Effects of Nylidrin, Isoproterenol and Phenoxybenzamine on Dogs Subjected to Hemorrhagic Shock

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ABSTRACT

The effects of beta-adrenergic receptor stimulants (nylidrin and isoproterenol) on the hemorrhagic shock state of anesthetized dogs were measured and compared to those of phenoxybenzamine to determine the therapeutic effectiveness of the combined cardiac stimulatory and peripheral vasodilatory actions of the former drugs. Anesthetized dogs were subjected to 3 hours of hypovolemia followed by the return of the shed blood. Nylidrin, isoproterenol (continuous infusion), and phenoxybenzamine were administered 1 hour after bleeding the animals and heart rate, arterial blood pressure, venous hematocrit, coronary blood flow, cardiac output, ventricular contractility, and survival rates were measured. Nylidrin and isoproterenol afforded significant protection against shock deaths, whereas phenoxybenzamine did not increase survival over control values. Mild to moderate intestinal hemorrhage and distention were noted in the isoproterenol- and phenoxybenzamine-treated animals, but not in the nylidrin-treated animals. Phenoxybenzamine gradually decreased the arterial blood pressure and additional quantities of blood had to be infused to maintain cardiac output and blood pressure. Ventricular contractile force progressively decreased in the phenoxybenzamine-treated animals, whereas isoproterenol and nylidrin enhanced the force of ventricular contractions. In the presence of existing hypotension, isoproterenol and nylidrin maintained cardiac output. These agents deserve further consideration as potentially useful therapeutic agents in the management of shock states.

ADDITIONAL KEY WORDS

hypovolemic shock survival rates intestinal necrosis

ventricular contractility bleeding volumes cardiac output
concomitant positive inotropic and chronotropic effects on the myocardium and peripheral vasodilation occurs. By directly augmenting cardiac contractility and cardiac output, the beta-receptor stimulants may have therapeutic advantages over other agents currently employed in the management of shock states. Because of this, we measured the effects of isoproterenol and nylidrin on the course of hemorrhagic shock in dogs and compared these with the effects of phenoxybenzamine, an alpha-receptor blocking agent.

**Methods**

**HEMORRHAGIC SHOCK AND DRUG PRETREATMENT**

Mongrel dogs of either sex weighing from 9 to 14 kg were fasted for 24 hours prior to each experiment and anesthetized with sodium pentobarbital (35 mg/kg, i.v.). Hemorrhagic shock was induced by modification of the methods of Lampson and DeTurk (6). In animals used to evaluate survival from hemorrhagic shock, an endotracheal tube was inserted to insure an open-air passage; the trachea was cannulated in animals used in acute experiments. The femoral artery was catheterized for recording blood pressure, using a Statham pressure transducer (P23AC) and a Model 5 Grass polygraph. The ipsilateral femoral vein was catheterized for injections and for subsequent transfusion of the withdrawn blood. The other femoral vein was catheterized with polyethylene tubing (PE 320) for withdrawal of blood. The shock state was induced by withdrawing blood into an open, elevated glass reservoir, the height of which could be adjusted to maintain the animal's blood pressure at any desired level. The animals were heparinized (5 mg/kg, i.v.) before bleeding, and an additional 1.0 mg/kg was added to the reservoir. Nylidrin, 0.75 mg/kg, i.v., or an equal volume of saline was administered intravenously one-half hour before bleeding the dog. Respiratory rate was measured by a thermocouple inserted in the tracheal cannula. Pulse rate was counted from the arterial blood pressure tracing, recorded at a speed of 25 mm/sec.

The following procedure was patterned after that described by Gourzis et al. (7). Irreversible hemorrhagic shock was accomplished by bleeding the dog over a 10-min period until the mean arterial pressure was 40 mm Hg and maintaining the pressure at this level for 1.5 hours. At the end of this time, the connection between the dog and the blood reservoir was clamped for a 2-hour period. If the mean pressure began to drop below 40 mm Hg, small transfusions were instituted to prevent complete cardiovascular collapse. At the end of the 2-hour period, the blood remaining in the reservoir was transfused into the animal via the femoral vein and the incisions were closed. The volume of blood withdrawn to lower mean arterial pressure to 40 mm Hg was recorded as the initial bleeding volume (IBV). The maximum volume of blood withdrawn during the shock-inducing procedure was recorded as the maximum bleeding volume (MBV). Arterial blood pressure and cardiac and respiratory rates were recorded throughout the shock-inducing procedure and up to one-half hour after transfusion of the shed blood. Animals alive after 24 hours were classified as survivors.

