Effect of Hemorrhage on the Cardiac Output and Its Distribution in the Rat

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With the technical assistance of Francesco Arcidiacono

The effects of moderate and severe hemorrhage on the cardiac output and its distribution have been studied in the rat. In moderate hemorrhage, cerebral and adrenal blood flow are well maintained through localized vasodilatation while most other organs show increased vascular resistance and diminished blood flow. After severe hemorrhage, despite further changes in territorial resistances, the blood flow is not maintained in any area of the body.

The circulatory response to acute hemorrhage involves a pattern of selective vasoconstriction and vasodilation which brings about a redistribution of the diminished cardiac output. It is generally agreed that the brain and myocardium are favored in this redistribution and that the skin suffers. There is less unanimity regarding other vascular beds. Although most evidence suggests that the splanchnic bed is indifferent or even favored, the teleological attractiveness of the contrary proposition often outweighs the evidence in the teaching of medical physiology. Though evidence has been presented that the blood supply to the kidney is all but completely sacrificed during circulatory embarrassment, there is equally impressive evidence to suggest that in many circumstances the kidneys are favored at the expense of the rest of the circulation during hemorrhage.

Most studies of this subject have been carried out in dogs; a few are based on observation and experiment in man. In most human studies, the effects of pure hemorrhage have been complicated by the coexistence of traumatic shock; this has also been true in some dog work.

The development of methods which can be applied to the measurement of the distribution of the cardiac output in the rat has prompted a series of investigations on the circulatory responses of this species to hemorrhage and shock. The present report is concerned with the early effects of single hemorrhages on the blood flow to various organs of rats.

Methods

The animals used in these studies were females of the Sprague Dawley strain which had been fasted 18 hours before use. Water was allowed during the fast. At the time of the experiment, the animals weighed 175 to 225 Gm. Sodium pentobarbital (40 mg./Kg. intraperitoneally) was used as the anesthetic.

Two levels of hemorrhage were employed, 10 ml./Kg. and 21 to 25 ml./Kg. The smaller hemorrhages were accomplished by withdrawal of blood from the femoral vein after the intravenous administration of 1 mg. heparin per rat. The larger hemorrhages were, in most cases, accomplished similarly. In some cases, the femoral artery and vein were cut together with a razor blade and the lost blood absorbed and weighed on cotton pledgets; bleeding usually stopped spontaneously after the loss of 21 to 25 ml. of blood/Kg. In a few cases, the hemorrhage was from a catheter in the carotid artery. The route of hemorrhage had no discernible effect on the results.
All measurements on hemorrhaged animals were made 10 to 20 min. after hemorrhage.

Mean arterial blood pressures were measured with a narrow bore mercury manometer in normal animals and those subjected to small hemorrhages. Accurate reading of pressure after large hemorrhages required a saline manometer (PE 50 tubing).

Cardiac outputs were measured by the indicator dilution technique, employing Rb86 as the indicator. The details of the method have been described elsewhere.1 The rate of sample collection varied from 22/min. (severe hemorrhage) to 90/min. (controls). The descending limbs of the dilution curves were always fixed by at least 4 points. Extrapolation was made as recommended by Hamilton et al.3

Fractional distribution of blood flow was measured by the indicator fractionation technique using Rb86 for all organs other than the brain and iodo131 antipyrine for the brain. This technique depends on the fact that all organs other than the brain have virtually the same extraction ratio for Rb86 as the whole body during the first minute after a single intravenous injection of the label. The brain and body have the same extraction ratio for iodo131 antipyrine in the same time. The uptake of Rb86 by any organ in this time will be related to total body uptake as is that organ’s blood flow to the cardiac output. Cerebral iodo131 antipyrine uptake is related to total uptake of this label in the same manner as cerebral blood flow is related to cardiac output. The theoretical basis of the technique, the details of its use, and its potential errors have been discussed elsewhere.1'2-4

The killing times chosen were 30 and 60 sec. First recirculation of Rb86 in the dilution curves of animals occurred at 15 to 30 sec. At the time of first recirculation, 92 to 99 per cent of the indicator had been transferred into the arterial circulation. No significant differences were observed in any organ’s uptake of indicator between 30 and 60 sec. Extrapolation to the situation of zero venous drainage required for the application of the indicator fractionation method9 was thereby simplified.

In converting flow fractions to actual flow values, the flow fraction was multiplied by the cardiac output. The cardiac output value used was estimated from the body weight and the value for cardiac output per kilogram determined on a group of rats subjected to treatment similar to that used in the group in which the flow fraction was determined. For simplicity in presentation, actual flow and resistance values are adjusted to those for a 200 Gm. rat.

The resistance values given are based on the ratio of arterial pressure in dynes/cm.·sec. to the derived flow values in cm.·sec.

Results

Cardiac Output and Blood Pressure of Rats After Hemorrhage

In the dog, hemorrhages of 10 and 25 ml./Kg. are tolerated quite well. Both levels are serious hemorrhages in the rat; the latter is eventually fatal.

The cardiac output of normal rats in this colony is 231 ± 43 (S.D.) ml./Kg./min.6 In 12 determinations at the 10 ml./Kg. level of hemorrhage, the cardiac output was 113 ± 30 (S.D.). At the 21 to 25 ml./Kg. level, in 10 determinations, the cardiac output was 29 ± 8 (S.D.)

