In irreversible shock caused by prolonged and severe oligemic hypotension there is damage to some vital cells and/or the release of lethal materials. The blood pressure progressively declines and death eventually ensues even though a transfusion of blood, plasma, or plasma expander may temporarily restore the pressure to normal. The cause of the circulatory failure seen following the replacement of the shed blood, must be due either to a decrease in cardiac output or to an extensive loss in overall peripheral vascular resistance, or both, since the systemic arterial blood pressure equals the product of cardiac output and calculated total peripheral resistance. This study tests the hypothesis that there is a collapse of peripheral vascular resistance to blood flow of such a magnitude as to explain a cardiovascular failure during severe hypotension and during the irreversible decline in blood pressure following reinfusion of the shed blood. If the peripheral resistance does not fail, then either a weakening of the myocardium or a deficit of cardiac filling must be the primary site of the failure in this type of shock.

Methods

Mongrel dogs, fasted overnight and anesthetized with 25 to 30 mg/kg of sodium pentobarbital (Abbott, veterinary Nembutal), were used. Extra anesthetic to the shock dog was unnecessary except in rare experiments late in the post-transfusion phase. Supplemental anesthetic doses during the control period were minimized so that at the beginning of hemorrhage the animals showed a slight eyelid reflex but no signs of pain. Heparin sodium (Nutritional Biochemicals) was used as an anticoagulant in a priming dose of 3 mg/kg body weight and a sustaining dose of about 10 mg/hr. The animals were intubated with auffed endotracheal tube. In all but a few experiments, the dogs were placed on their sides on a "V"-shaped dog board designed so that water at 40°C could be circulated through the table to maintain the rectal temperature between 37°C and 40°C. Control temperatures were between 37°C and 38.0°C. Total peripheral resistance was calculated during various phases of shock by measuring arterial blood pressure and cardiac output simultaneously in 34 dogs. Cardiac output was measured by the indicator dilution technique using indocyanine green* and a cuvette densitometer (Guilford, Model 103R). A spring-driven dye injector was used to inject 0.05 ml of dye (reproducibility error less than 0.5%) in about 0.5 second. The 0.5 mm I.D. polyethylene dye catheter, co-axial within a larger catheter, was inserted via a femoral vein until the tip was within 5 cm of the right atrium, was inflated via a femoral vein until the tip was within 5 cm of the right atrium, and was verified at autopsy. Blood sampling was made with a 1.6 mm I.D. polyethylene catheter inserted within 2 to 10 cm of the aortic valve via a femoral artery. Blood was withdrawn at 25 ml/min with a constant-rate withdrawal syringe. Immediately after each determination, the blood was returned to the dog and the system flushed with about 5 ml of saline.

Two 0.50 ml samples of 2.5 mg/ml dye (in the special water supplied) were diluted with 4.0 ml of distilled water for calibration. This was further diluted 1 to 1. Calibration solutions were made by adding 0.4 ml of either distilled water or the diluted dye to 9.6 ml of blood, using a 4.8 ml syringe-pipet to give 0, 10, and 20 mg/liter of dye. Later experiments have shown that dilution of the 2.5 mg/ml dye solution with saline gives more reproducible calibration factors, since the addition of a hypotonic aqueous solution to the blood causes small, but important, amounts of hemolysis.

The data were recorded on an Offner type R direct-writing oscillograph. A special circuit was designed to give the logarithm of the dye curve on another channel so that the straight downslope of this curve could be extrapolated to a value within about 2% of zero dye concentration. These extrapolated data were transferred to the linear dye concentration curve and the area was...
### TABLE 1
Factors in Hemorrhagic Shock in the Dog

