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Title The Effect of Changes in Cerebral Perfusion Pressure and Intracranial Pressure on the Development of Cerebral Oedema

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A Thesis submitted for the degree of Doctorate of Medicine at the University of Otago, Dunedin, New Zealand.

Date 1 January 1984
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ABSTRACT

The influence of intracranial pressure, systemic arterial pressure and cerebral perfusion pressure upon the development of vasogenic cerebral oedema is largely unknown. To study their relationship, an osmotic disruption of the blood-brain barrier was produced unilaterally in female rabbits by injecting 1 cc/Kg of 2 M Na Cl into the left internal carotid artery. The amount of vasogenic oedema produced was assessed by quantitation of the amount of Evans Blue extravasation into the area of maximum blood-brain barrier breakdown by optical densitometry following Formamide extraction of the Evans Blue from the oedematous cortex. Intracranial pressure was measured using a cisterna magna catheter into which mock CSF could be infused to a predetermined pressure. Systemic arterial pressure was controlled by exsanguination from a femoral artery catheter in those animals selected for blood pressure control.

In the initial 18 animals in which blood pressure was not controlled, no significant relationship between the intracranial pressure and the degree of Evans Blue extravasation was noted. In these animals, however, a significant direct relationship between cerebral perfusion pressure (defined as mean arterial pressure minus mean intracranial pressure) and Evans Blue extravasation was found (correlation coefficient = .630, \( p < .001 \)).

When intracranial pressure was maintained constant at 0-5 mmHg in 16 animals and different levels of blood pressure were produced by exsanguination, a significant direct relationship
between Evans Blue extravasation and the systemic arterial pressure was found (correlation coefficient = .786, p < .001).

In 20 animals the blood pressure was maintained constant at 90-100 mmHg and the intracranial pressure was varied between 0, 25, 50 and 75 mmHg with five animals at each pressure. There was a significant correlation indicating increasing Evans Blue extravasation at low levels of intracranial pressure (p < .001). This relationship may be exponential.

Cerebral blood flow determinations by the H₂ clearance method indicated loss of autoregulation in the areas of brain injured by the intracarotid hypertonic saline. In addition, a progressive fall in the cerebral blood flow with time was noted in the same areas. Electron microscopic studies of cortical samples demonstrated abnormal amounts of extracellular fluid in the neuropil surrounding capillaries, and swelling of astrocytic foot processes. Inter-endothelial tight junctions were not disrupted.

These results indicate a high systemic arterial pressure and low intracranial pressure (i.e., a large cerebral perfusion pressure) promote Evans Blue extravasation in this model of blood-brain barrier disruption. This finding has implications for the management of patients with vasogenic oedema. Vigorous control of intracranial hypertension and/or failure to treat systemic arterial hypertension may have detrimental consequences by promoting increased cerebral oedema.
This study arose out of a desperate situation I have been faced with on several occasions immediately following evacuation of an acute subdural haematoma. Having safely accomplished the haematoma removal, on these occasions the brain began to swell relentlessly and uncontrollably minute by minute filling and then exuding out of the craniotomy defect. In this situation the choice was to either remove large amounts of swollen brain or close up the head and allow the patient to die. A similar situation arose once in my experience after the successful removal of a huge left sphenoid wing meningioma in a 45 year old woman who presented with a VI nerve palsy as her only sign. The relatively straight-forward operation resulted in the patient initially awakening neurologically intact. Within 24 hours she began to deteriorate and eventually died of massive left hemisphere swelling.

In explaining this phenomenon, it seemed that removal of a compressing mass overlying an area of brain in which the blood-brain barrier was disrupted may promote oedema formation within that area of brain. This could possibly occur by either a direct hydrostatic effect or by allowing increased blood flow into the area. If this were the case, then a similar situation might also arise in the patient with a diffusely injured brain, swollen with oedema, in whom the intracranial pressure was iatrogenically lowered by the venting of CSF from a ventricular catheter. CSF venting is currently recommended for such patients with
intracranial hypertension in the belief, yet unproven, that a lower intracranial pressure may help the patient by reducing brain shift and increasing cerebral blood flow. I questioned if artificially reducing the intracranial pressure may in fact be detrimental to the injured brain by leading to further brain oedema. This study was initially designed to investigate the influence of intracranial pressure on brain oedema development. As the study progressed, however, I found that not only intracranial pressure but also the systemic arterial pressure and the derived cerebral perfusion pressure were directly related to cerebral oedema formation.

The study was undertaken during my neurosurgical residency at the University of Western Ontario, London, Ontario, Canada. The time spent working on the research project was considered part of my training by the Royal College of Surgeons of Canada. The laboratory experiments were performed in the Brain Research Laboratory, Victoria Hospital and the Cerebral Blood Flow Laboratory, University Hospital, University of Western Ontario. In addition to the guidance of Assistant Professor R. F. Del Maestro, M.D., PhD., FRCS(C) I wish to acknowledge the assistance of Associate Professor A. L. Amacher, M.D., FRCS(C), for help in formulating the study and Associate Professor J. K. Farrar, PhD., Department of Biophysics, for teaching me the hydrogen-clearance technique of cerebral blood flow analysis. I also wish to acknowledge the assistance of Messrs. W. MacDonald, BSc and
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P. Floyd, BSc for technical assistance in spectrophotometric analysis and the preparation of tissue for examination by the electron microscope.
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Unlike the lung or soft tissue of the limbs where oedema may develop consequent upon such problems as hypoalbuminaemia or cardiac failure, oedema of the brain occurs only as a consequence of a primary injury or disease process. Free entry of intravascular fluid, metabolites and protein into the brain is prevented by the "blood-brain barrier", an anatomical and physiological barrier. Histological study has shown the blood-brain barrier to be at the level of the cerebral capillary endothelium. (24). Unlike endothelium elsewhere in the body, the cerebral capillary endothelial cells are connected by continuous tight junctions. In addition, fenestrations, transendothelial channels and pinocytotic vesicles present in endothelial cells elsewhere are rarely demonstrated. Movement of metabolites such as glucose and amino acids across the blood-brain barrier is dependent upon their lipid solubility, molecular size and the presence of specific carrier-mediated transport systems. (23).