In blood pressure determinations via carotid catheter, 39 normal animals had a mean pressure of 121 ± 15 (S.D.) mm. Hg; 14 animals at the 10 ml./Kg. level of hemorrhage had a mean pressure of 90 ± 30 (S.D.) mm. Hg, and 25 animals at the 21 to 25 ml./Kg. level of hemorrhage had an arterial pressure of 28 ± 12 (S.D.) mm. Hg. The corresponding peripheral resistances for 200 Gm. rats were as follows: Normals –2.1 × 105 dyne sec./cm.5; 10 ml./Kg. hemorrhage, 3.1 × 105 dyne sec./cm.5; 21 to 25 ml./Kg. hemorrhage, 3.9 × 105 dyne sec./cm.5

Fractional Distribution of Blood Flow After Hemorrhage

Table 1 describes the fractional distribution of blood flow in the organs after the 2 types of hemorrhage employed. The values to all organs other than the brain are obtained from Rb86 distribution at 30 and 60 sec.; the brain values are obtained from iodo131 antipyrine distribution at the same times. Since no significant differences with killing times were observed, all values are reported together.

Table 1 describes the fractional distribution of blood flow in the organs after the 2 types of hemorrhage employed. The values to all organs other than the brain are obtained from Rb86 distribution at 30 and 60 sec.; the brain values are obtained from iodo131 antipyrine distribution at the same times. Since no significant differences with killing times were observed, all values are reported together.

It is important to emphasize here that, in the nature of the indicator fractionation technique, flow fraction of the cardiac output rather than blood flow is the primary datum. The values of table 1 do not depend on knowledge of the cardiac output.

The data of table 2 are derived from those of table 1, and the cardiac output values of similar groups of rats. An important technical
Organ blood flow in hemorrhage

Table 1

<table>
<thead>
<tr>
<th>Organ</th>
<th>Control</th>
<th>%</th>
<th>S.D.</th>
<th>N</th>
<th>10 ml./Kg. hemorrhage</th>
<th>%</th>
<th>S.D.</th>
<th>N</th>
<th>25 ml./Kg. hemorrhage</th>
<th>%</th>
<th>S.D.</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
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<td></td>
<td>0.31</td>
<td>11</td>
<td>2.3</td>
<td></td>
<td>0.88</td>
<td>26</td>
<td>4.1</td>
<td></td>
<td>0.85</td>
<td>11</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.22</td>
<td></td>
<td>0.06</td>
<td>16</td>
<td>0.53</td>
<td></td>
<td>0.14</td>
<td>22</td>
<td>0.46</td>
<td></td>
<td>0.16</td>
<td>19</td>
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<tr>
<td>Heart</td>
<td>2.9</td>
<td></td>
<td>0.48</td>
<td>34</td>
<td>3.8</td>
<td></td>
<td>0.62</td>
<td>22</td>
<td>5.7</td>
<td></td>
<td>2.36</td>
<td>55</td>
</tr>
<tr>
<td>Lungs</td>
<td>3.0</td>
<td></td>
<td>0.37</td>
<td>10</td>
<td>4.4</td>
<td></td>
<td>0.58</td>
<td>22</td>
<td>6.1</td>
<td></td>
<td>1.00</td>
<td>15</td>
</tr>
<tr>
<td>Kidneys</td>
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<td></td>
<td>2.2</td>
<td>30</td>
<td>18.5</td>
<td></td>
<td>3.0</td>
<td>22</td>
<td>11.1</td>
<td></td>
<td>4.0</td>
<td>55</td>
</tr>
<tr>
<td>Liver</td>
<td>6.7</td>
<td></td>
<td>1.5</td>
<td>30</td>
<td>9.7</td>
<td></td>
<td>2.0</td>
<td>22</td>
<td>6.2</td>
<td></td>
<td>2.8</td>
<td>55</td>
</tr>
<tr>
<td>Gut</td>
<td>18.5</td>
<td></td>
<td>2.7</td>
<td>30</td>
<td>21.7</td>
<td></td>
<td>2.0</td>
<td>22</td>
<td>17.3</td>
<td></td>
<td>4.5</td>
<td>55</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.1</td>
<td></td>
<td>0.42</td>
<td>30</td>
<td>1.5</td>
<td></td>
<td>0.33</td>
<td>22</td>
<td>0.6</td>
<td></td>
<td>0.30</td>
<td>55</td>
</tr>
<tr>
<td>Splanchnic bed</td>
<td>26.3</td>
<td></td>
<td></td>
<td>32.9</td>
<td></td>
<td>24.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>8.3</td>
<td></td>
<td>2.0</td>
<td>30</td>
<td>8.2</td>
<td></td>
<td>1.9</td>
<td>22</td>
<td>6.0</td>
<td></td>
<td>2.0</td>
<td>55</td>
</tr>
<tr>
<td>Carcass</td>
<td>44.2</td>
<td></td>
<td>5.1</td>
<td>30</td>
<td>38.8</td>
<td></td>
<td>3.1</td>
<td>22</td>
<td>51.1</td>
<td></td>
<td>7.5</td>
<td>55</td>
</tr>
</tbody>
</table>

*Based on fractional uptake of Iodine-thallium antipyrine (brain) or Rb*. All values are based on the ratio between organ content of label and the injected dose rather than the amount found in the whole animal.

In the normal rat, the sampling of arterial blood for the cardiac output determination involves the loss of about 30 cu. mm./sec., or roughly 3 per cent of the cardiac output. In rats subjected to severe hemorrhage, the bleeding rate is reduced to about 10 cu. mm./sec., and the cardiac output, however, is reduced to a value of the order of 100 cu. mm./sec. It seems possible that the procedure of sampling may in itself reduce cardiac output through the imposition of additional hemorrhage in an animal already in serious circulatory difficulties. The cardiac output value in animals after severe hemorrhage must, therefore, be regarded as minimum values; in the same way the flow values must be considered to be minimum values.

