**Cardiovascular response to blood loss during high intracranial pressure**

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The authors hypothesized that the combination of hemorrhage and increased intracranial pressure (ICP) has deleterious effects on cardiovascular function. The effect of blood loss during normal and increased ICP was studied in eight pigs. The mean arterial pressure (MAP), pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac output, and cerebrospinal fluid (CSF) pressure were measured. The regional tissue blood flow was determined with radioactive microspheres labeled with four different nuclides. High ICP (80% of MAP) was induced by infusion of artificial CSF into the cisterna magna. The response to rapid arterial bleeding of 25% of blood volume was measured. The decrease in blood flow to the intestine, skeletal muscle, and the kidneys after blood loss was significantly greater during high ICP. The decrease in blood flow to the spleen and pancreas tended to be greater during high ICP, whereas the changes in blood flow to the liver, adrenal glands, and heart muscle showed no such tendency. The fall in cardiac output and heart stroke volume after blood loss were more pronounced when the ICP was high, and the increase in systemic vascular resistance was considerably greater.

These observations suggest that during high ICP the physiological protective mechanisms against blood loss are impaired in the systemic circulation, and a loss of 25% of the blood volume, normally well compensated for, may induce a state of shock.

**KEY WORDS** • cardiovascular function • hemorrhagic hypotension • high intracranial pressure • organ blood flow • shock • pig

**Materials and Methods**

*Animals and Operative Technique*

This study was performed with the consent of the Norwegian Council of Animal Research according to the Code for the Care and Use of Animals for Experimental Purposes.

Eight juvenile Norwegian-bred landrace pigs of either sex weighing 18 to 28 kg were used. The animals were anesthetized by intraperitoneal injection of 25 mg/kg pentobarbital, and anesthesia was continued with 15 mg/kg/hour as a continuous infusion through an ear vein, supplemented with intermittent intravenous injections of 1 mg/kg pentobarbital as an analgesic. After tracheotomy, ventilation was established with 70% nitrous oxide and 30% oxygen by a serv ventilator at 20 breaths/minute (5–7 L/min) adjusted to maintain normocapnia according to blood gas measurements. Muscular paralysis was achieved with pancuronium (0.1 mg/kg given intravenously in repeated doses as needed) after the surgical procedure had been completed. With the animal in the supine position, an indwelling bladder catheter was inserted via a cystostomy. Fluid-filled catheters were inserted into the aorta through the right femoral and brachial arteries to monitor the arterial pressure and for...
blood and microsphere reference organ sampling. A pigtail catheter was inserted into the left heart ventricle through the left femoral artery for injection of radioactive microspheres. A Swan–Ganz catheter for measurement of right atrial pressure, pulmonary arterial pressure (PAP), and pulmonary arterial wedge pressure (PAWP) was inserted using the right external jugular vein. Blood temperature was measured through the thermoster probe, and body temperature was maintained with the use of a heating pad. Ringer-acetate solution (25 ml/kg/hour) was administered intravenously throughout the experiment.

After these preparations were made, the animal was turned to the prone position and a longitudinal midline incision extending from the glabella to the seventh cervical vertebra was made. The atlantooccipital membrane was defined, and two catheters were inserted into the cerebellomedullary cistern and held in position by a rubber membrane and rapid-setting methyl methacrylate. Both catheters were connected to pressure transducers and one to an infusion bottle containing artificial cerebrospinal fluid (CSF) (mmol/L: NaCl 123, KCl 3.75, KH₂PO₄ 1.25, NaHCO₃ 26, dextrose 5.0, MgCl₂ 1.0, CaCl₂ 2.0). The infusion bottle was elevated to achieve a steady high pressure when desired.

**Hemodynamic Measurements**

Catheters were connected to pressure transducers, the zero reference levels were leveled at midchest, and recordings were made on paper by a chart recorder. Systemic and pulmonary arterial, right atrial, and CSF pressures were recorded continuously, and other variables were measured intermittently. Mean arterial pressure (MAP) and mean PAP were calculated as the diastolic pressure plus one-third of pulse pressure. Heart rate was counted from the blood pressure curve. Systemic peripheral resistance was calculated as MAP/ cardiac output, and pulmonary vascular resistance as PAP–pulmonary capillary wedge pressure (PCWP)/cardiac output. Blood volume was assumed to be 61 ml/kg of body weight.