<table>
<thead>
<tr>
<th>Group</th>
<th>Unites</th>
<th>Mean ± SD Mean ± SD Mean ± SD</th>
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<tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>10</th>
<th>7</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major thoracic surgery</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Transfusion beyond reinfusion</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Body weight</td>
<td>kg</td>
<td>16.6 ± 3.6</td>
<td>17.5 ± 2.5</td>
</tr>
<tr>
<td>Control cardiac output (C.O.)</td>
<td>L/min</td>
<td>3.6 ± 1.3</td>
<td>3.6 ± 1.0</td>
</tr>
<tr>
<td>CO., after reinfusion</td>
<td>L/min</td>
<td>.33 ± .14</td>
<td>.48 ± .17</td>
</tr>
<tr>
<td>Control blood pressure (B.P.)</td>
<td>mm Hg</td>
<td>160. ± 17.</td>
<td>150. ± 10.</td>
</tr>
<tr>
<td>B.P., after reinfusion</td>
<td>mm Hg</td>
<td>314. ± 16.</td>
<td>91. ± 11.</td>
</tr>
<tr>
<td>Control TPR</td>
<td>mm Hg × min</td>
<td>62. ± 22.</td>
<td>46. ± 25.</td>
</tr>
<tr>
<td>Hematocrit ratio (bet), control</td>
<td>X 100</td>
<td>42.6 ± 7.1</td>
<td>43.1 ± 0.2</td>
</tr>
<tr>
<td>Het, pre-transfusion</td>
<td>X 100</td>
<td>42.7 ± 6.0</td>
<td>48.5 ± 6.4</td>
</tr>
<tr>
<td>Maximum bleeding volume</td>
<td>ml/kg body wt</td>
<td>32.0 ± 7.1</td>
<td>56.2 ± 12.9</td>
</tr>
<tr>
<td>Autotransfusion, per cent of max. bleed</td>
<td></td>
<td>30.0 ± 0.0</td>
<td>39.6 ± 1.1</td>
</tr>
<tr>
<td>Anesthesia to hemorrhage</td>
<td>min</td>
<td>91. ± 42.</td>
<td>152. ± 15.</td>
</tr>
<tr>
<td>Duration 50 mm hypotension</td>
<td>min</td>
<td>92.8 ± 2.8</td>
<td>92.9 ± 3.4</td>
</tr>
<tr>
<td>Hemorrhage to max. bleb</td>
<td>min</td>
<td>59. ± 23.</td>
<td>70.8 ± 13.</td>
</tr>
<tr>
<td>35 mm hypotension</td>
<td>min</td>
<td>74. ± 31.</td>
<td>145. ± 67.</td>
</tr>
<tr>
<td>Total hypotension</td>
<td>min</td>
<td>164. ± 31.</td>
<td>238. ± 65.</td>
</tr>
<tr>
<td>Survival after transfusion</td>
<td>min</td>
<td>152. ± 43.</td>
<td>474. ± 168.</td>
</tr>
<tr>
<td>Survival*</td>
<td>%</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Transfusion, blood</td>
<td>ml/kg body wt</td>
<td>9</td>
<td>38. ± 15.</td>
</tr>
<tr>
<td>Transfusion, plasma</td>
<td>ml/kg body wt</td>
<td>9</td>
<td>11. ± 15.</td>
</tr>
<tr>
<td>Transfusion, dextan</td>
<td>ml/kg body wt</td>
<td>9</td>
<td>14.0 ± 9.</td>
</tr>
<tr>
<td>TPR at maximum blood</td>
<td>PHU</td>
<td>80. ± 20.</td>
<td>75. ± 22.</td>
</tr>
<tr>
<td>TPR at pre-transfusion</td>
<td>PHU</td>
<td>74. ± 20.</td>
<td>63. ± 17.</td>
</tr>
<tr>
<td>Probability</td>
<td>P</td>
<td>.01</td>
<td>.02</td>
</tr>
<tr>
<td>Heart rate at max. bleed</td>
<td>b/min</td>
<td>215. ± 37.</td>
<td>217. ± 32.</td>
</tr>
<tr>
<td>Heart rate, pre-transfusion</td>
<td>b/min</td>
<td>284. ± 24.</td>
<td>188. ± 25.</td>
</tr>
<tr>
<td>Probability</td>
<td>P</td>
<td>.025</td>
<td>.05</td>
</tr>
<tr>
<td>Resp. rate at max. bleed</td>
<td>b/min</td>
<td>48. ± 20.</td>
<td>33. ± 21.</td>
</tr>
<tr>
<td>Resp. rate, pre-transfusion</td>
<td>b/min</td>
<td>33. ± 17.</td>
<td>26. ± 13.</td>
</tr>
<tr>
<td>Probability</td>
<td>P</td>
<td>.01</td>
<td>.1</td>
</tr>
</tbody>
</table>

*Two animals in Group A were killed at 240 and 480 minutes after transfusion when blood pressure was
112 and 200 mm Hg. Those were not included in the calculations of survival after transfusion. The hypotensive
time of the first was only 110 minutes, since a rapid takeoff of blood started at 105 minutes after hemo-
orrhage. The TPR of the second had progressively increased to 840 per cent of control and so had maintained
the arterial blood pressure to a value little different from that immediately after transfusion. The intestinal
tract showed typical hemorrhagic changes. In Group C, one dog was killed 700 minutes following transfusion
after the blood pressure had steadily declined to 40 mm Hg.
1Probability by paired comparison and "t" test between the value of "maximum bleed" and "pre-
transfusion."
unnecessary. Heart rate was determined from the arterial pressure record, and respiration rate from that of central venous pressure.

After at least two control cardiac output determinations, the dogs were hemorrhaged at the rate of about 60 ml/min until 10 ml/kg body weight was removed. After one to two minutes for blood pressure stabilization, cardiac output was determined. Another 10 ml/kg body weight was removed and the cardiac output was determined. Edding was then continued until the pressure was 50 mm Hg. Cardiac output was then measured within five minutes. Pressure was maintained at this level with the Lamson bottle technique so that an increase in pressure caused further hemorrhage and a decrease resulted in reinfusion of shed blood. Ninety minutes after the start of hemorrhage, the arterial pressure was lowered to 35 mm Hg. This pressure was maintained until there was 30% uptake of the maximum volume removed. All of the shed blood was then reinfused, pausing for cardiac output determinations when 20 and 10 ml/kg of body weight of blood were still to be replaced.

Three groups of experiments were conducted. Group A was given no extra transfusion beyond the reinfusion of the shed blood. Groups B and C received extra transfusions of blood, plasma, or dextran (table 1). Group C had had major thoracic surgery for the placement of a transducer around the left ventricle to evaluate cardiac function in another series of experiments about seven days prior to these studies.

Results

The control cardiac output of all 24 experiments was 3.1 ± 1.5 (SD) liter/min or 178 ± 56 (SD) ml/min per kg body weight. The reproducibility of the cardiac output determinations may be evaluated from the difference between the last two control values of each of the 24 experiments. This averaged −0.13 ± 0.42 (SD) liter/min. The coefficient of variation, i.e., the ratio of the standard deviation of the difference between the controls to the mean control determination, was 13%. Since 5 to 20 minutes elapsed between these determinations, much of this variation was physiological. There are wide variations in canine cardiac output. Howell et al.1 reported 2.96 ± 0.78 (SE) liter/min using the Fick method on 245 dogs. They noted a poorer correlation with surface area (0.22 ± 0.66 SE) and also with body weight (0.49 ± 0.50 SE). These conclusions are supported by the data of Smulyan et al.2 Therefore, evaluations were made by noting the percentage change from the control values of each animal, rather
than attempting to reduce the data to units of assumed surface area or body weight.

Early in the hypotensive phase, the average cardiac output of all experiments at a blood pressure of 50 mm Hg was only 0.54 liter/min. This averaged only 19.3 ± 6.6 (SD)% of the average control value. At the same time, the blood pressure was reduced to 33.5 ± 5.7 (SD)% of control. The total peripheral resistance was thus increased to an average of 199 ± 73 (SD)% of control (figs. 1 and 2).

