The Effect of Hemorrhage on Hepatic Blood Flow and Splanchnic Oxygen Consumption of the Dog

By LADD W. HAMRICK, JR., M.D. AND J. D. MYERS, M.D.

Using the BSP extraction technic, the hepatic blood flow of the dog was found to be reduced markedly following a single massive hemorrhage. However, increase in the arterial hepatic venous oxygen difference compensated for as much as 75% reduction in flow; hence, splanchnic oxygen consumption was maintained under these circumstances. Significant reduction of splanchnic oxygen consumption occurred only during sustained shock when hepatic blood flow was so seriously diminished that high oxygen extraction could not compensate for the lowered oxygen delivery to the liver.

Hepatic anoxia has been held responsible for many of the metabolic and circulatory abnormalities occurring during the shock syndrome. For example, the formation and destruction of humoral substances and alterations in carbohydrate and protein metabolism have been attributed to anoxia of the liver. Also, the reversibility of shock in the dog has been linked with deficient oxygen supply to the hepatic parenchyma. Practically all of these studies, however, have been in animals subjected to a degree and type of shock uncommonly observed in man.

Since non-fatal hemorrhage is one of the most frequently encountered clinical forms of the shock syndrome, the present study was designed to determine a) the alterations in hepatic blood flow (EHBf) and splanchnic oxygen consumption (SpO₂) in the dog following a single massive hemorrhage and b) the limit of the ability of the splanchnic area to maintain its oxygen consumption when hepatic blood flow is reduced. The applicability of the bromsulphthalein (BSP) extraction method for measurement of hepatic blood flow to the dog provided a means whereby such a study could be carried out in the intact animal.

METHODS

Eighteen adult mongrel dogs, fasted 12 to 18 hours prior to study, were given 0.09 to 0.12 grams of chloralose per kilogram of body weight, the drug being administered intravenously in 1 per cent solution in physiological saline. The anesthesia obtained was sufficiently light to insure good arterial oxygen saturation, and reflex activity and was usually well maintained. Small supplements of chloralose were occasionally necessary.

Control Studies: After an intravenous priming dose of 50 to 100 milligrams of bromsulphthalein (BSP), an infusion was begun in a foreleg vein and delivered through a calibrated Murphy drip at a rate of 0.065 to 0.13 mgm BSP/min/Kg of body weight. Then a number 7 or 8 cardiac type catheter was inserted via the external jugular vein into a large hepatic vein in either the right or left lobe of the liver, and an inlying needle was placed in a femoral artery. Following a 1 to 2 hour period to allow stabilization of the arterial BSP level and the anesthesia, 5 milligrams of heparin per kilogram were given intravenously. Four pairs of samples were drawn from the hepatic vein and femoral artery at intervals of 5 to 15 minutes over a 15 to 45 minute period for BSP determination. Hepatic venous blood for determination of oxygen content was taken midway between the first and second and third and fourth paired BSP samples. Hematocrit and arterial blood oxygen samples were drawn at the time of the second BSP sample. Arterial blood pressure was measured with a Lilly manometer before and following completion of the sampling, mean pressures being obtained by planimetric integration of the tracings.

Plasma BSP levels were measured colorimetrically as previously described and blood oxygen content

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was determined spectrophotometrically by the method of Hickam and Frayser. The latter procedure was adapted to dog blood by using 15% saponin and by making readings within 5 minutes of the time blood and saponin were mixed.

The hepatic blood flow was calculated using the steps outlined by Bradley and splanchnic oxygen consumption was derived from the product of the hepatic blood flow and the arterial-hepatic venous oxygen difference. Both hepatic blood flow and splanchnic oxygen consumption are expressed as ml/min/kg of body weight. In no instance did the arterial BSP concentration change at a rate of more than 0.0003 mgm/ml/min. Correction for such change was made by using the formula of Bradley.

When this correction was necessary the magnitude of the change in the final value for hepatic blood flow was generally so small as to be of little significance. The total blood volume was assumed to be 100.6 ml/kg of body weight, this value being derived from the data of Gibson and associates.

Single Hemorrhage: Immediately following the control determinations, thirteen animals were bled as rapidly as possible through the arterial needle until 32 to 65 per cent of the estimated total blood volume had been removed by a combination of bleeding through the arterial needle and the sampling during the control study and the first half of the post-hemorrhage determinations. Thirty to 60 minutes later all determinations were repeated.

