Beneficial Effects of Arachidonic Acid during Hemorrhagic Shock in the Dog

John T. Flynn and Allan M. Lefer

SUMMARY Arachidonic acid (AA), precursor of the biseinoic prostaglandins was infused at a rate of 120 μg/kg per min into the vena cava of dogs subjected to hemorrtagic shock to assess the effects of stimulation of the prostaglandin (PG) synthetase system on the shock state. Hemorrhagic shock was induced by bleeding to a mean arterial blood pressure (MABP) of 40 mm Hg for 150 minutes followed by reinfusion of all remaining shed blood. In sham shock dogs receiving AA vehicle (0.1 M Na₂CO₃), there were no significant changes in MABP, superior mesenteric artery flow (SMAF), renal artery flow (RAF), PGE₂ or PGF₂α concentrations, or in cathepsin D or myocardial depressant factor (MDF) activities during a 260-minute experimental period. During oligemia, untreated hemorrhagic shock dogs exhibited dramatic reductions in MABP, SMAF, and RAF which were transiently restored following reinfusion, but markedly decreased 100 minutes after reinfusion. Cathepsin D, MDF, PGE₂, and PGF₂α values increased significantly in these dogs. AA given during oligemia did not prevent changes in SMAF or RAF, but maintained MABP at near-normal values after reinfusion. AA also significantly protected against the plasma accumulation of both cathepsin D and MDF in hemorrhagic shock dogs. Circulating PGE₂ and PGF₂α values increased rapidly in AA-treated dogs and plateaued at 3.6 and 4.8 times control values, respectively, during oligemia. Hemorrhagic shock dogs receiving AA plus Na meclofenamate, a PG synthetase inhibitor, were not significantly different from shock dogs receiving vehicle except that the circulating PG concentrations did not increase. Thus, products of the PG synthetase system appear to prevent the plasma accumulation of lysosomal hydrolases and of MDF, and may significantly preserve MABP after hemorrhagic shock in the dog.

Methods

ANIMAL PREPARATION

Male dogs weighing 12-15 kg were anesthetized with pentobarbital sodium (30 mg/kg iv). After establishment of a patent airway, the dogs were allowed to breathe room air unassisted. Catheters were placed via the right femoral artery and vein into the descending aorta and inferior vena cava to monitor mean arterial blood pressure (MABP) and central venous pressure (CVP), respectively. An additional catheter was positioned within the right atrium via the left femoral vein, verified by pressure recordings, and used for drug or vehicle administration. A large bore arterial catheter was advanced from the left femoral artery into the thorax and was used to remove blood from the dog and to reinfuse shed blood. The arterial catheter was attached to a siliconized glass reservoir after passing through a Harvard peristaltic pump. The superior mesenteric artery was isolated by blunt dissection, and a Statham noncannulating electromagnetic flow probe was placed around the artery near its origin for the measurement of superior mesenteric artery flow (SMAF). The left renal artery was isolated, and a flow probe was placed on the vessel proximal to its bifurcation for the measurement of renal artery flow (RAF). Blood flows were monitored with Statham model SP 2202 blood flowmeters with nonocclusive zero. All blood pressures, blood flows, and lead III of the electrocardiogram (ECG) were continuously recorded on a Grass model 7 polygraph recorder. In addition, the output from the MABP amplifier was routed to an auxiliary channel of the recorder. An electronic servomechanism modified from the design of Culpepper et al., utilized-
PROSTAGLANDIN EXTRACTION

Blood samples (30 ml) were collected in plastic syringes containing 150 µg of indomethacin to inhibit in vitro PG synthesis. These samples were cooled, centrifuged at 12,000 g for 10 minutes at 4°C, and the plasma was frozen at −20°C under 100% nitrogen. These samples were extracted within 18 hours after collection by a modification of the method of Unger et al.16 Plasma samples (10 ml) were mixed with 10 ml of 0.9% NaCl, 20 ml of 95% ethanol, and a known amount of 3H-PGA, which was added to assess the percent recovery. The mixtures were washed with 80 ml of petroleum ether, and the pH was adjusted to 4.5 with 5% formic acid. The PG then were partitioned twice into 40-ml volumes of chloroform and the remaining plasma-alcohol phase was centrifuged to ensure complete recovery of the added chloroform. The chloroform was flash-evaporated at 40°C. The dry residues were dissolved in two washes of 70% ethanol, mixed with 250 mg of Fuller's Earth, and centrifuged at 2,000 g for 10 minutes. The prostaglandins were repartitioned into chloroform at pH 4.5, dried under nitrogen, and applied to silicic acid chromatography columns for the separation of A, E, and F series prostaglandins according to the method of Jaffe et al.,17 with minor modification of solvent ratios as previously described.18 The entire PGA fraction was collected, evaporated to dryness, and counted in a liquid scintillation spectrometer for the calculation of percent recovery throughout the extraction and chromatography procedures. The overall percent recovery of PGA averaged 62 ± 1% for a randomized sampling of 26 determinations.

