Experimental study of irreversible shock and the brain

PATRICK F. GOLDEN, M.D., AND JOHN A. JANE, M.D., PH.D.
Cleveland Veterans Administration Hospital, Cleveland, Ohio, and Department of Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia

The roles of various organ systems in preventing the phenomenon of irreversible hemorrhagic shock were studied in dogs by artificially maintaining or depriving these systems of circulation. It was found that depriving the abdominal viscera of circulation did not necessarily result in death if the heart and brain were perfused. If the heart was maintained at normal pressures while the rest of the body was subjected to what would have otherwise been a lethal period of shock, the animal nevertheless survived. Thus, in the standard "35 mm Hg shock model" the heart seemed to be crucial. However, in the "30 mm Hg shock model" death occurred even if the heart was adequately perfused, indicating that failure of neural mechanisms accounts for irreversibility at these levels of hypotension.

KEY WORDS brain hemorrhagic shock irreversible shock

DESPITE intensive clinical and experimental investigation of shock and the mechanism of so-called "irreversibility," there is as yet no adequate explanation of the fact that an organism subjected to a critical level and duration of hypovolemia will not survive even if volume is restored. As has been established by Lillehei, et al., the mortality rate associated with 4 hours of hemorrhagic shock at 35 mm Hg mean arterial pressure (MAP) is 90%. The reasons given for this high rate include defects in metabolism, circulating toxins, or the failure of a particular organ. This lack of certainty despite considerable investigation prompted us to postulate that the failure of certain organ systems to interact effectively to achieve homeostasis might determine survival or irreversibility. Since the central nervous system (CNS) is important in controlling cardiovascular, pulmonary, and endocrine responses, the preservation of this particular integrative capacity might be all-important in protecting the organism from the otherwise lethal effects of shock. Clinical observations in shock suggest that this capacity is important since not only are altered states of consciousness regularly noted but also there is a tendency for perfusion of the heart and brain to be maintained in many diverse situations at the expense of other organs, as for instance, in the diving reflex. It is interesting to note recent work on the role of the nervous system in shock and the regulation of circulation.

Previous Study

We have previously reported the technique of experimentally exaggerating this physiologically selective perfusion of the
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Heart, lungs, and brain, and have thereby increased tolerance to profound hypovolemia. The mortality rate associated with shock of 4 hours' duration was reduced in an animal preparation by the application of a large Silverstone clamp on the thoracic aorta just distal to the left subclavian artery. After the animal had been bled into shock, closure of this clamp redistributed residual blood volume to the heart, lungs, and brain, and restored near-normal perfusion to these organs.

Figure 1 demonstrates the basic experimental design. Control animals were bled to a mean arterial pressure (MAP) of 35 mm Hg and after 4 hours at this level were retransfused. Experimental animals were bled to a MAP of 25 mm Hg, after which the clamp was set to maintain normal pressures in the heart, lung, and brain but at a MAP of 25 mm Hg below the clamp, or in all abdominal organs and major portions of the body. Retransfusion was begun after 4 hours of shock or as required to maintain pressure.

Table 1 summarizes the results of measuring total bled volume, blood lactate levels, and the occurrence of hemorrhagic enteritis. (Bled volume is defined as the total amount of blood removed to bring the pressure to the desired level, and thus in the calculation of percent uptake represents the maximum volume removed.) The failure of a protease enzyme inhibitor (Trasylol) to protect the gut from the lesions of enteritis has been previously discussed. Excess lactate levels were also significant. All animals of both experimental and control groups therefore satisfied the usual criteria for hemorrhagic shock. The uptake of bled volume in animals with the clamp, however, was at a significantly lowered rate, indicating cardiovascular compensation during shock.

All 15 control animals were dead in 24 hours (Fig. 2). At 72 hours 50% of the experimental animals were alive, and the majority of these survived indefinitely. These results suggested that an intact central nervous system permits compensatory homeostasis, predominantly of cardiopulmonary origin, to operate and prevent an otherwise lethal outcome. This implies, therefore, that irreversibility is primarily related to failure of the heart, lung, and brain, and that other defects associated with shock are of secondary importance, whether mechanical, biochemical, or arising from abdominal organs.

The results of this earlier experiment, however, did not allow us to differentiate the relative importance of the heart, lung, and brain. The present experiment was therefore designed to consider the heart and lung as one unit and the brain as another, rather than the "heart-lung-brain unit" of the previous technique.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td><strong>Summary of criteria for shock in the three experimental groups</strong></td>
</tr>
<tr>
<td>clamp position</td>
</tr>
<tr>
<td>organs perfused</td>
</tr>
<tr>
<td>shock level (mm Hg)</td>
</tr>
<tr>
<td>bled volume (cc/kg)</td>
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<tr>
<td>excess lactate (mMoles/l)</td>
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<tr>
<td>hemorrhagic enteritis</td>
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Materials and Methods

A total of 16 mongrel dogs of both sexes weighing 8.2 to 12.5 kg were used in this study. The results were compared with those of the previous study including the control group consisting of 15 animals. The animals were anesthetized, intubated, and placed on a ventilator. A femoral artery cannula made of large-bore Teflon was inserted at least to the aortic bifurcation to permit rapid bleeding. Another arterial cannula was inserted into one of the common carotid arteries and positioned as described below.