The resistance values of the organs, shown in table 3, are based on the flow values of table 2. Consequently, the values in severe hemorrhage must be considered to be maximal.

The following changes are especially noteworthy:

In 10 ml./Kg. hemorrhage, the cardiac output is reduced to a little less than half its normal value and the blood pressure has declined significantly. This is associated with a diversion of blood flow from the tissues of the carcass (skeletal muscle, bone, etc.) to the internal organs. Of these, the brain and the adrenal profit disproportionately, but the heart, lungs, and splanchnic bed also profit. The kidney and skin maintain their relative positions.

In 21 to 25 ml./Kg. hemorrhage, the brain, adrenal, heart, and lungs become the chief beneficiaries of the circulatory reorganization. The burden of supporting these tissues, previously assumed by the carcass, is now shifted to the kidneys, skin, and splanchnic bed. In fact, the carcass now begins to take over an undue proportion of the diminished cardiac output.

The "compensatory" adjustments, though diminishing the full force of the circulatory catastrophe, are not very efficient. Though the internal organs, excepting the kidney, come off better than the carcass in mild hemorrhage, only the brain and adrenal approximate the normal flow level. In severe hemorrhage, no organ's blood supply is maintained.

The peripheral resistance responds in the same way to mild hemorrhage in every territory investigated except the brain, adrenal, and lungs. Even those organs whose flow fractions improve in mild hemorrhage, e.g. the heart, liver, and spleen, show increased resistance. Their improved standing with respect to other organs depends, not on the fact...
Table 2
Organ Blood Flows of Normal Rats, Rats Subjected to Mild Hemorrhage and Rats Subjected to Severe Hemorrhage
All values referred to 200 gram rat; values as ml/min/organ

<table>
<thead>
<tr>
<th>Organ</th>
<th>Control</th>
<th>Mild Hemorrhage</th>
<th>Severe Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>.56</td>
<td>.52</td>
<td>.24</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.10</td>
<td>0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart</td>
<td>1.34</td>
<td>.86</td>
<td>.13</td>
</tr>
<tr>
<td>Lung</td>
<td>1.38</td>
<td>.98</td>
<td>.35</td>
</tr>
<tr>
<td>Kidneys</td>
<td>8.20</td>
<td>4.02</td>
<td>.64</td>
</tr>
<tr>
<td>Liver</td>
<td>3.3</td>
<td>2.20</td>
<td>.56</td>
</tr>
<tr>
<td>Gut</td>
<td>5.54</td>
<td>4.90</td>
<td>1.00</td>
</tr>
<tr>
<td>Spleen</td>
<td>.50</td>
<td>.34</td>
<td>.035</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>12.14</td>
<td>7.44</td>
<td>1.40</td>
</tr>
<tr>
<td>Skin</td>
<td>4.0</td>
<td>1.9</td>
<td>.34</td>
</tr>
<tr>
<td>Carcass</td>
<td>29.5</td>
<td>8.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>46.8</td>
<td>24.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

that they have shown vasodilation while other organs have shown vasoconstriction, but rather on the fact that they vasoconstrict a little less vigorously than other organs. The brain and adrenal show an actual reversal of this picture while the lungs show no change.

In severe hemorrhage, the peripheral resistance picture is less clear, because of the uncertainty of the flow values. Nevertheless, it seems certain that the brain has further decreased its resistance, and probably that the heart and lungs have decreased theirs below their normal values. It also seems probable that the resistance of the carcass has fallen below its value in mild hemorrhage, and that the resistance of all of the other organs has risen substantially above its value in mild hemorrhage.

Discussion

It should be pointed out that the method of flow fractionation as employed here does not measure blood flow through shunts or through areas in which the blood is not brought into exchanging contact with tissues, but rather only that blood flow which actually "services" the tissues. Shunts can be detected by this method; they are displayed as precipitous tails in the indicator content of an organ during the time period when the curve of arterial indicator concentration is declining rapidly. In the present study, this time period was deliberately passed over since it was felt that the functional rather than the anatomical distribution of blood flow was of interest.

It is also important to emphasize that cardiac output and blood pressures were obtained in animals other than the ones in which flow fractions were measured. The greatest disturbance to the animal is involved in the measurement of the cardiac output; it seems probable that this is significant in the measurements of cardiac output after severe hemorrhage. Organ blood flows are, therefore, probably somewhat underestimated and organ resistances overestimated in these circumstances. In addition to this, it must be borne in mind that all values for absolute flow per organ are derived data based on 2 groups of animals of the same stock. No attempt has been made to carry out the statistical procedures required for evaluation of individual variation in these values.

In comparison of these results with those of others, 3 other points should be mentioned:

1. The responses described are not responses to pure hemorrhage, but rather to hemorrhage in the presence of anesthetic amounts of sodium pentobarbital.
2. The hemorrhages were single ones, accomplished over short periods of time; no attempt was made to adjust the bleeding to the arterial pressure level.
3. Hemorrhages of the magnitude employed are of much greater consequence in the rat than in the dog. This is shown by the substantial fall in cardiac output and blood pressure after the 10 ml./Kg. hemorrhage, which is trivial in the dog, and the catastrophic fall in blood pressure and cardiac output of rats subjected to the larger hemorrhages. It has been noted that hemorrhage of this magnitude is almost invariably fatal in the rat though it is almost never fatal in the dog.

