Hemodynamic physiology during perioperative intracranial hypertension
Kalmar, A.F.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2011

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Value of Cushing reflex as warning sign for brain ischaemia during neuroendoscopy.

Modified from

* Selected by the BJA editorial board as CME-article
** best poster award on the Annual meeting of the

Alain F Kalmar¹, Jozef Van Aken¹, Jacques Caemaert², Eric P Mortier¹, Michel MRF Struys¹

1. Department of Anaesthesia, Ghent University Hospital, Gent, Belgium
2. Department of Neurosurgery, Ghent University Hospital, Gent, Belgium
Abstract

Background: During an endoscopic neurosurgical procedure (ENP) a sudden increase in intracranial pressure (ICP) may occur at any time. In the literature little attention has been paid to the early detection of such an increase. In particular the occurrence of a ‘Cushing reflex’ has not been discussed in this context. We now present a prospective study of haemodynamic changes during ENP.

Methods: In 17 consecutive patients who underwent an ENP under general anaesthesia, physiological data was recorded over the whole operative procedure. Monitoring included invasive blood pressure, intracranial pressure, electrocardiogram, end-expired carbon dioxide, pulse oximetry and heart rate. Pressure- and ECG waveforms were recorded at 100Hz and evaluated in a subsequent off-line analysis.

Results: In almost every case, the occurrence of hypertension and tachycardia was clearly the result of an increase in ICP. Also, in almost every case where the cerebral perfusion pressure (CPP) dropped below 15mmHg, a Cushing reflex developed. The occurrence of bradycardia was rather occasional and not systematically associated with a low CPP.

Conclusion: In this study, we describe the haemodynamic effects of an increased ICP during ENP and their respective sequence of events at high temporal resolution. Although most clinicians rely on the occurrence of bradycardia to diagnose intracranial hypertension during ENP, we show that a simultaneous onset of hypertension and tachycardia is a much faster approach to determine impeded brain perfusion. Waiting for a persistent bradycardia to alert the surgeon during ENP could allow severe bradycardia or even asystole to develop.
Introduction

The Cushing reflex
Classically, the “Cushing reflex” has been reported as the occurrence of hypertension, bradycardia and apnoea following intracranial hypertension\(^1\). Various animal physiopathological studies, describing haemodynamic changes following sudden increases in intracranial pressure (ICP), refined the findings of Cushing by showing an initial tachycardia associated with an hypertension before the onset of bradycardia\(^2\). These initial changes have not always received sufficient attention in the literature on neuro-endoscopy. The increases of intracranial pressure resulting in haemodynamic instability used to be observed as a phenomenon following a time course of hours, days or months depending on the underlying pathology (e.g.: subdural haematoma, tumours, hydrocephalus,...). At the moment of clinical presentation, symptoms already consisted of bradycardia and hypertension.

Acute intracranial hypertension during neuro-endoscopy
Since the introduction of neuroendoscopy\(^3\) in the treatment of cerebral pathology, the problem of early recognition of any sudden increase in intracranial pressure has become crucial. During this procedure, continuous rinsing of the ventricular cavities might cause a sudden ICP increase. As direct measurement of the ICP via the endoscope is not always accurate as the single parameter to detect cerebral hypertension, the anaesthetist classically relies upon sudden haemodynamic changes to alert the surgeon. Many clinicians still use the occurrence of bradycardia and hypertension as an indication of acute intracranial hypertension\(^4-7\). In a retrospective study, we showed that only focussing on these late symptoms allows a long lasting intracranial hypertension risking a higher incidence of possible deleterious complications Therefore, we concluded that the occurrence of hypertension and tachycardia offers the most reliable warning sign of an increased ICP during neuro-endoscopy. This presumption was made on a review of animal studies\(^2\) and clinical observations published in the last century\(^8\).

Aim of the study
However, accurate simultaneous measurements of mean arterial blood pressure (MAP) and ICP are essential to diagnose a decrease in the underlying cerebral perfusion pressure (CPP). As a precise description of the haemodynamic changes in relation to the ICP during neuroendoscopy is still lacking in the literature, the aim of this prospective observational study was to offer a high resolution description of this phenomenon. Additionally, it was aimed at investigating the most suitable parameters to alert the surgeon to prevent deleterious brain ischaemia, together with possible strategies to keep the cerebral perfusion at a safe level.
Methods

Patients

After Institutional Ethics Committee approval and written informed consent was obtained, haemodynamic data of consecutive patients between 01/02/2003 and 01/02/2004 who underwent neuro-endoscopy for the treatment of obstructive hydrocephalus or tumour surgery under general anaesthesia were recorded during the whole operative procedure. Their ages ranged from 1 month to 84 years.