When there was a significant change in the hematocrit readings after bleeding, the plasma volume was corrected by using the formula PV = Total RBC - RBC removed

\[ PV = \text{Total RBC} - \text{RBC removed} \times 1 - \text{Hct}_b \]

where

\[ \text{Hct}_b = \text{hematocrit reading obtained during the post-hemorrhage determinations} \]

Sustained Shock: Five dogs subjected to a more profound type of circulatory collapse were studied by the above methods and, in addition, total oxygen consumption was measured during both the control and shock periods. A tracheal cannula was inserted and ventilatory volume was measured with a Tissot spirometer. Oxygen content of the expired air was determined every one to three minutes with a Pauling oxygen analyzer. Carbon dioxide content of the expired air was not measured since the type of shock studied in these animals does not alter the respiratory quotient (unpublished observations).

After the control determinations, shock was produced by allowing the dogs to bleed through a femoral artery cannula into an inverted bottle set at such a level that the mean arterial pressure was maintained at 22 to 45 mm. Hg. When blood had ceased entering the bottle (five to 15 minutes after onset of bleeding) all measurements were repeated. Since fluctuations in arterial BSP concentration occurred with regularity in these animals, it was necessary to include all BSP values obtained when the change was 0.0006 mgm/ml/min. or less, but the corrections were so small that there was no interference with the accuracy of the method.

Because of excess reflex activity induced by the operative procedures in three dogs, it was necessary to supplement the usual dose of chloralose with small amounts of morphine sulfate or sodium pentobarbital given intravenously prior to onset of the determinations.

RESULTS

Arterial Pressure

Single Hemorrhage: The mean arterial blood pressure in 12 dogs fell from a control average of 147 mm. Hg to 67 mm. Hg post-hemorrhage. Since chloralose has been shown to produce mild to moderate elevation of the arterial pressure in dogs, the height of the control value can probably be explained on this basis. Even though the decline in pressure in dogs 11 and 13 was only 12 and 16 mm. Hg respectively, the overall mean difference is still highly significant; it represents a pressure fall of 69 mm. Hg or more in each of the other animals.

Sustained Shock: In each of these five animals a consistent and marked diminution of arterial pressure was produced. The mean...
bromsulphthalein removal rate from the control period (0.097 mgm/min/Kg) to the post-hemorrhage period (0.094 mgm/min/Kg) and a consistent increase in the arterial-hepatic venous bromsulphthalein difference in the latter period. Arterial BSP concentration, however, rose from a mean of 1.60 mgm % to 2.42 mgm per cent. Thus, impairment of BSP removal during the post-hemorrhage studies was detectable only by the higher arterial level necessary for removal of essentially the same quantity of dye. Since the arterial bromsulphthalein (BSP) level was essentially constant during the post-hemorrhagic period, its initial rise was apparently occasioned by a more profound BSP removal during or shortly after active bleeding.

Sustained Shock: Removal of bromsulphthalein during sustained shock was more pronounced than that following a single hemorrhage. Even though the corrected BSP infusion rate was reduced from a control mean of 0.11 mgm/min/Kg to 0.076 mgm/min/Kg during shock, the arterial BSP concentration rose from a mean of 1.65 to 2.57 mgm per cent. Compared with the control period, bromsulphthalein removal during shock was sufficiently diminished to prevent excretion of a comparable quantity of dye in spite of the elevation of arterial BSP level.
Hepatic Blood Flow

Single Hemorrhage: A pronounced diminution of hepatic blood flow following hemorrhage occurred in every animal, the mean control flow being 47 ml/min/Kg and the post-hemorrhage value 18 ml/min/Kg (90 per cent reduction). In dogs 11 and 13, hepatic blood flow decreased in the absence of significant hypotension and the reduction would, therefore, seem to correlate better with the diminution of blood volume than with the fall in arterial blood pressure. This relation is borne out by the fact that the per cent reduction of hepatic blood flow for the entire group showed better correlation with the per cent of the total blood volume removed (r = 0.53, p = 0.05) than with the per cent reduction of the mean arterial blood pressure (r = 0.29, p > 0.4).

Sustained Shock: Hematocrit blood flow fell from a mean control value of 52 ml/min/Kg to 14 ml/min/Kg, the average reduction being 69 per cent. There was again a trend toward better correlation between the per cent reduction of the hepatic blood flow with the percent of the total blood volume removed than with the per cent reduction of the mean arterial pressure but, probably because of the limited number of observations, the difference was not statistically significant.

