Cardiovascular Effects of Sustained Norepinephrine Infusions in Dogs

IV. PREVIOUS TREATMENT WITH ADRENERGIC BLOCKING AGENTS

By Arthur J. Moss, M.D., and Eric A. Schenk, M.D.

ABSTRACT

Sustained infusions of norepinephrine (NE) are known to produce deleterious pathophysiologic effects on the circulatory system. The mechanisms responsible for these effects were investigated in 25 dogs; 17 were treated with selective block of alpha receptors by phenoxybenzamine or of beta receptors by propranolol, or by both agents, and then infused with NE (4 µg·kg⁻¹·min⁻¹) for 4 hours; 8 control animals were given only adrenergic blocking agents. Left ventricular and systemic pressure, cardiac output and arterial blood gases were measured at selected intervals throughout the infusion period, and histologic examinations of the heart and other vital organs were performed at the conclusion of each study. In animals with alpha-receptor blockade, NE infusions were associated with extensive subendocardial hemorrhage and focal myofiber fatty degeneration, yet blood pressure, cardiac output, and derived cardiac work parameters were well maintained. In animals with beta-receptor blockade, NE caused minimal pathologic changes in the heart despite significant reduction in cardiac output, minute and stroke work, and significant increase in left ventricular end-diastolic pressure (LVEDP) and peripheral vascular resistance. In animals receiving combined alpha- and beta-receptor blockade, NE infusions were not associated with significant hemodynamic or morphologic abnormality. These findings indicate: (1) the hemodynamic abnormalities are the result of the action of NE mediated primarily through alpha receptors; (2) the morphologic changes are produced by NE mediated mostly through beta receptors; and (3) the reductions in cardiac output and minute and stroke work and the increase in LVEDP produced by sustained NE infusions are not necessarily a consequence of the pathologic changes which develop in the heart muscle.

ADDITIONAL KEY WORDS

fatty myofiber degeneration phenoxybenzamine propranolol alpha and beta receptors

Sustained infusions of 1-norepinephrine (NE) in patients and experimental animals have been associated with a wide variety of cardiovascular lesions (1-3). Previous studies from this laboratory documented a progressive deterioration in cardiac function with 4-hour systemic infusions of NE (4). These circulatory abnormalities were correlated with the development of extensive myocardial lesions (5, 6) and it was postulated that the myocardial lesions accounted in large part for the low cardiac output that developed during NE administration (4).

Norepinephrine, by stimulating both alpha and beta receptors, produces constriction of the peripheral resistance vessels and a positive inotropic effect on the myocardium. To define more clearly the mechanisms responsible for the deterioration in cardiac function and for the cardiovascular lesions that develop during sustained NE infusions, selective adrenergic blocking agents were administered before NE.

From the Departments of Medicine and Pathology, University of Rochester School of Medicine and Dentistry, Rochester, New York 14620. This work was supported in part by U. S. Public Health Service Grants HE 10465-03 and HE 10251-05 from the National Heart Institute, a General Research Support grant and by the Ernest L. Woodward Research Fund.

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administration. The present report describes the results of these studies.

**Methods**

Twenty-five mongrel dogs weighing 10 to 34 kg were anesthetized with intravenous sodium pentobarbital, 25 mg/kg, and mechanically ventilated with room air through a cuffed endotracheal tube. Norepinephrine base was diluted in 40 ml of dextrose and water and infused into a femoral vein of the experimental animals for 4 hours at a dose of 4 μg·kg⁻¹·min⁻¹. The control animals were infused intravenously with 40 ml of 5% dextrose and water over a 4-hour period. This dose of NE was selected on the basis of previous experiments which demonstrated a moderate hypertensive effect and uniform pathologic changes (4, 5). Measurements of left ventricular and femoral artery pressure, cardiac output and arterial blood pH and oxygen saturation (4) were made before NE infusion, at 15 minutes and 1, 2, 3 and 4 hours during the infusions. The peripheral vascular resistance (PVR), left ventricular minute work (MW) and stroke work (SW) were calculated from the pressure and flow data. Autopsy examinations with particular attention to the cardiovascular system were performed on all animals within 15 minutes after the end of the infusion. A minimum of two blocks of tissue from each of the atria and ventricles and from the interventricular septum were used to prepare no less than 20 paraffin and frozen sections from each area. The paraffin sections were stained with hematoxylin and eosin and with acid fuchsin (7). Frozen sections cut on a cryostat were stained with oil red 0 for lipid, and by the tetrazolium method for lactic and succinic dehydrogenase (8).

