Changes in intraocular pressure during hemodialysis

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This study was designed to determine the changes in intraocular pressure (IOP) during hemodialysis in the uremic animal and to elucidate those parameters responsible for these changes. An increase in intraocular pressure averaging 41.8 per cent of the control occurred in uremic animals during dialysis. The rise started 21 minutes after dialysis was initiated and reached the maximum 45 to 75 minutes later. Changes in pCO₂ produced a significant increase in IOP. When the pCO₂ was constant, changes in pH did not affect IOP. Experimental changes in body water demonstrated that dehydration was associated with a reduction in IOP; overhydration resulted in a significant increase in IOP. When hyperosmolality without weight change was induced by adding solute to the bath solution there was a significant decrease in IOP. Hypoosmolality induced by lowering solute concentration of the bath solution caused a significant rise in IOP. Thus, changes in pCO₂, body water content, and plasma osmolality which can occur during dialysis may all contribute to changes in IOP. Slow dialysis, removal of up to 2.6 per cent of the body weight in fluid, and prior administration of acetazolamide could prevent a rise in IOP in uremic dogs undergoing hemodialysis. Furthermore, there was no rise in IOP when the drop in osmolality was prevented through addition of appropriate concentrations of urea to the bath solution.

During hemodialysis some patients with uremia may develop headache, nausea, vomiting, and extreme fatigue. Others may become confused, convulse, or develop cardiac arrhythmias and significant changes in blood pressure. These reactions cannot be readily explained by the usual measurements of changes in fluid and electrolyte balance. However, the rapid solute changes occurring during dialysis could affect significantly the transfer of water and adjustment of acid-base balance across the blood-brain barrier. Thus, the symptoms observed might be secondary to significant changes in intracranial pressure.

Interest in the blood aqueous barrier was stimulated by the fact that if there are parallel changes in the cerebrospinal fluid and aqueous humor pressures, tonometer readings can be used as an index of intracranial pressure changes during dialysis in the human. Therefore, a series of animal experiments was designed to correlate intracranial fluid pressure changes and aqueous humor pressure changes during dialysis. The purpose of this paper is to present the observed pressure changes of the aqueous fluid during dialysis and to relate these to shifts in solute concentration, body water, or acid-base balance.

Methods

Mongrel dogs ranging in weight from 20 to 30 kilograms were used for this study. At the begin-
ning of the experimental period they were anesthetized by intravenous injection of Pentothal sodium at a dose of 26.4 mg. per kilogram of body weight. Tracheotomies were performed, and the animals were kept breathing on a Harvard respirator at a constant respiratory rate of 23 strokes per minute. Stroke volume was adjusted to maintain a constant pCO₂. All observations were made with the dog lying horizontally on its right side on a platform scale accurate to a weight change of 4.5 grams. The anterior chamber of the left eye was punctured through the limbus of the cornea at the 12 o'clock position by a 24 gauge needle attached by polyethylene tubing (internal diameter 0.023 inch) to a Statham pressure transducer* connected to an oscillograph.† Simultaneous measurements of cerebrospinal fluid pressure were recorded by inserting a 20 gauge short spinal needle through the occipitotantoittaloid ligament into the cisterna magna. The needle was connected to a saline manometer. Intraocular pressure (IOP) and cerebrospinal fluid pressure (CSFP) were recorded every 10 to 15 minutes.

Hemodialysis was performed by the Kolff twin-coil technique,1 except that a single coil was used instead of the usual double unit. A solution of 6 per cent dextran in normal saline containing 10 mg. of heparin was used to prime the coil. The animal was given 10 mg. of heparin intravenously prior to dialysis. The solute composition of the bath solution was adjusted according to the experimental design, and any composition change from the standard* used for dialysis of the uremic animal is noted for each experimental group. A thermostat and electric heater maintained the bath temperature at 38° C. The dialysis circuit was completed through polyethylene catheters inserted into the femoral artery and vein. The flow rate through the coil unit was approximately 250 ml. per minute, and the duration of each dialysis was 2 hours, unless otherwise noted.