Procedure and data recording

The patients were given no premedication. Upon their arrival in the operating room the usual monitoring was applied: electrocardiogram (ECG), pulse oximetry and blood pressure by automated cuff. In children, if inhalation induction was indicated because of difficulty in obtaining intravenous access, sevoflurane was used to permit intravenous cannulation. After securing the intravenous access as quickly as possible the sevoflurane was discontinued and the intravenous sequence instituted. In adults, anaesthesia was induced with propofol 1–2 mg/kg, remifentanil 0.1 µg/kg/min and the trachea was intubated (facilitated with cisatracurium 0.15 mg/ kg i.v.). Anaesthesia was maintained with propofol 6 mg/kg/h, remifentanil 0.1–0.2 µg/kg/min, together with cisatracurium 0.15 mg/kg/h; the patients were ventilated with an oxygen/air mixture (FIO2 : 40%) to have an end-tidal CO2 between 30 and 35 mm Hg. After induction, a 20-gauge 8 cm PE catheter (Laeder Cath, Laboratoires pharmaceutiques, Vygon 95440 Ecouen, France) was inserted percutaneously into a radial artery, 1 cm proximal to the wrist. The catheter was connected via a 150 cm long (1.5 mm internal diameter) rigid pressure tubing, filled with saline to a continuous flush pressure-transducer system (Becton Dickinson Critical Care Systems, Singapore) to monitor beat-to-beat blood pressure. The heart rate (HR) was monitored continuously via the ECG. All patients remained flat in the supine position with the head flexed, so that the burr hole was located at the apex. Patients were kept normothermic by a forced-air warming system. Once stable profiles of capnography and blood pressure were reached, ventilatory and drug delivery settings were kept unchanged. All vital signs were monitored using an S5-monitor (Datex-Ohmeda, Helsinki, Finland).

The rigid Caemaert endoscope (Wolf, Knittlingen, Germany) with an outer diameter of 6 mm was used. After positioning the patient and infiltration with a local anaesthetic, a burr hole was made at the classical entry point for endoscopic entry to the lateral ventricle and the standard neuro-endoscopical introduction was done. Once the endoscope was introduced into the ventricle or the cystic space, the mandrins of the two irrigation channels and of the working channel were retracted, and the inlet and outlet irrigation tubes were connected. The outlet of the endoscope flushing system was connected with a 300 cm long pressure tubing to a pressure-
transducer for continuous monitoring of the ICP\textsuperscript{4,6}. The level of the foramen of Monro was used as the zero-reference point for both pressure transducers.

During the introduction of the endoscope the optical element was already inserted in the correct channel. We then began irrigation with Ringer lactate at body temperature. We made sure that the distal end of the outflow tube was fixed at the same level as the burr hole, so that there was no siphoning effect or raised ICP. At moderate flushing rate of the endoscope, the pressure value reliably represents the intracranial pressure at the bottom of the fourth ventricle, as long as no obstruction or increased resistance occurs inside the endoscope. The inflow of the rinsing fluid is managed by the surgeon. Using the same zero-reference point for both transducers allows a precise determination of the cerebral perfusion pressure, independent of patient positioning. Both systems were calibrated against atmospheric pressure and both pressure-transducers were connected to a S5-monitor (Datex-Ohmeda, Helsinki, Finland). All data from the monitor were recorded via the Collect Software\textsuperscript{®} (Datex-Ohmeda, Helsinki, Finland) for subsequent off-line analysis. There was a numerical recording of all parameters at 0.2 Hz. In addition, waveforms of ECG, invasive arterial pressure and intracranial pressure were registered at 100 Hz.

Data analysis and statistics
In subsequent off-line analysis, the data were transformed to an ASCII-file and imported in Microsoft\textsuperscript{®} Excel. Analysis of the waveforms was done using invasive arterial pressure (Art) signals and intracranial pressure (ICP) signals. After importing the values into Microsoft\textsuperscript{®} Excel, arterial and intracranial pressure waveforms, MAP, mean ICP, mean CPP en HR were determined. The CPP was calculated as MAP minus mean ICP. High-resolution waveforms at 100 Hz were visualised for detailed description of haemodynamic phenomena. Also trend curves were created at 1 Hz for whole-procedure evaluation of haemodynamic effects.

