Changes in Forelimb Weight and Segmental Vascular Resistances Following Severe Vascular Hemorrhage

By George J. Grega, James M. Schwinghamer, and Francis J. Haddy

ABSTRACT

The forelimb was used to study capillary fluid fluxes following hemorrhage in dogs anesthetized with sodium pentobarbital. Arterial hemorrhage (48 ml/kg) and 4 hours of hypovolemia produced decreases in forelimb weight, arterial and venous pressures, and skin and skeletal muscle blood flows. Segmental resistances (large artery, small vessel, large vein) in both skin and skeletal muscle increased markedly, and the increase was either completely or largely maintained throughout the hypovolemic period. The large arteries and large veins constricted proportionately more than the small vessels following hemorrhage. In animals that survived the hypovolemic period, the large arteries and large veins constricted almost proportionately, whereas in the animals that died, the large veins constricted proportionately more than the large arteries. The weight loss exceeded forelimb vascular volume, indicating that net extravascular fluid reabsorption occurred. In fact, the weight loss from 60-240 minutes after hemorrhage began appears to be largely attributable to extravascular fluid reabsorption, since resistance and, inferentially, blood volume were relatively constant in the forelimb capacitance vessels. These data fail to support the hypothesis that fluid filtration is a determinant of irreversibility but rather suggest that the compensatory responses to blood loss in the forelimb, i.e., vasoconstriction and net extravascular fluid reabsorption, persist during severe prolonged hemorrhagic hypotension.

KEY WORDS skin and skeletal muscle blood flows hematocrit arterial and venous pressures electrolytes capillary pressure intravascular blood volume extravascular fluid reabsorption anesthetized dogs

Transvascular fluid loss by filtration during the late hypovolemic and posttransfusion periods is frequently said to be an important determinant of irreversibility in hemorrhagic shock (1–3). It is felt that this fluid efflux largely represents filtration into skeletal muscle (4–6) subsequent to a rise in capillary hydrostatic pressure (5, 6) usually attributed to a fall in the ratio of pre- to postcapillary resistance: catecholamines induce postcapillary constriction while precapillary resistance wanes owing to an alleged accumulation of metabolic vasodilator substances (6). In an earlier experiment, we failed to find evidence for fluid efflux into forelimb skin and skeletal muscle in animals subjected to 25 or 50% reductions in blood volume and 4 hours of hypovolemia (7). The possibility exists, however, that the bleeding stresses were not sufficient to produce irreversibility. This prompted a study in which a more severe bleeding stress was used, one which caused death in a significant percent of the animals during the latter part of a prolonged hypovolemic period.

Methods

Dogs of either sex having an average weight of 16.5 kg were anesthetized with sodium pentobarbital (30 mg/kg iv) and allowed to breathe spontaneously through a cuffed endotracheal tube.

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COLLATERAL FREE FORELIMB

The skin of the right forelimb was circumferentially sectioned 3–5 cm above the elbow. The right brachial artery, forelimb nerves, and brachial and cephalic veins were isolated, and the muscles and remaining connective tissue were sectioned by electrocautery. The humerus was cut, and the ends of the marrow cavity were packed with bone wax. Blood entered the limb only through the brachial artery and exited only through the brachial and cephalic veins. The forelimb nerves (median, ulnar, radial, and musculocutaneous) were left intact and coated with an inert silicone spray to prevent drying. Heparin was administered in an initial dose of 10 mg/kg with hourly supplements of 2.5 mg/kg.

Intravascular pressures were measured with small-bore polyethylene tubes inserted into the following sites: (1) skin, small artery from the third superficial volar metacarpal artery on the undersurface of the paw; (2) muscle, small artery from a vessel supplying a flexor muscle in the upper portion of the forelimb; (3) skin, small vein from the second superficial dorsal metacarpal vein on the upper surface of the paw; (4) muscle, small vein from one of the deep vessels draining a flexor muscle in the middle portion of the forelimb; (5) skin, large vein from the cephalic vein via a side branch; (6) muscle, large vein from the brachial vein via a side branch. The small artery catheters were inserted in a downstream direction, while the small vein catheters were inserted in an upstream direction. A cannulated small vessel acts as an extension of the catheter, and thus the catheter measures pressure in the vessels to which the cannulated vessel connects. This pressure is a true lateral pressure as long as the cannulated vessel is patent and without valves (verified by the ability to freely withdraw blood from and to flush into the cannulated vessel). The presence of the catheter does not measurably alter the pressure in the arterial or venous system, because, in the canine forelimb, the cannulated vessel is a negligible fraction of the total cross-sectional area of the arterial or venous bed and there are abundant artery to artery and vein to vein anastomoses (8–10). Pressures were measured with low volume-displacement Statham transducers and recorded on a Sanborn direct-writing oscillograph.