Five groups of alpha- and beta-receptor blocking experiments were carried out (groups I-V). The hemodynamic and pathologic data from the previously reported studies in which NE was infused at the same rate (4, 5) are included as group VI so that the reader can more easily make comparisons between the effects of NE with and without adrenergic blockade (Table 1). Control hemodynamic measurements were made before adrenergic blockade, and baseline values were obtained after blockade but before beginning the 4-hour NE infusions. Phenoxybenzamine was administered in a single intravenous dose, 1 mg/kg, before either NE or dextrose infusion. Propranolol was given intravenously at an initial dose of 0.25 mg/kg, and at subsequent doses of 0.125 mg/kg, at hourly intervals throughout the 4-hour infusions.

These doses of the adrenergic blocking agents were selected on the basis of a few preliminary experiments. Phenoxybenzamine, 1 mg/kg, iv, prevented any increase in peripheral vascular resistance to challenging infusions of 4 μg·kg⁻¹·min⁻¹ NE. An initial dose of propranolol, 0.25 mg/kg, was selected because it produced an effective chronotropic block to sustained NE infusions. When similar hourly follow-up doses of propranolol were administered, the animals survived less than 2 hours during the NE infusion. For this reason, the hourly propranolol doses were reduced in half, i.e., to 0.125 mg/kg. Even then, three of seven group II dogs died between the third and fourth hour of NE administration.

**Results**

**HEMODYNAMIC DATA (TABLES 1 AND 2)**

During NE infusion alone (group VI), a progressive and significant increase in left ventricular end-diastolic pressure (LVEDP), heart rate and peripheral vascular resistance ensued and the cardiac output and minute and stroke work were significantly reduced without appreciable change in systemic pressure (4). When the alpha receptors were blocked (group I), the only significant hemodynamic change after 4 hours of NE infusion was an increase in heart rate. When beta receptors were blocked by previous treatment with propranolol (group II), infusions of NE produced significant increases in systemic pressure, LVEDP, and peripheral vascular resistance, and decreases in cardiac output, minute and stroke work, and heart rate. When NE was administered to animals in which both alpha and beta receptors were blocked, cardiac output and heart rate were diminished and peripheral vascular resistance was increased. No significant hemodynamic changes were observed in the control dogs whose alpha receptors were blocked, cardiac output and heart rate were diminished and peripheral vascular resistance was increased. Significant depression of cardiac function was evident in the control dogs whose beta receptors were blocked (group V).

The time course of the inter-relationship between left ventricular stroke work (LWSW) and LVEDP in all six groups is presented in Figure 1. In group II (beta-receptor block + NE) and group VI (NE), LWSW diminished and LVEDP increased progressively during the last 3 hours of the NE infusion. Beta-receptor blockade alone (group
SUSTAINED NOREPINEPHRINE INFUSION

**FIGURE 1**

Left ventricular stroke work (LVSW) in gram-meters/beat plotted against left ventricular end-diastolic pressure (LVEDP) in mm Hg for the six experimental groups. See text for drug dosage and details. The data for NE alone (group VI) are taken from a previous publication from this laboratory (4). C: control value; B: value after adrenergic blockade but before NE infusion; 15': 15 minutes of NE infusion; 1, 2, 3, and 4: the duration in hours of NE infusion. In group III, three of seven animals died between the third and fourth hour of NE infusion.

V) was associated with a progressive increase in LVEDP but without reduction in LVSW. In contrast, LVSW and LVEDP showed minimal change in groups I, III and IV animals throughout the 4-hour study.

Norepinephrine infusion in dogs whose
<table>
<thead>
<tr>
<th>Conditions and Times</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>LVEDP* (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Heart rate (beats)</th>
<th>PVRI $10^3$ dynes-sec/cm²</th>
<th>Minute work (kg·m/min)</th>
<th>Stroke work (g·m/beat)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I, alpha block + NE (5 dogs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>131 ± 11</td>
<td>4 ± 1.9</td>
<td>2.94 ± 1.1</td>
<td>135 ± 9</td>
<td>4.1 ± 1.1</td>
<td>3.50 ± 0.78</td>
<td>24.6 ± 6.6</td>
</tr>
<tr>
<td>After block</td>
<td>94 ± 11</td>
<td>5 ± 3</td>
<td>1.79 ± 0.4</td>
<td>150 ± 5</td>
<td>4.4 ± 0.5</td>
<td>2.87 ± 1.32</td>
<td>18.5 ± 3.7</td>
</tr>
<tr>
<td>15 min NE</td>
<td>102 ± 8</td>
<td>6 ± 2.0</td>
<td>3.29 ± 0.2</td>
<td>170 ± 14</td>
<td>2.5 ± 0.2</td>
<td>9.11 ± 1.80</td>
<td>51.8 ± 7.3</td>
</tr>
<tr>
<td>1 hr NE</td>
<td>108 ± 8</td>
<td>4 ± 2.0</td>
<td>2.68 ± 0.2</td>
<td>193 ± 5</td>
<td>3.3 ± 0.4</td>
<td>7.52 ± 1.24</td>
<td>38.2 ± 5.3</td>
</tr>
<tr>
<td>2 hr NE</td>
<td>108 ± 12</td>
<td>2 ± 1.2</td>
<td>2.56 ± 0.5</td>
<td>211 ± 23</td>
<td>4.0 ± 0.7</td>
<td>7.73 ± 1.05</td>
<td>37.0 ± 7.8</td>
</tr>
<tr>
<td>3 hr NE</td>
<td>119 ± 12</td>
<td>3 ± 1.1</td>
<td>2.55 ± 0.3</td>
<td>190 ± 14</td>
<td>3.8 ± 0.5</td>
<td>6.62 ± 0.63</td>
<td>34.8 ± 4.9</td>
</tr>
<tr>
<td>4 hr NE</td>
<td>110 ± 1.8</td>
<td>4 ± 1.7</td>
<td>2.29 ± 0.3</td>
<td>203 ± 111</td>
<td>4.0 ± 0.6</td>
<td>3.98 ± 1.10</td>
<td>19.9 ± 3.0</td>
</tr>
<tr>
<td><strong>Group II, beta block + NE (7 dogs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>106 ± 9</td>
<td>3 ± 1.5</td>
<td>2.42 ± 0.3</td>
<td>150 ± 10</td>
<td>3.9 ± 0.6</td>
<td>4.64 ± 0.77</td>
<td>26.0 ± 4.7</td>
</tr>
<tr>
<td>After block</td>
<td>109 ± 6</td>
<td>5 ± 1.4</td>
<td>2.24 ± 0.3</td>
<td>134 ± 6</td>
<td>4.5 ± 0.6</td>
<td>3.49 ± 0.28</td>
<td>25.0 ± 2.9</td>
</tr>
<tr>
<td>15 min NE</td>
<td>171 ± 9</td>
<td>9 ± 2.5</td>
<td>3.94 ± 0.4</td>
<td>120 ± 9</td>
<td>6.9 ± 1.2</td>
<td>6.21 ± 1.56</td>
<td>50.3 ± 8.1</td>
</tr>
<tr>
<td>1 hr NE</td>
<td>192 ± 12</td>
<td>11 ± 1.7</td>
<td>2.64 ± 0.8</td>
<td>111 ± 7</td>
<td>13.5 ± 3.2</td>
<td>5.01 ± 1.04</td>
<td>41.5 ± 11</td>
</tr>
<tr>
<td>2 hr NE</td>
<td>194 ± 10</td>
<td>9 ± 2.3</td>
<td>0.70 ± 0.1</td>
<td>130 ± 11</td>
<td>25.9 ± 3.5</td>
<td>5.31 ± 0.52</td>
<td>16.1 ± 3.4</td>
</tr>
<tr>
<td>3 hr NE</td>
<td>161 ± 14</td>
<td>15 ± 4.8</td>
<td>0.48 ± 0.1</td>
<td>128 ± 9</td>
<td>27.4 ± 2.7</td>
<td>1.19 ± 0.28</td>
<td>9.5 ± 3.0</td>
</tr>
<tr>
<td>4 hr NE</td>
<td>157 ± 29†</td>
<td>10 ± 2.0†</td>
<td>0.49 ± 0.11</td>