Arterial cannulas from the carotid and femoral arteries were connected via three-way stopcocks to pressure transducers (Statham p.23d).* Pressure measurements and electrocardiographic (ECG) and electroencephalographic traces (EEG) were displayed on an Electronics for Medicine recorder, Model DRS.† The EEG was a single-channel recording using leads from symmetrical points on each side of the parietal skull, avoiding the temporalis muscle. Esophageal and rectal temperatures were continuously monitored by indwelling probes (Yellow Springs Instruments Co.)‡

After baseline measurements of the above parameters were made, a left lateral thoracotomy was performed through the fourth intercostal space. The animal was given respiratory support with a Harvard respira-

*Statham pressure transducer p.23d manufactured by Statham Laboratories, Inc., Hato Rey, Puerto Rico.
†Recorder, Model DRS, manufactured by Electronics for Medicine, Inc., White Plains, N. Y.
‡Indwelling probes manufactured by Yellow Springs Instrument Company, Yellow Springs, Ohio.

§Respirator manufactured by Harvard Instruments.
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dextrose) citrate solution per 100 ml of blood.

The duration of shock at these levels was 4 hours. Reinfusion of bled volume was begun at this time or sooner as needed to support blood pressure. Bled volume, the time to initial reinfusion, and percentage of bled volume administered during shock were measured. During this period, the clamp was opened as soon as widening of the carotid pulse pressure occurred concomitant with a decrease in heart rate and elevation of the carotid MAP, indicating the trend toward hypervolemia in the circulation proximal to the clamp. Once the clamp was opened, it was disassembled and removed, and the chest was closed using standard suture technique. After a brief period of recording the vascular cannulas were removed, the wounds sutured, and the animals placed in a warm environment for observation of neurological function, stools and voiding, and time of death. Autopsies were performed on all animals.

During a control period just prior to shock and just before the end of the 4-hour period of shock, samples of blood were taken for analysis of lactate and pyruvate content. Blood was drawn from femoral artery catheters.

Animals were divided into groups as follows (Table 2). Group 1 consisted of the 15 control animals. Group 2 was composed of 20 animals with the heart, lung, and brain perfused, and the remainder of the body in shock. The results in these two groups were taken from our first experiment. Group 2 was further divided into subgroups for testing the effects of a protease enzyme inhibitor (Trasylol) in preventing hemorrhagic enteritis. Group 3 was composed of animals with heart-lung perfusion as described in this protocol.

**Results**

Because of some physiological differences between this and the first experiment, modification of the clamping technique was required. Presumably these differences were due partly to reflex vasomotor and cardiac changes mediated by carotid sinus mechanisms in response to diminished pressure in the aortic arch. Also, the effect of redistribution of blood volume caused by proximal aortic constriction was quite different from that in the first experiment, in which clamping induced a change in the desired directions, namely, a decrease in abdominal MAP and restoration of normal pressure in the heart, lung, and brain. In the present experiment, there was no damping effect of a peripheral vascular bed proximal to the clamp; the total vascular area distal to the clamp was greater, thus tending to cause greater fluctuation of blood pressures distal to the clamp in the first few minutes of shock. To prevent this, a loop of umbilical tape was passed around the aorta adjacent and distal to the clamp to aid the constricting mechanism. This stabilized the aortic constriction required to maintain the pressure differential on both sides of the clamp.

Variations from the desired pressures did not persist for any significant period except as demonstrated in Fig. 3. If a lower pressure persisted for longer than 5 minutes but less than 10 minutes, it was recorded as the lowest mean arterial pressure (LMAP). The duration of 10 minutes was determined by counting the time in a single interval of reduced pressure or an aggregate amount of time at reduced pressures. This occurred as a significant variation in 50% of the animals in each group in shock at a MAP of 30 and 35 mm Hg. No animals had reduced pressures for more than 10 minutes and no animal had an LMAP in an adverse

**TABLE 2**

Description of experimental groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Clamp Position</th>
<th>Organs Perfused</th>
<th>Shock (MAP mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: control</td>
<td>---</td>
<td>---</td>
<td>35</td>
</tr>
<tr>
<td>2: exp. no. 1</td>
<td>thoracic aorta</td>
<td>heart, lung, brain</td>
<td>25</td>
</tr>
<tr>
<td>3: exp. no. 2</td>
<td>ascending aorta</td>
<td>heart, lung</td>
<td>35 or 30</td>
</tr>
</tbody>
</table>
LOWEST MEAN ARTERIAL PRESSURE, mmHg

Fig. 3. Relation between the lowest mean arterial pressure seen by the brain and survival. There is a critical level of pressure at about 30 mm Hg below which survival does not occur.

direction from this shock group, e.g., animals in shock at 30 MAP with an LMAP no greater than 30 MAP.

