Canine Neonatally Induced Coarctation Hypertension in the Second Year

VARIEVY HYPERRESPONSIVE PLASMA RENIN ACTIVITY

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with Daniel K. Gray, Statistical Consultant

SUMMARY In canine neonatally-induced coarctation hypertension, we reported abnormally elevated plasma renin activity (PRA) during sodium restriction in 2-year-old dogs, but found normal PRA responses to sodium restriction ± furosemide in coarcted dogs studied serially over the first year postaortic banding (PAB). To resolve this apparent discrepancy in PRA response, longitudinal studies were extended to 2 years PAB. In two separately-studied groups, each with three coarcted and three littermate controls, measurements of indirect forelimb blood pressure (BP) at 15 to 18 months, direct brachial arterial BP at 24 months, and serial measurement of PRA and extracellular volume (ECV, as \(^{24}\)Na space) were made over a 15- to 24-month age range during three sodium-volume levels: ad libitum sodium intake (NS), low-sodium diet alone (LS), and low-sodium plus Lasix (LS/Lasix). While PRA in coarcted dogs of both groups was comparable to controls at NS and LS, PRA in Group 1 coarcted dogs significantly exceeded that of littermates during LS/Lasix in both 18- and 24-month studies. In contrast, PRA in Group 2 coarcted dogs was not hyperresponsive to LS/Lasix as compared to simultaneously-studied littermates. The hyperresponsive PRA in Group 1 coarcted dogs could not be attributed to larger absolute or relative ECV deficits. Overall, ECV in coarcted dogs of each group was higher on the average but was not statistically different from controls. Results indicate that the hyperresponsive PRA in this canine model is: 1) a variable feature, developing secondarily in the late established phase; 2) reproducible for a given animal; and 3) not attributed to exaggerated ECV deficits during the LS/Lasix protocol. (Hypertension 5: 328–335, 1983)

KEY WORDS • extracellular volume • inbred dogs • littermate control

THE genesis and maintenance of hypertension in thoracic aortic coarctation requires the presence of a kidney located distal to the vascular stenosis.\(^1\)\(^4\) Evidence supporting specific participation of the renin-angiotensin system is less definitive. In clinical coarctation hypertension, plasma renin activity (PRA) is consistently normal during unrestricted sodium intake\(^5\)\(^\text{-}^4\) but, in some patients, may show an exaggerated rise following stimulation.\(^6\)\(^\text{-}^4\) This variable hyperresponsiveness of PRA, usually construed as supportive of a renin-mediated mechanism, is of unknown pathophysiologic significance.

Inbred dogs subjected to thoracic aortic banding as neonates provide an animal model of coarctation hypertension. By virtue of slowly progressive aortic constriction from an early age, this model closely simulates the human disease.\(^15\)\(^\text{-}^16\) In 1975, we reported abnormally elevated PRA in 2-year-old neonatally-coarcted dogs studied only during sodium restriction.\(^15\) Unexpectedly, subsequent longitudinal studies in this model over the first year after banding, while documenting significant extracellular volume excess, demonstrated that PRA in coarcted dogs was clearly comparable to littermate controls: during ad libitum diet, during sodium restriction alone, and during sodium restriction plus diuretic.\(^16\)
This apparent discrepancy in stimulated PRA response between 0- to 1-year-old vs 2-year-old coarcted dogs prompted us to extend our longitudinal observations to 2 years postbanding. The present report describes the characteristics of proximal arterial blood pressure, extracellular fluid volume (ECV), and PRA responses during the second year of neonatally-induced coarctation hypertension.

Methods

Experimental Animals
Two separate groups of inbred Labrador dogs were each serially studied over a 15- to 24-month age range, representing the second-year postaortic banding. Group 1, born in 1977, consisted of three neonatally-coarcted and three littermate controls drawn from three litters; the Group 1 studies reported here were performed in 1979. Group 1 dogs were also included in 0- to 1-year studies reported previously. Group 2 dogs, born in late 1978, contained three coarcted and three littermate control dogs drawn from two litters; Group 2 studies reported here were carried out in 1980. The technique of neonatal aortic banding and the littermate-control experimental design have been previously described. While the two groups were studied separately in time, the dogs within each group were studied concurrently and their various plasma and urine samples assayed together.

