Research Report

Intracranial pressure (ICP) and optic nerve subarachnoid space pressure (ONSP) correlation in the optic nerve chamber: the Beijing Intracranial and Intraocular Pressure (iCOP) study

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Cerebrospinal fluid dynamics
Trans-optic canal pressure gradient

Abstract

Purpose: Because a lowered intracranial pressure (ICP) is a possible mechanism of optic neuropathy, we wished to study the CSF dynamics in the optic nerve chamber by recording possible changes in the optic nerve subarachnoid space pressure (ONSP) and the impact on it when acutely lowering ICP.

Methods: In eight normal dogs pressure probes were implanted in the left brain ventricle, lumbar cistern, optic nerve subarachnoid space and in the anterior eye chamber. Following CSF shunting from the brain ventricle we monitored changes of ICP, lumbar cistern pressure (LCP), ONSP and intraocular pressure (IOP).

Abbreviations: IOP, Intraocular pressure; ICP, Intracranial pressure; LCP, Lumbar cistern pressure; ONSP, Optic nerve subarachnoid space pressure; SAS, Subarachnoid space; CSFp, Cerebrospinal fluid pressure; TLPG, Trans-lamina cribrosa pressure gradient; TCPG, Trans-optic canal pressure gradient

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1. Introduction

Glaucoma, one of the optic neuropathies, is the second-leading cause of world blindness (Quigley and Broman, 2006). It leads to chronic, optic nerve degeneration characterized by cupping of the optic disk and visual field loss (Kwon et al., 2009). Elevated IOP is considered to be the main risk factor. However, in "normal tension" glaucoma (NTG) IOP is at control levels, yet patients still present progressive disk cupping and visual field loss. NTG is the most prevalent form of POAG in East Asian and Hispanic descent (Iwase et al., 2004; Quigley et al., 2001; Suzuki et al., 2006; Varma et al., 2004; Wang et al., 2011). But because an elevated IOP cannot explain NTG, the mechanism is still unclear.

One possible mechanism may be found in the brain, namely a lowered ICP. Indeed, the evidence is mounting for a role of the brain in optic neuropathy. Berdahl et al. (2008a, 2008b) and Ren et al. (2010) suggested that ICP is a critical event because when measured by lumbar puncture, it was found to be abnormally low in NTG patients. Yang et al. (2014) reported that the trans-lamina cribrosa pressure gradient (TLPG) was highest for IOP–ONSP, lower for IOP–LCP, and lowest for IOP–ICP (P < 0.001). During CSF shunting, the ICP gradually decreased in a linear fashion together with the ONSP ("ICP-dependent zone"). But when the ICP fell below a critical breakpoint, ICP and ONSP became uncoupled and ONSP remained constant despite further ICP decline ("ICP-independent zone").

Conclusions: Because the parallel decline of ICP and ONSP breaks down when ICP decreases below a critical breakpoint, we interpret this as a sign of CSF communication arrest between the intracranial and optic nerve SAS. This may be caused by obstructions of either CSF inflow through the optic canal or outflow into the intra-orbital cavity. This CSF exchange arrest may be a contributing factor to optic nerve damage and the optic nerve chamber syndrome which may influence the loss of vision or its restoration.

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reported that lowering ICP in monkeys could cause optic neuropathy. Fig. 1 illustrates the relationship between the different pressure compartments. It can be seen that when either the IOP rises or the ONSP drops, the pressure asymmetry at the lamina cribrosa is expected to increase which might lead to subsequent pathological pressure on the optic nerve. As a consequence, optic neuropathy may be caused by either one (or both) of the two pressure asymmetries: one from the eye side and the other from the brain side. Thus, either a high IOP or a low ICP could explain optic nerve damage. A presumed “eye disease” may, in fact, also be a “brain disease in disguise”.

While it is generally assumed that IOP influences on the lamina cribrosa alone can explain optic nerve head damage, it is still unclear how ICP and ONSP specifically relate to each other. To solve this open question we shunted CSF to acutely lower ICP and monitored pressure changes in the optic nerve chamber.