All data were analysed for possible events. Hereby, different classes of combined events were defined as shown in table 2. For changes in CPP, we defined an event as a decrease of CPP lower than 50 mmHg. Subsequent categories were defined as a CPP lower than 50, 40, 30, 20 and 15 mmHg. For changes in haemodynamics, we defined brady/tachycardia and hypo/hypertension as a change of 20 % from baseline during at least three seconds. Baselines were defined as the mean haemodynamic values in the minutes during the procedure before an increase of the ICP occurred. Since the administration of remifentanil was kept constant and this opiate may cause tolerance\textsuperscript{10} as well for analgesic as haemodynamic effects\textsuperscript{11}, rescaling of the baseline values was sometimes necessary. Haemodynamic changes during a CPP higher than 50 mmHg was defined as an isolated haemodynamic event and taken into account too.

A sensitivity/specificity analysis was done based on decreases of the CPP below certain levels and the incidences of cushing reflexes. In this assessment, we defined
a cushing reflex as a simultaneous occurrence of hypertension and tachycardia. The sensitivity of a cushing reflex to detect a CPP-drop below certain levels was determined as the number of CPP-drops coinciding a cushing reflex divided by the total number of these CPP-drops. The specificity of a cushing reflex in detecting a CPP-drop below a certain level, divided by the total number of observed cushing reflexes. For statistical analysis of the data, nonparametric correlations were determined using the SPSS 11.0 software (SPSS Inc, Chicago, USA).

Patient evaluation
All patients awoke in the operating room, and were directly transferred to the intensive care unit. For the assessment of post-operative complications, intensive-care files were evaluated for possible events. As described by Buxton and colleagues\textsuperscript{12}, possible complications in neuro-endoscopy are: delay in awaking, pneumoencephalus, pneumoventricle, convulsions, transient anisocoria, transient hemiparesis, haemorrhage, cerebral infarction, transient fever, meningism, infection, short-term memory loss, diabetes insipidus, inappropriate anti-diuretic hormone secretion, transient cerebrospinal leaks, chronic subdural haematomas, traumatic basilar aneurysm, hydrocephalus.

Results

Demographics
Data recorded (total recording time: 19.1 hours covering 10.9 hours of endoscopy) from 17 patients were analysed. Table 1 shows the individual demographics, haemoglobin and haematocrit level and glycaemia. Also shown is if there were clinical arguments for pre-operative intracranial hypertension of the patients. End-tidal CO\textsubscript{2} levels and body temperature stayed within limits in all patients.

Table 1 : biometrical and biochemical characteristics of the patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>V</td>
<td>V</td>
<td>M</td>
<td>M</td>
<td>V</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>8</td>
<td>9</td>
<td>21</td>
<td>19</td>
<td>84</td>
<td>71</td>
<td>20</td>
<td>3m</td>
<td>73</td>
<td>37</td>
<td>19</td>
<td>44</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>1m</td>
<td>62</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>27</td>
<td>40</td>
<td>78</td>
<td>70</td>
<td>60</td>
<td>70</td>
<td>70</td>
<td>3.4</td>
<td>54</td>
<td>58</td>
<td>70</td>
<td>80</td>
<td>45</td>
<td>37</td>
<td>44</td>
<td>3.15</td>
<td>83</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.2</td>
<td>12.4</td>
<td>16.1</td>
<td>12.1</td>
<td>11.8</td>
<td>13.7</td>
<td>14.0</td>
<td>8.6</td>
<td>11.4</td>
<td>14.4</td>
<td>14.0</td>
<td>12.7</td>
<td>14.9</td>
<td>13.3</td>
<td>13.4</td>
<td>9.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>37.2</td>
<td>35.3</td>
<td>45.5</td>
<td>37.7</td>
<td>35.0</td>
<td>41.6</td>
<td>39.6</td>
<td>27.5</td>
<td>34.8</td>
<td>40.6</td>
<td>39.5</td>
<td>35.4</td>
<td>42.5</td>
<td>38.6</td>
<td>41.3</td>
<td>29.3</td>
<td>37.5</td>
</tr>
<tr>
<td>Glucose (g/l)</td>
<td>0.96</td>
<td>0.82</td>
<td>1.14</td>
<td>1.09</td>
<td>0.91</td>
<td>0.84</td>
<td>0.96</td>
<td>1.11</td>
<td>1.13</td>
<td>1.09</td>
<td>1.04</td>
<td>1.34</td>
<td>0.83</td>
<td>1.11</td>
<td>0.9</td>
<td>0.66</td>
<td>1.54</td>
</tr>
<tr>
<td>Intracranial HT</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>