**Measurement of Flow With Microspheres**

In six animals, the cardiac output and regional tissue blood flow were measured with radioactive 15-μm diameter plastic microspheres suspended in 0.1% Tween 80. Microspheres labeled with four different nuclides (¹⁴¹Ce, ⁵¹Cr, ⁹⁵Nb, and ¹¹³Sn) were used, allowing four flow measurements in each animal. Approximately 10⁶ to 1.5 × 10⁷ spheres were used for each measurement. The suspension of microspheres was injected into the left heart ventricle over a period of 30 seconds, and the catheter was then flushed with 10 ml of isotonic saline. The arterial reference sample was withdrawn from the abdominal aorta at a constant rate, 4.45 ml/minute, with an infusion pump starting 30 seconds before injection and continuing for 120 seconds. Differently labeled microspheres were used in random order. No change in heart rate or blood pressure was observed during the injections.

At the end of the experiment the animals were killed and the location of the catheters was verified at autopsy. Tissue was taken from the heart, both kidneys, both adrenal glands, the liver, the spleen, the jejunum, the pancreas, the erector spinae muscle, and cancellous bone from spinous process. All tissue samples and the blood reference samples were weighed and placed in counting vials. Total radioactivity (cpm) of each isotope in all the samples from all animals was measured at the same time. The samples were placed in the center of a gamma scintillation spectrometer with the windows set over the highest energy peak of each isotope. Individual isotope activity of the samples was calculated with correction for background, crosstalk, and physical decay. To calculate the number of microspheres in each sample, aliquots of a known number of microspheres were counted together with the samples and the counts per minute of one microsphere were determined for each isotope. Because the reference blood samples were taken from a surrogate organ of known flow, tissue blood flow was calculated using the following formula:

\[
tissue \text{ blood flow} = \frac{\text{reference organ blood flow} \times cpm \text{ of tissue sample}}{cpm \text{ of reference sample}}
\]

and expressed as flow in ml/100 g/min. Cardiac output was calculated using the formula:

\[
\text{cardiac output} = \frac{\text{total number of microspheres injected} \times \text{reference blood flow}}{\text{number of microspheres in reference sample}}
\]

Even distribution of the microspheres was checked by comparing flow in the right and left kidney. The paired Student’s t-test was used for statistical analyses.

**Experimental Protocol**

The following variables were measured: organ blood flow (microspheres at four intervals); MAP; PAP; PCWP; cardiac output; heart rate; ICP; blood gases; and blood temperature. Baseline recordings were taken after a stabilizing period of at least 60 minutes. All measurements were repeated after withdrawing arterial blood until 25% of the blood volume had been removed. The animals were bled at a rate of approximately 4% of the blood volume per minute. The withdrawn blood was reinfused after 20 minutes. Following a stabilizing period of another 30 minutes, the CSF pressure was raised to approximately 80% of MAP, and all measurements were repeated before and after the withdrawal of 25% of the blood volume. The high ICP was stable for 5 minutes before the blood loss.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Organ Sample</th>
<th>Baseline</th>
<th>After 25% Blood Loss</th>
<th>During High ICP</th>
<th>After Blood Loss During High ICP</th>
<th>Blood Loss/ High ICP Baseline†</th>
<th>Blood Loss &amp; High ICP†</th>
</tr>
</thead>
<tbody>
<tr>
<td>spleen</td>
<td>646 ± 801</td>
<td>337 ± 489</td>
<td>461 ± 301</td>
<td>230 ± 334</td>
<td>0.43 ± 0.13</td>
<td>0.33 ± 0.24</td>
</tr>
<tr>
<td>intestine</td>
<td>96 ± 157</td>
<td>51 ± 54</td>
<td>56 ± 62</td>
<td>38 ± 43</td>
<td>0.97 ± 0.49</td>
<td>0.58 ± 0.22‡</td>
</tr>
<tr>
<td>pancreas</td>
<td>74 ± 59</td>
<td>31 ± 19</td>
<td>48 ± 25</td>
<td>25 ± 28</td>
<td>0.70 ± 0.41</td>
<td>0.46 ± 0.28</td>
</tr>
<tr>
<td>liver</td>
<td>86 ± 49</td>
<td>87 ± 76</td>
<td>92 ± 83</td>
<td>79 ± 46</td>
<td>1.05 ± 0.51</td>
<td>1.03 ± 0.54</td>
</tr>
<tr>
<td>rt adrenal</td>
<td>231 ± 134</td>
<td>211 ± 199</td>
<td>138 ± 89</td>
<td>246 ± 236</td>
<td>1.11 ± 0.59</td>
<td>1.13 ± 0.50</td>
</tr>
<tr>
<td>rt adrenal</td>
<td>196 ± 128</td>
<td>178 ± 135</td>
<td>136 ± 67</td>
<td>256 ± 256</td>
<td>1.12 ± 0.46</td>
<td>1.31 ± 0.55</td>
</tr>
<tr>
<td>rt adrenal</td>
<td>490 ± 203</td>
<td>351 ± 179</td>
<td>479 ± 436</td>
<td>209 ± 171</td>
<td>0.74 ± 0.22</td>
<td>0.42 ± 0.25‡</td>
</tr>
<tr>
<td>heart</td>
<td>541 ± 251</td>
<td>345 ± 185</td>
<td>449 ± 311</td>
<td>217 ± 184</td>
<td>0.71 ± 0.19</td>
<td>0.43 ± 0.24‡</td>
</tr>
<tr>
<td>skeletal muscle</td>
<td>7.5 ± 6.8</td>
<td>7.5 ± 5.1</td>
<td>4.2 ± 1.9</td>
<td>2.1 ± 3.1</td>
<td>0.82 ± 0.46</td>
<td>0.21 ± 0.17‡</td>
</tr>
<tr>
<td>bone</td>
<td>26 ± 23</td>
<td>16 ± 10</td>
<td>24 ± 9.4</td>
<td>12 ± 15</td>
<td>1.0 ± 0.61</td>
<td>0.52 ± 0.21</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations (ml/100 g/min).
† The change in each animal was calculated separately by dividing value after blood loss with baseline value.
‡ Significantly different from blood loss/baseline: p < 0.05.
§ p < 0.01.
High ICP and circulatory response to blood loss