Protocols
All observations were made in awake dogs. Studies in Group 1 dogs were performed at 15, 18, and 24 months after banding. The 15-month protocol included observations during "normal" sodium intake (2.1 ± 1.0 SE mEq Na+/kg/day; Blue Mountain Kibble) and again after 8 days of dietary sodium restriction (Na+ intake = 0.17 ± 0.01 mEq Na+/kg/day; HD Chow, Riviana Foods Inc., Indianapolis, Indiana). Dietary sodium intakes are based on prior metabolic balances. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third pulse pressure. In 24-month-old dogs, direct arterial pressure was measured via indwelling catheters as previously described. For each animal, the direct MAP value was derived from four 10- to 15-minute continuous recordings, each averaged over time. Systolic and diastolic pressures were recorded intermittently over the same period and the values averaged.

Extracellular Volume (ECV)
ECV was estimated by the space of distribution of 24Na according to methods detailed previously. Results are expressed as cubic centimeters per kilogram (cc/kg) of sodium-replete body weight.

Plasma Renin Activity (PRA)
Blood from upright dogs was collected in di Na EDTA just prior to ECV measurement; plasma was frozen at −20°C until assay. For each group, all samples collected during a given protocol were processed concurrently. Methods for pretreatment of plasma (di-isopropyl fluorophosphate, pH 6.2) and radioimmunoassay of angiotensin I (AI) have been reported. In this report, the term "hyperresponsive PRA" is defined as an exaggerated increase in PRA during stimulation to levels that are significantly increased over those of simultaneously-studied littermates.

Sodium Excretion
Twenty-four-hour urine specimens were collected in metabolic cages for measurement of daily urine sodium excretion (UoN) during each protocol condition. In 18-month Group 1 studies, cumulative sodium balances were also determined for 3 consecutive days beginning with institution of furosemide. Urinary sodium concentrations reported in table 1 were separately determined on fresh urine obtained by bladder catheterization. In 24-month studies, bladder catheterizations were performed on Days 6 and 13, the latter 5 days after the last diuretic dose. Sodium concentration was measured by flame photometer. Fecal sodium was determined by acid extraction according to the method of Leenen and deJong. In this report, the term "hyperresponsive PRA" is defined as an exaggerated increase in PRA during stimulation to levels that are significantly increased over those of simultaneously-studied littermates.

Statistical Analysis
Each variable was first examined by regression analysis for age-related changes. Age-dependent changes
TABLE 1. Indices of Sodium Excretion

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
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<th>Group 2</th>
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<tr>
<td></td>
<td>18 months</td>
<td>24 months</td>
<td>24 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS</td>
<td>LS/ furosemide Week 3*</td>
<td>LS</td>
<td>LS/ furosemide Day 5*</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>Week 1</td>
<td>LS</td>
<td></td>
</tr>
<tr>
<td>Coarcted</td>
<td>28 ± 12</td>
<td>1.8 ± 1.3</td>
<td>8.5 ± 8.8</td>
<td>34 ± 36</td>
</tr>
<tr>
<td>Control</td>
<td>23 ± 16</td>
<td>1.7 ± 0.8</td>
<td>5.1 ± 4.9</td>
<td>46 ± 48</td>
</tr>
<tr>
<td>Urinary [Na⁺] (mEq/liter)</td>
<td></td>
<td></td>
<td>49 ± 35</td>
<td>136 ± 109</td>
</tr>
<tr>
<td>Coarcted</td>
<td>43 ± 51</td>
<td>2.3 ± 3.2</td>
<td>0.9 ± 0.6</td>
<td>1.6 ± 1.1</td>
</tr>
<tr>
<td>Control</td>
<td>33 ± 16</td>
<td>6.3 ± 8.4</td>
<td>3.4 ± 3.7</td>
<td>55 ± 22</td>
</tr>
<tr>
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*Urine was collected 3 to 5 days after last furosemide dose.
Values are means ± SD; n = 3 coarcted and 3 control dogs for each entry. U_NaV = 24-hour urine Na⁺ excretion. Urinary [Na⁺] = sodium concentration in sterile urine sample from bladder catheterization.

