Blood volume, hemodynamic, and metabolic changes in hemorrhagic shock in normal and splenectomized dogs

SHU CHIEN, ROBERT J. DELLENBACK, SHUNICHI USAMI, DAVID A. BURTON, PAUL F. GUSTAVSON, AND VOJISLAV MAGAZINOVIC

Laboratory of Hemorhology, Department of Physiology, College of Physicians and Surgeons, Columbia University, New York City 10032

Hemorrhagic shock has been a subject of many experimental studies. The interpretation of the large body of literature, however, is often difficult. Some of the factors responsible for such difficulty are a) differences in responses among animal species and among individuals within a given species, b) the complicating effect of anesthesia, c) variations in the model used to produce hemorrhagic shock, and d) insufficiency of measurements made (8). Most of the experimental studies have been made on the dog. The extrapolation of these findings to man is hampered by the possession of a large, contractile spleen. Hemorrhage causes the release of cell-rich blood from the canine spleen, thereby changing the distribution of plasma and cell volumes in the circulation (12, 28) and altering the blood viscosity (9). In the present experiments the role of the spleen was evaluated by comparing the responses of normal dogs with those of splenectomized dogs. In order to avoid the complicating effects of general anesthesia (19, 27, 60), it was not used in these experiments. A large number of measurements were made on circulatory and metabolic functions at frequent intervals during various phases of hemorrhagic shock. In the analysis of the results, particular attention was paid to differences between survivals and nonsurvivals.

METHODS

Experimental Protocol

Twenty purebred, adult, male beagles were trained to lie quietly in a supine position without outward signs of discomfort. Ten dogs were splenectomized (SpX) at least 6 months before the experiment, and the other 10 dogs had the spleen intact (SpI). On the day of the experiment, the femoral region of one leg was exposed after local infiltration of lidocaine (Xylocaine, Astra Pharmaceutical Products, Inc., Worcester, Mass.). The femoral artery was cannulated, and a catheter was placed in the right ventricle via the femoral vein. One milliliter of 5,000 USP U/ml heparin was injected via the catheter. Sterile precautions were used in all operative and catheterization procedures.

A modified Wiggers' technique (59) was used to produce hemorrhagic shock. After a control period of 50 min, sufficient blood was removed to lower the arterial pressure to approximately 40 mm Hg. At this level of hypotension, the animal exhibited the clinical picture of hemorrhagic shock (27), with a lack or sluggishness of response to sound and visual stimuli. The oligemic hypotension was maintained for 3 hr by appropriate adjustments of the volume of blood removed. At the end of this oligemic period the shed blood, except for the samples removed for various measurements, was returned. Three hours after retransfusion, the femoral region was closed and 300 mg of lincomycin hydrochloride (Lincocin, The Upjohn Company, Kalamazoo, Mich.) was injected intramuscularly. The dog was then returned to his cage with free access to water. The animals that lived 24 hr after hemorrhage were considered to be survivors. Therefore, the experimental results will be presented as four groups:

SpI-S: dogs with spleen intact, survivals
SpI-D: dogs with spleen intact, nonsurvivals
SpX-S: splenectomized dogs, survivals
SpX-D: splenectomized dogs, nonsurvivals

Measurements of Blood Volume

The blood volume was measured by a dilution technique (12) with the use of three radioisotopes. The cell volume was measured with $^{51}$Cr-labeled autologous red blood cells.
(RBC), and the plasma volume was determined with dog albumin labeled with 131I and 125I by the iodine monochloride method (41). After a blank blood sample had been taken, a measured quantity of a mixture of RBC-51Cr and albumin-125I was injected into the venous catheter, and the catheter and the injection syringe were flushed 3 times with the animal's blood. The amounts injected were smallest in the control measurement and increased progressively in later injections as the background radioactivities rose. The quantities of radioactivity injected were 4–40 μc of 51Cr and 1–10 μc of 131I and 125I. Blood samples were taken from the arterial cannula every 10 min following the injection. One milliliter of the sample was pipetted into a counting tube. The radioactivities of the samples and diluted aliquots of the injection solution were assayed in a well-type scintillation counter connected to a three-channel gamma-ray spectrometer (Packard Instrument Co., Downers Grove, Ill.). The differences in gamma energy spectra allowed the calculation of the activity of each isotope by the following method. The energy settings for the three channels (channels 1, 2, and 3) were 3080, 320–500, and 240–360 kev, respectively. The interchannel ratio counts for 51Cr and 131I standards were designated as follows:

\[ R_1 : \text{channel 1}/\text{channel 3 ratio for 51Cr} \]
\[ R_2 : \text{channel 2}/\text{channel 3 ratio for 51Cr} \]
\[ R_3 : \text{channel 1}/\text{channel 2 ratio for 131I} \]
\[ R_4 : \text{channel 2}/\text{channel 3 ratio for 131I} \]

From the count rates of the blood samples in the three channels (B1, B2, and B3, respectively), the following equations were used to calculate the 51Cr activity of the blood sample in channel 3 (B3), 131I in channel 2 (B2), and 125I in channel 1 (B1):

\[ B_3 = R_3 (B_2 - B_1) / (R_4 - R_3) \]
\[ B_2 = R_2 (B_3 - B_1) / (R_1 - R_2) \]
\[ B_1 = R_1 (B_3 - B_2) / (R_3 - R_1) \]

These activities are in terms of counts per minute per milliliter blood, and they were changed into activities per milliliter cells (for 51Cr) or per milliliter plasma (for 131I and 125I) with the use of the hematocrit values. Preliminary experiments were conducted to test the accuracy of such simultaneous determination of three isotopes. Known amounts of these isotopes were added to blood in vitro to give concentrations similar to those obtained in the in vivo experiment. By using a counting time of 10 or 20 min, it was possible to obtain accuracies for 131I and 125I to better than 1%, but not for 51Cr. This was because of a) the considerable overlapping of energy spectra between 51Cr and 131I and b) the relatively low counting efficiency for 51Cr. The accuracy of 51Cr determination was improved after the removal of 131I. Therefore, after the first counting of radioactive activity, the 1-ml blood sample in the counting tube was centrifuged and most of the plasma was removed without losing any cells. The cells were washed twice by filling the counting tube (capacity approximately 20 ml) with 0.9% NaCl solution and centrifuging. The washed cells from the 1-ml blood sample were then used for the determination of 51Cr activity. Spectral analysis indicated that the washing procedure was adequate in removing the 131I and 125I activities. The use of both albumin-131I and albumin-125I allowed the injection of a plasma label every 30 min without affecting the 60-min disappearance curve following each injection. By extrapolating the semilog time-concentration (activity per milliliter plasma) curve to the time of injection, the zero-time concentration (C₀) was obtained. The plasma volume (PV) was calculated as:

\[ PV = Q/C₀ \]

where Q is the total radioactivity injected. Whenever a two-exponential decay was evident in the curve, the slowly declining second phase was used in the extrapolation. Since only one radioisotope was used for the determination of cell volume, successive injections of RBC-51Cr were made at least 60 min apart. Whenever there was evidence of a slow mixing of the injected RBC-51Cr, the concentrations (51Cr activity per milliliter RBC) obtained in the later, flat portion of the time-concentration curve were averaged to yield the mean 51Cr activity per milliliter RBC, C. The cell volume (CV) was calculated as:

\[ CV = Q'/C' \]

where Q' is the total 51Cr activity injected. The blood volume (BV) is equal to the sum of cell volume and plasma volume:

\[ BV = CV + PV \]