<td>119 ± 15†</td>
<td>20.6 ± 5.0†</td>
<td>1.61 ± 0.43†</td>
<td>8.6 ± 2.5†</td>
</tr>
<tr>
<td><strong>Group III, alpha and beta block + NE (5 dogs)</strong></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>147 ± 10</td>
<td>8 ± 3.5</td>
<td>3.50 ± 2</td>
<td>183 ± 10</td>
<td>3.2 ± 0.2</td>
<td>7.27 ± 0.87</td>
<td>37.5 ± 2.4</td>
</tr>
<tr>
<td>After block</td>
<td>120 ± 14</td>
<td>5 ± 1.6</td>
<td>2.31 ± 0.5</td>
<td>132 ± 5</td>
<td>4.5 ± 0.7</td>
<td>3.95 ± 0.96</td>
<td>25.5 ± 6.4</td>
</tr>
<tr>
<td>15 min NE</td>
<td>123 ± 12</td>
<td>7 ± 3.6</td>
<td>2.91 ± 0.1</td>
<td>153 ± 5</td>
<td>3.3 ± 0.4</td>
<td>6.29 ± 0.70</td>
<td>39.4 ± 5.3</td>
</tr>
<tr>
<td>1 hr NE</td>
<td>118 ± 13</td>
<td>5 ± 2.3</td>
<td>2.34 ± 0.3</td>
<td>138 ± 7</td>
<td>4.4 ± 0.9</td>
<td>4.21 ± 0.43</td>
<td>31.8 ± 4.6</td>
</tr>
<tr>
<td>2 hr NE</td>
<td>140 ± 10</td>
<td>6 ± 1.9</td>
<td>1.88 ± 0.4</td>
<td>119 ± 23</td>
<td>7.0 ± 3.9</td>
<td>4.17 ± 1.12</td>
<td>40 ± 10.2</td>
</tr>
<tr>
<td>3 hr NE</td>
<td>143 ± 15</td>
<td>4 ± 1.9</td>
<td>1.50 ± 0.2</td>
<td>109 ± 12</td>
<td>7.9 ± 1.2</td>
<td>3.90 ± 0.72</td>
<td>39.3 ± 7.7</td>
</tr>
<tr>
<td>4 hr NE</td>
<td>129 ± 6†</td>
<td>5 ± 3.9†</td>
<td>1.33 ± 0.11</td>
<td>118 ± 15†</td>
<td>8.8 ± 1.21</td>
<td>2.45 ± 0.23</td>
<td>18.6 ± 1.8</td>
</tr>
<tr>
<td><strong>Group IV, alpha block (4 dogs)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>130 ± 4</td>
<td>7 ± 25</td>
<td>2.75 ± 1.0</td>
<td>166 ± 9</td>
<td>3.1 ± 0.3</td>
<td>4.90 ± 0.61</td>
<td>35.5 ± 1.6</td>
</tr>
<tr>
<td>15 min</td>
<td>110 ± 17</td>
<td>7 ± 1.4</td>
<td>2.74 ± 0.4</td>
<td>130 ± 6</td>
<td>3.2 ± 0.5</td>
<td>4.07 ± 0.43</td>
<td>30.5 ± 2.9</td>
</tr>
<tr>
<td>1 hr</td>
<td>88 ± 4</td>
<td>5 ± 0</td>
<td>2.25 ± 0.1</td>
<td>130 ± 7</td>
<td>2.6 ± 0.4</td>
<td>3.72 ± 0.61</td>
<td>27.5 ± 3.4</td>
</tr>
<tr>
<td>2 hr</td>
<td>81 ± 6</td>
<td>9 ± 1.5</td>
<td>2.09 ± 0.1</td>
<td>111 ± 11</td>
<td>2.9 ± 0.2</td>
<td>2.75 ± 0.41</td>
<td>24.9 ± 2.4</td>
</tr>
<tr>
<td>3 hr</td>
<td>105 ± 15</td>
<td>9 ± 1.5</td>
<td>1.71 ± 0.4</td>
<td>118 ± 13</td>
<td>4.5 ± 0.3</td>
<td>2.24 ± 0.63</td>
<td>19.0 ± 3.9</td>
</tr>
<tr>
<td>4 hr</td>
<td>107 ± 19</td>
<td>7 ± 1.6</td>
<td>1.63 ± 0.4</td>
<td>115 ± 17</td>
<td>5.3 ± 0.5</td>
<td>2.50 ± 0.85</td>
<td>20.5 ± 4.5</td>
</tr>
</tbody>
</table>
alpha receptors were blocked (group I) produced a left ventricular systolic pressure which significantly exceeded systemic artery pressure during the first 2 hours of infusion. This was associated with a marked increase in myocardial oxygen demand (shaded area, Fig. 2). Onset of arterial hypotension occurred in all groups, but did not begin until after 2 hours of infusion. Sustained noradrenaline infusion (10 ng/kg.min) produced a marked increase in myocardial oxygen demand (shaded area, Fig. 2).