Blood pressure was recorded at 10 to 15 minute intervals by a mercury manometer connected to a polyethylene catheter inserted into the opposite femoral artery. Venous pressure was measured through a catheter inserted into the inferior vena cava and connected to polyethylene tubing containing heparinized saline. Readings were recorded at 10 minute intervals from a calibrated scale mounted beside the tubing. An indwelling catheter

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*5900 P23DD, 6 to 50 mm. Hg. 12 volts max. Statham Instruments, Inc., Hato Rey, Puerto Rico.
†Type S14-E; cat. No. A47732 G2, serial No. 9054-1; 115 volt, 60 cycle operation. Hathaway Instrument Company, Denver, Colo.

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Fig. 1. Measurement of IOP plotted against time in control groups.
was inserted into the urinary bladder of the non-
uremic animal and urine collected throughout the
experimental period.

All blood samples were drawn from the femoral
artery. These were analyzed as indicated for
osmolality (Fisk's freezing point technique),
hematocrit (capillary tube), sodium and potas-
sium (flame photometer), blood urea nitrogen
(Auto Analyzer), glucose (Auto Analyzer), and
CO₂ content (Natelson microgasometer). The
arterial pH and pCO₂ were determined every 30
minutes with the Astrop pH meter. The animal
weight was maintained constant throughout each
dialysis period by a continual drip of normal
saline into the dialysis system.

The uremic state was induced by surgical liga-
tion of both ureters. The experiment was carried
out 36 to 48 hours after the operation.

Results

Control studies. Experiments with 3 dogs
were performed in which all procedures
were identical to those used in the experi-
mental groups except for hemodialysis.
During a 3 hour observation period when
CO₂ tension was constant, there was no
significant change in IOP (Fig. 1). Since
it was preferable to use 6 per cent dextran
rather than dog blood for priming of the
coil, control experiments were performed
with circulation of blood through a dextran-
primed coil, but without dialysis, for a 2
hour period. The IOP did not change
significantly under these conditions (Fig.
1). For 10 to 15 minutes after anterior
chamber puncture, the IOP was elevated 3
to 5 mm. Hg. Thereafter, the pressure
steadied, and this reading was used as a
baseline pressure. There were minor fluc-
tuations which did not exceed 1 mm. Hg.
It was felt that the initial elevation of pres-
sure resulted from an increased volume
within the anterior chamber secondary to
the insertion of the needle.

Effects of changes in pCO₂ and pH. Dun-
calf and Weitzner² have demonstrated
changes in intraocular pressure with
changes in CO₂ tension. In this series, 4
animals were allowed to rebreathe 10 L.
of a mixture of 5 per cent CO₂ and 95 per
cent oxygen for 30 to 40 minutes. In Fig.
2, the measurements of IOP and CSFP are
plotted against the values for pCO₂. There
is a significant rise in IOP in association
with increases in pCO₂. The most marked
rise is observed at pCO₂ between 30 and
50 mm. Hg, which occurs within 10 to 15
minutes, and there is no further change in
IOP with a subsequent increase in pCO₂.
The corresponding changes in CSFP are
also shown in Fig. 2. When rebreathing
was stopped, the IOP and the CSFP re-
turned to normal within 10 minutes. All
animals showed a drop in pulse rate. Blood
pressure was either unchanged or showed
a slight reduction of up to 10 mm. Hg.
During the period of rapid rise in IOP, the
blood pH varied from 7.115 to 7.405.

