Renal Hemodynamic Response to Vasopressor Agents in the Treatment of Shock

By John H. Moyer, M.D., George Morris, M.D. and H. Liston Beazley, M.D.

Norepinephrine, when administered to normotensive subjects by continuous intravenous infusion produces a marked renal vasoconstriction and a reduction in renal blood flow. The opposite response is observed when this drug is given to patients in whom glomerular filtration rate and renal blood flow are already depressed due to shock. When the blood pressure in these patients is returned to normal with norepinephrine, there is an increase in both glomerular filtration rate and renal blood flow. There is also an increase in water and electrolyte excretion which is secondary to the increase in glomerular filtration rate.

Although vasopressor agents have been advocated for the treatment of shock, very few observations have been made on the hemodynamic responses of critical vascular beds to these compounds. Recently we have observed that when patients are made hypotensive with ganglionic blocking agents, blood flow through the kidneys and brain is reduced.1-2 When these same subjects are then rendered normotensive with vasopressor agents, the blood flow to these organs rapidly approaches the control observations.2-3 Although not analogous to shock, these observations present a paradox since if vasopressor agents are administered to normal subjects and the blood pressure raised to hypertensive levels, blood flow through the kidneys is reduced.4 These apparently confusing observations suggest a need for a better understanding of the pharmacodynamics of vasopressor agents when used either as primary treatment of hypotension or as an adjunct to other measures used in the treatment of shock. The current observations were made in order to assess the renal functional response to vasopressor agents when used for the treatment of shock due to numerous causes.

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Material and Methods

The patients in this study are divided into two groups. The first group was composed of patients admitted to the emergency room of a city-county hospital with untreated hemorrhagic and traumatic shock for which they received norepinephrine or Aramine (levo 1-(m-hydroxyphenyl)-2-amino-1-propanol). The second group consisted of hospitalized patients who received a vasopressor agent for the treatment of normovolemic shock due to numerous causes.

Renal function was determined, using inulin clearance as a measure of glomerular filtration rate (GFR) and low concentrations (2 to 4 mg. per 100 cc.) of para-aminobiphenyl (PAH) to measure renal plasma flow, methods and techniques previously described being used.5 6 In the normovolemic group who were already being treated with a continuous infusion of norepinephrine, the norepinephrine was discontinued long enough to obtain two or three 10-minute collection periods during hypotension. These were designated as the control observations. Norepinephrine infusion was then restarted and a variable number of additional 10-minute collection periods obtained.

In the hemorrhagic and traumatic cases, 1,000 to 1,500 cc. of 5 per cent glucose in water were given rapidly (intravenously) on arrival in the emergency room in order to insure satisfactory hydration for maximum urine formation under the circumstances. One to three 10-minute collection periods were then obtained while the patient was in shock. Patients who obtained a marked improvement in their clinical status on administration of the infusion of 5 per cent glucose, were discarded from the study. This served to eliminate patients who were border line and not seriously shocked. One such patient (T. H.-286—tables 1 to 4) is included for comparative purposes. Following the control observations two to six 10-minute periods were obtained during norepinephrine or Aramine induced normotension.
TABLE 1A.—Summary of Clinical Data on Patients Treated

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Race and Sex</th>
<th>Diagnosis</th>
<th>Etiology of Shock</th>
<th>Complicating Factors</th>
<th>Clinical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. D.-280</td>
<td>31</td>
<td>N/M</td>
<td>Lac. 1. forearm</td>
<td>Blood loss</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>W. H.-281</td>
<td>38</td>
<td>W/M</td>
<td>Mult. lac. scalp</td>
<td>Blood loss</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>E. B.-283</td>
<td>36</td>
<td>N/M</td>
<td>Lac. ulnar art.</td>
<td>Blood loss</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>L. M.-284</td>
<td>52</td>
<td>N/F</td>
<td>Hemopneumothorax. Mult. rib fract.</td>
<td>Trauma</td>
<td>Severe alcohol.</td>
<td>Recovered</td>
</tr>
<tr>
<td>T. H.-286</td>
<td>39</td>
<td>N/M</td>
<td>Stab wound shoulder</td>
<td>Alcohol &amp; min. blood loss</td>
<td>Alcohol.</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

Group 2—Patients with Normal Volume Shock

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Race and Sex</th>
<th>Diagnosis</th>
<th>Etiology of Shock</th>
<th>Complicating Factors</th>
<th>Clinical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. W.-287</td>
<td>70</td>
<td>W/M</td>
<td>Perforated gastric ulcer</td>
<td>Bile peritonitis</td>
<td>Closure leaked</td>
<td>Died in 4 days</td>
</tr>
<tr>
<td>L. H.-289</td>
<td>29</td>
<td>N/F</td>
<td>Criminal abortion</td>
<td>Intrauterine Lysol</td>
<td>Renal tub. necrosis</td>
<td>Recovered</td>
</tr>
<tr>
<td>J. N.-290</td>
<td>70</td>
<td>N/M</td>
<td>Ca. prostate</td>
<td>Mult. bony metastases. Terminal ca.</td>
<td>Metastases. No Uremia</td>
<td>Died in 4 days</td>
</tr>
<tr>
<td>V. W.-291</td>
<td>24</td>
<td>N/F</td>
<td>Postpartum—triplets</td>
<td>Postpartum—triplets</td>
<td>Schizophrenia</td>
<td>Recovered</td>
</tr>
<tr>
<td>G. H.-292</td>
<td>51</td>
<td>W/F</td>
<td>Cirrh., chr. pyeloneph., uremia</td>
<td>Hepatic coma</td>
<td>Chr. alcohol., dehydration</td>
<td>Died following day</td>
</tr>
<tr>
<td>J. M.-293</td>
<td>44</td>
<td>W/M</td>
<td>Lymph. leukemia</td>
<td>Electrolyte imbal. Plasma K = 2.2 mEq.</td>
<td></td>
<td>Recovered from shock in 24 hrs. after K corrected</td>
</tr>
<tr>
<td>D. L.-294</td>
<td>53</td>
<td>W/M</td>
<td>Myo. infarct.</td>
<td>Cardiogenic</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>T. R.-295</td>
<td>63</td>
<td>W/M</td>
<td>Myo. infarct.</td>
<td>Cardiogenic</td>
<td>Heart fail.</td>
<td>Died after 18 hrs. of therapy</td>
</tr>
</tbody>
</table>

Lac. = laceration.
Cirrh. = cirrhosis.
Pyeloneph. = pyelonephritis.
Lymph. = lymphatic.

The vasopressor agent was then discontinued and two more periods were collected after the blood pressure had again returned to shock levels. Following these observations, blood had become available and the patient was then transfused. Three to six more collection periods were obtained after stabilization of vital signs following the blood transfusion. In several cases follow-up studies were done after 24 hours or more. Mean arterial blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure.

RESULTS

The clinical observations on the patients of both groups I and II are summarized in tables 1A and 1B. There were seven patients who suffered from hemorrhagic shock (group I) and eight patients who were in shock from causes other than blood loss (group II). It is to be noted that the general status of the patients in group II was far worse than it was in those.
patients in group I. Had not another complication developed, all of the patients in group I would probably have recovered.

The effect of vasopressor agents on renal hemodynamics is summarized in table 2. The renal vascular resistance was increased in patients with hemorrhagic shock as well as in the patients with nonhemorrhagic shock. Although blood pressure prior to vasopressor therapy was depressed to about the same extent in both groups of patients, renal blood flow was more markedly depressed in the patients with nonhemorrhagic shock. This was probably due to the very poor condition of the patients in the latter group. The difference between the two groups in renal hemodynamic response to vasopressor agents is even more outstanding. In the patients with shock due to blood loss (group I), when the blood pressure was increased with the vasopressor agent glomerular filtration rate returned to or toward normal (table 3) and renal blood flow increased markedly in most of the patients (table 2). Although the renal blood flow and glomerular filtration rate increased, they did not return to within normal ranges in any of the patients with normovolemic shock. Likewise, the renal vascular resistance which was increased prior to therapy frequently did not decrease when norepinephrine was administered. Even patients with primary renal damage usually showed some improvement in function. One such example was patient 289—L. H. who suffered from renal damage due to Lysol administration. She showed a slight increase in renal blood flow when the blood pressure was increased with norepinephrine.

The effect of increasing the blood pressure with norepinephrine on glomerular filtration rate is summarized in table 3. There was a close parallel between the effect on glomerular filtration rate and renal blood flow. Glomerular filtration rate returned to or towards normal ranges in all but one of the patients in group I. By contrast, glomerular filtration rate did not increase to normal values in any of the patients in group II, although it increased somewhat in all of the patients, even in the patient (L. H.) with renal tubular necrosis.

When the vasopressor agents were discontinued prior to the administration of blood to the patients in group I, renal function was usually depressed again to a point approximating the observations made during the control periods. When compared with the control observations, both glomerular filtration rate and renal blood flow increased following blood transfusions in all of the patients in this group. It was quite a surprise to note that the immediate responses of glomerular filtration rate and renal

<table>
<thead>
<tr>
<th>Patient</th>
<th>Vasopressor Agent</th>
<th>Dose in microg.</th>
<th>Previous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1—Patients with Shock due to Hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. D.-280</td>
<td>Norepineph.</td>
<td>20</td>
<td>1200 cc. 5% glu. in H₂O</td>
</tr>
<tr>
<td>W. H.-281</td>
<td>Norepineph.</td>
<td>32</td>
<td>1000 cc. 5% glu. in H₂O</td>
</tr>
<tr>
<td>M. C.-282</td>
<td>Aramine</td>
<td>200</td>
<td>1000 cc. 5% glu. in H₂O</td>
</tr>
<tr>
<td>E. B.-283</td>
<td>Norepineph.</td>
<td>18</td>
<td>1000 cc. 5% glu. in H₂O</td>
</tr>
<tr>
<td>L. M.-284</td>
<td>Norepineph.</td>
<td>30</td>
<td>1000 cc. 5% glu. in H₂O</td>
</tr>
<tr>
<td>V. S.-285</td>
<td>A-Aramine</td>
<td>528</td>
<td>Eosph. balloon inserted just prior to study</td>
</tr>
<tr>
<td>T. H.-286</td>
<td>Norepineph.</td>
<td>22</td>
<td>1500 cc. 5% glu. in H₂O</td>
</tr>
</tbody>
</table>

| Group 2—Patients with Normal Volume Shock |
| G. W.-287 | Norepineph. | 12 | Simple closure 48 hours previously |
| L. H.-289 | Norepineph. | 84 | 500 cc. blood, DOCA, cortisone, glu. in H₂O (2000 cc.) |
| J. N.-290 | Norepineph. | 22 | Orchideet. T.U.R. 10 days before |
| V. W.-291 | Norepineph. | 17 | None |
| G. H.-292 | Norepineph. | 96 | 2000 cc. blood. I.V. fluids |
| D. L.-294 | Norepineph. | 4 | Sedation |
| T. R.-295 | Norepineph. | 32 | Sedation |

Glu. = glucose.
T.U.R. = transurethral resection.
Table 2.—Renal Hemodynamic Response to Vasopressor Agents During Shock

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean Blood Pressure mm. Hg</th>
<th>Renal Blood Flow ml/min.</th>
<th>Renal Vascular Resistance*</th>
<th>Hematocrit</th>
<th>Volume of Blood Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>V₁</td>
<td>V₂</td>
<td>B₁</td>
<td>B₂</td>
<td>C</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
<td>------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>R. D. 280</td>
<td>17 72 93 96 91</td>
<td>303 1248 1717 1159</td>
<td>1125 .05 .05 .06 .06</td>
<td>36 33 35 41 40</td>
<td>1000 cc.</td>
</tr>
<tr>
<td>W. H. 281</td>
<td>64 86 89 91 103</td>
<td>14 723 1321 338</td>
<td>-7 4.57 .12 .59 .25</td>
<td>-2</td>
<td>30 30 30 35 33</td>
</tr>
<tr>
<td>M. C. 282</td>
<td>64 73 84 84</td>
<td>122 245 550 548</td>
<td>-1 .52 .30 .15 .15</td>
<td>-</td>
<td>26 26 28 35</td>
</tr>
<tr>
<td>E. B. 283</td>
<td>50 85 95 99</td>
<td>126 1188 1320 1838</td>
<td>-</td>
<td>.43 .07 .07 .05</td>
<td>-</td>
</tr>
<tr>
<td>L. M. 284</td>
<td>43 76 85 76 83</td>
<td>53 510 650 850</td>
<td>868</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V. S. 285A</td>
<td>42 52 74</td>
<td>-</td>
<td>-</td>
<td>1291 1657</td>
<td>-</td>
</tr>
<tr>
<td>T. H. 286I</td>
<td>83 98 105 100</td>
<td>1266 1178 1120 1093</td>
<td>-</td>
<td>.07 .08 .09 .06</td>
<td>-</td>
</tr>
</tbody>
</table>

Group 1—Hemorrhagic Shock

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean Blood Pressure mm. Hg</th>
<th>Renal Blood Flow ml/min.</th>
<th>Renal Vascular Resistance*</th>
<th>Hematocrit</th>
<th>Volume of Blood Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. W. 287</td>
<td>83</td>
<td>101</td>
<td>-</td>
<td>-</td>
<td>118</td>
</tr>
<tr>
<td>L. H. 289</td>
<td>57</td>
<td>95</td>
<td>83</td>
<td>-</td>
<td>53</td>
</tr>
<tr>
<td>J. N. 290</td>
<td>67</td>
<td>89</td>
<td>113</td>
<td>-</td>
<td>347</td>
</tr>
<tr>
<td>V. W. 291</td>
<td>53</td>
<td>86</td>
<td>112</td>
<td>97</td>
<td>69</td>
</tr>
<tr>
<td>G. H. 292</td>
<td>37</td>
<td>74</td>
<td>92</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>J. M. 293</td>
<td>37</td>
<td>69</td>
<td>92</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>D. L. 294</td>
<td>49</td>
<td>72</td>
<td>71</td>
<td>92</td>
<td>293</td>
</tr>
<tr>
<td>T. R. 295</td>
<td>19</td>
<td>78</td>
<td>-</td>
<td>77</td>
<td>76</td>
</tr>
</tbody>
</table>

C—Control during shock.
V₁—Partial restoration of blood pressure with a vasopressor agent.
V₂—Complete restoration of blood pressure with a vasopressor agent.
B₁—Immediately after transfusion of blood.
B₂—Follow-up study completed. R. D., 24 hours after B₁; W. H., 5 days after B₂; L. M., 24 hours after B₂; L. H., 25 days after B₁; V. W., 6 days after V₂; D. L., 6 hours after V₂.