Statistical analysis used to determine significance of survival from hemorrhagic shock was done by the chi-square method. Student's t test was used to determine the significance of bleeding volumes, blood pressures, and heart rates.

**HEMORRHAGIC SHOCK AND INTERMEDIATE DRUG TREATMENT**

The animals in this series of experiments were initially prepared as previously described; however, the procedure was modified after that described by Zingg et al. (3) for the intermediate administration of hypotensive agents without excessive fluid replacement. The animal was rapidly bled to a mean arterial pressure of 40 mm Hg within 5 min and pressure was recorded as 40 min. Over the next 15 min, the mean arterial pressure was elevated to 70 mm Hg by reinfusion of a small quantity of blood; and the connection between the dog and reservoir clamped for a 2-hour period after which the withdrawn blood was reinfused to the animal. If the mean arterial pressure began to drop below 40 mm Hg, small quantities of blood were returned to the animal. The volume of blood withdrawn immediately before the clamp period was recorded as MBV. The same measurements were recorded as described in the previous section except that femoral venous hematocrits were also determined.

The drugs or an equal volume of saline were administered intravenously 1 hour after bleeding the dog (immediately following the clamping of the connection between the dog and the reservoir). The control animals received saline and the drug-treated animals received either isoproterenol (0.5 μg/kg per min, i.v.) continuously perfused during the 2-hour clamp period, nylidrin (0.5 mg/kg, i.v.) administered over a 15-min period, or phenoxybenzamine (0.1 mg/kg, i.v.). Isoproterenol was administered in a volume of 0.5 ml/min using a Sigmamotor pump (Model T8) to regulate the infusion rate.

**DETERMINATION OF CORONARY FLOW, CARDIAC OUTPUT, AND RIGHT VENTRICULAR FORCE DURING SHOCK**

Coronary flow, cardiac output, and force of...
right ventricular contractions were simultaneously
determined in another series of experiments
carried out at an intermediate point. The animals were
ventilated with 95% O_2-5% CO_2 using positive pres-
sure respiration (Mine Safety Appliance Respi-
rator) during implantation of the flo-probe and
strain gauge arch. The thoracic cavity was en-
tered at the left fourth intercostal space, using
an electrocautery to minimize bleeding. A
pericardium was incised and sutured to the chest
wall. The ascending aorta and a segment of
the left anterior descending coronary artery were
isolated and all extraneous tissue surrounding
them was removed to insure proper contact of
the vessels with the sensors of the flo-probe. A
2-mm flo-probe (Medicon M-4001) was placed
around the coronary artery and a 14-mm flo-
probe was placed around the aorta to determine
blood flow. A Walton-Brodie strain gauge arch
was sutured to the right ventricle to determine
force of contractions. The thoracic cavity was
closed, the pneumothorax was reduced, and the
animal was allowed to breathe air spontaneously.

Student's t test was used to evaluate the sig-
nificance of the data obtained.

For this group of animals, the dose of isopro-
ter enol was reduced to 0.25 \( \mu \)g/kg per min;
hower ever, cardiac arrhythmias were frequent and
3 animals died of ventricular fibrillation. The dose
of nylidrin was reduced to 0.35 mg/kg, i.v., and
was administered over a 15-min period (larger
doses produced a precipitous fall in blood pres-
sure necessitating fluid replacement to prevent
death). The dose of phenox ybenzamine was 0.1
mg/kg, i.v.

**Results**

**EFFECTS OF NYLIDRIN PRETREATMENT**

**Effects on Survival**

Nylidrin, administered one-half hour before
bleeding, produced a marked increase in sur-
vival \((P < 0.01)\) (Table 1). The IBV and
MBV did not differ significantly in the control
and nylidrin groups, which indicated that
both groups were subjected to the same de-
gree of stress. The time required to reach
the MBV in the control animals was less than
in the drug-treated animals.

