Influence of an increased intracranial pressure on cerebral and systemic haemodynamics during endoscopic neurosurgery: an animal model.

Modified from


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Abstract

Background: During endoscopic neurosurgery, direct mechanical stimulation of the brain by the endoscope and increased intracranial pressure (ICP) caused by the continuous rinsing can induce potentially lethal haemodynamic reflexes, brain ischaemia and excessive fluid resorption.

Methods: In a newly presented rat model of endoscopic neurosurgery, stereotactic access to the cerebrospinal fluid was secured and the ICP was increased by controlled infusion until complete suppression of the cerebral perfusion pressure (CPP). The haematocrit level was determined before and after the procedure. During the whole procedure, invasive arterial pressure, ICP and heart rate were continuously recorded and evaluated in a subsequent offline analysis. After the procedure, the animals were allowed to recover and seven days later they were killed for histological examination.

Results: Suppression of the CPP resulted in a severe hypertension combined with tachycardia or mild bradycardia. The haematocrit dropped from 41 to 35 over the minutes of CPP suppression. After cessation of the infusion, the ICP dropped to 37% of the plateau pressure within 2.5 seconds. In the first few minutes after restoration of normal ICP, five animals died because of pulmonary edema.

Conclusion: Upon complete suppression of the CPP, an obvious hypertension developed, often together with tachycardia, but no severe bradycardia. At high ICP levels we observed an important translocation of irrigation fluid to the vascular space. Fatality was not caused by ischaemia or arrhythmia but due to pulmonary edema.
Introduction

Background
The introduction of endoscopic neurosurgery has resulted in important advantages in the treatment of many pathologies such as hydrocephalus or brain tumours. During these procedures, the endoscope is advanced into the ventricles, where after continuous rinsing of the ventricular cavities is performed. Extensive rinsing however may increase the intracranial pressure (ICP), and consequently decrease cerebral perfusion pressure (CPP). As a result of the intracranial hypertension, a Cushing reflex may occur, which can evolve into dangerous haemodynamic instability. Secondly, the increased pressure of the cerebrospinal fluid (CSF) increases the arachnoidal reabsorption, eventually relocating rinsing fluid to the vascular space. Furthermore, direct stimulation of the bottom of the third ventricle can induce various haemodynamic responses. Initially it was supposed that an open outflow channel of the endoscope guarantees that the ICP does not increase too much. However, since then, many groups have reported severe haemodynamic changes that presumably can only be attributed to the intracranial manipulations.

Since extensive manipulation of cerebral structures during difficult surgical procedures often necessitates higher rinsing flows, it is impossible to clearly differentiate between direct stimulation of the brainstem and a genuine Cushing reflex as the cause of these haemodynamic changes.

Existing animal models
Ever since Cushing and others started investigating the haemodynamic effects of intracranial hypertension, all animal models were based on extradural volume expansion, using direct extradural fluid infusion, balloon inflation or traumatic injury. Since the intracranial hypertension during endoscopic neurosurgery is induced by ventricular volume expansion, the aforecited methods may not be accurate as a model for studying haemodynamic changes during neuroendoscopy.

Aim of the study
Therefore, in the present study, we propose a rat model of direct subarachnoidal volume expansion as an experimental model for intracranial hypertension during endoscopic neurosurgery. The aim of the present study is to evaluate the nature of the haemodynamic changes as a result of isolated intracranial hypertension and to elucidate the hydrodynamics of the rinsing fluid.
Methods

The experimental protocol was approved by the Ethical Committee for Animal experimentation of the faculty of medicine and health sciences, University of Ghent respecting the national guidelines for the treatment of experimental animals.