The overall cell percentage (H₀) in the entire circulation was calculated as:

\[ H₀ = 100 CV/BV \]

The hematocrit reading of each arterial blood sample was determined in duplicate after 5 min of centrifugation at 15,000 × g in a microcentrifuge. The reading was multiplied by a plasma-trapping correction factor of 0.97 (11) to give the corrected arterial hematocrit (Hₐ). The ratio of the overall cell percentage to the arterial hematocrit gives the \( F_{cells} \) factor, which reflects the uneven distribution of cells and plasma in the circulation (28):

\[ F_{cells} = H₀/Hₐ \]

The plasma protein concentration in each sample was determined in duplicate by a refractometric method (46).

**Hemodynamic Measurements**

The arterial pressure and the right ventricular pressure were monitored continuously with pressure transducers and a polygraph recorder (Grass Instrument Co., Quincy, Mass.). The cardiac output was determined by the dye-dilution method (31) using indocyanine green and a flow-through cuvette densitometer (Gilford Instrument Laboratories, Inc., Oberlin, Ohio). The total peripheral resistance (TPR) was calculated from the mean arterial pressure and cardiac output. The viscosity of heparinized blood samples was determined at a temperature of 37°C and at shear rates from 52 to 0.05 sec⁻¹ in an air-bearing Couette viscometer (13, 24).

**Metabolic Measurements**

Blood samples were drawn anaerobically from catheters placed in the femoral artery and in the right ventricle. The
Po2, Po2, and pH of the arterial and the mixed venous samples were immediately analyzed with ultramicro instruments (models 123 and 5A, Instrumentation Laboratory, Boston). Blood hemoglobin concentration was measured by the cyanmethemoglobin method (45). Twenty microliters of whole blood were mixed with 5 ml of Drahkin's solution (Unopette 5837, Becton, Dickinson & Co., Rutherford, N. J.), and the optical density was read in a Beckman model B spectrophotometer (Beckman Instruments, Inc., Fullerton, Calif.) at a wavelength of 540 mµ. From these measurements the base excess or deficit was calculated (56).

Enzymatic methods were used for the determination of arterial blood concentrations of pyruvate (P), lactate (L), and glucose and the plasma concentration of uric acid. In blood samples deproteinized with metaphosphoric acid (39), lactate concentration was determined from the conversion of NAD to NADH following the addition of lactic dehydrogenase, and pyruvate concentration was determined by the conversion in the opposite direction (enzyme kits from Boehringer Mannheim Corp., Mannheim, Germany). From the pyruvate and lactate values, the excess lactate was calculated as an index of anaerobic metabolism (34):

\[
\text{excess lactate} = L - P(L_0/P_0) \tag{9}
\]

where L0 and P0 are the control values for lactate and pyruvate, respectively. The blood glucose concentration in deproteinized samples was determined with glucose oxidase (Worthington Biochemical Corporation, Freehold, N. J.), which causes the formation of hydrogen peroxide and the subsequent oxidation of chromogen (52). The plasma concentration of uric acid was determined by following the decrease in absorbance at 29� mµ after the addition of uricase (38).

The oxygen consumption of the dog was determined with the use of a Blalock mask and a Benedict-Roth apparatus. Respiratory rate and pulmonary ventilation were obtained from the spirometer tracing.

**RESULTS**

**Blood Volume**

Control, expected, and measured blood volumes. Five of the 10 dogs with spleen intact died within 24 hr, and so did 5 of the 10 splenectomized dogs. The results obtained before hemorrhage are shown in Table 1. Serial determinations of the activities of three radioisotopes for one representative experiment are shown in Fig. 1. The absence of any influence of 51Cr injection on 131I activity and vice versa indicates the accuracy of the simultaneous determination of these isotopes with overlapping energy spectra. The slowness of the mixing of the injected isotopes can be seen during oligemia (e.g., the second albumin-131I injection in Fig. 1), but such delayed mixing was not observed in the posttransfusion period.

The effects of hemorrhagic shock on CV and PV are presented separately for the survivors (Fig. 2A) and for the nonsurvivals (Fig. 2B). The expected volumes (broken lines) were calculated from the control volumes minus the cumulative volumes removed by sampling and bleeding. With the onset of hemorrhage, the expected PV and CV decreased markedly. In the nonsurvivals the return of a portion of the shed blood was needed between 1-2 hr posthemorrhage, resulting in increases of the expected volumes. In the survivors, there was little uptake of the shed blood throughout the 3-hr oligemic period. For the maintenance of the same arterial pressure at 40 mm Hg, more blood was removed from the SpI dogs than the SpX dogs. The maximum bleeding volume of the SpI dogs was 65% of the control blood volume (or 59 ml/kg) and that of the SpX dogs was 62% (or 44 ml/kg). The difference between these two groups is statistically significant, especially in terms of milliliters per kilogram (Student t test P < 0.01). Retransfusion caused increases in the expected volumes, which did not return to the control levels because of the blood samples removed for the various measurements.

The measured CV and PV in all groups of animals decreased after hemorrhage and rose after retransfusion (Fig. 2). The measured volumes differed from the expected volumes, and the differences were calculated as percentages of the control volumes from the following equations:

\[
\%\Delta CV = 100(CV_m - CV_e)/CV_e \tag{10}
\]

\[
\%\Delta PV = 100(PV_m - PV_e)/PV_e \tag{11}
\]

\[
\%\Delta BV = 100(BV_m - BV_e)/BV_e \tag{12}
\]

where the subscripts m, e, and c refer to measured, expected, and control volumes, respectively.

