Cardiovascular Effects of Sustained Norepinephrine Infusions.
I. Hemodynamics

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

In the past ten years sustained infusions of L-norepinephrine (NE) have been used in the treatment of cardiogenic hypotension. In many of the reports the poor results and low rates of survival have been attributed to the severity of the underlying myocardial disease. Detailed studies of the cardiovascular effects of NE have focused on the hemodynamic changes during acute infusions of this catecholamine. During these short-term infusions norepinephrine increased peripheral vascular resistance and exerted a positive inotropic effect upon the myocardium. The cardiovascular effects of prolonged NE infusion are less clearly defined. Excessive doses of catecholamines administered to experimental animals have produced diffuse myocardial destruction. The purpose of this study was to investigate the hemodynamic changes in the cardiovascular system during prolonged infusions of relatively physiologic doses of NE.

Methods

Nineteen mongrel dogs weighing 8 to 16 kg were anesthetized with sodium pentobarbital, 25 mg/kg, and given artificial respiration mechanically with room air through a cuffed endotracheal tube. In each dog the femoral artery (SA) and the femoral vein were cannulated; catheters were passed retrograde to the left ventricle (LV) and right atrium (RA) via the left carotid artery and right jugular vein, respectively. Pressures (mm Hg) were recorded from the SA, RA, and LV using Statham 23Db transducers connected to a multichannel Sanborn 350 recorder. Using an RC filter with a time constant of $5 \times 10^{-2}$ seconds in the recording amplifier of the LV channel, the LV catheter-transducer-recording system had a flat frequency response to 16 cycles/sec and a 20 db per decade cutoff above 20 cycles/sec. High sensitivity tracings of LV pressures were taken to measure left ventricular end diastolic pressure (LVED). The first derivative of LV pressure ($dLV/dt$) was recorded using an analog RC differentiating circuit with a time constant of $4.4 \times 10^{-5}$ seconds. Paired cardiac outputs were obtained by the indicator dilution technique using RA injections of indocyanine green and SA sampling. After each dilution curve the blood was reinfused. The peripheral vascular resistance (PVR), LV minute work (MW) and stroke work (SW) were calculated from the pressure and flow data. Circulating blood volumes were measured by the radioactive iodine ($\text{I}^{131}$) technique.

The 19 dogs were divided into four groups of 4 or 5 dogs each. Group I served as the control and these animals were infused intravenously with 40 cc of 5% dextrose and water for four hours. Groups II, III, and IV were infused intravenously with 1, 2 and 4 $\mu$g/kg/min of NE base, respectively, in a total volume of 40 cc of 5% dextrose and water for four hours using a constant infusion pump.

Left ventricular, SA and RA pressures, $dLV/dt$, lead II of the electrocardiogram (ECC) and indicator dilution cardiac outputs were recorded during the base line pre-infusion state, at 15 minutes and one, two, three, and four hours of the infusion. At these times, blood hematocrit, arterial blood pH and arterial oxygen saturation were also obtained on 13 of the 19 dogs studied (4 in group I, 2 in group II, 3 in group III and 4 in group IV). The $\text{I}^{131}$ blood volumes were measured during the base line period and at two, three, and four hours of infusion in 11 dogs. The blood gas and blood volume determinations during each four hour study required about 50 cc of blood, and this volume was replaced in each animal with normal saline.
Graph of the average percentage change in cardiac output, mean systemic pressure and the rate of rise of left ventricular pressure (dLV/dt) during the four-hour infusions of norepinephrine (NE). Pre-infusion value is 100%. Vertical hatched rectangles are the control groups (C), and the black, white, and stippled rectangles are the 1, 2, and 4 μg/kg/min NE infused groups, respectively.

