The Effect of Adrenergic Blockade and Norepinephrine on Renal and Cardiovascular Hemodynamics Following Hemorrhage

By John H. Moyer, Carroll A. Handley, and Russell A. Huggins

Renal blood flow and other renal functions are depressed when the normotensive animal is made hypertensive by the administration of norepinephrine. By contrast, when the blood pressure is increased to normal with norepinephrine in the animal previously made hypotensive by hemorrhage, renal function and cardiac output increase.

Vasopressor agents produce renal vasoconstriction when administered to normotensive animals and man.1-4 Because of this vasoconstrictor activity, the question has been raised whether these agents might not actually be harmful5-7 to the kidney when used to elevate blood pressure for the treatment of shock. Observations made recently7,8 indicate that when renal and cerebral blood flow are markedly depressed due to hypotension resulting from ganglionic blocking agents, administering a vasopressor agent will actually increase blood flow to these vascular beds. Although the circumstances are not analogous to shock, these results do suggest a paradox since, when vasopressor agents are administered to normotensive subjects, and the blood pressure is raised to hypertensive levels, cerebral and renal blood flow are depressed. The current observations were made on dogs in order to determine whether the administration of vasopressor agents would increase renal blood flow in the presence of hypotension due to hemorrhage. Concurrent observations were made on cardiac output.

Since adrenergic blockade has been reported to decrease the mortality rate9,10 of experimental animals following hemorrhage, observations on the effect of adrenergic blockade on renal hemodynamics were made before and after hemorrhage.

Methods and Materials

Observations have been completed on 14 female dogs anesthetized with 30 mg. per kilogram of sodium pentobarbital administered intravenously. Dogs were divided into two groups. There were seven animals in group 1 in which the renal response to hemorrhage followed by norepinephrine was observed. Cardiac output studies were done on five of them. Creatinine was used to measure glomerular filtration rate (GFR) and para-aminohippurate (PAH), to measure renal plasma flow (RPF). Mean arterial blood pressure was measured directly with a mercury manometer as well as a Hamilton manometer in the five dogs on which cardiac outputs were estimated.11 Arterial blood for the analyses was collected through a manifold connected to an indwelling arterial needle. Except for minor modifications the techniques and analytic methods used in the renal studies have been previously described.12 Following suitable control observations (three successive 10-minute periods), animals were bled by the use of a graduated leveling reservoir until the mean blood pressure (determined by mercury manometer) was stabilized at 50 to 90 mm. Hg. Cardiac output and renal function studies were repeated during two consecutive 10-minute periods. These observations were designated as the first hemorrhage period (H1). The blood pressure was recorded every two minutes on each dog. There was some variation in blood pressure between the beginning of the period and the observations made 20 minutes later. Two of the animals (numbers 4 and 5), in which control blood pressures were particularly low, were bled until an amount of blood had been taken that was estimated (on the basis of

From the Department of Pharmacology, Baylor University College of Medicine, Houston, Tex.

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Following these observations a 1:100,000 solution of norepinephrine per minute. Observations were made during two successive 10-minute periods. Following these observations a 1:100,000 solution of norepinephrine was infused. The rate of infusion was adjusted so as to raise the blood pressure first to normotensive levels (V₁), which required 20 to 100 γ of norepinephrine per minute, and then to hypertensive levels (V₂), which required 100 to 300 γ of norepinephrine per minute. Observations were again made at each level of blood pressure during two successive 10-minute collection periods. Following these observations norepinephrine was discontinued. After a delay period of 15 to 20 minutes, observations on renal function were again made during two successive 10-minute periods. These observations are designated "C₄." All of the blood previously withdrawn from the dog was then replaced and four successive 10-minute clearance periods were obtained (designated T in tables). Cardiac outputs were estimated during each renal clearance period using the pulse contour method of Hamilton and Remington.¹

There were seven dogs in group 2. After three successive periods of control observation, similar to those on the dogs in group 1, five of the animals

