Absence of Hypertension Despite Chronic Marked Elevations in Plasma Norepinephrine in Conscious Dogs

BERNARD D. KING, DANIEL SACK, MARIANNE R. KICHUK, AND THOMAS H. HINTZE

SUMMARY To better define the mechanisms of blood pressure control in states of catecholamine excess, we infused norepinephrine for 28 days using subcutaneously implanted osmotic pumps in dogs previously instrumented for monitoring left ventricular dynamics and cardiac output. Plasma norepinephrine rose from 238 ± 27 to 4346 ± 952 pg/ml at 21 days, while epinephrine and dopamine levels did not change. Heart rate fell from 85 ± 4 to 63 ± 6 beats/min, while arterial pressure was unchanged from baseline. Total peripheral resistance rose 0.011 ± 0.003 mm Hg/ml/min from a control value of 0.029 ± 0.002 mm Hg/ml/min, and cardiac output decreased 1093 ± 292 ml/min from a baseline level of 3575 ± 156 ml/min. Since stroke volume did not change, the maintenance of arterial pressure is related to decreases in cardiac output secondary to bradycardia. Buffering mechanisms are responsible for maintenance of systemic arterial pressure because hexamethonium and atropine caused hypertension. Although left ventricular end-diastolic pressure, end-diastolic diameter, shortening, rate of change of pressure, velocity of myocardial shortening, cardiac work, stroke work, and the double product did not change significantly during the study, postmortem examination demonstrated biventricular hypertrophy. Thus, despite markedly elevated catecholamine levels and no elevation of systemic arterial pressure, myocardial hypertrophy developed. These studies lend support to the hypothesis that norepinephrine may be a direct myocardial tropic hormone and suggest that intense activation of reflex buffering mechanisms maintains blood pressure in the normal range during chronic catecholamine infusion. (Hypertension 9: 582-590, 1987)

KEY WORDS • bradycardia • hypertension • hypertrophy • catecholamines • total peripheral resistance • atropine

ELEVATIONS in catecholamine levels may be associated with a number of disease states, including mitral valve prolapse (MVP), chronic myocardial failure, and pheochromocytoma. These disease states may be characterized by sustained or episodic hypertension, myocardial dysfunction, and cardiomyopathy. Recently, it has been noted that certain patients with MVP, chronic myocardial failure, or pheochromocytoma have dysautonomia, manifested by abnormalities in heart rate or blood pressure response (or both) to orthostatic change or exercise. Some investigations of patients with MVP having dysautonomia are consistent with evidence of hyperadrenergic states and some with simultaneous hypervagotonia. Significant elevations in serum catecholamine levels have been observed in a group of symptomatic patients with MVP; these results have been confirmed by other workers. Patients with chronic myocardial failure, regardless of etiology, have elevated plasma norepinephrine (NE) levels. In addition, defects in baroreceptor reflex-mediated vasoconstrictor responses have been noted in dogs and in patients with marked myocardial dysfunction.

Several studies, summarized by Eckstein and Abboud, have evaluated the general effects of changes in plasma NE concentrations on cardiovascular function; few, however, have examined systematically the effects of altered regulatory mechanisms operating during chronic elevations in plasma NE.

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Initial studies by Laks et al., 21–23 in conscious dogs, showed that chronic elevations in plasma arterial NE concentration failed to increase ejection fraction or cause hypertension but resulted in myocardial hypertrophy. Recently, Young et al. 24 have shown that short-term infusions of NE to levels seen in many disease states in humans (2000–4000 pg/ml) were not associated with marked hypertension or changes in myocardial inotropic state.

The goals of our study were to determine alterations in myocardial function, cardiac output, and total peripheral resistance and to clarify the mechanisms responsible for the regulation of systemic arterial pressure in conscious dogs with prolonged (1 month), marked (2000–4000 pg/ml) elevations in plasma arterial NE. The primary focus of our study was the contribution of neural control mechanisms to the maintenance of systemic arterial pressure.

