Hemodynamic and Metabolic Effects of Hemorrhage in Man, with Particular Reference to the Splanchnic Circulation


Nearly all theories of the mechanisms involved in hemorrhagic shock depend upon observations made in anesthetized, infra-human species. Since anesthetics can modify circulatory responses and since species differences undoubtedly exist, it was elected to perform the present study in conscious human volunteers. The results differ in certain important respects from those previously observed or predicted during hemorrhage, and consequently they suggest the need for a more precise definition of what is meant by the term hemorrhagic shock.

Methods

Eleven healthy male volunteers were studied. Each reported to the laboratory in the early morning following an overnight fast. A medium antecubital vein was exposed under local anesthesia and a 100 cm Lehman catheter introduced into a right hepatic vein under fluoroscopic guidance. Following this, the right femoral artery was penetrated with a Cournand needle and subcutaneous limb electrodes were implanted to permit recording of the electrocardiogram. Arterial and venous pressures were transduced by Statham strain gauges and recorded, with the electrocardiogram, on a Grass polygraph. Mean pressures were obtained by electrical damping. The reference level for both pressures was 5 cm dorsal to the angle of Louis.

A 30 cm plastic catheter was placed in the left axillary or subclavian vein for use in dye injections, and another one was introduced into a right antecubital vein to permit both the infusion of indocyanine green and the injection of radioactive ($^{131}I$) iodinated human serum albumin. A blocking dose of Lugol's solution was given prior to the period of study.

Splanchnic blood flow was estimated at ten-minute intervals during a thirty minute control period using the method described by Caesar et al., with corrections introduced by Nielsen. Splanchnic blood volume was determined as indicated by Bradley et al. Splanchnic oxygen consumption was estimated by multiplying blood flow and arterio-venous oxygen difference as measured by the method of Van Slyke and Neill. Splanchnic vascular resistance was calculated as the mean flow rate divided by the mean perfusion pressure (mean arterial minus mean venous). Heart rate was counted from the electrocardiogram. Cardiac output and central blood volume were estimated by dye dilution, using either Evans blue or indocyanine green dye. A correction for catheter delay was applied in the estimation of central blood volume. Total blood volume was calculated from the dilution volume of plasma, obtained five minutes after the injection of radioactive serum albumin, multiplied by guest on July 9, 2017 http://circres.ahajournals.org/ Downloaded from http://circres.ahajournals.org/ Downloaded from
by the reciprocal of the "plasmacrit" (1-hematocrit). The hematocrit of arterial blood was determined in capped Wintrobe tubes spun for thirty minutes at 2300 g (at the tip).

The tensions of oxygen and carbon dioxide in arterial and venous blood were measured using an Instrumentation Laboratories electrode assembly model 102.

In most studies the concentrations of lactic and pyruvic acids in (whole) arterial and hepatic venous blood were measured, using enzymatic methods, and the arterio-venous and arterial "excess" lactate concentrations calculated as described by Huckabee.

After completion of the control measurements, bleeding was commenced from the antecubital vein catheter into a heparinized container and continued until an amount representing 15 to 20% of the estimated blood volume had been removed. Hemorrhage was completed in 25 to 35 minutes, following which a second thirty-minute period of study was commenced, and the measurements detailed repeated for a second time. During the final period, the blood lost in sampling (150 ml) was replaced with an equal volume of previously shed blood. Following the end of the study, the blood not needed for analysis was reinfused. In addition, approximately 200 ml of physiological saline solution were infused, either as the vehicle for the dye or in flushing the venous and arterial catheters. Since this infusion was presumably distributed throughout the entire extracellular fluid volume, no correction for it was made in the estimation of blood loss.

All data were analyzed statistically by means of paired "t" tests.