Four fatalities occurred in the control group
during the clamp period, and data from these
animals were not included; death in these
animals apparently resulted from respiratory
arrest. In 5 of the control animals, up to 30% of
the withdrawn blood needed to be rein-
fused during the clamp period to maintain
the blood pressure at the desired level. In the
nylidrin group, blood had to be returned in only 2 animals; this was less than 10% of the
withdrawn volume.

**TABLE 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of animals (died or survived)</th>
<th>Initial bleeding volume (ml/kg ± SE)</th>
<th>Maximum bleeding volume (ml/kg ± SE)</th>
<th>Percent survival Before hemorrhage</th>
<th>Mean arterial blood pressure (mm Hg ± SE)</th>
<th>1/4 Hour after reinfusion of shed blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>2 S</td>
<td>35.7 ± 1.0</td>
<td>57.0 ± 7.0</td>
<td>20</td>
<td>125 ± 10</td>
<td>110 ± 15</td>
</tr>
<tr>
<td></td>
<td>8 D</td>
<td>36.0 ± 0.01</td>
<td>56.0 ± 1.5</td>
<td>131 ± 2</td>
<td>121 ± 7</td>
<td>109 ± 7</td>
</tr>
<tr>
<td>Nylidrin (0.75 mg/kg, iv)</td>
<td>9 S</td>
<td>35.5 ± 0.05</td>
<td>56.3 ± 1.0</td>
<td>90</td>
<td>110 ± 5§</td>
<td>98 ± 4§</td>
</tr>
<tr>
<td></td>
<td>1 D</td>
<td>33.0</td>
<td>57.5</td>
<td>115</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>6 S</td>
<td>54.6 ± 1.0</td>
<td>141 ± 5</td>
<td>30</td>
<td>127 ± 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 D</td>
<td>53.3 ± 0.1</td>
<td>138 ± 4</td>
<td></td>
<td>124 ± 5</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>7 S§</td>
<td>54.0 ± 1.7</td>
<td>148 ± 7</td>
<td>70</td>
<td>134 ± 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 D</td>
<td>54.3 ± 1.0</td>
<td>140</td>
<td></td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Nylidrin (0.5 mg/kg, iv for 2 hr)</td>
<td>13 S</td>
<td>55.1 ± 0.8</td>
<td>144 ± 5</td>
<td>93</td>
<td>110 ± 4§</td>
<td>110 ± 4§</td>
</tr>
<tr>
<td></td>
<td>1 D</td>
<td>50.0</td>
<td>130</td>
<td></td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Phenox ybenzamine</td>
<td>2 S§</td>
<td>27.0 ± 2.0</td>
<td>145 ± 3</td>
<td>20</td>
<td>134 ± 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 D</td>
<td>55.8 ± 1.2</td>
<td>138 ± 3</td>
<td></td>
<td>126 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

*Administered one-half hour before bleeding.
†Administered 1 hour after bleeding.
‡Two dogs died before the end of the procedure and are not included in this table.
§P < 0.05.

_Circulation Research, Vol. XX, February 1967_
Nylidrin pretreatment decreased the mean arterial blood pressure (Table 1) and markedly increased mean heart rate (Table 2) before hemorrhage. One-half hour after return of the shed blood, mean arterial blood pressure in the nylidrin-pretreated animals was significantly lower than in the control animals ($P < 0.05$), whereas mean heart rates ($P < 0.05$) were significantly elevated over predrug and control rates, thus indicating that the pharmacological effects of the compound still persisted.

**EFFECTS OF THE INTERMEDIATE ADMINISTRATION OF NYLIDRIN, ISOPROTERENOL, AND PHENOXYBENZAMINE**

**Effects on Survival**

Thirty per cent of the control animals, 20% of the phenoxybenzamine-treated animals ($P > 0.05$), 70% of the isoproterenol-treated animals ($P < 0.05$), and 93% of the nylidrin-treated animals ($P < 0.01$) survived the shock procedure (Table 1). The MBV did not differ significantly in the control and drug-treated animals which indicated that the animals were subjected to the same degree of stress. In the isoproterenol-treated animals, 2 died of ventricular fibrillation but there were no cardiac arrhythmias in those that survived. When larger doses of isoproterenol were used, cardiac arrhythmias were frequent; the effect of these doses on survival were not investigated. Two phenoxybenzamine-treated animals died during the hypotensive period and data from these animals were not included. Up to 50% of the shed blood was returned during the clamp period in most of the phenoxybenzamine-treated animals to maintain arterial pressure at 40 mm Hg; however, 24 hour survival rates were not increased. When larger doses of phenoxybenzamine were administered, correspondingly greater quantities of blood had to be returned to the animals. Since these experiments were designed to evaluate the effects of drugs on survival, allowing for only minimal fluid replacement during the hypotensive period, a small dose of phenoxybenzamine capable of producing adrenergic blockade (as measured by blockade of the epinephrine pressor effect) was utilized. Five of the control animals required the reinfusion of up to 30% of the shed blood to maintain arterial pressure during the clamp period.

### Mean Heart Rates (Beats/min ± SE) in Dogs Subjected to Hemorrhagic Shock

| Drug | No of animals died or survived | 0 | 3 | 3½
|------|-------------------------------|---|---|---
| **Prior Treatment†** | | | | |
| Saline | 2 S | 138 ± 4 | | | 147 ± 5 |
| 8 D | 148 ± 10 | | | | 123 ± 9 |
| Nylidrin | 9 S | 221 ± 6* | | | 181 ± 9§ |
| (0.75 mg/kg, iv) | 1 D | 210 | | | |
| **Intermediate Treatment‖** | | | | |
| Saline | 6 S | 203 ± 5 | 222 ± 6 | 159 ± 4 |
| 14 D | 199 ± 11 | 219 ± 8 | 163 ± 9 |
| Isoproterenol | 7 S | 206 ± 13 | 237 ± 15 | 164 ± 12 |
| (0.5 mg/kg per min, iv) | 3 D¶ | 210 | 240 | 150 |
| Nylidrin | 13 S | 196 ± 10 | 215 ± 7 | 150 ± 7§ |
| (0.5 mg/kg, iv) | 1 D | 190 | 210 | 180 |
| Phenoxybenzamine | 2 S | 205 ± 3 | 240 ± 4 | 174 ± 3 |
| (0.1 mg/kg, iv) | 8 D¶ | 207 ± 10 | 233 ± 10 | 187 ± 12 |

*Shed blood returned at this time.
†Administered one-half hour before bleeding.
‡Prior to hemorrhage.
§$P < 0.01$.
¶$P < 0.05$.
‖Administered 1 hour after bleeding.
¶Two animals died before termination of the shock procedure and are not included in this table.

*Circulation Research, Vol. XX, February 1967*
Evidence of intense vasoconstriction and tissue ischemia (patchy white streaks) and of congestion and necrosis are prominent features of the intestine of an animal in irreversible shock. The small intestine is dark in appearance, distended and hard, resulting from the accumulation of considerable quantities of fluid in the extravascular compartment. These intestinal changes were observed in the present experiments and were most severe in the control animals, which always had bloody diarrhea. Isoproterenol and phenoxybenzamine attenuated these intestinal changes but mild to moderate distention and hemorrhage were noted in all animals treated by these drugs. In addition, the veins of the phenoxybenzamine-treated animals were widely dilated. Nylidrin prevented the development of these gross pathological changes.

Effects on Mean Blood Pressure and Heart Rate

During the clamp period, mean heart rates did not differ significantly within the control, isoproterenol, nylidrin, or phenoxybenzamine groups, although mean heart rates in the isoproterenol and phenoxybenzamine groups were consistently higher than rates in the other two groups (Table 2). Nylidrin reduced the mean arterial blood pressure to approximately 40 mm Hg during the clamp period, whereas isoproterenol either increased pulse pressure or only slightly decreased the mean arterial pressure. Phenoxybenzamine produced a steady decline in mean arterial pressure and additional quantities of blood were required to maintain the pressure at 40 mm Hg. One-half hour after return of the withdrawn blood, mean arterial pressure was significantly lower in the nylidrin-treated animals (Table 1) \((P < 0.05)\) than in controls; heart rates in the nylidrin-\((P < 0.05)\) and phenoxybenzamine-\((P < 0.05)\) treated animals were significantly higher than rates in controls.