The brachial and cephalic veins were partially transected 3–5 cm downstream from the sites of large-vein pressure measurements, and the distal end of each vessel was cannulated with a short section of polyethylene tubing (P.E. 320). Outflow from both veins was directed into a reservoir maintained at constant volume with a variable speed pump which continuously returned blood to the animal via a cannulated jugular vein. Blood flow was determined by timed collections of the two venous outflows. In this preparation, the median cubital vein represents the major anastomotic channel between the brachial and cephalic veins; this vessel was ligated in all experiments so that the brachial venous flow was predominantly from muscle, whereas cephalic flow was predominantly from skin. Although this approach does not accomplish complete anatomical isolation of skin and muscle, the degree of flow separation is sufficient to permit comparison of resistance changes in the two parallel coupled beds (7, 10–13).

When all cannulas were in position, the limb was suspended on a wire mesh platform attached to a strain-gauge balance which could be calibrated by adding known weights to the platform. The addition of a 2-g weight usually caused a pen deflection of 10–20 mm. Mean systemic arterial blood pressure was continuously monitored from a catheter in the lower abdominal aorta. After a 15-minute control period, all animals were bled (48 ml/kg) through a cannula in a carotid artery into a sterile container kept at 37°C. Limb weight was continuously monitored, and all pressures and flows were determined twice during the prehemorrhage control period, 2, 5, 10, and 15 minutes after initiation of bleeding, and every 15 minutes thereafter throughout a 4-hour hypovolemic period. After 4 hours, the animals were transfused with the shed blood (n = 10) or with an equal volume of 6% dextran 70 in saline (n = 10).Pressures and flows were determined 5, 15, 30, and 45 minutes after blood or dextran transfusion was initiated. Total and segmental (large artery, small vessel, large vein) vascular resistances in muscle and skin were calculated by dividing brachial or cephalic blood flows into corresponding pressure gradients. In addition, combined muscle and skin total and segmental vascular resistances in the forelimb (7, 12, 13) were calculated as:

\[
\text{Total forelimb resistance} = \frac{R_{sa} \times R_{sm}}{R_{sa} + R_{sm}}
\]

\[
\text{Total forelimb large artery resistance} = \frac{R_{sa} \times R_{ma}}{R_{sa} + R_{ma}}
\]

\[
\text{Total forelimb small vessel resistance} = \frac{R_{sva} \times R_{svm}}{R_{sva} + R_{svm}}
\]

\[
\text{Total forelimb large vein resistance} = \frac{R_{ve} \times R_{vme}}{R_{ve} + R_{vme}}
\]

where \( R = \) resistance in mm Hg min/ml 100 g⁻¹; \( t = \) total; \( s = \) skin; \( m = \) muscle; \( a = \) large artery; \( s-v = \) small vessel; \( v = \) large vein.

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Mean transmural pressure in each segment was obtained from the following relationship: 
\[ \frac{P_1 + P_2}{2} \]
where \( P_1 \) = inflow pressure and \( P_2 \) = outflow pressure for a given segment.

The systemic arterial plasma concentrations of sodium, potassium, calcium, and magnesium, the hematocrit, and the plasma osmolarity were determined on arterial blood samples drawn during the control period, at hourly intervals during the hypovolemic period, and at the end of the posttransfusion period. Sodium and potassium were measured with a flame photometer, calcium and magnesium by atomic absorption. Osmolarity was measured by the freezing-point depression method. Hematocrit ratios were determined in triplicate by the microcapillary technique. Arterial pH was measured with a Radiometer pH meter.