One animal with an LMAP of 35 mm Hg that did not survive had a very brief period of hypotension during shock (at 3.5 hours to a MAP level of 26 mm Hg for only 3 minutes), and survived for only 4 hours after shock. This was associated with steady deterioration including isoelectric flattening of the EEG but no focal neurological signs. Four animals at an LMAP of 32 mm Hg showed no neurological deficit and followed the average course of the other members of the group in shock at a MAP of 35 mm Hg. At an LMAP of 28 mm Hg, two animals did not survive, but showed no neurological deficits. Animals with an LMAP of 25 mm Hg survived only 9 hours after shock with 100% uptake of bled volume and neurological signs during shock. These consisted of dilated fixed pupils at 1 hour and isoelectric flattened EEG at 1½ hours during shock. Animals with an LMAP of 20 mm Hg showed the same neurological signs at 2 hours during shock and also had 100% uptake of bled volume. The LMAP in these four animals occurred prior to 2 hours in shock.

The MAP (systemic pressures) of all animals during a preshock control period ranged from 152 to 110 mm Hg, with a mean of 138 mm Hg. The aortic MAP (proximal to clamp) during shock ranged from 140 to 90 mm Hg, with a mean of 110. There were no episodes, however, when proximal pressures were depressed for a significant time. The pressures reported as abdominal aortic MAP also represent carotid artery MAP with no significant variation as determined in five animals.

Bled volume for Group 3 was 51 cc/kg, which compares closely with all other groups in the investigation. Uptake of bled volume is illustrated in Fig. 4. The significance of a small uptake of the bled volume has been shown by Lillehei, et al. When blood pressure is maintained at a MAP of 35 mm Hg, the percentage of uptake is quite small; but any level of pressure below this requires an increasing uptake of the bled volume to maintain that lower level of pressure. The greater the volume of transfusion of bled volume required to maintain desired pressures, the greater the cardiovascular decompensation. The high degree of correlation between low uptake and survival indicates the presence of compensating mechanisms in animals with a MAP of 35 mm Hg in the abdominal aorta.

Excess lactate demonstrates a significant level of anaerobic metabolism and therefore a severe degree of shock (Fig. 5). There was no significant difference between survivors and non survivors, which shows that the reason for survival is not that these animals sustained a lesser metabolic insult.

The results demonstrated a survival rate generally similar to that observed in the first experiment (Fig. 6). Control animals (Group 1) in shock for 4 hours at a MAP
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The survival curve for Group 3 is derived from data representing the 16 animals with the clamp on the proximal aorta but with distal pressures at two different values. Figure 3 relates LMAP to survival and analyzes the composition of the survival curve in Fig. 6. There was no survival beyond 36 hours unless the pressure was at least 31 mm Hg MAP. At this pressure there was an 88% survival rate. If we exclude the animals in the shock group at a MAP of 35 mm Hg, which had the brief period of severe hypotension, the survival rate would have been 100%. This suggests that the critical pressure for perfusion of the brain is a value near 31 mm Hg. A t-test demonstrates that the LMAP of survivors is significantly different (p = < .05) from the LMAP of non-survivors.

The 90% incidence of hemorrhagic enteritis in this series of animals was less severe than that in the previous experiment (Groups 1 and 2). There was no significant difference in lesions of animals in shock at a MAP of 30 or 35 mm Hg, and the extent of involvement of the gut was no more severe than the mild-to-moderate cases of enteritis in Groups 1 and 2. This may have been related to the observation that pulse pressure in the lower abdominal aorta was three to four times that in animals in shock at the levels of 25 mm Hg; this pulsatile quality of blood flow in the gut may prevent stagnation and severe ischemic changes.

Neurological deterioration manifested by third cranial nerve signs and EEG changes was correlated with lowered blood pressure. Ninety percent of the irreversible “fixed and dilated pupils” occurred in animals brought to a level of shock at a MAP of 30 mm Hg or below, and did not occur in the group at 35 mm Hg MAP.