Materials and Methods

Mongrel dogs of either sex, weighing 25 to 32 kg, were sedated with acepromazine (Ayerst, 0.2 mg/kg), and anesthetized with pentobarbital sodium (Butler, 25 mg/kg). Sterile techniques were used to make an incision in the left fifth intercostal space, and a Tygon catheter (Norton Plastics and Synthetic Division, Akron, OH, USA), was inserted into the descending thoracic aorta. Piezoelectric transducers (3 MHz) were implanted on opposing anterior and posterior epicardial surfaces of the left ventricle, and a solid-state pressure gauge (Model P6.5; Konigsberg Instruments, Pasadena, CA, USA), was inserted into the left ventricle through an apical stab wound in eight dogs to measure ventricular function. In eight additional dogs cardiac output (cardiac output minus coronary blood flow) was measured using an electromagnetic flow transducer (Carolina Medical Electronics, King, NC, USA) placed around the ascending thoracic aorta.

The wires from the instruments as well as the catheters were run subcutaneously and exited from the back of the dog's neck. The incision was then closed in layers, the pneumothorax was reduced, and the animals were allowed to recover. Antibiotics were given postoperatively. The dogs were trained to lie quietly on command. After bridle and fully recovered from the operation.

Arterial pressure was measured using the implanted catheter connected to a Statham P23ID strain gauge manometer (Oxnard, CA, USA). Left ventricular (LV) pressure was measured with the solid-state miniature pressure gauge, which was calibrated in vitro against a mercury manometer and in vivo against the arterial and left atrial pressure measurements. An ultrasonic transit-time dimension gauge 25 was used to measure LV diameter. This instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of 1.5 × 106 m/sec between the previously implanted 3-MHz piezoelectric crystals, thus giving a continuous record of LV diameter. The frequency of the dimension gauge is flat to 400 Hz. At a constant room temperature, the thermal drift of the instrument is minimal (i.e., <0.01 mm in 6 hours). Blood flow was measured with an electromagnetic flow meter (Model 501; Carolina Medical Electronics). Any drift in the measurement system, the instrument electronics, the data tape recorder, and the oscillograph was eliminated during the experiment by periodic calibrations. This calibration involved substituting pulses of known duration from a crystal-controlled pulse generator with a stability of 0.001%. The positions of all transducers and the piezoelectric crystals were confirmed at autopsy.

The data were recorded on a multichannel tape recorder (Model 3700B; Hewlett-Packard, Palo Alto, CA, USA) and played back on a direct-writing oscillograph (Model 2800S; Gould Brush, Cleveland, OH, USA). A carotid catheterometer (Model 9857B; Beckman Instruments, Palo Alto, CA, USA), triggered by the pressure pulse, provided instantaneous and continuous records of heart rate (HR). Continuous records of rate of rise of LV pressure (dP/dt) were derived from LV pressure signals using an operational amplifier (Model LM324; National Semiconductor, Santa Clara, CA, USA). LV dD/dt, the velocity of myocardial shortening, was also derived by differentiating the LV diameter signal. Triangular wave signals with known slopes were substituted for the pressure and dimension signals to calibrate the differentiator directly. Electrical resistance-capacitance filters with 2-second time constants were used to derive mean arterial pressure (MAP). An 8-Hz filter was used to derive mean aortic blood flow.

Arterial plasma NE was selectively increased by placing NE (Sigma) in Alzet osmotic pumps (Model 2MLM; Palo Alto, CA, USA) allowing continuous release over 28 days. In a previous study, 24 we found that an intravenous infusion rate of 0.5 μg/kg/min of NE results in plasma arterial concentrations of 2000 to 4000 pg/ml. We verified the delivery rate of the osmotic pumps used in this study by constructing dose-response curves, which allowed us to predictably produce plasma arterial concentrations of 4000 to 6000 pg/ml. At the time of recording, plasma arterial samples were taken to measure plasma catecholamines (NE, epinephrine, and dopamine), blood gases, plasma sodium and potassium levels, and hemocrit. Catecholamine levels were measured by high pressure liquid chromatography and confirmed by radioenzymatic methods.