Results

Twenty-four-hour urinary sodium excretion (U_NaV), together with the sodium concentration of random urine samples, are shown in table 1 for each protocol condition. Results document the potency of the volume-depleting stimuli and are comparable for coarcted and control dogs within each group. In Group 1 dogs at 18 months, urinary sodium concentration measured 4 to 5 days after the last diuretic dose supports complete dissipation of the natriuretic effect. Similarly, in 24-month studies for both groups, U_NaV and urinary sodium concentration indicate avid sodium conservation at 3 days after discontinuation of furosemide.

Plasma Renin Activity

In coarcted dogs of both groups, PRA during normal sodium intake was comparable to that of littermate controls (fig. 1). In sodium-replete Group 2 coarcted dogs at 18 months, PRA was 4.3 ± 1.9 (n = 6) vs 3.1 ± 1.5 (n = 5) ng Al/ml hr⁻¹ in controls (not significant). Similarly, during sodium restriction alone (Group 1, 15- and 18-month studies), PRA in coarcted dogs did not differ from controls. However, PRA response to the combination of furosemide plus sodium restriction differed between coarcted dogs of Group 1 vs those of Group 2 (p < 0.001). In Group 1 coarcted dogs, PRA (defined relative to simultaneously-studied littermates) following the low sodium/diuretic combination was significantly higher than that of littermate controls in both the 18-month and 24-month studies (p < 0.001). In contrast, coarcted dogs of Group 2 did not exhibit hyperresponsive PRA following the low sodium/diuretic combination at 24 months. PRA was significantly increased by each volume-depleting protocol (p < 0.001).
Extracellular Volume

Within each group, ECV in coarcted dogs was higher on the average but did not differ significantly from controls (fig. 1). In sodium-replete Group 2 coarcted dogs, ECV at 18 months was 295 ± 8 cc/kg (n = 6) vs 282 ± 20 (n = 5) in controls. ECV fell significantly in response to each of the volume-depleting protocols (p < 0.001).

To further examine the ECV response to sodium-volume depletion, ECV (in cc) measured during sodium-volume depletion, ECV (in cc) measured during sodi-

**Figure 1.** Plasma renin activity, extracellular volume, and proximal arterial blood pressure during the second year of neonatally induced coarctation hypertension. PRA = plasma renin activity; ECV = extracellular volume; BP = blood pressure; NS = normal sodium diet; LS = low sodium diet alone; LS/Lasix = combined low sodium diet plus furosemide (see Methods); (n) = no observations. Each point represents the mean ± sd.
um depletion was expressed for each dog as a percentage of the sodium-replete ECV. Results for 18- and 24-month studies are presented in figure 2.

In Group 1 coarcted dogs at 18 months, the percentage decrease in ECV following 2 weeks of sodium restriction alone (−2.6% ± 1.6%) or with diuretic added (−9.8% ± 5.0%) was comparable to that of controls (−2.7% ± 3.0% and −6.9% ± 2.1%) (fig. 2, top panel). Similarly, in 24-month studies, the volume deficit induced by simultaneous sodium restriction and diuretic treatment was similar in coarcted and control dogs of each group (fig. 2, bottom panel).

**Sodium Deficit**

Cumulative sodium losses following the addition of furosemide were measured in Group 1 dogs at 18 months. For the 3-day period beginning with the institution of furosemide, cumulative sodium deficits were 191 ± 13 mEq (5.8 ± 0.6 mEq/kg) in the three coarcted dogs vs 177 ± 31 mEq (5.1 ± 0.6 mEq/kg) in three littermate controls (not significant).

Thus, neither an absolutely nor a relatively excessive volume deficit following the low sodium/diuretic combination provided a consistent explanation for the differing PRA responses in Group 1 vs Group 2 coarcted dogs as compared to their respective littermate controls.

**Hematocrit**

Hematocrit values in coarcted dogs of each group were similar to their respective littermate controls and were comparably and significantly (p < 0.001) increased by LS/furosemide. At 24 months, means (± sd) were, for NS and LS/furosemide, respectively, 46.5 ± 0.7 and 52.7 ± 0.3 vol % in Group 1 coarcted dogs, 43 ± 1.4 and 50.2 ± 0.8 vol % in Group 1 controls; 48.6 ± 3.4 and 51.9 ± 1.0 vol % in Group 2 coarcted dogs, and 46.3 ± 3.1 and 53.8 ± 2.9 vol % in Group 2 controls.