Effect of Hemorrhage on Cardiac Output, Arterial Pressure, and Total Peripheral Resistance (TPR)

The blood pressure fell about 25 per cent in rats subjected to hemorrhages of 10 ml./
ORGAN BLOOD FLOW IN HEMORRHAGE

Kg. At the same time, the cardiac output fell a little more than 50 per cent. The TPR correspondingly increased almost 50 per cent. More severe hemorrhages produced a further lowering of the cardiac output and blood pressure. The TPR increased further to almost double its basal value.

Rises in TPR are characteristically observed in oligemic shock in dogs. H. C. Wiggers and Middleton\textsuperscript{13} and C. J. Wiggers\textsuperscript{14} have stressed that these rises are less regular than is generally believed. In considering individual animals rather than the whole group, we have noted that the same is true of the rat. The reduction in cardiac output after mild hemorrhage was quite regular; the arterial pressure, on the other hand, might, in different animals, remain at the control level or fall to less than the control value. In the whole group, the blood pressure was better preserved than the cardiac output; but some individuals showed the opposite picture. Since our territorial resistance values were based on groups rather than individuals, we were not able to determine what particular vascular areas, if any, were involved in the decline of the total peripheral resistance in these individuals. Substantially, the same type of variability in the TPR was noted in the animals subjected to severe hemorrhage.

Myocardial Blood Flow Fraction, Myocardial Blood Flow, Myocardial Vascular Resistance

The rat after hemorrhage shows an increased myocardial blood flow fraction, i.e., a greater part of the diminished cardiac output perfuses the myocardium than is the case before hemorrhage. Despite this, at both levels of hemorrhage employed, the coronary flow was not increased or maintained, but rather reduced. In the low level hemorrhage the coronary flow was reduced one-third, and with larger hemorrhages, three-fourths. The coronary resistance was increased, though only slightly so, after mild hemorrhage; the coronary resistance in severe hemorrhage was a little less than normal. When allowance is made for the error in cardiac output deter-

Table 3

<table>
<thead>
<tr>
<th>Organ</th>
<th>Controls</th>
<th>Mild hemorrhage</th>
<th>Severe hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x10^5$</td>
<td>$x10^5$</td>
<td>$x10^5$</td>
</tr>
<tr>
<td>Brain</td>
<td>173</td>
<td>138</td>
<td>94</td>
</tr>
<tr>
<td>Adrenal</td>
<td>960</td>
<td>600</td>
<td>800</td>
</tr>
<tr>
<td>Heart</td>
<td>72</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>Lungs</td>
<td>70</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>Kidneys</td>
<td>11.8</td>
<td>17.9</td>
<td>34.8</td>
</tr>
<tr>
<td>Liver</td>
<td>31</td>
<td>33</td>
<td>62</td>
</tr>
<tr>
<td>Gut</td>
<td>11.3</td>
<td>14.7</td>
<td>22.5</td>
</tr>
<tr>
<td>Spleen</td>
<td>194</td>
<td>212</td>
<td>644</td>
</tr>
<tr>
<td>Splanchnic bod</td>
<td>7.96</td>
<td>0.96</td>
<td>10.04</td>
</tr>
<tr>
<td>Skin</td>
<td>25.2</td>
<td>35.8</td>
<td>64.4</td>
</tr>
<tr>
<td>Carcass</td>
<td>4.24</td>
<td>7.40</td>
<td>6.76</td>
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<tr>
<td>TPR</td>
<td>2.09</td>
<td>3.19</td>
<td>3.86</td>
</tr>
</tbody>
</table>

minution, (see Results) this fall is probably more important than it appears.

There is fairly general agreement that coronary blood flow is reduced in hemorrhage. It was first suggested by Wiggers and Werle\textsuperscript{15} that irreversible shock might be associated with impaired coronary flow. Opdyke and Foreman\textsuperscript{16} showed later that there was, in fact, reduced coronary inflow during hypotension. Edwards and his collaborators, Frank et al.,\textsuperscript{18} Theilon et al.,\textsuperscript{19} Takaes\textsuperscript{20} and Horvath et al.,\textsuperscript{21} have all noted a fall in coronary blood flow during oligemic hypotension or in crush shock.

The increase in coronary flow fraction is also well documented. In the experiments of Frank et al.,\textsuperscript{18} the coronary flow fraction was more than tripled in hemorrhage. In Edwards' series, the coronary flow fraction increased more than threefold. Takaes found a threefold increase in coronary flow fraction. Hackel and Goodale observed a similar increase.\textsuperscript{22}

Most authors find coronary resistance to be decreased in hypotension. The data of Frank et al.,\textsuperscript{18} and those of Edwards et al.,\textsuperscript{17} suggest that coronary resistance is reduced about one-
third. In the latter study, coronary flow was measured by the nitrous oxide method. Faulty equilibration, which might be expected in the presence of diminished flow, tends to overestimate the flow. The true flow values may have been lower than the measured ones, and the resistance, consequently, somewhat higher. Opdyke and Foreman found "potential" coronary flow to be substantially elevated in dogs made hypotensive by oligemia.

Our finding of increased coronary resistance in mild hemorrhage is apparently at variance with the above. It should, however, be noted that in the studies referred to decreased coronary resistance was observed at very low arterial pressures. We have not been able to find direct studies of coronary resistance when arterial pressure is reasonably well maintained. It may, however, be of interest that Opdyke and Foreman's "potential" coronary flow fell strikingly to nearly normal values on reinfusion which elevated the arterial pressure. One hour after hemorrhage, coronary resistance was normal in the experiments of Horvath et al.