Cerebral oedema may develop when the blood-brain barrier is disrupted. It has been categorized into three types; vasogenic, cytotoxic and transcellular. In vasogenic oedema, the primary pathological process is disruption (by either anatomical or physiological means) of the blood-brain barrier allowing entry of intravascular components (protein, water) into the cerebral extracellular space. Vasogenic oedema may
develop as the consequence of tumour, trauma, infection or from drug induced blood-brain barrier breakdown. (26).

In cytotoxic oedema, disturbances of cellular metabolism (for example resulting from anoxia) result in loss of water and ion hemeostasis at the cellular level with consequent fluid entry into the cell and resultant cellular swelling. Transcellular oedema arises in hydrocephalus when ventricular fluid under increased pressure moves by bulk flow from the ventricle into the cerebral extracellular space.

Cerebral oedema leads to brain swelling and shifting within the cranium, cerebral ischaemia and elevated intracranial pressure. In addition, experimental evidence suggests that oedema fluid or its effects within the cerebral extracellular space may be harmful to the neuropil. (4, 10).

Recent reported advances in the management of patients with vasogenic cerebral oedema and brain swelling from trauma have stressed the necessity to control intracranial pressure (ICP) to near normal levels. (18, 20, 27). The aim of this treatment is two-fold: (1) to prevent shift of the brain downward through the tentorial hiatus (herniation) and thus reduce pressure on the vital brain stem centers and (2) to improve cerebral blood flow inside the head by improving the cerebral perfusion pressure. However, the effect of control of the intracranial pressure on brain oedema formation in man is unknown. According to Starling's Law manipulation of the
intracranial pressure might be expected to influence movement of
intravascular fluid across a disrupted blood-brain barrier. (15).

All neurosurgeons at some time have seen the development of
rapid (within minutes) uncontrollable brain swelling from cerebral
oedema following acute decompression of an injured brain by the
evacuation of an acute subdural haematoma. This brain swelling
can also be seen rarely following removal of a large meningioma.
The phenomenon has been termed "malignant" cerebral oedema. The
progressive swelling over the ensuing 1 to 12 hours often leads
to the patient's demise. In animals subjected to an acute cryogenic
brain injury, decompressive craniectomy over the injury site has
been shown to increase local cerebral oedema formation. (7).

This study was initially undertaken to investigate this
phenomenon of increased brain oedema formation occasionally
seen following removal of a cerebral compressive lesion. It
investigates the hypothesis that elevated intracranial pressure
(either local as in the case of a haematoma, or generalized
as the result of a diffuse brain injury with swelling) may
retard movement of oedema fluid across a disrupted blood-
brain barrier, and thus reduce vasogenic oedema formation.
As the study progressed, it became clear that the systemic
arterial pressure may also significantly influence cerebral
oedema formation. Again applying Starling's Law, it is reason-
able to hypothesize that variations in the cerebral intra-
vascular hydrostatic pressure in areas of brain in which the
blood-brain barrier has been disrupted may lead to increased vasogenic oedema.

In normal brain, cerebral autoregulation maintains the cerebral blood flow and capillary hydrostatic pressure constant between a wide range of systemic arterial pressures, if the intracranial pressure is constant. (Figure 13)(21). This phenomenon is called autoregulation. Diseases which disrupt the blood-brain barrier (e.g. trauma, ischaemia) may lead to disordered autoregulation. In this situation, variations in the blood pressure are reflected by variations in the cerebral capillary hydrostatic pressure. If the amount of fluid flowing across the disrupted blood-brain barrier were to vary, then alterations in vasogenic oedema formation would presumably occur. Some evidence already exists in animals subjected to traumatic or ischaemic brain injury that increased blood pressure may be associated with an increase in vasogenic oedema formation. (6, 16, 19, 26). In humans with brain injury, the effect of blood pressure changes on cerebral oedema development has not been investigated. It may be an important factor to be considered in the management of brain-injured patients. Of additional importance is that therapy with induced hypertension has become part of the standard treatment for certain types of cerebral ischaemia including ischaemia from vasospasm resulting from subarachnoid hemorrhage. (13). If in this situation blood-brain barrier disruption has already occurred, induced hypertension may be harmful to the patient by promoting
This study has been undertaken with rabbits to ascertain the influence of various levels of both the intracranial pressure, the systemic arterial pressure and the derived cerebral perfusion pressure (defined as mean arterial pressure minus mean intracranial pressure) (21) upon the development of vasogenic cerebral oedema. A relatively pure model of vasogenic cerebral oedema can be produced in animals by osmotic disruption of the blood-brain barrier by the direct injection of hypertonic saline into the internal carotid artery of a rabbit. (8, 9). Disruption of the blood-brain barrier is produced within five minutes of injection by a direct effect of the hypertonic saline upon the capillary endothelium. (11). The period immediately following blood-brain barrier disruption is an ideal time to investigate the relationship of the blood pressure and intracranial pressure upon oedema formation. As a marker for the amount of oedema formation, experimental studies in animals have shown that Evans Blue is ideal because of its immediate complete binding to albumen following intravenous injection. (29). Thus, it will only enter into the extra-vascular space when the blood-brain barrier has been disrupted and oedema fluid (containing albumen) enters the brain.
CHAPTER 2
MATERIALS AND METHODS

Because of their proven reliability for studying hypertonic saline cerebrovascular injury and cerebral oedema, rabbits weighing 2.3 - 2.8 kg were selected. Females were used because evidence exists that there are different permeability characteristics of the blood-brain barrier of male and female rabbits. An anaesthetic agent that provided an anaesthetized immobile and physiologically stable animal initially breathing spontaneously was sought. After attempts at using Ketamine alone (which failed to anaesthetize the animal in about 20 percent of cases) intramuscular Pentobarbital, and inhalational agents (which resulted in frequent death from cardiorespiratory arrest), a combination of Ketamine Hydrochloride (Ketalar) 100 mg/kg and Xylazine (Rompun) 10 mg/kg, intramuscular was found to consistently provide satisfactory anaesthesia. In addition, once attached to a ventilator the animal did not fight ventilation.