Sources of Supplies and Equipment

The model 900B servventilator was manufactured by Siemens, Solna, Sweden; the pressure transducer, model AE 840, by Sensonor, Horten, Norway; and the pressure amplifier and chart recorder, model ES2000, by Gould, Cleveland, OH. Microspheres were supplied by New England Nuclear, Boston, MA. The infusion pump was manufactured by Braun Melsungen, Melsungen, Germany and the auto-gamma scintillation spectrometer, model ES2000, by Gould, Cleveland, OH. Microspheres were supplied by New England Nuclear, Boston, MA. The model 900B servventilator was manufactured by Siemens, Solna, Sweden; the pressure transducer, model AE 840, by Sensonor, Horten, Norway; and the pressure amplifier and chart recorder, model ES2000, by Gould, Cleveland, OH. Microspheres were supplied by New England Nuclear, Boston, MA.

Results

The number of microspheres in the reference samples was well above 1000, and in the tissue samples there were more than 400 microspheres for the intestine, pancreas, and adrenal glands, more than 1000 for liver and spleen, and more than 3500 for heart and kidneys. The number of microspheres was relatively low in muscle samples (mean 91 microspheres per sample) and bone samples (mean 72 microspheres per sample).

Organ Blood Flow Changes

Organ blood flow after loss of 25% of the blood volume is shown in Table 1. Blood loss caused a decrease in blood flow to the spleen, kidneys, and pancreas during both normal and high ICP (p < 0.05), whereas blood flow to the intestine also tended to decrease, but not significantly. Blood flow to skeletal muscles tended to decrease after blood loss during normal ICP (p = not significant), but decreased significantly after bleeding during high ICP (p < 0.05). Blood flow to the myocardium, liver, and adrenal glands showed no significant changes after blood loss during normal or high ICP (Table 1). High ICP during normovolemia tended to decrease blood flow to the spleen, intestine, pancreas, adrenal glands, heart, and skeletal muscle, but none of the changes was significant. The changes from baseline in organ blood flow after blood loss with normal and high ICP are also shown in Table 1. The decrease in blood flow to the intestine, skeletal muscle, and the kidneys after blood loss was significantly greater during high ICP. The decrease in blood flow to the spleen and pancreas tended to be greater during high ICP (p = not significant), whereas the changes in blood flow to the liver, adrenal glands, and myocardium showed no such tendency.