Before implantation of the osmotic pumps, cardiovascular function, including each parameter to be followed during the study, was measured on at least three separate occasions, thus allowing each dog to serve as its own control. The amount of NE necessary to produce desired levels (equivalent to 0.5 μg/kg/min for 28 days) was divided into two pumps that were implanted subcutaneously along the midline in the dorsal aspect of the neck, using sterile surgical techniques and local lidocaine anesthesia.
Effects of Elevated Plasma Norepinephrine on Left Ventricular Function

In dogs instrumented for study of LV function, LV pressure, LV end-diastolic pressure (LVEDP), LV dP/dt, MAP, HR, and internal LV dimensions were measured before and 1, 3, 5, 7, 14, 21, and 28 days after implantation of the pumps.

Effects of Elevated Plasma Norepinephrine on Cardiac Output and Peripheral Vascular Resistance

In dogs instrumented for this portion of the study, MAP, HR, and cardiac output were measured and peripheral vascular resistance, stroke volume, stroke work, and cardiac work were calculated before and 1, 3, 5, 7, 14, 21, and 28 days after implantation of the pumps. To prevent a decline in plasma NE levels noted on Day 14 in the first portion of the study, an additional pump, containing 30% of the original dose of NE, was implanted on Day 10 in each dog.

Effects of Atropine and Hexamethonium on Arterial Pressure, Left Ventricular Function, and Peripheral Resistance in Dogs with Elevated Norepinephrine Levels

In five dogs, hexamethonium (20 mg/kg) was administered on Day 21 to assess the blood pressure, HR, and function responses. In six dogs, atropine methylbromide (0.1 mg/kg) was administered while MAP, HR, and cardiac output were measured. Stroke volume and total peripheral resistance also were calculated in each instance.

To determine whether longer recording sessions would reveal consistent hypertension, three dogs were instrumented with a Tygon catheter and allowed to fully recover. On Day 14 after elevation in plasma NE arterial pressure in each dog was recorded continuously for 6 hours.

Effects of Elevated Plasma Arterial Norepinephrine on Cardiac Size (Hypertrophy)

Following the completion of each experiment (at 28 days), each dog was anesthetized with pentobarbital sodium and killed with an overdose of potassium chloride. The hearts were excised immediately and weighed on a Mettler balance (Florham Park, NJ, USA). The right ventricular (RV) free wall was separated from the left ventricle and septum and weighed. The LV free wall and septum were weighed separately. Control values were obtained from a cohort of 33 conditioned, male mongrel dogs, similarly instrumented, studied during this and other concomitant experiments in our laboratory.

Statistical Analysis

All data were stored in a DEC Pro 350 computer (Digital Equipment, Maynard, MA, USA). Cardiac work was calculated by multiplying mean aortic pressure by mean aortic blood flow (1 mm Hg = 1.36 g/cm^2), and stroke work was calculated as cardiac work divided by HR. Index of cardiac effort (double product) was calculated by multiplying peak LV pressure by HR. Resistance was calculated as the quotient of MAP and cardiac output. Statistical analysis of the data from the study was performed using a one-way analysis for linear contrast to compare points within a group. All data are expressed as means ± SE. Linear regression analysis was performed using a least-squares method with programs written for a Hewlett-Packard 97 calculator.

Results

Effects of Elevated Plasma Norepinephrine on Left Ventricular Function

Figure 1 shows arterial plasma catecholamines on the control day and on each experimental day in dogs used to study LV function. Before implantation of the pumps, plasma NE, epinephrine, and dopamine levels were 268 ± 48, 83 ± 34, and 42 ± 8 pg/ml, respectively. Following pump implantation, arterial NE was increased 10-fold to 20-fold (peak, 4449 ± 927 pg/ml), while epinephrine (peak, 148 ± 47 pg/ml) and dopamine (peak, 85 ± 55 pg/ml) levels did not change significantly from control, thus indicating that NE elevations were not of adrenal origin. Hemodynamic data observed on Day 21 will be discussed in the text, although all data are shown in figures and tables.

LV end-diastolic diameter (LVEDD) and LVEDP were measured as indices of preload, while LV dP/dt, LV dD/dt, and shortening (i.e., LVEDD minus LV end-systolic diameter) were calculated as indices of myocardial function (Table 1). Preload did not increase significantly (LVEDD: 1.5 ± 0.9 from 35.1 ± 1.8 mm; LVEDP: 1 ± 1.5 from 10 ± 1 mm Hg), nor were any significant changes in LV contractility by HR. Resistance was calculated as the quotient of MAP and cardiac output. Statistical analysis of the data from the study was performed using a one-way analysis for linear contrast to compare points within a group. All data are expressed as means ± SE. Linear regression analysis was performed using a least-squares method with programs written for a Hewlett-Packard 97 calculator.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Time course of plasma catecholamines before and after implantation of miniosmotic pumps in eight dogs used to study left ventricular function. While dopamine (DOP) and epinephrine (EPI) levels did not change for the 28 days of this study, plasma norepinephrine (NE) increased almost 20-fold from control (C).
tile state observed (LV dP/dt: 652 ± 201 from 3287 ± 165 mm Hg/sec; LV dD/dt: 14 ± 4 from 76 ± 7 mm/sec; shortening: 1.8 ± 1.0 from 8.4 ± 1.1 mm) despite greater than 10-fold increases in arterial NE. Importantly, however, MAP did not change (5 ± 3 from 100 ± 3 mm Hg) whereas HR significantly declined (11 ± 5 from 85 ± 4 beats/min; p<0.05; see Table 1).

**Effects of Elevated Plasma Norepinephrine on Cardiac Output and Peripheral Vascular Resistance**

To further define mechanisms of arterial pressure regulation in the face of marked NE excess, eight dogs were instrumented to measure cardiac output and arterial pressure. As in the first series of experiments, after 21 days epinephrine and dopamine had not changed while plasma NE rose from 238 ± 27 pg/ml to 4346 ± 952 pg/ml following implantation of the minipumps (Table 2). NE levels in the latter portion of the month remained substantially elevated compared with the first series of experiments because of the implantation of the additional minipump on Day 10 (see Table 2).

By Day 21, MAP was again unchanged (—2 ± 3 from 101 ± 1.9 mm Hg) while heart rate decreased 20% (15 ± 4 from 82 ± 5.3 beats/min; p<0.01). Cardiac output also declined significantly (895 ± 320 from 3575 ± 156 ml/min; p<0.01; Figure 2). Calculated total peripheral resistance increased significantly (0.008 ±0.003 from 0.0286 ± 0.0017 mm Hg/ml/min; p<0.02).

As shown in Table 3, stroke volume (4.6 ± 3.0 from 44.5 ± 2.7 ml) and stroke work (0.009 ± 0.004 from 0.061 ±0.004 kg/m/beat) were unchanged while cardiac work fell (1.39 ±0.03 from 4.89 ±0.21 kg/m/min; p<0.05).

To characterize hemodynamic relationships we plotted MAP (r = 0.16), cardiac output (r = 0.67), and HR (r = 0.94) against NE concentrations and performed linear regression analysis (Figure 3). Whereas there was no significant correlation between arterial pressure and plasma NE, there was a significant negative correlation between both cardiac output and HR and plasma NE.

**Effects of Atropine and Hexamethonium on Arterial Pressure, Left Ventricular Function, and Peripheral Resistance in Dogs with Elevated Norepinephrine**

Dogs maintained their blood pressures and HR within fairly narrow limits during recording sessions that generally lasted 5 to 6 hours. We have plotted the average readings from three dogs recorded on Day 14 of the experiment (Figure 4). Nevertheless, during several experimental sessions, while the dogs were resting quietly or sleeping, spontaneous rises in MAP occurred. These episodes suggest that the expected effect of NE infusion (hypertension) was buffered by an intrinsic control mechanism that intermittently and transiently failed.

We attempted to interrupt reflex buffering mechanisms by administering the ganglionic blocker hexamethonium (20 mg/kg i.v.) to five dogs. These dogs became hypertensive: MAP rose to 170 ± 16 mm Hg from 102 ± 5 mm Hg (p<0.05); HR rose to 171 ± 6 beats/min from 75 ± 6 beats/min; and LV dP/dt increased from 3369 ± 190 mm Hg/sec to 5516 ± 625 mm Hg/sec.

**Table 1. Hemodynamic Responses Before and After Norepinephrine Infusions**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>100 ± 3</td>
<td>106 ± 4</td>
<td>103 ± 4</td>
<td>109 ± 6</td>
<td>102 ± 6</td>
<td>105 ± 3</td>
<td>106 ± 3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>85 ± 4</td>
<td>66 ± 3*</td>
<td>60 ± 3*</td>
<td>69 ± 6*</td>
<td>63 ± 6*</td>
<td>74 ± 6*</td>
<td>65 ± 7*</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>127 ± 3</td>
<td>141 ± 6</td>
<td>140 ± 9</td>
<td>146 ± 9</td>
<td>144 ± 12</td>
<td>134 ± 5</td>
<td>136 ± 7</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10 ± 1</td>
<td>12 ± 3</td>
<td>14 ± 1</td>
<td>12 ± 2</td>
<td>10 ± 2</td>
<td>11 ± 3</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>35.1 ± 1.8</td>
<td>34.8 ± 2.2</td>
<td>36.0 ± 2.1</td>
<td>34.8 ± 1.5</td>
<td>34.3 ± 2.3</td>
<td>33.6 ± 1.1</td>
<td>35.4 ± 3.2</td>
</tr>
<tr>
<td>Shortening (mm)</td>
<td>8.4 ± 1.1</td>
<td>9.5 ± 2.4</td>
<td>10 ± 1.8</td>
<td>8.8 ± 1.2</td>
<td>8.3 ± 1.3</td>
<td>6.6 ± 1.3</td>
<td>8.8 ± 4.0</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3287 ± 165</td>
<td>4147 ± 400</td>
<td>3840 ± 365</td>
<td>3429 ± 352</td>
<td>3372 ± 458</td>
<td>2635 ± 225</td>
<td>3470 ± 691</td>
</tr>
<tr>
<td>LV dD/dt (mm/sec)</td>
<td>76 ± 7</td>
<td>92 ± 14</td>
<td>101 ± 13</td>
<td>87 ± 8</td>
<td>74 ± 9</td>
<td>62 ± 12</td>
<td>60 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SEM. LV = left ventricular; LVSP = LV systolic pressure; LVEDP = LV end-diastolic pressure; EDD = end-diastolic diameter; dP/dt = rate of change of pressure; dD/dt = velocity of myocardial shortening.

*p<0.05, compared with control value.

**Table 2. Plasma Arterial Catecholamine Concentrations**

<table>
<thead>
<tr>
<th>Catecholamine (pg/ml)</th>
<th>Control</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>238 ± 27</td>
<td>3654 ± 722*</td>
<td>4267 ± 1159</td>
<td>4346 ± 952*</td>
<td>2905 ± 570*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>70 ± 24</td>
<td>61 ± 30</td>
<td>67 ± 26</td>
<td>177 ± 107</td>
<td>139 ± 40</td>
</tr>
<tr>
<td>Dopamine</td>
<td>45 ± 14</td>
<td>29 ± 10</td>
<td>24 ± 5</td>
<td>24 ± 7</td>
<td>18 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*p<0.01, compared with control value.
To further define the responsible efferent neural mechanism, we administered atropine methylbromide (0.1 mg/kg) intravenously to the eight dogs instrumented for cardiac output determination. An example is shown in Figure 5. In the control state (i.e., before pump implantation), atropine administration produced a 7% increase in MAP (from 102 ± 1 to 109 ± 3 mm Hg) but, following implantation of the pumps and with markedly elevated NE levels (2250 ± 463 pg/ml), injection of atropine produced a 61% increase in MAP (from 106 ± 6 to 172 ± 14 mm Hg; \( p < 0.05 \), compared with change in control state). HR increased more than 150% (from 86 ± 6 to 215 ± 14 beats/min) after muscarinic receptor blockade in control dogs but increased 235% (from 75 ± 3 to 249 ± 12 beats/min; \( p < 0.01 \)) after atropine in the presence of increased NE levels. Cardiac output increased 44 ± 7% (from 3650 ± 132 to 5275 ± 390 ml/min) in the control state and 56 ± 14% with elevated NE levels (from 3080 ± 392 to 4780 ± 70 ml/min; \( p < 0.05 \)). Peripheral vascular resistance, however, decreased 25 ± 4% (from 0.028 ± 0.001 to 0.021 ± 0.001 mm Hg/ml/min) following atropine in control animals but did not change.

### Figure 2

**Time course of the effects of elevations of plasma norepinephrine on heart rate (HR), mean arterial pressure (MAP), and cardiac output (CO).** While HR fell significantly, MAP did not change. CO fell in parallel with decreases in HR.

### Figure 3

**Linear regression analysis of plasma norepinephrine (NE) and heart rate (HR) and cardiac output (CO).** Linear regression demonstrated a significant relationship between elevations in NE levels and reductions in CO (\( r = 0.67 \)) and HR (\( r = 0.94 \); both, \( p < 0.05 \)). Each individual data point is depicted by triangles and the solid line, while mean data points for each experimental day are shown by circles and dashed lines.

### Table 3

**Effects of Increases in Plasma Arterial Norepinephrine on Cardiac and Peripheral Vascular Function**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>101 ± 2</td>
<td>106 ± 0.3</td>
<td>108 ± 4</td>
<td>99 ± 5</td>
<td>97 ± 5</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>3575 ± 156</td>
<td>3100 ± 250*</td>
<td>3083 ± 271</td>
<td>2680 ± 343*</td>
<td>3283 ± 207*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>82 ± 5.3</td>
<td>67 ± 5*</td>
<td>70 ± 6*</td>
<td>67 ± 4*</td>
<td>74 ± 6*</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min)</td>
<td>0.029 ± 0.002</td>
<td>0.036 ± 0.004*</td>
<td>0.037 ± 0.004*</td>
<td>0.037 ± 0.003*</td>
<td>0.031 ± 0.002*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>44.5 ± 2.7</td>
<td>41.7 ± 5</td>
<td>45.2 ± 4</td>
<td>39.9 ± 4</td>
<td>43.5 ± 4</td>
</tr>
<tr>
<td>LV cardiac work (kg/m/min)</td>
<td>4.89 ± 0.2</td>
<td>4.44 ± 0.4</td>
<td>450 ± 0.4</td>
<td>3.5 ± 0.4*</td>
<td>4.34 ± 0.4</td>
</tr>
<tr>
<td>LV stroke work (kg/beat)</td>
<td>0.061 ± 0.004</td>
<td>0.068 ± 0.008</td>
<td>0.066 ± 0.006</td>
<td>0.052 ± 0.005</td>
<td>0.055 ± 0.005</td>
</tr>
<tr>
<td>Double product (mm Hg/beat/min)</td>
<td>10,433 ± 740</td>
<td>10,580 ± 1330</td>
<td>9405 ± 1302</td>
<td>9894 ± 661</td>
<td>8488 ± 861</td>
</tr>
</tbody>
</table>

*Values are means ± SEM. LV = left ventricular.

*\( p < 0.05 \), compared with control value.
ABSENCE OF HYPERTENSION WITH CHRONIC NOREPINEPHRINE/ King et al.

FIGURE 4. Time course of mean arterial pressure (MAP) and heart rate (HR) measurements taken every 5 minutes for 6 hours in three chronically instrumented dogs 14 days after implantation of norepinephrine-filled osmotic pumps. Each point represents the average of values in three dogs.

Effects of Elevated Plasma Arterial Norepinephrine on Cardiac Size (Hypertrophy)

Left and right ventricular hypertrophy occurred despite a reduction in cardiac output and absence of arterial pressure elevation (i.e., without a significant alteration in cardiac work; Table 4). Furthermore, the reduced HR and the absence of alterations in contractile state, afterload (MAP), LV systolic pressure, double product, and LV cardiac work indicate that myocardial oxygen demand was not markedly increased and, indeed, probably decreased slightly. In these dogs, LV weight, RV weight, and the LV weight and RV weight to body weight ratios were all increased significantly when compared with those of the control group.

To fully characterize the response of dogs to the presence of high plasma NE levels, the blood chemistry and general health of the dogs were monitored closely. Body weight, hematocrit, pH, oxygen tension, carbon dioxide tension, plasma sodium, and plasma potassium did not change during the 1-month study.