*Changes in cell, plasma, and blood volumes.* In all four groups of animals, there was a ΔCV of approximately −10% at 110 min posthemorrhage, and this difference between the measured and expected values was statistically significant (Student t test P < 0.05). In the survivors (dashed lines in Fig. 3), retransfusion did not cause a further loss of cell volume within 3 hr, though there was a ΔCV of −20% on

<table>
<thead>
<tr>
<th>TABLE 1. Control blood volume measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal dogs (spleen intact)</td>
</tr>
<tr>
<td>Survivals (n = 5)</td>
</tr>
<tr>
<td>Body Wt, kg</td>
</tr>
<tr>
<td>13.6 ± 1.1</td>
</tr>
<tr>
<td>Volumes, ml/kg (CV)</td>
</tr>
<tr>
<td>44.0 ± 3.1</td>
</tr>
<tr>
<td>48.5 ± 3.9</td>
</tr>
<tr>
<td>92.5 ± 4.6</td>
</tr>
<tr>
<td>Corrected Arterial Hematocrit, %*</td>
</tr>
<tr>
<td>1.00 ± 0.04</td>
</tr>
<tr>
<td>F-cells Factor*</td>
</tr>
<tr>
<td>6.34 ± 0.16</td>
</tr>
<tr>
<td>PP, g/100 ml</td>
</tr>
<tr>
<td>Nonsurvivals (n = 5)</td>
</tr>
<tr>
<td>13.4 ± 2.1</td>
</tr>
<tr>
<td>42.4 ± 3.0</td>
</tr>
<tr>
<td>45.3 ± 4.3</td>
</tr>
<tr>
<td>87.6 ± 2.1</td>
</tr>
<tr>
<td>46.9 ± 2.1</td>
</tr>
<tr>
<td>0.99 ± 0.04</td>
</tr>
<tr>
<td>6.33 ± 0.20</td>
</tr>
<tr>
<td>Splenectomized dogs</td>
</tr>
<tr>
<td>Survivals (n = 5)</td>
</tr>
<tr>
<td>14.8 ± 1.7</td>
</tr>
<tr>
<td>26.9 ± 1.2</td>
</tr>
<tr>
<td>46.9 ± 3.3</td>
</tr>
<tr>
<td>73.8 ± 0.9</td>
</tr>
<tr>
<td>38.3 ± 1.2</td>
</tr>
<tr>
<td>0.91 ± 0.04</td>
</tr>
<tr>
<td>6.02 ± 0.17</td>
</tr>
<tr>
<td>Nonsurvivals (n = 5)</td>
</tr>
<tr>
<td>12.7 ± 1.0</td>
</tr>
<tr>
<td>24.8 ± 1.3</td>
</tr>
<tr>
<td>44.0 ± 4.5</td>
</tr>
<tr>
<td>68.8 ± 3.2</td>
</tr>
<tr>
<td>38.3 ± 0.6</td>
</tr>
<tr>
<td>0.91 ± 0.04</td>
</tr>
<tr>
<td>6.43 ± 0.06</td>
</tr>
</tbody>
</table>

Values given are means ± SE. * Student t test between normal and splenectomized dogs: P < 0.01. † Plasma protein concentration.
FIG. 1. Results from an unanesthetized dog (spleen intact) showing triple-isotope technique of determining blood volume in hemorrhagic shock. Dots and open circles represent radioactivities of albumin-125I and albumin-131I, respectively, solid triangles denote radioactivity of RBC-51Cr. Delayed equilibration of injected RBC-51Cr in control measurement is attributable to slow mixing of injected tracer in spleen. Note slow mixing of injected radiiodinated albumin in several plasma volume measurements made during oligemia: first points in PV curves marked 379 ml and 340 ml.

FIG. 2. Expected and measured cell volume (CV) and plasma volume (PV) in hemorrhagic shock. Volumes are expressed as percentages of control volume. A: survivals. B: nonsurvivals. In both A and B, left panels show results on SpI dogs and right panels denote data on SpX dogs. Note that measured CV generally was less than expected and that measured PV generally was more than expected, except in posttransfusion period of nonsurvivals. Decreases of expected CV and PV during control period and posttransfusion periods were result of blood samples removed.

the next day. In the nonsurvivals (solid lines in Fig. 3), \( \Delta CV \) became increasingly negative during the 3-hr posttransfusion period.

Twenty minutes after hemorrhage, \( \Delta PV \) was approximately +10%. The SpI-D group (solid lines in Fig. 3A) had the greatest initial gain in PV, but their PV fell as oligemia proceeded. In the three other groups, the gain in PV increased progressively to reach maxima of 22% (SpI-S), 27% (SpX-S), and 33% (SpX-D), and these gains were maintained throughout the remainder of the oligemic period. One hour after retransfusion of the shed blood, the PV of the survivals became essentially the same as the PCV, and there was no loss of PV even on the next day. In the nonsurvivals, however, the \( % \Delta PV \) after retransfusion showed a progressive decrease, especially for the SpI-D group.

The values of \( \Delta BV \) (Fig. 3) reflect the combined effect of CV and PV changes. A positive \( \Delta BV \) was found throughout oligemia in all groups except the SpI-D dogs, which showed mainly a negative \( \Delta BV \). Following retransfusion, the \( \Delta BV \) was nearly zero in the survivals but significantly negative (\( P < 0.01 \)) in the nonsurvivals, especially the SpI-D dogs.

The \( F_{selis} \) value (equation 8) did not change significantly in the SpX-S dogs, but decreased slightly (\( P < 0.05 \)) in the SpX-D group, both during oligemia and following retransfusion (Fig. 3). The \( F_{selis} \) value of the SpI dogs was higher than that of the SpX dogs in the control period (\( P < 0.01 \)), decreased in oligemia to levels comparable to those obtained in the SpX dogs with corresponding fates, and rose again after retransfusion.

Hematocrit and plasma proteins. The changes of hematocrit and plasma protein concentration were generally parallel to each other (Fig. 4). Both measurements decreased in oligemia, especially in the SpX dogs. The hematocrit and plasma protein concentration of the SpI-D group rose in late oligemia and overshot the control levels following retransfusion. The total circulating plasma proteins (TPP, in grams) were calculated as the product of the plasma volume and the plasma protein concentration. The calculated TPP was compared with the expected TPP (= control TPP - plasma proteins removed), and the difference was expressed as a percentage of the control TPP:

\[
% \Delta TPP = \frac{PV_m \times PP_m - TPP_{expected}}{PV_c \times PP_c} \times 100
\]

HOURS AFTER HEMORRHAGE

where PP refers to the plasma protein concentration, and the subscripts c and m denote control values and values measured following hemorrhage, respectively. Except for a decrease of less than 10% in the SpI-D dogs, the measured TPP during oligemia showed good agreement with the expected values. Therefore, the increase in plasma volume during oligemia was essentially a gain in protein-free fluid. This ultrafiltrate gain (Fig. 4) was calculated as:

\[
\% \text{ ultrafiltrate gain} = \% \Delta \text{PV} - \% \Delta \text{TPP} \tag{14}
\]

The ultrafiltrate gain reached maximum values approximately 80 min after hemorrhage (Fig. 4). In the SpI-D dogs there was a decrease in ultrafiltrate gain after the attainment of this maximum, indicating a transcapillary loss of protein-poor fluid in late oligemia. In the other groups the maximum ultrafiltrate gain was relatively well maintained throughout oligemia.

\[n\text{ ultrafiltrate gain} = \% \Delta \text{PV} - \% \Delta \text{TPP} \tag{14}\]

Hemodynamic Functions

Cardiac output and total peripheral resistance. During the early phase of oligemic hypotension at 40 mm Hg, the nonsurvivals showed similar or greater bleeding volumes than the corresponding survivals (Fig. 5). In the SpI-D dogs there was a decrease in ultrafiltrate gain after the attainment of this maximum, indicating a transcapillary loss of protein-poor fluid in late oligemia. In the three other groups the maximum ultrafiltrate gain was relatively well maintained throughout oligemia.