**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>6 ± 1.5</td>
<td>2.95 ± 0.19</td>
<td>145 ± 12</td>
<td>3.4 ± 3</td>
<td>5.38 ± 0.81</td>
<td>36.3 ± 6.8</td>
<td>33.0 ± 2.8</td>
</tr>
<tr>
<td>30 min</td>
<td>8 ± 3.5</td>
<td>3.38 ± 0.15</td>
<td>12 ± 9</td>
<td>4.2 ± 3</td>
<td>5.07 ± 0.42</td>
<td>33.6 ± 6.8</td>
<td>28.2 ± 2.8</td>
</tr>
<tr>
<td>1 hr</td>
<td>10 ± 2.0</td>
<td>1.98 ± 0.20</td>
<td>109 ± 10</td>
<td>4.9 ± 8</td>
<td>3.28 ± 0.42</td>
<td>29.8 ± 3.3</td>
<td>27.8 ± 4.1</td>
</tr>
<tr>
<td>2 hr</td>
<td>9 ± 2.2</td>
<td>1.60 ± 0.35</td>
<td>94 ± 5</td>
<td>5.4 ± 1.2</td>
<td>2.67 ± 0.40</td>
<td>29.8 ± 6.0</td>
<td>28.0 ± 6.0</td>
</tr>
<tr>
<td>3 hr</td>
<td>10 ± 2.0</td>
<td>1.38 ± 0.31</td>
<td>85 ± 4</td>
<td>5.6 ± 3.6</td>
<td>2.16 ± 0.43</td>
<td>24.0 ± 6.0</td>
<td>26.0 ± 6.0</td>
</tr>
<tr>
<td>4 hr</td>
<td>14 ± 2.4</td>
<td>1.28 ± 0.31</td>
<td>81 ± 8</td>
<td>3.5 ± 1.4</td>
<td>2.41 ± 0.23</td>
<td>26.5 ± 6.3</td>
<td>25.5 ± 6.3</td>
</tr>
</tbody>
</table>