Autopsy findings are the subject of another report; generally, in addition to enteritis, these animals showed the usual pathological changes associated with shock in kidney, liver, and spleen. From gross observation, it was found that pulmonary atelectasis, focal hemorrhages, hemorrhagic pulmonary edema, and changes in the heart occurred with less frequency and severity compared with the findings in Group 2 animals. This might be expected in the experiment with near-normal perfusion of
the heart. It may also indicate that circulating toxins from ischemic viscera, if present at all, are not of primary importance. The gross appearance of the dog brain at autopsy was not characteristic for each group. The brains of those animals that did not survive longer than 36 hours, and especially those with pressures below 30 mm Hg MAP, were pale in color with collapsed cortical vessels and some signs of brain swelling.

Discussion

The data suggest that the brain is the critical organ in the preservation or mediation of homeostatic mechanisms that permit survival (Table 3). In the control group of animals, shock at 35 mm Hg MAP held for a period of 4 hours gave a uniformly lethal result. This was consistent with other investigations of hemorrhagic shock in which a significantly prolonged level of hypotension or hypovolemia produced irreversible damage. In dogs, hemorrhagic enteritis always accompanies fatal shock. If, however, the perfusion of the heart, lungs, and brain is maintained at levels significantly greater than those in the remainder of the body, as occurs when the major portion of the body is held at 30 to 35 mm Hg MAP for a period of 4 hours, a high percentage survive despite the 100% incidence of severe hemorrhagic enteritis.

Our initial conclusion from evaluation of the data from Group 2 animals (Table 3) was that the brain is the more sensitive and critical organ, but that cardiopulmonary functions are important in preventing death in shock at 35 mm Hg MAP. This assumed near-normal perfusion of the heart and lung. This may not be the case, however.

<table>
<thead>
<tr>
<th>Organs Perfused (Normal Pressure)</th>
<th>Shock (MAP mm Hg)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>none (controls)</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>heart, lung, brain</td>
<td>25</td>
<td>+</td>
</tr>
<tr>
<td>heart, lung</td>
<td>35</td>
<td>+</td>
</tr>
<tr>
<td>heart, lung</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

Pulmonary circulation pressures were not monitored and if venous return from the systemic circulation was poor, as was usual in hypovolemic shock, then lung perfusion may not have been adequate. Only coronary circulation could be said to have been near normal. On the other hand, this was an open-chest experiment, and some of the standard criteria for determining pulmonary perfusion based on systemic venous return thus may not apply. Furthermore, survival could occur only if the brain were not anoxic or irreversibly hypoxic, and this demands adequate ventilation-perfusion in the lung. Therefore, while the lack of measurements in lung perfusion may be criticized, this should not be a severe limitation to our original concept that the heart and lung can be considered as a unit when isolated for perfusion while the remainder of the body is subjected to shock at a MAP of 35 and 30 mm Hg. This would separate the function of the brain and cardiopulmonary systems as the variable factors in the experimental model.

This separation of systems was the primary purpose of this study. It was shown that if the heart and lungs alone were perfused at normal pressures while the rest of the body, including the brain, were held at a MAP of 30 to 35 mm Hg, survival could occur. This suggested to us that the key organs in 35 mm Hg shock must indeed be the heart and lungs. Recent work on the myocardial depressant factor\(^3\) suggests that the heart itself is probably most important. Because of the severity of the ischemic process, it appears certain that the myocardial depressant factor would have been present in our experimental models, and yet survival occurred. It seems likely that this factor or others must work in conjunction with a myocardium already damaged by low perfusion.

Finally, if pressure in the circulation to the brain drops below a MAP of 30 mm Hg for even relatively short periods of time, death occurs. This is also in general agreement with the findings of most investigators that arterial pressures below 30 mm Hg MAP in standard hemorrhagic shock models are uniformly fatal and that this outcome may well be of central nervous system origin.

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In summary, our contention is that death in “35 mm Hg shock” is cardiopulmonary, but well may involve interaction of a toxic substance with a susceptible myocardium, while in “30 mm Hg shock” it is due to the failure of the central nervous system. It was surprising that the functions of heart and lung seemed less resistant to hypotension than the brain, but our data suggest no alternative explanation. While it is difficult to say what is most important, it seems that metabolic or toxic factors or the perfusion of the abdominal organs are less critical than the state of the end organs, namely heart and lung, and secondarily, brain. This critical level of pressure has been observed in experiments in which cerebral autoregulation failed at about 30 mm Hg but the brain remained resistant.

We believe that death in standard “35 mm Hg shock” is due to failure of some element of cardiopulmonary function since it does not occur if the heart is adequately perfused. Death in “30 mm Hg shock” is related to the central nervous system because it occurs even if normal pressure is maintained in the heart. In brief, survival in profound hypovolemia is dependent on adequate cardiovascular and pulmonary functions integrated by an intact nervous system, and the differential failure of these organs accounts for the phenomenon of irreversibility.

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Present address for Dr. Golden: Forum Building, 777 High Street, Eugene, Oregon.

Address reprint requests to: John A. Jane, M.D., Department of Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia.