Effect of blood transfusion, dopamine, or normal saline on neurogenic shock secondary to acutely raised intracranial pressure


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An experimental model to simulate acutely raised intracranial pressure due to a rapidly expanding intracranial space-occupying lesion was used to produce neurogenic shock. Forty-one rats in neurogenic shock (defined as a mean systemic arterial pressure (SAP) of less than 60 mm Hg) were subjected to various treatments to increase the mean SAP to a level of more than 80 mm Hg. The control group with neurogenic shock received no treatment, and the six treatment groups received infusions of: whole blood, packed cells, plasma, normal saline, dopamine, or a combination of dopamine and saline. Detrimental effects were observed after transfusion of packed cells or whole blood, which caused further deterioration of mean SAP. Although dopamine or the combination of dopamine and saline were both effective (p = 0.0001) for reversing hypotension, the combination was the most effective. If this rat paradigm correlates with human disease, these results indicate that, in the absence of hypovolemia, neurogenic shock due to acute intracranial hypertension should be treated with a combined transfusion of dopamine and normal saline, but not blood since the latter could have a detrimental effect.

KEY WORDS • neurogenic shock • head injury • dopamine • saline • intracranial pressure • rat
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tunities for organ transplantation. In the same study, all patients treated with epinephrine alone succumbed to cardiac arrest within 48 hours of brain death with no clear explanation, in spite of adequate respiratory and fluid management.

For the present study, a model of severe mechanical brain injury caused by a rapidly expanding intracranial balloon was developed in rats and used to produce neurogenic shock defined as a mean systemic arterial pressure (SAP) of less than 60 mm Hg (corresponding to systolic/diastolic values of 80/50 mm Hg). The normal mean SAP in these rats was approximately 130 mm Hg. Animals in shock were treated by infusion of whole blood, packed cells, plasma, normal saline, dopamine, or a combination of dopamine and saline with the goals of restoring mean SAP to 80 mm Hg or higher and of prolonging survival. Details of the cardiovascular effects of the acute intracranial hypertension observed with this model, including catecholamine changes, myocardial pathology, and electrocardiographic (EKG) abnormalities are reported separately.79

Materials and Methods

Animal Preparation and Monitoring

Fifty male Wistar rats,* each weighing 350 to 500 gm, were anesthetized with chloralose (75 mg/kg) and urethane (525 mg/kg) intraperitoneally. These agents were chosen because they are not toxic to the myocardium and minimally affect cardiovascular neurogenic tone.4 The right femoral artery and vein were cannulated with polyethylene (PE 50) catheters containing a mixture of heparin and saline (10 IU heparin/ml saline). The femoral artery cannula was connected to a pressure transducer.‡ A pressure amplifier and chart recorder provided continuous recording of blood pressure.‡ The femoral artery cannula was also used for sampling arterial blood gases and hematocrit, and the femoral vein was used for infusion of drugs and other agents.

The temperature was monitored using a rectal probe and a teletetherometer, and normal temperature was maintained by means of a warming blanket. After a tracheostomy was performed, the animal was attached via a T connector to a Harvard small-animal volume-controlled ventilator.§ All animals were given a muscle relaxant intravenously (pancuronium, 0.6 mg initially then a 0.5-mg maintenance dose every 45 minutes thereafter, if necessary), and ventilated at a rate of 50/min using a 20:1 mixture of pressurized air and oxygen. Arterial blood gases were monitored|| and were maintained within the physiological range. The rats were then placed on the operating room table with the head fixed in a head-holder.

Production of Intracranial Hypertension

A 10-mm midline scalp incision was made extending from the coronal suture to the junction of the lambdoid sutures. With an air drill, two burr holes were made, one on each side of the midline 7 mm behind the orbit and 2 mm lateral to the midline. It was important to place these burr holes at least 1 mm anterior to the lambdoid sutures to prevent venous hemorrhage. The dura mater was opened and, with a small nerve hook, the subdural space was probed on each side. Through the left burr hole, a No. 3 French Fogarty arterial embolectomy catheter was introduced anteriorly into the subdural space so that the whole length of the balloon was inserted intracranially. The catheter was fixed to the skull around the burr hole with Fleck's zinc cement to prevent displacement of the balloon catheter during inflation.

For ICP measurements, a PE 50 catheter filled with normal saline was placed subdurally through the right burr hole, cemented to the skull, and connected to a pressure transducer. Electrocardiographic needle electrodes were inserted into both forelegs and the right back leg. The animals were then allowed to stabilize for 15 minutes, during which time the cement solidified, and arterial blood samples were obtained for determination of blood gases and hematocrit.

In order to inflate the Fogarty catheter balloon in a consistent fashion, an automatic spring-loaded injector was used; this inflated the balloon to its maximum volume of 0.3 ml of liquid over a 2-second interval. Inflation was accomplished with a tuberculin syringe filled with 0.3 ml of distilled water attached to the Fogarty catheter (Fig. 1) and mounted in the injector. The balloon was kept inflated for 15 seconds, and then deflated rapidly. During this entire period, mean SAP and ICP measurements and EKG recordings were obtained.

Experimental Protocol

As described below, 41 (82%) of the 50 injured rats showed systemic hypertension, widening of the pulse pressure, and arrhythmias, followed by hypotension. These 41 animals showed a reduction of mean SAP to less than 60 mm Hg (defined as neurogenic shock) and were randomly allocated after injury into seven groups: Group 1 was a control group and received no treatment; Group 2 received an infusion of normal saline; Groups 3 and 4 were treated with an infusion of dopamine (4.5 mg/ml), or a combination of dopamine (2 mg/ml) and

* Wistar rats supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts.
‡ Pressure transducer, Model 4-327-010, manufactured by Bell & Howell, Pasadena, California.
§ Rodent respirator, Model 680, manufactured by Harvard Apparatus Co., Inc., Dover, Massachusetts.
¶ Blood gas systems BMS, manufactured by MK III Radiometer, Copenhagen, Denmark.
TABLE 1
Volume or weight of agents infused to restore mean systemic arterial pressure for duration of experiment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: control</td>
<td>5</td>
<td>10.6 ± 1.0 ml</td>
</tr>
<tr>
<td>2: normal saline</td>
<td>6</td>
<td>14.0 ± 3.7 ml</td>
</tr>
<tr>
<td>3: normal saline &amp; dopamine</td>
<td>7</td>
<td>14.0 ± 8.0 mg dopamine</td>
</tr>
<tr>
<td>4: dopamine</td>
<td>8</td>
<td>2.1 ± 0.5 ml</td>
</tr>
<tr>
<td>5: whole blood</td>
<td>5</td>
<td>7.2 ± 1.0 ml</td>
</tr>
<tr>
<td>6: packed cells</td>
<td>5</td>
<td>6.2 ± 2.7 ml</td>
</tr>
<tr>
<td>7: plasma</td>
<td>5</td>
<td>5.6 ± 0.8 ml</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations.

normal saline; and Groups 5 to 7 received rat whole blood, plasma, or packed cells, respectively, prepared as described below (Table 1).

The aim of the treatment in Groups 2 to 7 was restoration of the mean SAP to 80 mm Hg or higher for a minimum of 3 hours and, accordingly, the rate of infusion of these agents was adjusted in an attempt to achieve this goal. This value corresponds to a systolic/diastolic pressure of approximately 100/70 mm Hg. As described below, this goal could not be achieved in most animals in terms of the level of mean SAP attained and the duration of restoration of mean SAP.

Preparation of Blood Products for Transfusion

Large male Wistar rats were anesthetized with pentobarbital (3 mg/100 gm intraperitoneally), the jugular vein was cannulated, and the animals were given 500 IU/kg of heparin intravenously. Both carotid arteries were then exposed and, with the animal inverted over a heparinized funnel and flask, the arteries were transected. Approximately 12 ml of blood was collected from each animal during a 1-minute period, and the blood was stored in a citrated bag.*

To obtain packed cells and plasma, whole blood was centrifuged at 2500 G for 2 minutes in a Sorvall GLC-1 centrifuge with an HL-4 rotor,† after which the plasma and packed cells were placed in citrated bags for future use. The volume of each blood product infused is shown in Table 1. An infusion pump‡ was used to infuse the blood products, with the speed of infusion titrated according to the mean SAP response (see below).

Statistical Analysis

Since multiple treatment groups and two time intervals were involved, both linear (one-way analysis of variance) and nonlinear (Kruskal-Wallis test) statistical analyses were performed. Probability values less than 0.05 were considered significant after correction for multiple-hypothesis testing. The effect of treatment was expressed as percent change in mean SAP.

Results

After inflation of the balloon, 41 (82%) of the 50 rats developed immediate arterial hypertension, widening of the pulse pressure, and arrhythmia, followed by severe hypotension to a mean SAP of less than 60 mm Hg within 30 minutes of injury. In the other nine rats mean SAP remained above this level, and they were excluded from the study; indeed, six of these nine rats maintained a mean SAP higher than 80 mm Hg. Therapy was initiated in the 41 rats in neurogenic shock as soon as the mean SAP dropped below 60 mm Hg. Table 1 shows the volume or weight of the agents required to restore mean SAP to more than 80 mm Hg for as long as possible, as described below. Table 2 shows the mean SAP before injury, at the maximum mean SAP response due to balloon inflation, and then after injury (pretreatment values). Statistical analysis of the mean SAP values at all these pretreatment times (preinjury, injury, and postinjury) revealed no significant differences between the seven groups (p > 0.05).

Table 2 also shows the mean SAP 5 minutes after onset of treatment and indicates that preinjury mean

* CPB blood pack unit supplied by Fenwal Laboratories, Division of Travenol Laboratories, Inc., Deerfield, Illinois.
† HL-4 rotor manufactured by Ivan Sorvall, Inc., Norwalk, Connecticut.
‡ Infusion pump, Model 2620, manufactured by Harvard Apparatus Co., Inc., Millis, Massachusetts.
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TABLE 2

Mean systemic arterial pressure before, during, and after injury, and during treatment*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Rats</th>
<th>A: Pre-injury</th>
<th>B: Injury Peak</th>
<th>C: Postinjury Pretreatment</th>
<th>D: Posttreatment (5 min)</th>
<th>Significance: D vs. C</th>
<th>E: Posttreatment (30 min)</th>
<th>Significance: E vs. C</th>
<th>Significance: E vs. D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: control</td>
<td>5</td>
<td>135 ± 13</td>
<td>196 ± 11</td>
<td>51 ± 9</td>
<td>51 ± 8</td>
<td>NS</td>
<td>53 ± 5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>2: normal saline</td>
<td>6</td>
<td>126 ± 24</td>
<td>194 ± 17</td>
<td>51 ± 9</td>
<td>52 ± 11</td>
<td>NS</td>
<td>60 ± 17</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>3: normal saline &amp; dopamine</td>
<td>7</td>
<td>129 ± 7</td>
<td>165 ± 48</td>
<td>47 ± 13</td>
<td>131 ± 21</td>
<td>0.0001</td>
<td>81 ± 8</td>
<td>0.0001</td>
<td>0.0004</td>
</tr>
<tr>
<td>4: dopamine</td>
<td>8</td>
<td>115 ± 19</td>
<td>177 ± 44</td>
<td>49 ± 8</td>
<td>137 ± 34</td>
<td>0.0001</td>
<td>73 ± 12</td>
<td>0.005</td>
<td>0.0001</td>
</tr>
<tr>
<td>5: whole blood</td>
<td>5</td>
<td>133 ± 19</td>
<td>187 ± 19</td>
<td>48 ± 14</td>
<td>46 ± 5</td>
<td>NS</td>
<td>53 ± 6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>6: packed cells</td>
<td>5</td>
<td>146 ± 15</td>
<td>177 ± 61</td>
<td>57 ± 14</td>
<td>44 ± 10</td>
<td>NS</td>
<td>66 ± 17</td>
<td>NS</td>
<td>0.0001</td>
</tr>
<tr>
<td>7: plasma</td>
<td>5</td>
<td>143 ± 10</td>
<td>192 ± 17</td>
<td>60 ± 5</td>
<td>58 ± 4</td>
<td>NS</td>
<td>63 ± 25</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviation (mm Hg). NS = not significant.

SAP values were restored only in those animals treated with dopamine or a combination of dopamine and normal saline (p < 0.0001). However, even with these, the mean SAP could not be maintained (as described below), and there was a significant drop in values within 30 minutes of onset of treatment despite continuous administration of the agents. At 30 minutes posttreatment, the mean SAP in all treated groups except animals receiving whole blood was above 60 mm Hg. Statistical analysis showed that the mean SAP in the dopamine group and dopamine plus saline group was still higher than the control group (p = 0.02). It should be noted that, during this treatment period, the infusion of dopamine or dopamine and saline was increased in rats with diminishing mean SAP, but uncontrollable arrhythmias occurred and the mean SAP deteriorated further. The changes in mean SAP during the treatment period are shown as a percentage of the postinjury pretreatment values in Table 3. The positive effects of dopamine and the combination of dopamine and saline are seen, as well as the ineffectiveness of transfusion of whole blood, plasma, or packed cells. Actually, a further drop in mean SAP was observed in injured rats receiving a transfusion of packed cells or whole blood. This deterioration in blood pressure usually occurred immediately after transfusion and continued for 3 to 5 minutes (Fig. 2). Also, in the group treated with packed cells, there was a significant rise in mean SAP between 5 and 30 minutes after transfusion (Table 2), although only 20% of the animals achieved a mean SAP greater than 80 mm Hg (Table 4).

The percentage of injured rats achieving a mean SAP over 80 mm Hg and the period during which this level of blood pressure could be maintained are shown in Table 4. The results indicate that dopamine and normal saline followed by dopamine alone were the two best treatment methods for maintaining mean SAP after neurogenic shock due to severe head injury. With combined dopamine and normal saline, the average period during which SAP was maintained over 80 mm Hg was 88 ± 22 minutes (± standard deviation), and with dopamine alone the average was 35 ± 17 minutes.

TABLE 3

Changes in mean systemic arterial pressure (mSAP) at 5 and 30 minutes after treatment*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% Change in mSAP at 5 Min</th>
<th>Significance</th>
<th>% Change in mSAP at 30 Min</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: control</td>
<td>1 ± 5</td>
<td>NS</td>
<td>5.2 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>2: normal saline</td>
<td>3 ± 15</td>
<td>NS</td>
<td>19 ± 27</td>
<td>NS</td>
</tr>
<tr>
<td>3: normal saline &amp; dopamine</td>
<td>223 ± 193</td>
<td>0.0001</td>
<td>94 ± 90</td>
<td>0.0001</td>
</tr>
<tr>
<td>4: dopamine</td>
<td>192 ± 121</td>
<td>0.0001</td>
<td>50 ± 28</td>
<td>0.005</td>
</tr>
<tr>
<td>5: whole blood</td>
<td>5 ± 40</td>
<td>NS</td>
<td>19 ± 35</td>
<td>NS</td>
</tr>
<tr>
<td>6: packed cells</td>
<td>22 ± 16</td>
<td>NS</td>
<td>19 ± 35</td>
<td>NS</td>
</tr>
<tr>
<td>7: plasma</td>
<td>3 ± 10</td>
<td>NS</td>
<td>6.5 ± 48</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations, expressed as a percentage of postinjury pretreatment levels. NS = not significant.

Discussion

The cardiovascular effects of increased ICP have been of major interest to clinicians and investigators for more than 170 years. As early as 1824, Cooper noted a relationship between increased pressure inside the head and changes in the cardiovascular system, and in 1892,
Spencer and Horsely\textsuperscript{82} published their observations “on the changes produced in the circulation and respiration by increase of ICP or tension.” However, Harvey Cushing was the first to methodically investigate the cardiovascular consequences of raised ICP. In 1901, he stated: “as a result of these experiments, a simple and definite law may be established, namely that an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla. It is thus seen that there exists a regulatory mechanism on the part of the vasomotor center which, with great accuracy, enables the blood pressure to remain at a point which is just sufficient to prevent the persistence of an anemic condition of the bulb, demonstrating that the rise is a conservative act and not one such as is consequent upon a more reflex sensory irritation.\textsuperscript{91,98}

Later, Denny-Brown and Russell\textsuperscript{20} clearly delineated the immediate rise in SAP, and the subsequent fall to hypotensive levels which was accompanied by peripheral vasoconstriction. These and subsequent investigators used a variety of models for studying the cardiovascular changes due to intracranial hypertension. The models have varied from direct mechanical brain injury with elevation of ICP to models with elevation of ICP alone, such as saline infusion into the cisterna magna or lumbar subarachnoid space.\textsuperscript{2,5,7,18,21,27,28,32,39,43,61,76,77,83,84}

The role of the autonomic nervous system in producing these cardiovascular changes was gradually recognized during the present century.\textsuperscript{11,19,32,39,43,53,65,66,76,77,81,91} The current opinion is that an imbalance between the sympathetic and parasympathetic nervous systems\textsuperscript{77,53,54,90} causes a spectrum of cardiovascular changes ranging from hypotension to hypertension, bradycardia to tachycardia, and bradyarrhythmia to tachyarrhythmia.\textsuperscript{76} There are also biochemical and histological changes in the heart suggestive of myocardial ischemia.\textsuperscript{8,9,12,13,26,37,38,40,49,50,58,59} Alpha adrenergic blockade\textsuperscript{31,43,76} or beta adrenergic blockade\textsuperscript{48,49,73,76} has been successful in preventing some of these cardiovascular changes. In particular, the role of the vagus nerve in the pathogenesis of the arrhythmias has been investigated.\textsuperscript{27,42,53,70,81,92} Most reports show that vagotomy or blockade of the parasympathetic nervous system has been successful in preventing bradycardia and arrhythmias due to intracranial hypertension.

As early as 1934, it was noted that EKG abnormalities accompany head injury\textsuperscript{3} and, since then, EKG changes simulating myocardial ischemia have been found in patients with intracranial disorders ranging from meningitis to intracranial tumors.\textsuperscript{17,29,41,67} In patients with subarachnoid hemorrhage and intracerebral hemorrhage, these findings have been especially frequent.\textsuperscript{36,55} In some cases, there was elevation of myocardial specific creatine phosphokinase\textsuperscript{26,37,49,58} and histologically defined focal myocardial ischemic changes.\textsuperscript{36,40,55}

High levels of both local and circulating catecholamines reflecting an increase in sympathetic tone were found to be associated with intracranial hypertension.\textsuperscript{9,11,48,59,76,86} This catecholamine response was implicated in the genesis of a variety of target organ changes including central neurogenic pulmonary edema,\textsuperscript{44,65,73,78,85} focal myocardiocontracture,\textsuperscript{36,38,40,66} and generalized hypermetabolism.\textsuperscript{77} It has been known since the early 1900’s that surgical and chemical sympathectomy could prevent or modify the cardiovascular changes accompanying high ICP.\textsuperscript{4,8,31,32,65,95} Adrenalectomy or depletion of catecholamines from the nerve terminals by pharmacological agents were shown to prevent the reactive rise in circulating catecholamines in intracranial hypertension.\textsuperscript{75,76} Studies of the anatomical localization of the centers in the brain that mediate these cardiovascular changes due to high ICP have shown that an intact medulla oblongata and floor of the fourth ventricle are required.\textsuperscript{22,45,91} However, higher centers (in particular, the posterior and anterior hypothalamic nuclei, and even specific areas of the frontal lobes and the orbital gyrus) have been shown to modify the response of the vasomotor centers of the brain stem to intracranial hypertension.\textsuperscript{30,33,34,67}

Figure 3 shows diagrammatically the sequence of events leading to neurogenic shock due to mechanical brain injury caused by the inflation of the subdural balloon in the present experiment. The pathophysiology of cardiac arrest in patients with brain death due to severe head injury and intracranial hypertension is not well understood.\textsuperscript{94} Although brain death leads to hemodynamic and metabolic deficiencies due to loss of brain-stem function, with adequate hemodynamic management such patients can usually be stabilized for purposes of organ donation. The best means of establishing such stabilization are the subject of debate. For example, in one study, 144 brain-dead patients considered for kidney donation received dopamine, dobutamine, and norepinephrine to maintain adequate mean SAP; it was found that the type of catecholamine administered made no difference to the incidence of initial or delayed establishment of renal function, or to

### Table 4

Percentage of animals achieving mSAP > 80 mm Hg and duration of maintaining that level

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Rats</th>
<th>% of Rats</th>
<th>Mean SAP &gt; 80 mm Hg</th>
<th>Mean Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: control</td>
<td>5</td>
<td>20</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2: normal saline</td>
<td>6</td>
<td>65</td>
<td>10.3 ± 10.8</td>
<td></td>
</tr>
<tr>
<td>3: normal saline &amp; dopamine</td>
<td>7</td>
<td>100</td>
<td>88.0 ± 22.0</td>
<td></td>
</tr>
<tr>
<td>4: dopamine</td>
<td>8</td>
<td>100</td>
<td>35.0 ± 17.0</td>
<td></td>
</tr>
<tr>
<td>5: whole blood</td>
<td>5</td>
<td>40</td>
<td>8.4 ± 14.0</td>
<td></td>
</tr>
<tr>
<td>6: packed cells</td>
<td>5</td>
<td>20</td>
<td>2.0 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>7: plasma</td>
<td>5</td>
<td>40</td>
<td>16.0 ± 30.0</td>
<td></td>
</tr>
</tbody>
</table>

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whether renal function was successfully restored at all. 63 In a recent clinical study, Yoshioka, *et al.*, 34 found that ADH plays an important role in the hemodynamic maintenance of brain-dead patients: the addition of ADH significantly reduced the dose of dopamine required to maintain mean SAP. Some patients were successfully maintained for more than 1 month after cerebral death was established. This observation is compatible with earlier reports by Cowley, *et al.*, 15 who showed that, in sinoaortic baroreceptor-denervated animals and decapitated animals, pressor sensitivity to ADH and noradrenaline was increased 11-fold and 8000-fold, respectively. Kidney and liver function in brain-dead patients who received a combination of ADH and epinephrine was normal even after a prolonged period. 94

The present study not only showed clearly that transfusion of whole blood, packed cells, or plasma failed to improve hypotension due to neurogenic shock as a result of brain injury, but also showed that whole blood or packed cell transfusion usually led to further deterioration of blood pressure. This deterioration usually occurred immediately after transfusion and continued for 3 to 5 minutes (Fig. 2) and may represent further stress on the failing heart caused by increased cardiac preload. However, in the experimental group treated with packed cells, there was a significant rise in mean SAP between 5 and 30 minutes after transfusion (Table 2), although only 20% of the animals achieved a mean SAP between 5 and 30 minutes after transfusion (Table 2), although only 20% of the animals achieved a mean SAP greater than 80 mm Hg (Table 4). This could be explained on the basis of decreased cardiac preload and improved cardiac function, since transfusion was discontinued in the face of deteriorating mean SAP in this group of rats.

The present study supports the hypothesis that this type of shock is caused by neurogenically induced cardiac failure (Fig. 3). In a companion study of the vascular changes affecting the heart in this model, the microfil perfusion technique showed that in 10 of 12 injured rats the heart showed perfusion abnormalities with multiple areas of contraction band necrosis associated with focal areas of vascular spasm and irregularity. 79 In addition, it was demonstrated that our model of acutely increased ICP caused massive elevation of plasma catecholamines. 79

These results are compatible with other investigations of increased ICP which have shown a severe peripheral vasoconstriction due to sympathetic hypertonia and high levels of circulating catecholamine. 7,10,11,39,43,48,71, 72,76–78 With his model of increased ICP, Cushing 18 commented in 1901 that “If a coil of small intestine be exposed, during such a compression experiment as has been described, the splanchnic vessels can be seen to contract during the rise in blood pressure.” Tsubura 88 showed that there is no increased cardiac output although there is peripheral vasoconstriction. Rodbard and Stone 74 concluded from their experiments on high ICP that there are two phases in the pathogenesis of peripheral vasoconstriction: the first or immediate phase is neurogenic vasoconstriction; and the second phase, with a lag of 10 to 15 seconds, is consistent with the release into the venous system of a pressor material which requires time to reach the arterioles. Although cardiac output was not measured in the present study, Richardson, *et al.*, 71 found in dogs that, as the ICP was rapidly elevated by the injection of fluid into the parietal subarachnoid space, there was an initial massive peripheral vasoconstriction accompanied by increased right atrial pressure and no change in the cardiac output. However, if high ICP was maintained for several minutes, this was then followed by a decrease in vasoconstriction and increased cardiac output, as long as the animals did not decompensate.

Denny-Brown and Russell 20 in their study of the cardiovascular effects of cerebral concussion, noted three phases in the changes affecting the peripheral vasculature: first, a massive peripheral vasoconstriction, followed by a period of recovery, and finally an end-stage of intense vasoconstriction. Eichbaum and Bissetti 24 showed that, in dogs with head injury and acute intracranial hypertension, there was an initial short-lasting hypertension followed by late hypotension, often reaching shock levels. A significant fall in the diastolic blood pressure, observed by Hayreh and Edwards 99 in the late stage of their experiments on vascular responses to acute intracranial hypertension, induced by injection of normal saline in the cisterna magna of the rhesus monkey, was thought to be due to reduced vasomotor tone of the arterioles and a fall in peripheral vascular resistance. Other aspects of the cardiovascular changes due to high ICP were studied by the same authors, who also noted a significant rise in the pressure of the internal jugular vein and superior sagittal sinus as a result of intracranial hypertension.

In our experiments, the infusion of dopamine (a drug which produces an inotropic effect on the myocardium, resulting in increased cardiac output), or a combination of normal saline and dopamine improved neurogenic
The effect of blood transfusion and dopamine on neurogenic hypotension due to spinal cord injury at T-1 in rats was studied by Dolan and Tator.\(^2\) In contrast to brain injury, the hypotension after cord injury was less responsive to dopamine infusion than to blood transfusion. Table 5 summarizes the differences in cardiovascular responses secondary to acute brain and cervical spinal cord injury. In general, neurogenic shock after head injury and increased ICP is due to cardiac failure, mainly secondary to myocardial ischemia. In contrast, after spinal cord injury the major hemodynamic deficits are due to sympathetic hypotonia, unopposed vagotonia, and reduced cardiac output. These differences in the mechanisms underlying neurogenic shock in brain trauma and spinal cord injury should be considered, so that appropriate treatment can be given.

Conclusions

The relative value of transfusion of whole blood, packed cells, or plasma, or the infusion of normal saline, dopamine, or a combination of dopamine and normal saline was determined for the resuscitation of head-injured rats with neurogenic hypotension (shock) due to mechanical brain injury and raised ICP. Dopamine or a combination of dopamine and normal saline improved the mean SAP to preinjury blood pressure levels (\(p < 0.0001\)). However, this effect was not long-lasting, and a significant drop in blood pressure was observed at 30 minutes in spite of continuing treatment. It is our conclusion that the failure of dopamine to maintain the blood pressure in head-injured animals is caused by the initial sympathetic hypertonia and the resultant high levels of catecholamine which are injurious to the myocardium. It is hypothesized that the high levels of both local and circulating catecholamines cause cardiac vasospasm, ischemia, necrosis, and primary pump failure. Transfusion of blood or its components did not improve the hypotension; indeed, whole blood and packed cell transfusion caused further acute but temporary deterioration in the hypotension, which supports the hypothesis that primary pump failure is the cause of the reduction of blood pressure.

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References

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22. Doba N, Reis DJ: Localization within the lower brainstem of a receptor area mediating the pressor response to increased intracranial pressure (the Cushing response). Brain Res 47:487-491, 1972


40. Heinrich D, Muller W: Focal myocardial necrosis in cases of increased intracranial pressure. Eur Neurol 12:369-376, 1974


42. Heymans C: The control of heart rate consequent to changes in the cephalic blood pressure and in the intracranial pressure. Am J Physiol 85:498-506, 1928


Treatment of neurogenic shock secondary to intracranial hypertension

91. Weinstein JD, Langfitt TW, Kassell NF: Vasopressor response to increased intracranial pressure. Neurology 14: 1118-1131, 1964
94. Yoshioka T, Sugimoto H, Uenishi M, et al: Prolonged hemodynamic maintenance by the combined administra-


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