Splanchnic Oxygen Consumption

Single Hemorrhage: The ability of the splanchnic area, and presumably the liver, to
three instances in which hepatic blood flow was most drastically reduced (Dogs 19, 23, and 24) splanchnic oxygen consumption during shock was 60 per cent or less of the control value. In dogs 23 and 24 the control oxygen consumption was considerably higher than in any other experiments, hence the reduction observed in these instances may have been an artefact. Splanchnic oxygen consumption during shock in Dog 24 was so low, however, that there seems little doubt that a significant reduction was produced. In all three of these animals the reduction of the hematocrit reading by hemodilution during shock may have contributed significantly toward diminution of oxygen delivery to the splanchnic area in spite of maintenance of good arterial oxygen saturation. The oxygen saturation of the hepatic venous blood was strikingly diminished during shock in each of the five animals, the mean during shock being 19 per cent and

<table>
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<tr>
<th>Dog</th>
<th>Hematocrit %</th>
<th>Arterial oxygen consumption</th>
<th>Arterial-hepatic venous oxygen difference</th>
<th>Splanchnic oxygen consumption ml/min/kg</th>
<th>Total oxygen consumption</th>
<th>( \text{SpO}_2/\text{Total O}_2 ) %</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Post hemorrhage</td>
<td>Control</td>
<td>Post hemorrhage</td>
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**TABLE 2—Single Hemorrhage**

**Sustained Shock**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Hematocrit %</th>
<th>Arterial oxygen consumption</th>
<th>Arterial-hepatic venous oxygen difference</th>
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<th>Total oxygen consumption</th>
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<td>19</td>
<td>30.4</td>
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<td>92</td>
<td>98</td>
<td>4.0</td>
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**Mean**

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<tr>
<th>Hematocrit %</th>
<th>Arterial oxygen consumption</th>
<th>Arterial-hepatic venous oxygen difference</th>
<th>Splanchnic oxygen consumption ml/min/kg</th>
<th>Total oxygen consumption</th>
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</tr>
</thead>
<tbody>
<tr>
<td>38.5 ± 1.3</td>
<td>26.8 ± 5.4</td>
<td>94 ± 1.1</td>
<td>11.3 ± 0.70</td>
<td>1.9 ± 0.15</td>
<td>1.7 ± 0.15</td>
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</table>

**Mean Difference**

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<th>Arterial oxygen consumption</th>
<th>Arterial-hepatic venous oxygen difference</th>
<th>Splanchnic oxygen consumption ml/min/kg</th>
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<tr>
<td>-8.7 ± 1.7</td>
<td>11.3 ± 0.70</td>
<td>1.9 ± 0.15</td>
<td>1.7 ± 0.15</td>
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<tr>
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<th>Total oxygen consumption</th>
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<tr>
<td>&lt;0.01</td>
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* Morphine sulfate 7 mg/m. 1 hr. 40 min. before study, 7.5 mg/m. 45 min. before study, 7.5 mg/m. 25 min. before study—total 1.7 mg/m/kg.

**Mean**

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**Sustained Shock:** Although sustained shock did not consistently diminish hepatic blood flow beyond the maximal degree of reduction observed following a single hemorrhage, in the three instances in which hepatic blood flow was
the control value 60 per cent. In Dog 24 the value fell to 10 per cent.

Total Oxygen Consumption

During shock there was uniformly a striking reduction of total oxygen consumption. This was most pronounced immediately following the onset of bleeding but a rise occurred thereafter in spite of the maintenance of low arterial blood pressure. The control mean of 6.7 ml/min/Kg of body weight was reduced to a mean of 3.7 ml/min/Kg during shock but this was not accompanied by a consistent change in the ratio of the splanchnic oxygen consumption to total oxygen consumption. In only one instance (Dog 24) was the ratio significantly reduced. Again, these data are difficult to interpret because of the high control splanchnic oxygen consumption values in Dogs 23 and 24.

Discussion

Determination of hepatic blood flow in the dog by the BSP extraction technic has usually given values higher than those obtained by other methods and, for this reason, Werner and Horvath have questioned the validity of the BSP method. However, evidence has been presented that, despite a small positive error, the results are in no way invalidated.

Of all the reported studies of hepatic blood flow in the dog by the BSP extraction technic, only that of Pratt and associates was performed on unanesthetized animals. The remainder were carried out on animals anesthetized with sodium pentobarbital, an agent known to produce varying and unpredictable alterations in circulatory function. In the present study, chloralose was used in an attempt to more nearly approach the unanesthetized state as far as the circulation is concerned. The mean control hepatic blood flow of 48 ml/min/Kg is in agreement with the value of 49 ml/min/Kg reported by Pratt and associates and is, therefore, probably more representative of the true status of the hepatic circulation than the values obtained when sodium pentobarbital anesthesia was used.