**INTACT FORELIMB**

Six dogs (mean weight 24 kg) were positioned so that the intact right forelimb rested on the balance platform with the shoulder joint acting as a fulcrum. This method provides a reliable means of following the direction of weight change (8). Estimated blood volume was depleted by 48 ml/kg, and limb weight and systemic pressure were continually monitored throughout a 4-hour hypovolemic period and for 45 minutes after transfusion of the shed blood began. Severe blood loss will decrease right atrial pressure and increase resistance in the large vein segment between the elbow and the right atrium. These two factors which tend to lower and raise capillary hydrostatic pressure, respectively, are absent in the collateral free forelimb preparation, because the vessels between the elbow and right atrium are bypassed by diverting the venous flow through tubes with a fixed outflow pressure. With the intact limb preparation, it was possible to determine if there was a qualitative difference in the weight response to bleeding when these two determinants of capillary hydrostatic pressure were operative. In addition, the surgical trauma associated with the collateral free forelimb preparations was eliminated.

**Results**

**COLLATERAL FREE FORELIMB**

Responses in Animals Surviving 4 Hours of Hypovolemia.—Thirty-four dogs were used in this part of the study. Only 20 of 34 survived 4 hours of hypovolemia as a result of the severity of the bleeding stress. Of the 14 dogs that died, 6 survived less than 90 minutes. The data from these 6 animals are not included. All data are reported as the mean or the mean ± se. Student's t-test was used to determine if responses following hemorrhage were significantly different from those in the control period.

**Bleeding Time.**—The rate of blood loss was adjusted so that systemic pressure remained at least 40 mm Hg throughout the bleeding period. In the first 30-45 minutes (rapid bleeding phase), blood volume was depleted by 40 ml/kg; an additional 60-75 minutes...
was required to remove the final 8 ml/kg (slow bleeding phase).

Forelimb Weight.—The limbs (430 ± 21 g) were isogravimetric prior to bleeding. Hemorrhage always produced a continuous decline in forelimb weight which averaged 27.9 ± 1.4 g after 4 hours of hypovolemia (P < 0.05) (Fig. 1). With dextran transfusion, limb weight increased but was still significantly below (−6.2 ± 1.0 g) control 285 minutes after hemorrhage began (P < 0.05). With blood transfusion, limb weight also increased but was still significantly below (−11.6 ± 1.4 g) the prehemorrhage control value 285 minutes after hemorrhage began (P < 0.05).

Pressure.—Hemorrhage consistently produced rapid reductions in all arterial and venous pressures (Figs. 1-3), and they remained significantly below prehemorrhage control levels throughout the hypovolemic period (P < 0.05).

All transmural pressures (Table 1) fell during the first hour of hemorrhage. From 60–240 minutes, transmural pressure either


TABLE 1
Effects of Arterial Hemorrhage on Large Artery, Small Vessel, and Large Vein Mean Transmural Pressure (mm Hg) in Forelimb Skeletal Muscle and Skin

<table>
<thead>
<tr>
<th></th>
<th>Control 0 minutes</th>
<th>15 minutes</th>
<th>60 minutes</th>
<th>120 minutes</th>
<th>165 minutes</th>
<th>240 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Large artery</td>
<td></td>
<td></td>
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<tr>
<td>S</td>
<td>96</td>
<td>39</td>
<td>42</td>
<td>42</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>D</td>
<td>108</td>
<td>39</td>
<td>43</td>
<td>41</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Small vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
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<td>19</td>
<td>21</td>
<td>21</td>
<td>14</td>
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</tr>
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<td>Large vein</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>11.0</td>
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<td>3.3</td>
<td>3.2</td>
<td>3.5</td>
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<td>2.7</td>
<td>3.0</td>
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<td></td>
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<tr>
<td>Large artery</td>
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<td>41</td>
<td>42</td>
<td>42</td>
<td>37</td>
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<tr>
<td>D</td>
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<td>38</td>
<td>40</td>
<td>40</td>
<td>27</td>
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<tr>
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<td></td>
<td></td>
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<tr>
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<tr>
<td>D</td>
<td>48</td>
<td>18</td>
<td>18</td>
<td>19</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Large vein</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>7.5</td>
<td>3.8</td>
<td>4.0</td>
<td>4.1</td>
<td>4.3</td>
<td>4.3</td>
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<tr>
<td>D</td>
<td>6.4</td>
<td>1.8</td>
<td>3.6</td>
<td>3.8</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

S = animals which survived the hypovolemic period (n = 20); D = animals which died after 165 minutes of hypovolemia (n = 8). The arterial hemorrhage was 48 ml/kg body weight.

decreased slightly (large artery and small vessel segments) or remained constant (large vein segments).