* Renal Vascular Resistance = Mean Blood Pressure / Renal Blood Flow
† Insufficient blood replacement at time of study, transferred to surgery.
‡ Sulfa drug therapy interfered with PAH determinations.
§ Undeterminable due to extremely low PAH clearance.
|| Patient clinically in shock but blood pressure was normal following the infusion of 1500 cc. of 5% glucose. Renal functions were not depressed.

CASE REPORTS

The following cases are given in more detail because they present pertinent points in the study.

Patients in shock due to blood loss and trauma (group I)

Case 1. R. D., a patient with moderate hemorrhagic shock. This patient was a 31-year-old Negro man who had an extensive laceration of the arm. His systolic blood pressure was 50 mm. Hg. after the rapid instillation of 1,200 cc. 5 per cent glucose in water. The diastolic pressure was not obtainable. Renal function was restored to normal levels with norepinephrine. Comparable values were obtained after restoration of blood volume with 1,000 cc. blood. The laceration was repaired and recovery was uneventful (tables 1 to 4).

Case 2. W. H. Patient W. H., a typical case of shock due to hemorrhage and lacerations of the scalp. This patient illustrates the response from a moderate degree of hemorrhagic shock. He was a
**TABLE 3.—Effect of Vasopressor Agents During Shock on Glomerular Filtration Rate and Renal Plasma Flow**

| Patient | Glomerular Filtration Rate || Renal Plasma Flow || Filtration Fraction* |
|---------|---------------------------|-----------------|-----------------|---------------------|
|         | C | V₁ | V₂ | B₁ | B₂ | C | V₁ | V₂ | B₁ | B₂ | C | V₁ | V₂ | B₁ | B₂ |
| R. D. −280 | 29 | 43 | 115 | 119 | 103 | 194 | 799 | 1116 | 684 | 675 | .15 | .05 | .10 | .17 | .15 |
| W. H. −281 | 3 | 114 | 92 | 67† | 155 | 10 | 504 | 715 | 233† | —† | .30 | .23 | .13 | .29 | —† |
| M. C. −282 | 10 | 63 | 78 | 82† | — | 90 | 181 | 396 | 356† | — | .11 | .33 | .20 | .23 | — |
| E. B. −283 | 11 | 86 | 85 | 78 | — | 77 | 713 | 792 | 974 | — | .14 | .12 | .11 | .08 | — |
| L. M. −284 | —§ | 5 | 16 | 23 | 119 | —§ | 255 | 493 | 612 | 538 | —§ | —§ | .02 | .03 | .04 | .22 |
| V. S. −285A | —§ | 66 | 94 | — | — | —§ | 865 | 1090 | — | — | —§ | —§ | .08 | .09 | — | — |
| V. S. −285B | 31 | 53 | 58 | 48 | — | 205 | 376 | 397 | 455 | — | .15 | .14 | .15 | .11 | — |
| T. H. −286 | 128 | 137 | 140 | 184 | — | 823 | 766 | 728 | 1016 | — | .16 | .18 | .19 | .18 | — |

**Group 1—Hemorrhagic Shock**

**Group 2—Non-hemorrhagic Shock of Varied Etiology**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Glomerular Filtration Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>G. W. −287</td>
<td>5</td>
</tr>
<tr>
<td>L. H. −289</td>
<td>9</td>
</tr>
<tr>
<td>J. N. −290</td>
<td>33</td>
</tr>
<tr>
<td>V. W. −291</td>
<td>33</td>
</tr>
<tr>
<td>G. H. −292</td>
<td>5</td>
</tr>
<tr>
<td>J. M. −293</td>
<td>3</td>
</tr>
<tr>
<td>D. L. −294</td>
<td>48</td>
</tr>
<tr>
<td>T. R. −295</td>
<td>12</td>
</tr>
</tbody>
</table>

C—Control during shock.
V₁—Partial restoration of blood pressure with a vasopressor agent.
V₂—Complete restoration of blood pressure with a vasopressor agent.
B₁—Immediately after transfusion of blood.
B₂—Follow-up study—R. D., 24 hours after B₁; W. H., 5 days after B₁; L. M., 24 hours after B₁; L. H., 25 days after V₂; V. W., 6 days after V₂; D. L., 6 hours after V₂.