Results

The principal findings are shown in tables 1 to 3. On the average, seventeen per cent of the blood volume was removed from the subjects studied. This hemorrhage produced significant reductions (P < 0.01) in splanchnic blood volume, indocyanine green dye clear-

<table>
<thead>
<tr>
<th>No.</th>
<th>MABP mm Hg</th>
<th>H.R. beats/min</th>
<th>C.O. liters/min</th>
<th>Initial bleeding vol liters</th>
<th>Bleeding vol liters</th>
<th>Per cent red %</th>
<th>Signs and symptoms</th>
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<td>84</td>
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<td>19</td>
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Means 91 86 78 81 6.5 6.5 6.1 1.04 17
Sig. none none none

*All subjects exhibited pallor.
†Fainted after second flow measurement.
H.R.: heart rate (values are averages of three individual measurements).
C.O.: cardiac output.
Initial blood vol: total initial blood volume. Figures in parentheses are estimated from body weight.
Bleeding vol: blood removed.
Per cent red.: percentage reduction in blood volume caused by hemorrhage.
C: measurements during control period.
E: measurements during experimental period.
Sig.: significance of changes observed during hemorrhage.
No.: subject number.

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TABLE 2
Local Hemodynamic Changes Following Hemorrhage

<table>
<thead>
<tr>
<th>No.</th>
<th>SBF (liters/min)</th>
<th>SVR (mm Hg/liter/min)</th>
<th>SBV (liters)</th>
<th>CBV (liters)</th>
<th>HVP</th>
<th>CICG (liters/min)</th>
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<td>51</td>
<td>54</td>
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Means: 1.81 ± 1.04

Sig.: none

P < 0.001

SBF: splanchnic blood flow (values are averages of three individual measurements).
SVR: splanchnic vascular resistance (values are averages of three individual measurements).
SBV: splanchnic blood volume.
HVP: hepatic venous pressure (values are averages of three individual measurements).
CICG: clearance of indocyanine green dye in liters of plasma per minute.
C: measurements during control period.
E: measurements during hemorrhage.
Sig.: significance of observed changes during hemorrhage.
No.: subject number.

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TABLE 3
Metabolic Changes Following Hemorrhage

<table>
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<tr>
<th>No.</th>
<th>L\textsubscript{A}/P\textsubscript{A}</th>
<th>L\textsubscript{V}/P\textsubscript{V}</th>
<th>XL (V-A)</th>
<th>XL (A\textsubscript{A}-A\textsubscript{O})</th>
<th>Q\textsubscript{O}</th>
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Means: 10.49 ± 11.24

Sig.: none

P < 0.003

L\textsubscript{A}/P\textsubscript{A}: arterial blood lactate-pyruvate ratio.
L\textsubscript{V}/P\textsubscript{V}: hepatic venous blood lactate-pyruvate ratio.
XL (V-A): splanchnic "excess" lactate production in mEq/liter.
XL (A\textsubscript{A}-A\textsubscript{O}): arterial "excess" lactate production (hemorrhage vs. control).
Q\textsubscript{O}: splanchnic oxygen consumption in ml/min (STP).
C: measurements during control period.
E: measurements during hemorrhage.
Sig.: significance of observed changes during hemorrhage.
No.: subject number.
ance, and hematocrit. Of the blood removed, half was apparently contributed by the splanchnic viscera, which lost roughly 40% of their initial volume. In contrast, the central blood volume was depleted by only 10%. Hepatic venous oxygen tension was reduced by a similar amount ($P < 0.05$). Splanchnic blood flow, oxygen consumption, arterio-venous "excess" lactate, and vascular resistance were unaltered, as were cardiac output, central blood volume, heart rate, mean arterial blood pressure, and arterial "excess" lactate. Hepatic venous pressure was slightly (0.9 mm Hg) but significantly ($P < 0.05$) diminished.

The dissociation between the responses of flow and indocyanine green dye (ICG) clearance was caused by a significant ($P < 0.05$) diminution in ICG extraction during the period of hypovolemia. The arterial blood tension of carbon dioxide was unchanged, but $P_{aO_2}$ was significantly ($P < 0.01$) reduced, from 98 to 89 mm Hg, during hemorrhage.

**Discussion**

These results suggest that the splanchnic circulation functions as an important blood reservoir in man, and that it can be preferentially depleted by a mechanism which does not result automatically in increased vascular resistance. Since by far the largest resistances in this circulation lie upstream from the portal vein, and since constriction of the vessels of the portal venous tree occurs readily in response to stimulation of the local nerve supply (hepatic plexus of nerves), it seems theoretically possible to explain the present results on the basis of active venoconstriction without coincident arteriolar participation. There is direct evidence for such a dissociation in the response to sympathetic activation in the case of the feline gut, but no available information concerning the liver. The "restricted" venous perfusion shown by Daniel et al. could, perhaps, explain the reduction in ICG clearance observed by us. The failure of oxygen consumption to decline coincidentally is, however, puzzling. It could be theorized that hemorrhage caused the restricted area still adequately perfused to respire at an increased rate, but this explanation also requires the existence of an underperfused, hypoxic area, and the measurements of lactate and pyruvate do not support this notion. A more likely possibility is that ICG extraction was reduced because transit time through the liver was markedly diminished.