At the conclusion of each study complete postmortem examinations were performed on each dog.9

Results

The hemodynamic findings in the control (group I) and NE infused (groups II, III and IV) animals are recorded in tables 1 and 2. A comparison of the percentage change in CO, SA and dLV/dt at the different infusion rates is presented in figure 1. Neither the hemodynamic parameters nor the electrocardiogram changed significantly in group I. In groups II, III, and IV the initial increase in SA, dLV/dt, CO, MW, and SW during the first 15 minutes of NE administration was not sustained, and a progressive dose-related decline in these parameters was observed during the remaining three and three-quarter hours of the infusion period. The right atrial mean pressure did not change significantly in any of the three groups during the NE infusion. In groups III and IV, electrocardiographic ST segment elevation, QRS amplitude diminution and Q wave abnormality developed within the first hour of NE infusion (fig. 2), and these electrocardiographic changes preceded the deterioration in cardiovascular dynamics. The effects of NE on the interrelationship between left ventricular SW and LVED are presented in
## TABLE 1

Hemodynamic Measurements During Control and Norepinephrine Infusions*

<table>
<thead>
<tr>
<th>Conditions and times</th>
<th>Mean systemic pressure</th>
<th>LVED†</th>
<th>dLV/dt†</th>
<th>Cardiac output</th>
<th>Heart rate</th>
<th>PVR†</th>
<th>Minute work</th>
<th>Stroke work</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>%</td>
<td>liters/min</td>
<td>beats/min</td>
<td>10^6 dyne • sec/cm²</td>
<td>kg • m/min</td>
<td>g • m/beat</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>base line</td>
<td>124 ± 7</td>
<td>2.2</td>
<td>100</td>
<td>2.12 ± .3</td>
<td>150 ± 12</td>
<td>4.9</td>
<td>.5</td>
<td>3.81 ± .67</td>
</tr>
<tr>
<td>15 min</td>
<td>124 ± 8</td>
<td>1.0</td>
<td>102 ± 2</td>
<td>2.11 ± .3</td>
<td>150 ± 10</td>
<td>4.9</td>
<td>.5</td>
<td>2.80 ± .67</td>
</tr>
<tr>
<td>1 hr</td>
<td>121 ± 9</td>
<td>1.6</td>
<td>106 ± 5</td>
<td>2.06 ± .3</td>
<td>151 ± 13</td>
<td>4.9</td>
<td>.4</td>
<td>3.68 ± .66</td>
</tr>
<tr>
<td>2 hr</td>
<td>112 ± 10</td>
<td>1.6</td>
<td>100 ± 8</td>
<td>2.14 ± .38</td>
<td>160 ± 19</td>
<td>4.7</td>
<td>.7</td>
<td>3.48 ± .74</td>
</tr>
<tr>
<td>3 hr</td>
<td>118 ± 11</td>
<td>2.0</td>
<td>108 ± 13</td>
<td>1.80 ± .35</td>
<td>153 ± 22</td>
<td>6.0</td>
<td>.9</td>
<td>3.05 ± .72</td>
</tr>
<tr>
<td>4 hr</td>
<td>127 ± 10</td>
<td>3.4</td>
<td>85 ± 21</td>
<td>1.80 ± .25</td>
<td>174 ± 20</td>
<td>6.0</td>
<td>.9</td>
<td>3.26 ± .60</td>
</tr>
<tr>
<td><strong>Norepinephrine, 1.0 µg/kg/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>base line</td>
<td>118 ± 7</td>
<td>5.7</td>
<td>100</td>
<td>1.52 ± .17</td>
<td>162 ± 5</td>
<td>6.3</td>
<td>.4</td>
<td>2.47 ± .40</td>
</tr>
<tr>
<td>15 min</td>
<td>100 ± 10†</td>
<td>7.3</td>
<td>169 ± 7†</td>
<td>2.18 ± .32</td>
<td>148 ± 9</td>
<td>6.3</td>
<td>.9</td>
<td>4.82 ± .82‡</td>
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<tr>
<td>1 hr</td>
<td>139 ± 8</td>
<td>5.0</td>
<td>160 ± 10</td>
<td>1.10 ± .42</td>
<td>157 ± 18</td>
<td>5.9</td>
<td>.24</td>
<td>1.99 ± .76</td>
</tr>
<tr>
<td>2 hr</td>
<td>125 ± 2</td>
<td>5.3</td>
<td>148 ± 14</td>
<td>1.33 ± .26</td>
<td>162 ± 21</td>
<td>8.8</td>
<td>.24</td>
<td>2.32 ± .49</td>
</tr>
<tr>
<td>3 hr</td>
<td>125 ± 9</td>
<td>4.5</td>
<td>153 ± 25</td>
<td>1.31 ± .29</td>
<td>176 ± 22</td>
<td>8.9</td>
<td>.21</td>
<td>2.37 ± .65</td>
</tr>
<tr>
<td>4 hr</td>
<td>121 ± 13</td>
<td>4.5</td>
<td>145 ± 26‡</td>
<td>1.21 ± .27</td>
<td>183 ± 22</td>
<td>9.3</td>
<td>.22</td>
<td>2.13 ± .63</td>
</tr>
</tbody>
</table>