All incision lines were infiltrated with .5% Lidocaine (Xylocaine, Astra) to reduce the amount of general anaesthetic required. Fifteen minutes later, the animal was turned prone, its head placed in a headholder and the atlanto-occipital membrane was exposed via a mid-line incision. Following complete haemostasis, the membrane and arachnoid were incised just below the foramen magnum and a PE-60 Intramedic polyethylene catheter inserted 2-3 mm into the cisterna magna with the end lying free in the sub-arachnoid space. The dural opening was made water tight by the insertion of
FIGURE 1

Method of measurement and elevation of the intracranial pressure (ICP) via a cisterna magna catheter. The rate of the infusion pump was adjusted to infuse normal saline at 37° to produce the desired ICP.
a muscle plug into the hole beside the catheter. The catheter was secured in position with acrylic glue. The catheter was then attached to a Statham (Statham Laboratories, Inc., Puerto Rico) pressure transducer (#1) via a three-way stop-cock allowing simultaneous recording of the intracranial pressure (ICP) and the infusion of 0.9% normal saline at 37°C when required to elevate the ICP (Fig. 1). The animal was then turned supine, and via a mid-line neck incision, a tracheostomy and left external jugular venous catheter with normal saline running at 5 cc per hour were inserted. The animal was then attached to a volume-cycled ventilator and the rate and tidal volume adjusted to ventilate the rabbit to a PaCO$_2$ of 39 ± 4 mmHg. The left common, internal and external carotid arteries were exposed, and the external carotid artery ligated with 3-0 silk close to the bifurcation (Fig. 2). The common carotid artery was then ligated 1 cm proximal to the bifurcation, and a PE-60 catheter attached to a Statham pressure transducer (#2) inserted into the distal common carotid artery for measurement of stump pressure and when required, the simultaneous infusion of 2.0 M NaCl to produce blood-brain barrier breakdown. A third PE-60 catheter attached to a Statham pressure transducer (#3) was inserted into the proximal common carotid artery to allow systemic arterial pressure (SAP) measurement and removal of blood for PaO$_2$, PaCO$_2$ and pH. The three Statham pressure transducers were attached to a Gould (Gould Inc., Cleveland, OH) multi-channel chart recorder allowing simultaneous recording of
FIGURE 2

The method used to perfuse the rabbit left internal carotid artery territory with 1 cc/kg 2M NaCl at a pressure 15-30 mmHg higher than systemic arterial pressure. The time taken to infuse the volume of 2M NaCl was 30-60 seconds.
FIGURE 3a, b

Superior (a) and inferior (b) views of a typical left hemisphere lesion demonstrating Evans Blue extravasation. Note also some extravasation into the right anterior cerebral territory.
the three pressures. (Figs. 4 & 6).

The left femoral artery was exposed and cannulated to allow removal of blood in those animals selected for blood pressure control. All arterial catheters were kept patent with the slow infusion of heparinized normal saline solution.

The experiment was then conducted in three stages. In the first stage, the influence of increased ICP (without the SAP being controlled) upon cerebral oedema development was investigated. Eighteen animals were used to study the effect of 3 randomly allocated levels of ICP (6 animals each at 0, 25 and 50 mmHg) upon oedema formation as measured by Evans Blue (EB) extravasation in the cortex. Blood-brain barrier disruption was produced by infusing 1 cc/kg of 2.0 M Na Cl into the left internal carotid artery. (Fig. 3). Because elevated cerebral arterial pressure has been shown to disrupt an intact blood-brain barrier (25) the injection pressure was restricted to 15-30 mmHg above the SAP. The brains of the rabbits studied weighed 6-8 gms. If the average cerebral blood flow (CBF) is assumed to be 50 ml per 100 gram per minute, the rabbit brain normally receives only 3-4 cc per minute of blood. Approximately 1/3 is supplied by each internal carotid artery. At initial trials, 1 cc/kg of 2.0 M Na Cl solution was found to produce a consistent reproducible disruption of the blood-brain barrier. Infusion of that volume of hypertonic saline at 15-30 mmHg greater than SAP takes approximately 40-60 seconds. Upon completion of the hypertonic saline injection, the ICP was
FIGURE 4

Tracings of the stump, systemic arterial (SAP) and intracranial (ICP) pressures from a first stage animal with the ICP elevated to 50 mmHg. Note the large reflex increase in stump pressure and SAP in response to intracarotid hypertonic saline injection and ICP elevation.
immediately elevated to the predetermined level (0, 25 or 50 mmHg) by infusing 0.9% NaCl at 37°C intracranially via the cisterna magna catheter using a Sage (Orion Research Inc., Cambridge, MA) infusion pump. (Fig. 4). Upon reaching the desired ICP, 2 cc/kg of 2 gm/100 ml Evans Blue (Fisher Scientific, Fair Lawn, New Jersey) in distilled water (0.270 Osm) was injected intravenously. The ICP was then kept at the desired level for 10 minutes, arterial blood gases were drawn, and the animal was sacrificed by injecting a bolus of intravenous air. Both external jugular veins were then cut, the right atrium opened and 100 cc of 0.9% NaCl infused into the left internal carotid catheter by gravity at 100 cm of water pressure to flush out the cerebral intravascular contents. (8, 9). The brain was then removed, examined and the area and degree of EB extravasation recorded. (Fig. 3). This was always maximum in the cerebral cortex.