Blood Flow.—Total forelimb blood flow fell from a control value of 29.4 ± 3.2 to 1.3 ± 0.3 ml/min 100 g⁻¹ after 4 hours of hypovolemia (P < 0.05) (Fig. 1). Muscle (Fig. 2) and skin (Fig. 3) blood flows decreased from 13.6 ± 2.0 and 16.0 ± 2.0 ml/min 100 g⁻¹, respectively, to 0.6 ± 0.1 and 0.7 ± 0.2 at 240 minutes (P < 0.05).

Total Resistances.—Total forelimb resistance increased from 4.3 ± 0.5 to 38.1 ± 3.0 (mm Hg min)/(ml 100 g⁻¹) at the end of the hypovolemic period (P < 0.05) (Fig. 4) while total muscle (Fig. 5) and skin (Fig. 6) resistances increased from 9.7 ± 1.1 and 7.7 ± 0.9 (mm Hg min)/(ml 100 g⁻¹) to 89.1 ± 4.0 and 93.3 ± 25.0 (P < 0.05).

Segmental Resistances.—Large artery, small vessel, and large vein resistances in skin (Fig. 6) increased from 2.0 ± 0.2, 5.4 ± 1.0, and 3.0 ± 0.3 (mm Hg min)/(ml 100 g⁻¹), to 32.9 ± 8.0, 50.1 ± 7.0, and 8.5 ± 2.2 after 4 hours of hypovolemia (P < 0.05). Muscle large artery, small vessel and large vein resistances (Fig. 5) increased from 2.3 ± 0.5, 7.3 ± 0.9, and 0.28 ± 0.8 (mm Hg min)/(ml 100 g⁻¹) respectively, to 35.8 ± 9.0, 45.5 ± 6.5, and 4.0 ± 1.2 after 4 hours of hypovolemia (P < 0.05). The mean values reported in Figures 5 and 6 indicate that all vascular segments remained constricted throughout the hypovolemic period. However, for 5 of 20 dogs in this series, skin and muscle total and segmental vascular resistances were maximal during the first hour of hypovolemia and decreased 60-240 minutes after hemorrhage began. This partial waning of the hemorrhage-induced vasoconstriction was always associated with a slowly declining arterial blood pressure. For the remaining 15 dogs, all vascular resistances in skin and muscle either remained elevated or increased further during the last 3 hours of hypovolemia.

The large artery-large vein resistance ratios (Table 2) were usually unchanged relative to control in muscle and skin (P >
The prevenous-venous resistance ratio (ratio of large artery plus small vessel to large vein) was decreased in both muscle and skin throughout the hypovolemic period ($P < 0.05$).

Table 3 shows percent of total skin and muscle resistance residing in each of the three series-coupled vascular segments during the prehemorrhage control period and at the end of the hypovolemic and posttransfusion periods. During the late part of the hypovolemic period, the large vessel segments accounted for a greater percent of the total resistance in skin and muscle than they did during the control period, while the small vessel segment accounted for a smaller percent of the total resistance relative to control.

**Hematocrit, pH, Osmolarity, and Electrolytes.**—Arterial pH, Na$^+$ and Ca$^{2+}$ did not change significantly during the hypovolemic period.

---

**FIGURE 4**

*Effect of arterial hemorrhage on forelimb total and segmental vascular resistances—(mm Hg min)/(ml 100 g$^{-1}$). Symbols and $n$ values correspond to those in Figure 1.*

**FIGURE 5**

*Effect of arterial hemorrhage on total and segmental vascular resistances in forelimb muscle. Symbols and $n$ values correspond to those in Figure 4.*
period or after blood transfusion. Osmolarity, hematocrit, $K^+$, and $Mg^{2+}$ increased significantly ($P<0.05$) during hypovolemia and were maintained at these elevated levels after blood transfusion (Table 4). Hematocrit decreased significantly ($P<0.05$) with dextran transfusion.