Though the coronary circulation is reduced in hemorrhage, it is clear that it is not reduced nearly so much as is the work of the heart. In the present experiments, the work of the heart was reduced more than 60 per cent by mild hemorrhage, but the coronary circulation was reduced only one-third. Severe hemorrhage, reducing the coronary flow to one quarter of its normal value was associated with a thirtyfold reduction in the work of the heart. It would appear, as Opdyke has suggested, that in relation to its work, the heart in hypotension is exceptionally well provided for. Another expression of the same finding is that the hypotensive heart has become highly inefficient, as was suggested by Edwards et al. In effect, though the myocardial circulation is supported at the expense of the circulation to other tissues, the support is wastefully expended. Viewed in this light, it would seem unlikely that myocardial ischemia is at fault in the changes of irreversible shock.

But the changes can be viewed in another light. Bing and Michal have suggested that 20 per cent of the energy utilized by the heart is required for cellular maintenance rather than the performance of external work. At very low work loads, this fixed basal obligation may become significant in relation to the total energy required by the heart. In these circumstances, the heart would appear inefficient even in the absence of alterations in biochemical or physical mechanisms for energy utilization.

It would appear probable that when coronary perfusion rates fall below the absolute basal level required for the maintenance of myocardial cellular integrity, there would be irreversible changes in the myocardium, even though the myocardium were exceedingly well perfused in relation to its work load. Irreversibility in shock might then be, as was suggested by Wiggers and Werle, a function of myocardial ischemia. The interesting findings of Sarnoff et al. on the lowering of left atrial pressure in late hemorrhagic shock by coronary perfusion come at once to mind.

Cerebral Blood Flow Fraction, Cerebral Blood Flow, and Cerebral Vascular Resistance

Except for the adrenal, the largest increase in flow fraction observed in any area in mild hemorrhage was noted in the brain. The flow fraction increase was so great, in fact, that cerebral blood flow was maintained at normal levels, despite the decrease in arterial blood pressure. The cerebral vascular resistance was, correspondingly, decreased. In severe hemorrhage, there was a further increase in the cerebral flow fraction, and a further decrease in cerebral vascular resistance, but flow was no longer maintained, falling to less than half the control value.

Though it has long been accepted as established fact that the circulatory adjustments of hemorrhage serve to maintain the cerebral blood flow, we are not familiar with any previous evidence that this is the case. Very few studies have been made on cerebral blood flow in hemorrhage.

Hemorrhage has been reported to reduce...
the cerebral vascular resistance in dogs by Frank et al. and in humans by Stone et al.

In addition, the data given by Fazekas et al. on humans in shock suggest a reduction in cerebral vascular resistance. Despite this fall in the resistance, cerebral blood flow was reduced in all these studies.

Our results, taken in conjunction with these others, suggest that the cerebral blood supply is indeed guarded in the hemorrhaged animal, but that the protection of cerebral blood flow is effective only when the hemorrhage is small to moderate.

Adrenal Blood Flow Fraction, Adrenal Blood Flow, and Adrenal Vascular Resistance

The adrenal gland is the only organ other than the brain which preserves and may even improve its blood flow after a mild hemorrhage. The adrenal blood flow fraction rises from the control value of 0.22 to 0.53 per cent in mild hemorrhage. Adrenal resistance is reduced one-third.

The behavior of the adrenal in severe hemorrhage is a little different. Though the adrenal flow fraction is still well above the normal, its flow is reduced to less than one-third of the normal value. The resistance, though not at normal levels, has risen.

Information on adrenal blood flow in hemorrhage is sparse. It has been reported that the adrenal blood flow of the normal rat is of the order of 0.16 per cent of the cardiac output. It was noted that traumatic procedures (other than hemorrhage) produced an irregular increase in adrenal blood flow, but blood pressure was not measured. ACTH, presumably released in hemorrhage, increases adrenal blood flow markedly.

Frank et al. noted that severe hemorrhages (blood pressure reduced to 30 mm. Hg) in the dog reduced the adrenal blood flow to less than one-fifth normal. The 'normal' values, however, were obtained in animals which had been subjected to surgical manipulation, ether anesthesia, etc. The authors noted that these values may have been unduly high. If our animals after mild hemorrhage are comparable to these controls, the blood flow reductions are quite comparable.

Bronchial Flow Fraction, Bronchial Blood Flow, Bronchial Resistance

The fact that the dilution curve for Rb injected intravenously differs a little from that observed with T-1824 shows that there is a small reservoir in the pulmonary circulation for the alkali metal. Thus the pulmonary content of label represents not only that which is delivered by way of the bronchial circulation, but also some which is taken up by the reservoir. The pulmonary uptake fraction of Rb, therefore, probably overestimates the bronchial flow fraction.

The measurements of Bruner and Schmidt and of Salisbury et al. suggest that that portion of the bronchial blood flow which drains into the pulmonary veins is of the order of 1 per cent of the cardiac output of the dog. The discrepancy between this value and that obtained in the present experiments indicates the need for caution in accepting these values as true measurements of bronchial blood flow. However, the value obtained by the indicator technic may be considered to describe that fraction of the cardiac output which is brought into exchanging contact with the cells of the pulmonary parenchyma, whether contact is made through the capillaries of the bronchial or the pulmonary circulation.

Whatever its route, about 3 per cent of the cardiac output is normally brought into such contact. This value rises almost 50 per cent in mild hemorrhage and is more than doubled in severe hemorrhage. So far as actual flow values are concerned, there is a 30 per cent fall in mild hemorrhage and a 75 per cent fall in severe hemorrhage. Using systemic arterial pressure for the calculation of the resistance of this circuit, it can be seen to remain constant in mild hemorrhage and to decrease a little in severe hemorrhage.