The effects of change in pH on IOP
were also studied when the pCO₂ was held
constant. In 2 animals acidosis was induced
during dialysis by reducing the bicarbonate
content of the bath to 8.9 mEq. per liter.
Changes in IOP did not exceed the fluctua-
tions observed in the control groups. In the
experiment shown in Fig. 3 the blood pH
dropped from 7.49 to 7.29 and the CO₂ con-
tent from 22 to 14.8 mEq. per liter.
Changes in the other experiments were of a similar range. In 2 animals alkalosis was induced by raising the bath concentration of bicarbonate to 59.4 mEq per liter. There was no significant change in IOP. In the experiment shown in Fig. 3 blood pH increased from 7.415 to 7.605, and the CO₂ content rose from 21.7 to 32.6 mEq per liter. The results of the other experiments were similar.

Fig. 3. Effect on IOP of changes in blood pH in typical experiments.

Fig. 4. Effect on IOP and CSFP fluid removal produced by dialysis.
Table I. Effect on IOP of overhydration induced by injection of 1,000 ml. of either 0.9 per cent saline or 5 per cent glucose in water

<table>
<thead>
<tr>
<th>Intravenous injection</th>
<th>Weight of dog (Kg.)</th>
<th>Δ IOP (%)</th>
<th>Onset* (minutes)</th>
<th>Maximum† (minutes)</th>
<th>Return‡ (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9 NaCl</td>
<td>20</td>
<td>+17</td>
<td>15</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>+18</td>
<td>10</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Average</td>
<td>20</td>
<td>+17.5</td>
<td>12.5</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>(16 to 18.7 mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 per cent glucose</td>
<td>22</td>
<td>+18</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>+20</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Average</td>
<td>22</td>
<td>+19</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>(15 to 17.9 mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Time of initial change of IOP after starting infusion.
†Time of maximum rise of IOP after beginning of infusion.
‡Time that IOP returned to normal after completion of infusion.

Effect on IOP of changes in total body water. In 4 animals dehydration was produced during dialysis by increasing the filtration pressure in the dialysis unit. The water loss achieved ranged from 2.7 to 3.3 per cent of body weight. In all instances there was a decrease in IOP which averaged 26.5 per cent of the control value. There is a continued drop in IOP throughout the progressive dehydration period. The results of a typical experiment are shown in Fig. 4. The CSFP varied in the same direction, although the change was not as marked. Plasma osmolality and pCO₂ did not change in these experiments. In all animals there was a reduction of venous pressure ranging from 20 to 25 mm. saline. Blood pressure was unchanged in 3 experiments, but there was a reduction of 20 mm. Hg in one experiment.

Overhydration was induced in 2 animals by intravenous infusion of 1,000 ml. of 0.9 per cent saline and in 2 animals by intravenous infusion of 1,000 ml. of 5 per cent glucose in water. The changes in intraocular pressure are summarized in Table I. There is a significant and comparable increase in IOP with both types of infusion. After saline infusion there was no change in pCO₂ and plasma osmolality. The hematocrit drop averaged 13.5 per cent of the control value, and the venous pressure increased 25 mm. saline. After glucose infusion the pCO₂ was constant. Plasma osmolality dropped 5 mOsm. per liter. The decrease in the hematocrit averaged 14 per cent of the control value, and the venous pressure increased 20 mm. saline.

Effects on IOP of changes in plasma osmolality. Four different solutes (glucose, urea, NaCl, and Travert sugar*) were added to the bath solution to raise the total osmolality to 500 mOsm. per liter. There were 3 experiments in each group; the effects on IOP are shown in Table II. There is a reduction in IOP in all experiments, irrespective of the type of solute used to raise serum osmolality. The decrease in IOP is comparable when glucose, urea, and NaCl are used, although the rise in plasma osmolality in the glucose group averages 30 mOsm. per liter, whereas it averages 70 mOsm. per liter for the urea group and 75 mOsm. per liter for the NaCl group. When Travert sugar is used, the drop in intraocular pressure averages 11

*Travert sugar is a Travenol preparation containing 50 per cent glucose and 50 per cent fructose.
Table II. Effect on IOP of hyperosmolality induced by addition of (A) glucose, (B) Travert sugar, (C) urea, and (D) NaCl to the dialysis fluid