The amount of oedema was measured by quantitation of the amount of EB extravasation into the cortex. 0.10 to 0.15 gm of cerebral cortex was removed from the area of greatest EB extravasation (the lesion) and from an identical area in the opposite hemisphere (the control). The samples were then cut into quarters and soaked in 1 cc of Formamide (Fisher Scientific, Fair Lawn, New Jersey) for 72 hours to extract the EB. This method of EB extraction was originally described by Nachman. (22). More recently it was used by Ackerman in studying blood vessel permeability in liver tumors. (21). The fluid containing the extracted
EB was then removed and the optical density measured at 620 nm using a Perkin-Elmer 559A double beam spectrophotometer (Perkin-Elmer, Oak Brook, IL) with Formamide in the reference cuvette. (Fig. 5) A standard curve was prepared using EB diluted in Formamide and the results expressed as \( \mu \text{gm EB/gm cortical weight} \). The amount of EB crossing the blood-brain barrier was assessed by subtracting the EB extracted from the control sample from that extracted from the lesion sample. This method of EB extraction and quantitation by optical densitometry has not previously been used for the study of cerebral oedema.

The second stage of the experiment consisted of maintaining the ICP constant (at 0-5 mmHg) after infusion of the hypertonic intracarotid saline and then altering the SAP in each animal to a predetermined level by exsanguination from the femoral artery catheter. This was achieved by drawing blood into a 50 cc heparinised saline syringe as required to maintain the predetermined arterial pressure. Ten animals were studied and the range of randomly allocated mean SAP's was from 24-120 mmHg. The experiment was otherwise identical to that of the first stage.

The third stage of the experiment was identical to the first stage except that the SAP was kept at a constant mean level of 90-100 mmHg by the controlled removal of blood from the left femoral artery catheter, i.e. the hypertensive response (precipitated by (i) the infusion of hypertonic intracarotid saline and (ii) the elevation of the ICP by the cisterna magna infusion.
FIGURE 5

Cortical samples soaked in 1 cc of Formamide for 72 hours. Left is from the lesion cortex showing distinct blue colouring of the Formamide caused by extracted Evans Blue. Right is from the control cortex and shows minimal colouring.
FIGURE 6

Tracings of the stump, systemic arterial (SAP) and intracranial (ICP) pressures from a third stage animal with the ICP elevated to 50 mmHg. The reflex increase in SAP has been prevented by controlled exsanguination. The SAP is kept constant at 90-100 mmHg mean.
saline) was prevented. (Fig. 6).

Twenty animals were studied in the 3rd stage with the ICP kept at 0, 25, 50 or 75 mmHg (five animals at each pressure level).
CHAPTER 3
RESULTS OF OEDEMA QUANTITATION

First Stage Protocol

The systemic arterial pressure (SAP), intracranial pressure (ICP) and degree of Evans Blue (EB) extravasation from the first eighteen animals are recorded in Appendix 1. The variation in levels of SAP's should be noted because this parameter was not controlled in the first stage of the experiment. The mean and standard deviation of the EB extravasation are recorded in Table 1. As outlined in Chapter 2, the degree of oedema fluid is represented by the "lesion-control" values.

ICP's of 0, 25, and 50 mmHg were not associated with a statistically significant difference in the amount of extravasation of EB. The degree of EB extravasation at an ICP of 50 mmHg tended to be less than that occurring at 0 or 25 mmHg. The cerebral perfusion pressure (CPP), which takes account of both the SAP and the ICP (see Page 40), was then calculated for each animal five minutes after lesion creation and plotted against the lesion-control value for the EB extravasation. A significant linear relationship (correlation coefficient = .680, p < 0.001) was found between the CPP and the degree of EB extravasation. (Fig. 7). The six animals which had an ICP of 0 (* in Fig. 7) appeared to show a possible linear relationship between the SAP and EB extravasation. To investigate this relationship an additional 10 animals with varying degrees of SAP between 24-120 mmHg were then studied (second stage).
TABLE 1

Mean and standard deviation of the amount of Evans Blue (EB) extravasation into the cerebral cortex of the 18 first stage rabbits at an intracranial pressure (ICP) of 0, 25 or 50 mmHg. Systemic arterial pressure was not controlled. There is no statistically significant difference between the lesion-control values.

<table>
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<tr>
<th>ICP</th>
<th>Evans Blue Extravasation (μ gm EB) (gm cortex)</th>
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<tr>
<td></td>
<td>Lesion</td>
</tr>
<tr>
<td>0</td>
<td>142.7±60.7</td>
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<tr>
<td>25</td>
<td>147.2±32.8</td>
</tr>
<tr>
<td>50</td>
<td>109.6±56.6</td>
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FIGURE 7

Results of the first stage protocol plotting Evans Blue (EB) extravasation against cerebral perfusion pressure. The correlation coefficient for these 18 animals is .630 and the relationship is significant, $P < .001$. The results of the six animals with an ICP of 0 are indicated by an asterisk.
Second Stage Protocol

The results of the second stage experiments are tabulated in Appendix 2. The wide range of SAP's was produced by controlled exsanguination from the left femoral artery catheter. The degree of EB extravasation related to variations in SAP with the ICP kept constant at 0-5 mmHg in the 16 (6 from the 1st stage) animals demonstrated a highly significant linear relationship (correlation coefficient = .786, p < .001). Increasing SAP led to increasing EB extravasation. (Fig. 8).

Third Stage Protocol

In the third stage, 20 animals were randomly allocated to an ICP of 0, 25, 50 and 75 mmHg. The experiment was conducted as in the first stage except that the large rise in SAP which occurred in response to both the intra-arterial hypertonic saline injection and the elevated ICP was prevented by controlled exsanguination. (Fig. 6). The SAP of each animal was consequently maintained at 90-100 mmHg. The values of EB extravasation for each of these 20 animals are recorded in Appendix 3. The mean and standard deviation of the values from the five animals at each of the four ICP's are recorded in Table 2. The value at an ICP of 0 is significantly less than at ICP's of 25, 50 and 75 mmHg (p < .001). When plotted on a graph (Figure 9) the line of best fit may be curvilinear suggesting an exponential relationship between the ICP and the amount of EB extravasation.
FIGURE 8

Results of the second stage protocol plotting Evans Blue (EB) extravasation against systemic arterial pressure (SAP). The intracranial pressure was kept at 0-5 mmHg. The plots marked with an asterisk are from the six first stage protocol animals which had an ICP of 0. The linear correlation coefficient is .786 and is significant (P < .001).
Mean and standard deviation of the amount of Evans Blue (EB) extravasation into the cortical samples of the 20 third stage animals at four levels of intracranial pressure (ICP). The mean systemic arterial pressure was maintained at 90-100 mmHg. The degree of EB extravasation at an ICP of 0 is significantly less than at an ICP of 25, 50 or 75 mmHg. The results are plotted graphically in Figure 6.

