Renin, Aldosterone, Body Fluid Volumes, and the Baroreceptor Reflex in the Development and Reversal of Goldblatt Hypertension in Conscious Dogs

By Jean-Francois Liard, Allen W. Cowley, Jr., Robert E. McCaa, Connie S. McCaa, and Arthur C. Guyton

ABSTRACT

The renal artery to a sole remaining kidney was constricted in unanesthetized dogs while renal arterial pressure was recorded distal to the occluder. Following the constriction, mean arterial blood pressure, which was continuously monitored 24 hours a day for 1 week, exhibited a biphasic increase. The first peak in pressure correlated with a large increase in plasma renin activity; the second peak correlated with an increase in plasma volume brought about by positive sodium and water balances. Renin activity was returning to normal when the second peak occurred. Increased drinking played a major role in the positive water balance. Plasma aldosterone concentration was moderately and transiently increased for only a few hours following the constriction. The experiment was repeated in sinoaortic baroreceptor-denervated dogs; apparently, the baroreceptor reflex significantly slows the time course of the arterial blood pressure increase during the first few days of constriction but does not alter the magnitude of the pressure increase after 1 week. After release of renal artery constriction, mean arterial blood pressure decreased progressively over a 3-day period, during which time significant negative sodium and fluid balance occurred. The slow return of the pressure back to normal correlated highly with a decrease in plasma volume. In the baroreceptor-denervated dogs, the initial fall in arterial blood pressure apparently also resulted at least partly from a decrease in plasma renin activity, but this effect was not observed in the intact dogs because the renin activities in these dogs had already decreased to normal prior to constrictor release. The effects of the baroreceptor reflex on the time course of the pressure decrease did not seem to be as significant as those on the time course of the pressure increase.

KEY WORDS arterial blood pressure heart rate sodium space sodium potassium continuous data collection fluid balance studies plasma volume

The magnitude and the time course of the increase in mean arterial blood pressure following constriction of the renal artery to a sole remaining kidney (Goldblatt hypertension) depend on the interaction of a number of mechanisms: the release of renin by the kidney (1, 2), the retention of sodium and water, the expansion of fluid volumes (1, 3–6), the buffering action of the baroreceptor reflexes, and still other arterial blood pressure control systems are all involved. However, few studies have attempted to evaluate simultaneously the role of all of these pressure control systems and to compare the experimental results with the predictions made from their known physiological characteristics, especially with respect to response time and maximum feedback gains (7). Also, no definite explanation has yet been provided for the return of blood pressure to normal following release of the renal artery constriction (8–12). The role of the kidney’s excretory function in this process is controversial. For instance, it has been reported that the return of blood pressure to normal can be obtained without any (10) or with a normal urinary excretion (11), although marked diuresis and natriuresis have been observed after unclamping in the one-kidney Goldblatt hypertensive rat (13).

Therefore, we attempted to conduct a comprehensive study of the transient changes in arterial blood pressure, heart rate, fluid volumes, sodium and water balance, plasma renin activity, aldosterone concentration, and other factors during

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the development and the reversal of Goldblatt hypertension in unanesthetized dogs. The results were also compared in intact and baroreceptor-denervated dogs to determine the role that the baroreceptor reflex plays in modulating the transient changes in blood pressure.

Important methodological aspects of this study must be emphasized. Recently described computer techniques (14) allowed precise analysis of continuously recorded hemodynamic data. Surgery and anesthesia at the time of the constriction were avoided, and the degree of renal artery constriction was precisely measured in the conscious dogs. These techniques allowed a detailed careful analysis of some important aspects of the transients associated with Goldblatt hypertension.

### Methods

#### Animal Preparation.

Seventeen mongrel dogs, 10 male and 7 female, were used for these experiments; their initial body weight averaged 22.5 ± 1.0 kg. Eight were studied with their baroreceptor reflexes intact (referred to as intact dogs). Four of the intact dogs later underwent sinoaortic baroreceptor denervation and constituted, with 9 other dogs, a group of 13 baroreceptor-denervated dogs.

In a first surgical step, the right kidney was removed, and chronic indwelling catheters were placed in the aorta and the vena cava through the femoral vessels on one side. A second operation was performed 1-2 weeks later to place an occluder around the left renal artery and a chronic indwelling catheter in the renal artery distal to the occluder by the method of Herd and Barger (15, 16). Care was taken not to strip the renal nerves when the renal artery was exposed. Also, for the sinoaortic baroreceptor-denervated dogs, the baroreceptors were denervated during this second operation using a previously described procedure (14) which involves surgery on the carotid sinus, the aortic arch, and the sympathetic-depressor-vagal trunks. In five dogs, the thoracic surgery was not performed. There was no noticeable difference in the efficacy of the denervation in the dogs not subjected to the thoracic surgery.