<table>
<thead>
<tr>
<th>Solute used</th>
<th>Plasma</th>
<th>Intraocular fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Glucose (mg. %)</td>
<td>Δ mOsm./L.</td>
</tr>
<tr>
<td>Glucose</td>
<td>+501</td>
<td>+23</td>
</tr>
<tr>
<td>(A)</td>
<td>+526</td>
<td>+30</td>
</tr>
<tr>
<td></td>
<td>+743</td>
<td>+39</td>
</tr>
<tr>
<td>Average</td>
<td>+590</td>
<td>+30.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Sugar¹ (mg. per cent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travert sugar</td>
<td>+514</td>
<td>+24</td>
</tr>
<tr>
<td>(B)</td>
<td>+536</td>
<td>+35</td>
</tr>
<tr>
<td></td>
<td>+592</td>
<td>+32</td>
</tr>
<tr>
<td>Average</td>
<td>+592</td>
<td>+30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ BUN (mg. per cent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>+151</td>
<td>+51</td>
</tr>
<tr>
<td>(C)</td>
<td>+207</td>
<td>+75</td>
</tr>
<tr>
<td></td>
<td>+230</td>
<td>+85</td>
</tr>
<tr>
<td>Average</td>
<td>+196</td>
<td>+70.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Na (mEq./L.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl</td>
<td>+40</td>
<td>+73</td>
</tr>
<tr>
<td>(D)</td>
<td>+42</td>
<td>+75</td>
</tr>
<tr>
<td></td>
<td>+44</td>
<td>+77</td>
</tr>
<tr>
<td>Average</td>
<td>+42</td>
<td>+75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Time of initial change of IOP after starting dialysis.
†Time that IOP returned to normal after completion of dialysis.
¹Glucose and fructose.

Table III. Effect on IOP of hypoosmolality achieved by reducing the osmolality of the dialysis solution to 240 mOsm. per liter

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Plasma</th>
<th>Intraocular fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Na</td>
<td>Δ mOsm./L.</td>
</tr>
<tr>
<td>1</td>
<td>-17</td>
<td>-30</td>
</tr>
<tr>
<td>2</td>
<td>-22</td>
<td>-40</td>
</tr>
<tr>
<td>3</td>
<td>-26</td>
<td>-45</td>
</tr>
<tr>
<td>Average</td>
<td>-21.7</td>
<td>-38.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Time of initial change of IOP after starting dialysis.
†Time that IOP returned to normal after completion of dialysis.
per cent of the control; this might not be considered a significant change, although it consistently dropped in each experiment. The change in plasma osmolality is the same as for the glucose group.

In 3 animals hypoosmolality was induced by use of a dialysis bath solution with solute concentration of 240 mOsm. per liter. The changes in plasma sodium and osmolality and in intraocular pressure are shown in Table III. The average increase in intraocular pressure is 37 per cent of the control. The average decrease in osmolality is 38 mOsm. per liter. The control osmolality in these 3 animals averages 297 mOsm. per liter. The average decrease in serum sodium is 21.7 mEq. per liter. In all animals the venous pressure drop ranged from 15 to 20 mm. saline, and the blood pressure drop ranged from 10 to 20 mm. Hg.

**Hemodialysis in uremic animals.** Four uremic animals were dialyzed for a 2 hour period. The predialysis blood urea nitrogen (BUN) ranged from 128 to 196 mg. per cent. The predialysis intraocular pressure ranged from 12 to 18 mm. Hg. The results are shown in Table IV. The average rise in IOP is 41.8 per cent. The rise in IOP occurs 15 to 40 minutes after starting dialysis, attains a maximum level at 45 to 75 minutes during dialysis, and returns to normal 20 to 30 minutes after completing dialysis. These changes are associated with an average drop in BUN of 57 mg. per cent and in plasma osmolality of 22 mOsm. per liter. There was no precise quantitative relationship between the drop of plasma osmolality and the extent of the rise in IOP. The pCO₂ and the weight remained constant. The average increase in CSFP in these experiments was 75.8 per cent of the control. The other difference noted was the longer time period required for the CSFP to return to normal. This ranged from 2 to 4 hours, as compared with 20 to 30 minutes for the IOP. A typical experiment illustrating changes in both IOP and CSFP is shown in Fig. 5.