* Filtration Fraction = Glomerular Filtration Rate
Renal Plasma Flow

† Insufficient blood replacement at time of study.
‡ Sulfa drug therapy interfered with PAH determinations.
§ Undeterminable due to extremely low inulin and PAH clearance.
|| Normal values for glomerular filtration rate in this laboratory are 100 to 140 cc per minute and for renal plasma flow are approximately 600 to 800 cc per minute.

38-year old white man who had multiple lacerations of the head and a mean blood pressure prior to treatment of 52 to 60 mm. Hg. He was given 1,000 cc. of 5 per cent glucose in distilled water which did not affect his blood pressure appreciably. Following norepinephrine infusion sufficient to restore mean blood pressure to a range of 85 to 90 mm. Hg, both renal blood flow and glomerular filtration rate were restored to nearly normal levels. After an increase in the blood volume with 1,000 cc. of blood the mean blood pressure ranged from 89 to 93 mm. Hg and glomerular filtration rate increased almost to normal, but renal blood flow remained depressed. This was probably due to inadequate blood replacement. His initial blood volume, while in shock immediately after the rapid infusion of 1,000 cc. 5 per cent glucose in water, was 4,519 cc. which may be high due to the temporary presence of a large portion of the crystalloid infusion in the vascular compartment. Five days later his blood volume was 5,740 cc. and his glomerular filtration rate was in the high normal range. Due to an intercurrent infection, the patient was given sulfonamide. As a result, it was not possible to determine renal blood flow during the follow-up study since sulfonamides interfere with the chemical analysis of para-aminobipurpurate.

As the glomerular filtration rate increased with both the vasopressor agent and the blood transfusion, there was a sharp increase in urine volume (fig. 1B). This was associated with a moderate initial and sustained increase in sodium and potassium excretion. The increase in sodium excretion was more marked after blood replacement than after blood pressure elevation with the vasopressor agent.
### Table 4.—Effect of Vasopressor Agents During Shock on Water and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urine Volume mI/min.</th>
<th>Plasma Sodium mEq/L</th>
<th>Plasma Potassium mEq/L</th>
<th>Sodium Excretion mEq/min.</th>
<th>Potassium Excretion mEq/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>V₁</td>
<td>V₂</td>
<td>B₁</td>
<td>B₂</td>
<td></td>
</tr>
<tr>
<td>R. D.-280</td>
<td>1.0</td>
<td>1.2</td>
<td>2.8</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>W. H.-281</td>
<td>0.1</td>
<td>0.8</td>
<td>0.8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>M. C.-282</td>
<td>0.7</td>
<td>2.3</td>
<td>2.8</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>E. B.-283</td>
<td>0.2</td>
<td>0.8</td>
<td>2.4</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>L. M.-284</td>
<td>0.0</td>
<td>1.0</td>
<td>2.4</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>V. S.-285A</td>
<td>0.0</td>
<td>0.4</td>
<td>1.4</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>V. S.-285B</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>T. H.-286</td>
<td>0.6</td>
<td>1.1</td>
<td>5.1</td>
<td>12.6</td>
<td></td>
</tr>
</tbody>
</table>

#### Group 1—Hemorrhagic Shock

- G. W.-287
  - 0.1
  - 0.9
  - 130
  - 124
  - 133
  - 3.4
  - 2.8
  - 3.9
  - 18
  - 87
  - 137
  - 3
  - 38

- J. N.-280
  - 0.8
  - 1.5
  - 4.9
  - 124
  - 120
  - 3.8
  - 3.6
  - 3.0
  - 30
  - 68
  - 34
  - 38
  - 38
  - 59
  - 59

- V. W.-281
  - 0.2
  - 0.6
  - 0.6
  - 2.6
  - 130
  - 124
  - 151
  - 5.1
  - 4.8
  - 3.0
  - 9
  - 10
  - 17
  - 62
  - 8
  - 8
  - 14
  - 22

- G. H.-282
  - 1.4
  - 4.0
  - 4.4
  - 143
  - 134
  - 133
  - 3.4
  - 2.8
  - 3.9
  - 18
  - 87
  - 137
  - 3
  - 38
  - 38
  - 59
  - 59

- J. M.-283
  - 0.2
  - 1.5
  - 6.2
  - 143
  - 141
  - 4.3
  - 3.9
  - 4.0
  - 40
  - 300
  - 24
  - 36
  - 24

- D. L.-294
  - 0.4
  - 1.6
  - 143
  - 141
  - 4.3
  - 3.9
  - 4.0
  - 40
  - 300
  - 24
  - 36
  - 24

- T. R.-295
  - 0.2
  - 0.8
  - 0.3
  - 143
  - 140
  - 138
  - 4.6
  - 4.0
  - 3.8
  - 21
  - 82
  - 16
  - 26
  - 30
  - 17

C—Control during shock.
V₁—Partial restoration of blood pressure with a vasopressor agent.
V₂—Complete restoration of blood pressure with a vasopressor agent.
B₁—Immediately after transfusion of blood.
B₂—Follow-up study—R. D., 24 hours after B₁; W. H., 5 days after B₁; L. M., 24 hours after B₂; L. H., 25 days after V₂; V. W., 6 days after V₂; D. L., 6 hours after V₂.
* Insufficient blood replacement at time of study.