### 2. Results

The average pressures at baseline were as follows: IOP of $181.4 \pm 11.4$ mm H$_2$O, ICP of $105.3 \pm 14.1$ mm H$_2$O, LCP of $87.9 \pm 14.3$ mm H$_2$O, and an ONSP of $59.3 \pm 8.7$ mm H$_2$O (Table 1).

Table 1 - Intracranial pressure (ICP), lumbar cistern pressure (LCP), optic nerve subarachnoid space pressure (ONSP), and intraocular pressure (IOP) at baseline in all study dogs (mm H$_2$O; mean ± SD).

<table>
<thead>
<tr>
<th>Animal</th>
<th>IOP</th>
<th>LCP</th>
<th>ONSP</th>
<th>IOP–ICP</th>
<th>IOP–LCP</th>
<th>IOP–ONSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120.7±5.0</td>
<td>110.0±6.6</td>
<td>70.9±6.3</td>
<td>190.2±1.2</td>
<td>69.5±4.6</td>
<td>80.1±6.3</td>
</tr>
<tr>
<td>2</td>
<td>85.2±1.7</td>
<td>71.3±1.9</td>
<td>45.8±1.9</td>
<td>163.4±5.4</td>
<td>76.1±6.2</td>
<td>90.0±6.2</td>
</tr>
<tr>
<td>3</td>
<td>95.2±2.1</td>
<td>76.2±1.6</td>
<td>54.9±2.9</td>
<td>174.7±2.4</td>
<td>79.5±4.0</td>
<td>98.4±3.6</td>
</tr>
<tr>
<td>4</td>
<td>108.9±4.0</td>
<td>92.1±4.4</td>
<td>49.3±3.4</td>
<td>185.5±3.9</td>
<td>76.6±6.0</td>
<td>83.4±6.2</td>
</tr>
<tr>
<td>5</td>
<td>93.2±2.7</td>
<td>71.4±3.1</td>
<td>63.3±2.5</td>
<td>167.8±3.4</td>
<td>74.6±4.4</td>
<td>96.4±4.9</td>
</tr>
<tr>
<td>6</td>
<td>123.0±5.6</td>
<td>93.8±4.6</td>
<td>67.4±1.4</td>
<td>185.6±0.5</td>
<td>62.6±5.4</td>
<td>91.7±4.8</td>
</tr>
<tr>
<td>7</td>
<td>117.2±4.5</td>
<td>102.4±5.9</td>
<td>62.6±2.7</td>
<td>195.6±0.9</td>
<td>78.4±4.9</td>
<td>93.1±6.4</td>
</tr>
<tr>
<td>8</td>
<td>99.1±5.5</td>
<td>85.8±4.4</td>
<td>60.6±2.0</td>
<td>188.4±0.7</td>
<td>89.3±5.4</td>
<td>102.6±4.7</td>
</tr>
<tr>
<td>Mean</td>
<td>105.3±14.1</td>
<td>87.9±14.3</td>
<td>59.3±8.7</td>
<td>181.4±11.4</td>
<td>75.8±7.7</td>
<td>92.0±7.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent ICP (%)</th>
<th>IOP–ICP</th>
<th>IOP–LCP</th>
<th>IOP–ONSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.0</td>
<td>127.3</td>
<td>87.4</td>
<td>115.9</td>
</tr>
</tbody>
</table>

We have identified three features of the ICP–ONSP relationship: an ICP-dependent zone, a breakpoint, and an ICP-independent zone. They show that the ICP–ONSP correlation is non-linear: while ONSP and ICP both drop linearly at high ICP levels (ICP-dependent zone), at or below a certain breakpoint this linearity is lost and ONSP remains stable despite further ICP decline (ICP-independent zone).

What are the clinical implications of these findings? It is conceivable that if ICP is in the ICP-independent zone, the “optic nerve chamber syndrome” develops. Thus, if the ICP is too low, CSF flow from the intracranial SAS into the optic nerve SAS stops and CSF drainage from the optic nerve SAS is interrupted as well. Our observations are compatible with Jaggi et al. (2007, 2010) who carried out sheep experiments and studied patients with optic nerve sheath meningioma. They reported that CSF sequestration by interruption of CSF flow from the intracranial SAS into the optic nerve SAS could lead to optic nerve damage.

Our findings of the two zones contrast proposals by Morgan et al. (1995, 1998) who suggested a linear correlation between ICP and ONSP, i.e. that the ONSP and ICP decline together. However, in our normal dogs this was only true for higher ICP levels. At lower ICP levels below a certain critical “breakpoint” which varied between different animals, ICP and ONSP were uncoupled. Comparing the two experiments, it can be seen that on the one hand, our pressure measurement error is $\pm 1.0$ mm H$_2$O and their error is $\pm 1.0$ mm Hg, that is to say, we can measure more accurately and find more subtle differences. For example, if the difference is below $1$ mm Hg (about $13$ mm H$_2$O), it cannot be found in their experiment but it is a bigger variation in our research. On the other hand,

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Table 1 - Intracranial pressure (ICP), lumbar cistern pressure (LCP), optic nerve subarachnoid space pressure (ONSP), and intraocular pressure (IOP) at baseline in all study dogs (mm H$_2$O; mean ± SD).
The ICP

(100% equation ((lines are drawn and the equations are determined the ICP in independent zone. Using the same method we also calculated the relative ONSP percent change over baseline (ONSP %) and CSF drainage for the group analyses. In this manner we normalized the pressure values and were able to identify the ICP-taking the baseline ICP value of each dog as 100% and then calculated the ICP percentage change over baseline (ICP %) during them, ranging from 57% to 89% of their respective individual baseline value (Table 2). Therefore, we normalized the data by and the ICP-independent zone for each dog. The breakpoint was not the same in all dogs but varied considerably among

\[ y = 0.11x + 55.9; r = 0.809 \]  

In contrast, in the “ICP-independent zone”, ONSP remains relatively constant despite a decreasing ICP (regression equation: \( y = 0.02x + 45.8; r = 0.157 \)). The breakpoint between the dependent and independent zone is at about 40 mm H₂O. Part B: The two separate regression lines were calculated after the data were split by the breakpoint between the ICP-dependent and the ICP-independent zone for each dog. The breakpoint was not the same in all dogs but varied considerably among them, ranging from 57% to 89% of their respective individual baseline value (Table 2). Therefore, we normalized the pressure values and were able to identify the ICP-independent zone. Using the same method we also calculated the relative ONSP percent change over baseline (ONSP %) and determined the ICP–ONSP curve and displayed it as change of ICP%–ONSP% curve for all animals combined. The regression lines are drawn and the equations are \( y = -0.01x + 64.70 \ (r = 0.049) \) in the “ICP-independent zone” and \( y = 0.24x + 75.01 \ (r = 0.797) \) in the “ICP-dependent zone”. The breakpoint of ONSP% is at about 68% (Table 1). Then, putting it back into the equation \( y = 0.24x + 75.01 \) will calculate the ICP% (around –30%). Because the ICP declines from the baseline (100%) through the ICP–ONSP dependent zone and the breakpoint to ICP–ONSP independent zone, the breakpoint of ICP% is just equal to 70% (100% – 30%); that is, the ICP–ONSP dependent zone is 30% and the ICP–ONSP independent zone is 70%.

### Table 2: Optic nerve subarachnoid space pressure (ONSP) at baseline and in the ICP-independent zone.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Baseline ONSP (mm H₂O) ICP-independent zone</th>
<th>ICP-independent ONSP (%)</th>
<th>ICP-independent/ONSP-Baseline*100%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70.9 ± 6.3</td>
<td>46.3 ± 1.8</td>
<td>65.30</td>
</tr>
<tr>
<td>2</td>
<td>45.8 ± 1.9</td>
<td>29.9 ± 0.8</td>
<td>65.28</td>
</tr>
<tr>
<td>3</td>
<td>54.9 ± 2.9</td>
<td>38.5 ± 0.7</td>
<td>70.13</td>
</tr>
<tr>
<td>4</td>
<td>49.3 ± 3.4</td>
<td>28.2 ± 2.7</td>
<td>57.20</td>
</tr>
<tr>
<td>5</td>
<td>63.3 ± 2.5</td>
<td>45.3 ± 5.5</td>
<td>71.56</td>
</tr>
<tr>
<td>6</td>
<td>67.4 ± 1.4</td>
<td>37.8 ± 0.9</td>
<td>56.08</td>
</tr>
<tr>
<td>7</td>
<td>62.6 ± 2.7</td>
<td>45.4 ± 2.7</td>
<td>72.52</td>
</tr>
<tr>
<td>8</td>
<td>60.6 ± 2.0</td>
<td>53.9 ± 0.3</td>
<td>88.94</td>
</tr>
<tr>
<td>Mean</td>
<td>59.3 ± 8.7</td>
<td>40.7 ± 8.7</td>
<td>68.38 ± 10.34</td>
</tr>
</tbody>
</table>

if we use the same method as Morgan et al. did to put all of the data together to analyze, we also can get the results as well as they did. Then ICP and ONSP correlate linearly, despite the ICP-independent zone and we could not find the breakpoint. So, our study clearly revealed for the first time not only that the baseline ONSP is markedly lower than the ICP (only about 60%), but that there is a breakpoint in the ICP–ONSP curve which divides it into two zones: ICP-dependent and ICP-independent zone.

### 3.1. Optic nerve chamber anatomy and fluid dynamics

To explain the pressure dynamics between the ICP and the ONSP, let us consider the normal anatomical situation. The optic nerve (ON) passes through three different cavities: the intraocular, the intra-orbital and the intracranial cavity (Fig. 3A). Because CSF in the optic nerve SAS originates from the intracranial cavity, it was long thought that ONSP simply mirrors ICP. But the pressures are, in fact, not the same in the different compartments, with ICP > LCP > ONSP. Thus, not only is the ONSP much lower than the ICP, but the optic nerve is exposed to three different pressure influences: the IOP, ONSP and ICP. This exposes the optic nerve to two pressure gradients: the TLPG between the IOP and ONSP and the trans-optic canal pressure gradient (TCPG) between ICP and ONSP. In our results, TLPG was highest for IOP–ONSP, lower for IOP–LCP, and lowest for IOP–ICP. As for TCPG, under normal conditions ICP directly controls ONSP levels because of normal fluid communication between the optic nerve and the intracranial SAS through the optic canal. But when ICP drops too low, the breakpoint is reached and CSF flow stops.

To illustrate how the pressures conditions affect the optic nerve chamber, Fig. 3 shows three cavities and their pressure relations: CSF flows from the intracranial cavity through the optic nerve SAS into the intra-orbital cavity. In the higher.
Fig. 3 - The water pond CSF dynamics theory. Part A shows a cartoon of the different pressure compartments that act on the optic nerve. Part B is an illustration of the pressure conditions showing CSF inflow to and outflow from the optic nerve chamber. When ICP drops below 70%, the pressure in the optic nerve SAS remains constant at 40% of ICP. In the “ICP-dependent zone” (ICP from 100% to 70%, accordingly ONSP from 60% to 40%), the ICP is sufficient to assure a free CSF-flow into the optic nerve SAS which then exits into the drainage system. However, in the “ICP-independent zone” (ICP from 70% and below, accordingly ONSP is stable at 40%), ICP is insufficient and the CSF-flow through the optic canal stops. The optic canal creates apparently a certain optic canal resistance (OCR) because otherwise ONSP and ICP would be equal. But the two pressures, ICP and ONSP, are not equal because of a natural resistance by the optic canal, here illustrated by the inflow hump. Therefore, according to the formula TCPG = ICP – ONSP – which is 70% – 40% = 30% in our dogs –, we conclude that the optic canal resistance (OCR) in normal dogs is about 30%. When TCPG is higher than 30% (TCPG > OCR), i.e. when there is sufficient pressure of the CSF to push the CSF over the hump, CSF can freely flow through the optic canal. When the TCPG is < 30%, TCPG < OCR, CSF flow stops. On the other hand, because the stable ONSP is 40%, it can be inferred that the outflow resistance is at least 40%. In other words, ONSP should be higher than 40% so to allow normal drainage of CSF out of the optic nerve SAS. Given that the inflow breakpoint is 70% and the outflow breakpoint is 40%, (ICP > 70% and ONSP > 40%), CSF can flow from the intracranial SAS to the optic nerve SAS and then drain to the intra-orbital cavity. But if the pressure is below this breakpoint (ICP < 70 and ONSP ≤ 40%), CSF cannot flow in and out the optic nerve SAS, and a healthy “CSF-pond” turns into a “dead-pond”, leading to the optic nerve chamber syndrome.

pressure ICP-dependent pressure zone (ICP 70–100%; ONSP 40–60%), ICP is sufficient to assure CSF flow into the optic nerve SAS. In contrast, in the lower pressure ICP-independent zone (when ICP <70%) the ONSP remains stable at about 40%, despite further ICP decline. This means that the ICP is too low for CSF to freely flow through the optic canal. The optic canal apparently creates a certain optic canal resistance (OCR), which is at about 30%, and the outflow resistance consequently is at about 40% (see caption of Fig. 3). We assume that a healthy CSF flow is required for the optic nerve to be able to receive sufficient nutrients and to dispose toxic waste from the optic nerve chamber. Below a critical value, which is 70% in normal dogs, CSF cannot flow in or out of the optic nerve SAS, and a healthy “CSF-pond” may turn into a “dead-pond”. This will then create the CSF compartment syndrome or the chamber syndrome of optic nerve damage.

One can think of the optic nerve SAS as a CSF compartment with an inflow and outflow channel. Like a water pond that has water coming in on one side of the pond and flowing out on the other side, any flow of CSF into the optic nerve SAS due to higher ICP needs to be matched by appropriate outflow to maintain a dynamic fluid equilibrium. However, if ONSP does no longer change as ICP declines below the breakpoint, this is a sign that the optic nerve SAS is like a compartment in a stationary (stable) pressure state. To stay with the analogy of the water pond, if the inflow of water stops there is no longer any outflow either; now the pond has only the pressure created by its own liquid volume. When fluid exchange stops, there is no more inflow of nutrients and no more drainage of toxic substances; it is like a dead pond’s ecosystem that is seriously disturbed.

Furthermore, we identified a critical breakpoint in normal dogs suggesting a natural resistance caused by anatomical constraints. However, there may very well be some pathological conditions which could lead to a rise of the breakpoint because of additional obstructions: traumatic or inflammatory events with optic nerve swelling, fibrous dysplasia due to optic canal bone thickening, optic nerve sheath meningioma, or an intra-orbital tumor. In such pathological situations CSF flow is expected to be reduced or stopped in the optic nerve SAS despite normal ICP levels, creating the CSF compartment syndrome. A reduced CSF flow would be expected to interrupt nutrition and reduce outflow of toxic substances that build up...
over time, damaging the optic nerve. This could be the reason why some patients suffer NTG despite normal ICP. The “breakpoint”, therefore, may be a pathologically relevant marker which reflects the CSF dynamic status in the optic nerve SAS.

3.2. CSF drains from the cul-de-sac

Free CSF exchange in the optic nerve chamber is not only a function of proper inflow but also of unobstructed outflow. If drainage is obstructed, the pressure in the optic nerve chamber rises and greater inflow-pressure is needed to maintain CSF free flow. Thus, the breakpoint may not only be determined by the optic canal obstruction but also by certain outflow pressure conditions.