Animal preparation
Male albino Wistar rats (weight, 250-500 g) (iffa credo, Brussels, Belgium) were anaesthetized with sevoflurane 2% in a mixture of O₂ (30%) and N₂ (70%). After spontaneous movements stopped, the concentration was increased to 4% ; we waited for another 30 seconds and the animal was put on his back. The tail artery was cannulated with a PE-50 tubing for monitoring of arterial pressure, periodic blood sampling and for drug administration. During cannulation a little funnel was placed over the head for administration of sevoflurane 4%. The animals were orally intubated with a 16-gauge catheter. To facilitate intubation, sevoflurane 8% was administered through the catheter under direct vision of the vocal cords until they were immobile and standing wide open. Then the animals could smoothly be intubated. After securing the airway, sevoflurane was set at 2% and the animals were positioned in a stereotaxic frame. A syringe pump with a constant flow rate of 0.02 ml/min was connected to the arterial line.

Stereotactic access to the CSF
An incision of the skin, 2 mm in length, directly overlying the occipito-vertebral junction was made on the dorsal side of the neck. An 18-gauge catheter needle (Laeder Cath, Laboratoires pharmaceutiques, Ecouen, France) was stereotactically introduced between the scull and the atlas into the cisterna magna for access to the cerebrospinal fluid (CSF). The stereotactical coordinates consistently were 2.5 mm above the level of the earpins and 4 mm posterior to the level of the earpins in the median plane. Before insertion, the needle was connected to a pressure transducer (PMSET 1DT-XX Becton Dickinson Critical Care Systems Pte Ltd, Singapore) and a syringe filled with Ringer solution. The needle-transducer system was completely filled with the solution; the syringe was placed in a syringe pump (model 600-0, Harvard apparatus, Dover, Mass.) and a flow of 0.04 ml/h was initiated.

As the needle was advanced slowly through the tissues with a micromanipulator, a linearly increasing pressure was recorded. Upon entering the subarachnoidal space, the pressure reading dropped to a pulsatile waveform matching a normal ICP of 5 ± 2 mmHg. Low frequency ventilatory pulsations are superimposed to high frequency cardiac pulsations. (See fig. 1).

Then, the needle was left in place for continuous ICP monitoring and ICP-manipulation.
As no spontaneous movement was observed during the animal preparation, the degree of analgesia and hypnosis was considered adequate. Then, the animals were paralysed with cisatracurium 0.2 mg/kg and ventilated by controlled intermittent positive pressure ventilation with a tidal volume of 12 ml/kg and a frequency of 50 min⁻¹. After an equilibration period of 5 minutes, arterial blood samples were taken for Hct, pH, PO₂ and PCO₂. If necessary, ventilator settings were adjusted to obtain an arterial PCO₂ between 32 and 38 mmHg. A rectal temperature probe was placed for core temperature monitoring, which was maintained at 37.0°C by a heating pad. In total, twenty animals were used. After baseline measurements with 5 min of stabilisation, another dose of cisatracurium was given.

**Data recording**
The arterial pressure and ICP were monitored using an S5 monitor (GE Health Care, Helsinki, Finland). Both pressure transducers were placed at the level of the external acustic meatus. Locating both pressure transducers at the same level allows accurate calculation of the CPP (CPP = MAP – ICP). Both pressure waveforms were continuously recorded at 100Hz on a PC using the S5 collect® software for subsequent off-line analysis.

**Induction of intracranial hypertension and haemodynamic management**
The ICP was then slowly increased using the syringe-pump connected to the ICP-pressure transducer. After each increase of the infusion rate, the ICP was observed until a plateau was reached. The infusion rate was gradually increased until the ICP exceeded the systolic pressure. During suppression of the CPP, a distinctive Cushing reflex developed as expected ⁵ ⁷. When the MAP increased, we increased the ICP in order to sustain total CPP suppression. The infusion rates were continuously recorded. If haemodynamic collapse occurred, no attempt at resuscitation was made. Complete CPP suppression was maintained for different periods ranging from 90 to 514 seconds, after which the syringe-pump was stopped. ICP recording was continued after cessation of fluid infusion; the one-way valve of the pressure transducer prevented intracranial fluid to flow back through the needle. Then, the
total volume of fluid infused into the subarachnoidal space was recorded and an arterial blood sample was taken for Hct, pH, PO$_2$ and PCO$_2$. During the procedure, the eyes of the rats were examined on colour and pupil-size. It was assessed that no fluid had leaked alongside the needle.