### Table 1

**Effect of Hemorrhage Followed by Norepinephrine on Renal Hemodynamics (Group 1 Dogs)**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Mean Blood Pressure (mm Hg)</th>
<th>Renal Blood Flow* (ml/min)</th>
<th>Renal Vascular Resistance</th>
<th>Blood Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C, H₁, H₂, V₁, C₄, T</td>
<td>C, H₁, H₂, V₁, C₄, T</td>
<td>C, H₁, H₂, V₁, C₄, T</td>
<td></td>
</tr>
<tr>
<td>RH 1</td>
<td>155 92 50 90 154 116 157 417 214</td>
<td>319 176 284 201 0 45 0 120 29 25 8 0 20 0 25 0 44 1 20 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH 2</td>
<td>175 78 50 127 185 4 110 300 332 135</td>
<td>275 51 75 120 0 55 0 230 440 460 360 50 0 55 0 40 50 0 150</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>RH 3</td>
<td>156 76 50 100 150 56 110 165 49 20 45</td>
<td>181 95 150 200 0 22 0 50 0 20 0 100 0 40 0 20 0 20 0</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>RH 4</td>
<td>84 52 28 75 100 48 94 106 116</td>
<td>—— 50 52 —— —— —— —— —— —— —— —— —— 0 68 14 2 57</td>
<td>0 61 250 320</td>
<td></td>
</tr>
<tr>
<td>RH 5</td>
<td>78 54 48 100 185 50 115 185 167</td>
<td>19 155 20 120 180 72 0 40 0 32 0 230 0 60 0 40 0 61 178 220</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>141 92 71 126 145</td>
<td>150 118 161 112</td>
<td>61 20 113 110 0 70 0 68 2 0 7 7 25</td>
<td>11 13 000 350</td>
</tr>
<tr>
<td>7</td>
<td>131 105 65 131 175</td>
<td>146 145 155</td>
<td>74</td>
<td>106 68</td>
</tr>
<tr>
<td>Mean…</td>
<td>131 78 54 108 157 53</td>
<td>120 209 214 107 161</td>
<td>—— 152 0 71 0 60 1 12 1 16</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table 2

**Effect of Hemorrhage Followed by Norepinephrine or Blood Transfusion**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Glomerular Filtration Rate (ml/min)</th>
<th>Renal Plasma Flow (ml/min)</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C, H₁, H₂, V₁, C₄, T</td>
<td>C, H₁, H₂, V₁, C₄, T</td>
<td>C, H₁, H₂, V₁, C₄, T</td>
</tr>
<tr>
<td>RH 1</td>
<td>70 77 54 64</td>
<td>37 40</td>
<td>53 232 275 154</td>
</tr>
<tr>
<td>RH 2</td>
<td>84 66 25 68</td>
<td>16 20</td>
<td>38 241 239 104</td>
</tr>
<tr>
<td>RH 3</td>
<td>39 8 5 14</td>
<td>1 1</td>
<td>30 122 37 23</td>
</tr>
<tr>
<td>RH 4</td>
<td>43 3 0 0</td>
<td>0 0</td>
<td>0 19 113 1 0</td>
</tr>
<tr>
<td>RH 5</td>
<td>44 33 4 32</td>
<td>6 18</td>
<td>21 109 112</td>
</tr>
<tr>
<td>6</td>
<td>30 33 24 17</td>
<td>6</td>
<td>—— 35</td>
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<tr>
<td>7</td>
<td>42 26 12 40</td>
<td>21</td>
<td>—— 41 100</td>
</tr>
<tr>
<td>Mean…</td>
<td>50 36 20 34 12 18 34</td>
<td>142 125 62 104 34 72 108 32 31 27 26 25 25</td>
<td>30</td>
</tr>
</tbody>
</table>

% of Control: 72 40 68 24 36 68 88 44 73 24 51 76 97 84 51 78 78 94

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* Renal Plasma Flow

† Mean Blood Pressure

‡ Mean for only six observations

§ Observations not made

C—Control Observations (average of three periods).
H₁—After first hemorrhage.
H₂—After second hemorrhage.
V₁—Blood pressure returned to normotensive levels with norepinephrine.
V₂—Blood pressure increased to hypertensive levels with norepinephrine.
C₄—Second control period after the vasopressor agent was discontinued.
T—All blood replaced which was previously lost.
in group 2 were given an adrenergic blocking dose of Dibenzyline (phenoxybenzamine hydrochloride) (5 mg. per kilogram). After three successive renal clearance periods were completed the animals were bled until blood pressure was reduced to 50 to 60 mm. Hg; following which three renal clearance periods were again completed. The two remaining dogs in group 2 were bled (before administering Dibenzyline) similarly to the dogs in group 1 and renal clearance studies carried out. When the blood pressure had stabilized at 50 to 60 mm. Hg, they were given 5 mg. per kilogram of Dibenzyline in order to produce adrenergic blockade. Observations were then made on renal function. Because of the adrenergic blockade, norepinephrine was not administered to the animals in group 2 and cardiac output studies were not made.

RESULTS

The Effect of Hemorrhage and Norepinephrine on Renal Hemodynamics. Renal hemodynamic studies are presented in table 1. Following the initial hemorrhage, renal blood flow and glomerular filtration rate were with two exceptions (dogs 3, 4), not markedly depressed. After the second hemorrhage, the blood pressure was reduced further and both glomerular filtration rate and renal blood flow were depressed in all of the animals. Renal vascular resistance was increased in only about one-half of the animals. When norepinephrine was administered, both glomerular filtration rate and renal blood flow usually returned towards the control values but never completely reached it. When the blood pressure was increased to hypertensive levels, renal blood flow and glomerular filtration rate were markedly depressed (fig. 1). Renal function in the animals which were bled most severely apparently was not

![Diagram of renal hemodynamics](image)

**Fig. 1.** A comparison of the response to norepinephrine in a normotensive dog and one previously made hypotensive. When norepinephrine is infused into a normotensive dog, the blood pressure increases and renal plasma flow is depressed. As the rate of infusion is increased further, both glomerular filtration rate (GFR) and renal plasma flow (RPF) are depressed. Following blood loss in an incremental fashion, RPF is first depressed and then both GFR and RPF are depressed. When the blood pressure is increased to hypertensive levels both RPF and GFR are again depressed.
improved when the blood pressure returned to normotensive values. However, if the blood volume was partially restored, norepinephrine had a beneficial effect on renal function (fig. 2). The improvement in renal function was frequently associated with an increase in cardiac output when norepinephrine was given.

The effects on water and electrolyte excretion are presented in table 2. Following hemorrhage, water and sodium excretion were markedly depressed. This occurred without alteration in plasma sodium. When the norepinephrine was given, glomerular filtration rate increased as the blood pressure approached the control levels. This was associated with an increase in sodium and water excretion. However, this never approximated the control levels and when the blood pressure was raised above the control levels the excretion rates of water and electrolytes were again depressed.
**TABLE 3**

Effect of Dibenzyline on Renal Hemodynamic Response to Hemorrhage (Group 2)

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Mean Blood Pressure (ml/min.)</th>
<th>Renal Blood Flow (ml/min.)</th>
<th>Renal Vascular Resistance</th>
<th>Hematocrit</th>
<th>Blood Loss (ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>Bi</td>
<td>Bh1</td>
<td>Bh2</td>
<td>Ch</td>
</tr>
<tr>
<td>8</td>
<td>93</td>
<td>74</td>
<td>55</td>
<td>53</td>
<td>130</td>
</tr>
<tr>
<td>9</td>
<td>150</td>
<td>85</td>
<td>76</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>153</td>
<td>97</td>
<td>80</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>11</td>
<td>164</td>
<td>82</td>
<td>82</td>
<td>40</td>
<td>40</td>
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<tr>
<td>12</td>
<td>160</td>
<td>92</td>
<td>71</td>
<td>57</td>
<td>56</td>
</tr>
</tbody>
</table>

Mean... 134 86 77 55 54 146 | 175 165 137 140 1.00 | 0.52 | 0.49 | 0.40 | 0.40 | 36   | 36   | 32  | 30   | 296 |

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Glomerular Filtration Rate (ml/min.)</th>
<th>Renal Plasma Flow (ml/min.)</th>
<th>Filtration Fraction</th>
<th>TNF mg./min.</th>
<th>WT Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Bi</td>
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<td>12</td>
<td>33</td>
<td>38</td>
<td>32</td>
<td>27</td>
<td>24</td>
</tr>
</tbody>
</table>

Mean... 39 38 35 27 27 93 | 111 106 93 98 | 42 35 34 30 | 28 | 117 | 106 | 106 | 104 | 105 | 11.2 |

Effect of Hemorrhage Following Adrenergic Blockade

B1—First period (10 minutes) following adrenergic blockade with 5 mg/Kg. of Dibenzyline.
B2—Average of second and third 10-minute periods after adrenergic blockade.
BH1—Effect of blood loss following adrenergic blockade (first period).
BH2—Average of second and third periods after hemorrhage.
H1—First period after hemorrhage without adrenergic blockade.
H2—Average of second and third periods after hemorrhage prior to adrenergic blockade.
HB1—First period after adrenergic blockade in animal from which blood was previously taken.
HB2—Average of second and third periods after adrenergic blockade in animal from which blood was previously taken.