Two types of renal artery occluder were used. The first one was similar in principle to the occluder described by Ferrario et al. (17); it consisted of two stainless steel parts which snapped together around the renal artery. A small screwdriver could be passed through an exteriorized polyvinyl tube to reach a screw housed in the upper portion of the occluder to open and close the clamp following recovery of the dogs. The second type of occluder was a Silastic cuff filled with saline that was used in four dogs in place of the steel occluder. This externally inflatable cuff was 1 cm long and had an inside diameter of 5 mm (Hazan Everett, Malwh, N. J.).

#### Collection and Analysis of Hemodynamic Data.

Due to the great sensitivity of arterial blood pressure to external stimuli in the baroreceptor-denervated dogs, special techniques were used to continuously record arterial blood pressure and heart rate on a Grass model 7 polygraph, at low paper speed (10-15 mm/min) in an isolated room (14). Analysis of the data was performed using a fiber-optic curve-scanning system (18) that read the chart records and was linked through an analog-to-digital converter to a PDP-9 computer (14). In addition to very accurate mean values, these techniques permitted calculation of the relative frequency of occurrence of any value of each variable, thus allowing generation of frequency-distribution curves over any desired period of time.

#### Balance Studies.

The individual experiments were performed in a metabolic cage. Urinary volume was measured daily. Distilled water was provided ad libitum, and the volume ingested daily was carefully measured. Daily sodium and potassium concentrations or contents were measured in the urine, the food, and the feces by flame photometry. Feces and food were incinerated, and the residues were dissolved in 1M HCl. The daily sodium intake varied between 1 and 4 mg/kg, and the balance was obtained by subtracting the amount of sodium excreted in the urine and the feces from this intake. Sodium and potassium balance, drinking water intake, and urinary volume were expressed per kilogram of body weight, which was measured every other day.

#### Other Measurements.

Blood samples were taken from the aortic catheter before the dogs were fed. After removal of the plasma, the blood cells were reinjected in isotonic saline. Plasma renin activity was measured by a radio-immunoassay technique for angiotensin I (19), and plasma aldosterone concentration was also measured using a radioimmunoassay procedure (20). Plasma cortisol determinations were made by the competitive protein-binding procedure described by Murphy (21). Plasma sodium and potassium concentrations were measured by flame photometry. Creatinine was measured in both urine and plasma using a Technicon autoanalyzer to allow calculation of endogenous creatinine clearance from the daily urinary volume. Plasma volume was measured by spectrophotometry in three samples collected after injection of Evans blue dye. The sodium space was measured by collecting three samples 2.5, 3, and 3.5 hours after injection of 22Na.

#### Experimental Protocol.

Following recovery from the second operation, control measurements were started. When the dogs had been in approximate sodium balance for at least 2 consecutive days, the renal artery was constricted. Continuous measurement of arterial blood pressure and heart rate was instituted at least 24 hours before the constriction, and control values for plasma volume and sodium space were obtained either the day before or the day of renal artery constriction. Control measurements of aldosterone, cortisol, creatinine, sodium, and potassium concentrations in the plasma as well as control measurements of plasma renin activity, osmolality, and hematocrit were obtained several times during the days preceding the constriction. All of these measurements were then repeated periodically following constriction and also following subsequent release of the constriction.

The renal artery was constricted while arterial blood pressure was being recorded distal to the occluder. Renal perfusion pressure was reduced in one step to approximately 50 mm Hg. This procedure was carried out with no local or general anesthesia. Arterial blood...
pressure distal to the occluder was recorded continuously for the first hour following constriction, and additional intermittent measurements 5 minutes to several hours in duration were made every day.

Seven days after constriction of the renal artery, the constriction was released in the conscious dogs while the pressure in the renal artery was being measured distal to the occluder. Six experiments were performed on six intact dogs, and seven experiments were performed on five baroreceptor-denervated dogs.

Unless otherwise stated, all values are expressed as means ± SE. Statistical significance was accepted for a P value less than 0.05.

Results

ONSET TRANSIENTS

Hemodynamic Data.—Figure 1 depicts the average changes in mean arterial blood pressure during the first hour following constriction of the renal artery in 11 experiments performed on 8 intact dogs and in 16 experiments performed on 13 baroreceptor-denervated dogs. The illustrated changes are the differences between the mean pressure averaged by the computer for each 5-minute period following constriction and the mean pressure for the 30-minute period prior to constriction (116 ± 4.7 mm Hg in the intact group [N = 11] and 109 ± 6.6 mm Hg in the denervated group [N = 16]).