In the first group of rats (N-group, n=5), the procedure was carried out as described above. Because of the high mortality rate (3 out of 5) in these rats, probably due to excessive fluid infusion and severe hypertension, the procedure was modified in order to differentiate the cause of the fatality between brain ischaemia and haemodynamic reasons. In order to attenuate the cardiovascular consequences of the Cushing reflex, rats were pre-treated with repetitive boluses of labetalol 50 µg until additional boluses didn’t generate any further lowering of the MAP (L-group, n=3).

In another group of rats, increasing concentrations of inspiratory sevoflurane were administered until the systolic pressure was lowered to 55 mmHg before the ICP was increased (S-group, n=12). In this way, the necessary increase in ICP to suppress the CPP was lower. During the ICP-increase, the inspiratory sevoflurane was altered depending on haemodynamic needs.

After normalisation of the ICP, the animals were kept anaesthetized for at least one hour until haemodynamic stability was reached. During this period ICP-monitoring was maintained. If necessary the sevoflurane concentration was increased to at most 6% in order to control rebound hypertension. If possible, the inspiratory sevoflurane concentration was lowered to 1%. One hour after the ischaemic event, the animals were taken out of the stereotactic frame, the arterial catheter was removed, wounds were closed and the animals were allowed to breathe room air spontaneously. When coughing reflexes occurred, the tracheal tube was removed. The animals were closely observed the following hours. Any abnormal behaviour or motoric dysfunction was registered. If suffering was suspected, the animal was euthanized (intraperitoneal pentobarbital 150 mg/kg).

Analysis of pressure waveforms
During offline analysis after the experiment, arterial and ICP waveforms, MAP, mean ICP and heart rate (HR) were analysed. The CPP was calculated as the difference between mean arterial pressure and mean ICP. High-resolution waveforms at 100 Hz of the arterial pressure, ICP and CPP were visualized for detailed description of the haemodynamic phenomena.

The ICP-level upon entering the subarachnoidal space was determined (ICP$_{Baseline}$). In order to evaluate the influence of the ICP on the cerebral perfusion, several parameters were examined. The MAP and HR prior to the initiation of the CPP-suppression, the ICP and CPP values at the onset of the Cushing Reflex and the period of total CPP suppression were determined. The highest value of the ICP, MAP
and HR during CPP-suppression was registered. The evolution of the MAP and HR during the procedure was graphically represented.

The Pulse Pressure of the ICP (PP\textsubscript{ICP}) was calculated as the difference between the systolic and diastolic ICP-pressure and graphically represented together with the MAP, ICP and CPP waveform. The lowest and highest PP\textsubscript{ICP} during the procedure were detected and analysed in relation to the ICP and CPP. It was assessed whether PP\textsubscript{ICP} suppression occurred at the moment of CPP ≤ 0 mmHg.

At different infusion rates of Ringer solution into the CSF, the plateau-pressure (ICP\textsubscript{Plateau}) was determined, together with the MAP. The time constant tau – being the time required for the ICP to return to 1/e (=37%) of its baseline value after stopping the fluid infusion\textsuperscript{8} – was also calculated based on the pressure waveforms and related to the MAP.

**Histological evaluation**

On day 8 of the experiment, the animals were euthanized with an intraperitoneal injection of pentobarbital 150 mg/kg and were decapitated. The animals that died during the procedure, or that were euthanized in the first 24 hours after it, were excluded from histological analysis.

The brain was fixed in 10% buffered formaldehyde for at least 12 hours. After adequate fixation, the brain was embedded in paraffin, and serial sections (5 micrometer thick) were cut and stained with hematoxylin and eosin, prior to histological evaluation. Serial sections were evaluated by light microscopy to determine the presence of haemorrhagic lesions. In order to estimate ischaemic injury, the number of pycnotic cells in the CA1-pyramidal cell layer of the hippocampus was counted\textsuperscript{9}.