**Incidence and nature of haemodynamic events**

Table 2 shows for each patient the incidence of Hypertension (H), Tachycardia (T), Bradycardia (B) or Cushing reflex (H+T) in the seconds following a drop of the CPP to a certain level, together with the nature of the performed procedure and age of the patient. Also the incidences of haemodynamic changes with a normal CPP are mentioned (= isolated cases). Hypertension associated with tachycardia was prominently present when the CPP dropped below 15 mmHg. In higher CPP levels, less prominent changes were observed. In the last row, sum of all the events in the respective category is shown. The procedures are: revision of a ventriculoperitoneal shunt (revision), diagnostic ventriculoscopy (ventr.scopy), Pineal tumour resection (Tumour), third ventriculostomy (3VS), fenestration of a ventricular cyst (fenestr.) or biopsy of a pineal tumour (biopsy).

**Table 2 : incidence of haemodynamic events in related to the drop of the CPP.**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Procedure</th>
<th>Isolated</th>
<th>40 &lt; CPP &lt; 50</th>
<th>30 &lt; CPP &lt; 40</th>
<th>20 &lt; CPP &lt; 30</th>
<th>15 &lt; CPP &lt; 20</th>
<th>CPP &lt; 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>9</td>
<td>Ventr.scopy</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>Tumour</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>3VS</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>3VS</td>
<td>H+B</td>
<td>H+B</td>
<td>H+B</td>
<td>H+B</td>
<td>H+B</td>
<td>H+B</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>3VS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>3m</td>
<td>3VS</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>3VS</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>3VS</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>11</td>
<td>19</td>
<td>Tumour</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>12</td>
<td>44</td>
<td>fenestr.</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>13</td>
<td>11</td>
<td>3VS</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>Tumour</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>biopsy</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>16</td>
<td>1m</td>
<td>3VS</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>17</td>
<td>62</td>
<td>biopsy</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
<td>H+T</td>
</tr>
<tr>
<td>SUM</td>
<td>20</td>
<td>60 &lt; CPP &lt; 50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The sensitivity and specificity of a cushing reflex ( = a simultaneous occurrence of hypertension and tachycardia, defined as a 20% increase in HR and MAP ) to determine a decreased CPP is shown in table 3. Because in patient 14 multiple haemodynamic events occurred during tumour retraction, haemodynamic changes may have been induced by direct stimulation of the brainstem. Moreover, it was the only patient where severe bradycardia and hypertension was seen during a decreased CPP. Therefore, the sensitivity analysis was done using all patients and also with all patients except patient 14.

**Table 3 : The sensitivity and specificity of the cushing reflex to detect low CPP**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patient 14 excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>CPP &lt; 15 mmHg</td>
<td>93%</td>
<td>54%</td>
</tr>
<tr>
<td>CPP &lt; 20 mmHg</td>
<td>53%</td>
<td>65%</td>
</tr>
<tr>
<td>CPP &lt; 30 mmHg</td>
<td>29%</td>
<td>77%</td>
</tr>
<tr>
<td>CPP &lt; 50 mmHg</td>
<td>13%</td>
<td>77%</td>
</tr>
</tbody>
</table>

29
Figure 1 shows the relation between the CPP and the relative change in heart rate and MAP.

**Figure 1 : Relationship between CPP and Heart rate and MAP.**

![Graph showing the relation between CPP and heart rate and MAP.](image)

Figure 2 shows the relation between the ICP and the relative change in heart rate and MAP.