The changes in mean arterial blood pressure were significantly greater in the baroreceptor-denervated dogs throughout the first hour. In the intact dogs, the average peak increase in mean arterial blood pressure during the first hour was 20 ± 2.6 mm Hg, occurring after 50 ± 4 minutes. The average peak increase for the baroreceptor-denervated dogs was 50 ± 3.0 mm Hg, occurring after 39 ± 3 minutes. Both the magnitude of this maximum increase and the time at which it occurred were significantly different between the two groups.

Figure 2 shows that the much greater increase in pressure in the baroreceptor-denervated group was due to a greater pressor sensitivity to plasma renin activity as a result of baroreceptor debuffering rather than to a greater renin release. Cowley and Guyton (22) have seen differences of the same magnitude during the infusion of angiotensin or norepinephrine into conscious intact or baroreceptor-denervated dogs.

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**FIGURE 1**

Changes in mean arterial blood pressure during the first hour following constriction of the renal artery in intact (11 experiments) and baroreceptor-denervated dogs (16 experiments). Values are means ± SE.

**FIGURE 2**

Relation of the change in mean arterial blood pressure from control following constriction of the renal artery to the change in plasma renin activity from control after 15 minutes (triangles), 30 minutes (squares), and 60 minutes (circles) in intact dogs (solid symbols), and baroreceptor-denervated dogs (open symbols).
Hourly Plot of Mean Arterial Blood Pressure Changes over 6 Days following Constriction.—The 24-hour control mean arterial blood pressure averaged 104 ± 4.0 mm Hg in 8 experiments in seven intact dogs and 102 ± 3.7 mm Hg in 11 experiments in nine baroreceptor-denervated dogs. Figure 3 summarizes the average changes in mean arterial blood pressure for 6 days following the constriction; Figure 3A presents the data for the intact dogs and Figure 3B presents those for the baroreceptor-denervated dogs. The results were obtained by subtracting the 24-hour control mean arterial blood pressure from the mean arterial blood pressure obtained for each hour following the constriction in each dog. During the 2 days indicated by the hatched areas at the top of Figure 3A, the changes measured in the baroreceptor-denervated dogs (Fig. 3B) were significantly greater than those occurring in the intact dogs (Fig. 3A). It is apparent from Figure 3B that the baroreceptor-denervated dogs showed all their change in pressure during the first 24 hours after the constriction, whereas the arterial blood pressure continued to increase for 4 days in the intact dogs. By the sixth day after constriction the average increase in mean arterial blood pressure was 37 ± 5.1 mm Hg in the intact group and 40 ± 1.5 mm Hg in the baroreceptor-denervated group (not statistically different).

It should be noted that in both the intact and the baroreceptor-denervated dogs the general pattern of increase in mean arterial blood pressure was biphasic with an initial peak pressure occurring during the first and second hours and a second rise starting after approximately 6 hours in the baroreceptor-denervated dogs and after 18 hours in the intact dogs.

The heart rate averaged 90 ± 2.3 beats/min in the intact dogs for the 24-hour control period and 110 ± 4.8 beats/min in the baroreceptor-denervated dogs (difference significant). The relation of heart rate changes to mean arterial blood pressure was different in the intact dogs compared with that in the baroreceptor-denervated dogs for the 6 days following constriction of the renal artery. In the intact dogs, heart rate decreased significantly following the constriction, reaching its lowest value during the second day after constriction (73 ± 4.0 beats/min). It then gradually returned to its control value over the next 4 days. In contrast, the baroreceptor-denervated dogs responded with an increase in heart rate; for the duration of the experiment, their heart rate remained slightly higher (average 5 beats/min) than that during the control period.

Frequency-Distribution Analysis of Daily Pressure Changes.—Figure 4 compares 24-hour frequency-distribution curves of mean arterial blood pressure for the same dog before (A) and after (B) baroreceptor denervation. These distribution curves are included to demonstrate that, despite the variability of daily arterial blood pressure in baroreceptor-denervated dogs, precise quantification of the data was possible by using such frequency-distribution analyses of the pressure changes. The first curve on the left in both
Figure 4A and Figure 4B represent the distribution of the continuously monitored pressure during the 24-hour control period preceding renal artery constriction. The curve for the baroreceptor-denervated state typically shows a broader distribution of pressure (14). The control 24-hour blood pressure in this dog was 89 ± 8.1 mm Hg (SD) before denervation and 82 ± 15.1 mm Hg (SD) following denervation.