Throughout the hypotensive period, the cardiac output did not change significantly ($P = 2.59; d.f. = 2.46; P > 0.1$). Usually, the total peripheral resistance decreased progressively and significantly ($P = 27.15; P < 0.01$) (figs. 1 and 2). Associated with the circulatory failure during the latter part of the hypotensive phase requiring autoreinfusion, the TPR decreased 12.1 ± 4.0 (SE) mm Hg X min ($P < 0.01$) from the value obtained shortly after the time of the maximum shed volume until the transfusion of all the shed blood. In some experiments, the maximum shed volume occurred during the 50 mm Hg phase. Since the blood pressure was subsequently reduced to 35 mm Hg in these experiments, not only was the TPR significantly reduced, but also the blood pressure by an average of $4.0 ± 1.4$ (SD) mm Hg. Changes in blood pressure complicate the analyses of changes in vascular resistance. A value was available in 22 of the experiments in the early part of the 35 mm Hg phase. Even during this shorter period of analysis, the total peripheral resistance was significantly decreased by $6.1 ± 2.9$ (SD) PRU ($P < 0.05$).

The major portion of the decrease in TPR during this period is not attributable to changes in hematocrit ratio since in nine experiments from which data early in the 35 mm Hg phase were available, the hematocrit significantly increased $7.8 ± 0.9$ (SD) units. The hematocrit ratio was generally higher than control just before transfusion (table 1).

In addition to the decline in TPR, the heart rate and the respiration rate also declined from the high level seen following hemorrhage (table 1). Combining the data of all 24 experiments, the average change from the value during the beginning of autoreinfusion following the time of maximum hemorrhage to that just before reinfusion of the remainder of the shed blood was: heart rate, $-27.6 ± 5.5$ (SE) beats/min ($P < 0.001$) and respiration rate, $-10.7 ± 3.2$ (SE) breaths/min ($P < 0.005$). The probability values were obtained using paired comparisons and the "t" test.

At the completion of the transfusion, which required 10-15 min, the blood pressure was allowed to stabilize before determining the cardiac output. In all 24 experiments, the blood pressure was less than the control value. The cardiac output in 17 experiments, and the TPR in 15 experiments was less than the control value. In 8 of the 24 experiments, the blood pressure, following transfusion, increased to only 65% of the control value or less (avg $58.4\%$). The cardiac output in all eight of these experiments was less than control (avg $65.7\%$), whereas the total peripheral resistance was not significantly different from control (100.2%). Thus, the cause of the poor pressor response to transfusion in these experiments was a reduced cardiac out-
TFR IN SHOCK

During the subsequent progressive fall in blood pressure, the cardiac output again declined to a greater extent than the blood pressure, thereby providing evidence for a compensatory increase in total peripheral resistance.

Finally, with blood pressure of 60 mm Hg or less, the cardiac output was less than control in all 24 experiments, whereas the total peripheral resistance had increased in 15 experiments. There was little or no change in three, and a decrease in only six of the experiments. Among the latter nine experiments with a terminal reduction in TPR, all but one had had a greater than control TPR sometime between transfusion and death. However, considering the degree of blood pressure reduction, the apparent peripheral vasodilation was reduced from that seen earlier during the rapid hemorrhage to comparable blood pressures.

Transfusions of blood, plasma, or dextran prolonged survival after the hemorrhagic hypotension, but were inadequate for long term survival (table 1). In animals given the extra transfusions, the total peripheral resistance also rose as the blood pressure fell (fig. 2). In Group C, those with previous surgery, the average post-transfusion rise in TPR (fig. 2) was smaller. After the blood pressure had declined to about 60 mm Hg, a 20 ml/kg transfusion of dextran caused a reduction of vascular resistance to below control. A major part of this reduction in TPR is attributable to a decrease in blood viscosity caused by the dextran, reducing the hematocrit ratio.

As shown in figures 1 and 2, the slow progressive phase of circulatory failure was not the result of collapse of peripheral resistance. However, the sudden terminal decline in pressure from already hypotensive levels may have been speeded by generalized vasodilation. However, the TPR could not be measured in this series because of the added serious insult of even a 35 ml hemorrhage needed to measure cardiac output by the indicator dilution technique. Therefore, this point could not be definitely established.