<table>
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<th>Control</th>
<th>Lesion-Control</th>
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<tr>
<td>0</td>
<td>140.9±33.4</td>
<td>25.2±11.6</td>
<td>115.7±31.9</td>
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<tr>
<td>25</td>
<td>62.4±52.8</td>
<td>24.3±18.3</td>
<td>38.2±36.0</td>
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<tr>
<td>50</td>
<td>32.8±14.6</td>
<td>16.8±8.5</td>
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<td>75</td>
<td>20.5±20.6</td>
<td>26.0±16.9</td>
<td>5.6±7.7</td>
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</table>
Results of the third stage protocol plotting mean and standard deviation of Evans Blue (EB) extravasation against mean intracranial pressure (ICP). The systemic arterial pressure (SAP) was maintained constant at 90-100 mmHg in these 20 animals. Five animals were randomly allocated at each ICP level of 0, 25, 50 and 75 mmHg. EB extravasation at ICP = 0 is significantly less than at 25, 50 and 75 mmHg (P < .001).
CEREBRAL BLOOD FLOW

To better understand the pathophysiology of oedema formation produced by this method, measurement of cerebral blood flow (CBF) was undertaken in four animals in whom the intracranial pressure (ICP) was not elevated. A platinum needle electrode was inserted (Fig. 10) into the cortex of each hemisphere (middle cerebral artery distribution) and the CBF (as determined by the initial slope index) was measured by the hydrogen clearance technique described by Young. (30). This method of CBF measurement utilizes the principle that dissolved hydrogen previously deposited within the cerebral interstitium (by having had the animal breathe hydrogen gas) will be "washed out" of the brain at a rate depending upon the CBF when the animal ceases breathing hydrogen. The concentration of \( \text{H}_2 \) is measured by a quantitative polarographic technique using the principle that the oxidative reaction

\[
\text{H}_2 \rightarrow 2\text{H}^+ + 2\text{e}^-
\]

generates electricity. A platinum electrode is inserted into the cerebral cortex, a calomel reference electrode is placed into muscle in the posterior neck, and a polarity of +350 mV placed across the two electrodes. The current generated by the platinum electrode linearly estimates tissue \( \text{H}_2 \) concentration. This method has been shown to correlate well with other methods of CBF measurement, including the \( ^{14}\text{C} \) antipyrine autoradiographic technique, radioactive microsphere injection and \( ^{133}\text{Xenon} \) gas
FIGURE 10

Diagram of platinum needle electrode inserted into cerebral cortex for measurement of cerebral blood flow (CBF). The wire is completely insulated from all structures except the cortex. The electrode is inserted with a microdrive and held firmly in position by dental cement placed into the skull opening.
clearance methods. (30). The advantages of the hydrogen clearance technique over these other methods include its ability to record CBF in any small area where a platinum needle can be inserted, it can be used for multiple flow determinations from the same area of brain, and it is not dependent on the absolute value of the $H_2$ signal but the clearance rate of the $H_2$. Finally, it is an inexpensive method.

Figure 11 demonstrates three recordings of the $H_2$ depletion (represented by the polarographic current) from the injured hemisphere of a rabbit. The blood flow responsible for each of these recordings is obtained by the Fick principle.

\[
\frac{dQ_1}{dT} = F_1(C_a-C_v) \text{where}
\]

\[
\frac{dQ_1}{dT} = \text{the amount of tracer taken up by the tissue per unit time}
\]

\[
F_1 = \text{the quantity of tracer brought by the arterial inflow}
\]

\[
C_a = \text{the arterial blood tracer concentration}
\]

\[
C_v = \text{the venous blood tracer concentration}
\]

In the situation where brain is already saturated with $H_2$ (which has a partition coefficient approaching 1) the arterial tracer concentration when the animal ceases breathing $H_2$ is assumed to be 0. The Fick equation can be thus solved for blood flow per unit volume, i.e.:

\[
\text{CBF} = -\frac{\ln(C_i/C_o)}{T}
\]
Cerebral blood flow (CBF) recordings using the Hydrogen clearance technique of changes in CBF in the lesion cortex of a rabbit both before and after injection of hypertonic saline into the left internal carotid artery. Each CBF value is calculated from the initial slope index. Following hypertonic saline injection the left hemisphere CBF is greatly reduced (POST-LESION #1). However, because of loss of autoregulation, hypertension induced by I.V. angiotensin (indicated on the SAP recording) results in a marked increase in the CBF (POST-LESION #2).
The blood flow can be estimated from the half life, $T_\frac{1}{2}$, the time required by the $H_2$ concentration to fall to $\frac{1}{2}$ its original value. Therefore $\text{CBF (in ml/100 gm/min)} = \frac{\ln \left(\frac{1}{2}\right) \times 100 \times 60}{T_\frac{1}{2}} = \frac{4192}{T_\frac{1}{2}}$

This determination of the CBF is called the initial slope index.