*All values are mean ± standard error.

†LVED: left ventricular end diastolic pressure; dLV/dt: rate of rise of left ventricular pressure; PVR: peripheral vascular resistance; NE: norepinephrine.

‡Indicates a significant (P < 0.05) change of the 15-minute and 4-hour values from the base line reading.
### TABLE 2

**Hemodynamic Measurements During Norepinephrine Infusion**

<table>
<thead>
<tr>
<th>Conditions and times</th>
<th>Mean systemic pressure</th>
<th>LVED+</th>
<th>dLV/dt+</th>
<th>Cardiac output</th>
<th>Heart rate</th>
<th>PVR+</th>
<th>Minute work</th>
<th>Stroke work</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Norepinephrine, 2 µg/kg/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>base line</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>%</td>
<td>liters/min</td>
<td>beats/min</td>
<td>10^6 dyne • sec/cm²</td>
<td>kg • m/min</td>
<td>g • m/beat</td>
</tr>
<tr>
<td>137 ± 13</td>
<td>5.4 ± 1.1</td>
<td>100</td>
<td>2.37 ± 0.36</td>
<td>180 ± 18</td>
<td>5.4 ± 1.5</td>
<td>4.37 ± 0.50</td>
<td>24.6 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>174 ± 24</td>
<td>6.5 ± 1.6</td>
<td>185 ± 13†</td>
<td>3.29 ± 0.46</td>
<td>158 ± 21</td>
<td>5.0 ± 1.3</td>
<td>8.20 ± 2.0†</td>
<td>55.6 ± 9.1†</td>
</tr>
<tr>
<td>1 hr</td>
<td>165 ± 9</td>
<td>6.0 ± 0.8</td>
<td>175 ± 9</td>
<td>2.43 ± 0.52</td>
<td>157 ± 10</td>
<td>6.8 ± 1.8</td>
<td>5.34 ± 0.98</td>
<td>34.5 ± 5.8</td>
</tr>
<tr>
<td>2 hr</td>
<td>143 ± 10</td>
<td>4.8 ± 1.7</td>
<td>160 ± 15</td>
<td>1.72 ± 0.39</td>
<td>156 ± 9</td>
<td>9.6 ± 3.8</td>
<td>3.46 ± 0.88</td>
<td>23.0 ± 6.1</td>
</tr>
<tr>
<td>3 hr</td>
<td>132 ± 8</td>
<td>6.0 ± 1.4</td>
<td>137 ± 14</td>
<td>1.29 ± 0.27</td>
<td>176 ± 13</td>
<td>11.5 ± 3.7</td>
<td>2.36 ± 0.55</td>
<td>13.9 ± 3.7</td>
</tr>
<tr>
<td>4 hr</td>
<td>122 ± 8</td>
<td>6.4 ± 0.87</td>
<td>123 ± 12†</td>
<td>1.27 ± 0.29</td>
<td>180 ± 9</td>
<td>11.6 ± 3.9</td>
<td>2.01 ± 0.45†</td>
<td>11.4 ± 2.7‡</td>
</tr>
<tr>
<td><strong>Norepinephrine, 4 µg/kg/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>base line</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>%</td>
<td>liters/min</td>
<td>beats/min</td>
<td>10^6 dyne • sec/cm²</td>
<td>kg • m/min</td>