**Proximal Arterial Blood Pressure**

Coarcted dogs of group 1 exhibited significant proximal systolic, diastolic, and MAP hypertension (p < 0.001 for each) by indirect measurement at 18 months (fig. 1). In the three sodium-repleted Group 2 coarcted dogs, indirect forelimb pressures at 18 months (not shown in fig. 1) were, for systolic/diastolic/MAP: 181 ± 32/88 ± 9 mmHg (119 ± 17 mmHg) as compared to 156 ± 16/92 ± 10 mm Hg (114 ± 12 mm Hg) in the three Group 2 controls (not significant). No sodium-depleted indirect pressure data are available for Group 2.

At 24 months, coarcted dogs of both groups exhibited significant direct proximal systolic (p < 0.01), diastolic (p < 0.01) and MAP (p < 0.005) hypertension. There were no statistically significant differences in direct proximal blood pressure measurements between coarcted dogs of Group 1 vs those of Group 2. However, the marked variability in proximal arterial BP among sodium-repleted Group 1 coarcted dogs (fig. 1) is due to unusually low BP in one coarcted dog. The latter had been clearly hypertensive in 18-month studies (186/101 mm Hg, MAP 129 mm Hg by indirect measurement, which underestimates direct diastolic and MAP15) and was again so during the LS/furosemide protocol at 24 months, suggesting that transient pathophysiologic or technical factors may have been operative. Individual proximal BP values in sodium-repleted Group 1 coarcted dogs at 24 months were 149/91 mm Hg (114), 205/130 mm Hg (165), and 251/157 mm Hg (193) as compared to sodium-depleted values of 182/109 mm Hg (140), 185/127 (152), and 186/115 (142).

There were no significant changes in proximal blood pressure during the sodium-depleting protocols in either group. However in Group 1 coarcted dogs at 24 months, responses were again variable. While there was an apparent rise in proximal BP during sodium depletion in the one coarcted dog, there were substantial BP falls in the other two.

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**Figure 2.** Change in extracellular volume (ECV) during sodium-depleting protocols, expressed as a percent change (% Δ) from the sodium-replete value. LS = low sodium diet; LS/Lasix = low sodium diet plus furosemide (see Methods).
Discussion

Exaggerated increase in PRA in response to stimulation (i.e., hyperresponsive PRA) has been observed in 28 of 51 (55%) appropriately studied patients with thoracic aortic coarctation.6-14 The mechanism(s) and significance of this variable abnormality are unknown. We reported similarly hyperresponsive PRA in 2-year-old neonatally coarcted dogs studied during severe sodium restriction and compared to age-matched (but not littermate) controls.15 However, subsequent longitudinal studies in this canine model, performed over the first year after aortic banding, demonstrated normal PRA responses to sodium restriction alone and to sodium restriction plus furosemide, as well as to acute converting-enzyme inhibition, in each case as compared to littermate controls.16-18 These latter studies, while documenting significant extracellular and plasma volume excess in coarcted dogs (and thus a relatively abnormal PRA), nonetheless indicate that an overtly hyperresponsive PRA is not essential to the generation or first-year maintenance of canine coarctation hypertension.16

The present report extends our longitudinal studies to the second year of the neonatal coarctation model in order to reassess the incidence, mechanism, and significance of the exaggerated PRA response to stimulation. Interpretation of our results is based on comparison of coarcted dogs with simultaneously studied littermate controls. Results indicate, first, that as in human coarctation hypertension, PRA hyperresponsiveness in this canine model is a variable feature occurring in three of six coarcted dogs observed during the second year postbanding. Review of PRA results from our original studies in 2-year neonatally coarcted dogs shows that seven of 10 exhibited overtly hyperresponsive PRA.19 Second, when present, the hyperresponsive PRA pattern is reproducible in a given subject, as demonstrated by the concordance of the 18- and 24-month responses of Group 1 coarcted dogs (fig. 1). Third, the hyperresponsive pattern was not demonstrable with sodium restriction alone, but only after the combination of sodium restriction plus intravenous furosemide. Finally, the longitudinal design of the present study, wherein all animals were subjected to the identical LS/furosemide protocol at both 1 and 2 years postbanding (S. Bagby, unpublished data),16 permits the conclusion that, when present, the exaggerated PRA response to stimulation is a secondary development evolving in the late established phase of the hypertensive process. The possibility that Group 2 coarcted dogs might develop PRA hyperresponsiveness if followed longer cannot be excluded.

Our extended longitudinal studies therefore indicate that hyperresponsive PRA occurs as a late variable feature of neonatally-induced canine coarctation hypertension with a frequency (50% to 70%) comparable to that seen in human coarctation hypertension.6, 9-14 The pathophysiologic significance of the hyperresponsive PRA pattern is not known; it is clearly not essential for either the generation or maintenance of canine coarctation hypertension, as shown by our present study and previously.16 However, it may reflect other aspects of the coarcted state that are potentially relevant to clinical assessment and management. For example, PRA hyperresponsiveness might indicate diffuse renovascular damage due to distal hypertension and thus a decreased likelihood of long-term hypertensive cure following corrective surgery.

Therefore, to glean maximum information from the discrepant PRA responses, we have compared the hyperresponsive coarcted dogs of Group 1 with those of Group 2, bearing two goals in mind: 1) to assess the immediate mechanism(s) of renin stimulation operative specifically during the LS/furosemide protocols; and 2) to identify any chronic features of the coarcted state which, by virtue of association with the hyperresponsive PRA pattern, might provide clues to its pathophysiologic significance. We fully recognize that, in view of the small number of subjects, this comparison cannot be definitive; we rather intend that it define areas worthy of future study.

Several mechanistic factors affecting renin release could, singly or in combination, account for the PRA hyperresponsiveness and potentially provide clues to its significance. These factors include: 1) excessive volume deficits during the more potent sodium-depleting protocols; 2) compromised renal perfusion pressure and/or blood flow during severe volume depletion; 3) exaggerated sympathetic outflow in response to volume depletion; and 4) augmented prostaglandin release in response to furosemide.21,22 The present results address the first of these factors.

The ECV in coarcted dogs of both groups, although higher on the average, was not significantly different from littermate controls. Specifically during the periods of PRA excess in Group 1 coarcted dogs, absolute ECV values were never smaller, nor ECV deficits larger, as compared to those seen in identically treated littermate controls. Finally, relative (%) changes in ECV during sodium-volume depletion were not exaggerated in the Group 1 coarcted dogs exhibiting excess PRA. Thus, the PRA hyperresponsiveness developing late in the course of some neonatally-coarcted dogs did not appear attributable to altered ECV responses.

The augmented rise in PRA in Group 1 coarcted dogs relative to their littermates was demonstrable only in the presence of furosemide. In the clinical study of Alpert et al.,13 the pattern of hyperresponsive PRA was similarly observed, not during sodium restriction alone, but only after furosemide. In an additional 13 coarctation patients reported9, 10, 12, 14 the effective stimulus for exaggerated PRA rise included furosemide. Since furosemide has been recently shown to stimulate prostaglandins,21,22 the hyperresponsive PRA could reflect an abnormal prostaglandin response to furosemide. However, the fact that our original 2-year-old coarcted dogs exhibited hyperresponsive PRA during severe sodium restriction alone, without a diuretic,12 suggests that the factors involved are not specific to furosemide. Furthermore, Van Way et al.11 elicited an exaggerated PRA response in three
coarctation patients simply by treadmill exercise. Our observations do not exclude a contribution of prostaglandins in mediating the exaggerated PRA responses.

Indices of urinary sodium excretion during the various volume-depleting protocols were comparable in coarcted and control dogs within each group. Furthermore, cumulative sodium balance over the 3 days following furosemide in 18-month Group 1 studies indicated similar net sodium deficits in experimental and control animals. These observations are in keeping with the normal ECV responses observed in coarcted dogs.

It is also feasible that Group 1 dogs operated at a lower ECV setpoint and thus were exposed to a lower ECV in absolute terms following LS/furosemide as compared to Group 2. A more potent hypovolemic stimulus in Group 1 might thus unmask the hyperresponsive PRA of the coarcted dogs. However, all observations are against this hypothesis: sodium-replete Group 1 dogs tended to have, if anything, higher ECV and lower PRA than Group 2 dogs (fig. 1). The relatively low sodium excretion (table 1) in 24-month Group 1 dogs on an ad libitum diet does not appear representative of the chronic state of these animals.