Effects on Venous Hematocrit

Throughout the shock procedure, hematocrits were significantly lower in the nylidrin group \((P < 0.05)\) than in the control animals (Table 3); hematocrits in the phenoxybenzamine and isoproterenol-treated animals were significantly lower than values in control animals only at the one-half hour period after drug administration.

### Table 3

<table>
<thead>
<tr>
<th>No of animals (died or survived)</th>
<th>Hours after hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Control (saline)</td>
<td></td>
</tr>
<tr>
<td>7 D</td>
<td>43.1 ± 3.6</td>
</tr>
<tr>
<td>Isoproterenol (0.5 mg/kg per min, iv)</td>
<td>47.9 ± 3.5</td>
</tr>
<tr>
<td>Nylidrin (0.5 mg/kg, iv)</td>
<td>42.3 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>40.5 ± 2.34</td>
</tr>
<tr>
<td></td>
<td>45.1 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>53.4 ± 2.9</td>
</tr>
<tr>
<td>Phenoxybenzamine (0.1 mg/kg, iv)</td>
<td>42.7 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>38.8 ± 1.8†</td>
</tr>
<tr>
<td></td>
<td>41.6 ± 1.5‡</td>
</tr>
<tr>
<td></td>
<td>51.1 ± 1.8§</td>
</tr>
<tr>
<td>6 D§</td>
<td>44.0 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>41.1 ± 3.0‡</td>
</tr>
<tr>
<td></td>
<td>47.1 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>54.1 ± 2.0</td>
</tr>
</tbody>
</table>

*Shed blood returned at this time.
†Drugs administered 1 hour after bleeding.
‡\(P < 0.05\).
§Two animals died during the clamp period and data from these animals were not used.
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TABLE 4
Mean Cardiac Output (ml/min ± se) in Dogs Subjected to Hemorrhagic Shock

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Weight (kg)</th>
<th>1</th>
<th>1½</th>
<th>3*</th>
<th>3½</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>9-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (saline)</td>
<td>596 ± 85   (45)</td>
<td>536 ± 139 (48)</td>
<td>550 ± 149 (42)</td>
<td>1088 ± 376 (74)</td>
<td></td>
</tr>
</tbody>
</table>

Isoproterenol (0.25 µg/kg per min, ivf)

| 3 | 9-12 | 540 ± 46 (45) | 551 ± 58 (47) | 509 ± 62 (39) | 940 ± 55 (70) |

Nylidrin (0.35 mg/kg, ivf)

| 6 | 10-14 | 603 ± 64 (42) | 762 ± 96 (56) | 788 ± 88 (58) | 1758 ± 194 (107) |

Phenoxybenzamine (0.1 mg/kg, ivf, §)

| 6 | 9-13 | 553 ± 58 (43) | 550 ± 120 (40) | 488 ± 130 (36) | 880 ± 350 (63) |

*Shed blood returned at this time.

†Drugs administered 1 hour after bleeding the animals.

‡P < 0.05.

§Approximately 50% of shed blood returned during clamp period to maintain cardiac output.

Numbers in parentheses = percent of prehemorrhage values.

TABLE 5
Coronary Blood Flow (ml/min ± se) in Dogs Subjected to Hemorrhagic Shock

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Hours after hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10.5 ± 2</td>
</tr>
</tbody>
</table>

Isoproterenol (0.25 µg/kg per min, ivf)

| 3 | 12.2 ± 1 | 15.8 ± 1 | 13.6 ± 2 | 17.3 ± 1 |

Nylidrin (0.35 mg/kg, ivf)

| 6 | 14.8 ± 2 | 22.0 ± 3* | 19.8 ± 28| 21.2 ± 4 |

Phenoxybenzamine (0.1 mg/kg, ivf)

| 6 | 12.5 ± 1 | 11.1 ± 1 | 8.0 ± 0.5| 15.3 ± 1 |

*Shed blood returned at this time.

†Drugs administered 1 hour after bleeding the animals.

‡P < 0.01.