Responses in Animals that Did Not Survive the Hypovolemic Period.—Eight animals died between 165 and 180 minutes of hemorrhage. Control resistances and systemic pressures (Figs. 1-6) were consistently higher in these animals compared to the group that survived the hypovolemic period. The hemorrhage-induced increases in all vascular resistances (Figs. 4-6) were usually larger in the

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Control 0 minutes</th>
<th>Hypovolemia 60 minutes</th>
<th>Hypovolemia 120 minutes</th>
<th>Hypovolemia 165 minutes</th>
<th>Hypovolemia 240 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin S</td>
<td>D</td>
<td>S</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Large Artery to Large Vein</td>
<td>6.6 ± 0.8</td>
<td>3.6 ± 0.8</td>
<td>4.8 ± 1.7</td>
<td>4.2 ± 1.0</td>
<td>6.6 ± 2.2</td>
</tr>
<tr>
<td>Skeletal muscle S</td>
<td>7.2 ± 1.2</td>
<td>5.4 ± 0.8</td>
<td>7.6 ± 1.7</td>
<td>7.9 ± 1.9</td>
<td>8.4 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>13.0 ± 1.6</td>
<td>8.0 ± 2.4</td>
<td>8.9 ± 2.4</td>
<td>6.6 ± 1.5</td>
</tr>
<tr>
<td>Prevenous to Venous</td>
<td>Skin S</td>
<td>D</td>
<td>S</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.2 ± 6.0</td>
<td>17.0 ± 4.1</td>
<td>21.0 ± 5.0</td>
<td>18.4 ± 2.7</td>
<td>17.0 ± 4.3</td>
</tr>
<tr>
<td>Skeletal muscle S</td>
<td>31.4 ± 4.0</td>
<td>19.1 ± 3.1</td>
<td>22.4 ± 5.0</td>
<td>23.0 ± 3.6</td>
<td>21.2 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>52.0 ± 7.0</td>
<td>30.3 ± 9.4</td>
<td>36.0 ± 8.3</td>
<td>26.0 ± 6.8</td>
</tr>
</tbody>
</table>

S = animals that survived the hypovolemic period ($N = 20$); D = animals that died during the hypovolemic period ($N = 8$). All values are means ± SE. The arterial hemorrhage was 48 ml/kg body weight.
### TABLE 3
Effects of Arterial Hemorrhage on the Percent of Total Resistance Residing in Large Arteries, Small Vessels, and Large Veins

<table>
<thead>
<tr>
<th></th>
<th>Skin</th>
<th>Skeletal muscle</th>
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<tbody>
<tr>
<td></td>
<td>Large arteries</td>
<td>Small vessels</td>
</tr>
<tr>
<td><strong>Animals that Survived the Hypovolemic Period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>26%</td>
<td>69%</td>
</tr>
<tr>
<td>240 minutes*</td>
<td>36%</td>
<td>53%</td>
</tr>
<tr>
<td>Dextran Blood</td>
<td>39%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>26%</td>
<td>66%</td>
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<tr>
<td><strong>Animals that Died during the Hypovolemic Period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>24%</td>
<td>73%</td>
</tr>
<tr>
<td>285 minutes†</td>
<td>35%</td>
<td>73%</td>
</tr>
</tbody>
</table>

The arterial hemorrhage was 48 ml/kg body weight.
*End of the hypovolemic period.
†End of the posttransfusion period.