Often during the control period in the uremic animals the IOP was lower than during the same control period in normal animals. The data for all experiments are summarized in Table V. In 50 normal animals the IOP ranges from 12 to 23 mm.

**Table IV. Effect on IOP of hemodialysis in uremic animals**

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Δ BUN (mg. %)</th>
<th>Δ mOsm./L.</th>
<th>Δ IOP (%)</th>
<th>Onset* (minutes)</th>
<th>Return† (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-28</td>
<td>-11</td>
<td>+33</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>-50</td>
<td>-20</td>
<td>+80</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>-71</td>
<td>-27</td>
<td>+28</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>-79</td>
<td>-30</td>
<td>+26</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Average</td>
<td>-57</td>
<td>-22</td>
<td>+41.8</td>
<td>21.3</td>
<td>25</td>
</tr>
</tbody>
</table>

*Time of initial change of IOP after starting dialysis.
†Time that IOP returned to normal after completion of dialysis.

**Table V. The intraocular pressure in normal and uremic animals**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>IOP range (mm. Hg)</th>
<th>Mean (mm. Hg)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>50</td>
<td>12 to 23</td>
<td>18.3</td>
<td>2.65</td>
</tr>
<tr>
<td>Uremic</td>
<td>20</td>
<td>12 to 18</td>
<td>15</td>
<td>1.73</td>
</tr>
</tbody>
</table>
Hg, with a mean of 18.3 mm. Hg. In the 20 uremic animals the IOP ranges from 12 to 18 mm. Hg, with a mean of 15 mm. Hg.

Methods of modifying changes in IOP during dialysis in uremic animals. To prevent the rapid changes in plasma osmolality, dialysis was performed slowly over a prolonged period of time. Four uremic dogs were dialyzed for 4 hours at a flow rate of 80 ml. per minute instead of the usual 250 ml. per minute. In 2 animals there was no change in IOP; in the other 2 animals the increase was minimal, occurring 10 to 20 minutes after initiating dialysis and returning to normal at 30 minutes in 1 animal (Fig. 6) and at 120 minutes in the other animal. In contrast, there was a significant rise in CSFP which averaged 89.8 per cent of the control. There was an average drop of BUN of 87.3 mg. per cent and of plasma osmolality of 33.8 mOsm. per liter. This represented a change in osmolality of 8.5 mOsm. per liter per hour instead of the 11 mOsm. per liter per hour.
observed when the flow rate was 250 ml. per minute.

In 4 uremic animals, dehydration was induced during dialysis. The results are shown in Table VI. The average fluid loss is 2.6 per cent of the body weight. The intraocular pressure shows a transient increase ranging from 10 to 14 per cent of the control, starting 10 to 20 minutes after beginning dialysis, and reaching a maximum at 30 minutes. Then the IOP decreases and attains an average maximum drop of 20 per cent between 60 and 70 minutes after starting dialysis. There was a reduction of venous pressure in all experiments, ranging from 10 to 20 mm. saline. Arterial blood pressure was unchanged in 2 animals, but in the other two there was a reduction of 15 to 20 mm. Hg.

The effect of intravenous administration of acetazolamide (Diamox) upon IOP was studied in both control and uremic animals. No change in IOP occurred in normal animals with acetazolamide doses of 3 mg. per kilogram or 100 mg. per kilogram. When the dose was increased to 150 mg. per kilogram there was an initial rise of IOP lasting approximately 30 minutes; this was followed by a fall of IOP which averaged 27 per cent and reached a maximum within 2 hours.

