Hemodynamic physiology during perioperative intracranial hypertension
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General discussion and future perspectives
Newly implemented surgical practices offer improved treatment options in many clinical conditions. The advent of new imaging techniques, improved endoscopic surgical equipment and the introduction of robotic technology have allowed many advances in surgical care, commonly referred to as ‘minimal invasive surgery’. However, in several of these newly introduced surgical interventions, direct surgical manipulations of cerebral structures or extreme patient positioning is likely to severely disturb intracranial pressure, cerebral perfusion and oxygenation. This perturbation of cerebral homeostasis may imply important risks for irreversible brain damage, making these surgical improvements much less minimal invasive than previously supposed. A better understanding of the physiological changes induced by and during these procedures might optimize patient care.

A surgical field where minimally invasive techniques offer great potential for improved patient outcome is endoscopic neurosurgery. Since endoscopic techniques allow for intracranial interventions with minimal damage to healthy brain tissue, these advances are a major benefit in this particular surgical area. Because these procedures are associated with bleeding into the ventricles, active rinsing of the ventricular cavities is imperative to remove blood to improve the operative view. This rinsing may induce very fast increases in intracranial pressure. Even more, in many cases deliberately applied controlled intracranial hypertension is a surgical technique to control bleeding, which allows for more complex procedures to be successfully performed with endoscopic techniques.

From 2002 to 2008, I had the privilege to collaborate on neurosurgical patient care in the Gent University hospital with a neurosurgical team that were among the pioneers in endoscopic neurosurgery. Their experience with the technique allows them to attempt ever more delicate procedures. An essential skill to perform these intricate operations successfully is the manipulation of the rinsing flow to control intraventricular fluid volume and pressure.

During these procedures, we often observed unexpected, but very severe haemodynamic changes during a stable anaesthetic regimen, which could only be caused by the intracranial manipulations. It was also remarkable that such events always occurred during difficult manipulations or during heavy rinsing. After our communication and subsequent retraction of the working instruments or diminishing of the flow, there was a fast normalisation of the haemodynamics.

Harvey Cushing was the first to describe in 1903, based on his clinical experience as a neurosurgeon, a triade of hypertension, bradycardia and apnea as a result of intracranial hypertension. Although Heymans showed in 1928 in animal research that there is an initial short-lasting tachycardia before the onset of bradycardia, it is only since the introduction of neuro-endoscopy, this has become clinically relevant. Relying on the experience with relatively slow-evolving processes such as subdural haematoma, hydrocephalus or cerebral tumors, many clinicians still consider
bradycardia and hypertension as the first haemodynamic sign of intracranial hypertension. However, in our clinical experience, we have observed that tachycardia occurs more frequently than bradycardia during neuro-endoscopy and might be considered an earlier warning sign making interventions safer.

Since the precise haemodynamic effects of endoscopically induced hyperacute intracranial hypertension were never thoroughly investigated, we developed a methodology for synchronous recording of the intracranial and arterial pressure waveforms during endoscopic neurosurgery. Using our custom-written software for analysis and visualization of these data, we were able to precisely describe the haemodynamic effects of induced intracranial hypertension and to determine the most suitable parameters for detection and prevention of harmful complications.

Contrary to the conventional view of the Cushing reflex being a combination of hypertension and bradycardia, we discovered that the initial phase of the Cushing reflex in hyperacute intracranial hypertension consists of a combination of hypertension and tachycardia. We demonstrated that tachycardia is always the first sign of severely increased ICP. Waiting for a persistent bradycardia could allow severe complications to develop. Secondly, we demonstrated that during endoscopic neurosurgery, the main determinant for brain perfusion is the cerebral perfusion pressure, and an increased intracranial pressure does not cause a distinctive Cushing reflex as long as an adequate perfusion pressure is preserved. While in adults, this insight may allow tolerance of higher rinsing pressure, it implies that in babies it is essential that much lower thresholds are used. Moreover, in literature it is often postulated that babies are protected against Cushing reflexes by their open fontanel. We proposed safety measures to prevent brain ischaemia in these particularly vulnerable patients and strategies for adequate patient monitoring.