We are not familiar with any other reports on the magnitude of the bronchial circulation in hemorrhage. We wish to stress again that the significance of the values given here is clouded.
Renal Blood Flow Fraction, Renal Blood Flow, and Renal Vascular Resistance

The renal blood flow fraction was essentially unchanged in mild hemorrhage; in severe hemorrhage it was drastically reduced. The renal blood flow was reduced to half its normal value after mild hemorrhage, and to less than one-twelfth its normal value in severe hemorrhage. The renal vascular resistance increased about 50 per cent in mild hemorrhage and showed almost a threefold increase in severe hemorrhage. The increase in renal vascular resistance in response to severe hemorrhage was the largest in the major circulatory areas examined.

The behavior of the renal circulation in hemorrhage and shock has been extensively studied. Most authors, but not all, find that renal blood flow is reduced in oligemia. The renal resistance has been reported to increase by some, and to decrease by others.

Despite the prevailing opinion to the contrary, most studies indicate that the renal blood flow fraction is actually increased in the animal after bleeding. For example, Blalock and Levy making direct measurements observed that the renal blood flow of dogs was diminished by hemorrhage. The cardiac output, however, was diminished more so that the renal fraction of the cardiac output rose. Frank et al. made similar observations. Goodyer and Jaeger found the effective renal plasma flow to remain normal after non-shocking hemorrhage. Though cardiac output was not measured, it must be presumed that it had fallen. Phillips et al. found that the renal circulation was maintained at the expense of the remainder of the circulation after moderate hemorrhages.

The response of the renal vascular resistance to hemorrhage appears to depend on the severity and duration of the hemorrhage. Using large hemorrhages, renal vascular resistance was found to increase by Brandfonbrener and Geller, and Selkurt. Small, non-shocking hemorrhages, used by Goodyer and Jaeger, and Moyer et al. and, in man, by de Wardener and McSwiney resulted in lowering of the renal vascular resistance. Similar relationships are apparent in the findings of Corcoran and Page.

The belief that the renal circulation suffers disproportionately in hemorrhage, as it were, conserving the diminished cardiac output for those areas which had more pressing claims upon it through exclusion of the kidneys from the circulation appears to rest primarily upon the observation of Phillips et al. in the dog and of Lauson et al. in man.

Phillips et al. observed that after a series of bleedings during which renal blood flow was well maintained, there might result a "renal debacle" in which the renal circulation failed more extensively than the cardiac output. Such an outcome was also noted occasionally after single large hemorrhages. Lauson et al. studying men in shock, found the renal fraction of the cardiac output to be depressed many fold in almost all subjects. In both these studies, renal blood flow was estimated by clearance methods. Although Phillips et al. had presented evidence that the extraction ratio of the clearance substance used for the measurement remained the same in circumstances of reduced renal blood flow, Selkurt had suggested that the bladder clearance of PAH might grossly underestimate renal blood flow after renal ischemia. By direct methods, he was able to show that the renal blood flow was considerably reduced in severely hypotensive dogs. Supporting the idea that the diminished cardiac output is preferentially diverted from the kidneys, he stated that the renal fraction of the cardiac output was reduced. Unfortunately, the cardiac output values which were used in the estimation of the renal flow fraction were assumed rather than measured.

In our experiments the kidneys suffered at both levels of hemorrhage. Small hemorrhages reduced renal blood flow and increased renal vascular resistance, but not disproportionately. After large hemorrhages, there was indeed a renal "debacle" in which the circulation to the kidney was compromised not only by the diminished perfusion pressure, but also...
by a dramatic rise in renal vascular resistance. In these circumstances, the liquidation of the kidney contributed to the support of the remainder of the failing circulation.

**Splanchnic Blood Flow, Splanchnic Blood Flow Fraction, Splanchnic Resistance**

The splanchnic circulation is easily seen, both macroscopically and microscopically. It is, therefore, not surprising that when, in hemorrhage, the flow of blood is reduced everywhere, it should be noticed easily in the splanchnic bed. Neither is it surprising that it should be assumed that because the reduction in splanchnic blood flow is obvious, it is excessive.

The idea that the splanchnic blood flow is disproportionately curtailed in hemorrhage has about it, further, a teleological attractiveness which has withstood observations to the contrary for more than 30 years. This is the more astonishing in the face of the fact that no affirmative evidence has been advanced in favor of the proposition that the splanchnic bed suffers to an undue extent in hemorrhage.

The first to show that the splanchnic bed was favored in the animal bleeding were Rous and Gilding. Subsequently, Blalock and Levy, Frank et al., Reynell et al., and Sapirstein et al. observed that the splanchnic fraction of the cardiac output was increased by hemorrhage.

So regular was the finding that the splanchnic blood flow was reduced less than the cardiac output in hemorrhage that it seemed almost as if the splanchnic bed were supported by the remainder of the circulation in circulatory difficulties. Indeed, some studies made it appear that the splanchnic arterioles did not participate in the vasoconstrictor response to hemorrhage of the rest of the circulation.