All values are means ± SE. Noradrenaline dose was 4 μg/kg.min. *LVDEP = left ventricular end-diastolic pressure, PVR = peripheral vascular resistance. †Indicates significant (P < .05) change from control by paired sample analysis. ‡The data for Group VI (NE alone) are taken from a previous publication from this laboratory (4).
Alpha-receptor blockade followed by NE infusion (group I). Extensive subendocardial and intramyocardial hemorrhages are present in both the left and right ventricles, and there is slight ventricular dilatation.

FIGURE 3
Alpha-receptor blockade followed by NE infusion (group I). There is focal myofiber fatty degeneration. Oil red O stain × 100.

Alpha-receptor blockade followed by NE infusion (group I). Groups of myofibers show both a loss of lactic dehydrogenase and clumping of the enzyme in the form of coarse granules adjacent to the intercalated discs. Tetrazolium method for lactic dehydrogenase × 100.

Beta-receptor blockade followed by NE infusion (group II). Prominent biventricular dilatation is present and only slight focal subendocardial hemorrhage is evident.
TABLE 2
Systolic Pressures in the Left Ventricular Outflow Tract during Adrenergic Blockade and Norepinephrine (NE) Infusions

<table>
<thead>
<tr>
<th></th>
<th>Baseline LV*</th>
<th>2 hr NE System*</th>
<th>4 hr NE System*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (alpha block + NE)</td>
<td>117 ± 15</td>
<td>204 ± 37</td>
<td>135 ± 11</td>
</tr>
<tr>
<td>Group II (beta block + NE)</td>
<td>125 ± 5</td>
<td>216 ± 14</td>
<td>167 ± 36</td>
</tr>
<tr>
<td>Group III (alpha and beta block + NE)</td>
<td>118 ± 12</td>
<td>133 ± 14</td>
<td>150 ± 13</td>
</tr>
</tbody>
</table>

All values are means ± se, in mm Hg.
*LV = left ventricular systolic pressure (mm Hg); System = systemic arterial systolic pressure (mm Hg); †Significantly reduced below LVS when analyzed by paired sample analysis (P < .05).

TABLE 3
Arterial Blood pH Changes during Adrenergic Blockade with and without Norepinephrine (NE) Infusions

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline†</th>
<th>2 hr NE</th>
<th>4 hr NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (alpha block + NE)</td>
<td>7.39 ± .02</td>
<td>7.34 ± .02</td>
<td>7.33 ± .02</td>
</tr>
<tr>
<td>Group II (beta block + NE)</td>
<td>7.49 ± .03</td>
<td>7.39 ± .02</td>
<td>7.23 ± .04</td>
</tr>
<tr>
<td>Group III (alpha and beta block + NE)</td>
<td>7.38 ± .03</td>
<td>7.33 ± .03</td>
<td>7.36 ± .02</td>
</tr>
<tr>
<td>Group IV (alpha block)</td>
<td>7.44 ± .01</td>
<td>7.44 ± .01</td>
<td>7.39 ± .01</td>
</tr>
<tr>
<td>Group V (beta block)</td>
<td>7.42 ± .01</td>
<td>7.40 ± .01</td>
<td>7.39 ± .01</td>
</tr>
</tbody>
</table>

Values are means ± se. †After administration of blocking agents.

TABLE 4
Morphologic Changes in Animals Receiving Norepinephrine with Adrenergic Blockade

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiac dilation</th>
<th>Subendocardial hemorrhage</th>
<th>Myofiber degeneration</th>
<th>Adrenalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (alpha block + NE)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Group II (beta block + NE)</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Group III (alpha and beta block + NE)</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group IV (alpha block)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group V (beta block)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group VI (NE)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Grading scale: 0 = absent; + = slight; ++ = moderate; +++ = severe.

in mitochondrial size and staining, and loss of respiratory enzyme activity were present focially and to a slight degree in these three animals.