Immediately following retransfusion of shed blood, the arterial pressure and cardiac output showed nearly parallel increases in all groups. After these initial rises, the arterial pressure and cardiac output fell, and the TPR increased in all groups. The posttransfusion values for pressure and flow were significantly lower for the nonsurvivals than for the corresponding survivals ($P < 0.05$). Following retransfusion, the TPR of the SpI-D dogs was higher than that in the other groups ($P < 0.05$).

Blood viscosity and vascular hindrance. The blood viscosity values (η) at two shear rates (52 and 0.05 sec$^{-1}$) are plotted in Fig. 6. The control η values of the SpI dogs were higher than those of the SpX dogs ($P < 0.01$). This difference can be attributed mainly to the discrepancy in control hematocrit values. The transcapillary influx of protein-poor fluid during oligemia led to a decrease in η. This decrease in η was least prominent in the SpI-D dogs, which actually showed an increase of η in late oligemia. Following retransfusion, η rose with the hematocrit and plasma protein concentration significantly greater ($P < 0.01$) for the SpI dogs (Fig. 5A) than for the SpX dogs (Fig. 5B). The TPR of SpI dogs rose immediately after hemorrhage; it tended to decrease in late oligemia, but remained higher than the control values (Fig. 5A). The TPR of SpX dogs decreased to below control levels in late oligemia (Fig. 5B). Generally, there was no statistically significant difference in cardiac output or TPR between the survivals and the corresponding nonsurvivals during oligemia.


HOURS AFTER HEMORRHAGE

The decrease in cardiac output during oligemia was sig-
HEMODYNAMICS AND METABOLISM IN SHOCK

Vascular hindrance was estimated from the ratio of TPR to the blood viscosity measured at 52 sec⁻¹. As shown in Fig. 6, the TPR/η ratio increased in oligemia for all groups. For both the SpI and SpX dogs, the TPR/η ratio in the nonsurvivals was higher than that of the survivals in early oligemia, but this high TPR/η ratio was not well maintained in late oligemia. Immediately following retransfusion, the ratio TPR/η either decreased or remained the same as in late oligemia (Fig. 6). The SpI-D dogs showed an increase of TPR/η in the late posttransfusion period.

Heart rate and right ventricular pressure. The heart rate increased during the first 5 min of the rapid bleeding period (Fig. 7). Following a partial recovery, there was a continued increase in heart rate during the early phase of oligemia, reaching a peak value of approximately 230 beats/min in all groups. The stroke volume decreased precipitously during oligemia (Fig. 7). Retransfusion of shed blood caused a reduction in heart rate in all groups. In the posttransfusion period the nonsurvivals showed significantly higher heart rate and lower stroke volume than the survivals (P < 0.05).

The systolic and end-diastolic right ventricular pressures (RVP, and RVPd, respectively) decreased following hemorrhage and showed a transient rise after retransfusion (Fig. 7). Between 1 and 3 hr after transfusion, the RVPd remained essentially constant in the survivors, but it declined progressively in the nonsurvivals. These changes are similar to those found for the cardiac output (Fig. 5).

The relations of RVPd to cardiac output are shown in Fig. 8. In early oligemia, the decrease in RVPd was accompanied by a reduction in cardiac output. As oligemic hypotension was maintained for 1–2 hr, the data for the SpI dogs moved to the left of the initial line connecting the control and the early oligemic points (not shown in Fig. 8), indicating an increase in myocardial performance possibly due to sympathetic stimulation (54). Such evidence for an increase in contractility was absent in the SpX dogs. Retransfusion of shed blood in the SpI dogs caused a shift of the data points to the left of the initial lines. In the SpX dogs, however, retransfusion of shed blood resulted in a shift of the data points to the right of the initial lines, suggesting a deficiency in cardiac emptying power (29, 54), especially in the SpX-D group.

The above suggestion of the occurrence of myocardial failure in the nonsurviving SpX dogs is supported by the findings that pathological change in the ventricular myocardium (endocardial and subendocardial hemorrhage) was most severe in this group (Table 2). In contrast, the normal dogs showed less myocardial damage and greater intestinal lesions in the form of mucosal hyperemia, sloughing, and hemorrhage (Table 2).

Metabolic and Respiratory Functions

Oxygen consumption and pulmonary ventilation. The oxygen uptake decreased after bleeding, returned partially toward control in the midoligemic period, and decreased again in
late oligemia (Fig. 9). Retransfusion caused a rise in $O_2$ uptake to or above the control level. Between 2 and 3 hr posttransfusion $O_2$ uptake tended to decrease in the nonsurvivals. The tidal volume and pulmonary ventilation increased in

**TABLE 2. Frequency and severity of hemorrhagic lesions in ventricular myocardium and intestinal mucosa**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Myocardial Lesions</th>
<th>Intestinal Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Severity</td>
</tr>
<tr>
<td>SpI-S</td>
<td>3/5</td>
<td>+</td>
</tr>
<tr>
<td>SpI-D</td>
<td>4/5</td>
<td>+</td>
</tr>
<tr>
<td>SpX-S</td>
<td>3/5</td>
<td>++</td>
</tr>
<tr>
<td>SpX-D</td>
<td>5/5</td>
<td>+++</td>
</tr>
</tbody>
</table>

**FIG. 7.** Heart rate, stroke volume, systolic right ventricular pressure ($RVP_s$), and end-diastolic right ventricular pressure ($RVP_d$) in hemorrhagic shock. Vertical bars denote 1 SE. A (left): SpI dogs. B (right): SpX dogs.