<td>g • m/beat</td>
</tr>
<tr>
<td>127 ± 3</td>
<td>6.0 ± 1.0</td>
<td>100</td>
<td>2.52 ± 0.20</td>
<td>146 ± 4</td>
<td>4.2 ± 0.3</td>
<td>4.40 ± 0.39</td>
<td>30.2 ± 3.1</td>
<td></td>
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<tr>
<td>15 min</td>
<td>155 ± 8‡</td>
<td>12.0 ± 1.4‡</td>
<td>184 ± 14‡</td>
<td>3.73 ± 0.27‡</td>
<td>136 ± 11</td>
<td>3.6 ± 0.3</td>
<td>7.32 ± 0.38‡</td>
<td>57.2 ± 7.7‡</td>
</tr>
<tr>
<td>1 hr</td>
<td>144 ± 3</td>
<td>11.6 ± 3.1</td>
<td>140 ± 15</td>
<td>2.31 ± 0.43</td>
<td>164 ± 9</td>
<td>5.7 ± 0.9</td>
<td>4.42 ± 0.87</td>
<td>27.6 ± 6.5</td>
</tr>
<tr>
<td>2 hr</td>
<td>128 ± 5</td>
<td>11.8 ± 3.8</td>
<td>127 ± 18</td>
<td>1.39 ± 0.21</td>
<td>185 ± 8</td>
<td>8.2 ± 1.3</td>
<td>2.29 ± 0.34</td>
<td>12.6 ± 2.2</td>
</tr>
<tr>
<td>3 hr</td>
<td>121 ± 5</td>
<td>11.2 ± 2.8</td>
<td>116 ± 13</td>
<td>1.01 ± 0.17</td>
<td>210 ± 5</td>
<td>10.7 ± 1.9</td>
<td>1.56 ± 0.25</td>
<td>7.5 ± 1.1</td>
</tr>
<tr>
<td>4 hr</td>
<td>101 ± 13</td>
<td>14.6 ± 3.2‡</td>
<td>93 ± 14</td>
<td>0.95 ± 0.18‡</td>
<td>210 ± 12‡</td>
<td>10.0 ± 2.0‡</td>
<td>1.15 ± 0.20‡</td>
<td>5.3 ± 0.7‡</td>
</tr>
</tbody>
</table>

*All values are mean ± standard error.
†Same as on table 1.
‡Indicates a significant (P < 0.05) change of the 15-minute and 4-hour values from the base line reading.
Electrocardiographic changes (lead II) during a four-hour, 4 μg/kg/min infusion of norepinephrine (NE). A bradycardia develops during the first 15 minutes, and thereafter a progressive tachycardia ensues. Within the first hour, the QRS amplitude diminishes, Q-wave abnormalities develop and there is slight elevation of the ST segment. Thereafter, the ST segment becomes isoelectric and T-wave inversion develops. Paper speed 50 mm/sec.

Figure 2

Electrocardiographic changes (lead II) during a four-hour, 4 μg/kg/min infusion of norepinephrine (NE). A bradycardia develops during the first 15 minutes, and thereafter a progressive tachycardia ensues. Within the first hour, the QRS amplitude diminishes, Q-wave abnormalities develop and there is slight elevation of the ST segment. Thereafter, the ST segment becomes isoelectric and T-wave inversion develops. Paper speed 50 mm/sec.