The observation that no distinct Cushing reflex is induced, even at very high rinsing pressures, as long as an adequate cerebral perfusion pressure is preserved, raises the question of what happens with the cerebral blood flow in these cases, and to what degree the different stages of the Cushing reflex occur in relation to the cerebral blood flow. Based on our synchronous recordings of intracranial and arterial pressure and Doppler measurements of the blood flow through the middle cerebral artery, we could clearly demonstrate the exact sequence of haemodynamic changes resulting from impeded brain perfusion. This shows that it takes about ten seconds after abolition of brain perfusion, before a Cushing reflex – consisting of hypertension and tachycardia – arises. These Doppler readings also demonstrate that the Cushing reflex is a protective and effective mechanism to preserve some brain perfusion despite massively increased intracranial pressure.

Knowledge of the nature of the Cushing reflex is essential to comprehend the meaning of such haemodynamic changes. Misinterpretation might result in inappropriate pharmacological intervention to reduce blood pressure, thereby
allowing persistent deleterious intracranial hypertension to persist, whilst interfering with this protective mechanism. In this scenario it is far better to maintain the blood pressure but inform the surgeon.

During clinical surgery, moments of intracranial hypertension resulting from excessive rinsing often coincide with direct mechanical stimulation of the brainstem. Therefore, we developed a rat model to study the haemodynamic and hydrodynamic effects of isolated intracranial hypertension. In this model, we confirmed convincingly that the first sign of acute intracranial hypertension is a concurrent arterial hypertension and tachycardia. A particular advantage of our model is the ability to exactly quantify the amount of rinsing fluid that is translocated from the ventricular cavity to the vascular compartment. A striking result of this investigation is the observation that very significant fluid translocations occur at high intracranial pressures, resulting in drop in haematocrit and fatal pulmonary oedema. A third important finding is the observation that animals that apparently recovered smoothly from the procedure, and showed completely normal behavior after 24 hours, nevertheless had very significant histologically confirmed loss of hippocampal neurons. The obvious clinical message is that we should be reserved in claiming optimal patient care simply because patients show normal postoperative behavior. These findings demonstrate that, aside from acute haemodynamic disturbances, severe perioperative intracranial hypertension induces subclinical irreversible brain damage. Moreover, even without distinctive haemodynamic changes, a high ICP may induce important complications.

The obvious conclusion of these discoveries is that it is imperative to develop and determine optimal strategies to monitor and control intracranial pressure during endoscopic neurosurgery. The most practical locations to monitor this pressure is at the inflow or outflow channel of the neuro-endoscope. Both locations are used in literature with no solid arguments in favor of either methods. Since – remarkably – there has never been a sound study determining the reliability of these measurements in a realistic clinical situation or simulation, we built an in-vitro model to determine the validity of these pressures during clinically relevant rinsing flows. As we discovered that neither a pressure measurement at the inflow nor the outflow reliably reflects the true intraventricular pressure, we developed a new strategy for perioperative intracranial pressure monitoring and demonstrated this reflects the true intraventricular pressure at any rinsing flow pattern. We convincingly provided evidence that reliable noninvasive ICP-monitoring is only possible using a transendoscopic sensor or catheter.

With our prospective patient study, we demonstrated that close monitoring of the haemodynamic changes is indispensable during these procedures. However, currently this is only possible using invasive arterial blood pressure monitoring, while using indwelling catheters in the radial artery has important risks, especially in small children. An attractive alternative would be continuous non-invasive blood pressure monitoring using piezo-electric pressure sensors at the radial site. However, despite
its unmistakable advantages, this technology has not reached the clinical practicality yet, because of its inability to deliver a stable reliable reflection of the arterial pressure changes. Therefore, we conducted a study to determine different physiological and technical sources of artifacts. In this study, we identified some technical, and some physiological causes of unreliable pressure readings that must be resolved before this technology can be used in these procedures.

Another major innovation in surgery of recent years is the introduction of robotic technology in the operating theatre. This silent revolution in endoscopic surgery allows for much more accurate surgical manipulations and introduces the option of endoscopy as an alternative to the classical approach in several indications. Again however, although this “minimal invasive” character is certainly advantageous in the surgical area of the procedure, the highly unphysiological patient positioning combined with the need for CO\textsubscript{2}-pneumoperitoneum raises major concerns for the physiological homeostasis of the patient, especially for intracranial pressure, brain perfusion and oxygenation.