**FIG. 8.** Correlation of cardiac output and right ventricular end-diastolic pressure in hemorrhagic shock. Data in control period (circles), oligemia (squares, 2 points indicating 20 and 175 min post hemorrhage), and posttransfusion stage (triangles, 2 points representing 20 and 180 min posttransfusion). A (left): SpI dogs. B (right): SpX dogs.


all groups, whereas the changes in respiratory rate were less consistent (Fig. 9). The increase in pulmonary ventilation appears to follow the pattern of the bleeding volume. The uptake of shed blood in late oligemia was associated with a decrease in pulmonary ventilation.

**Blood gases and acid-base balance.** During oligemia, arterial $P_{O_2}$ increased and arterial $P_{CO_2}$ decreased; the arteriovenous differences in $P_{O_2}$ and $P_{CO_2}$ widened (Fig. 10). These changes in blood gases recovered partially after retransfusion. Oligemia caused a decrease in arterial pH (Fig. 10). The SpX-D dogs did not show a lower pH than the SpX-S dogs until the last sample of oligemia ($P < 0.05$). The SpI-D dogs showed a lower pH than the SpI-S dogs ($P < 0.05$) during early oligemia, but the difference was reversed following the uptake of shed blood by the SpI-D dogs in late oligemia. Retransfusion caused the pH to increase in all groups, and the values were not lower in the nonsurvivals. Even samples taken immediately before cardiac arrest
showed a nearly normal pH, provided that respiration had not failed. The metabolic acidosis in oligemia was partially compensated by the lowering of arterial Pco₂ due to hyperventilation. The calculation of base excess showed a base deficit (negative values in Fig. 10) during oligemia and a partial recovery following retransfusion. Although the mixed venous blood showed a higher Pco₂ and lower pH than the simultaneous arterial values \( P < 0.01 \), the calculated base deficit showed no significant arteriovenous difference.

**Lactate, pyruvate, and glucose.** Oligemia caused the blood lactate and pyruvate concentrations to increase (Fig. 11). The increase in lactate concentration was generally more than one-half of the base deficit incurred (Fig. 10). Since lactate increased proportionally more than pyruvate, the calculated excess lactate rose. During early oligemia, the excess lactate was higher in the nonsurvivals than the corresponding survivals \( P < 0.05 \). This difference continued in late oligemia for the SpX dogs. For the SpI dogs, however, the uptake of shed blood by the nonsurvivals (Fig. 5) was associated with a decrease of excess lactate (Fig. 11). Following retransfusion, excess lactate decreased to near zero for all groups, regardless of their fate. The lactate/pyruvate concentration ratio \( (L/P) \) showed a similar trend to the excess lactate, except that a slight increase in \( L/P \) was found in the SpI-D dogs in the late posttransfusion period.

Hemorrhage causes an increase in blood glucose concentration, mainly as a result of sympathoadrenal stimulation (21). The increase in blood glucose concentration in early oligemia was greater \( P < 0.05 \) in the nonsurvivals than the corresponding survivals (Fig. 11). In late oligemia, the glucose concentration of the survivals continued to rise, but that of the nonsurvivals decreased with the uptake of shed blood. In the SpI-D dogs the decline in glucose concentration was associated with a simultaneous decrease in lactate. Retransfusion caused a decline in blood glucose concentration in all groups, and hypoglycemia was found in the nonsurvivals.

The uric acid concentration increased throughout oligemia in all groups (Fig. 12). In late oligemia, the uric acid concentration of the nonsurvivals was significantly higher than that of the corresponding survivals \( P < 0.05 \). Following retransfusion, uric acid decreased in all groups but the difference between nonsurvivals and survivals remained.

**DISCUSSION**

The multitude of measurements made in the present study has made it possible to correlate different parameters and to gain further insights into the pathophysiology of hemorrhagic shock. Thus, from the results on plasma volume, plasma proteins, and cell volume, one can calculate the transcapillary shifts of fluids and proteins and estimate the degree of volume sequestration. From the data on TPR and blood viscosity, the vascular hindrance can be estimated. The simultaneous determination of several metabolic parameters allows an evaluation of their relative merits as indexes of anaerobic metabolism. By comparing the present...
results on unanesthetized dogs with the data on anesthetized dogs in the literature, the effect of general anesthesia in hemorrhagic shock can be assessed. The use of splenectomized (SpX) dogs as well as dogs with spleen intact (SpI) permits an evaluation of the role of the spleen. Finally, the comparison of results between the survivals and nonsurvivals gives some indication of the pathophysiologic mechanism of decompensation in hemorrhagic shock.

Blood Volume

Inasmuch as the initial disturbance in hemorrhagic shock is the loss of blood volume, it is incorrect that blood volume is one of the least commonly measured circulatory parameters in hemorrhagic shock. Because of the uneven distribution of cells and plasma in the circulation, an accurate determination of the total blood volume necessitates the simultaneous measurements of the cell volume and the plasma volume (12, 26). In low-flow states, there may be a marked delay in the equilibration of test substances administered for volume measurement (47, 55). Hence it is essential to obtain a complete time-concentration curve for the proper calculation of the blood volume. In the present study, a triple-isotope technique was utilized: $^{51}$Cr-labeled RBC for the cell volume and $^{14}$C- and $^{125}$I-labeled serum albumin for the plasma volume. Alternate injections of two types of labeled albumin allowed frequent measurements of the plasma volume without curtailing the time-concentration curve following each injection. A delayed mixing of the injected isotopes was often seen during oligemia (Fig. 1), but not in the posttransfusion period.

In general agreement with the results on anesthetized dogs (2, 18, 43), the measured CV and PV in our unanesthetized dogs were often significantly different from the respective volumes expected, and the difference varied according to animal groups and the stage of hemorrhagic shock (Fig. 3). Therefore, the circulating blood volume cannot be simply predicted from the volume bled. The results on blood volume measurements indicate a decrease in the circulating blood volume at the time of uptake of shed blood in late oligemia (Figs. 3 and 5). This finding, which agrees with the results of others (22, 25, 33, 51), suggests that the circulatory deterioration in late oligemia may result partially from reductions in the circulating blood volume and the venous return.

Combination of equations 6, 7, and 8 yields

$$H_a = 100 CV / (F_{cells}(CV + PV))$$

Therefore, the arterial hematocrit is determined by the cell volume, the plasma volume, and the $F_{cells}$ factor, which reflects the distribution of cells between large and minute vessels. Among these three parameters the plasma volume generally showed the greatest change after hemorrhage (Fig. 3). Therefore, hematocrit variations (Fig. 4) may be used as a rough indicator of alterations in plasma volume. Since the cell volume and the $F_{cells}$ factor also changed simultaneously, however, one must be cautious in deducing information on plasma volume from the hematocrit.