The renal hemodynamic response to blood pressure reduction with adrenergic blockade and adrenergic blockade plus hemorrhage is presented in Table 3. Blood pressure reduction by adrenergic blockade did not alter glomerular filtration or renal blood flow appreciably. When these animals were then bled, only a fraction of the blood was taken from the animal that was necessary in the group 1 dogs in order to obtain the same degree of blood pressure reduction. This was reflected in a relatively insignificant depression of renal function, as compared with the group 1 animals despite slightly greater reductions in blood pressure in the animals in group 2. This absence of depressed renal function probably
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nerves. Even when Dibenzyline was given indicates at least partial blockade of the renal
function was not depressed to the same degree
that was observed with an equivalent degree
of reduction in blood pressure without block-
Hemorrhage following adrenergic blockade
did not depress sodium excretion to the same
degree that it did in the animals which did not
receive Dibenzyline.

Effect of Hemorrhage and Norepinephrine on
Cardiac Output. Following the initial hemor-
raghe (no. 1 or H), typical hemorrhage pulse
contours were observed and the cardiac out-
put was usually depressed. The second hemorrhage depressed
the cardiac output further with an inconstant
effect on peripheral resistance. The variability
of the effect of hemorrhage on cardiac output
and the total peripheral resistance agrees with
the observations of Remington and his associ-
ates. When the blood pressure was returned
to control levels by the intravenous infusion
of norepinephrine, the cardiac output either
increased or it was not altered. It was not
significantly depressed even when the pressure
was increased to levels which were consider-
ably above the control levels. The administra-
tion of norepinephrine was associated with an
increase in peripheral resistance. This was
most marked when the blood pressure was
raised to markedly hypertensive levels (period
“V”). Following reinfusion of blood, the cardiac
output increased above the control levels. If
the cardiac output was greatly increased above
the control levels immediately following blood
replacement, this gradually decreased toward
the control levels during the subsequent period
of 20 minutes.

**DISCUSSION**

It is quite obvious that erroneous conclu-
sions are reached when vasopressor agents are
administered to normal animals for evaluating
the pharmacodynamics of these compounds as
therapeutic agents for the treatment of hypo-
tensive states. When norepinephrine is ad-
ministered to a normal animal, renal blood
flow is at first depressed without altering
glomerular filtration rate. However, as the
rate of infusion is further increased, the blood
pressure rises further and glomerular filtration
rate as well as renal blood flow are depressed.
Contrariwise, when the blood pressure is
raised by administering norepinephrine to an
hypotensive animal, both glomerular filtration
rate and renal blood flow are actually increased
provided that the blood loss is not excessive.
These observations suggest that if blood volume
is not totally inadequate, the administration

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### Table 4: Effect of Dibenzyline and Hemorrhage on Water and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>C</th>
<th>B1</th>
<th>B2</th>
<th>BH1</th>
<th>BHs</th>
<th>Sodium mEq/L.</th>
<th>Potassium mEq/L.</th>
<th>Sodium µEq/Min.</th>
<th>Potassium µEq/Min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.8</td>
<td>1.5</td>
<td>1.5</td>
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<td>1.8</td>
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<td>150</td>
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<td>143</td>
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<td>1.6</td>
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<td>135</td>
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<td>140</td>
<td>140</td>
<td>140</td>
<td>139</td>
</tr>
</tbody>
</table>

See table 3 for key to abbreviations.
of norepinephrine for the treatment of hypotensive states due to hemorrhage can be expected to increase renal blood flow and improve renal function. If the hemorrhage is too severe, vasopressor agents seem to aggravate the reduction in renal blood flow, and blood volume replacement is the most effective method for improving renal function. These data further suggest that vasopressor agents would be beneficial to the kidney when used in the treatment of normal volemic shock.

Summary and Conclusions

The renal and cardiovascular hemodynamic response to norepinephrine was studied in dogs made hypotensive by repeated hemorrhage. Cardiac output, renal blood flow and glomerular filtration rate were reduced by small to moderately severe hemorrhage. When the blood pressure was then increased to approximately control levels with norepinephrine, both cardiac output and renal function improved. However, if the blood pressure was increased to hypertensive levels, renal function was markedly depressed, quite similarly to normal animals which have not been bled but have been made hypertensive with a norepinephrine infusion. In the severely hemorrhaged animals which did not show improvement of renal function following norepinephrine, when the blood loss was partially replaced, glomerular filtration rate and renal blood flow increased when norepinephrine was administered, and the blood pressure returned to control levels. This indicates that in the presence of excessive blood loss, blood volume replacement is superior to vasopressor agents for improving renal function and cardiac output.

REFERENCES


The Effect of Adrenergic Blockade and Norepinephrine on Renal and Cardiovascular Hemodynamics Following Hemorrhage

JOHN H. MOYER, CARROLL A. HANDLEY and RUSSELL A. HUGGINS

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