**Results**

**Procedure**

The induction of anaesthesia, arterial cannulation, tracheal intubation and positioning of the head in the stereotactic frame was well tolerated by all animals. In all animals, except one (animal S9), the subarachnoidal space was entered without difficulties. In this animal, no reliable ICP waveform could be obtained; it was excluded from further analysis.

Upon entering the subarachnoidal space, a waveform with cardiac pulsations superimposed on respiratory oscillations confirmed correct placement of the needle (see fig.1). The initial ICP was 5 ± 2 mmHg (mean ± SD, n = 15) in all animals.
A summary of all measured values is given in table 1: For the N-group (no precautions), L-group (labetalol), and S-group (sevoflurane), following parameters are shown (mean ± SD): the baseline intracranial pressure (ICP) after access to the CSF; the baseline mean arterial pressure (MAP) and heart rate (HR) before inducing intracranial hypertension; the maximal ICP, MAP and HR during intracranial hypertension; the total ischaemic time; the minimal pulse pressure (PP) during suppression of the cerebral blood flow and the maximal PP during increased ICP; the total volume of infused fluid.

Table 1: Summary of all measured values in the different groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>ICP baseline (mm Hg)</th>
<th>MAP baseline (mm Hg)</th>
<th>HR baseline (beats min⁻¹)</th>
<th>ICP max (mm Hg)</th>
<th>MAP max (mm Hg)</th>
<th>HR max (beats min⁻¹)</th>
<th>Ischaemic time (s)</th>
<th>PP min (mm Hg)</th>
<th>PP max (mm Hg)</th>
<th>Infused fluid (ml)</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>89 (10)</td>
<td>346 (36)</td>
<td>214 (22)</td>
<td>179 (29)</td>
<td>371 (74)</td>
<td>231 (128)</td>
<td>1 (0.44)</td>
<td>14 (7.96)</td>
<td>13.25 (2.75)</td>
<td></td>
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<tr>
<td>L</td>
<td>99 (5)</td>
<td>529 (34)</td>
<td>216 (27)</td>
<td>148 (12)</td>
<td>545 (19)</td>
<td>207 (94)</td>
<td>2 (0)</td>
<td>11 (5.52)</td>
<td>14.16 (5.29)</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>38 (5)</td>
<td>185 (74)</td>
<td>175 (42)</td>
<td>116 (21)</td>
<td>345 (53)</td>
<td>276 (135)</td>
<td>1 (0.5)</td>
<td>7 (3.43)</td>
<td>14.00 (3.08)</td>
<td></td>
</tr>
</tbody>
</table>

Haemodynamic changes
The evolution of the MAP and Heart Rate in the first 200 seconds of induction of intracranial hypertension is presented in figure 2.

At time 0, the ICP is increased. A two-fold increase of the initial arterial pressure is seen in group N and L compared to a three-fold increase in group S. In all three groups, the MAP increases significantly after induction of intracranial hypertension (p<0.01).

In the N-group, tachycardia as well as bradycardia is observed following induction of intracranial hypertension. In the L-group there is a tendency towards bradycardia. In the N-group and L-group no significant change in heart rate is observed after induction of intracranial hypertension.

In the S-group, there is a significant induction of tachycardia within seconds after induction of intracranial hypertension (p<0.01).

Compared to the N group, there was no significant decrease of the initial MAP (p=0.06) or HR (p=0.53) in the L-group; but there was a significant decrease of initial MAP (p<0.01) and HR (p<0.01) in the S-group.
Figure 2: Haemodynamic changes following induction of intracranial hypertension.

In a first series of experiments (N-group, n=5) the CPP was suppressed for 231 ± 125 seconds. In all animals a Cushing reflex, consisting of a clear hypertension and bradycardia or tachycardia occurred following induction of intracranial hypertension (fig. 2a, 2d, 3). The PP_{ICP} dropped from a maximal value of 14 ± 8 mmHg to 1 mmHg when the ICP increased above the systolic pressure. Of the five animals in the N-group, two animals survived the procedure. The three animals that did not survive showed severe pulmonary edema, with pink frothy fluid obstructing the tracheal tube.