The three curves labeled postconstriction 1, 2, and 3, represent the 24-hour frequency-distribution curves of mean arterial blood pressure for the first, second, and third days, respectively, after the constriction, both before (A) and after denervation (B). Before denervation the arterial blood pressure increased progressively, whereas after denervation the three curves following constriction were superimposed. The mean 24-hour arterial blood pressure for the third day after constriction was 120 ± 8.1 mm Hg in the intact state and 121 ± 23.2 mm Hg in the baroreceptor-denervated state.

**Aortorenal Pressure Gradient.**—The difference between the mean aortic pressure and the mean pressure measured from the catheter implanted in the renal artery was constant and very small before constriction: 4 ± 1.8 mm Hg in the intact dogs and 4 ± 1.3 mm Hg in the baroreceptor-denervated dogs. Immediately after constriction, the pressure gradient across the constrictor was increased to 63 ± 5.1 mm Hg in the intact dogs and to 64 ± 3.5 mm Hg in the baroreceptor-denervated dogs. These values did not change significantly during the duration of the experiment. Since the change in mean arterial blood pressure 6 days after the constriction of the renal artery was approximately 40 mm Hg in both groups, the renal perfusion pressure at that time was approximately 20 mm Hg less than its preconstriction value.

In the following sections, the results obtained in the intact and the baroreceptor-denervated dogs are combined, since there was no significant difference in most of the variables studied.

**Plasma Renin Activity, Aldosterone and Cortisol Concentrations, Plasma Electrolytes, Osmolality, and Hematocrit.**—The results are summarized in Table 1. They confirm the well-known pattern of transiently increased plasma renin activity. Plasma aldosterone concentration was nearly doubled at 1 and 6 hours after constriction; it then returned toward its control value. The changes in aldosterone concentration correlated significantly with the changes in plasma renin activity. Hematocrit fell in the intact dogs from 36.5 ± 1.5% to 33.0 ± 1.4% after 6 days. In the baroreceptor-denervated dogs, hematocrit fell from 33.5 ± 1.4% to 31.6 ± 1.4% after 6 days.

**Changes in Water Intake and Urinary Volume.**—The results are summarized in Table 2. Drinking water intake increased markedly the first day after constriction, with more than half the first day's intake occurring during the first 6 hours. Water intake was increased to some extent during the entire experiment. Since the urinary output did not change markedly after constriction, the difference between the water intake and the urinary volume or the "fluid balance," became significantly positive.
Sodium and Potassium Balance.—The constriction of the renal arterial induced a significant retention of sodium. For the 2 days preceding the constriction, sodium balance was $-0.26 \pm 0.21 \text{ mEq/kg day}^{-1}$ $(N = 19$, intact and baroreceptor-denervated combined). The first day after constriction, sodium balance was $+1.36 \pm 0.22 \text{ mEq/kg day}^{-1}$. During the following days, still more sodium was retained so that after 6 days the cumulative sodium balance calculated from the day of the constriction was $+4.15 \pm 0.69 \text{ mEq/kg}$.

The changes in sodium balance were essentially due to the changes in urinary excretion of sodium. Urinary concentration of sodium fell from $78.5 \pm 8.0 \text{ mEq/liter}$ $(N = 19)$ for the 2 days before constriction to $46.8 \pm 5.7 \text{ mEq/liter}$ the day after constriction. Endogenous creatinine clearance was reduced following constriction of the renal artery from an average preconstriction value for the 2 preceding days of $1.97 \pm 0.13 \text{ ml/kg min}^{-1}$ to $1.21 \pm 0.18 \text{ ml/kg min}^{-1}$ the first day after constriction; it was still significantly reduced 6 days after constriction $(1.46 \pm 0.12 \text{ ml/kg min}^{-1})$. Using creatinine clearance as an estimate of glomerular filtration rate, the fraction of filtered sodium that was excreted in the urine decreased slightly but not significantly following constriction.

Measurements showed that renal artery constriction did not cause significant changes in potassium balance from the control period apart from a slight retention the first day after constriction. Urinary concentration of potassium was unchanged by constriction.

Body Fluid Volumes.—Control plasma volume averaged $58.7 \pm 2.0 \text{ ml/kg body weight}$ $(N = 19)$. One day after constriction it was increased by $9.8 \pm 2.1 \text{ ml/kg}$, and 6 or 7 days after constriction the increase from the control value was $10.2 \pm 1.6 \text{ ml/kg}$.