Discussion

EARLY HYPOTENSION

In a recent review of the physiology of the peripheral circulation in shock, Green concluded that "there appears to be minimal to no significant net increase in TPR and, therefore, probably only minimal active generalized contraction of arteriolar vessels (resistance vessels) as a compensation for hypotension induced by hemorrhage." If major surgery, or slow hemorrhage were involved, only a small increase in TPR was seen by some investigators. Indeed, some authors have noted a non-significant decline in vascular resistance during hemorrhagic hypotension. These results and conclusions are not supported by our data. Furthermore, numerous other workers reported data indicating an increase in the TPR in response to hemorrhage.

Using electromagnetic flow meters in unanesthetized dogs, Gregg reported only a mild increase in peripheral resistance. However, the rate of hemorrhage was slow, requiring an hour or more to reach 35 to 45 mm Hg. During this time, metabolic agents with vasodilating action might be expected to accumulate to counteract, at least in part, a neurogenic vasoconstriction. In the intact dog, following rapid hemorrhage, our data show a 33% increase in TPR resulting from only a 10 ml/kg hemorrhage. Ochs and Billig reported similar findings. Following hemorrhage at a rate which rapidly reduced blood pressures to 30 to 40 mm Hg, a decrease in cardiac output to less than 20% of control has been observed.

PROLONGED HYPOTENSION

Dilation of peripheral resistance vessels (arterioles) due to accumulation of vasodilator materials or consequent to failure of the vasomotor center generally has not been considered to be an important factor during hemorrhagic shock. Although total failure does not occur, quantitative measurement of progressive changes in the overall state of
the resistance vessels has not been reported because accurate methods for sequential cardiac output determinations were not available. The data of H. C. Wiggers et al. and Waud and Waud support our conclusion that the total peripheral resistance often declines during the period of autoreinfusion. Contrarily, no significant change in TPR during hypotension was reported by Gilmore et al. or Crowell and Guyton. Gilmore and co-workers did not provide evidence that their animals were in irreversible shock. Several lines of evidence predict a decline in TPR from an early high level during the period of oligemia. (a) Vasodilator materials are released into the portal blood during the later part of the hypotensive period. (b) Vasodepressor materials are released into the blood following prolonged intestinal ischemia, a syndrome similar to hemorrhagic shock. (c) Catecholamine concentrations in the blood, which had been increased to about 100 times control, decline later in the hypotensive period. (d) Not only does the catecholamine concentration decrease but the pressor response to norepinephrine declines. (e) The vasomotor response to epinephrine decreases. (f) There is often a reduction in the neurogenic vasoconstrictor tone of the resistance vessels of skeletal muscle during severe hypotension.

The decline in total peripheral resistance occurs despite the slow progressive increase in renal vascular resistance during hypotension and the increase in hematocrit ratio (table 1) seen in the experiments reported here.

The data presented support the hypothesis that neurogenic control of the cardiovascular system progressively decreases during severe, prolonged hypotension in most dogs, and support the conclusions of Fine et al. that the dog takes back shed blood during hemorrhagic hypotension because "compensatory vasodilation is failing and peripheral vascular collapse is beginning." However, although the decline in TPR suggests generalized tissue damage, TPR itself is not probably the primary cause of the autoreinfusion phenomenon since the changes are slight and not seen in all experiments.

The variable, but significant, decline of TPR during severe hypotension suggests a reduced tone of the capacitance vessels and so might account for the autoreinfusion. However, the data of Mellander suggest that a decline in sympathetic activity from a high level would reduce resistance vessel constriction before causing a significant reduction in capacitance vessel tone. The capacitance vessels tend to attain a maximum constriction (minimal volume) at a lower level of either sympathetic fiber stimulation or catecholamine infusion than the resistance vessels. More recent data of Lewis and Mellander show that prolonged skeletal muscle ischemia produced by reducing the perfusion pressure causes a much more rapid and extensive decline in resistance vessel response than in capacitance vessel response. If this relationship continues throughout the autoreinfusion period, the small, but statistically significant, change in resistance suggests an even smaller change in capacitance vessel tone. These authors have suggested that following prolonged ischemia, the activity of the pre-capillary resistance vessels is impaired to a greater extent than the activity of the post-capillary vessels. As a result, the mean capillary pressure tends to rise, leading to an outward movement of fluid from the vasculature. Extensive studies of the relationship between pre-capillary and post-capillary resistance during hemorrhagic hypotension are indicated.