**Figure 2 : Relationship between ICP and Heart rate and MAP.**

![Graph showing the relation between ICP and heart rate and MAP.](image)

Table 4 shows the Spearman’s rho correlation coefficients between intracranial pressure/ cerebral perfusion pressure (ICP/CPP) and relative change in heart rate (%ΔHR) and mean arterial pressure (MAP). The correlation coefficients are calculated for all patients (all) and with patient 14 excluded (excl pt 14). A good correlation was found between the MAP and the ICP/CPP. Also a good correlation was found between the degree of tachycardia and the ICP/CPP. A weak correlation was found between the degree of bradycardia and ICP/CPP. Notably, there is a stronger correlation between the tachycardia/MAP and CPP than between tachycardia/MAP and ICP.
Table 4: Spearman’s rho correlation coefficients between ICP/CPP and ΔHR/ΔMAP.

<table>
<thead>
<tr>
<th></th>
<th>%ΔHR tachycardia</th>
<th>%ΔHR bradycardia</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP</td>
<td>0.589 / 0.638</td>
<td>-0.176 / 0.355</td>
<td>0.617 / 0.596</td>
</tr>
<tr>
<td>CPP</td>
<td>-0.659 / -0.687</td>
<td>0.256 / -0.248</td>
<td>-0.628 / -0.576</td>
</tr>
</tbody>
</table>

Figure 3: Illustrative cases of haemodynamic changes during neuro-endoscopy

Out of all events, we selected 3 illustrative cases. Figure 3A shows a particular haemodynamic event. A sustained ICP of 50 mmHg over 90 seconds induced no haemodynamic changes. This may be explained by the fact that the CPP was over 35 mmHg. At second 2490, the ICP further increased resulting in a drop of the CPP and the occurrence of a tachycardia and hypertension. After alerting the surgeon, the pressure was released leading to normalisation of the ICP and haemodynamics.
within 120 seconds. Figure 3 B plots a slower increase of ICP accompanied with a marginal increase in MAP and an initial moderate decline of the heart rate. At 4285 seconds, a sudden additional increase in ICP is seen together with an abrupt severe bradycardia. After 20 seconds, the heart rate recovers promptly. In figure 3 C, a manifest Cushing reflex in a baby of only 3 months old is illustrated. In this case, the baseline CPP was 39 mmHg since the normal MAP is much lower at that age. In this patient, we see hypertensive adaptation at an ICP of 10 mmHg and tachycardia at 34 mmHg. Neither patient suffered any of the post-operative complications mentioned by Buxton and colleagues.

**Discussion**

During neuro-endoscopic procedures, early recognition of an excessive increase in ICP, jeopardizing brain perfusion, is of major importance for preserving cerebral homeostasis. Isolated or combined bradycardia and hypertension are commonly used during neuro-endoscopy to alert the surgeon for increased ICP or mechanical stimulation of the floor of the third ventricle. ICP or Doppler flow measurements have been used to evaluate cerebral perfusion. However, in a retrospective study, Van Aken and colleagues concluded that tachycardia occurred as frequently as bradycardia during neuro-endoscopy. It was hypothesised that the tachycardia coincided mostly with an increase in ICP, caused by high-speed fluid irrigation or obstruction of the outflow tube. The observed tachycardia was nearly always accompanied by systemic hypertension. These signs might be seen as an atypical Cushing response. Unfortunately, no ICP was registered in the retrospective study, because at that time, the surgeon started his endoscopic procedures using a two-channel cystoscope, not allowing measurement of the ICP. The classic response, as described by Cushing in 1901, consists of apnoea, increased blood pressure and bradycardia. Therefore, it might be interesting to further prospectively evaluate the adequacy of the occurrence of haemodynamic alterations for assessing the cerebral perfusion status during these procedures by simultaneously measuring heart rate, arterial and intracranial pressure.

We investigated the correlation between CPP and the occurrence of haemodynamic changes. We defined haemodynamic changes as a change of 20% from baseline for at least three seconds. Rescaling of the baseline values was sometimes necessary to eliminate slow haemodynamic changes caused by long-term anaesthesia, but it was only done after at least two minutes of haemodynamic steady-state and ICP-levels below 5 mmHg. In our opinion, this is defendable and desirable since we are focusing mainly on the fast haemodynamic changes following increased ICP and decreased CPP. As shown in table 2, a drop of the cerebral perfusion pressure (CPP) to below 15 mmHg always results in a Cushing reflex. In 14 of the 15 cases, hypertension
accompanied by tachycardia occurred, in 1 of the 15 cases, a combination of hypertension and bradycardia was revealed.