Discussion

The augmented cardiac performance observed within the first 15 minutes of NE infusion was not sustained with any of the three dose rates employed in this study. With continued NE infusion the mean arterial pressure returned to, or was slightly below, the control level. The magnitude of the decline in cardiac output below the pre-infusion value was related to the dose rate of NE infused. At the two highest doses of NE (2 and 4 μg/kg/min), left ventricular function declined after the first hour, and deteriorated progressively thereafter with a decrease in left ventricular MW and SW below base line values. The rate of rise of LV pressure did not decline below base line values during the NE infusion. This dissociation in the performance characteristics of the LV as evaluated by classical LV function curves and by dLV/dt¹⁰ is unexplained.

The processes which lead to hypotension, low cardiac output and left ventricular dysfunction during sustained NE infusions are complex. During the first 15 minutes of NE infusion, the cardiac output increased to a relatively greater degree than the mean systemic pressure, and the calculated PVR declined. However, after the first hour of NE infusion a progressive dose-related increase in the PVR was noted. The development of the increasing PVR was related in time to a progressive decline in cardiac output and a
SUSTAINED NOREpinephrine INFUSIONS

FIGURE 3

Left ventricular stroke work (SW) in gram meters/beat is plotted against left ventricular end diastolic pressure (LVED) for the control, and the three norepinephrine (NE) infused groups. B: base line value; 15': 15 minutes of NE infusion; 1, 2, 3, and 4: the duration, in hours, of NE infusion. At the two highest dose rates of NE infusion, there is a progressive deterioration in cardiac function with diminished SW at the same or an increased LVED.

deterioration in left ventricular function. These findings are similar to the results of others using higher dose rates of NE.\textsuperscript{11-13}

A vasodepressor state with a decline in PVR due to NE tachyphylaxis\textsuperscript{14} or release of a vasodepressor substance\textsuperscript{15,16} was not observed in this study.

With prolonged and sustained arteriolar vasoconstriction, organ perfusion diminishes and tissue hypoxia develops.\textsuperscript{17} In sepsis from gram negative bacteria, endotoxin potentiates the pressor response of catecholamines,\textsuperscript{18} and the resultant vasoconstriction and the ischemic hypoxia are thought to be key factors in the development of shock.\textsuperscript{19} Metabolic acidosis which develops during tissue hypoperfusion may also depress cardiac contractility,\textsuperscript{20} but this point is controversial.\textsuperscript{21} Moderate acidosis (pH 7.27 to 7.30) was observed in two of the control animals during the four-hour anesthesia period without significant hemodynamic consequences. In the animals receiving NE, marked acidosis (pH < 7.20) developed in two of nine dogs in which the pH was measured. In these two animals the acidosis developed during the third and fourth hours of the high dose NE infusion. This extreme acidosis may have contributed to the hemodynamic deterioration observed since the degree of cardiovascular impairment was slightly more marked in the more acidotic animals. Other investigators, however, have noted that correction of the acidosis associated with NE infusion does not improve cardiovascular dynamics.\textsuperscript{11}

Lillehei\textsuperscript{19} pointed out that circulatory hypovolemia may develop during hypotension due to sepsis from gram negative bacteria, and he postulated excess catecholamine release as a possible etiologic factor in this condition. In the present study the change in the blood volume in the control and NE infused groups during the four-hour infusion periods was very variable. Sustained hypovolemia was not
documented during the NE infusions, and the increase in LVED during the later periods of high dose NE infusion is further evidence against a significant hypovolemic state. Since the whole blood hematocrit increased within the first 15 minutes of NE infusion, and remained elevated throughout the duration of the infusion, it must be concluded that in the absence of a hypovolemic state the circulating red cell mass increased. The probable explanation for this augmented erythrocyte volume is the splenic release of red cells by NE stimulation. The diminution in the calculated plasma volume may reflect an increase in the postcapillary to precapillary resistance ratio with a transudation of fluid from the vascular compartment. Although viscosity was not measured, it must have increased in association with the augmented hematocrit. This viscosity factor would further reduce tissue perfusion in association with the augmented PVR.