EARLY POST-TRANSFUSION

Total peripheral resistance decreases following transfusion of shed blood as shown by these data and those of others. Arterial blood pressure was always less than the control value. A reduction in cardiac output from control generally accounted for the reduced blood pressure. Continuing vasodilation of some vascular beds, (i.e., reactive hyperemia), following transfusion could have reduced the effectiveness of overall peripheral
constriction, since vasoconstrictor outflow, as monitored by an isolated skeletal muscle preparation appears to continue. Although an increase in total peripheral resistance might be expected as a homeostatic response to the hypotension, the reduced cardiac output appears to be the primary cause of reduced blood pressure. This deficiency in cardiac output is even more striking in those experiments in which the pressor response to transfusion was poor.

**TERMINAL "NORMOVOLUMIC" SHOCK**

In 1950, C. J. Wiggers concluded from the data then available that generalized vasoconstriction was minor in sustaining arterial pressure in hemorrhagic shock and that the general trend during the irreversible stage was toward a decrease. However, we generally have seen a compensatory increase in TPR during the progressive deteriorating phase following transfusion. In the majority of experiments, the data seem to lead to the same conclusion. The TPR decreased to control values, or less, only when the blood pressure had declined to severe hypotensive levels as a result of inadequate cardiac output. An unknown, but possibly important component of the increase in TPR may have resulted from changes in blood viscosity due to increases in hematocrit ratio or sludging or clotting of blood in the vasculature. Although such changes might partially account for a reduction in effective venous pressure and so cardiac output, they do not support a hypothesis of massive collapse of peripheral vascular resistance.

Although Wegrzyn et al. noted a steady and pronounced decrease in TPR following transfusion, and attributed the fundamental failure to this, extensive surgery was involved in these preparations. From more recent work and data presented in this paper, it would appear that a sharp decrease of the TPR occurs only in cases of fulminant cardiovascular failure.

Because the TPR generally increased, whereas the cardiac output in all but one experiment was less than control, the progressive fatal decline in blood pressure was primarily the result of failure of cardiac output. Since one cause of this decrease in output may be a decrease in the effective circulating blood volume, the phase of deterioration following transfusion may well be due to the development of a second phase of oligemia, and thus the term "normovolemic shock" is probably inappropriate in describing this phase of the syndrome, especially late after transfusion.

**Summary**

Cardiac output in the dog was measured by indocyanine green dilution in 24 hemorrhagic shock experiments. Total peripheral resistance (TPR) was calculated from the cardiac output and systemic arterial blood pressure. Early in the hypotensive phase resulting from hemorrhage to 50 mm Hg blood pressure, the cardiac output was 19.3 ± 6.6 (SD) % of control and the total peripheral resistance was 199 ± 73 (SD) % of control. During the hypotensive phase the peripheral resistance declined significantly. This decline in TPR was associated with a significant decrease in respiration and heart rates, indicating a partial failure of the neurogenic control of the cardiovascular system. Following transfusions of the shed blood, the TPR decreased to the control value, but during subsequent progressive decline in blood pressure, vascular resistance again increased. Occasionally, TPR again fell terminally as the blood pressure decreased below 60 mm Hg. Although there is evidence for partial failure of peripheral resistance vessel tone during severe hypotension and some evidence for this following reinfusion of the shed blood, this failure, when observed, is a minor component of the progressive cardiovascular failure and is not the cause of irreversibility.

**References**


TPR IN SHOCK

Control of Total Vascular Resistance in Hemorrhagic Shock in the Dog

CARL F. ROTHE, JAMES R. LOVE and EWALD E. SELKURT

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