The PGE and PGF fractions were evaporated to dryness under 100% nitrogen and assayed by specific radioimmunoassay.

PG RADIOIMMUNOASSAY

The dried PGE and PGF residues, representing 10 ml of plasma, were dissolved in 1.0 ml of 95% ethanol. Samples were transferred to plastic assay tubes and evaporated to dryness under nitrogen. Both the PGE and PGE assays were carried out in 0.06 M phosphate buffer containing 0.1% gelatin at pH 7.3. After a 1-hour incubation period at room temperature, bound and free hapten were separated by adding dextran-coated charcoal followed by centrifugation at 1,500 g for 10 minutes. Supernatant fluids were decanted into liquid scintillation vials, dissolved in a suitable counting medium, and counted in a liquid scintillation spectrometer. After calculation of disintegrations per minute (dpm) the percent binding of 3H-PG was determined for a set of samples comprising a standard curve and the unknown samples for each assay. Sample values were corrected for percent recovery and are reported as picograms of PG per milliliter of plasma. The PGE antibody was used at a final dilution of 1:15,000, whereas the antibody used for the determination of PGE was used at a final dilution of 1:5,000. Interassay precision for both assays is shown in Table 1. Cross-reactivity of the PGE antibody with prostaglandins of other series or with major metabolites was found to be negligible. The antibody used to measure PGE was directed against PGB and a cross-
reactivity was utilized to measure PGE\textsubscript{2}. The PGB\textsubscript{2} antibody did not cross-react with prostaglandins of the F series or with major PGE metabolites. This fact, coupled with the column chromatographic procedure, allowed for the specific measurement of PGE\textsubscript{2}.

**STATISTICS**

Student's \(t\)-test of significance for unpaired data was used throughout to compute statistical significance.\textsuperscript{18}

**Results**

Administration of AA (i.e., sodium arachidonate) to dogs in hemorrhagic shock resulted in significant increases in circulating plasma PG concentrations. Figure 1 illustrates the PGF\textsubscript{2a} concentrations in the four major groups of dogs. Sham shock dogs exhibited low, stable PGF\textsubscript{2a} concentrations over the entire 260-minute observation period. In contrast, dogs subjected to hemorrhagic shock exhibited a progressive increase in their plasma PGF\textsubscript{2a} concentration, which reached a plateau about 150 minutes after the onset of hemorrhage. After reinfusion of all remaining shed blood, the PGF\textsubscript{2a} concentration remained elevated at about 300 pg/ml. Dogs subjected to hemorrhagic shock receiving AA exhibited a very rapid increase in their PGF\textsubscript{2a} concentration which remained stable during the entire period of arachidonate infusion. After cessation of the arachidonate infusion and reinfusion of the shed blood, the PGF\textsubscript{2a} concentration decreased to a value that was not significantly different from that observed in the vehicle-treated, hemorrhagic shock dogs. Arachidonate infusion did not significantly increase the peak PGF\textsubscript{2a} concentration above that of the vehicle-treated dogs (i.e., the 150-minute PGF\textsubscript{2a} concentrations of both groups of shock dogs were not statistically different). However, the difference in the elapsed time necessary to achieve a maximal concentration was significantly different. Dogs receiving arachidonate experienced high PG concentrations for at least 100 minutes before comparable increases occurred in untreated shock dogs. The administration of sodium meclofenamate alone (not shown in Figure 1) or meclofenamate plus arachidonate prevented increases in the PGF\textsubscript{2a} concentration in dogs subjected to hemorrhagic shock to the extent that these values were not significantly different from those of the sham shock dogs given vehicle.

