

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

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**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 (Hct) 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 7 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 Hct decreased from 41 to 35 over the minutes of CPP suppression. After cessation of the infusion, the ICP decreased to 37% of the plateau pressure within 2.5 s. In the first few minutes after restoration of normal ICP, five animals died because of pulmonary oedema.

**Conclusions.** 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 oedema.

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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, whereafter 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,<sup>1</sup> 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<sup>2–4</sup> 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 necessitate 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.

Ever since Cushing<sup>5</sup> and others started investigating the haemodynamic effects of intracranial hypertension, all animal models were based on epidural volume expansion, using direct epidural fluid infusion, balloon inflation, or traumatic injury. Since the intracranial hypertension during endoscopic neurosurgery is induced by ventricular volume expansion, the aforesaid methods may not be accurate as a model for studying haemodynamic changes during neuroendoscopy.

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 O<sub>2</sub> (30%) and N<sub>2</sub> (70%). After spontaneous movements stopped, the concentration was increased to 4%; we waited for another 30 s 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

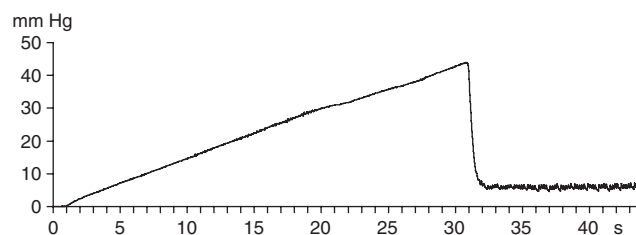
facilitate intubation, sevoflurane 8% was administered through the catheter under direct vision<sup>6</sup> of the vocal cords until they were immobile and standing wide open. Then, the animals could smoothly be intubated. After securing the airway, sevoflurane was set at 2% and the animals were positioned in a stereotaxic frame. A syringe pump with a constant flow rate of 0.02 ml min<sup>-1</sup> was connected to the arterial line. 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 skull and the atlas into the cisterna magna for access to the 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's 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, MA, USA) and a flow of 0.04 ml h<sup>-1</sup> 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 decreased to a pulsatile waveform matching a normal ICP of 5 (SD 2) mm Hg (Fig. 1).

Then, the needle was left in place for continuous ICP monitoring and ICP manipulation.

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 acoustic meatus. Locating both pressure transducers at the same level allows accurate calculation of the CPP [CPP=mean arterial pressure (MAP)–ICP]. Both pressure waveforms were continuously recorded at 100 Hz on a PC using the S5 collect<sup>®</sup> software for subsequent offline analysis.

As no spontaneous movement was observed during the animal preparation, the degree of analgesia and hypnosis



**Fig 1** Example of pressure waveform during placement of the occipital needle. A linear pressure increase during tissue penetration is followed by a sudden decrease upon entering into the cisterna magna. At that moment, a pulsatile waveform matching a normal ICP of around 6 mm Hg is observed. Low-frequency ventilatory pulsations are superimposed to high-frequency cardiac pulsations.

was considered adequate. The animals were then paralysed with cisatracurium  $0.2 \text{ mg kg}^{-1}$  and ventilated by controlled intermittent positive pressure ventilation with a tidal volume of  $12 \text{ ml kg}^{-1}$  and a frequency of 50 bpm. After an equilibration period of 5 min, arterial blood samples were obtained for haematocrit (Hct), pH,  $P_{\text{O}_2}$ , and  $P_{\text{CO}_2}$ . If necessary, ventilator settings were adjusted to obtain an arterial  $P_{\text{CO}_2}$  between 32 and 38 mm Hg. A rectal temperature probe was placed for core temperature monitoring, which was maintained at  $37.0^\circ\text{C}$  by a heating pad. In total, 20 animals were used. After baseline measurements with 5 min of stabilization, another dose of cisatracurium was given.

### *Induction of intracranial hypertension*

The ICP was then slowly increased using the syringe-pump connected to the ICP 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 arterial pressure. During suppression of the CPP, a distinctive Cushing reflex developed as expected.<sup>5,7</sup> 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 s, 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. The total volume of fluid infused into the subarachnoidal space was recorded and an arterial blood sample was obtained for Hct, pH,  $P_{\text{O}_2}$ , and  $P_{\text{CO}_2}$ . 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 (three out of five) 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 pretreated with repetitive boluses of labetalol  $50 \mu\text{g}$  until additional boluses did not 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 arterial pressure was lowered to 55 mm Hg 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 normalization of the ICP, the animals were kept anaesthetized for at least 1 h 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 in the following hours. Any abnormal behaviour or motoric dysfunction was registered. If suffering was suspected, the animal was killed (intraperitoneal pentobarbital  $150 \text{ mg kg}^{-1}$ ).