### TABLE 4
Effects of Arterial Hemorrhage on Systemic Arterial pH, Hematocrit, Osmolarity, Na⁺, K⁺, Ca²⁺,
and Mg²⁺

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0 minutes</th>
<th>60 minutes</th>
<th>120 minutes</th>
<th>180 minutes</th>
<th>240 minutes</th>
<th>Posttransfusion</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>285 minutes</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Ss</td>
<td>40</td>
<td>46*</td>
<td>45*</td>
<td>46*</td>
<td>46*</td>
<td>45*</td>
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<td>D</td>
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<td>39</td>
<td>36</td>
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<td>27*</td>
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<td>Osmolarity</td>
<td>Ss</td>
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<td>304*</td>
<td>305*</td>
<td>306*</td>
<td>307*</td>
<td>308*</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>288</td>
<td>304*</td>
<td>306*</td>
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<tr>
<td>Na⁺</td>
<td>Ss</td>
<td>154</td>
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<td>Ca²⁺</td>
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<td></td>
<td>D</td>
<td>4.4</td>
<td>4.2</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>Ss</td>
<td>2.08</td>
<td>2.20*</td>
<td>2.23*</td>
<td>2.29*</td>
<td>2.40*</td>
<td>2.24*</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1.92</td>
<td>2.18*</td>
<td>2.77*</td>
<td></td>
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</tr>
</tbody>
</table>

Ss = animals transfused with shed blood after 4 hours of hypovolemia (n = 10); D = animals which died after 165 minutes of hypovolemia (n = 7); SB = animals transfused with dextran after 4 hours of hypovolemia (n = 5). The arterial hemorrhage was 48 ml/kg body weight.
*P < 0.05 (Student's t-test).

dogs that died. In four animals, total and segmental vascular resistances (especially in the small vessels) waned from 60 to 165 minutes. In the other four animals, all
resistances continued to increase from 60 to 165 minutes. The large artery-large vein and the prevenous-venous resistance ratios (Table 2) were decreased ($P < 0.05$) throughout the hypovolemic period. The large arteries and veins accounted for a greater percent of the total resistance at 165 minutes than during the control period, and the small vessels accounted for a smaller percent of the total resistance at this time (Table 3).

The hematocrit did not change significantly, whereas the pH of arterial blood decreased in the animals which died. In addition, the increases in plasma osmolarity, $K^+$, and $Mg^{2+}$ ($P < 0.05$) were larger than those observed in animals that survived the hypovolemic period (Table 4).

We have recently published data for the forelimb of control dogs followed continuously for 5 hours (12). Forelimb weight and systemic pressure were unchanged relative to control throughout the entire observation period. Total skin and skeletal muscle vascular resistances increased slightly but significantly during this time; the resistance increases were largely confined to constriction of the small vessel segment. In these control animals, muscle and skin total resistances increased to 150% of control at the end of a 5-hour period. In this study, resistance in muscle increased to 900% of control, while resistance in skin increased to 1200% of control after 4 hours. Hence, the marked changes in forelimb weight, systemic pressure, and segmental vascular resistances in this study must largely be attributed to the blood loss due to arterial hemorrhage and not to the deterioration of the preparation with time.

**INTACT FORELIMB**

**Weight Changes in the Intact Forelimb.**—During a 5-minute control period, the limbs gained an average of 2 g. Hemorrhage always produced a continuous decline in forelimb weight which averaged 21 g by 60 minutes, 31 g by 120 minutes, 38 g by 180 minutes, and 44 g by 240 minutes ($P < 0.05$). Following transfusion with blood, limb weight increased but was still 24 g below control at the end of the posttransfusion period (285 minutes) ($P < 0.05$).

**Discussion**

**WEIGHT RESPONSE**

Forelimb weight fell rapidly initially and then more slowly throughout the remainder of the hypovolemic period. Theoretically, this weight loss could be attributed to a decreased vascular compartment or extravascular compartment or both. The weight loss was associated with marked increases in all segmental vascular resistances which were either largely maintained or further increased during the remainder of the hypovolemic period. This suggests that mean vessel caliber decreased and, inferentially, that forelimb blood volume also decreased. Clearly, all of the weight loss is not attributable to a decreased intravascular volume, since it exceeded the weight of all the blood in the forelimb. Based on data from Baker's studies (14), normal canine forelimb blood volume is approximately 4 g/100 g forelimb weight; the average weight loss in these experiments was approximately 7 g/100 g forelimb weight. Hence, the weight loss, in part, must be attributable to net extravascular fluid reabsorption. In fact, the weight loss during the last 3 hours of the hypovolemic period may well have resulted largely from a decreased extravascular compartment volume. Total forelimb small vessel and large vein resistances were relatively constant during this time ($P < 0.05$), suggesting a reasonably constant blood volume in these capacitance vessels (Fig. 4). Both collateral free and intact forelimbs continuously lost weight; therefore, bypassing the veins between the elbow and the right atrium did not artificially lower capillary hydrostatic pressure in the collateral free forelimbs.