Figure 2 illustrates the PGE\textsubscript{2} concentrations in the four major groups of dogs. These data are quite similar to those obtained for PGF\textsubscript{2a}. There was a more rapid increase in the circulating plasma concentration of PGE\textsubscript{2} in the dogs

**Table 1** Radioimmunoassay Binding of Prostaglandins F\textsubscript{2a} and E\textsubscript{2}

<table>
<thead>
<tr>
<th>Prostaglandin (ng)</th>
<th>PGF\textsubscript{2a} (% binding)</th>
<th>PGE\textsubscript{2} (% binding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00</td>
<td>5.1 ± 0.1</td>
<td>20.2 ± 1.2</td>
</tr>
<tr>
<td>2.50</td>
<td>8.5 ± 0.2</td>
<td>27.6 ± 1.6</td>
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<tr>
<td>1.25</td>
<td>15.5 ± 0.3</td>
<td>37.1 ± 2.0</td>
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<tr>
<td>0.62</td>
<td>25.7 ± 0.2</td>
<td>50.0 ± 3.2</td>
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<tr>
<td>0.32</td>
<td>42.2 ± 0.7</td>
<td>61.9 ± 3.4</td>
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<tr>
<td>0.16</td>
<td>59.4 ± 1.1</td>
<td>74.5 ± 3.6</td>
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<td>0.09</td>
<td>71.6 ± 2.2</td>
<td>83.5 ± 3.0</td>
</tr>
<tr>
<td>0.04</td>
<td>87.7 ± 0.8</td>
<td>93.7 ± 2.6</td>
</tr>
</tbody>
</table>

All values are means ± SEM for eight determinations.

*Figure 1* Prostaglandin F\textsubscript{2a} concentration in central venous plasma. O = sham + vehicle; □ = hemorrhage + vehicle; ■ = hemorrhage + arachidonic acid; ○ = hemorrhage + meclofenamate. All values of hemorrhage + vehicle group after 50 minutes posthemorrhage are significantly greater than those of sham + vehicle group (\(P < 0.05\)). Fifty-minute and 100-minute PGF\textsubscript{2a} concentrations of hemorrhage + arachidonic acid group are significantly greater than those of hemorrhage + vehicle group (\(P < 0.05\)). Values in this and all other figures are mean ± SEM.

*Figure 2* Prostaglandin E\textsubscript{2} concentration in central venous plasma. O = sham + vehicle; □ = hemorrhage + vehicle; ○ = hemorrhage + arachidonic acid; ■ = hemorrhage + meclofenamate. Significant increases in PGE\textsubscript{2} are observed at all times after 30 minutes posthemorrhage in the hemorrhage + vehicle group, and at all times posthemorrhage in the hemorrhage + arachidonic acid group as compared to sham + vehicle controls (\(P < 0.05\)).
subjected to hemorrhagic shock given arachidonate compared to those given its vehicle. The plasma PGE2 concentration achieved in dogs given arachidonate was within the physiological range. The major difference between the PGE2 and PGF2α data is that the PGE2 concentrations were approximately double those of PGF2α at all times during hemorrhage in both the shock plus vehicle and the shock plus arachidonate groups. However, meclofenamate given alone (not shown in Figure 2) or in combination with arachidonate infusion resulted in PGE2 concentrations not statistically different at any time period from those of the sham shock dogs given vehicle.

MABP for the four groups of dogs are shown in Figure 3. Sham shock dogs receiving the vehicle for arachidonate exhibited a MABP of 120 mm Hg which was maintained for the entire experimental period. Dogs subjected to hemorrhagic shock exhibited comparable initial blood pressures. However, within 5 minutes after bleeding, all of these dogs exhibited aortic blood pressures of 40 mm Hg which were maintained at that value for the entire oligemic period. After reinfusion of all remaining shed blood at 150 minutes posthemorrhage, the MABP of all groups of dogs that had been bled increased to about 100 mm Hg. This pressure was not well maintained, and within the next 100 minutes fell to pre-reinfusion values in all groups that had been bled except the one given AA. This latter group of dogs demonstrated a MABP that was not significantly different from that of the sham shock dogs at 250 minutes. Dogs in hemorrhagic shock receiving only meclofenamate exhibited arterial pressures that were not significantly different from those of dogs in hemorrhagic shock given either the vehicle or AA plus meclofenamate.