Discussion

To better understand disease states characterized by elevations in plasma NE, we studied blood pressure regulation using osmotic pumps that allowed us to maintain prolonged, markedly elevated NE levels in conscious dogs that were instrumented and trained to allow recording in an unanesthetized state.

Following implantation of the pumps, arterial plasma NE rose 10-fold to 20-fold while epinephrine and dopamine levels were unchanged. Despite such dramatic elevations, no changes in LV contractile state, as assessed by LV dP/dt, LV dD/dt, or shortening, occurred. Preload (LVEDD) was also unchanged. In addition, MAP remained at baseline levels while HR decreased significantly. Several dogs became hypertensive spontaneously, suggesting that baroreceptor-mediated reflex control intermittently and transiently failed. Responses to ganglionic blockade further suggested the importance of reflex control, since administration of the ganglionic blocker resulted in fulminating hypertension. The latter two observations establish the presence of active circulating NE and functioning, though potentially somewhat down-regulated, adren-

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>After 28 days of NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (kg)</td>
<td>22.4 ± 0.8</td>
<td>23.7 ± 0.9</td>
</tr>
<tr>
<td>LV/body wt (g/kg)</td>
<td>3.35 ± 0.08</td>
<td>4.03 ± 0.13*</td>
</tr>
<tr>
<td>RV/body wt (g/kg)</td>
<td>1.55 ± 0.04</td>
<td>1.94 ± 0.10*</td>
</tr>
<tr>
<td>RV/LV (g/g)</td>
<td>0.46 ± 0.01</td>
<td>0.47 ± 0.02</td>
</tr>
<tr>
<td>LV (g)</td>
<td>74.5 ± 2.9</td>
<td>95.5 ± 4.4*</td>
</tr>
<tr>
<td>RV (g)</td>
<td>34.9 ± 1.7</td>
<td>45.2 ± 2.2*</td>
</tr>
<tr>
<td>Septum (g)</td>
<td>30.3 ± 1.7</td>
<td>31.9 ± 2.0</td>
</tr>
</tbody>
</table>

Values are means ± SEM. NE = norepinephrine; LV = left ventricle; RV = right ventricle.

*p < 0.01, compared with control value.
ergic receptors. Receptor regulation, however, was not specifically assessed in this study.

Study of a second group of dogs instrumented for measurements of pressure and cardiac output confirmed that the development of bradycardia was entirely responsible for maintenance of blood pressure following implantation of the pumps. Cardiac output fell in direct proportion to HR, while peripheral resistance rose and stroke volume did not change. Muscarinic receptor blockade in these dogs resulted in marked tachycardia and hypertension, confirming the essential role of vagal efferent activity in arterial pressure control. Myocardial hypertrophy developed in both groups of dogs, however, despite maintenance of arterial pressure.

Previous studies using NE infusions generally have involved short-term experiments with infusions lasting several minutes to a few hours. Results of these studies have largely focused on two particular features: historical evidence of myocarditis (catecholamine cardiomyopathy) and demonstration of hypertension and bradycardia. To determine threshold levels for its metabolic effects, Silverberg et al. infused NE in stepwise fashion in doses from 0.1 to 5 μg/min over 60 minutes. At the highest dose in these short-term studies (plasma levels of 2150 ± 66 pg/ml), systolic and diastolic arterial blood pressures rose while HR fell. They found that steady state plasma NE concentrations in excess of 1000 pg/ml were required to produce measurable hemodynamic responses.

Similarly, in a previous study, Young et al. demonstrated that serum NE levels in excess of 1000 pg/ml were required to produce small (10%), although statistically significant, changes in blood pressure, HR, or LV contractility. Accordingly, we calculated doses for infusion in the present study to yield serum NE levels of 2000 to 4000 pg/ml, which were well above threshold levels for a hemodynamic response.

Such NE levels have uniformly been associated with profound systemic effects in short-term experiments. In intact conscious dogs, NE increased MAP and LV dP/dt significantly while HR decreased. "There is controversy as to whether the parasympathetic nervous system influences myocardial contractility, but at least one study, using a model similar to ours, concluded that the parasympathetic nervous system was antagonistic to the actions of catecholamines on contractility."

In our first group of experiments, we noticed that several dogs became markedly hypertensive during routine recording sessions unrelated to environmental stress. We suspected that blood pressure was well buffered most of the time but that neural control intermittently failed.

First with ganglionic blockade and then with muscarinic receptor blockade, we were able to confirm the importance of the vagal efferents to blood pressure control. The dogs remained normotensive despite increases in peripheral vascular resistance, since bradycardia alone accounted for the decrease in cardiac output. Myocardial contractility and stroke volume were unchanged. Despite normal systemic arterial pressure and the reduction in HR that occurred without increasing stroke work, the heart of each dog in this study demonstrated marked biventricular hypertrophy at autopsy.

Gans and Cater administered NE in oil chronically to a series of dogs and demonstrated increases in heart weight. It is, however, difficult to interpret the physiological bases of these results since no hemodynamic measurements were included. To our knowledge, the only other investigators to use a model similar to ours were Laks et al., who, in a series of publications, described hemodynamic responses to prolonged infusions of NE. An initial study in 1971 described a dose-response curve to NE in which progressive increases in NE delivery resulted in increases in HR, blood pressure, cardiac output and total peripheral resistance. A later study by these authors examined the effects of prolonged (6–63 weeks) NE infusion. A dose for infusion was chosen that did not produce hypertension. Thus, they produced much lower plasma NE levels. Yet, despite the absence of hypertension, LV weight and wall thickness increased while RV weight remained unchanged. Subsequently, Laks and his colleagues reported increases in stroke volume and ejection fraction at 3 months, as measured using left ventriculography. These studies are difficult to interpret, since infusions were stopped 30 minutes before angiographic study.

Laks and Morady have proposed NE as the "myocardial hypertrophy hormone." They suggest that hypertrophy is produced preferentially because of afterload differences between the two ventricles. However, it is also conceivable that the NE-as-myocardial-hypertrophy-hormone hypothesis is more consistent with our results (i.e., production of both right and left ventricular hypertrophy). Indeed, Lee and Downing performed short-term infusions of NE in rabbits and assessed LV function 2 days later. The maximum LV dP/dt was depressed, but overall LV function was intact. The ratios of LV weight to body weight were
significantly higher in the rabbits, but the ratios of LV weight to total heart weights were not significantly different, indicating increased mass in all parts of the heart.

We have not directly studied the mechanism of myocardial hypertrophy, although no obvious physiological basis for hypertrophy (e.g., afterload, preload, cardiac output, or HR) was observed. We cannot, however, exclude the possibility that subtle alterations in ventricular wall stress may have occurred. Alternatively, Simpson et al. has demonstrated that NE can stimulate hypertrophy in cultured neonatal rat heart cells through α-adrenergic receptors. Hence, hypertrophy might have resulted from a direct stimulatory effect of NE.

Certain important clinical consequences are suggested by the results of this study. First, in some states characterized by catecholamine excess, hypertension appears to be prevented by parasympathetic efferent control. Many patients with elevations in levels of plasma catecholamines are reported to have dysautonomia. Yet in the circumstances described in these experiments, parasympathetic control is entirely appropriate; perhaps essential, for homeostatic control. Nevertheless, excesses in catecholamine levels may produce myocardial dysfunction. In addition, parasympathetic nervous system dysfunction has been reported in patients with ventricular dysfunction. Second, our studies suggest that mechanisms of heart failure and hypertrophy may need to be reexamined, since NE may be both cardiotoxic and, as others have reported, cardiotoxic.

In summary, we have demonstrated that, despite extremely high levels of plasma NE, hypertension did not occur in our dogs. Reflex-mediated vagal reduction in cardiac output secondary to a reduction in HR is entirely responsible for the maintenance and regulation of arterial pressure at rest, yet myocardial hypertrophy occurred in the absence of hypertension or other obvious physiological stimuli.

Acknowledgments

The authors extend their thanks and appreciation to Maria DeLeonardis and Jeffrey Shapiro, not only for their technical assistance but also for their enthusiasm and dedication.

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Hypertension. 1987;9:582-590
doi: 10.1161/01.HYP.9.6.582

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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