Measurements were taken of the CBF both before and after the intracarotid hypertonic saline injection, and the state of autoregulation was determined by the CBF measurement following induction of hypertension (by infusion of angiotensin 0.04 mM/ml at 0.15 mls/min and following hypotension (after discontinuation of angiotensin).
Results

All readings reported were those obtained from the platinum hydrogen electrode that was inserted into the middle cerebral artery territory of the left hemisphere. In all animals autoregulation (as determined by the lack of change in CBF in response to angiotensin-induced hypertension) was found to be intact before the hypertonic saline lesion was produced. The value of the CBF immediately before and after the hypertonic saline injection in four animals are recorded in Table 3. A reduction in CBF after the hypertonic saline lesion was produced was present in each of the animals. However, with animals 3 and 4, in response to angiotensin induced hypertension, the CBF was restored to its pre-lesion value, indicating loss of autoregulation in the lesioned hemisphere. This response to hypertension was repeated in each of animals 3 and 4 to confirm its reproducibility. The change in the CBF related to the level of systemic arterial pressure for rabbit #3 is recorded graphically in Figure 9. Following cessation of the angiotensin in animals 3 and 4, the CBF returned to the pre-angiotensin level. However, as noted in Table 3, the CBF fell to an even lower value. Further studies in animals 3 and 4 demonstrated a progressive reduction in the CBF over the two hours following lesion creation.

CBF studies were also recorded from the middle cerebral artery territory of the control hemisphere in animals 2, 3 and 4.
TABLE 3
Cerebral blood flow (CBF) recordings (initial slope index) from four rabbits before and after intracarotid hypertonic saline injection. Post-lesion #1 CBF was taken within 10 minutes of the injection with the animal normotensive. Post-lesion #2 was taken in animals 3 and 4 following induction of hypertension by intravenous angiotensin. Post-lesion #3 was obtained following restoration of normal systemic arterial pressure (SAP). A fall in the CBF was noted following hypertonic saline lesion creation. CBF was restored to pre-lesion levels following angiotensin induced hypertension (rabbit #3, #4) indicating loss of autoregulation. With time, a progressive decline in CBF was noted despite a normal SAP. (rabbit #2, #3, #4).

<table>
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CBF - (ml/100 gm/min)
No alteration occurred in the CBF before and after the left hemisphere lesion was created, or in response to angiotensin-induced hypertension. This confirmed normal autoregulation in the unaffected control hemisphere.
HISTOLOGICAL STUDIES

Histological specimens were taken from the lesion hemisphere ten minutes after lesion creation to ascertain the pathology of intra-arterial hypertonic saline induced oedema. For light microscopic study, cortical samples were fixed in 20% formalin, eight micron paraffin sections were cut and stained with PTAH.

Specimens were prepared for electron microscopy as described by Auer et. al. (2). Immediately following sacrifice of the animal, a solution containing 1% glutaraldehyde, 1% paraformaldehyde, 5% sucrose and 0.1 M sodium cacodylate buffer at pH 7.4 was infused into the left internal carotid artery at a pressure of 100 cm H$_2$O for 20 minutes. This was followed by an infusion of an identical volume of a more concentrated solution containing 2.5% glutaraldehyde and 2.0% paraformaldehyde. The brain was then removed and cortical samples taken from the area of maximum blood-brain barrier breakdown. These samples were post-fixed for 90 minutes in a solution containing 1% osmium tetroxide, 0.1 M sodium phosphate at pH 7.3 and 5% sucrose. Samples were then soaked in 2% uranyl acetate (Fisher Scientific, Fair Lawn, NH) overnight, embedded in Spurr (Taab Laboratories, Reading, England) and examined with a Philips E.M.-201 electron microscope.

Examination of the light microscopic sections demonstrated obvious per-capillary fluid extravasation. Thrombi were not seen in any vessels. There were no areas of haemorrhage present. (Fig. 12a). By electron microscopic examination, fluid was seen
FIGURE 12a

Light microscopic picture taken from lesion cortex 10 minutes after hypertonic saline injection. Peri-capillary fluid extravasation into neuropil is seen. Note vessels are patent. PTAH x 45.
to have collected under the capillary basement membrane and within the extra-cellular space. (Fig. 12b). Marked swelling of the astrocytic foot processes was also seen. Examination of tight junctions demonstrated no obvious disruption or discontinuity. (Fig. 12c). I was unable to quantitate pinocytotic vesicles or transendothelial channels, findings which have been described previously in other models of osmotic blood-brain barrier injury. (11).
FIGURE 12b

Electron microscopic picture of the peri-capillary neuropil taken from the lesion cortex. Note the collection of fluid between the capillary endothelium and basement membrane ( ), and in the extra-cellular space of the neuropil ( ). V = intracytoplasmic fluid-filled vacuoles within astrocytic foot processes. P = pericyte, l = capillary lumen. (x 35,000)
FIGURE 12c

Electron microscopic picture of intact capillary inter-endothelial tight junction from the lesion cortex (→). 1 = capillary lumen. (x 35,000)
CHAPTER 5

DISCUSSION

Control of an elevated intracranial pressure (ICP) to a value of less than 20 mmHg by the use of surgical decompression, ventriculostomy with intermittent venting of CSF, osmotic diuresis and hyperventilation has become standard treatment for the head injured patient with brain swelling from contusion and oedema. (18, 20, 27). Theoretically, control of intracranial hypertension has two aims: to improve circulation to ischaemic areas of brain by increasing the cerebral perfusion pressure (implicit in this concept is the belief that there are areas of the brain in which the cerebral autoregulation is not functioning normally) and to reduce brain shift caused by focal areas of swelling and pressure. Despite some encouraging reports comparing patients who have undergone aggressive treatment of elevated ICP with patients reported in earlier series in whom such aggressive treatment had not been instituted, no controlled trials confirming the benefits of aggressive control of intracranial hypertension on the outcome from severe head injury have been reported. (18, 20).

Brain swelling that occurs following a severe head injury may be the result of vasogenic oedema. (28). This is thought to develop because of physical disruption of the blood-brain barrier. (14, 26). In addition to producing brain swelling with its resulting effects on the ICP, brain shift and cerebral perfusion, the oedema fluid may have a direct toxic effect on
the neuropil. (4, 10).