In addition to specific mechanisms known to directly affect renin release, chronic features reflecting the severity of coarctation hypertension may prove relevant in identifying indirect mechanisms influencing PRA hyperresponsiveness. Thus, factors such as duration of hypertension, magnitude of proximal hypertension, magnitude of pressure gradients, and presence/magnitude of distal hypertension could be important in the secondary evolution of an abnormal renin response to stimulation. The present results bear on the first two factors.

Our observations suggest that duration of hypertension, taken alone, is not sufficient to explain the variable development of hyperresponsive PRA. Thus, the pattern was apparent by 18 months in Group 1 coarcted dogs but not yet by 24 months in Group 2.

In considering indicators of coarctation severity in terms of their chronic impact, it is of note that the sodium-replete state represents the usual condition for these dogs over their lifespan to date, whereas sodium-deplete conditions have been imposed only intermittently for short periods. Thus, observations made during ad libitum sodium intake should most validly reflect the chronic state. Although there were no statistically significant differences in the magnitude of proximal blood pressure demonstrable between the coarcted dogs of Group 1 vs those of Group 2, several points bear emphasis. First, forelimb BP in 18-month-old sodium-repleted Group 1 coarcted dogs was distinctly higher than that of Group 2 coarcted dogs, although the paucity of Group 2 observations at 18 months precludes any statistically meaningful comparison of indirect blood pressures between the two groups. Second, in the 24-month studies, the striking proximal hypertension (MAP, 165 and 193 mm Hg) during ad libitum sodium in two Group 1 coarcted dogs, together with the longitudinal evidence that the apparently normotensive value of the third was not reflective of the chronic state, suggest a potentially relevant difference from the MAP range of 136–150 mm Hg in sodium-repleted Group 2 coarcted dogs. Taken together, these results can suggest, although certainly not document, that the pattern of hyperresponsive PRA may be a correlate of more severe proximal hypertension.

It is also interesting to note that the two Group 1 coarcted dogs exhibiting severe chronic (i.e., in their usual sodium-repleted state) hypertension also showed distinct proximal pressure falls in response to the LS/furosemide protocol at 24 months. In contrast, none of the Group 2 coarcted dogs exhibited proximal pressure changes in response to LS/furosemide. It is thus tempting to suggest that, in at least two of the three Group 1 coarcted dogs, PRA hyperresponsiveness reflects a decreased capacity to maintain blood pressure during volume depletion. However, the stability of proximal MAP in the 18-month studies, despite comparably hyperresponsive PRA, is not supportive of relative hypertension as a consistent mechanism of renin stimulation during LS/furosemide.

The present results in 15- to 24-month-old dogs do not statistically document the previously reported 4% to 5% ECV excess noted in coarcted dogs studied over the first-year postaortic banding. However, overall mean values for coarcted dogs in the present report exceeded that of controls at each sodium/diuretic condition: during ad libitum diet, 292 ± 9 cc/kg in coarcted (n = 19) vs 285 ± 16 cc/kg (n = 18) in controls; during sodium restriction, 279 ± 18 (n = 8) vs 261 ± 11 cc/kg (n = 8); during LS/furosemide, 255 ± 18 (n = 9) vs 253 ± 23 cc/kg (n = 9). Because of the small magnitude of the expected ECV difference and fewer observations in these older dogs, we can neither document nor exclude a persistent ECV excess in the second-year postbanding. On the other hand, comparing the present results with those of our prior studies prompts our working hypothesis that, if present, the magnitude of the ECV excess likely declines between 1 and 2 years after banding.

The role of renal hemodynamics and the distal circulation in the variably hyperresponsive PRA will be addressed in a separate report.

In summary, exaggerated PRA rise following stimulatory maneuvers in canine neonatally-induced coarctation hypertension: 1) is a variable feature developing secondarily in the late phase of the model; 2) is reproduducible for a given animal; and 3) cannot be attributed to exaggerated ECV deficits during sodium-volume depletion. Our findings suggest, but do not document, that the hyperresponsive PRA pattern may be associated with more severe proximal hypertension.

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