Adrenalitis characterized by extensive polymorphonuclear cell infiltration in the adrenal cortex was present in all cases in this group. No abnormal structural changes were seen in any other organs.

Group III.—The hearts from three animals in this group showed very slight focal

wall. In four cases this was of a moderate degree, in the other three it was slight. In all cases in this group (Fig. 5), the degree of subendocardial hemorrhage was less than that seen in group I animals. Microscopic sections showed subendocardial hemorrhage with slight focal intramural extension in five animals. Myofiber degeneration and necrosis of a slight focal nature were seen within areas of hemorrhage in three animals. Lipid droplet accumulation, a change
subendocardial hemorrhages in the left ventricle. None of the hearts appeared to be
dilated and there were no structural abnor-
malities of the myofibers on microscopic
examination. No evidence of adrenalitis was
found.

Groups IV and V.—The hearts from three
animals in each of these groups showed very
slight focal subendocardial hemorrhages in the
left ventricle. None of the hearts appeared to be
dilated and there were no structural abnor-
malities of the myofibers on microscopic
examination. The adrenals were normal.

Group VI.—Detailed pathologic examina-
tion has been presented in a previous report
(5). In summary, cardiac dilatation, subendo-
cardial hemorrhage, myofiber degeneration
and adrenalitis were present to a marked
degree.

Discussion
In previous investigations from this labora-
tory, the progressive decline in cardiac perfor-
mance during sustained NE infusions was
ascribed in large part to the myocardial lesions
produced by NE (4-6). These assumptions
could not be substantiated in the present set
of experiments in which we administered
selective adrenergic blocking agents before
NE infusion. The myocardial lesions of
subendocardial hemorrhage (myofiber necro-
sis and fatty myocellular degeneration) oc-
curred primarily during activation of beta
receptors by NE (group I: alpha-receptor
block + NE) when circulatory pressure and
flow were well maintained. Hemodynamic
abnormalities of decreased cardiac output and
minute and stroke work, and increased
LVEDP and peripheral vascular resistance
developed during activation of alpha receptors
by NE (group II: beta-receptor block + NE)
when only slight myofiber necrosis was
evident on histologic examination. These
circulatory disturbances in group II animals
were qualitatively similar to those observed
during unblocked NE infusions (group VI)
(4). These findings indicate that the circula-
tory disturbances produced by NE are not
necessarily a consequence of the histologic
changes in the heart muscle.

The protection of the myocardium from
extensive NE-induced pathologic changes by
propranolol is in agreement with the recent
report of Hoak et al. (9). In contrast, Nash
observed that the myocardial hemorrhage
produced by epinephrine was unaffected or
increased by propranolol (10). The discrepan-
cy between Nash’s results and ours may relate
to the different agents used in the two studies,
the total dose of agonist and antagonist given,
or the frequency of propranolol administra-
tion. Nash administered epinephrine, 10
µg • kg⁻¹ • min⁻¹, for 2 hours, and only one dose
of propranolol, 2 mg/kg, iv, at the onset of
epinephrine infusion. In the present study, we
administered 4 µg • kg⁻¹ • min⁻¹ of NE for 4
hours; an initial dose of propranolol was given
before the onset of NE infusion and was
followed by additional propranolol doses at
hourly intervals to a total dose of 0.625
mg/kg. Although a number of investigators
have observed some protection against cate-
cholamine-induced myocardial lesions with a
variety of alpha-receptor blocking agents (3,
11-15), the discrepancy in experimental de-
sign between these studies and the present
investigation makes any comparison difficult.