The effect of alteration of the ICP on the development of vasogenic cerebral oedema has not been fully investigated. Cooper et. al. reported a significant increase in local cerebral oedema in monkeys with a cold-induced cortical injury in whom the bone flap overlying the injury had been removed to provide a decompression. (7). Much of this oedema may, however, have resulted from the effects of strangulation of the cortex by the margins of the craniotomy as the brain protruded through. Klatzo et. al. demonstrated that removal of CSF (with consequent lowering of the ICP) will promote clearing of oedema fluid from injured brain. (15). The lowered ICP promoted bulk flow of oedema fluid from the cerebral extracellular space into the ventricular system. The effect of lowered ICP on the actual formation of the oedema fluid at the capillary level was not studied however.

Some evidence exists that variations in the systemic arterial pressure (SAP) may influence the formation and spread of cold-induced vasogenic cerebral oedema in animals. (6, 16, 19). Marshall et. al. showed that hypertension following gas percussion cortical injury in cats increased the amount of brain swelling from vascular congestion and oedema. (19). They attributed this effect to a loss of cerebral autoregulation leading to greater blood flow to the injured brain.

Recently, Avery et. al. demonstrated blood-brain barrier disruption following an ischaemic injury in gerbils. (3).
Induction of hypertension in the post-ischaemic period in these animals resulted in a marked increase in the amount of Evans Blue leakage into the brain.

To better delineate the influence of the SAP, ICP and the derived cerebral perfusion pressure (CPP), (defined as mean SAP - mean ICP) (21) on the formation of vasogenic oedema demonstrated visually by Evans Blue (EB) extravasation, I studied a rabbit model initially described by Del Maestro and Arfors (8, 9). This method utilizes hypertonic saline injected into the internal carotid artery to disrupt the blood-brain barrier. The method results in rapid (within five minutes) oedema formation which may be demonstrated visually by EB extravasation.

Histological studies of the cerebral cortex injured by hypertonic saline in this study demonstrated peri-capillary extra-cellular fluid and swollen astrocytic foot processes impinging upon the capillary lumen. (Fig.12a,b). These findings are typical of the vasogenic cerebral oedema described previously in association with traumatic brain swelling and brain tumors (14, 28). Of note, no obvious disruption of the inter-endothelial tight junctions was present. (Fig.12c). The mechanisms by which osmotic injury may disrupt the blood-brain barrier have been elucidated by Houthoff et. al. (11). They demonstrated that rather than actually disrupting inter-endothelial tight junctions, osmotic injury seems to result in an increase in pinocytotic activity and possibly to an opening of trans-endothelial
41

channels. My findings would certainly lend support to the observations of Houthoff.

Evans Blue is almost completely bound to albumin within the bloodstream immediately following intravenous injection. (29). Thus, measurement of interstitial EB provides an assessment of protein extravasation in the oedema fluid. Although water content is the true index of brain oedema, a strong correlation between EB labelled albumin extravasation and brain water content has been found by others in areas of vasogenic cerebral oedema. (5). If extraction of EB from a sample of cortex could be performed, then quantitation of the passage of protein-laden oedema fluid and thus quantitation of vasogenic oedema would be achieved. Previous reports quantitating EB extravasation have relied upon visual grading to a 1+, 2+, 3+, 4+ or similar scale. Demonstration by Nachman et. al. (22) and Ackerman (1) that EB can be completely extracted from skin or liver by incubation with Formamide provided an ideal method for accurate quantitation of cerebral oedema fluid in my rabbits. Incubation of the cortical samples containing extravasated EB in Formamide for three days resulted in complete extraction of the EB into the Formamide. The amount of EB could then be quantitated by optical densitometry, (Fig. 5).

The anatomical variation in the territory of supply of each carotid artery to the rabbit brain, and variation in the pressure at which the hypertonic saline is injected manually,
may account for a variation in the distribution of maximum blood-brain barrier breakdown that was encountered in this model. Thus, brain specimens were selected from the cortex of the left hemisphere where maximal blood-brain barrier disruption was visualized. A control sample was taken from the identical area in the opposite right hemisphere, although this control hemisphere was occasionally seen to have some degree of EB extravasation (particularly in hypertensive animals). Subtraction of the EB extracted from the control sample from that extracted from the lesion sample corrected for any EB remaining intravascularly. Thus, a true value for interstitial EB (and thus vasogenic cerebral oedema) was derived.

Intracranial pressure was elevated by the infusion of normal saline at 37°C into the cisterna magna. (Fig. 1). This method has been shown to produce identical ICP elevation in both the infra and supratentorial compartments in normal dogs. (12).

My study was initially undertaken to investigate the relationship between intracranial hypertension produced by cisterna magna infusion of normal saline and the formation of vasogenic cerebral oedema. The results indicate that when the ICP is elevated with no attempt being made to control the SAP (which rises both in response to the injection of intracarotid hypertonic saline and to the elevation of intracranial pressure), no significant effect upon the amount of EB extravasation is seen. (Table 1). However, a significant correlation between the CPP and the amount of the EB extravasation is present,
When the intracranial pressure is kept at 0-5 mmHg (i.e. a normal level) while manipulating the SAP to a different level in each animal, a highly significant relationship \((p < 0.001)\) between increasing SAP and an increasing amount of EB extravasation in the area of blood-brain barrier disruption is found. \((p < 0.001)\) This confirms previously reported findings in animals with cold-induced or traumatic cortical injury. \((6, 19)\).

When the SAP is maintained constant at 90-100 mmHg mean by using controlled exsanguination from the femoral artery catheter, a decrease in the amount of EB extravasation is seen with increasing ICP. \((p < 0.001)\) The shape of the graph plotting EB extravasation against the ICP with the SAP kept constant may indicate an exponential relationship \((p < 0.001)\) (i.e. low levels of ICP result in a much greater degree of extravasation).

