Acute Hypertension in a Nonhuman Primate: Humoral and Hemodynamic Mechanisms

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SUMMARY The present study assessed the contribution of the renin-angiotensin system (RAS), dietary sodium, and cardiac output (CO) to the genesis of primate hypertension in a one-kidney model which was developed to test species-specific renin inhibitors. Reduction of renal perfusion pressure increased mean arterial pressure (MAP) from 105 ± 4 to 127 ± 3 mm Hg ($p < 0.0005$), associated with increased plasma renin activity (PRA) from 4.9 ± 0.7 to 13.8 ± 1.1 ng·ml^{-1}·hr^{-1} ($p < 0.0005$). Correlation of MAP with PRA yielded an r value of 0.662 ($p < 0.0005$). Significant blood pressure elevation was obtained with both regular (R) and low sodium (LS) diet ($p < 0.0005$), although the MAP change was greater with LS. With both R and LS diet, hypertension was associated with increased PRA ($p < 0.0005$), and normotensive pressures were achieved with converting enzyme inhibitor (teprotide). The hemodynamic change with hypertension was an increase of systemic vascular resistance (SVR) from 0.89 ± 0.12 to 1.17 ± 0.09 units ($p < 0.05$); cardiac output (CO) and central blood volume did not change significantly. Thus, acute hypertension, mediated by the RAS, was developed in a one-kidney primate model. The hemodynamic correlate of hypertension was increased SVR; CO and volume redistribution were not initiating factors. (Hypertension 4: 219–225, 1982)

KEY WORDS • *Macaca fascicularis* monkeys • renin-angiotensin system • hemodynamics
• converting enzyme inhibitor • hypertension

CURRENT knowledge regarding mechanisms of hypertension in the nonhuman primate is limited. This reflects in part the difficulty of producing a model that may be studied in both acute and chronic stages of the disease. A better understanding of such mechanisms is necessitated by primate studies, which have demonstrated a correlation of hypertension with cardiac and cerebrovascular atherosclerosis, analogous to human pathologic conditions.[1,2] A primate model of hypertension is also necessary to test species-specific peptide inhibitors of renin.[3,4]

The generation of angiotensin II (AII) by renin plays a major role in the genesis of some models of hypertension,[5,6] but this is not a universal phenomenon.[7-9] Several authors have noted that the degree of hypertension produced, and its response to

angiotensin blockade, is influenced by sodium depletion.[10,11] These factors remain to be evaluated in primate hypertension.

Increased cardiac output and volume expansion have been found during the development of some forms of renal hypertension.[12,13] However, this may not be a critical determinant since the development of renovascular hypertension may also be secondary to increased peripheral resistance,[14,15] or a combination of increased peripheral resistance and cardiac output.[16] Of special interest are the hemodynamic alterations that occur at the very inception of hypertension, prior to compensatory regulation.

Since both humoral and hemodynamic factors may participate in the onset of primate hypertension, we assessed an acute model of hypertension in the primate *M. fascicularis*.

Methods

Male cynomolgus monkeys *(M. fascicularis)* weighing 4 to 6 kg were maintained on a combination of chow (Purina), fresh fruit, and water, except as specified below. All experiments were performed in conscious, unanesthetized monkeys, seated in upright chairs the evening prior to study and fasted overnight. Ketamine, 5 mg/kg intramuscularly, was used for

transfer of monkeys to and from the chairs, but experiments were not performed in the 12 to 16 hours following its administration. The monkeys sat quietly and comfortably in the chairs, without appreciable change in behavior; 24-hour intraarterial blood pressure recordings have shown that blood pressure and heart rate remain stable with this technique.[17]

Surgical Preparation

The experimental preparation is demonstrated in figure 1; surgery was performed under nitrous oxide anesthesia, and ketamine 10 mg/kg intramuscularly. Through a left flank, retroperitoneal approach, an inflatable chronic Silastic cuff (Hazen Everett, Mahwah, New Jersey) was placed around the abdominal aorta, above the origin of the left renal artery. The inflation side-arm was externalized. The cuff was below the origin of the right renal artery, superior mesenteric