Superior mesenteric artery flow (SMAF) rates are summarized in Figure 4. Sham shock dogs did not exhibit significant changes in SMAF during the entire 260-minute experimental period. In contrast, there were marked decreases in SMAF in the dogs in hemorrhagic shock. Those dogs receiving AA vehicle demonstrated a slower decrease in flow over the first 5 minutes of bleeding than did the dogs given either AA alone or in combination with meclofenamate. This difference soon disappeared, and the flows of all groups in hemorrhagic shock were not significantly different from one another during the remainder of the hypovolemic period. After reinfusion, SMAF increased markedly in all groups that had been bled. However, these SMAF values declined within 100 minutes following reinfusion in all groups that had been bled.

Renal artery flow (RAF) was virtually identical to the time course changes seen with SMAF. All groups of dogs exhibited comparable initial RAF values of about 150 ml/min. After hemorrhage, RAF declined very rapidly to values of 10–20 ml/min and remained at these low values until reinfusion. After reinfusion, there was a transient increase in flow in all groups that had been bled. This increase in flow was not sustained. At no time during the 260-minute experimental period were there any significant differences in renal artery blood flow between any of the groups that had been bled.

Cathepsin D activities for the major experimental groups are summarized in Figure 5. Sham shock dogs receiving vehicle exhibited no significant increase in cathepsin D activity over the entire experimental period. Hemorrhagic shock proved to be a potent stimulus for the release of lysosomal enzymes, resulting in large increases in circulating cathepsin D activity. In contrast, the administration of AA to dogs that had been bled significantly attenuated the plasma accumulation of this protease. This action did not appear to be a direct effect of AA, since dogs that had been bled and received AA plus meclofenamate exhibited cathepsin D activities indistinguishable from those of vehicle-treated dogs that had been bled. Moreover, dogs in hemorrhagic shock that received only meclofenamate also exhibited cathepsin D activities that

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**Figure 3**  Mean arterial blood pressure (MABP). ○ = sham + vehicle; □ = hemorrhage + vehicle; ● = hemorrhage + arachidonic acid; ■ = hemorrhage + arachidonic acid + meclofenamate. The MABP of the hemorrhage + arachidonic acid group is significantly greater than those of either the hemorrhage + vehicle or the hemorrhage + arachidonic acid + meclofenamate group at 250 minutes (P < 0.001).

**Figure 4** Superior Mesenteric Artery Flow (SMAF). ○ = sham + vehicle; □ = hemorrhage + vehicle; ● = hemorrhage + arachidonic acid; ■ = hemorrhage + arachidonic acid + meclofenamate. The SMAF of the hemorrhage + arachidonic acid group and the hemorrhage + arachidonic acid + meclofenamate group are significantly lower than that of the hemorrhage + vehicle group at 5 minutes posthemorrhage (P < 0.05).
were not significantly different from vehicle-treated shocked dogs.

Plasma activities of a myocardial depressant factor (MDF), present 100 minutes after reinfusion, are summarized in Figure 6. MDF activity in the vehicle-treated dogs that had been bled was significantly higher than in sham shock dogs. MDF activity was also high in the dogs that had been bled and were given AA plus meclofenamate or meclofenamate alone. However, MDF accumulation was significantly lower ($P < 0.01$) in the AA-treated dogs that had been bled than in other dogs subjected to hemorrhage.

Table 2 summarizes the bleedout volumes in milliliters per kilogram of body weight of the four groups of bled dogs. Peak bleedout volumes occurred within the first 50 minutes following hemorrhage. After this time, the reservoir volume progressively declined as the dogs took up shed blood to maintain an arterial pressure at 40 mm Hg. The bleedout volume of the dogs receiving AA was significantly less than those of the other three groups at 50 minutes posthemorrhage. However, this difference was not maintained, and no further significant differences were observed. None of the other groups that had been bled exhibited significant alterations in bleedout volume compared with the vehicle-treated bled dogs.

Discussion

Infusion of AA resulted in 4- to 5-fold increases in circulating PGE$_2$ and PGF$_{2a}$ concentrations. AA also significantly attenuated the plasma accumulation of cathepsin D and MDF during hemorrhagic shock, and resulted in the maintenance of mean systemic blood pressure near control values following reinfusion of shed blood.