Four uremic dogs were then given 150 mg. per kilogram of acetazolamide intravenously 2 hours prior to dialysis. The results are shown in Table VII. In 3 animals there is no change in IOP during dialysis, while 1 animal shows a slight rise, approximately 12 per cent of the control. The average drop in plasma osmolality is 26 mOsm. per liter, and the average drop in BUN is 68 mg. per cent. A rise in pCO₂ was observed in all animals and ranged.

Table VI. Effect on IOP of fluid removal during dialysis in uremic animals

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Δ Weight (%)</th>
<th>Δ BUN (mg. %)</th>
<th>Δ mOsm./L.</th>
<th>Initial rise (%)</th>
<th>Onset* (minutes)</th>
<th>Fall (%)</th>
<th>Max. dropf (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-2.1</td>
<td>-53</td>
<td>-20</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>-2.5</td>
<td>-81</td>
<td>-30</td>
<td>14</td>
<td>10</td>
<td>13</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>-2.5</td>
<td>-50</td>
<td>-25</td>
<td>10</td>
<td>20</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>-2.8</td>
<td>-62</td>
<td>-25</td>
<td>16</td>
<td>10</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>Average</td>
<td>-2.6</td>
<td>-63.8</td>
<td>-25</td>
<td>12.5</td>
<td>12.5</td>
<td>20</td>
<td>62.5</td>
</tr>
</tbody>
</table>

*Time of initial change of IOP after starting dialysis.
†Time of maximum drop of IOP after starting dialysis.

Table VII. Effect on IOP of acetazolamide (150 mg. per kilogram) given intravenously 2 hours prior to dialysis in uremic animals

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Δ BUN (mg. %)</th>
<th>Δ mOsm./L.</th>
<th>Δ IOP (%)</th>
<th>Onset* (minutes)</th>
<th>Return† (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-49</td>
<td>-20</td>
<td>0</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>-52</td>
<td>-20</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>-80</td>
<td>-30</td>
<td>+12</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-91</td>
<td>-35</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>-68</td>
<td>-26.3</td>
<td>+3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Time of initial change of IOP after starting dialysis.
†Time that IOP returned to normal after completion of dialysis.
from 6 to 15 mm. Hg. The average increase in CO₂ content was 6.1 mEq. per liter, and the average rise of pH was 0.058. In 2 animals there was an increase in CSFP of 18 and 25 per cent. CSFP did not change in the other 2 animals.

In 3 animals the usual drop in osmolality observed during dialysis was prevented by adding appropriate concentrations of urea to the bath solution and dextran priming solution. In these experiments there was no significant change in the IOP, and only the minor fluctuations comparable to those observed in the control group occurred. The changes of plasma osmolality were within ±5 mOsm. per liter. There was no change in pCO₂.

Discussion

Hertel showed that injection of hypertonic solution of urea produced a drop of IOP in animals. Recently, hypertonic solutions of urea or mannitol have been used to decrease intraocular pressure in acute glaucoma. In these experiments there were significant shifts in the body fluids. Our experiments differed in that when hyperosmolality was induced during dialysis the body weight and pCO₂ were kept constant. In this situation there was also a significant drop in IOP. Earlier studies revealed that hypoosmolality induced by injection of hypotonic solutions increased intraocular pressure, but was associated with a significant increase in body fluid. In our dialysis experiments hypoosmolality was induced without significant change in body weight. There was also a definite increase in IOP in these experiments. Thus, IOP can be changed significantly by raising or lowering solute concentration in the body fluids without changing total body water. Hemodialysis in uremic animals is also representative of a sudden solute change without changes in body water, and, as might be expected, there is an increase in IOP.

Other factors that may affect IOP during hemodialysis are changes in pCO₂ or significant changes in body fluid. In our studies changes in pCO₂ produced a definite change in IOP in normal animals; similar effects might be expected in humans undergoing hemodialysis when there is a change in pCO₂. However, if the pCO₂ is maintained at a constant level, changes in pH between a range of +0.19 and -0.20 have no effect on IOP. Increases in hydration are associated with a rise in IOP, and dehydration is usually associated with a drop in IOP. The rise in IOP in the water-loading test for glaucoma probably results from changes in both body water and osmolality.