§P < 0.05.

tain cardiac output at levels necessary for survival. One-half hour after return of the shed blood, cardiac output in the nylidrin-treated animals was significantly higher than in controls (P < 0.05) (Table 4).

Mean coronary flow in the nylidrin-treated animals was significantly increased over control values at the 1½- and 3-hour time intervals (P < 0.01) (Table 5). In the dogs treated with isoproterenol and phenoxybenzamine, coronary blood flow did not significantly increase during the period of hypovolemia but did increase sharply one-half hour after return of the shed blood.

Nylidrin and isoproterenol increased ventricular contractile force at 1½ (P < 0.01) and 3 hours (P < 0.01) after hemorrhage (Table 6), while contractility progressively decreased in the phenoxybenzamine-treated animals. One-half hour after return of the shed blood, ventricular contractility was still significantly increased in the nylidrin-treated animals as compared to contractility in the control animals (P < 0.01).
TABLE 6

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Hours after hemorrhage</th>
<th>Control (saline)</th>
<th>Isoproterenol (0.25 µg/kg per min, iv)</th>
<th>Nylidrin (0.35 mg/kg, iv)</th>
<th>Phenoxylbenzamine (0.1 mg/kg, iv)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>3/4</td>
<td>3</td>
<td>3½</td>
</tr>
<tr>
<td>6</td>
<td>+ 3 ± 8</td>
<td>− 7 ± 6</td>
<td>− 22 ± 10</td>
<td>− 17 ± 11</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+ 1 ± 7</td>
<td>+ 28 ± 5§</td>
<td>+ 32 ± 1§</td>
<td>− 13 ± 7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+ 5 ± 5</td>
<td>+ 34 ± 8§</td>
<td>+ 23 ± 4§</td>
<td>+ 32 ± 9§</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+ 6 ± 3</td>
<td>+ 13 ± 6</td>
<td>− 30 ± 6</td>
<td>− 11 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

*Percent change from prehemorrhage values ± SE.
†Shed blood returned at this time.
‡Drugs administered 1 hour after bleeding the animals.
§P < 0.01.

Discussion

The effects of drugs on physiological systems during hemorrhagic shock have been tested mainly in pretreated animals; this may not give a true indication of the effects of the drug on the shock state but rather a measure of drug-induced response of the physiological system to hemorrhage. After demonstrating protection with nylidrin pretreatment, the experimental design was altered to evaluate the effects of drug administration at an intermediate point on survival rates and on cardiovascular function in dogs subjected to hemorrhagic shock. For intermediate therapy, drugs were administered 1 hour after bleeding, since return of the shed blood at this time results in over 90% survival. Thus, drugs capable of delaying the development of the irreversible shock state should be effective if administered at this time in the shock procedure. The doses of the drugs employed in this study were selected so as to elicit the characteristic pharmacological effects of these agents and yet require minimal blood volume replacement.

Nylidrin pretreatment and intermediate treatment both provided marked protection against the lethal effects of hemorrhagic shock. Nylidrin maintained cardiac output during the period of hypovolemia and after return of the shed blood, and increased the coronary flow and ventricular contractile force throughout the period of hypovolemia. Nylidrin simultaneously decreases peripheral resistance and increases ventricular contractility; these combined peripheral and cardiac effects maintain an adequate circulating blood volume during hemorrhagic hypotension. In contrast, phenoxylbenzamine, a potent vasodilator without positive inotropic effects, did not maintain cardiac output when administered during hypovolemia, and additional quantities of blood had to be infused to prevent cardiovascular collapse.

It has been reported that maximal oxygen transport during hemorrhagic shock occurs in animals with hematocrits between 35 and 40 (8). Nylidrin maintained the hematocrit at approximately 40 throughout the period of hypovolemia.