Blalock and Levy, by direct measurement of hepatic blood flow in unanesthetized dogs, found a mean reduction of 53 per cent in 5 to 10 minutes following hemorrhage equivalent to 2.1 to 3.4% of body weight. Werner and associates, using the BSP extraction technic, observed a 20 per cent reduction immediately after blood loss equal to 1 per cent of body weight. Heinemann and his collaborators, by the same method, found that hepatic blood flow uniformly showed marked reduction (mean 63 per cent) during the first 10 minutes after hemorrhage but increased toward and, in a few instances, reached control values over the next 10 to 60 minutes in spite of maintenance of low arterial pressure. However, no correlation was made between the amount of blood removed and the persistence of reduction of hepatic blood flow.

The present study, in which blood loss from a single hemorrhage was 3.2 to 6.5 per cent of body weight, revealed no tendency for hepatic blood flow to return to control values during the post-hemorrhage studies, none of which were terminated in less than 50 minutes following hemorrhage. Furthermore, hepatic blood flow remained relatively stable during the post-hemorrhage study period in the dogs subjected to sustained shock. In the dogs subjected to a single hemorrhage good correlation existed between the amount of blood removed and the degree of reduction of hepatic blood flow. It would appear, therefore, that immediately following a single hemorrhage of more than 1 per cent of body weight hepatic blood flow is reduced and that the amount of blood lost determines in large part the degree of reduction and whether or not there is subsequently a return to the pre-hemorrhage level. Thus, the decline in arterial pressure following a single hemorrhage is a poor index of the degree of circulatory embarrassment of the liver, particularly during the phase when peripheral vasoconstriction is pronounced and the arterial blood pressure may be normal or only slightly reduced.

Several studies of splanchnic oxygen consumption in the dog have been reported previously. Blalock and Mason, by direct measurement of hepatic blood flow, found a mean splanchnic oxygen consumption of 1.6 ml/min/
Kg. Others have reported mean values of 1.5 to 2.4 ml/min/Kg. In view of the fact that these values represent wide variations in both hepatic blood flow and arterial-hepatic venous oxygen difference, they are in remarkable agreement with the mean of 2.1 ml/min/Kg obtained in the present study.

Werner and associates found that the slight reduction of hepatic blood flow produced by blood loss of 1 per cent of body weight was not accompanied by a significant change in splanchnic oxygen consumption. Bradley reported similar findings following blood loss of 1.3 to 3.9 per cent of body weight although measurements of splanchnic oxygen consumption were apparently made on only four animals. In the present study, splanchnic oxygen consumption was maintained following a single hemorrhage of 6.5 per cent of body weight and the increase in arterial-hepatic venous oxygen difference compensated for as much as a 79 per cent reduction of hepatic blood flow. Significant reduction of splanchnic oxygen consumption occurred only during sustained shock when there was more profound reduction of hepatic blood flow. These findings reveal a remarkable ability of the splanchnic area to maintain its oxygen consumption by increasing oxygen extraction when hepatic blood flow is reduced and indicate that splanchnic oxygen consumption does not fail until oxygen delivery and removal approach one another. Maintenance of splanchnic oxygen consumption when hepatic blood flow is reduced does not necessarily imply that the oxygen is being utilized through normal metabolic pathways, and the results of this study cannot be interpreted to mean that liver cell function is undisturbed as long as splanchnic oxygen consumption is maintained. The extremely low oxygen content of hepatic vein blood noted in several instances in which splanchnic oxygen consumption was maintained, was undoubtedly associated with profound reduction of oxygen tension in spite of any acidosis which may have been present. This alteration in hepatic metabolism may, in part, account for the early histologic alterations in liver cells following moderate degrees of clinical shock. More severe and sustained circulatory collapse has usually preceded the finding of central necrosis of the liver and it seems probable that in such instances hepatic oxygen consumption was drastically reduced for a prolonged period of time.

SUMMARY

Hepatic blood flow in the dog was found to be reduced markedly 30 to 60 minutes following a single hemorrhage equivalent to 32 to 65 per cent of the estimated total blood volume. The reduction in flow showed better correlation with the percentile blood volume removed than with the magnitude of the arterial pressure fall. There was a striking increase in the arterial-hepatic venous oxygen difference and, accordingly, no change in splanchnic oxygen consumption; Bromsulphthalein removal was moderately reduced.

When hemorrhage was greater and fall in arterial pressure more severe, there was greater reduction in hepatic blood flow and Bromsulphthalein clearance and there was a marked diminution in total oxygen consumption. Splanchnic oxygen consumption was not uniformly maintained under these circumstances.

It is concluded that a single massive hemorrhage in the dog reduces hepatic blood flow but does not alter splanchnic oxygen consumption. The latter fails only during circulatory collapse when hepatic oxygen delivery and removal approach one another.

ACKNOWLEDGEMENT

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