Changes in Hemodynamic Variables

The relationship between ICP and MAP at the time of measurement of blood flow is shown in Fig. 1. Blood loss during normal ICP caused the MAP and PAWP to decrease significantly (p < 0.01), whereas the cardiac output, stroke volume, and PAP also tended to decrease, but not significantly (Table 2). Blood loss during high ICP caused a decrease in cardiac output (p < 0.005), MAP (p < 0.01), and heart stroke volume (p < 0.001), and an increase in heart rate (p < 0.005) and systemic vascular resistance (p < 0.05). High ICP during normovolemia caused an increase in systemic vascular resistance (p < 0.05) and tended to increase MAP and pulmonary vascular resistance (p = not significant). The changes in hemodynamic variables from baseline after blood loss are also shown in Table 2. The fall in cardiac output and heart stroke volume was more pronounced during high ICP.

Table 2

<table>
<thead>
<tr>
<th>Hemo-dynamic Variables</th>
<th>Baseline</th>
<th>After 25% Blood Loss</th>
<th>During Blood Loss/ High ICP/</th>
<th>Blood Loss/ High ICP/</th>
<th>Blood Loss/ High ICP/</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>3.97 ± 2.06</td>
<td>3.65 ± 2.39</td>
<td>3.57 ± 0.86</td>
<td>2.17 ± 1.37</td>
<td>0.87 ± 0.17</td>
</tr>
<tr>
<td>HR</td>
<td>121 ± 42</td>
<td>135 ± 48</td>
<td>119 ± 43</td>
<td>184 ± 63</td>
<td>1.14 ± 0.33</td>
</tr>
<tr>
<td>MAP</td>
<td>108 ± 30</td>
<td>81 ± 31</td>
<td>123 ± 15</td>
<td>81 ± 29</td>
<td>0.76 ± 0.10</td>
</tr>
<tr>
<td>PAP</td>
<td>17 ± 4.6</td>
<td>16 ± 2.4</td>
<td>23 ± 6.3</td>
<td>16 ± 7.0</td>
<td>1.01 ± 0.34</td>
</tr>
<tr>
<td>PCWP</td>
<td>8.0 ± 5.9</td>
<td>5.5 ± 4.5</td>
<td>10 ± 8.2</td>
<td>6.7 ± 4.7</td>
<td>0.56 ± 0.13</td>
</tr>
<tr>
<td>SV</td>
<td>34.3 ± 11.7</td>
<td>27.7 ± 12.0</td>
<td>33.4 ± 16.3</td>
<td>11.9 ± 5.8</td>
<td>0.83 ± 0.28</td>
</tr>
<tr>
<td>SVR</td>
<td>29.6 ± 10.7</td>
<td>27.1 ± 14.7</td>
<td>36.9 ± 13.2</td>
<td>46.3 ± 28.8</td>
<td>0.89 ± 0.17</td>
</tr>
<tr>
<td>PVR</td>
<td>3.0 ± 1.5</td>
<td>4.1 ± 2.5</td>
<td>4.2 ± 3.4</td>
<td>5.1 ± 3.8</td>
<td>1.63 ± 0.78</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>3.99 ± 1.0</td>
<td>4.08 ± 0.71</td>
<td>4.08 ± 0.45</td>
<td>3.83 ± 0.95</td>
<td>0.96 ± 0.17</td>
</tr>
<tr>
<td>ICP</td>
<td>9.7 ± 5.5</td>
<td>10 ± 6.6</td>
<td>96 ± 16</td>
<td>89 ± 15</td>
<td>1.23 ± 0.65</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard deviation. CO = cardiac output; HR = heart rate; PAP = mean pulmonary arterial pressure; PaCO₂ = partial arterial carbon dioxide pressure; PCWP = mean pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance (PAP-PCWP/CO); SV = heart stroke volume (CO/HR); SVR = systemic vascular resistance (MAP/CO).
† The change in each animal was calculated separately by dividing value after blood loss with baseline value.
‡ Significantly different from animal blood loss/baseline: p < 0.01.

Fig. 1. Mean arterial pressure and intracranial pressure at the time of measurements of blood flow.
and the increase in systemic vascular resistance was greater.

Discussion

This study shows that the effects of blood loss on systemic circulation are considerably enhanced by high ICP. The decreases in blood flow to the intestine, skeletal muscle, and kidneys were greater during high ICP, the fall in cardiac output was more pronounced, and the systemic vascular resistance was increased.