The changes of plasma protein concentration in the various groups were generally parallel to those of the hematocrit. The measured total plasma protein during oligemia showed good agreement with the expected values (Fig. 4). Therefore, the increase in plasma volume during oligemia (Fig. 3) was essentially a gain in protein-free fluid. This ultrafiltrate gain (Fig. 4) was calculated by the use of equation 14. In this formulation, the alteration in plasma volume (%ΔPV) is subdivided into a component that is protein free (% ultrafiltrate gain) and a component that contains the circulating plasma protein concentration, and this second component of PV change is equal to %ΔTPP. This concept is similar to that used in renal physiology to partition the urine flow into a free-water clearance and an osmotic clearance. The decrease in plasma volume following retransfusion in the non-survivals (Fig. 3) was accompanied by a reduction in TPP (Fig. 4), indicating a loss of protein-rich fluid rather than ultrafiltrate from the circulation. The calculated ultrafiltrate gain remained positive following retransfusion.

Ultrafiltrate shifts are attributable to alterations in transcapillary fluid exchange between the plasma and the interstitial fluid. A loss in protein-containing fluid, however, may represent either a transcapillary efflux of protein-rich fluid or a sequestration of plasma in some parts of the circulation, or both. These two possibilities may be separated by considering the ΔCV at the same time. Since it is rather unlikely for large amounts of cells to traverse the capillary wall, except in frank hemorrhage, a negative value for %ΔCV usually indicates a sequestration of cells. Therefore, a loss of protein-containing plasma accompanied by a parallel de-
crease in cells would suggest a sequestration of whole blood or frank hemorrhage, whereas such plasma loss unac-
companied by decrease in CV would indicate a transcapillary efflux of plasma only. Since the posttransfusion loss of TPP (Fig. 4) in the nonsurvivals was similar in magnitude to the decrease in CV (Fig. 3), the data suggest a progressive se-
questration or loss of cells and plasma following retransfu-
sion in these animals. This is in agreement with the sugges-
tion in the microvasculature (1, 35) in hemorrhagic shock shown a reduction in red cell deformability (6) and a stag-
nation in the microvasculature (1, 35) in hemorrhagic shock. As there was no slow-mixing phase in the indicator-
dilution curves after retransfusion, the sequestered or lost volume was essentially completely excluded from the cir-
culation.

**Hemodynamic Measurements**

The total peripheral resistance is determined by blood viscosity (η) and vascular hindrance (36). There is ample evidence that vasoconstriction occurs in many regions of the circulation in hemorrhagic shock (5, 8) and that coronary circulation is the only region that undergoes vasodilation. Nevertheless, TPR determinations often fail to show a large increase in hemorrhage (8). The present study indicates that the decrease in η during oligemia may mask the con-
tribution of vasoconstriction to TPR, and the degree of vasoconstriction (or vascular hindrance) can be estimated from the ratio TPR/η. The calculation of this ratio involves some difficulty. The value of η depends on the shear rate, which shows considerable spatial and temporal variations in the circulation (9). In the normal circulation, the shear rate is probably of the order of several hundred seconds⁻¹. During oligemia, as the cardiac output decreased to approxi-
mately one-fifth of the control (Fig. 5), the shear rate would also decrease in a similar fashion. Because of the uncertainty of the exact shear rate involved, we have chosen to use the viscosity at a shear rate of 52 sec⁻¹ (the highest shear rate used in our viscometric measurements) for all calculations. Since η does not change markedly with shear rates above 50 sec⁻¹ (13), the use of a constant shear rate of 52 sec⁻¹ probably does not introduce a large error, even for the control values. It should be emphasized that such a TPR/η ratio can only be regarded as a rough estimate of the degree of vasoconstriction, since the correction for η is merely approx-
imate. As shown in Fig. 6, the TPR/η ratio increased in oligemia for all groups. This is in agreement with the signs of vasoconstriction seen during oligemia, including the decrease of cutaneous temperature, dryness of the oral mu-
cous membrane, and the lack of urine flow. Therefore, the lack of significant increases in TPR can be explained by the masking effect of the concomitant hemodilution and a de-
crease in η. The decrease of the TPR/η ratio of the nonsur-
vivals in late oligemia probably reflected vasodilatation re-
sulting from a decrease in sympatho-adrenal activity and an increase in acid metabolites (8, 42).

**Indexes of Anaerobic Metabolism**

The decrease in oxygen consumption in oligemia (Fig 9) was a consequence of the reduction in oxygen delivery which was not adequately compensated by an increase in the ex-
traction ratio. The reduction in oxygen delivery, in turn, resulted from the decrease in cardiac output (Fig. 5) and a reduction of O₂ carrying capacity as evidenced from the lowering of hematocrit (Fig. 6). The cumulative change in O₂ uptake, \( \int (\Delta VO_2) dt \), has been calculated for the present experiments on unanesthetized dogs (Fig. 12). It should be pointed out that such a calculation does not give a quanti-
tative indication of the O₂ deficit. During oligemia the stimulation of respiration in the unanesthetized dogs (Fig. 9) and the activation of the sympatho-adrenal system (44) would increase the oxygen requirement above that of the control period. Therefore, O₂ deficit was probably greater than that indicated by the cumulative decline in O₂ uptake.

Studying hemorrhagic shock in anesthetized dogs with intact spleen, Crowell and Smith (17) found a correlation between the mortality and the accumulated O₂ debt, but such correlation was not observed by Routie (50). In the present study on unanesthetized SpI dogs, the cumulative decrease in O₂ uptake was greater in the nonsurvivals than survivals both during oligemia and following retransfusion.

During early oligemia, the lactate increased proportion-
ally more than the pyruvate concentration and the cal-
culated excess lactate rose, especially in the nonsurvivals (Fig. 11). The excess lactate tended to decrease with the uptake of shed blood and fell to near zero following retrans-
fusion in all groups. Therefore, the excess lactate serves as a prognostic index only when determined in early oligemia. The prognosis of clinical patients in hemorrhagic shock has also been correlated with the initial blood lactate or excess lactate obtained upon admission (7, 20). The time courses of changes in the lactate and glucose concentrations (Fig. 11) suggest that the decrease in lactate may sometimes reflect a decrease of its carbohydrate precursors. The lactate/glucose concentration ratio (L/G) was fairly constant in the survivals. The L/G ratio of the nonsurvivals also did not change significantly during early oligemia, but it rose slightly in late oligemia and increased further following retransfusion. Since the L/P ratio reflects the severity of anaerobic me-
tabolism during early oligemia, the product of these two ratios, (L/P)(L/G), has been calculated as an index of anaerobic metabolism throughout the hemorrhagic shock experi-
ment (Fig. 12).