Sodium space measurements averaged $316.8 \pm 5.7 \text{ ml/kg body weight}$ $(N = 19)$ before constriction; they increased $35.0 \pm 5.5 \text{ ml/kg}$ 6-7 days after constriction.

OFFSET TRANSIENTS

Hemodynamic Data.—Six intact dogs were submitted to release of the renal artery constriction. The average 24-hour mean arterial blood pressure before constriction was $102 \pm 5.0 \text{ mm Hg}$, and 7 days after constriction it had risen to an average of $137 \pm 3.2 \text{ mm Hg}$ for the 24 hours preceding the release. The corresponding values for the continuously recorded heart rates were $96 \pm 5 \text{ beats/min}$ for the 24 hours before constriction and

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82 ± 1.0 beats/min for the 24 hours preceding release of constriction (difference not significant).

Seven release experiments were performed in five baroreceptor-denervated dogs. The average mean arterial blood pressure before constriction was 98 ± 5 mm Hg, and it had increased to 138 ± 2.8 mm Hg for the 24 hours preceding release. The heart rate was 105 ± 7.3 beats/min for the 24 hours preceding the constriction and 107 ± 9.2 for the 24 hours preceding the release.

The aortorenal arterial blood pressure gradient averaged 4 ± 2.7 mm Hg before constriction in the intact dogs and 60 ± 3.2 mm Hg before release. In the baroreceptor-denervated dogs this value averaged 2 ± 1.4 mm Hg before constriction and 65 ± 5.9 mm Hg before release.

**Mean Arterial Blood Pressure and Heart Rate after Release of Constriction.**—Immediately following release of the occluder, the aortorenal pressure gradient fell in each experiment to a value not significantly different from its preconstriction value.

In all the dogs, mean arterial blood pressure decreased over a 3-day period to preconstriction values or slightly lower (Fig. 5). At the end of 24 hours, mean arterial blood pressure had fallen in the intact dogs to 122 ± 6.5 mm Hg, at the end of the second day, it reached 109 ± 4.0 mm Hg, and, at the end of the third day, it was 98 ± 3.7 mm Hg. During this reversal of hypertension, heart rate increased above the prerelease level by 5–10 beats/min on the average.

In the baroreceptor-denervated dogs, mean arterial blood pressure showed an initial rapid decrease during the first 6 hours; it then plateaued for 24 hours and finally decreased to its preconstriction value over the next 2 days (Fig. 5B). At the end of the first day, mean arterial blood pressure had fallen to 121 ± 3.2 mm Hg, at the end of the second day, it reached 110 ± 4.9 mm Hg, and, at the end of the third day, it was 93 ± 4.8 mm Hg. Heart rate decreased following release of constriction by 6–11 beats/min during the period of decreasing pressure.

Figure 5 shows the average hourly changes in mean arterial blood pressure following release of the renal artery constriction in intact (5A) and baroreceptor-denervated dogs (5B). These changes were calculated by averaging the individual differences between the 24-hour mean arterial blood pressure before the release and the mean arterial blood pressure for the specified hour. During most of the first day, the average decrease
in mean arterial blood pressure of the baroreceptor-denervated dogs was greater than that of the intact dogs, but a statistically significant difference was reached only during the second hour after release as indicated by an asterisk on Figure 5A.

In the following sections, the results obtained in the intact and the baroreceptor-denervated dogs are combined unless significant differences were found.

Changes in Water Intake and Urinary Output.—Table 3 shows that drinking water intake decreased markedly following release. At the same time, urinary output increased significantly during the first day after release. The overall effect on fluid balance was a marked decrease from the prerelease value. As described before, the cumulative fluid balance measured from the day of the constriction up until the time of the release was markedly positive; this balance returned toward zero during the 3 days following unclamping of the renal artery. There was a positive, significant correlation between the changes in fluid balance and the changes in sodium space induced by unclamping (see the following sections) with a correlation coefficient of 0.63.