These experiments showed that several different approaches to preventing a rise in IOP during hemodialysis may be effective. It can be accomplished by slow dialysis, by removing significant amounts of fluid during dialysis, by administration of acetazolamide, and by preventing a drop in plasma osmolality by adding urea to the bath solution. These experiments further confirm the observation that three factors which can change during hemodialysis may all contribute to observed changes in intraocular pressure, namely, changes in hydration, pCO₂, and osmolality.

One purpose of this study was to establish the relationship between changes in CSFP and IOP during dialysis, particularly in the uremic animal. In the majority of the animal experiments the changes in IOP were in the same direction as that of CSFP. However, the rise in IOP did not persist as long as the increase in CSFP. In many instances the IOP returned to normal shortly after the end of dialysis, whereas the change in CSFP might persist for several hours. Quantitatively, the per cent increase in IOP above the control level was less than the per cent increase in CSFP. Thus, in relating measured changes of IOP in patients during dialysis to probable changes in CSFP based on the data presented, one would assume a change to be somewhat smaller on a percentage basis and the total effect to be of shorter duration. This perhaps might be explained by Davson’s demonstration that the turnover
rate of the aqueous fluid is higher than that of the cerebrospinal fluid, namely, 1 and 0.4 per cent, respectively.

REFERENCES

Discussion

Dr. Mansour F. Armaly, Iowa City, Iowa. This is a very provocative presentation. It emphasizes the complexity of utilizing the intact anesthetized animal for studies of intraocular fluid dynamics and the need to maintain the "internal environment" within the physiologic range. It also brings out important aspects of the effect of change in plasma osmolality on intracranial pressure.

In order to keep the present results in the appropriate perspective and to maximize the future contribution of this sophisticated preparation to the understanding of the effect of various parameters of the "internal environment" on intraocular fluid dynamics, I wish to make briefly the following remarks:

1. The intraocular pressure level is not a definitive index or measure of the blood aqueous barrier or aqueous dynamics. It reflects, as a resultant, the blood aqueous barriers, inflow rate of aqueous, aqueous outflow facility, and the pressure in the extraocular aqueous recipient vessels. Thus, absence of change in intraocular pressure does not mean that the blood aqueous barrier or the aqueous dynamics was not altered. This is especially true in the case of the factors in question, since they are known to produce changes in capillary permeability and in the caliber of small arteries and veins by direct action as well as by triggering neural or hormonal mechanisms. Thus, an enlightened evaluation of the results requires the following: (A) an indicator of the intactness of the blood aqueous barrier in this preparation and under the influence of the various factors investigated; aqueous protein determination may prove adequate; (B) a measure of outflow facility of aqueous by perfusion of this cannulated eye; and (C) a measure of pressure in the episcleral veins.

2. The pressure in the femoral artery and inferior vena cava, outside of being a gross indicator of systemic shock, does not inform us, quantitatively, or qualitatively, of the critically important behavior of the episcleral venous pressure. This latter need be definitively measured.

3. While the dog is a suitable animal for dialysis, its eye may not be a suitable model for the human eye from the standpoint of aqueous dynamics. This reservation should be clearly emphasized when transferring observations from dog to man. For instance, the nature of the effect of Diamox in the dog and the dose required to produce it are markedly different from those in man; therefore, the Diamox modification of the dialysis effect on intraocular pressure may not have its counterpart in man and, if it did, it may utilize a different mechanism.

4. The effect of pCO₂ is shown in a hyperventilated dog. The pCO₂ of alveolar air and arterial blood in man and presumably in the dog is around 40 mm. Hg. Since intraocular pressure changes occur in the range of 30 to 50 mm. Hg, it would be important to start with the physiologic pCO₂ level and investigate the effect of changes in either direction.