Since the lactate forms a major proportion of the base deficit, the relation between lactate and glucose concentra-
tions indicates that the base deficit may also be similarly affected by changes in glucose concentration. The portion of base deficit that is not affected by the anaerobic produc-
tion of lactate is calculated as the alactacid base deficit:

\[
\text{alactacid base deficit} = (\text{BE}_0 - \text{BE}) - (L - L_0) \quad (16)
\]

where \( \text{BE}_0 \) and \( \text{BE} \) are the base excess values for the control and experimental blood samples respectively. This partitioning of base deficit into a lactacid component and an alactacid component is similar to such subdivision of oxy-
gen debt in exercise (40). The other metabolic products of anaerobic glycolysis, e.g., pyruvate, have not been sub-
tracted from the total base deficit because of their relatively low concentrations. Although the base deficit and lactate concentra-
tion both decreased during late oligemia and fol-
lowing retransfusion in the nonsurvivals (Figs. 10 and 11), the alactacid base deficit remained elevated and was sig
sufficiently higher than that of the corresponding survivals (Fig. 12). These results suggest that alactacid base deficit is a sensitive index of anaerobic metabolism and prognosis. The alactacid base deficit probably is composed of mostly inorganic anions (49), especially the phosphates generated from the breakdown of organic phosphate compounds, e.g., creatine phosphate and ATP. Measurements of serum free fatty acids in several experiments showed a decrease during oligemia. Therefore, free fatty acids probably did not contribute to the alactacid base deficit.

Uric acid is a terminal metabolic product of the adenosine nucleotides when ATP breakdown proceeds in anaerobic conditions. The plasma uric acid concentration depends on a balance between the rates of production and excretion. The marked decrease in urine flow during oligemia should contribute to an increase in the plasma uric acid concentration. The rate of uric acid excretion in the urine was determined in control animals and found to be 0.009 mmole/hr. Hence, even a complete cessation of urinary excretion cannot totally account for the rate of rise of uric acid concentration seen in late oligemia, and there must have been an increase in uric acid production. The uric acid concentration of the nonsurvivals was significantly higher than that of the corresponding survivals in late oligemia and following retransfusion. Therefore, these results support the findings of Cowsert et al. (15) that the plasma uric acid concentration is a useful index of the severity of anaerobic metabolism and the fate of the animal in hemorrhagic shock.

**Influence of General Anesthesia on Hemorrhagic Shock**

General anesthesia is known to affect the cardiovascular functions and alters the response of experimental animals to hemorrhagic shock (10, 19, 27, 60). In the present study on unanesthetized SpI dogs, hemorrhagic hypotension at 40 mm Hg was associated with a maximum bleeding volume of 59 ml/kg. This is considerably higher than the values reported in the literature for anesthetized SpI dogs of 40-45 ml/kg (58). Therefore, at the same level of hemorrhagic hypotension, the volume of blood loss is considerably greater in the unanesthetized dogs. The use of unanesthetized animals also reveals certain cardiopulmonary changes in hemorrhagic shock which are blunted by general anesthesia. In pentobarbitalized dogs, the control heart rate is usually above 150 beats/min and hemorrhagic shock caused relatively insignificant and unpredictable changes in heart rate (58). In the unanesthetized dogs, one can demonstrate a biphasic pattern of cardiovascular acceleration: an immediate, transient increase in heart rate during the first 5 min of oligemic hypotension followed by a more gradual, secondary rise to approximately 230 beats/min (Fig. 7). The respiratory response (hyperventilation) in our unanesthetized dogs (Fig. 9) was also much more prominent than that observed in the anesthetized dogs (30, 53). As a result, the arterial $P_{CO_2}$ decreased in late oligemia to an average of 10 mm Hg (Fig. 10), which is much lower than the values reported for the anesthetized animals (23, 30, 53). Therefore, the unanesthetized dogs appear to have stronger cardiovascular and respiratory responses and a greater tolerance to blood loss than the dogs under general anesthesia.

**Role of Spleen**

With the presence of a spleen, the SpI dogs had higher control values for the cell volume and the hematocrit than the SpX dogs ($P < 0.01$), but the control plasma volumes were comparable (Table 1). As a result, the salient hemodynamic differences between the two groups are the presence of a larger blood volume (Table 1) and a higher blood viscosity (Fig. 6) in the SpI dogs.

The control $F_{cells}$ factor averaged 0.91 in the SpX dogs, reflecting the existence of a lower cell percentage in the extraplenic minute vessels than in the large vessels (28). In the SpI dogs, the control $F_{cells}$ factor was near unity, indicating that the low cell percentage in the extraplenic minute vessels was balanced by the high cell percentage in the splenic sinusoids (28). During oligemia, the contraction of the spleen in the SpI dogs resulted in an $F_{cells}$ factor essentially the same as that of the SpX dogs (Fig. 3).

Due to the presence of the splenic reservoir, the SpI dogs can tolerate a larger volume loss than the SpX dogs. The maximum bleeding volume was 59 ml/kg for the SpI dogs and only 44 ml/kg for the SpX dogs. Therefore, the two groups of dogs were actually subjected to different degrees of hemorrhage at the same level of oligemic hypotension. The larger bleeding volume of the SpI dogs was associated with greater decreases in $RVP_d$ (Fig. 7) and cardiac output (Fig. 5). A consideration of the relation between $RVP_d$ and cardiac output indicates an increase in myocardial contractility during oligemia for the SpI dogs. Such myocardial stimulation in oligemia was not seen in the SpX dogs, which instead showed evidence of a decrease in myocardial contractility after retransfusion, especially in the SpX-D group (Fig. 8). Autopsy also indicated that the SpX-D group showed the most severe damage in the ventricular myocardium (Table 2).

The results on plasma volume and plasma proteins indicate that the SpI dogs had less transcapillary ultrafiltrate gain than the SpX dogs during oligemia and that retransfusion caused a transcapillary fluid loss only in the SpI-D group. These fluid shifts were associated with higher values of hematocrit and blood viscosity in the SpI-D dogs in late oligemia and after retransfusion. The transcapillary fluid loss seen in the SpI-D dogs probably reflects a rise in the postcapillary to precapillary resistance ratio in the limb vessels (8, 26, 32, 42), and a portion of this fluid loss may occur in the intestine (14, 48). It is interesting to note that, of the four groups studied, pathologic changes in the intestine were most pronounced in the SpI-D dogs (Table 2).