The microsphere method is considered the most accurate technique for determining the circulation in various organs provided that certain requirements are fulfilled. The method is based on the assumption that the microspheres are distributed proportionally to regional blood flow and become permanently entrapped during the first circulation in the tissues. The main factor affecting the accuracy and reproducibility of the blood flow measurements by this method is the number of microspheres that are entrapped in the tissue samples. The precision of the method thus depends on the dose of microspheres injected. Except for the samples from skeletal muscle and bone with low flow, the doses we have used were high enough to assure more than 400 microspheres in all tissue samples. The doses used in this study yielded approximately 90 microspheres in the low-flow tissue samples like muscle, and 3500 in the high-flow samples like kidney. The theoretical variation due to random distribution of the microspheres would be approximately 20% at the 95% confidence level for the samples from skeletal muscle, and approximately 3% for the samples from the kidney. The error due to the random component of microsphere distribution was within acceptable limits when the large differences on which our conclusions are based are taken into account.

Our method of increasing the ICP does not distort the brainstem in the same way a unilateral mass lesion or even diffuse brain swelling does. We would expect a mass lesion, which in addition to causing ICP also causes distortion or herniation, to have even greater effects on physiological equilibrium.

We did not choose random sequences of normal and high ICP combined with hypovolemia because the physiological insult to the brain and cardiovascular system by a rather moderate blood loss is small. Combined with high ICP, however, the insult is so extensive that conditions comparatively close to baseline conditions are difficult to achieve afterward, even with resuscitation and long stabilization. Our conclusions probably would have been strengthened by a double-hypovolemia control group in addition to our experimental group, but this was not part of the study design.

We specifically used a hemorrhage protocol that would replicate rapid blood loss by removing a certain part of the blood volume very quickly, as happens in accidental bleeding. This may have some advantages over the more commonly used fixed-pressure model in studies of traumatic or perioperative blood loss because the fixed-pressure model creates an artificial steady state, unlike the dynamic situation seen in accidental blood loss. The changes seen with the model used in this study may readily be compared to most other studies involving hemorrhagic hypotension and show the well-known physiological responses to blood loss, including changes in heart rate, MAP, cardiac output, and redistribution of blood flow to various organs. The cardiovascular effects of increased ICP have also been extensively studied. As early as 1824, a relationship between high ICP and changes in systemic cardiovascular variables was reported.

Our results showed that blood loss during high ICP resulted in a greater than normal decrease in cardiac output and stroke volume. A reduction of cardiac output to 53% corresponds to a blood loss of half the blood volume during intracranial normotension. The MAP reduction was greater during high, as opposed to normal ICP, but the MAP was also at a higher level before bleeding at high ICP, so that the posthemorrhagic MAP did not differ in the two situations. The systemic vascular resistance was increased by the combination of blood loss and high ICP to a point at which the peripheral circulation could be expected to be impaired and the animals expected to be in shock. That this was indeed the case was confirmed by the results of the renal blood flow and skeletal muscle flow measurements. The combination of blood loss and high ICP caused the renal blood flow to drop to 36% of baseline values (Table 1). The skeletal muscle blood flow after blood loss dropped to 82% of baseline during normal ICP and to 21% during high ICP. Such low values for kidney and skeletal muscle blood flow are normally caused by loss of more than half the blood volume, and were followed by death from shock in one-third of the pigs in one study.

Skeletal muscle blood flow is probably a critical factor for survival after massive hemorrhage, because skeletal muscle constitutes the greatest single source for transcapillary fluid exchange and restoration of blood volume and is also an important source of lactic acid in low-flow states.

The cardiovascular responses that preserve the systemic blood flow during blood loss and high ICP are similar. Thus, high ICP had probably exhausted the defense mechanisms against hemorrhage so that a simultaneous moderate blood loss resulted in a greater decrease in cardiac output, stroke volume, and peripheral organ blood flow than would normally occur. There are no previous studies of the response to blood loss during high ICP, but it has been shown that brain injury combined with hemorrhage induces a greater catecholamine response than hemorrhage alone.

Conclusions

The results of this study lead us to suggest that the compensatory mechanisms for preservation of the systemic
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circulation during hemorrhage are impaired in high ICP, and a blood loss of 25% of the blood volume, which normally is well compensated, can produce a state of shock. This observation may partly explain the serious consequences of hypotensive episodes in head-injured patients. It might also be an important consideration when attempting to achieve hemodynamic stabilization during surgery in the large group of neurosurgical patients with increased ICP.

References

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