In the L-group (n=3), administration of labetalol decreased the initial MAP and HR. The CPP was suppressed for 207 ± 54 seconds. Again, the PP_{ICP} was suppressed from a maximal 11 ± 2 mmHg to 2 mmHg. The hypertension was blunted to a maximum MAP of 148 ± 11 mmHg (fig. 2b). A modest bradycardia was observed in two of the animals. No tachycardia was seen in this group (fig. 2e). Two of the three animals died during the procedure; one of them showed obvious pulmonary edema. The animal that did survive showed a spastic paralysis of the hind paws, which resolved within 24 hours.
The nature of the Cushing reflex

As an example, figure 3 shows a typical recording of the sudden change in arterial blood pressure in response to an increased ICP during an S group experiment. Inspiratory sevoflurane concentration of 8% results in a low initial ABP and causes brady-arrhythmia. Five seconds after increasing the ICP, the arrhythmia resolves and a Cushing reflex initiates. Notice a low Pulse Pressure of the ICP \( PP_{ICP} \) at 0-7 sec; an absent \( PP_{ICP} \) when ICP>ABP and relatively high \( PP_{ICP} \) when ICP = MAP.

Figure 3: Typical recording of haemodynamic changes.

In the S-group (n=12), administration of sevoflurane 8% strongly decreased the MAP and the HR. In five animals, brady-arrhythmia developed before the induction of intracranial hypertension because of the high sevoflurane concentration; this condition subsided within seconds after increasing the ICP. (See fig 3). The CPP was suppressed for 247 ± 101 seconds. The MAP increased only to 116 ± 21 mmHg and the HR to 345 ± 33. In all animals, the Cushing reflex consisted of an unambiguous onset of hypertension and tachycardia (fig. 2f). The \( PP_{ICP} \) was suppressed from 7 ± 3 mmHg to 1 ± 0 mmHg during total CPP suppression. At the moment of maximal \( PP_{ICP} \), the CPP was 4 ± 5.8 mmHg.

After the intracranial fluid infusion was stopped, most animals showed an initial hypotension, followed by a prominent hypertension, which could efficiently be controlled by increasing the sevoflurane concentration during several minutes. Within 30 minutes, the arterial pressure tended to normalize. In the postischaemic period, the ICP did not show any important increase.

Intracranial Fluid resorption

During CPP suppression, an important amount of fluid is absorbed from the subarachnoid space into the circulation (14 ± 3.08 ml) as indicated by the haematocrit, dropping from 41.1 ± 3.0 % before CPP suppression to 35.2 ± 3.6 % (p < 0.001, n=10) afterwards.
Figure 4 shows the drop in Haematocrit level for the individual animals. The levels before and after CPP suppression indicate the infused fluid was resorbed into the vascular compartment. All samples are from the sevoflurane group. Since in some of the animals the second blood sampling via the tail artery was not possible, only 10 coupled data points were obtained.

Figure 4: Drop in Haematocrit level for the individual animals.

Outcome and analysis
All the animals of the S-group, survived the entire procedure. Six animals showed normal behaviour one hour after recovery from anaesthesia. Five animals showed a transient paralysis of the hind legs, which resolved within 24 hours. One animal (S11, with the longest CPP-suppression time of 563 seconds) showed persistent paraplegia, and was therefore euthanized after 24 hours. The remaining animals completely recovered of the ischaemic insult and were euthanized at the end of the observation period of 7 days.

In order to differentiate the cause of haemodynamic collapse between fluid overload and brain ischaemia, different parameters were assessed to evaluate true suppression of the cerebral blood flow (CBF). In all animals paling of the eyes and onset of mydriasis was clearly present during CPP-suppression. Paling of the eyes was particularly easy to evaluate in these albino animals.