Sodium and Potassium Balance.—The daily sodium balance became significantly negative during the first 3 days after release of the renal artery constriction. The value for 2 days before the release was $+0.84 \pm 0.14$ mEq/kg body weight day$^{-1}$ ($N = 13$), which changed to $-2.21 \pm 0.45$ mEq/kg the first day after release, $-1.29 \pm 0.38$ mEq/kg the second day after release, and $-1.25 \pm 0.34$ mEq/kg the third day after release. The sodium balance 4-6 days after release was not significantly different from zero. In these 13 dogs, the retention of sodium from the day of constriction up to the day of release was $+4.42 \pm 0.67$ mEq/kg.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Control value for 2 days prerelease</th>
<th>Changes from control after release*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>Drinking water intake</td>
<td>$51.8 \pm 9.4$</td>
<td>$-26.2 \pm 2.1\dagger$</td>
</tr>
<tr>
<td>Urinary volume (ml/kg day$^{-1}$)</td>
<td>$37.0 \pm 5.9$</td>
<td>$+8.1 \pm 2.7\dagger$</td>
</tr>
<tr>
<td>Fluid balance (ml/kg day$^{-1}$)</td>
<td>$14.8 \pm 6.0$</td>
<td>$-34.3 \pm 3.0\dagger$</td>
</tr>
</tbody>
</table>

Results were obtained from six experiments in intact and seven experiments in baroreceptor-denervated dogs. All values are means $\pm$ SE.

*Calculated by subtracting the control value from the value after release.

$\dagger$Denotes a significant change, $P < 0.05$.  

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body weight. This cumulative sodium balance returned to zero within 3 days after release (−0.33 ± 0.62 mEq/kg body weight).

Increased urinary sodium concentration was the primary reason for the change in sodium balance. The fraction of the filtered sodium excreted in the urine, which was 0.80 ± 0.14% for the 2 days preceding the release, rose significantly to 1.27 ± 0.16% the first day after release, 1.2 ± 0.18% the second day, and 1.19 ± 0.20% the third day.

Potassium balance was altered only slightly by the unclamping with a significantly negative potassium balance occurring during the first and third days following release.

Creatinine clearance before constriction in these 13 dogs was 1.89 ± 0.31 ml/kg body weight min⁻¹ and it was depressed during the entire period of constriction. During the 3 days following release, creatinine clearance returned to values not significantly different from the preconstriction values (1.87 ± 0.22 ml/kg min⁻¹ the first day, 1.55 ± 0.20 ml/kg min⁻¹ the second day, and 1.87 ± 0.23 ml/kg min⁻¹ the third day).

Fluid Volume Changes. — Plasma volume averaged 59.1 ± 3.2 ml/kg body weight (N = 13) before the constriction, plasma volume was still elevated by the time the constriction was released. One day after release, plasma volume was increased to 69.1 ± 1.1 ml/kg with respect to the preconstriction value. By the third day plasma volume had returned to the preconstriction value (difference: −0.8 ± 1.6 ml/kg).

Return of plasma volume to its preconstriction level was delayed in a manner similar to the return of mean arterial blood pressure to its control value. There was a positive, significant correlation (r = 0.82) between the changes in mean arterial blood pressure measured after 24 and 72 hours and the changes in plasma volume measured at the same times. It is particularly significant that, in those few instances in which the plasma volume returned to its preconstriction value more rapidly than it did in most other experiments, the mean arterial blood pressure did likewise.

The sodium space before constriction averaged 310.3 ± 10.3 ml/kg (N = 13), and it had increased by 35.0 ± 6.6 ml/kg before the release of the constriction. Three days after release, the difference in sodium space (3.4 ± 4.3 ml/kg) from the preconstriction value was not significantly different from zero. There was a positive, significant correlation between the changes in sodium space and the changes in sodium balance during both the on and the off transients (r = 0.81).

Changes in Plasma Renin Activity, Aldosterone, and Cortisol Concentrations. — Unlike most other variables measured in this study, plasma renin activity was significantly different in the intact and the baroreceptor-denervated dogs immediately before the release (Table 4). Following release of the constriction, plasma renin activity fell rapidly below the preconstriction value in both groups of dogs. Measurements made in four dogs 1 hour after release showed some decrease in two of the four dogs. As shown in Table 4, neither aldosterone nor cortisol concentrations showed significant changes