### *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 MAP 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 ( $\text{ICP}_{\text{Baseline}}$ ). In order to evaluate the influence of the ICP on the cerebral perfusion, several parameters were examined. The MAP and HR before 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 ( $\text{PP}_{\text{ICP}}$ ) was calculated as the difference between the systolic and diastolic ICP and graphically represented together with the MAP, ICP, and CPP waveform. The lowest and highest  $\text{PP}_{\text{ICP}}$  during the procedure were detected and analysed in relation to the ICP and CPP. It was assessed whether  $\text{PP}_{\text{ICP}}$  suppression occurred at the moment of  $\text{CPP} \leq 0 \text{ mm Hg}$ .

At different infusion rates of Ringer's solution into the CSF, the plateau pressure ( $\text{ICP}_{\text{Plateau}}$ ) 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<sup>8</sup>—was also calculated based on the pressure waveforms and related to the MAP.

### *Histological evaluation*

On day 8 of the experiment, the animals were killed with an intraperitoneal injection of pentobarbital  $150 \text{ mg kg}^{-1}$  and then decapitated. The animals that died during the procedure, or that were killed in the first 24 h after it, were excluded from histological analysis.

**Table 1** Experimental parameters. N group, no precautions; L group, labetalol; S group, sevoflurane. ICP, intracranial pressure; MAP, mean arterial pressure; HR, heart rate; PP, pulse pressure

Group	ICP baseline (mm Hg)	MAP baseline (mm Hg)	HR baseline (beats min <sup>-1</sup> )	ICP max (mm Hg)	MAP max (mm Hg)	HR max (beats min <sup>-1</sup> )	Ischaemic time (s)	PP min (mm Hg)	PP max (mm Hg)	Infused fluid (ml)
N group, mean (sd)	5 (1)	80 (10)	346 (36)	214 (23)	179 (29)	371 (74)	231 (125)	1 (0.44)	14 (7.66)	13.25 (2.75)
L group, mean (sd)	5 (2)	68 (5)	329 (34)	216 (57)	148 (11)	345 (49)	207 (54)	2 (0)	11 (1.52)	14.16 (6.29)
S group, mean (sd)	4 (1)	38 (5)	183 (74)	175 (42)	116 (21)	345 (33)	276 (135)	1 (0.5)	7 (3.43)	14.00 (3.08)

The brain was fixed in 10% buffered formaldehyde for at least 12 h. After adequate fixation, the brain was embedded in paraffin, and serial sections (5  $\mu$ m thick) were cut and stained with haematoxylin and eosin, before 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.<sup>9</sup>

## Results

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

Upon entering the subarachnoid space, a waveform with cardiac pulsations superimposed on ventilatory oscillations confirmed correct placement of the needle (Fig. 1). The initial ICP was 5 (2) mm Hg [mean (sd),  $n=15$ ] in all animals. A summary of all measured values is given in Table 1. The evolution of the MAP and HR in the first 200 s of induction of intracranial hypertension is presented in Figure 2.

In a first series of experiments (N group,  $n=5$ ), the CPP was suppressed for 231 (125) s. In all animals, a Cushing reflex (Fig. 3), consisting of a clear hypertension and bradycardia or tachycardia, occurred after induction of intracranial hypertension (Fig. 2A and D). The PP<sub>ICP</sub> decreased from a maximal value of 14 (8) to 1 mm Hg when the ICP increased above the systolic arterial pressure. Of the five animals in the N group, two animals survived the procedure. The three animals that did not survive showed severe pulmonary oedema, 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) s. Again, the PP<sub>ICP</sub> was suppressed from a maximal 11 (2) to 2 mm Hg. The hypertension was blunted to a maximum MAP of 148 (11) mm Hg (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 oedema. The animal that did

survive showed a spastic paralysis of the hind paws, which resolved within 24 h.