Forelimb weight increased in response to either whole blood or dextran transfusion, but was still well below prehemorrhage control levels at the end of the posttransfusion period. The posttransfusion weight gain is attributable to an increased vascular volume subsequent to a fall in all vascular resistances and also, in part, to fluid filtration.
Extravascular fluid reabsorption would occur if the transmural capillary hydrostatic pressure gradient fell or if it fell proportionately more than the transmural capillary colloid osmotic pressure gradient. A fall in the transmural hydrostatic pressure gradient is suggested since all forelimb vascular pressures decreased. Osmolarity rose in arterial plasma. If the osmotically active particles came predominantly from tissues other than skin and muscle, consideration must be given to the possibility that part of the weight loss resulted from loss of intracellular water. Additional experiments are necessary to investigate this possibility. Small vein pressure, which represents a minimum for capillary hydrostatic pressure, was decreased throughout the hypovolemic period in both skin and skeletal muscle. A fall in capillary hydrostatic pressure would occur despite a rise in precapillary resistance if the latter were overwhelmed by the fall in aortic pressure and a rise in postcapillary resistance. It is likely that capillary hydrostatic pressure fell even if the precapillary-postcapillary resistance ratio actually decreased.

\[ P_c = \frac{(r_a/r_a) \cdot pA + pV}{1 + r_a/r_a}, \]

where \( P_c \) = capillary hydrostatic pressure, \( r_a \) = postcapillary resistance, \( r_p \) = precapillary resistance, \( pA \) = aortic pressure, and \( pV \) = right atrial pressure. The hemodynamic changes during severe hemorrhagic hypotension predict a fall in capillary hydrostatic pressure and transcapillary water reabsorption. Capillary pressure is determined not only by the precapillary-postcapillary resistance ratio, but also by aortic and right atrial pressures. When these pressures are normal or elevated, changes in the resistance ratio can have a great effect on both the direction and rate of transcapillary water fluxes. When aortic and right atrial pressures are low, the resistance ratio is less important as a determinant of net transcapillary water movement. For example, during severe hypovolemia, aortic pressure is usually 30-40 mm Hg and right atrial pressure is approximately zero. Under this condition, if the resistance ratio falls from a control of 4 to as low as 1, capillary hydrostatic pressure will still be between 15.0 and 20.0 mm Hg — values well below plasma colloid osmotic pressure. Therefore, extravasation of water in skeletal muscle and elsewhere would be unlikely during severe hemorrhagic hypotension unless microvascular membrane permeability to proteins increased greatly.

A survey of the literature indicates that the evidence for fluid filtration in circulatory shock, resulting either from blood loss or endotoxin, has been largely inferred from changes in plasma volume measured with dilution techniques and changes in hematocrit in dogs. Plasma volume markedly decreases while hematocrit markedly increases with time (15); these changes are maximal after 3-4 hours, and they have been attributed to extensive net fluid efflux into tissue. This fluid filtration is said to begin during the hypotensive period (as soon as 20 minutes after initiating bleeding) and to continue following the return of the shed blood (6). Other data also support this hypothesis. Shock in dogs is generally associated with a profuse bloody diarrhea (15). At autopsy, the small intestine is engorged and the lumen frequently contains blood, indicating that fluid is lost by filtration into the intestinal wall and by bleeding from necrotic tissue. Other findings, however, are difficult to reconcile with the fluid filtration hypothesis. Plasma volume measured with dilution techniques fails to increase in splenectomized dogs and primates (monkeys) subjected to circulatory shock, and hematocrit fails to increase relative to control (16-21). Other investigators (16, 19, 22-24) employing these same techniques have failed to find evidence for significant transvascular fluid efflux in dogs (intact spleens) subjected to shock, i.e., the magnitude of the measured decrease in plasma volume was small. In man, the available data, although sparse and fragmentary, fail to provide evidence for fluid filtration in circulatory shock (15, 25, 26). Some of the discrepancies appear to be related to species variation. The bloody diarrhea and intestinal necrosis is not found in...
primates including man (15, 27-29). It has been shown that the volume of fluid lost via the intestinal route in dogs is relatively small and is of insufficient magnitude to be of primary importance in the development of irreversibility (30). Enterectomy in dogs does not significantly alter the hemodynamics of the shock state or survival rates (31, 32). The administration of atropine to dogs prevents the intestinal necrosis but fails to alter survival time or survival rates (33).