Close observation of the MAP and ICP waveforms shows the exact duration of zero-CPP, caused by an ICP which is maintained slightly above the systolic pressure, resulting in a complete suppression of the CBF\(^{10}\).

Analysis of the ICP pressure waveform shows a very reproducible pattern of the PP\(_{ICP}\) in relation to the CPP. Figure 5 illustrates that when the ICP is increased slowly towards the arterial pressure, the PP\(_{ICP}\) increases and has its maximum when the ICP equals the diastolic pressure. When the ICP increases further to above the systolic pressure, the PP\(_{ICP}\) decreases to almost zero.
After cessation of the infusion, a fast drop of the ICP occurs. Figure 6 shows the exponential descent of the ICP from 100.3 mmHg to its baseline value. In this case, the pressure drops to 1/e (= 37%) of the plateau pressure value within 2.4 seconds, thus \( \tau = 2.4 \) seconds.

For all cases, \( \tau \) was 2.5 ± 1.2 seconds (mean ± SD), illustrating a fast recurrence of the ICP to baseline values after cessation of the infusion.

Histologic analysis showed that except for one animal, no haemorrhagic injury was inflicted during the procedure. In this animal, a haemorrhagic zone was observed in the periventricular white matter. All animals were evaluated for signs of ischaemia in the hippocampal neurons. No infarctions could be demonstrated. In the animals of the S-group that survived the procedure, 22 ± 23 % (mean ± SD) of hippocampal CA1-cells were pycnotic.
Discussion

Neuroendoscopy is increasingly applied in the treatment of intracranial pathology. Despite the minimal invasive nature of this technique, important morbidity and even mortality can occur as a result of intracranial circulatory insufficiency and haemodynamic reflexes. Since extensive manipulation of cerebral structures during difficult surgical procedures often coincides with higher rinsing flows, it is impossible to clearly differentiate the cause of these haemodynamic changes between direct stimulation of the brainstem and a genuine Cushing reflex.

In order to investigate the cerebral hydrologic and haemodynamic impact of intracranial hypertension as a result of an isolated high rinsing pressure, we used a simple model for ICP related manipulation of cerebral blood flow, devoid of any direct traumatic effects on brain structures.

Our technique of providing stereotactic access to the CSF has the advantage of a very reproducible and minimal invasive setup, which permits precise control of the ICP without direct manipulation of the brain structures. This method allows investigation of the influence of isolated intracranial hypertension on the haemodynamics without interference caused by direct cerebral stimulation or distortion of brain structures. Because of the minimal invasive nature, the animals can easily be awakened after the procedure to allow post-interventional evaluation. Additionally, this model allows precise determination of the rate of fluid resorption related to the ICP. Our previous research indicated that a remarkably high ICP up to 150 mmHg can arise very quickly during neuroendoscopy, which may remain unnoticed when no ICP-monitoring is used. These high pressures occur for instance when heavy rinsing is required for surgical reasons. Since this might induce important translocation of rinsing fluid to the vascular system, we determined the rate of intracranial fluid resorption related to the ICP.

In the N-group, a very pronounced hypertension (fig. 2a) occurred together with a relatively modest bradycardia or tachycardia (fig. 2d). In order to determine the haemodynamic effects of sustained CPP suppression, we kept increasing the ICP in order to maintain the ICP above the systolic pressure. Despite a complete suppression of the CPP, only a modest change in heart rate is observed. Although the arterial pressure tended to decrease during minute-long CPP-suppression, it still remained well above the initial arterial pressure for many minutes. Several minutes after lowering the ICP to baseline levels, three of the five animals died from obvious pulmonary edema.

This phenomenon has two important consequences that must be solved. The Cushing reflex generates a morbid hypertension that may have a direct impact on the brain and in many cases results in haemodynamic collapse as a result of pulmonary
edema. Secondly, the high MAP necessitates very high intracranial infusion rates of up to 8 ml/min in order to suppress the CPP. The haemodynamic collapse can be caused either by brain ischaemia or by an extreme Cushing reflex due to the intracranial hypertension. In order to differentiate between these two causes, we developed a strategy to lower the initial MAP and to blunt the Cushing reflex, necessitating only a modest secondary increase of the ICP to keep the CPP suppressed.