The marked sympathetic discharge provoked by hypovolemia is thought to result in a decrease in flow through the peripheral microcirculation resulting in ischemia and subsequently necrosis and irreversible shock (9). The intestinal necrosis found in animals subjected to prolonged hypotensive periods indicates a marked reduction in the peripheral circulation. The small intestine was distended and bloody in the control animals; but not in the nylidrin-treated animals. These observations demonstrate that nylidrin prevents the progressive gastrointestinal deterioration associated with prolonged periods of hypovolemia and suggests that nylidrin maintains splanchnic blood flow.
Isoproterenol produced the same salutary effects on survival as did nylidrin, which suggests that protection probably results from cardiovascular effects mediated by beta-receptor stimulation. It is emphasized that there is no significant difference between the survival rates of the isoproterenol- or nylidrin-treated dogs. The increased survival rate in the isoproterenol-treated animals agrees with the results obtained by Pierce et al. (10) in animals with cardiogenic shock and by Vick et al. (11) in animals with endotoxin shock. Cardiac contractility was enhanced during the infusion of isoproterenol, again suggesting that the direct cardiac effects of the beta-receptor stimulants contribute significantly to maintaining cardiac output when these agents are administered in the presence of hypovolemia. Cardiac arrhythmias were frequent when higher doses of isoproterenol were employed and the potential cardiotoxic effects of this agent were manifest in the cardiovascular studies even though the dose was reduced. Higher doses of nylidrin did not induce cardiac arrhythmias, although fluid replacement was necessary to maintain the arterial pressure at the desired level. These results suggest that the electrocardiogram should be carefully monitored when isoproterenol is employed in the treatment of shock states. Since isoproterenol is such a potent cardiac stimulant, a more desirable hemodynamic pattern might have been obtained if the dose had been carefully titrated for each animal rather than employing a fixed dosage schedule. Moreover, initial clinical studies with this agent have been encouraging and cardiotoxic effects have not been reported (12).

Phenoxybenzamine pretreatment with doses of as little as 0.1 mg/kg have been reported to provide marked protection in animals subjected to hemorrhagic shock. This dose of phenoxybenzamine is capable of blocking the pressor effects of injected epinephrine. Conflicting results have been obtained when this agent is administered at an intermediate point in the shock procedure, perhaps reflecting differences in experimental design. In this study, the intermediate administration of phenoxybenzamine did not increase survival. Lotz et al. (13) found that the administration of phenoxybenzamine one-half hour after bleeding the animals increased survival; however, when it was administered 85 min after bleeding the animals and followed by return of the shed blood, it did not improve survival rates. In their procedure, the connection between the animal and blood reservoir was not clamped, and since it is known that hypotensive agents cause return of the shed blood to the animal, no comparison can be made with our results as they did not report the volume of blood taken up in those animals that survived. Lillehei et al. (9) reported that phenoxybenzamine, administered 30 to 60 min after the induction of endotoxin shock, did not improve survival unless accompanied by 25 ml/kg of plasma.

In our procedure, cardiac output and ventricular contractile force continued to decline after the administration of phenoxybenzamine, and up to 50% of the shed blood needed to be returned to prevent cardiovascular collapse. Several factors may contribute to the poor results obtained with phenoxybenzamine. It is known that even upon intravenous administration, the time required to produce complete adrenergic blockade is relatively long. Rather high doses of phenoxybenzamine are required to abolish the effects of sympathetic nerve stimulation and the doses required are much higher than those employed in most shock experiments. Since it is well established that phenoxybenzamine pretreatment provides marked protection against shock deaths, it may be assumed that pretreatment with this agent produces resistance to shock. For example, Nickerson (14) has found that the plasma volume is markedly increased in phenoxybenzamine-pretreated animals before the induction of shock. Also, its alpha-receptor blocking effects probably prevent the development of intense vasoconstriction in the peripheral vasculature during the hypovolemic period. The fact that ventricular contractile force remained below prehemorrhage values after return of the shed blood suggests that the simultaneous admin-
istration of cardiac stimulants might be used to insure normal cardiac functioning when phenoxybenzamine is employed in shock therapy. The beta-receptor stimulants are capable of maintaining cardiac output during hypovolemia and deserve further consideration as potentially useful therapeutic agents in the management of hemorrhagic hypotension.

Acknowledgment
The authors are indebted to Dr. B. S. Jandhyala for technical assistance in the various experiments.

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Effects of Nylidrin, Isoproterenol and Phenoxybenzamine on Dogs Subjected to Hemorrhagic Shock

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Circ Res. 1967;20:253-261
doi: 10.1161/01.RES.20.2.253

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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