5. The effect of the uremic state on intraocular pressure is not clear. The group with uremia had a significantly lower intraocular pressure than the control group. On the other hand, when the uremic state was controlled by slow dialysis, the pressure did not change, suggesting that the difference among groups was not due to uremia.
It would be important to compare in the same animal the intraocular pressure before and after the uremic state with application or MacKay-Marg tonometry.

The most prevalent notion regarding the effect of change in plasma osmolality on intraocular pressure is that based on the osmotic attraction of water. Numerous investigators have pointed out that this mechanism can have little effect, if any, because of the presence of the ciliary pump and of the circulation or turnover of aqueous. The authors report a set of characteristics which clearly indicates that osmotic attraction of water cannot be the mechanism responsible for the effect of change in plasma osmolality on intraocular pressure: (A) the effect on intraocular pressure was not related to the magnitude of the osmotic force or gradient; (B) similar osmotic gradients produced by different solutes had different effects on intraocular pressure; (C) the change in intraocular pressure induced by the introduction of an osmotic gradient recovered in spite of maintaining that gradient constant, or was maintained after the osmotic gradient had been eliminated; (D) large changes in plasma osmolality could be introduced without an associated change in intraocular pressure; and (E) the effect on intraocular pressure was dependent upon the solute and the rate of onset of the osmotic change and not upon the magnitude of the change in plasma osmolality.

The above indicate clearly that the effect cannot be explained by simple osmotic attraction of water, but must include the parameters influencing the steady state intraocular pressure. Changes in plasma osmolality have been shown to alter the caliber of blood vessels, to induce a sympathetic and parasympathetic activity of the Edinger-Westphal nucleus. This well-controlled preparation offers a real possibility to pin down the effect of plasma osmolality on vascular and aqueous dynamics of the steady state intraocular pressure by measurement of the appropriate parameters.

Dr. Sitprija (closing). We wish to thank Dr. Armaly for his lucid and interesting comments. We agree that measurement of intraocular pressure does not represent a total index of physiologic changes in the eye, and that it would be important to study at the same time the "intactness" of the blood aqueous barrier, the outflow facility, and the episcleral venous pressure. However, we do want to emphasize that changes in fluid and electrolyte balance can affect significantly pressure relationships within the eye. To the internist and the physiologist, because of its accessibility, the study of the eye in relation to changes in other parts of the body may provide useful information regarding mechanisms of transfer of solute and water, and also be of value diagnostically in assessing such changes in other parts of the body.

It is interesting that the dog required a larger dose of Diamox and a longer time to reduce the intraocular pressure in comparison with the human eye. Dr. Armaly mentioned that the dog eye differs from the human eye from the standpoint of aqueous dynamics. However, to put this into proper perspective, it will be necessary to correlate changes in the eye with changes in function of other organs such as the kidney.

In answering Dr. Armaly's fourth remark, the pCO₂ in dogs is slightly lower than that in humans. In our series, it ranged from 30 to 35 mm Hg; therefore, in these experiments, we started with a baseline pCO₂ of 30 mm Hg. In one experiment, the dog was hyperventilated until pCO₂ dropped to 10 mm Hg, but there was no drop in intraocular pressure. This area will require further study.

A lower intraocular pressure in the uremic group is most likely related to dehydration. Our dogs lost about 1.5 pounds during the time period from the ligation of the ureters to the measurements made in the uremic state. This was the result of vomiting, which always occurred in these animals as uremia developed. It would be important to measure the intraocular pressure before ligation of the ureters to compare in the same animal with the pressure obtained after induction of uremia. However, it should be pointed out that the metabolism in uremia may be altered and this in turn may affect the functional activity of various organs in the body. For example, studies of the salivary flow in uremic patients show a marked reduction in rate of flow and significant increases in the concentration of potassium and sodium. The increased potassium concentration is currently being studied, but increases of this magnitude have not been observed in any other abnormality of the salivary glands. We are hopeful that our studies of the eye in uremia may contribute to a better understanding of the total metabolism in the uremic patient.