis in that a different method for examining the physiological significance of the RAA system was employed and renal clearances of salt and water were sequentially examined. The larger number of dogs studied, the longer period of observation, and the different criterion used for adequate TIVCC in the present experiments (which produced significant variation in the degree of vena cava constriction) allowed for greater variability in the timing and sequence of events than noted by Watkins and co-workers,\textsuperscript{24} and permitted an important modification of their hypothesis. That is, PRA, plasma and urine aldosterone, and BP response to saralasin in caval dogs correlate with the state of sodium balance rather than a fixed time schedule or fixed course of events. In addition, because of this close relationship, the data suggest that either there is a common stimulus for increasing sodium excretion and suppression of the RAA system (extracellular volume expansion) or the increased sodium excretion (possibly through the macula densa-juxtaglomerular apparatus mechanism) leads to RAA system inhibition.

In the present study, GFR and C\textsubscript{PAH} were similar in normal and both types of caval dogs, so that renal sodium retention in the latter cannot be accounted for by alterations in renal hemodynamics. In contrast, acute TIVCC often produces marked renal hemodynamic changes associated with, and, probably, contributing to increased tubular sodium reabsorption.\textsuperscript{1, 3, 5, 6, 14} Thus, it would appear that the mechanism(s) for sodium retention also changes, as does the mechanism for maintenance of BP, but the former does so earlier and, possibly, not entirely due to initial sodium retention.

The transient BP increase noted in type 1 caval dogs preceding the decrease in BP can be attributed to the agonistic effect of saralasin. Support for this view may be derived from the inverse linear relationship between the magnitude of the pressor response and PRA (Fig. 1). That is, dogs with the highest PRA would have the fewest free binding sites and, therefore, the smallest agonistic effect.

It is of interest that PRA increased after saralasin
infusion only in type 1 caval dogs in which a decrease in BP was noted, suggesting a baroreceptor mechanism regulating renin release during angiotensin II blockade in these animals, since PRA remains unchanged in normal and type 2 caval dogs in which a fall in BP does not occur following the same dose of saralasin.

The present study may have relevance to clinical conditions associated with sodium retention, such as congestive heart failure, cirrhosis of the liver, and the nephrotic syndrome in which both elevated and normal PRA and serum aldosterone levels have been demonstrated. This has led to some confusion. Moreover, patients with these conditions, and particularly cirrhotics may undergo a spontaneous diuresis followed by a return to avid salt retention. It is possible that dynamic physiological adjustments similar to those described in the present experiments account for some of the variability in findings and clinical courses in these disease states, in addition to explaining the discrepancies in the literature concerning caval dogs.

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