It only makes sense to use this detection technique if a high sensitivity/specificity level can be reached. Therefore, a sensitivity and specificity analysis was performed as shown in table 3. It can be seen that a simultaneous occurrence of hypertension and tachycardia, defined as a 20% increase in HR and MAP, has a sensitivity of 93% to detect a decrease of the CPP below 15 mmHg. Furthermore, the single case where no tachycardia was seen, was in patient 14 during tumour retraction where we saw an abrupt bradycardia, which may have prevented the emergence of tachycardia because of direct stimulation. A drop of the CPP to between 15 and 30 mmHg often results in a Cushing reflex, but frequently causes a clean hypertension without tachycardia or bradycardia. A drop of the CPP to between 30 and 40 mmHg almost never results in a Cushing reflex. When we omit patient 14 in the analysis, the sensitivity of a cushing reflex to detect a severely decreased CPP becomes even stronger. The occurrence of a simultaneous hypertension and tachycardia during the endoscopic procedure has a specificity of 77% (20/26) in detecting a decrease of the CPP to below 30 mmHg.

It has to be stated that a CPP lower than 50 mmHg not always resulted in haemodynamic changes as observed in table 2. Moderate lowering of the CPP evokes an isolated adaptive hypertension within seconds due to an unexplained mechanism. Remarkably, this - often modest – increase in blood pressure induces an increase in CPP. In all cases where the blood pressure increased following a moderate CPP drop, the hypertension seemed controlled and aiming for a normalisation of the CPP at a level between 35 and 50 mmHg, as illustrated in figure 3A. Since the adaptive increase of the MAP may result in a normalisation of the CPP, one can consider such phenomena as a protective and effective action of the brain for preserving an adequate CPP despite an increased ICP. Beiner and colleagues proved that such an increase in the mean systemic arterial pressure restores the cerebral blood flow to approximately normal levels\textsuperscript{15}.

Only when the increase of the ICP was too fast for adaptation and consequently the CPP dropped below a threshold level between 15 and 30 mmHg a tachycardia developed. Within seconds after the CPP dropped below a threshold (in most patients around 15mmHg), a prominent uncontrolled increase in MAP and HR occurred resulting in a considerable overshoot of the CPP. Though, if the CPP is restored quickly (due to the increased MAP or due to decreased ICP), a normalisation of the MAP and HR is seen within minutes. Even in these instances, if an increased ICP imposes an increased MAP for preserving the CPP, the MAP only normalises up to the required value. Therefore, one can state that exclusively measuring the ICP, without taking into account the MAP, might result in misleading conclusions regarding cerebral perfusion. As observed in two small children aging 1 and 3 month, an ICP considered tolerable in general, may in some instances of low MAP be unacceptably high. This is in agreement with previous observations by

33
Fabregas and colleagues\textsuperscript{6,13}. They have tried to solve the problem of early recognition of any increase in intracranial pressure (ICP) by measuring the pressure inside the neuro-endoscope. They observed a lack of systemic changes accompanying high peak intra-endoscopic pressures, making it difficult to believe that these pressures really reflect the ICP.

These results might suggest to pharmacologically increase the MAP in order to allow higher ICP-values, though this could also increase the risk of bleeding or other adverse effects. An optimal MAP could be determined together with the surgeon, based on the patient’s risk factors and type of procedure.

Haemodynamic alterations occurred more frequently when lowering the CPP, as concluded from figures 1A and B. When considering the changes in heart rate, a more pronounced incidence of tachycardia was seen at lower CPP. As shown in table 4 there is a stronger correlation of 0.589 and −0.659 between the degree of tachycardia and the ICP/CPP respectively than the weaker correlation of −0.176 and 0.256 found between the degree of bradycardia and the ICP/CPP respectively.

Direct stimulation of the floor of the third ventricle may induce both hypertension and hypotension, together with bradycardia or tachycardia\textsuperscript{16}. Possibly, the underlying cause of bradycardia is different from tachycardia, as postulated by El-Dawaty\textsuperscript{5}. He specifically focused on the incidence of bradycardia during endoscopic third ventriculosity. It was postulated that the bradycardia is the result of stimulation of the floor of the third ventricle by the endoscope\textsuperscript{4,5}, or caused by distortion of the posterior hypothalamus\textsuperscript{17}. As can be seen in table 2, the initial manifest bradycardia following a CPP drop was seen only in one patient, although in this patient it was seen multiple times. As such, this patient represents all episodes of bradycardia at CPP levels lower than 50 mmHg in our table 2. All these cases of isolated bradycardia coincided with manipulation of the tumour and may well be due to direct mechanical stimulation; the increased ICP may well be coincidental and not the cause of the bradycardia, as suggested in figure 1A and 1B.