The adrenalitis that develops during sus-
tained NE infusions in the dog (5) is related
to the alpha adrenergic effects of NE that may
cause a local ischemia due to excessive
constriction of the adrenal vasculature. How-
ever, the extent of polymorphonuclear cell
infiltration of the adrenal cortex seems out of
proportion to the minor degree of cortical cell
nuclear pycnosis and cytoplasmic eosinophilia.
As yet, we have no adequate explanation for
this acute NE-induced change.

Complete beta-receptor blockade was not
obtained in this study. The increase in cardiac
output during the first hour of NE administra-
tion to the animals with beta-receptor block-
ade (group II) suggests incomplete inotropic
blockade. On the other hand, stability of the
heart rate below control values throughout the
4-hour NE infusion in group II indicates
effective blockade of the chronotropic effects
of NE. A higher propranolol dose was not
given because in preliminary experiments
larger doses did not allow completion of the 4-hour NE infusion (see Methods). Even at the dose of propranolol used, three of seven NE-infused animals with beta-receptor blockade (group II) died after the third hour of NE. These three animals had the highest LVEDP at the third hour of NE infusion.

Phenoxybenzamine produced effective alpha-receptor blockade in group I animals since the peripheral vascular resistance (PVR) did not increase during the 4-hour NE infusion. However, the increased PVR in group III (alpha and beta receptor + NE block) during the last 2 hours of NE infusion indicates incomplete alpha-receptor blockade. This effect may be due to an unmasking of alpha-receptor activity by beta-receptor blockade with propranolol (16). This mechanism may also explain the fact that PVR was augmented to a greater degree in group II (beta-receptor block + NE) than in group VI when NE was infused alone.

The mechanisms by which NE, or more particularly, the action of NE that is mediated through the beta receptors, produces its characteristic morphologic effects on the heart remain speculative. The lesions are similar to the morphologic abnormalities associated with sympathetic nerve stimulation (17) and isoproterenol (18). The subendocardial hemorrhage and the diffuse myofiber degeneration are two very distinctive lesions, and they may be mediated by entirely different mechanisms.

Subendocardial hemorrhage is due to capillary or venular rupture probably from mechanical causes. Gauer has postulated that NE produces a sustained isometric contraction which persists following initial ejection (19). If the heart volume is small, the subendocardial surfaces of the heart may contract against themselves, and the shearing and squeezing forces may produce a mechanical disruption of the delicate vascular channels. This postulation is supported by the observations in the present study. The subendocardial hemorrhage was most marked in the group I (alpha-receptor block + NE) animals which had a low LVEDP and developed a significant systolic pressure difference between the left ventricle and the systemic circulation. Aortic outflow tract pressure differences have also been observed during the administration of the pure beta-receptor agent, isoproterenol (20). This pressure difference, which was most marked in the second hour of NE infusion in the group I animals, suggests catheter entrapment in a small left ventricular cavity.

The myofiber degeneration during beta-receptor stimulation with NE suggests a biochemical rather than a mechanical muscular mechanism. The NE lesions are associated with accumulation of small lipid droplets within the myofiber and with loss of respiratory enzyme activity. An hypoxic mechanism with either an oxygen supply deficit or "oxygen wasting" has been postulated in the pathogenesis of the catecholamine-induced cardiac lesions (11, 21-23). The recent metabolic studies of Regan during epinephrine and norepinephrine infusions do not support an ischemic theory (24, 25). Furthermore, dissimilarities between catecholamine lesions (5, 9, 17, 18) and the morphologic (26) and biochemical (27) lesions of ischemic necrosis raise serious doubt about the traditionally postulated hypoxic mechanism. Enhanced triglyceride uptake by the myocardium during NE stimulation has been well documented (9, 25) and the lipid which accumulates within the myocellular elements may be a cause rather than a result of myofiber degeneration which ensues.

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Cardiovascular Effects of Sustained Norepinephrine Infusions in Dogs: IV. PREVIOUS TREATMENT WITH ADRENERGIC BLOCKING AGENTS
ARTHUR J. MOSS and ERIC A. SCHENK

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