Several interesting aspects of the AA infusion may be examined. First, the beneficial action of AA on cathepsin D and MDF activities and on MABP were dissociated from a vehicle effect and from a direct effect of the AA molecule. The use of sodium meclofenamate as a PG synthetase inhibitor effectively blocked PG synthetase in our dogs. Under these conditions, AA was of no significant benefit in improving the cardiovascular or cellular status of these dogs. They could not be distinguished from bled dogs receiving the arachidonate vehicle. Clearly, any beneficial action of AA is via the PG synthetase pathway. Our measurements of PGE$_2$ and PGF$_{2a}$ indicate significant activation of the PG synthesizing system. However, it is not known at present which substance(s) formed in this system (e.g., PGG$_2$, PGH$_2$, thromboxane A$_2$, PGE$_2$, PGF$_{2a}$, PGD$_2$, etc.) may be the active agent. Prostaglandins of the E and F series have been shown to stabilize lysosomal membranes in vitro$^{19,20}$ and in vivo during endotoxic shock$^{21}$ and to improve survival during shock.$^{21-23}$

A second interesting aspect of the effect of AA in hemorrhagic shock is that the beneficial effects were observed at concentrations of PGE$_2$ and PGF$_{2a}$, which were not substantially higher than those which the dogs are capable of attaining without substrate supplementation. The major difference was the longer duration of the elevated PG concentrations in the AA-treated shock group. Dogs receiving AA developed high circulating PG concentrations almost immediately after being bled, whereas a period of between 100 and 150 minutes was necessary for the bled dogs receiving vehicle to attain similar PG concentrations. This suggests that the earlier a relatively high PG concentration can be attained, the greater the potential benefit to the dog.

It is conceivable that the endogenous PG concentrations measured during hemorrhagic shock may have resulted from production of prostaglandins in the blood reservoir following hemorrhage with subsequent reinfusion into the...
dog. If this were true, one would expect to see very large increases in the plasma PG concentrations between the time of reinfusion (i.e., 150 minutes) and the 200-minute sampling period. However, there were no increases in either PGE₂ or PGF₂α in the vehicle-treated bled dogs after reinfusion, and more notably, the PGE₂ and PGF₂α concentrations decreased dramatically in the AA-treated dogs after reinfusion and cessation of the drug infusion. These findings support the assumptions that little or no prostaglandins were synthesized in the blood reservoir and that the infused AA was the primary substrate from which the circulating prostaglandins were synthesized.

The precise mechanism of the protective action of products of the PG synthetase system during hemorrhagic shock is not presently known. One possibility is that the significantly reduced reservoir volume in the bled dogs given AA is a reflection of a less severe shock model in these dogs. Dogs that were bled and received AA plus meclofenamate demonstrated reservoir volumes similar to those of the untreated shock group (i.e., those receiving only the vehicle). It therefore follows that the reservoir volume was lower in the AA-treated dogs as a direct result of the activation of the PG synthetase system. This reduced volume could be due either to a generalized vasodilation or to an increase in capillary permeability which would result in a loss of circulating fluid necessitating a reduced reservoir volume to maintain the systemic blood pressure at 40 mm Hg.

Although we have no data on the effects of AA on capillary permeability, our findings argue against vasodilation resulting in a less severe shock protocol as the mechanism of action of AA. The net effect of arachidonate administration was to stabilize lysosomal membranes and to attenuate the production of MDF. That a major portion of the circulating MDF is formed in the pancreas has been demonstrated in the spleen of the dog. The findings that AA attenuated the release of cathepsin D and MDF support the contention that products formed by the PG synthetase system may have either directly stabilized lysosomal membranes and prevented MDF production, or preserved liver phagocytic cell integrity allowing cathepsin D and MDF to be cleared more efficiently from the circulation.