In the S group ( $n=12$ ), administration of sevoflurane 8% strongly decreased the MAP and the HR. In five animals, bradyarrhythmia developed before the induction of intracranial hypertension because of the high sevoflurane concentration; this condition subsided within seconds after increasing the ICP (Fig. 3). The CPP was suppressed for 247 (101) s. The MAP increased only to 116 (21) mm Hg and the HR to 345 (33) beats min<sup>-1</sup>. In all animals, the Cushing reflex consisted of an unambiguous onset of hypertension and tachycardia (Fig. 2F). The PP<sub>ICP</sub> was suppressed from 7 (3) to 1 (0) mm Hg during total CPP suppression. At the moment of maximal PP<sub>ICP</sub>, the CPP was 4 (5.8) mm Hg.

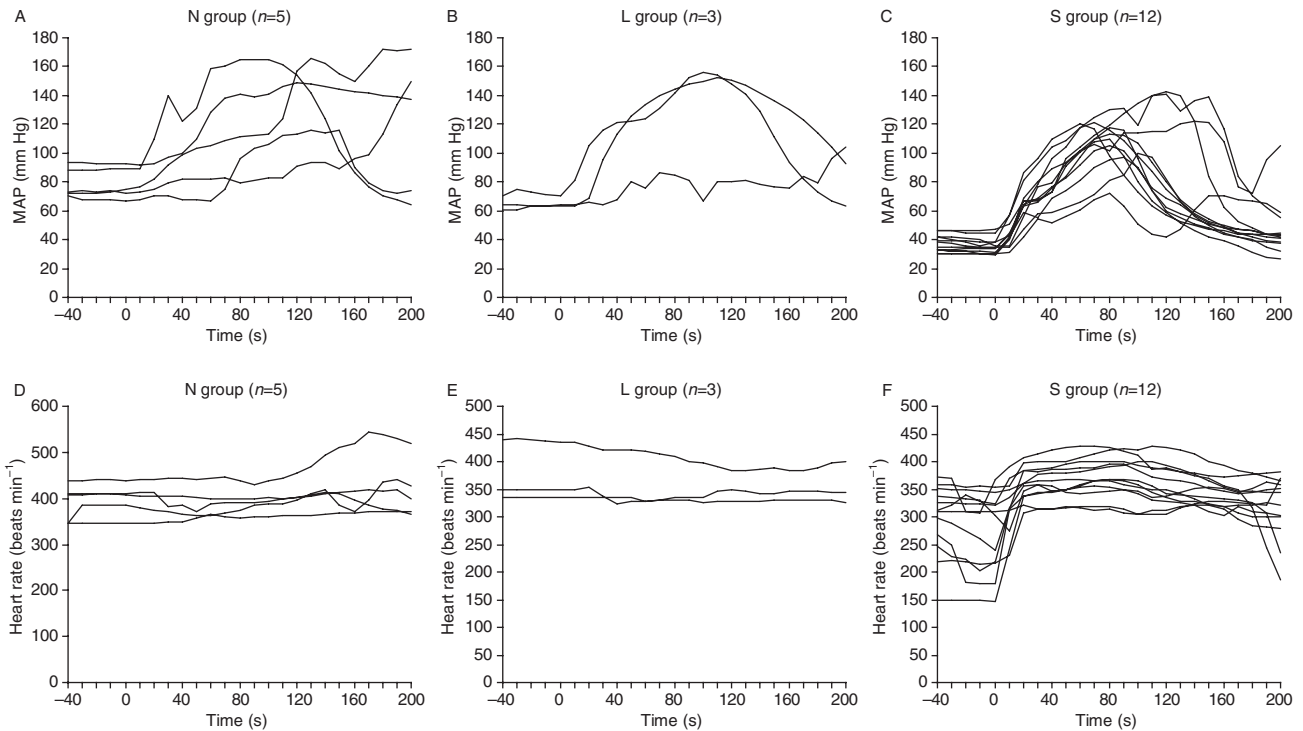
After the intracranial fluid infusion was stopped, most animals showed an initial hypotension, followed by a prominent hypertension, which could efficiently be controlled by increasing the sevoflurane concentration during several minutes. Within 30 min, the arterial pressure tended to normalize. In the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

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 Hct, decreasing from 41.1 (3.0)% before CPP suppression to 35.2 (3.6)% ( $P<0.001$ ,  $n=10$ ) afterwards. Figure 4 shows the decrease in Hct level for individual animals.

All the animals of the S group survived the entire procedure. Six animals showed normal behaviour 1 h after recovery from anaesthesia. Five animals showed a transient paralysis of the hind legs, which resolved within 24 h. One animal (S11, with the longest CPP suppression time of 563 s) showed persistent paraplegia, and was therefore killed after 24 h. The remaining animals completely recovered from the ischaemic insult.

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



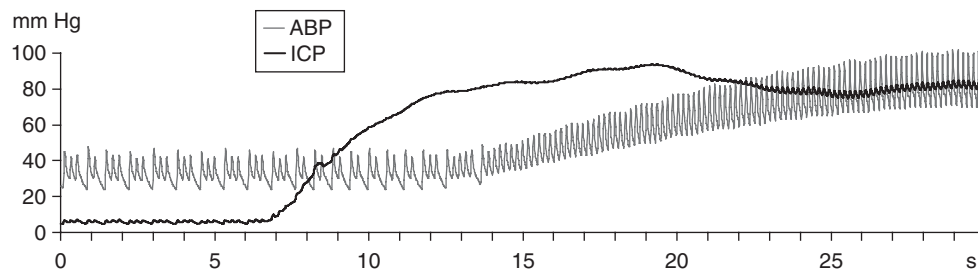
**Fig 2** The evolution of the MAP and HR during the first 200 s upon induction of intracranial hypertension. At time 0, the ICP is increased. A two-fold increase of the initial arterial pressure is seen in Groups N and L compared with a three-fold increase in Group S. In all three groups, the MAP increases significantly after induction of intracranial hypertension ( $P < 0.01$ ). In the N group, tachycardia and bradycardia are observed after induction of intracranial hypertension. In the L group, there is a tendency towards bradycardia. In the N and L groups, no significant change in HR 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 with 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.

complete suppression of the CBF.<sup>10</sup> Analysis of the ICP pressure waveform shows a very reproducible pattern of the  $PP_{ICP}$  in relation to the CPP. When the ICP is increased slowly towards the arterial pressure, the  $PP_{ICP}$  increases and has its maximum when the ICP equals the diastolic arterial pressure. When the ICP increases further to above the systolic arterial pressure, the  $PP_{ICP}$  decreases to almost zero (Fig. 5).

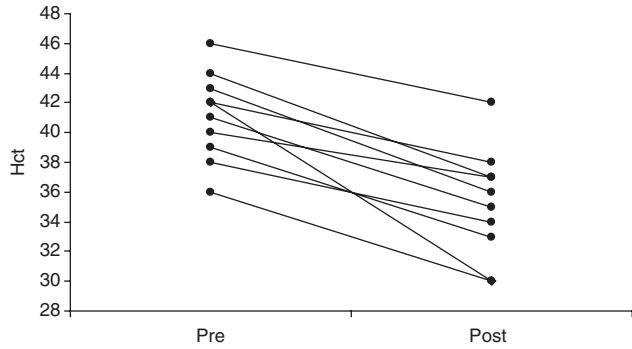
After cessation of the infusion, a fast decrease of the ICP occurs. Figure 6 shows the exponential descent of the ICP from 100.3 mm Hg to its baseline value. In this case, the pressure decreases to  $1/e$  ( $=37\%$ ) of the plateau

pressure value within 2.4 s ( $=\tau$ ). For all cases,  $\tau$  was 2.5 (1.2) s [mean (SD)], illustrating a fast recurrence of the ICP to baseline values after cessation of the infusion.

Histological 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 neurones. 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.



**Fig 3** Typical recording of the sudden change in arterial blood pressure (ABP) in response to an increased ICP during an S group experiment. Inspiratory sevoflurane concentration of 8% results in a low initial ABP and causes bradyarrhythmia. 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 s, an absent  $PP_{ICP}$  when  $ICP > ABP$ , and relatively high  $PP_{ICP}$  when  $ICP = MAP$ .



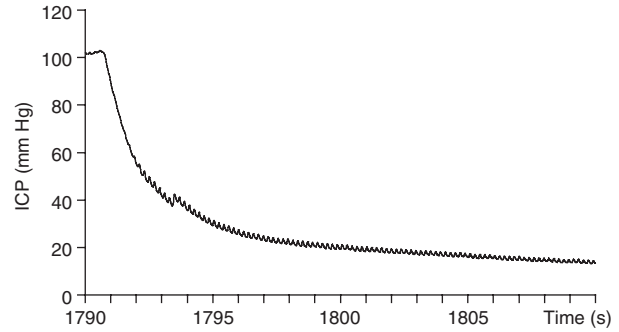
**Fig 4** Hct levels before and after CPP suppression indicate the infused fluid was resorbed into the vascular compartment. All samples are from the sevoflurane group. Since in some of the animals, the second blood sampling via the tail artery was not possible, only 10 coupled data points were obtained.