Thus, the existing evidence supports the concept of fluid filtration in dogs with intact spleens only (16). It is evident that a large body of literature fails to provide evidence for fluid filtration in circulatory shock, especially in splenectomized dogs and primates including man (15). Our findings are consistent with this segment of the literature, and, in addition, fail to provide evidence for fluid filtration into skin and skeletal muscle in dogs with intact spleens subjected to severe prolonged hemorrhagic hypotension. This agrees with our previous findings for dogs subjected to endotoxin shock (13) and to less severe hemorrhagic hypotension (7). Recently, Hinshaw and Owen, utilizing the same canine forelimb preparation employed in this study, also failed to find evidence for fluid filtration into skin and skeletal muscle during irreversible endotoxin shock (34). Since the alleged fluid filtration in circulatory shock is frequently attributed to catecholamine-induced vasoconstriction, transcapillary fluid fluxes were also examined in irreversible catecholamine shock (12). In these studies, only evidence for net extravascular fluid reabsorption was found during a 3-hour intravenous infusion of either epinephrine or norepinephrine in doses which caused death shortly after cessation of the infusion. These combined findings suggest that the concept that fluid filtration occurs during severe prolonged hypotension resulting from circulatory shock needs to be critically reexamined.

RESISTANCE RESPONSE

Constriction of all vascular segments contributed to the sustained increases in vascular resistances. In the animals that survived 4 hours of hypovolemia, the large arteries and veins constricted almost proportionately (Table 2). In animals that died after 165 minutes of hypovolemia, the large veins constricted proportionately more than the large arteries (Table 2). The large arteries and large veins both constricted proportionately more than the small vessels in all animals. Thus following hemorrhage, a far greater percent of the total resistance resides in the large arteries and veins (Table 3), while a smaller percent resides in the small vessels. This indicates that constriction of these large vessels contributed greatly to the rise in pre- and postcapillary resistance following severe blood loss. In addition, the large veins constricted proportionately more than the combined large artery plus small vessel segments in all animals (Table 2).

The resistance increases during the first hour of hypovolemia can be ascribed to active and passive decreases in vessel caliber and to a rise in blood viscosity (hematocrit). The resistance increases during the remainder of the hypovolemic period can be largely attributed to active decreases in vessel caliber alone, for transmural pressures and hematocrit were nearly constant.

In 5 of 20 dogs surviving the hypovolemic period, there was some waning of total and segmental vascular resistances in both skin and skeletal muscle during the last 3 hours of hypovolemia. There was also a fall in all vascular resistances, especially in the small vessels, in 4 of 8 dogs that died. Our findings appear to be consistent with those of Bond et al. (35) and Fell (36), namely a partial waning of resistance in some animals after several hours of hypovolemia. The partial waning of resistance observed in these animals was associated with a fall in pressures and, therefore, does not represent active vasodilation due to an increased baroreceptor stimulus or passive vasodilation due to a rise in transmural pressure. This resistance decline could have represented a gradual failing of the remote or local vasoconstrictor mechanisms due to cerebral ischemia or the
accumulation of vasodilator metabolites, respectively, or a combination of both.

Blood flow increases substantially more in animals transfused with dextran rather than autologous whole blood. This effect, undoubtedly, reflects differences in blood viscosity as indicated by the lower hematocrits in animals transfused with dextran. Although viscosity reduction appears to be an effective means of improving peripheral blood flow following severe hypovolemia, the influence of such therapy on oxygen delivery and survival rates remains to be demonstrated.

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References
TRANSCAPILLARY FLUID FLUXES IN SHOCK


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