Arterial desaturation was observed in some of the animals in both the control and NE infused groups despite mechanical ventilation. The desaturation probably reflects venous admixture through hypoventilated atelectatic segments. Since the control and NE infused animals were ventilated in like manner, and since the degree of desaturation was similar in both groups, the hemodynamic and pathologic findings observed with NE can not be attributed to the arterial desaturation per se. However, since tissue hypoxia may complicate catecholamine induced vasocnstriction, co-existing arterial desaturation may further compound the tissue hypoxia and may contribute to the development of more severe acidosis observed in high dose NE animals.

The electrocardiographic changes during the NE infusion indicated a significant and progressive deterioration in electrical activity of the myocardium. In addition, throughout the NE infusion there was a progressive dose-related release of lactic dehydrogenase from the heart. As pointed out in an accompanying paper, the gross and microscopic findings in the hearts of these animals at autopsy revealed cardiac hemorrhages related to NE dosage, focal myofiber loss of oxidative enzyme activity and lipid accumulation, and myocellular necrosis. These myocardial lesions may account in large part for the low cardiac output that develops during sustained NE infusions.

Myocardial lesions have been observed with NE infusions by other investigators, but very large doses of NE have been used and a limited number of cardiac parameters have been measured. A more physiologic dose range of NE doses was used in the present study. Preliminary experiments revealed that a 0.5 µg/kg/min NE dose rate produced a negligible change in cardiovascular dynamics. On the basis of these findings, the lowest dose rate selected for study was 1.0 µg/kg/min and increments at two and four times this concentration were also investigated. Although these dose rates are larger than those usually employed clinically, they are not excessive in the dog when viewed in terms of species sensitivity.

The mechanisms responsible for the production of the myocardial lesions and the associated cardiac dysfunction can only be speculated upon at the present time. Norepinephrine increases the demand for oxygen by the myocardium. The myocardial oxygen supply may be augmented either by increasing the oxygen extraction across the coronary arterio-venous circuit, or by increasing coronary flow, or by a combination of both mechanisms. Since the myocardial oxygen extraction is almost maximal at rest, any augmentation in myocardial oxygen supply depends largely on an increase in coronary flow. During acute NE infusions calculated coronary resistance changes little or not at all, and the coronary flow is directly proportional to the systemic artery pressure. During sustained NE infusions, the initial increase in systemic pressure is not maintained and coronary flow and myocardial oxygen supply may decline as the pressure falls to pre-infusion values. However, NE stimulation of the myocardium increases the demand for oxygen, and this effect is inde-
pendent of the external cardiac work performed. The sustained increase in dLV/dt during prolonged NE infusions suggests continued adrenergic stimulation and, in all probability, a sustained increase in the myocardial oxygen requirement. Thus, prolonged NE infusions may produce a dissociation between myocardial oxygen supply and demand, and the end result of this sequence of events appears to be the development of hypoxic myocardial lesions and cardiac dysfunction.

**Summary**

Norepinephrine (NE) in graded doses of 1, 2, and 4 μg/kg/min was infused for four hours into 14 dogs; 5 dogs served as controls. The systemic pressure and flow, blood volume, hematocrit, arterial blood pH, and oxygen saturation were measured at selected intervals throughout the infusion period. Cardiovascular performance was augmented during the first 15 minutes of the NE infusions, but this effect was not sustained. Thereafter, there was a dose-related decline in cardiac output, systemic pressure and left ventricular work, and an increase in the calculated peripheral vascular resistance. At the highest NE dose rate employed, significant left ventricular failure developed by the second hour of NE administration. The hematocrit increased during the first 15 minutes of NE infusion and remained elevated throughout the infusion period. Sustained hypovolemia was not found during the prolonged NE administration, and severe acidosis (pH < 7.20) was inconstant. The processes which lead to cardiovascular dysfunction during prolonged NE infusion are discussed.

**References**

18. GOURZIS, J. T., HOLLENBERG, M. W., AND NICKERSON, M.: Involvement of adrenergic


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