### Fig. 1

**A**

A typical renal hemodynamic response to a vasopressor agent and to blood replacement in a patient with shock due to blood loss. In this instance, renal blood flow did not return to normal following the blood transfusion probably because of inadequate blood replacement. **(B)**

Typical response of water and electrolyte excretion to vasopressor agent and to blood transfusion in a patient in shock due to blood loss. (Patient W. H.)
The following case represents the response to Aramine, a vasopressor agent which is longer acting than norepinephrine.

Case 3. M. C. A 45-year old white man was admitted to the Receiving Ward, having vomited an estimated 2 quarts of blood due to gastrointestinal hemorrhage. He have no history of peptic ulcer. His blood pressure was 70/50, the pulse rate was 120, and other clinical manifestations of shock were evident. The patient was given 1,000 cc. of 5 per cent glucose in water. Following the control observations on renal function, an infusion of Aramine in a concentration of 200 mg. per liter was started. There was a gradual increase in blood pressure to 104/76. This was associated with sharp increases in glomerular filtration rate and renal blood flow from about 10 per cent of normal values to about two-thirds and one-half of normal, respectively. After the observations on renal function were complete, the Aramine was discontinued and the patient was given 2,500 cc. of blood. The glomerular filtration rate and renal blood flow remained about the same as they had been during the Aramine infusion. However, the patient continued to bleed and he was taken to the surgical service where a gastrectomy was performed. Soon thereafter he again developed shock and it became necessary to administer another 2,500 cc. of blood before his blood pressure stabilized. The bleeding point was never found and hemorrhage recurred.

Comment: The renal hemodynamic response to Aramine in this patient was quite similar to previous observations made on the response to norepinephrine. Following blood pressure elevation, renal blood flow and glomerular filtration rate increased. As the glomerular filtration rate increased, sodium, potassium and water excretion also increased (fig. 2B). The response to Aramine was about the same as the response to the blood transfusion.

The following case represents an example of a relatively poor initial renal hemodynamic response to both norepinephrine and blood transfusions in a patient who was in severe shock from blood loss and trauma.

Case 4. L. M. This 52-year old Negro woman was admitted to the hospital after being hit by an automobile. She was in shock associated with multiple fractured ribs, a left pneumothorax, subcutaneous emphysema, and hemorrhage into the pleural space. The pulse rate was 110 and the blood pressure was 70/30 following the administration of 1,000 cc. of 5 per cent glucose in water. The patient was completely anuric. Therefore, renal blood flow and glomerular filtration rate could not be estimated. Norepinephrine was administered by continuous intravenous infusion and the blood pressure in-
creased to normotensive ranges. Despite a marked increase in renal blood flow, glomerular filtration rate did not show a parallel improvement. A similar response to blood transfusion was observed. However, 24 hours later the glomerular filtration rate had increased to within normal range with no further therapy. Despite a minimal initial increase in glomerular filtration rate, water and electrolyte excretion increased sharply as the blood pressure was elevated with either blood transfusions or norepinephrine.

Patients in normo-volemic shock (Group II)

Case 5. D. L. This 53-year old white man had had an anterolateral myocardial infarction. His blood pressure on admission was 70/35 (fig. 3). The patient was given norepinephrine by continuous infusion at a rate of 4 micrograms per minute and his blood pressure increased to 98/60. The urine output rose from 0.4 cc. to 1.6 cc. per minute. The glomerular filtration rate increased from 48 cc. per minute to nearly normal. Recovery was uneventful.

Case 6. T. R. This 63-year old white man was admitted to the hospital in shock due to a large anterior myocardial infarction (fig. 4). His systolic blood pressure was 56 mm. Hg. The diastolic pressure was unobtainable. When the blood pressure was increased to 90/75 with norepinephrine, the glomerular filtration rate increased from approximately 12 cc. per minute to 37 cc. per minute. This was only a partial response since the normal glomerular filtration rate for this man was 110 cc. per minute. He required increasing amounts of norepinephrine in order to maintain the blood pressure, and death occurred 15 hours after therapy was started. There was a progressive deterioration of renal function during this period.

Case 7. L. H. This 29-year old Negro woman was admitted, having produced a criminal abortion three days previously with concentrated Lysol (R). Secondary infection had occurred. She had been oliguric for three days and was in shock on admission. Her blood pressure was 54/8. Her temperature was 102 F. The white blood cell count was 40,000 and the blood urea nitrogen was 38 mg. per 100 cc.