FIGURE 1. *Model of one-kidney hypertension resulting from acute aortic constriction and reduction of renal perfusion pressure. The inflatable Silastic cuff was placed as described in the text. Right nephrectomy was then performed, and chronic catheters placed as described. Note that the origin of the celiac axis and superior mesenteric artery are above the cuff.*

artery, and celiac axis in all cases. Following cuff placement, monkeys were returned to their cages with normal activity and diet. After 1 week of recovery, the monkeys were returned to surgery for catheter placement and right nephrectomy, using the anesthetic preparation previously described. Chronic indwelling catheters were placed via a right paramedial, retroperitoneal approach. These were positioned in the lower inferior vena cava, high thoracic aorta, and lower abdominal aorta via the iliac vein and artery respectively. The catheters were polyvinyl chloride with an internal diameter of 0.64 mm (inferior vena cava, lower abdominal aorta) and 0.38 mm (upper thoracic aorta). They were externalized and color-coded for later identification. Right nephrectomy was performed through a midline laparotomy. The monkeys were dressed in cloth-covered steel mesh jackets to prevent their manipulation of the catheters. Catheters were flushed a minimum of three times per week with 0.9% saline. A postoperative period of 1 week ensued with full activity and normal diet, prior to the onset of physiologic experiments.

Hypertension Studies

Monkeys were transferred to chairs as described previously. The upper thoracic and lower abdominal aortic catheters were flushed with saline and connected to two Statham transducers whose outputs were recorded simultaneously on a Grass polygraph. Blood pressure from both catheters was recorded (in mm Hg) as either phasic or electronically-integrated mean arterial pressure (MAP). The pulse contour was not attenuated through either catheter. Heart rate (HR, bpm) was recorded by a cardiotachometer, as determined from the blood pressure signal. The inferior vena cava catheter was used for sampling of plasma renin activity (PRA) and for drug injection. A total of 10 studies was performed in five monkeys; no monkey had two studies within the same 24-hour period. The onset transient of hypertension was by inflation of the cuff with physiologic saline to constrict the aorta just above the left renal artery. A MAP gradient of 60 mm Hg was developed over several seconds, so that the lower aortic (and left renal artery) MAP was approximately 40 mm Hg. Pressure below the cuff was maintained at 40 mm Hg throughout the experiment, even after the subsequent development of hypertension above the cuff. Normal color and temperature, spontaneous movement, and withdrawal from stimuli indicated good lower extremity perfusion throughout the experiment. After 1 hour, the cuff was deflated. The MAP was recorded from both catheters for an additional 30 to 60 minutes until it had returned to baseline. PRA samples were obtained during the control period, at 20 and 60 minutes of inflation, and 30 minutes after deflation.

Effect of Diet and Converting Enzyme Inhibition

A total of seven studies were performed in four monkeys while on a regular diet. No monkey had two studies within the same 24-hour period. A 24-hour
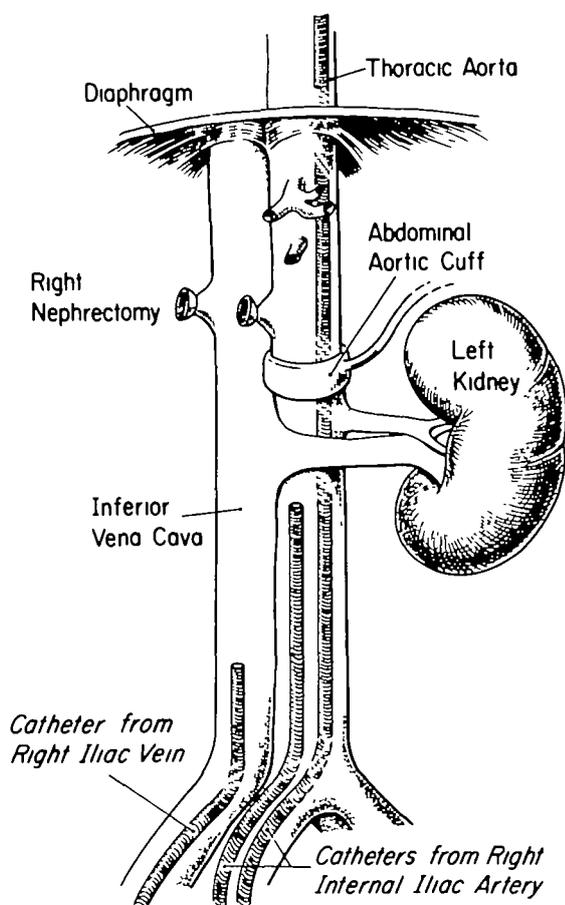
collection of urine for sodium determination was obtained just prior to the hypertension protocol. Following the onset of hypertension with 1 hour of cuff inflation, nonapeptide converting-enzyme inhibitor (CEI) was given as a 1 mg/kg bolus through the inferior vena cava catheter. No adjustment of cuff volume was made during the period of CEI administration and response. Following the nadir response to CEI, the cuff was deflated. PRA samples were obtained at control, peak hypertension, post-CEI, and postdeflation periods.

Seven studies were then performed in four monkeys during a low sodium state, which was achieved by a fruit for chow exchange and administration of furosemide 1 mg/kg intravenously. The latter was given daily for 1 week prior to study. A 24-hour collection of urine for sodium determination was obtained just prior to performing the hypertension protocol. Cuff inflation with development of hypertension, CEI administration, and sampling for PRA were then performed as stated for monkeys on regular diet.

Hemodynamic Studies

The hemodynamic response to cuff inflation and subsequent hypertension was assessed in four monkeys, using indocyanine green dye dilution to obtain cardiac output.[18] Monkeys were seated upright in chairs and connected to transducers as outlined above. Dye was rapidly administered as a 0.15 bolus through the inferior vena cava catheter with continuous sampling from the lower aortic catheter, withdrawing blood through a densitometer at 30 ml per minute. The dye curve was recorded, and cardiac output was determined by the method of Hamilton et al.[19] Blood was returned to the monkey after the inscription of each curve. Neither spurious distortion of cardiac output curves nor dampened blood withdrawal occurred during cuff inflation. MAP, via the thoracic aorta catheter, and heart rate were recorded throughout cardiac output determination. Hemodynamic values were obtained during the control period, immediately after cuff inflation, at 1 hour of cuff inflation, immediately after cuff deflation, and when MAP had returned to its control value.

Cardiac output (CO) was expressed as milliliters per minute per kilogram weight (ml·min⁻¹·kg⁻¹). Systemic vascular resistance (SVR) was calculated by dividing MAP by CO, and expressed as arbitrary units (U). Stroke volume was calculated by dividing CO by HR, and was expressed in milliliters per minute per kilogram body weight (ml·min⁻¹·kg⁻¹). Central blood volume (CBV) was calculated by the formula: CBV = (CO × MTT)/60, where MTT is the mean transit time from dye injection to the initial dye curve inscription.[20] CBV was expressed as milliliters of blood per kilogram body weight.

Biochemical Analysis

PRA was measured by radioimmunoassay according to the method of Haber and coworkers.[21] Inferior vena cava blood samples (1 ml) were placed in cold tubes containing ethylenediaminetetraacetic acid (EDTA). Following centrifugation, the plasma was frozen, and the assay was performed at a later date. Values were expressed as nanograms of angiotensin I (AI) generated per milliliter per hour (ng·ml⁻¹·hr⁻¹).

Aliquots of 24-hour urine specimens were analyzed for sodium concentration by the flame photometric technique. Values were corrected for 24-hour urine volume and expressed as milliequivalents per 24 hours (mEq/24 hrs).

Converting Enzyme Inhibitor

The nonapeptide converting enzyme inhibitor (<Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) was synthesized for use in this study.[22] It was dissolved in physiologic saline to a concentration of 2 mg per milliliter.

Statistical Analysis

Because each monkey served as its own control, analysis of the probability of differences was by paired *t* test. All values in this study were expressed as means ± 1 standard error of the mean (SEM). Correlation of variables was by linear regression. The 0.05 level of probability was used to indicate statistical significance.

Results

Response to Aortic Constriction

A MAP gradient of approximately 60 mm Hg was developed in response to the aortic constriction produced by cuff inflation (fig. 2). Within 20 minutes, the MAP increased from 105 ± 4 to 115 ± 3 mm Hg ($p < 0.001$). Blood pressure continued to increase gradually over 60 minutes of inflation, to 127 ± 3 mm Hg, with significance of $p < 0.0005$ compared to control. Phasic recordings indicated an increase of both systolic and diastolic pressures. Following cuff deflation, lower aortic MAP was equal to thoracic aortic MAP at hypertensive levels indicating no residual gradient. Blood pressure gradually decreased to 110 ± 2 mm Hg by 30 minutes postdeflation, which was not significantly different from the control level. During cuff inflation, there was no significant change in heart rate from the baseline of 196 ± 7 bpm. Initially following cuff deflation the heart rose to 203 ± 8 bpm ($p < 0.01$ compared to control), but by 30 minutes following deflation, the heart rate of 200 ± 8 bpm was not significantly different from control or hypertensive values. PRA increased from 4.9 ± 0.7 to 9.6 ± 1.3 ng·ml⁻¹·hr⁻¹ at 20 minutes of inflation ($p < 0.001$) and continued to rise to 13.8 ± 1.1 ng·ml⁻¹·hr⁻¹ by 60 minutes of inflation ($p < 0.0005$). By 30 minutes following deflation, PRA decreased significantly ($p < 0.001$) to 9.2 ± 1.1 ng·ml⁻¹·hr⁻¹. PRA required 60 to 90 minutes to return to baseline in all studies. When MAP values at control, 20 minutes inflation, and 60 minutes inflation were correlated with corresponding
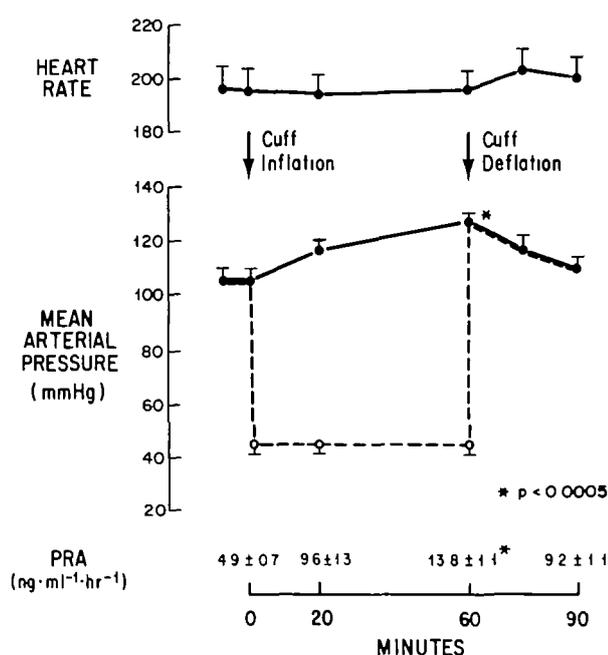
FIGURE 2. *Heart rate, blood pressure, and plasma renin activity (PRA) responses to cuff inflation (aortic constriction) and cuff deflation in 10 studies. Mean arterial pressure (MAP) above the cuff was measured via the thoracic aorta catheter (solid line). The MAP below the cuff was measured via the abdominal aorta catheter (dashed line). Cuff inflation (aortic constriction) was performed to decrease lower aortic (and renal artery) perfusion pressure to approximately 40 mm Hg where it was maintained throughout the experiment until cuff deflation. Following cuff deflation, MAP recorded via both catheters was at hypertensive levels, gradually decreasing to baseline over 30 to 60 minutes.*
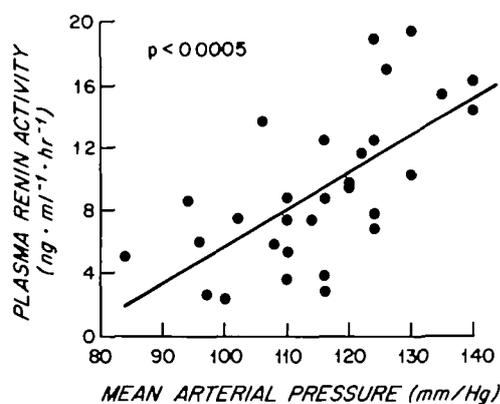

MEAN ARTERIAL PRESSURE (mm/Hg)

FIGURE 3. *Measurements of simultaneous mean arterial pressure (MAP) and plasma renin activity (PRA) made at control, 20 minutes of inflation, and 60 minutes of inflation in 10 studies, for a total of 30 determinations. This correlation resulted in values of* r = 0.662, *and* p < 0 0005.

PRAs at these times, an *r* value of 0.662 and significance of *p* < 0.0005 were obtained (fig. 3).

Four sham studies were performed with the aortic cuff placed below both renal arteries. With a control MAP of 107 ± 5 mm Hg, inflation was performed as above, producing a gradient of 56 ± 4 mm Hg which was maintained for 1 hour. At 1 hour of inflation MAP was 105 ± 8 mm Hg, unchanged from control. Heart rate change was also nonsignificant (186 ± 18 to 192 ± 23 bpm). In subsequent observations of sham studies, blood pressure remained unchanged during a cuff inflation of 2 to 3 hours duration.

Effects of Diet and Converting Enzyme Inhibition

In seven studies, monkeys were studied on a regular diet. Urinary sodium was 4.0 ± 0.6 mEq/24 hours and PRA was 4.4 ± 0.7 ng·ml^{-1}·hr^{-1}. Following 60 minutes of cuff inflation, MAP increased from 109 ± 3 to 125 ± 2 mm Hg (*p* < 0.0005) (fig. 4). Administration of CEI resulted in a decrease of MAP to 110 ± 3 mm Hg (*p* < 0.0005) which was not significantly different than the control pressure. There was no significant change in blood pressure following cuff deflation. Heart rate did not change significantly from the control value of 206 ± 8 bpm. The PRA increased from 4.4 ± .7 to 13.1 ± 1.6 ng·ml^{-1}·hr^{-1} (*p* < 0.0005). Following CEI administration, there was a further increase to 22.8 ± 2.3 ng·ml^{-1}·hr^{-1} (*p* < 0.0001) due to blockade of the negative feedback inhibition of renin release by AII generation.[23] There was a subsequent downward trend of PRA following cuff deflation.

Seven studies were then performed in monkeys during a low sodium state. Urinary sodium was 0.6 ± 0.3 mEq/24 hrs and PRA was 16.3 ± 2.2 ng·ml^{-1}·hr^{-1}, representing a fall to one-sixth of control and a four-fold increase respectively, compared with regular diet studies. After 60 minutes of cuff inflation, MAP increased from 99 ± 3 to 124 ± 2 mm Hg (*p* < 0.0005). CEI administration resulted in a prompt decrease of MAP to 97 ± 5 mm Hg (*p* < 0.0005). Following cuff deflation there was a further decrease of MAP, which did not achieve statistical significance compared with control values. The heart rate changes with cuff inflation and following CEI were not significant. However, the change of heart rate from the control of 192 ± 7 to 213 ± 4 bpm following deflation was significant (*p* < 0.001). With cuff inflation, PRA increased from 16.3 ± 2.2 to 43.2 ± 3.9 ng·ml^{-1}·hr^{-1} (*p* < 0.001); following CEI, there was a further increase to 56.9 ± 4.7 (*p* < 0.05). There was a downward trend of PRA following deflation.

Hemodynamic Changes During the Development of Hypertension

First, the hemodynamic changes produced by cuff inflation itself were assessed. Immediately following cuff inflation, the change of MAP (114 ± 7 to 117 ± 6 mm Hg) was not significant (table 1). However, cardiac output decreased from 168 ± 22 to 142 ± 29 ml·min^{-1}·kg^{-1}, associated with an increase of systemic resistance from 0.69 ± 0.06 to 0.89 ± 0.12 U.
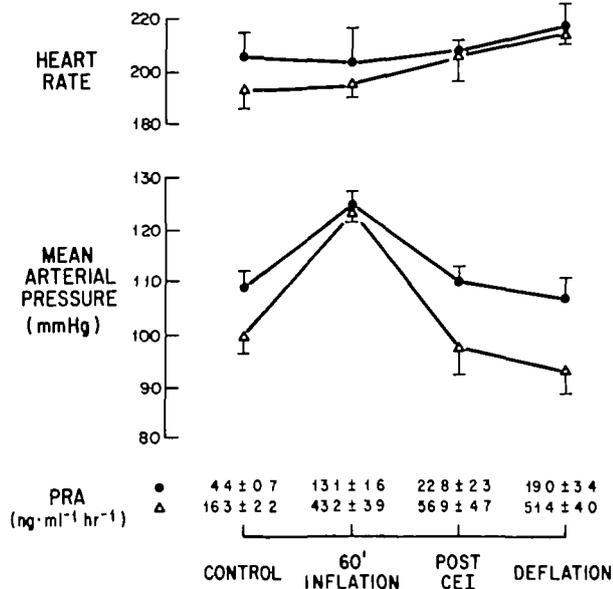
FIGURE 4. *Heart rate, mean arterial pressure (MAP), and plasma renin activity (PRA) determinations in monkeys receiving regular diet (black circles) and during sodium depletion (open triangles) Details are as given in the text.*

Although stroke volume also decreased from 0.72 ± 0.06 to 0.59 ± 0.02 ml·min⁻¹·kg⁻¹, central blood volume and heart rate did not change appreciably. These changes represented the immediate hemodynamic response to aortic constriction. In the subsequent 60 minutes of cuff inflation, MAP increased from 117 ± 6 to 137 ± 7 mm Hg ($p < 0.0005$). The principal hemodynamic alteration during the development of hypertension was increase of systemic resistance from 0.89 ± 0.12 to 1.17 ± 0.09 U ($p < 0.05$). There were no significant changes in cardiac

output, stroke volume, or central blood volume. Heart rate decreased from 188 ± 13 to 181 ± 14 bpm. Immediately after cuff deflation, the MAP recorded from both catheters was 128 ± 8 mm Hg, which was significantly greater than the control and immediate postinflation values ($p < 0.02$). This was due to persistent increase in systemic resistance (0.98 ± 0.15 U) and increase of flow from 121 ± 6 to 140 ± 24 ml·min⁻¹·kg⁻¹. Blood pressure gradually decreased and achieved a stable level 30 to 60 minutes following cuff deflation. The value of 118 ± 7 mm Hg was not significantly different from the initial control level. This return to baseline was associated with further reduction of systemic resistance to 0.80 ± 0.05 U, and an increase of CO to 150 ± 16 ml·min⁻¹·kg⁻¹. These values were not significantly different from baseline values. Central blood volume and stroke volume were unchanged.

Discussion

This model is useful because of its reliable production of renin-dependent hypertension in repeated studies, providing a better understanding of primate renin. More important, species-specific peptide analogs of renin substrate and antirenin antibodies can be studied in a physiologic milieu. Such studies have been initiated[24] and are currently under investigation.

The application of the aortic cuff above the left renal artery allows normal perfusion of all major vascular beds, and avoids the hemodynamic alterations seen with constriction of the thoracic aorta.[25, 26] There was no evidence that hypertension was a direct response to mechanical impedence by the cuff. A two-kidney model, with the aortic cuff placed above both renal arteries, was not technically feasible because of anatomic limitations.

In response to aortic constriction and decreased renal perfusion pressure, both MAP and PRA in-

TABLE 1. *Hemodynamic Changes with the Development of Hypertension*

	Control	Immediate post inflation	1-hour post inflation	Immediate post deflation	Return to baseline
Mean arterial pressure (mm Hg)	114 ± 7	117 ± 6	137 ± 7	128 ± 8	118 ± 7
Heart rate (bpm)	195 ± 4	188 ± 13	181 ± 14	177 ± 5	176 ± 9
Cardiac output (ml · min⁻¹ · kg⁻¹)	168 ± 22	142 ± 29	121 ± 6	140 ± 24	150 ± 16
Systemic vascular resistance (units)	0.69 ± 0.06	0.89 ± 0.12	1.17 ± 0.09	0.98 ± 0.15	0.80 ± 0.05
Central blood volume (ml · min⁻¹ · kg⁻¹)	18 ± 2	19 ± 2	19 ± 3	17 ± 2	17 ± 1
Stroke volume (ml · min⁻¹ · kg⁻¹)	0.72 ± 0 06	0.59 ± 0.02	0.60 ± 0.03	0.66 ± 0 06	0.80 ± 0.09

Although blood pressure did not change immediately following cuff inflation, there was an appreciable change in the flow/resistance relationship. From this new baseline, the subsequent development of hypertension was due to a significant ($p < 0.05$) increase in resistance. The gradual reduction of blood pressure following release of the cuff was due to return of resistance to baseline.

creased significantly over 1 hour. The highly signifi-
cant correlation of these two variables indicates a ma-
jor role for the renin angiotensin system in the genesis
of this acute form of hypertension, with the early
characteristics of one-kidney Goldblatt hypertension.
Preliminary studies indicate that hypertension can be
maintained chronically.