For the most part, however, hemorrhage has been found to increase the vascular resistance of the splanchnic bed. This increase is, in general, the same as or a little smaller than the increase of the total peripheral resistance. Thus, Werner, McCanon, and Horvath found the estimated hepatic blood flow and cardiac output to fall in exact proportion to each other after small hemorrhages in the dog. Splanchnic resistance and total peripheral resistance both increased to the same extent. Moore and Lawson noted that the splanchnic fraction of the cardiac output remained fixed in the face of hemorrhage, indicating that the behavior of the splanchnic resistance and that of the total peripheral resistance was comparable. A similar conclusion was reached by Sapirstein who observed constancy of the splanchnic fraction of the cardiac output in rats and dogs after hemorrhage, using the indicator fractionation technic. Gilmore presented data which suggested a slight rise of splanchnic resistance in hemorrhage; the data of Hamrick and Myers on single hemorrhages show a similar rise in resistance in the splanchnic bed; in sustained shock the resistance appeared to fall. Selkurt and Brecher observed a 30 per cent increase in the splanchnic vascular resistance in dogs in hemorrhagic shock though they did not regard the results as statistically significant; and Selkurt, Alexander, and Patterson had previously noted an early increase of 55 per cent in the mesenteric vascular resistance of similar dogs.

The present observations show that the splanchnic blood flow fraction is increased some 25 per cent in mild hemorrhage; severe hemorrhage reduced the flow fraction a little. The splanchnic blood flow is less embarrassed than the cardiac output at low levels of hemorrhage; but its value is, nevertheless, not maintained. The splanchnic vascular resistance, which increases somewhat less than the TPR in mild hemorrhage, is nevertheless increased 25 per cent, while in severe hemorrhage the splanchnic resistance is nearly doubled.

It must be emphasized that the finding that the splanchnic flow fraction is not reduced as much as the cardiac output in mild hemorrhage; severe hemorrhage reduced the flow fraction a little. The splanchnic blood flow is less embarrassed than the cardiac output at low levels of hemorrhage; but its value is, nevertheless, not maintained. The splanchnic vascular resistance, which increases somewhat less than the TPR in mild hemorrhage, is nevertheless increased 25 per cent, while in severe hemorrhage the splanchnic resistance is nearly doubled.

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abolic effects, the fact that this ischemia is not so great as it might be does not alter the qualitative fact that the ischemia exists. Although it is probable that increased splanchnic extraction of oxygen in mild hemorrhage\textsuperscript{42, 49, 50, 52} serves to compensate for the reduced blood flow, the blood flow reduction in severe hemorrhage is too great to be so compensated.

Further, it should not be taken from these findings that the splanchnic blood volume does not occupy a special place in the regulation of circulatory homeostasis. As was pointed out by Reynell et al.,\textsuperscript{42} splanchnic venular and venous blood may be made available to the circulation by constriction of these vessels without significant effect on splanchnic vascular resistance.


Clinically, the cutaneous circulation is more easily visualized than any other. The cold, pale skin of the patient in hemorrhagic shock is so conspicuous that this vascular area is regarded as among the first to be sacrificed in the circulatory readjustments. Yet, the evidence which indicates that the cutaneous circulation is disproportionately impaired is remarkably sparse. Only in the studies of Zweifach, Lowenstein, and Chambers\textsuperscript{12} was there evidence of earlier impairment of the cutaneous circulation than of that of another vascular bed (mesenteric). These authors noted that in the rat there was visible reduction in cutaneous blood flow at levels of bleeding less than those required to reduce mesenteric blood flow.

There is abundant evidence to indicate that skin blood flow (rather than the relationship between skin blood flow and cardiac output) is reduced by hemorrhage. Most studies have been based on direct observation of cutaneous blood vessels or plethysmography.\textsuperscript{53-57}

The nature of previous observations of skin blood flow in hemorrhage makes it impossible to draw conclusions regarding the resistance of cutaneous vessels. Direct observation of skin vessels cannot yield the quantitative flow values required for the resistance calculation. Plethysmography is invariably confounded by the fact that muscular tissue and bone are involved in the measurement.

The present results indicate that the cutaneous fraction of the cardiac output is maintained at normal levels after mild hemorrhage; the skin blood flow is reduced and its vascular resistance elevated, but not excessively so. After severe hemorrhage, the skin’s fraction of the cardiac output is reduced, indicating that cutaneous vasoconstriction is now greater than that of the rest of the body: blood is, consequently, diverted from the skin to other areas.

Carcass Blood Flow Fraction, Carcass Blood Flow, Carcass Resistance

The ‘‘carcass’’ measurement in these experiments was made on all the tissues remaining after removal of the internal organs and the skin. Presumably, the value obtained was largely determined by the blood flow to skeletal muscle.

The literature on skeletal muscular blood flow in hemorrhage is very limited. It has been shown that arterial blood flow is decreased and resistance increased in the legs of dogs subjected to shock from intestinal manipulation\textsuperscript{58} or hemorrhage,\textsuperscript{59} but the nature of the methods used for the measurement makes it uncertain that muscular rather than cutaneous responses were dominant. On the other hand, the thoracic cage, though its blood flow is decreased, suffers somewhat less than other organs of the animal after hemorrhage, perhaps because of the increased respiratory activity.\textsuperscript{60}

Our results suggest that there is a substantial increase in peripheral resistance of the skeletal muscles after mild hemorrhage. This is of greater degree than the increase in total peripheral resistance. In this way, the diminished cardiac output is conserved for other organs. In more profound hemorrhage, this effect disappears, and is, in fact, reversed. The carcass now receives more than its normal share of the cardiac output. Its resistance has increased, but less than that of the body as a whole.
The relationship of our observations to those made in unanesthetized men, in whom, during the post-hemorrhagic faint, there is believed to be muscular vasodilation, is not at all clear. It seems possible that the picture in man has no animal counterpart; or that the effects of anesthesia override it.