Administration of labetalol prior to the initiation of the CPP suppression clearly reduces the initial MAP and the secondary hypertension. Still, important hypertension occurred, which necessitated high inflow rates to maintain the CPP suppressed. In these animals, we saw a tendency towards relative bradycardia but even after minutes of complete CPP-suppression there was no evolution to severe bradycardia. The absence of tachycardia was expected after the administration of labetalol. Again, only several minutes after CPP-suppression, two of the three animals in the L-group died, because of pulmonary edema.

As we had no a priori knowledge of the expected outcome, no statistical sample size determination was performed. Since the mortality rate in the N- and L-group was so high, it was considered unethical and useless to continue this strategy. As a second strategy to mitigate the cardiovascular consequences of the Cushing reflex, we increased the sevoflurane concentration to 8%. This induced a significant initial decrease of the MAP (fig. 2c) and HR (fig. 2f). After increasing the ICP, a very reproducible increase of the MAP together with an obvious tachycardia developed. Initially, it was not known whether the animals would awaken after complete CPP suppression of several minutes. As the animals awoke normally, in the subsequent experiments, the time of CPP suppression was increased in order to be able to determine the sequence of haemodynamic events during long-lasting CPP suppression and to differentiate the cause of morbidity or mortality between brain ischaemia and other reasons. In none of the animals, bradycardia was observed. This indicates that when relative bradycardia is induced by anaesthetic drugs, this may completely mask the bradycardia of the Cushing reflex, while still allowing a very important tachycardia to develop. Anyway, in the sequence of events in every animal in the three groups, we never saw a sudden severe bradycardia during the hypertensive phase. The fact that a comparable degree of CPP suppression occurred in all three groups, suggests that the animals in the N and L group died as a result of haemodynamic collapse or pulmonary edema, but not because of cerebral ishaemia. The higher infusion rates in the N and L group potentially could induce fatal brain herniation, but the late onset of haemodynamic collapse and the clinical presentation point towards a genuine cardiovascular collapse as the cause of death.

When the ICP is higher than the MAP, theoretically the CBF should be interrupted. We assessed this assumption in different manners. Observation of the eyes of these albino-rats showed a distinct pallor at the moment of CPP suppression. Also, the naturally existing miosis turns into a mydriasis. After return of the CPP to the original
value, there is an immediate return of the reddish colour of the eyes and a return of
the miosis a few minutes later. Close evaluation of the pulse pressure of the ICP-
waveform also suggests true CBF-suppression. When the ICP is low, only a modest
$PP_{ICP}$ can be seen. When the ICP equals the MAP, the $PP_{ICP}$ increases to its
maximal value. When the ICP increases further above the MAP, the $PP_{ICP}$ decreases
and minimizes to almost zero when the ICP is above the systolic pressure (fig. 5).
This observation could be of clinical significance. Since the measurement of the
actual ICP is not always accurate in human neuro-endoscopic procedures\(^{12}\), an
observed increase of the $PP_{ICP}$ suggests that the ICP is approximating the MAP,
even when the measured ICP-level might suggest otherwise (fig. 5).

We witnessed a very remarkable capacity of the CSF autoregulative system to resorb
the infused fluid at high ICP. In animal N5, 25 ml of fluid is resorbed in two minutes
time. This equals $\pm$ 5% of the body weight. More evidence of the high rate of fluid
resorption is the remarkably fast drop of the ICP within a few seconds (fig. 6) after the
continuous flow is suddenly stopped. Thus, the total amount of infused fluid is
translocated into the circulation. In these rats of 500 g, an ICP of 100 mmHg induces
a fluid translocation of 2 ml/min; an ICP of 190 mmHg induces a fluid translocation of
even 8 ml/min. It is very speculative to extrapolate these flows to human cases, but if
a weight ratio is used, which is probably an overestimation, in a person of 60 kg this
ICP of 100 mmHg would result in a translocation of 240 ml/min. Although no one
would deliberately induce such an ICP, our previous work\(^2\)\(^{12}\) has shown that these
pressures do occur sometimes and may remain unnoticed if the CPP remains
adequate; certainly if the reflective (and protective) hypertension and tachycardia is
not recognised as a genuine Cushing reflex and no ICP-monitoring is done.