The full role of prostaglandins in circulatory shock still remains to be firmly established. The use of nonsteroidal anti-inflammatory drugs to inhibit PG synthesis during shock is complicated by the fact that many of these agents have direct effects unrelated to their ability to inhibit PG synthesis. Several investigators have suggested that endogenous prostaglandins might act as a brake on sympathetically mediated vasoconstriction during development of the shock state in a manner similar to that described by Hedqvist and that endogenous prostaglandins protect the renal vasculature during shock. The administration of exogenous prostaglandins appears to attenuate the accumulation of lysosomal acid hydrolases and MDF during circulatory shock, and to support systemic arterial blood pressure. Our findings of improved circulatory function after stimulation of the PG synthetase system with AA in hemorrhagic shock support the physiological role of prostaglandins in either stabilizing lysosomal membranes or protecting phagocytic cell function during shock and thus maintaining the hemodynamic status of the shock animal by preventing the action of toxic materials on the cardiovascular system. However, the long-term efficacy of stimulation of endogenous PG production or of exogenous PG administration as therapeutic regimens for circulatory shock remains to be fully established:

Acknowledgments
We acknowledge the competent technical assistance of George Osman, Jr., Frances Kubler, and Genevieve Deutsch during the course of this investigation. We also acknowledge the generous gift of sodium meclofenamate by Dr. Clifford Beck of Parke, Davis and Company, Ann Arbor, Michigan. The antibodies used in this study were generously donated by Dr. Lawrence Levine, Department of Biochemistry, Brandeis University, Waltham, Massachusetts.

References

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**Table 2: Reservoir Volumes in Hemorrhaged Dogs**

<table>
<thead>
<tr>
<th>Group</th>
<th>Reservoir vol (ml/kg body wt)</th>
<th>50 min posthemorrhage</th>
<th>100 min posthemorrhage</th>
<th>150 min posthemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic shock plus vehicle</td>
<td>7</td>
<td>40.6 ± 3.0</td>
<td>36.2 ± 2.9</td>
<td>28.3 ± 7.5</td>
</tr>
<tr>
<td>Hemorrhagic shock plus PGE₂</td>
<td>7</td>
<td>27.5 ± 3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic shock plus PGF₂α</td>
<td>6</td>
<td>45.7 ± 3.0</td>
<td>34.4 ± 4.0</td>
<td>25.1 ± 6.1</td>
</tr>
<tr>
<td>Hemorrhagic shock plus meclofenamate</td>
<td>5</td>
<td>41.1 ± 6.0</td>
<td>34.1 ± 7.5</td>
<td>34.6 ± 6.1</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SEM; n = number of dogs in each group. *Significantly different from hemorrhagic shock plus vehicle (P < 0.01).
agents on myocardial ischemia. J Pharmacol Exp Ther 8: 582-593, 1976

Development of Left Ventricular Hypertrophy in Young Spontaneously Hypertensive Rats after Peripheral Sympathectomy

ANTHONY F. CUTILLETTA, LYNDA ERINOFF, ALFRED HELLER, JOHN LOW, AND SUZANNE OPARIL

SUMMARY The effects of peripheral sympathectomy with nerve growth factor antiserum (NGFAS) on blood pressure, systemic hemodynamics, myocardial function, myocardial hypertrophy, and renin were studied in male spontaneously hypertensive (SH) rats of the Okamoto strain and normotensive control Kyoto-Wistar (WKY) rats. NGFAS prevented the development of hypertension in the SH rats but did not alter blood pressure in the WKY rats. NGFAS-treated SH rats developed the same hemodynamic abnormalities as the sham-treated rats, including increased peripheral vascular resistance and depressed cardiac output. Indices of left ventricular performance, including peak flow velocity, stroke power, stroke work, dP/dt max, and flow acceleration (d/dt) were diminished in the SH rats compared to the WKY rats. NGFAS treatment further depressed ventricular function in the SH rats, but had little effect on the WKY rats. Plasma renin activity in both the SH and WKY rats was unaffected by NGFAS treatment. Although NGFAS treatment effectively prevented the development of hypertension in the SH rats, it did not influence the development of left ventricular hypertrophy as reflected by increases in left ventricular mass, RNA, DNA, and hydroxyproline content. The data suggest that the development of myocardial hypertrophy and myocardial dysfunction in the SH rat is in part independent of hypertension and plasma renin activity.

The spontaneously hypertensive (SH) rat of the Okamoto strain appears to be an excellent model for the study of genetically determined hypertension and its effect on the cardiovascular system.8-10 Our previous studies4 and those of others 4-6 have demonstrated the presence of hemodynamic abnormalities accompanied by myocardial hypertrophy in the hypertensive adult rat. We also have been able to show that hypertension can be prevented by interventions in the immature rat which deplete central or peripheral catecholamines, or both.7-8 Administration of an antiserum to nerve growth factor to SH rats in the 1st week of life interferes with the development of sympa-
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