**Circulatory Readjustments in Hemorrhage**

These findings show that the rat after bleeding redistributes its cardiac output to favor certain organs at the expense of others. The organs favored are the adrenals, brain, heart, and lungs. Their support is accomplished by diversion of blood from skeletal muscle, skin, kidneys, and splanchnic bed.

In mild hemorrhage, the redistribution is so effective that the favored organs maintain a nearly normal blood supply. The circulation to the brain and adrenal is completely preserved; though the myocardial blood supply is reduced, it is reduced less than the work of the heart. The skin, skeletal muscle, kidneys, and splanchnic bed suffer in the redistribution.

In severe hemorrhage, the compensatory mechanisms are no longer adequate to maintain the blood supply of any organ. Despite a decrease in cerebral vascular resistance and further increase in the TPR, the cerebral blood flow is less than half normal. The pattern of vasoconstriction is also shifted. In mild hemorrhage, the resistance of the skin, carcass, and kidney all increase about 50 per cent; the splanchnic vascular resistance increases about 25 per cent. In severe hemorrhage, the resistance of the carcass no longer increases; at the same time, there are spectacular increases in the resistances of kidneys, skin, and splanchnic bed.

It may be noted that if in severe hemorrhage the resistance of the carcass increased to the same extent as that of the kidneys, skin, and splanchnic bed, enough of the cardiac output would be preserved to maintain cerebral, coronary, and bronchial blood flow at normal levels, with some to spare. Conceivably, vascular resistance of the carcass has increased maximally with the smaller hemorrhage. Alternatively, larger hemorrhages may have nervous and endocrine concomitants which increase the activity and metabolic rate of somatic musculature. Local responses to the metabolic alterations might then override the centrally dictated call to vasoconstriction as was proposed by Remington et al. Muscle tissue in a futile response to the circumstances of hemorrhage may thus disable the compensatory mechanisms which are available for its own exclusion from the circulation. The cause of this disability, and its significance in the final vascular collapse of shock remain to be investigated.

**Summary**

Hemorrhages of 10 ml./Kg. in the rat reduce the cardiac output about 50 per cent. Hemorrhages of 21 to 25 ml./Kg. reduce the cardiac output 85 per cent. The arterial pressure falls from 121 (normal) to 90 mm. Hg after the lower level of hemorrhage and to 28 mm. Hg after the larger hemorrhages. The total peripheral resistance increases from 2.1 \( \times \) 10^5 (normal) to 3.2 \( \times \) 10^5 dyne sec/cm.² in 10 ml./Kg. hemorrhage, and to 3.9 \( \times \) 10^5 dyne sec/cm.² in 25 ml./Kg. hemorrhage.

The circulation to the adrenal gland and brain is maintained after the smaller hemorrhage. The myocardial blood flow, though reduced, is reduced less than the work of the heart. Blood flow to all other areas is reduced; the lungs and splanchnic bed show smaller reductions than kidneys, skin, or carcass.

After large hemorrhages, the cerebral blood flow is no longer maintained, though the cerebral vascular resistance falls. Coronary blood flow is very low. Large increases in resistance occur in the kidneys, splanchnic bed, and skin. The vascular resistance of the carcass (skeletal muscle) does not increase correspondingly.

It is suggested that centrally induced activity of skeletal muscle or local metabolic factors are involved in the failure of the carcass to increase its resistance in the same manner as the internal organs after large hemorrhage and that this failure may be related to the final vascular collapse.
Summario in Interlingua

Hemorrhagias amontante a 10 ml per kg de peso corporeo in rats reduce le rendimento cardince per circa 50 pro cento. Hemorrhagias amontante a inter 21 e 25 ml per kg de peso corporeo reduce le rendimento cardince per 85 pro cento. In le prime de iste casos, le tension arterial descende ad le nivello normal de 111 mm de Hg. In le seconde caso, le tension arterial descende a 28 mm de Hg. Le total resistencia peripherie monta ab 2, 1 X 10^5 dyna-sec/cm^2, le valor normal, usque a 3,2 X 10^5 dyna-sec/cm^2 in hemorrhagias de 10 ml per kg de peso corporeo e usque a 3,0 X 10^5 dyna-sec/cm^2 in hemorrhagias de 25 ml per kg de peso corporeo.

Le circulation al glandulas suprarenales e al cerebro es mantene post le plus leve hemorrhagia. Le fluxo de sanguine myocardial es reducite, sed iste reducicio non augenta su resistencia in lo mesme maniera. Post forte hemorrhagias, le fluxo de sanguine cerebral non es mantenite, ben que le resistencia cerebrovascular descende. Le fluxo de sanguine coronaria es molto basse. Marcate augmentos occurre in le resistential del renes, le pulmiones, le pelle, o le carcassa.

Post forte hemorrhagias, le fluxo de sanguine cerebral non es mantenite, ben que le resistencia cerebrovascular descende. Le fluxo de sanguine coronaria es molto basse. Marcate augmentos occurre in le resistential del renes, le pulmiones, le pelle, o le carcassa.

Le resistencia vascular del carcasas (musculo skeletico) non cresce correspondemente. Es suggerito lo possibilitate quo un eontntemente mai meno la resistential del renes, le pulmiones, le pelle, o le carcassa.

Post forte hemorrhagias, le fluxo de sanguine cerebral non es mantenite, ben que le resistencia cerebrovascular descende. Le fluxo de sanguine coronaria es muito basse. Marcate augmentos occurre in le resistential del renes, le pulmiones, le pelle, o le carcassa.

References


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