### Table 4

<table>
<thead>
<tr>
<th>Change from prerelease value*</th>
<th>6 hours</th>
<th>1 day</th>
<th>2 days</th>
<th>3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng AI/ml hour⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>1.3 ± 0.2</td>
<td>1.5 ± 0.6 †</td>
<td>−0.9 ± 0.6 †</td>
<td>−1.2 ± 0.5 †</td>
</tr>
<tr>
<td>Denervated</td>
<td>1.6 ± 0.6</td>
<td>4.6 ± 1.0 §</td>
<td>−3.5 ± 1.4 †</td>
<td>−4.1 ± 1.0</td>
</tr>
<tr>
<td>Aldosterone (ng/100 ml)</td>
<td>38.1 ± 1.4</td>
<td>9.2 ± 1.2</td>
<td>−0.6 ± 1.3</td>
<td>−1.4 ± 1.2</td>
</tr>
<tr>
<td>Cortisol (μg/ml)</td>
<td>1.3 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>0.1 ± 0.3</td>
<td>0.2 ± 0.3</td>
</tr>
<tr>
<td>Sodium (mEq/liter)</td>
<td>143.0 ± 1.0</td>
<td>142.8 ± 0.8</td>
<td>−0.9 ± 0.4</td>
<td>0.4 ± 0.8</td>
</tr>
<tr>
<td>Potassium (mEq/liter)</td>
<td>3.89 ± 0.11</td>
<td>4.10 ± 0.10</td>
<td>−0.05 ± 0.10</td>
<td>−0.13 ± 0.08</td>
</tr>
<tr>
<td>Osmolality (mosmoles/liter)</td>
<td>302.9 ± 5.0</td>
<td>303.2 ± 6.1</td>
<td>−9.2 ± 6.6</td>
<td>−9.5 ± 3.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34.9 ± 1.6</td>
<td>32.7 ± 1.6</td>
<td>−0.3 ± 0.8</td>
<td>1.5 ± 0.9</td>
</tr>
</tbody>
</table>

All values are means ± SE.

*Calculated by subtracting the value before release from the value after release.
†Indicates that values for intact and baroreceptor-denervated dogs are significantly different (P < 0.05).
‡Indicates a significant change from the value before release (P < 0.05) from the value before constriction.
§Indicates that values for intact and baroreceptor-denervated dogs are significantly different (P < 0.05).
following unclamping, in contrast with the changes in plasma renin activity.

Changes in Sodium and Potassium Concentrations, Plasma Osmolality, and Hematocrit.—The results are summarized in Table 4.

Macroscopic Examination of the Kidneys.—The right kidneys weighed 51.2 ± 3.6 g when they were removed 3–4 weeks before constriction of the left renal artery. At the end of the experiments the left kidneys were 25.6 ± 7.2 g heavier than their right counterparts. Gross examination did not reveal significant damage to the left kidneys. In two instances, two or three small depressed areas were noted on the surfaces of the kidneys. The two experiments performed on these two dogs did not differ from the others.

Discussion

The use of special techniques for continuous measurements and analysis of hemodynamic data in conscious dogs made it possible to discern many quantitative details of the mechanisms involved in the development and reversal of renovascular hypertension. Also, by using externally adjustable occluders, the effects of surgery and anesthesia on the renin-angiotensin system, sodium and fluid balance, and baroreceptor reflex were avoided.

Role of the Baroreceptor Reflex.—The absence of the baroreceptor reflexes significantly accelerated the development of Goldblatt hypertension but did not affect the final level of arterial pressure 1 week after constriction. Alexander and DeCuir (23) did not show an effect of the baroreceptor reflex on the rate of development of renal hypertension; however, they did not measure arterial blood pressure during the first 24 hours and they applied a progressive hypertensive stimulus instead of the single-step renal artery constriction used in this study.

Also, the fact that we recorded arterial blood pressure continuously in a quiet environment probably explains why the average basal levels of pressure and the plateau pressure elevations induced by the renal artery constriction were not significantly higher in baroreceptor-denervated dogs than they were in intact dogs. Other investigators have measured an increase in the magnitude of renal hypertension following partial or total sinoaortic deafferentiation (24–27).

Therefore, it appears that the only contribution made by the buffering action of baroreceptors to the level of arterial blood pressure occurs during the first few days following a step change in renal perfusion pressure. This finding is best explained by progressive adaptation of the baroreceptors to the increased arterial blood pressure. Evidence for baroreceptor adaptation in experimental hypertension has been presented by McCubbin (28).

During the reversal of the hypertension, the baroreceptor reflex did not have much effect on the time course of the arterial blood pressure changes. Even the initial difference that occurred during the first hours seems to have been more related to a difference in the prerelease renin level than to the presence or the absence of the baroreceptor reflex.

Role of the Renin-Angiotensin-Vasoconstrictor System.—Secretion of renin following constriction of the renal artery has often been shown to be the factor responsible for the immediate increase in mean arterial blood pressure (1, 2, 29). Following release of the constriction, the renin-angiotensin system did not appear to play a significant role in the reduction of blood pressure in the intact dogs, since the decrease in plasma renin activity was of very small magnitude and had a very different time course from that of the arterial blood pressure changes. In the baroreceptor-denervated dogs, however, the decrease in renin involved an amount known to have significant pressure effects and could easily have been responsible for the initial fall in pressure. The reason for the difference between intact and baroreceptor-denervated dogs with respect to plasma renin activity one week after the constriction might have been a slightly more pronounced renal artery constriction in the baroreceptor-denervated dogs, as indicated by an increase in the aortorenal pressure gradient of 63 mm Hg at the time of the release in baroreceptor-denervated dogs compared with 56 mm Hg in the intact dogs.