## 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<sup>11</sup> 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 CBF, devoid of any direct traumatic effects on brain structures.

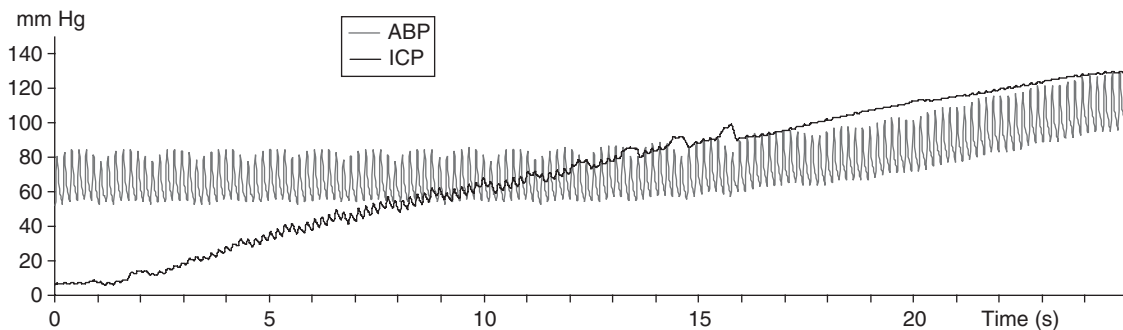
Our technique of providing stereotactic access to the CSF has the advantage of a very reproducible and minimal invasive setup, which permits precise control of the ICP without direct manipulation of the brain structures. This method allows investigation of the influence of isolated intracranial hypertension on the haemodynamics without interference caused by direct cerebral stimulation or



**Fig 6** After cessation of the infusion, the ICP decreases exponentially from 100.3 mm Hg to its baseline value. Within 2.4 s, the ICP has decreased to  $1/e$  (=37%) of its baseline value, thus  $\tau=2.4$  s.

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<sup>2 12</sup> indicated that a remarkably high ICP up to 150 mm Hg 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 occurred together with a relatively modest bradycardia or tachycardia. 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 arterial pressure. Despite a complete suppression of the CPP, only a modest change in HR 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 oedema.



**Fig 5** The pulse pressure of the ICP ( $PP_{ICP}$ ) shows a very reproducible pattern in relation to the CPP. When the ICP is low, a low  $PP_{ICP}$  is seen; when the ICP increases towards the ABP, the  $PP_{ICP}$  increases to its maximum, and when the ICP increases to above the systolic arterial pressure, the  $PP_{ICP}$  decreases to almost zero.

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 oedema. Secondly, the high MAP necessitates very high intracranial infusion rates of up to  $8 \text{ ml min}^{-1}$  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 before 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 oedema.

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 groups 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 and HR. 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 groups died as a result of haemodynamic collapse or pulmonary oedema, but not because of cerebral ischaemia. The higher infusion rates in the N and L groups 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 arterial pressure. This observation could be of clinical significance. Since the measurement of the actual ICP is not always accurate in human neuroendoscopic procedures,<sup>12</sup> an observed increase of the  $PP_{ICP}$  suggests that the ICP is approximating the MAP, even when the measured ICP level might suggest otherwise.

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 2 min. This equals  $\pm 5\%$  of the body weight. More evidence of the high rate of fluid resorption is the remarkably fast decrease of the ICP within a few seconds 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 mm Hg induces a fluid translocation of  $2 \text{ ml min}^{-1}$ ; an ICP of 190 mm Hg induces a fluid translocation of even  $8 \text{ ml min}^{-1}$ . 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 mm Hg would result in a translocation of  $240 \text{ ml min}^{-1}$ . Although no one would deliberately induce such an ICP, our previous work<sup>2, 12</sup> 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 recognized as a genuine Cushing reflex and no ICP monitoring is done.

A ubiquitous decrease in Hct during the few minutes of CPP suppression confirms that the fluid is translocated to the vascular compartment. 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, although some had transient paresis of the hind paws, which resolved after 24 h. Histological analysis, however, showed signs of ischaemic injury with an increased number of pycnotic neurones 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 and Momota<sup>13</sup> 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.<sup>14</sup> 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<sup>2 12 15</sup> 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 neuroendoscopy. 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 (1.2) s, 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.

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