But the outflow mechanism is still an unsolved riddle, as CSF cannot escape in the optic nerve head region. The optic nerve sheath forms a sealed pouch pocket, which does not communicate with the intraocular cavity; this is a “dead end” for CSF-flow (“cul-de-sac”). As our dog experiments show, CSF cannot flow back into the intracranial SAS when the ICP is considerably higher than the ONSP (Fig. 3B). Therefore, other options of the CSF fate must be considered. Several animal models (Liu et al., 2012; Murtha et al., 2014) suggested possible sites of CSF drainage/resorption including the olfactory cribiform plate, nasal submucosa and cervical lymphatics. Other authors (Brinker et al., 1997; Ludemann et al., 2005) proposed rapid drainage of CSF into the lymphatic system through pore-like openings in a thin neuroepithelial layer along the optic nerve extending into the lymphatic system and even a brain lymphatic system was recently identified (Louveau et al., 2015). Whether lymph vessels around the ON support CSF drainage to the intra-orbital cavity remains to be studied. Based on our results we speculate that the ONSP in the chamber syndrome is equal to the pressure in the lymphatic system around the ON which is another resistance force concerning CSF drainage. Only if ONSP is higher than this equilibrium pressure, the CSF drainage works properly and the optic nerve is kept in a healthy state (provided sufficient inflow, of course).

Several authors already suggested that the chamber syndrome is the cause of optic nerve damage (Jaggi et al., 2010; Killer, 2013; Orgul, 2012), but they did not specify possible mechanisms. Our dog study suggests that the chamber syndrome may be the result of an imbalance of several pressure gradients, which arrest CSF flow into and out of the optic nerve chamber. If CSF flow stops it is like a “dead pond” with a disturbed ecosystem. Thus, healthy CSF flow into the optic nerve chamber depends on (i) the absolute ICP, (ii) a normal, but not pathological, pressure obstruction of the optic canal (OCR), and (iii) sufficient outflow (drainage) pressure.

Of course, dog and human physiology are not the same, and it is still not clear whether or not it is true in human beings. On the other hand, the dog is not as well as mankind upright walking, and our experiments were done in supine position, i.e. the results cannot be translated to humans directly, especially given their erect position.

Future studies are needed to identify whether these results could be used in human and in what pathological conditions the breakpoint may be raised and result in glaucoma or optic neuropathy. In addition, we need to learn whether there is an obstructions on the inflow and/or the outflow (drainage) side of the optic nerve SAS. To the extent that results obtained in dogs can be confirmed in humans, it appears that the brain and its CSF pressures may play a critical role in the development of some ophthalmological diseases, such as glaucoma. This may guide our further search for underlying mechanisms and help discover new therapeutic approaches for preventing further vision loss or enhancing vision restoration.

4. Experimental Procedure

4.1. Animal preparation

Eight mixed-breed beagle dogs were studied in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, the ethical standards laid down in the 1964 declaration of Helsinki and its later amendments and all applicable institutional and/or national guidelines for the care and use of animals. To implant pressure probes, the animals were anesthetized with an intramuscular injection of ketamine HCL (20 mg/kg) and midazolam (0.2 mg/kg), with repeated injections of ketamine (10 mg/kg) as needed during the examinations and surgery.

4.2. Pressure transducer and probe

To measure the pressure conditions simultaneously in the 4 cavities, hydraulic pressure transducers were custom fabricated by Biological Mechanics Laboratory, Beijing University of Aeronautics & Astronautics. One transducer each was implanted into the left ventricle, left optic nerve SAS, the lumbar cistern, and the anterior chamber of the left eye, respectively (Fig. 4A). The devices consisted of a computer, an amplifying device, pressure sensors, and probes. The absolute pressure measurement error for each transducer was ±1.0 mm H2O. Each manometry probe was connected to the pressure sensor by a three-way union and connected with the amplifier device. The pressure signals were converted into electrical signals and recorded in real-time so that the four pressures, ICP, LCP, ONSP and IOP could be recorded simultaneously.