The low plasma renin activity that occurred following release of the renal artery constriction is worth special mention, since significant sodium and water losses were induced by unclamping.

Role of the Renal-Body Fluid Mechanism.—Both fluid volume expansion and sodium retention in Goldblatt hypertension are well documented (1, 3–6). Interestingly, altered water intake appeared to be involved in the observed changes in fluid balance both during the on and the off transients in the present experiments. Fluid volume changes appeared to follow closely the alterations in fluid balance. This phenomenon was indicated by a positive correlation between changes in sodium space and fluid balance and by the fact that during the off transients the changes in plasma volume were more...
pronounced as the fluid balance became more negative following unclamping. The large increase in plasma volume measured 1 day after renal artery constriction may have been caused partly by a shift in capillary dynamics.

The effect of the changes in plasma renin activity on the alterations in drinking observed at the on and off transients of Goldblatt hypertension in these experiments is not known. Fitzsimmons (30) recently reviewed the possible role of renin in thirst. We observed that after constriction of the renal artery the increased drinking was particularly pronounced when renin was highest. Furthermore, osmolality was generally decreased following constriction and, therefore, could not have been a prime factor in the increased drinking observed.

As for the dependence of arterial blood pressure changes on fluid volume changes, the evidence comes from the observation that, following constriction of the renal artery in the baroreceptor-denervated dogs, the mean arterial blood pressure reached a plateau after 24 hours, which corresponded to the time of maximum increase in plasma volume. Furthermore, during the on transients, plasma volume and mean arterial blood pressure both decreased together, that is, arterial blood pressure did not return to its preconstriction value until plasma volume had decreased to control. A detailed presentation of the mechanisms which could relate changes in fluid volumes and changes in mean arterial blood pressure has been given recently (31).

The present experiments provide evidence that, at both the onset and the offset transients of Goldblatt hypertension, changes in sodium and fluid balance and their effects on body fluid volumes are important factors in determining the mean arterial blood pressure. We do note, however, that other workers have found decreases in arterial blood pressure following either release of the constriction or introduction of a normal kidney in the circulation of a hypertensive animal without changes in the amounts of sodium and water excreted (10–12, 32, 33). The present results appear to diverge from the results of these other studies, but measurement of fluid balances is very difficult, and the results can easily be altered by anesthesia, operative procedures to apply or remove Goldblatt clamps, failure to measure intake as well as output, or even intermittent disturbance of the animals. In these experiments, special attempts to avoid all these problems were made. Yet, there could be other mechanistic differences in the results that are not now understood.

Renal Perfusion Pressure in Goldblatt Hypertension.—A feature of interest was the dependence of the renal perfusion pressure on other factors as well as the systemic arterial blood pressure. The aortorenal pressure gradient was not constant, presumably because of changes in renal blood flow. For instance, heart rate and aortorenal pressure gradient often changed simultaneously, which indicated that changes in sympathetic tone to the kidney might have been responsible for many of the alterations in pressure gradient. Also, Harris and Ayers (34) and Thomas et al. (35) have shown that changes in total intrarenal vascular resistance can markedly affect the pressure gradient under a Goldblatt clamp.

Aldosterone Concentration.—Previous work done on uncomplicated one-kidney Goldblatt hypertension has shown that aldosterone secretion is generally unchanged (36, 37) or sometimes depressed (38). Blair-West et al. (39) have shown that there is often a temporary increase in plasma aldosterone concentration at the onset, part of which could be related to release of adrenocorticotropic hormone in response to surgery. In our experiments aldosterone showed a moderate initial increase, which correlated significantly with the change in plasma renin activity. During the reversal of hypertension following the release of the renal artery constriction, there was no significant change in aldosterone concentration, which contrasted with the decrease in plasma renin activity.

References

6. SWALES, J.D., THURSTON, H., QUEIROZ, F.P., AND MEDINA, A.: Sodium balance during the development of experimen-
560

LIARD, COWLEY, McCAA, McCAA, GUYTON


40. COWLEY, A.W., JR., AND GUYTON, A.C.: Sensitivity to angiotensin II in sino-aortic denervated dogs (abstr.).
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