A ubiquitous drop in haematocrit during the few minutes of CPP-suppression
confirms that the fluid is translocated to the vascular compartment (fig. 4). Conversely, this indicates that when rinsing activity of the ventricular cavities during
clinical practice induces high ICP-levels, important translocation of fluid will occur.

Interestingly, although brain ischaemia was induced for several minutes, many of the
animals recovered without any obvious sign of cerebral damage; some had transient
paresis of the hind paws, which resolved after 24 hours. Histological analysis
however showed signs of ischaemic injury with an increased number of pycnotic
neurons in the hippocampus. This indicates that a normal awakening of the patient
after an apparently uneventful narcosis may not exclude important CPP suppression
and even ischaemic injury. The number of pycnotic cells in the most vulnerable brain
regions of the rats show that a clinically ‘complete recovery’ may not be equal to
perfect cerebral protection during the procedure.

A limitation of the study is the use of high doses of sevoflurane to control the
haemodynamic reflex. Artru\(^{13}\) demonstrated that up to 3.7% of sevoflurane has no
influence on CSF formation or reabsorption, but the used concentrations in our study
may have had an effect on the CSF translocation. Sevoflurane impairs CBF autoregulation\textsuperscript{14}; however, since the CPP was decreased very fast to zero, the influence of the high concentration on the time of complete CPP suppression should be small.

In conclusion this study shows that in rats, when haemodynamic reflexes are induced by isolated intracranial hypertension, it always consists of hypertension, but the absence of bradycardia does not exclude even complete CPP suppression. Moreover, in many cases, a severe tachycardia is the only and very distinct constituent of the induced Cushing reflex. The only instances of severe bradycardia we witnessed were after multiple minutes of stern CPP-suppression when total haemodynamic collapse was near. Furthermore, this bradycardia only developed after the animal was already severely hypotensive; thus we never saw a severe bradycardia in the hypertensive phase. This partially confirms our clinical observations\textsuperscript{2,12–15} that hypertension and tachycardia should be the first sign to look for when severe intracranial hypertension is suspected. Additionally we have shown that important translocation of the rinsing fluid may occur during high rinsing pressures. As these high rinsing pressures may not induce observable haemodynamic changes as long as the CPP is adequate, we would suggest using ICP-monitoring to detect intracranial hypertension.

Even if pharmacological intervention prevents haemodynamic disturbance caused by a severe Cushing reflex, a high iatrogenous ICP may induce important morbidity or even mortality, possibly because of uncontrolled rinsing fluid translocation. Although in this experimental setup the sevoflurane group had a clearly higher survival rate than the other groups, in our opinion no conclusion can be drawn on the protective therapeutic potentials of these agents for the management of patients.

These results confirm that in clinical practice, both invasive arterial pressure monitoring and ICP-monitoring are imperative during neuro-endoscopy. Since high ICP-levels will remain concealed on arterial pressure monitoring as long as the CPP is adequate and ICP-monitoring alone is not always accurate, both measurements are indispensable to protect the patient against the hazards of endoscopic neurosurgery. Moreover, the onset of a Cushing reflex can be used as the ultimate monitoring tool whenever a dangerously decreased CPP would remain concealed. However, the histological examination shows that the cause of the Cushing reflex should be defined immediately and remedied as soon as possible.

The swift increase of the ICP after initiation of the fluid infusion, together with a tau of $2.5 \pm 1.2$ seconds, demonstrates that this model allows an accurate control of the duration of the whole brain ischaemia. Moreover, histological evaluation shows that this method rarely induces cerebral bleeding.
References

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