The forces acting across a cerebral capillary membrane and responsible for the flow of oedema fluid across the membrane when the blood-brain barrier is disrupted, is derived from Starling's Law. \((15)\). It can be summarized:

\[
J_v = L (p_{\text{plasma}} - p_{\text{tissue}} - \rho (\Pi_{\text{plasma}} - \Pi_{\text{tissue}}))
\]

where

\(L\) = hydrolic conductivity of the endothelial membrane
\(p_{\text{plasma}}\) = intravascular hydrostatic pressure
\(p_{\text{tissue}}\) = extracellular hydrostatic pressure
\(\Pi_{\text{plasma}}\) = osmotic pressure of plasma
\[ \Pi_{\text{tissue}} = \text{osmotic pressure of tissue} \]

\[ \mathcal{g} = \text{osmotic reflection coefficient} \]

Starling's Law predicts that an increase in EB extravasation may result from a high SAP and/or a low ICP (i.e. factors leading to an increased CPP). A low ICP results in a low \( P_{\text{tissue}} \) which acts to increase fluid movement across the capillary membrane. Similarly, a high \( P_{\text{tissue}} \) (caused by a high ICP) will result in decreased oedema formation.

In normal brain, cerebral blood flow is maintained relatively constant at approximately 50cc/100gms/min between a mean CPP range of 50 and 150 mmHg. (21) (Fig. 13). This phenomenon is called autoregulation and probably arises by both myogenic and metabolic mechanisms. The \( p_{\text{plasma}} \) in normal brain with intact cerebral autoregulation should also remain constant between CPP's of 50 and 150 mmHg. Pressures above the upper limit of autoregulation will produce an increase in \( p_{\text{plasma}} \), promoting increased movement of fluid across the capillary wall. This movement of fluid increases significantly if the blood-brain barrier is disrupted. If autoregulation is impaired, the \( p_{\text{plasma}} \) will increase at lower levels of the CPP leading to increased cerebral oedema formation. Results of the study of CBF following osmotic blood-brain barrier disruption demonstrate that autoregulation has ceased to function normally (Chapter 4), supporting this hypothesis. Marshall et. al. also postulated disordered autoregulation as the cause of increased oedema.
Relationship between cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) in normal brain indicating autoregulation to both falling blood pressure (ΔMAP) or increasing intracranial pressure (ΔICP), (From Miller, J. D. et. al., see Reference 21). CBF is maintained until the CPP falls below 50 mmHg.
formation resulting from hypertension in their cat model of percussion brain injury. (19). A lowering of the upper limit of autoregulation in other models of cerebral oedema has not been seen, however. (16).

The marked increase in EB extravasation seen at low levels of ICP in the third stage of this experiment (Fig. 9) may possibly be related to two factors. Not only is Ptissue reduced when the ICP is zero, but Pplasma (due to loss of autoregulation) is increased. In contrast, in the second stage only one factor, Pplasma, is altered, perhaps thus accounting for the linear relationship between EB extravasation and SAP. (Fig. 8)

Maintenance of a normal (or even elevated) SAP and control of intracranial hypertension are recommended for the management of patients with brain injury from trauma or ischaemia. (13, 20). The reason for this is the belief that they act in part to promote improved blood flow to ischaemic areas of brain. My study has not examined this important aspect of alteration of arterial and intracranial pressure. As noted in Chapter 4, however, a progressive decline in the CBF not accounted for by any significant change in the ICP was observed in the lesion hemisphere of the rabbits following hypertonic saline injection. (Table 3). This fall in the CBF could theoretically arise from the increased oedema fluid within the cortical interstitium leading to capillary compression. Alternatively, the fall in CBF may have resulted from intravascular thrombosis or endothelial swelling
although these latter findings were not observed histologically in our specimens taken 10 minutes after injury. Whatever the cause, the reduction in CBF may well lead to secondary ischaemic cortical injury.

The results of my study do indicate that changes in the systemic arterial and intracranial pressures influence oedema development. Although these results cannot be applied directly to humans, they do raise serious questions about current recommended management of the patient with cerebral oedema. Perhaps automatic manipulation to reduce the ICP to a set figure (e.g. 20mmHg) as is currently accepted practice in many centers is harmful to the patient by increasing oedema and brain swelling and then paradoxically reducing the cerebral blood flow. If a patient has elevated ICP from brain swelling but appears unchanged clinically, then it may be better to leave the intracranial hypertension untreated. If the patient does show signs of deterioration with the intracranial hypertension (e.g. dilating a pupil or demonstrating an extensor response to pain indicating transtentorial herniation), then no one would argue that it should be treated. Similarly if the ICP climbs to a level where the CPP is reduced to the lower limit of normal autoregulation (50 mmHg) mean, then the risks of causing cerebral ischaemia increases and the ICP should probably be lowered to improve the CPP and increase the CBF.

The question of what SAP level is best for the patient should
also be examined in the light of results of this study. Patients with a severe brain injury frequently are hypertensive despite having a normal ICP (i.e. the Cushing reflex is not acting). It would seem appropriate to lower the SAP to a normal level with anti-hypertensive agents to reduce cerebral oedema formation. Again, care must be taken not to induce cerebral ischaemia by reducing the CPP below the lower limit of autoregulation.


7. Cooper PR, Hagler H, Clark WK, Barnett P. *Enhancement of experimental cerebral edema after decompressive craniectomy:*
Implications for the management of severe head injuries.


pp. 359-373.


APPENDIX 1

Values of ICP, SAP and CPP and Evans Blue (EB) extravasation obtained from the 18 first stage animals.

<table>
<thead>
<tr>
<th>Rabbit #</th>
<th>ICP (mmHg)</th>
<th>SAP (mmHg)</th>
<th>CPP (mmHg)</th>
<th>Control (μ Gm EB) (gm cortex)</th>
<th>Lesion (μ Gm EB) (gm cortex)</th>
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ICP = mean intracranial pressure
SAP = mean systemic arterial pressure 5 minutes after lesion
CPP = cerebral perfusion pressure 5 minutes after lesion
APPENDIX 2

Values of SAP and Evans Blue (EB) extravasation for the 10 second stage animals.

<table>
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<th>Rabbit #</th>
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SAP = mean systemic arterial pressure
### APPENDIX 3

Values of ICP and Evans Blue (EB) extravasation from the 20 third stage animals.

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(Cont'd. on next page)
Evans Blue Extravasation (µ gm EB) (gm cortex)

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ICP = mean intracranial pressure