Sodium retention and volume expansion may result
in sustained hypertension,[27] but it is well documented
that sodium depletion augments the degree of hyper-
tension produced in renin-dependent models, through
further stimulation of the renin-angiotensin system.[10]
In our present study, acute hypertension developed
with both regular diet and low sodium diet; the change
of blood pressure was greater with low sodium diet,
however. Regardless of diet, development of hyper-
tension was associated with a significant increment of
PRA, even though low sodium diet resulted in a four-
fold increase of basal renin, compared to regular diet.
Similar findings have been reported for the dog.[10]

The potential nonspecific inhibition of carboxy-
dipeptidase activity by teprotide CEI is contro-
versial,[28] but the major effect of this compound is in-
hibition of AII generation.[6, 29] We found that the
hypertension produced by aortic constriction was
blocked by CEI, thereby returning blood pressure to
control levels, regardless of regular or low sodium
diet. During the latter condition, post-CEI blood
pressure was somewhat lower than control, which is
compatible with the enhanced dependence of vascular
tone on the renin-angiotensin system during sodium
depletion.[11, 28, 30, 31]

There was no significant change in blood pressure
immediately following aortic constriction, but there
was an appreciable change in the flow/resistance rela-
tionship. Bradycardia was not associated with the
decrease in cardiac output in all cases, but a baro-
receptor response to cuff inflation cannot be excluded.
Offsetting stimuli may be responsible for the absence
of significant heart rate change. Since the cardiac out-
put curves did not change qualitatively during cuff
inflation, an artifactual decrease in output was not
likely. The major importance of the hemodynamic
determinations however, was that systemic vascular
resistance continued to increase progressively from
the new equilibrium point immediately after cuff infla-
tion until the development of significant hypertension
1 hour postinflation. At this new level of blood pres-
sure, the major hemodynamic change was a signifi-
cant increase of systemic resistance, which gradually
returned to baseline values after abrupt release of aor-
tic constriction. Therefore, the increased systemic
resistance was not simply due to cuff impedance (table
1). This progressive increase of resistance at the incep-
tion of hypertension is compatible with the data of
Bianchi et al.[32] In both situations, cardiac output did
not play an initiating role in the immediate hyperten-
sive response. Based on the humoral findings in our
study, the increase of peripheral resistance is most
likely secondary to the generation of AII by increased
PRA, with subsequent vasoconstriction. With the
offset transient of aortic constriction and gradual

reduction of AII levels (reflected by decreased PRA),
both resistance and MAP gradually returned to base-
line. As central blood volume and stroke volume did
not change appreciably throughout the study, central
redistribution of blood, and volume expansion, did not
play a significant role in the acute phase of hyperten-
sion.

References

1 Hollander W, Prusty S, Kirkpatrick B, Paddock J, Nagraj S·
   Role of hypertension in ischemic heart disease and cerebral
   vascular disease in the cynomolgus monkey with coarctation of
   the aorta Circ Res 40 and 41: (suppl I) I-70, 1977
2 Pick R, Johnson PJ, Glick G· Deleterious effects of hyper-
   tension on the development of aortic and coronary athero-
   sclerosis in stumptail Macaques (Macaca Speciosa) on an
   atherogenic diet Circ Res 35: 472, 1974
3. Haber E, Burton J· Inhibitors of renin and their utility in
   physiologic studies Fed Proc 38: 2768, 1979
4 Cody RJ, Burton J, Evin G, Poulsen K, Herd JA, Haber E. A
   substrate analog inhibitor of renin that is effective in vivo.
   Biochem Biophys Res Comm 97: 230, 1980
5 Miller ED Jr, Samuels AI, Haber E, Barger AC· Inhibition of
   angiotensin conversion in experimental renovascular hyper-
   tension Science 177: 1108, 1972
6 Pals DT, Masucci FD, Denning GS Jr, Sipos R, Fessler DC.
   Role of the pressor action of angiotensin II in experimental
   hypertension Circ Res 29: 673, 1971
7 Davis JO· The pathogenesis of chronic renovascular hyper-
   tension. Circ Res 40: 439, 1977
8 Johnson JA, Davis JO, Braverman B· Role of angiotensin II in
   experimental renal hypertension in the rabbit. Am J Physiol
   228: 11, 1975
9 Richardson D, Stella A, Leonetti G, Bartorelli A, Zanchetti A
   Mechanisms of renal release of renin by electrical stimulation
   of the brainstem in the cat. Circ Res 34: 425, 1974
10 Fray JCS, Johnson MD, Barger AC· Renin release and pressor
   response to renal arterial hypotension· effect of dietary sodium
   Am J Physiol 233: H191, 1977
11 Gavras H, Brunner HR, Vaughan ED Jr, Laragh JH. Angio-
   tensin-sodium interaction in blood pressure maintenance of
   renal hypertensive and normotensive rats Science 180: 1369,
   1973
12 Ferrario CM, Page IH Current views concerning cardiac out-
   put in the genesis of experimental hypertension. Circ Res 43:
   821, 1978
13 Ledingham JM, Cohen RD· Role of the heart in the patho-
   genesis of renal hypertension Lancet 2: 979, 1963
14 Ledingham JM, Pelling D. Cardiac output and peripheral
   resistance in experimental renal hypertension. Circ Res 20 and
   21 (suppl II) II-187, 1967
15 Olmsted F, Page IH Hemodynamic changes in trained dogs
   during experimental renal hypertension. Circ Res 16: 134, 1965
16 Maxwell MH, Lupu AN, Viskoper RJ, Aravena LA, Waks
   UA Mechanisms of hypertension during the acute and inter-
   mediate phases of the one-clip, two kidney model in the dog.
   Circ Res 40 and 41 (suppl I)· I-24, 1977
17 Dews PB, Herd JA: Behavioral activities and cardiovascular
   function· effects of hexamethonium on cardiovascular changes
   during strong sustained static work in Rhesus monkeys J Phar-
   macol Exp Ther 189: 12, 1974