Probably, the Cushing reflex was obscured by mechanical stimulation in an attempt to remove a pineal tumour. One of the severe bradycardic periods in this patient is illustrated in figure 3B. In table 4, the correlation coefficients are shown for all patients and with patient 14 omitted. Remarkably, after exclusion of patient 14, the correlation between the CPP and bradycardia even reverses. Most importantly, the correlation between ICP/CPP and bradycardia is almost absent while the correlation between ICP/CPP and tachycardia becomes even stronger.

These data suggest that under a stable anaesthetic condition, severe haemodynamic changes that are not associated with tumour retraction are most likely due to compromised CPP. Furthermore, in these cases, we almost exclusively observed tachycardia and hypertension, and no bradycardia. The anaesthetic used (TIVA and remifentanil) tends to give relatively slow heart rates, which may explain why relative bradycardia is less frequently seen, since the analysis is based on relative changes to baseline. It might be that other general anaesthesia techniques give different
haemodynamic responses. Nevertheless, other causes of haemodynamic changes must be considered during endoscopy. For instance, bradycardia might be caused by the pressor reflex (end of figure 3A), due to iatrogenous hypertension, during normal brain perfusion. In these cases, only precise knowledge of the CPP values can permit us not to disturb the surgical proceeding. Therefore, it is crucial to correlate the observed haemodynamic instability with the ICP measured via the endoscope. As observed in traumatic brain injury in infants, open fontanels and/or sutures do not preclude the development of intracranial hypertension. We recorded a clear Cushing reflex in a 1 and 3 month old child as illustrated in figure 3C.

In the literature, there is no consensus about safe ICP-values during neuroendoscopic interventions. Our research suggests that the seeking of such a safe and convenient ICP value is doomed to fail, since the brain perfusion is regulated by the CPP. Our observations of the haemodynamic effects of the ICP and CPP show that no observable effects are seen with a CPP above 40 mmHg, independent of the ICP.

Due to ethical and medical considerations, we did not investigate the haemodynamic effect during long lasting periods of a decreased CPP. When an increased ICP coincided with a haemodynamic change, the surgeon was informed and the ICP was lowered immediately. As a result, we have not evaluated possible post-tachycardial bradycardia as classically described by Heymans. Further animal experiments could be done to confirm this sequence of events during longer lasting iatrogenous ICP-increases.

**Conclusion**

We have shown that the onset of a Cushing reflex is a reliable sign of unsafe increase in intracranial pressure (ICP) and hence a dramatic decrease in CPP during neuroendoscopy. We showed that in most cases a sudden decrease of the CPP below a threshold of 20-30 mmHg is quickly followed by a Cushing reflex. In contrast, a slow decrease of the CPP is often corrected by an adaptive increase of the MAP. The meticulous assessment of the perfusion pressure is the only valid variable to assess brain perfusion and not the ICP on itself. Nevertheless, one must always be aware of possible erroneously low measured ICP values. For instance, in one case, we noticed a sudden drop of the ICP and a disappearance of the cardiac pulsations on the ICP waveform. A few seconds afterwards an abrupt tachycardia and hypertension occurred. This event was at a moment that a lot of debris was floating in the rinsing fluid. An obstruction of the outflow was the cause of this event. Shortly after retraction of the endoscope, the heart rate and blood pressure normalised. A continuous assessment of the irrigation pressure could be useful for early detection in such cases. Since outflow obstruction could be a serious cause of sudden rise in ICP, a safety system to detect such problems should be considered.
These observations have important repercussions on the clinical plan in neuroendoscopic procedures, including in small children. It is imperative to assess subtle cardiovascular changes, in particular hypertension coupled with tachycardia/bradycardia as fast as possible in order to alert the surgeon. Our study shows that looking for and identification of a Cushing reflex, together with continuous monitoring of the arterial and intra-endoscopic pressure and the surgical manoeuvres is a reliable and valuable adjunct to the existing monitoring techniques to protect the patient undergoing a neuro-endoscopic procedure.

References