The present study indicates that the transcapillary loss of protein-poor fluid in oligemia can be prevented by the removal of the spleen. Hollenberg et al. (33) have shown that this fluid loss in the normal dogs can be reduced by the use of phenoxybenzamine (POB), an $alpha$-adrenergic blocking agent. Since POB blocks the splenic contraction after hemorrhage (33), the protective effect of POB against transcapillary fluid loss may be partially attributable to this functional splenectomy, in addition to the reduction of postcapillary-to-precapillary resistance ratio elsewhere. Sympathetic activity and splenic contraction may be synergistic in causing the circulatory deterioration in hemorrhagic shock. Pro-
Hemodynamics and Metabolism in Shock

Longed oligemia causes a loss of vascular reactivity to sympatheic stimulation in the precapillary segments, which may then undergo vasodilation in response to the acid metabolites in the tissue (42). Thus, sympatheic activity would cause a preferential rise of the postcapillary hindrance and an increase in the post-to-precapillary hindrance ratio (8). The increase in blood viscosity due to splenic contraction would be most prominent in the postcapillary segments, where the shear rate is the lowest in the circulation (9). Therefore, splenic contraction would lead to a preferential rise of the postcapillary viscosity and an increase in the post-to-precapillary viscosity ratio (9). These changes in postcapillary hindrance and viscosity in late oligemia caused respectively by sympatheic activity and splenic contraction would both raise the postcapillary resistance and increase the post-to-precapillary resistance ratio. Therefore, the posthemorrhage sympatheic activity and splenic contraction in the SpI dogs may result in a vicious cycle involving transcapillary fluid loss, elevation of blood viscosity, and reducition in venous return (8, 9). Hence, in contrast to the relative importance of myocardial involvement in the SpX dogs, alterations in the peripheral circulation appear to be the prominent factor in the SpI dogs.

Optimum Hematocrit for Oxygen Transport and Survival

The decrease in hematocrit during hemorrhage has a dual effect on oxygen delivery to tissues. The resulting decrease in blood viscosity tends to improve blood flow, but the concomitant reduction in O₂ capacity tends to lower the arterial O₂ content. In organs in which the control O₂ extraction ratio is low (e.g., the skeletal muscle) the posthemorrhage lowering of arterial O₂ content can be compensated by an increase in O₂ extraction, and the predominant effect of hemodilution is flow improvement. In the coronary circulation, where the control O₂ extraction ratio is already high (4), the posthemorrhage lowering of arterial O₂ content would lead to a decrease in the volume of O₂ extracted from each unit volume of blood. Therefore, with extreme hemodilution, such a decrease in coronary O₂ extraction may outweigh the flow improvement and cause a reduction in myocardial O₂ uptake. Hence, the heart may become the limiting organ in hemodilution. This is in agreement with the physiological and pathological evidence of the preferential occurrence of myocardial damage in the SpX-D dogs, which had the lowest hematocrit values (22%) among the four groups studied. The minimum hematocrit in the SpX-S was approximately 25%. The decrease in myocardial O₂ uptake may act together with other factors causing myocardial depression in hemorrhagic shock, e.g., the myocardial depressant factor released from the ischemic pancreas (37).

Among the SpI dogs, the minimum hematocrit was 42% for the SpI-D and 38% for the SpI-S group. The high hematocrit in the SpI-D dogs suggests that the limiting factor in O₂ transport in the presence of the spleen is the associated high viscosity and flow resistance. Therefore, the present study supports the concept that the fundamental disturbance in hemorrhagic shock is a decrease in oxygen transport and serves to illustrate the interaction between the two components of oxygen transport in influencing surivivals. For the splenectomized dogs, which have low hematocrits, the limiting factor is the low arterial O₂ content; whereas for the SpI dogs, which have high hematocrits, the limiting factor is the high viscous resistance. These results are in agreement with the findings in anesthetized dogs that the optimum hematocrit for surviving hemorrhagic shock is 30-35% (16). The data also support the contention that pathophysiological changes in hemorrhagic shock are complex and that different mechanisms may become the limiting factor in varying experimental conditions (8, 16, 50).

In Conclusion—1) The unanesthetized dogs used in the present study tolerated a larger bleeding volume and showed stronger circulatory and respiratory responses to hemorrhagic shock than the anesthetized dogs.

2) The maintenance of the same degree of hemorrhagic hypotension necessitated the removal of a larger volume of blood from the dogs with spleen than from the splenectomized dogs, and the resulting mortality was comparable in these two groups.

3) During oligemia, the dogs with spleen had less transcapillary fluid influx than the splenectomized dogs (Figs. 3 and 4). As a result, the dogs with spleen had higher values for the hematocrit and blood viscosity (η), which were in turn associated with a higher TPR (Fig. 5). The ratio TPR/η, which reflects the degree of vasoconstriction, increased to a greater extent in the nonsurvivals than in the survivals during early oligemia, but this difference disappeared in late oligemia (Fig. 6).

4) Following retransfusion, the arterial pressure and cardic output were lower for the nonsurvivals than the corresponding survivals. During this period, the nonsurviving normal dogs (SpI-D group) showed a progressive loss of the circulating blood volume (Fig. 3) and elevations in η and TPR (Figs. 5 and 6). These rheological changes may aggravate flow stagnation and oxygen deficit, thus contributing to circulatory and metabolic deterioration in the SpI-D dogs. The absence of similar elevations in η and TPR in the nonsurviving splenectomized dogs (SpX-D) indicates that such a viscosity factor is relatively unimportant in the absence of the spleen.

5) In the nonsurviving splenectomized dogs, measurements of cardiac output, right ventricular pressure and blood volume suggest the occurrence of myocardial failure in the late posttransfusion period (Figs. 7 and 8). Pathological studies showed greater myocardial damage in this group than others (Table 2). One of the factors responsible for the severe myocardial damage may be the excessive hemodilution (Fig. 4) and the associated decrease in myocardial O₂ uptake.

6) During oligemia, nonsurvivals showed a more severe degree of stagnant hypoxia and metabolic acidosis than the corresponding survivals (Figs. 10 and 11). The increase in blood lactate concentration during oligemia accounted for more than one-half of the base deficit. In late oligemia, the lactate and base deficit of nonsurviving dogs decreased together with the blood glucose concentration. Retransfusion caused a recovery of blood gases and acid-base balance, and these parameters became essentially normal even in the preterminal samples.

7) In all groups, the oxygen uptake decreased in oligemia and increased after retransfusion (Fig. 12). The cumula-
tive decrease in O\textsubscript{2} uptake of the nonsurviving dogs was greater than that of the survivors, probably reflecting the more severe flow stagnation. Plasma uric acid concentration, blood (L/P)/(L/G) and the alactacid base deficit provided useful indexes of oxygen deficit and prognosis (Fig. 12).

8) The results of circulatory and metabolic studies indicate that pathophysiological changes in hemorrhagic shock are complex. Different mechanisms may become the limiting factor in survival under varying experimental conditions.

The authors appreciate the excellent technical assistance of Ignacio Alvarez de la Campa, Orlando M. Leyva, and Juan Rodriguez. This investigation was supported by Research Grant HL 06139

REFERENCES