18 Herd JA, Low PA, Rodger RF, Hartley LH Hemodynamics of arterial hypertension in cynomolgus monkeys *In* The Use of Nonhuman Primates in Cardiovascular Diseases, edited by Kalter SS. Austin, Texas: University of Texas Press, 1980, p 326

19 Hamilton WF, Moore JW, Kinsman JM, Spurling RG Studies on the circulation IV Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Am J Physiol 99: 534, 1932

20 Yang S, Bentivoglio LG, Maranhao V, Goldberg H From Cardiac Catheterization Data to Hemodynamic Parameters. Philadelphia FA Davis Company, 1978, p 154

21 Haber E, Koerner T, Page LB, Kliman B, Purnode A Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects J Clin Endocr 29: 1349, 1969

22 Watkins L, Burton J, Haber E, Cant JR, Smith FW, Barger AC The renin angiotensin system in congestive failure in conscious dogs J Clin Invest 57: 1606, 1976

23 Samuels AI, Miller ED Jr, Fray JCS, Haber E, Barger AC Renin-angiotensin antagonists and the regulation of blood pressure Fed Proc 35: 2512, 1976

24 Burton J, Cody RJ Jr, Herd JA, Haber E. Specific inhibition of renin by an angiotensinogen analogue: studies in sodium depletion and renin-dependent hypertension Proc Natl Acad Sci USA 77: 5476, 1980

25. O'Rourke MJ, Cartmill TB. Influence of aortic coarctation on pulsatile hemodynamics in the proximal aorta Circulation 44: 281, 1971

26 Stokland O, Miller MM, Ilebekk A, Kiil F Mechanism of hemodynamic responses to occlusion of the descending thoracic aorta Am J Physiol 238: H423, 1980

27 Guyton AC, Coleman TG, Cowley AW Jr, Manning RD Jr, Norman RA Jr, Ferguson JD A systems analysis approach to understanding long-range arterial blood pressure control and hypertension Circ Res 35: 159, 1974

28 McCaa RE. Studies in vivo with angiotensin I converting enzyme (kininase II) inhibitors. Fed Proc 38: 2783, 1979

29 Collier JG, Robinson BF, Vane JR. Reduction of pressure effects of angiotensin I in man by synthetic nonapeptide (B P P 9a or SQ20881) which inhibits converting enzyme Lancet 1: 72, 1973

30 Hall JE, Guyton AC, Smith MJ Jr, Coleman TG Chronic blockade of angiotensin II formation during sodium deprivation Am J Physiol 237: F424, 1979

31. Conway J, Hatton R, Keddie J, Dawes P The role of angiotensin in the control of blood pressure during sodium depletion. Hypertension 1: 402, 1979

32 Bianchi G, Baldoli E, Lucca R, Barbin P Pathogenesis of arterial hypertension after the constriction of the renal artery leaving the opposite kidney intact both in the anesthetized and in the conscious dog. Clin Sci 42: 651, 1972

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