4.3. Implantation of pressure transducer

To implant the probes, dogs were anaesthetized (see above) and suspended in prone position, with front legs hanging down through a fenestrated sheet, and the rest of the body supported by a sling. The head was fixed with a maxilla bite clamp connected to the operating table. The concrete operation process was shown in Fig. 4A. To accurately puncture, we first connected the pressure transducer and measured the zero-pressure baseline. Then we slowly punctured the optic nerve sheath while simultaneously monitoring the pressure. As the needle punctured the dura, the successful entry of the probe was clearly noticeable by a sharp real-time pressure rise. Pressure was then monitored for at least 5 min to assure stable CSF baseline pressure. Thereafter, we fixed the needle and pressure probe with the biological glue (ECglue; Guangzhou Baiyun Medical Glue Company, China) which also closed the puncture site to prevent CSF leaks.
4.4 Data processing

Calculations of pressures were performed with MATLAB (MathWorks Inc, Natick, Massachusetts, USA). To avoid interpretation errors, all pressure recordings were manually inspected for any unusual artefacts and/or fluctuations. For each 1.0 s period, pressures were calculated as the mean of unfiltered pressure; using 10th order Butterworth zero phase filters we removed slow respirator waves (high pass cut-off frequency 0.5 Hz).

To calculate the pressures, we first measured the distances between the puncture points and operating table and the probes were then connected with the pressure monitoring system, which revealed the hydrostatic zero-pressure-baseline. Thereafter, we placed the pressure probes for each puncture point to collect baseline values for ICP, LCP, ONSP and IOP for at least 5 min. The pressure values were determined by calculating the real time values minus the starting point (zero-pressure-baseline) values. A standard recording showing the correlation between ICP and ONSP was shown in Fig. 4B.

The relative pressure coefficient was determined by calculating the slope of a linear regression of ICP, LCP, ONSP, and IOP. ONSP was found to be essentially constant at low ICP levels (see results) which were used to determine the

Fig. 4 – Puncture pattern diagram and standard investigation. Part A shows the puncture positions of the pressure probes at the intraocular cavity (A), optic nerve subarachnoid space (B), intracranial cavity (ventricle) (C), and lumbar cistern (D). To measure the LCP, a skin incision was made over the 4th lumbar vertebra and a laminotomy was performed to cannulate the lumbar cistern with a catheter using blunt dissection. Electrocoagulation and electrotomy avoided bleeding and vertebra bone was removed to access dura mater. Then, a catheter connected to a pressure sensor was implanted into the lumbar cistern. Next, the IOP was measured with a 25-gauge cannula that was connected with a pressure transducer after it was inserted through the peripheral cornea into the anterior eye chamber. Furthermore, for measuring the ICP, a burr hole was drilled on each side 1 cm lateral of the sagittal midline halfway between the occipital prominence and a line between both lateral canthi. Thereafter, the dura was incised, and the lateral ventricle was punctured by a Frazier’s ventricular needle. A catheter was then placed into the frontal horn of the lateral ventricle on each side. The left catheter was connected to a pressure sensor while the right catheter served as pressure control of possible CSF volume alterations. Finally, lateral orbitotomy was performed to expose the left retrobulbar optic nerve sheath. Extreme care was taken when puncturing the optic nerve sheath with a sharp needle (28-gauge) into the optic nerve SAS. The tubes were filled with normal saline (NS) and any residual air was removed. Through the three-way union, a washing device could be linked with the pressure measurement system to ascertain that if the front-end of the needle was plugged up by tissue debris, it could be washed without removing the probe. Part B is a typical recording of the correlation between ICP and ONSP during step-wise drainage of CSF from the ventricle. It shows a baseline registration (A), followed by removal of CSF samples from the ventricle (B) and the subsequent decreased ICP as indicated by the pressure decline (C). Black lines show the regulated pressure levels as they declined during ICP shunting. All pressure probes were continuously monitored, including the 5 min baseline, and 3–5 min for every shunting event. To achieve a reliable and stable depiction of a pulsatility curve, ICP values were divided into 10 mm H2O intervals. Intervals with fewer than three values were discarded to minimize the influence of noise and the median was used to reduce the influence of single outlier values.
“breakpoint”. This was defined as the value representing the transition between the "ICP-dependent zone" – where ICP and ONSP values dropped in parallel—and the "ICP-independent zone", where further ICP loss was no longer accompanied by ONSP loss.

4.5. Statistics

IOP, ICP, LCP, and ONSAS pressure values were compared using paired t-tests with Origin Statistics (V.9.1; OriginLab Corporation, Northampton, USA). A p-value <0.05 was considered statistically significant.

Conflict of interest

None.

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