The patient was given 2,000 cc. of 5 per cent glucose in distilled water, and the blood pressure stabilized at 65/50. Control observations on renal function were made. Control urine volume was 0.4 cc. per minute. Norepinephrine was then started and the blood pressure increased to normotensive ranges. Although renal function was markedly depressed prior to norepinephrine administration, as the blood pressure increased glomerular filtration rate showed a three-fold increase and renal blood flow a two-fold increase. The patient was given antibiotics and supportive therapy. After 24 hours it was no longer necessary to administer a vasopressor agent. She showed evidence of increasing azo-

temia for the next two days, following which urinary function gradually returned toward normal and recovery was uneventful. Her blood urea nitrogen had risen as high as 96 mg. per 100 cc. on one occasion during her illness. Renal function studies repeated
after three weeks indicated that glomerular filtration rate had returned to normal and para-aminomelipurate clearance (approximate renal plasma flow) was about 50 per cent of normal.

Case 8, G. H., was a 51-year-old white woman with pneumonia, cirrhosis of the liver, and renal failure due to chronic pyelonephritis. On admission, the blood urea nitrogen was 175 mg. per 100 cc., the white blood cell count was 28,300 and hemoglobin was 5.8. The patient was hydrated with 2,000 of 5 per cent glucose in distilled water. The blood pressure was 50/24. Despite a glomerular filtration rate of only 5 cc. per minute, the urine volume was 1.4 cc. per minute. As soon as the blood pressure was increased to normotensive ranges with norepinephrine the glomerular filtration rate increased to 11 cc. per minute and the urine output increased to 4 cc. per minute, indicating that improvement in renal function can be expected even in the presence of severe primary renal disease. These observations are considered qualitative and directional only since accurate estimations of renal blood flow cannot be made under these circumstances.

Discussion

Laboratory Observations. There is no doubt that vasopressor agents are renin vasoconstrictors when administered to the normotensive animal in adequate amounts. Furthermore, this renal vasoconstrictor effect can be blocked off with Dibenzyline, a potent adrenergic blocking agent. This is well demonstrated in figure 6. When either Aramine or norepinephrine were administered to this animal, renal blood flow and glomerular filtration rate were reduced. However, if adrenergic blockade was produced with Dibenzyline and then Aramine was administered at four times the rate previously, renal vasoconstriction did not occur. We have made similar observations after unilateral adrenergic blockade of one kidney by the intra-arterial injection of Dibenzyline. Before Dibenzyline was injected into the left renal artery, norepinephrine infusion (intravenous) produced marked vasoconstriction in both kidneys. After the blocking dose of Dibenzyline was injected into the left renal artery, norepinephrine continued to produce vasoconstriction in the contralateral unblocked kidney but had no effect on the blocked side (left).

By contrast to the normotensive animal
FIG. 6. Renal hemodynamic response to vasopressor agents before and after adrenergic blockade in the dog. (Courtesy American Heart Journal).

FIG. 7. Renal hemodynamic response to hemorrhage (in a dog) followed by blood pressure elevation with norepinephrine. Renal blood flow was reduced with hemorrhage and increased when the blood pressure was raised with norepinephrine. However, if the pressure was raised to hypertensive levels, renal blood flow and glomerular filtration rate were again depressed.

which is made hypertensive, a different response is observed when vasopressor agents are administered to animals previously made hypertensive by hemorrhage. In the latter animals, renal blood flow and glomerular filtration rate are reduced due to bleeding. When norepinephrine is then administered, renal blood flow and glomerular filtration rate are increased toward the control values although there is usually only partial return (fig. 7).

Clinical Observations. The effect of vasopressor agents on the human kidney in the normotensive subject is quite similar to that observed in the laboratory animal. As the blood pressure increases renal blood flow is first reduced. If the rate of infusion is great enough, glomerular filtration rate may also be reduced (table 5). However, the renal hemodynamic response to vasopressor agents in the presence of shock is entirely different than when these agents are administered to normal subjects. In the shocked patient there exists a marked reduction in renal blood flow and glomerular filtration rate which is due to a combination of renal vasocstriction and hypotension (tables 2 and 3). When the blood pressure is now increased with a vasopressor agent, some of the renal vasoconstrictor response is relieved and the intraglomerular filtration pressure increases. As a result, renal blood flow, glomerular filtration rate, and urine output are increased.

When glomerular filtration rates before and after treatment with vasopressor agents or blood transfusions are plotted (graphed) against blood pressure in the hemorrhagic shock patients (group I), one can see that the degree of increase in glomerular filtration rate after blood replacement is well interspersed with the response to vasopressor agents, indicating very minor differences, if any, in the overall response. When glomerular filtration rate is plotted against urine volume after blood pressure elevation with either vasopressor

<table>
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<th>Table 5.—Renal Hemodynamic Response in Control Subjects Made Hypertensive By an Infusion of Norepinephrine (9 Subjects)</th>
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<tr>
<td>Control</td>
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<tr>
<td>---------</td>
</tr>
<tr>
<td>Mean B.P. (mm. Hg)</td>
</tr>
<tr>
<td>GFR (cc/min.)</td>
</tr>
<tr>
<td>RPF (cc/min.)</td>
</tr>
<tr>
<td>RBF (cc/min.)</td>
</tr>
<tr>
<td>Renal Vascular Resistance</td>
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</table>

1 Mean for per cent of control value of 9 subjects.
GFR = glomerular filtration rate.
RPF = renal plasma flow.
RBF = renal blood flow.
agents or blood transfusions, one observes that although urine volume increases, the increase in glomerular filtration rate appears to be the primary response. Although the control values for renal function are not considered as quantitative estimations, these observations certainly indicate directional changes following the administration of vasopressor agents and blood since the observations made after blood pressure elevation can be considered more or less accurate because urine volume was quite adequate at this time.

In mild to moderate hemorrhagic shock, blood transfusions do not appear to be superior to vasopressor agents for increasing glomerular filtration rate and renal blood flow (table 2). The increase in blood pressure frequently does not have to be very great in order to produce a rather sharp increase in glomerular filtration rate. If blood loss is too great and very large amounts of norepinephrine are required to raise the blood pressure, improvement in renal function is not observed after the administration of vasopressor agents. However, if part of the normal blood volume is replaced, norepinephrine now produces a significant improvement in renal function (fig. 8). This response was observed even though the transfusion was not great enough to have a significant effect on blood pressure.

These responses to vasopressor agents speaks against a humoral agent being responsible for the renal vasoconstriction associated with hemorrhagic shock in man, especially since glomerular filtration rate and renal blood flow return to normal ranges. If a circulating agent were responsible for the renal vasoconstriction which occurs in shock, one would not anticipate that the administration of a second vasoconstrictor would relieve the vascular constriction produced by the first. It is possible, however, but not likely, that norepinephrine directly antagonizes circulating vasoconstrictor substances which are liberated by the patient in shock.

In the patients with normovolemic shock there is a consistent increase in renal blood flow and glomerular filtration rate but they never approach normal ranges. Even though the increase in glomerular filtration rate is not great, there is a rather consistent increase in urine volume and electrolyte excretion.

**Summary and Conclusions**

1. Renal function studies have been made in patients suffering with clinical shock due to various etiologies. Renal function was determined during shock, during norepinephrine-induced normotension, and in traumatic cases, after blood volume replacement.

2. Although norepinephrine administration to normotensive human subjects increases renal vascular resistance and depresses renal blood flow, when administered to patients who are in shock the opposite effect results. This ambivalent action of norepinephrine is thought to result from a differential vasoconstriction between the kidney and the remainder of the general circulatory bed. The elevation in blood pressure incident to the administration of norepinephrine to patients in shock is due to an overall increase in peripheral vascular resistance but the lesser renal vasoconstrictor effect results in an increase in renal blood flow and glomerular filtration rate with an actual reduction in renal vascular resistance.

in all types of clinical shock. In moderate hemorrhagic shock norepinephrine may return renal function to normal. Partial restoration of renal function may be effected with the drug in severe hemorrhagic shock, but complete restoration occurs only if the blood volume is increased towards normal.

(4) It is suggested that norepinephrine is probably useful in protecting the kidneys in cases of hemorrhagic and traumatic shock while awaiting blood volume replacement.

SUMMARIO IN INTERLINGUA

1. Studios del function renal eseva executate in patientes con choc clinic a varie etiologias. Le function renal eseva determinate durante le choc, durante normotension induite per norepinephrina, e—in casos traumatic—post reimplaciamen del volumine de sanguine.

2. Ben que le administration de norepinephrina a individuos normotensive augmenta le resistentia vascular renal e reduce le fluxo sanguine renal, le effecto opposite es observe in casos de choc. Nos opina que iste ambivalenta del effecto de norepinephrina resulta de un differentia del vasoconstriction in le renes e in le resto del circulation general. Le elevation del pression sanguine effectuate per norepinephrina in casos de choc resulta de un augmento general del resistentia vascular peripheric, sed le reducece effecto de vasoconstriction renal resulta in un augmento del fluxo sanguine renal e del filtration glomerular con un effective reduction del resistentia vascular renal.

3. Norepinephrina meliora le function renal in omne typos de choc clinic. In casos de moderate choc hemorrhagic, le effecto de norepinephrina pote esser le retorno del function renal al normal. Un restauración partial del function renal pote resultar del uso del droga in casos de choc hemorrhagic sever, sed un complete restauración resulta solmente si le volumine del sanguine es augmentate usque a valores normal.

4. Nos opina que norepinephrina es probablemente utile in proteger le renes in casos de choc traumatic e hemorrhagic durante le intervallo ante le reimplaciamen del volumine sanguine.

REFERENCES


Renal Hemodynamic Response to Vasopressor Agents in the Treatment of Shock
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