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/hr (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 (teprolide). 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.1-3 A primate model of hypertension is also necessary to test species-specific peptide inhibitors of renin.4,4

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

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transfer of monkeys to and from the chairs, but ex-
periments 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 in-
flatable 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
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 place-
ment and right nephrectomy, using the anesthetic
preparation previously described. Chronic indwelling
catheters were placed via a right paramedial, retro-
peritoneal 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 con-
nected 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 in-
ferior 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 con-
strict 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 through-
out the experiment, even after the subsequent develop-
ment of hypertension above the cuff. Normal color
and temperature, spontaneous movement, and with-
drawal 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 ob-
tained 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 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. 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. 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, and when MAP had returned to its control level.

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⁻²). 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. 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. 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. 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.

Following cuff deflation, the heart rate of 200 ± 8 bpm 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 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 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 the control level.
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 ± 0.7 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 AI1 generation. 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.
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 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. There was no evidence that hypertension was a direct response to mechanical impedance 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**

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

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.
increased significantly over 1 hour. The highly significant correlation of these two variables indicates a major 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, but it is well documented that sodium depletion augments the degree of hypertension produced in renin-dependent models, through further stimulation of the renin-angiotensin system. 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 hypertension was associated with a significant increment of PRA, even though low sodium diet resulted in a fourfold increase of basal renin, compared to regular diet. Similar findings have been reported for the dog.

The potential nonspecific inhibition of carboxypeptidase activity by teprotide CEI is controversial, but the major effect of this compound is inhibition of All generation. 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.

There was no significant change in blood pressure immediately following aortic constriction, but there was an appreciable change in the flow/resistance relationship. Bradycardia was not associated with the decrease in cardiac output in all cases, but a baroreceptor response to cuff inflation cannot be excluded. Offsetting stimuli may be responsible for the absence of significant heart rate change. Since the cardiac output 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 inflation until the development of significant hypertension 1 hour postinflation. At this new level of blood pressure, the major hemodynamic change was a significant increase of systemic resistance, which gradually returned to baseline values after abrupt release of aortic constriction. Therefore, the increased systemic resistance was not simply due to cuff impedance (table 1). This progressive increase of resistance at the inception of hypertension is compatible with the data of Bianchi et al. In both situations, cardiac output did not play an initiating role in the immediate hypertensive response. Based on the humoral findings in our study, the increase of peripheral resistance is most likely secondary to the generation of All by increased PRA, with subsequent vasoconstriction. With the offset transient of aortic constriction and gradual reduction of All levels (reflected by decreased PRA), both resistance and MAP gradually returned to baseline. 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 hypertension.

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References

5 Miller ED Jr, Samuels AI, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. Science 177: 1108, 1972
8 Johnson JA, Davis JO, Braverman B: Role of angiotensin II in experimental renovascular hypertension in the rabbit. Am J Physiol 228: 11, 1975
13 Ledingham JM, Cohen RD: Role of the heart in the pathogenesis of renovascular hypertension. Lancet 2: 979, 1963
17 Dew PB, Herd JA: Behavioral activities and cardiovascular function: effects of hexamethonium on cardiovascular changes during strong sustained static work in Rhesus monkeys. J Pharmacol Exp Ther 189: 12, 1974


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