Griffith and Emery, who were the first to investigate the vasomotor control of the liver circulation during hemorrhage, reported that (in the cat) "(the) contraction of liver volume... may be sufficient to sustain the blood pressure; this reaction... is abolished by section of the hepatic plexus." Ether anesthesia or prolonged chloralose anesthesia also abolished the liver reflexes. Unfortunately, these authors did not measure splanchnic vascular resistance. A study largely similar to ours was performed by Reynell and his associates in dogs anesthetized with pentobarbital. Hemorrhage equal to one-third of the blood volume in their study reduced splanchnic blood flow only as it diminished cardiac output, and splanchnic vascular resistance was unchanged. In contrast, splanchnic blood volume was halved; splenectomy did not materially alter these results. The disproportionately large reduction in splanchnic blood volume in both studies naturally suggests an active response. Assuming this to be so, it is worth remarking that the reflex involved must be able to discriminate between stimuli necessitating changes in volume and in resistance. There are situations, such as exercise, in which the appropriate adjustment would appear to be (and in fact is) that of increased resistance and diminished volume.

It should be mentioned that some previous studies of the splanchnic circulation during hemorrhage have demonstrated an increase in splanchnic vascular resistance. On the other hand, most previous studies have been done on anesthetized animals, and all have involved moderate to profound arterial hypotension. In the most recent of these, a hemorrhage consisting of 22% of the blood volume reduced arterial pressure to 40 mm Hg and was ultimately fatal to each of nine Macaca monkeys. Not only does this represent an
agonal situation, but the interpretation of changes in vascular resistance when arterial pressure also changes is difficult and possibly misleading. On the other hand, a more severe hemorrhage might well have been accompanied by evidence of arteriolar constriction in our subjects. This belief is supported by the fact that the only subject (no. 1) who did experience a "faint" at the termination of the period of study had a twofold elevation in splanchnic vascular resistance just prior to this event when his arterial pressure was still essentially normal (this datum is not shown in table 2).

Our failure to demonstrate a significant reduction in central blood volume during hemorrhage also contrasts with previous work. Possible explanations are: 1) that the measurement may depend (spuriously) upon changes in cardiac output, since mixing of the dye may not be complete in a single passage; 2) that peripheral vasoconstriction may have obscured real central changes; 3) that the previously reported changes may have resulted in part from arterial hypotension, which did not occur in our subjects. We have no reason to doubt that changes in the pulmonary circulation did occur in our subjects, both because such changes have previously been demonstrated during a more moderate hemorrhage and because increases in the A-a oxygen difference (inferred from the reduction in PaO₂ with PaCO₂ remaining normal) were found in eight of ten cases studied by us. On the other hand, the pulmonary blood volume is a minor fraction of that subsumed under the term "central blood volume," and changes in one may not be reflected in the other.

Since neither total peripheral resistance, splanchnic vascular resistance, nor cardiac rate was elevated during hemorrhage in this study, there is perhaps reason to question whether an increase in sympathetic nervous activity did occur. Our evidence on this point is indirect, but persuasive, since we were unable to study hemorrhage during ganglionic blockade because of the development of alarming hypotension in response to a relatively minor blood loss.

**Summary**

1. Eleven normal subjects were studied before and after removal of 15 to 20% of their blood volume within 35 minutes.

2. This amount of blood loss did not produce conspicuous effects upon any of the usually measured circulatory or metabolic parameters.

3. The results suggest that the splanchnic circulation functions as an important blood reservoir in man, that it can be preferentially depleted of blood by a mechanism which does not automatically increase vascular resistance, and that the ability of our subjects to tolerate blood loss was attributable in large part to this response.

**References**


8. Hucklebee, W. E.: Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and...
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