From 2008 to 2009, I was again extremely privileged to perform anaesthesia care together with an urological team in the OLV-hospital in Aalst, Belgium who have played a pioneering role in the use of robotic urological surgery. As they developed their technique and surgical approaches, professional anaesthesiological care matured to assess the boundaries of the feasibility. Despite the hours of positioning in steep Trendelenburg position – which is essential for the surgery - patient recovery was surprisingly fast. However, since the occurrence of postoperative cognitive disorders cannot easily be objectively quantified, the absence of obvious deficits does certainly not automatically imply perfect perioperative management of cerebral homeostasis. Secondly, the influence of this extreme positioning on cardiovascular and pulmonary physiology in this elderly population was never examined before. Therefore, we investigated its influence on the cardiopulmonary system, and on cerebral perfusion and oxygenation. Our findings showed that – taking into account the essential precautions for an adequate anaesthesiological approach – haemodynamic, pulmonary and cerebral parameters remained within a clinical acceptable range. Together with a general illumination of an adequate management and details of optimal patient positioning, this scientific confirmation of adequately preserved homeostasis is important to allow broader application of these novel surgical approaches. In addition it was unknown to what degree the end-tidal CO\textsubscript{2} concentration reliably reflects the arterial CO\textsubscript{2} in this patient positioning, and consequently how it must be interpreted to optimize ventilation. Our work described that a Pa\textsubscript{CO}_2 between 3.40-4.66 kPa results in a Pa\textsubscript{CO}_2 between 4.66-6.00 kPa. This knowledge is essential as Pa\textsubscript{CO}_2 is a key determinant for brain perfusion – a central concern in this circumstance.

Although cerebral oxygenation – as measured with Near-infrared technology - is a fundamental parameter for safeguarding the cerebrum, it only shows part of the
picture. From our clinical experience, it was obvious that important homeostatic disturbances do occur, since a reversible phase of postoperative confusion is frequently observed. Because of the clinical evolution of this confused status, with very fast recovery within an hour, cerebral oedema was the main suspect. In order to quantify objectively the degree of resistance to cerebral blood flow, we designed a study protocol to elucidate the influence of this patient positioning on the main parameters of the cerebral circulation. Using transcranial Doppler waveform registrations at the level of the middle cerebral artery and the radial arterial blood flow waveforms, we were able to depict the evolution of these parameters over the course of the procedure. As no commercial software exists for this particular analysis, we needed to write our own software for precise synchronization of the different waveform data, and for the determination of the derived physiological parameters of brain perfusion. This analysis showed that the two principal descriptive parameters of cerebral microvascular blood flow – pulsatility index and resistivity index – remained acceptable, although significant alterations do occur.

Our algorithm-based methodology to determine these parameters, using a high-resolution analysis of synchronized pressure and flow waveforms, is the most mathematically and physiologically accurate. However, since this method is far too elaborate to be useful in clinical practice, some formula-based methods have been proposed and validated in several clinical conditions. These formula-based methods thus far were never validated in this particular clinical setting of combined extreme Trendelenburg position and CO₂-pneumoperitoneum. Therefore, together with our descriptive analysis of the evolution of the different brain flow parameters over the course of the procedure, we also evaluated the different formula-based methods on their validity in this clinical situation. We discovered that of the several proposed formulae, only the one proposed by Czosnyka remains reliable in every patient position. This knowledge allows for much more practical real time monitoring of brain perfusion parameters in this patient positioning. It also supports the thesis that the theoretical basis for this formula is a reliable reflection of the true physiological reality.

In many institutions, anaesthetists are reluctant to offer this favorable patient positioning for surgical interventions because of safety concerns. This may deny optimal surgical care to many patients. We hope this work may relieve these concerns and provide some accurate underlying insight in order to select the best treatment options to a large patient population.

**Future perspectives :**

Our research has convincingly demonstrated that during endoscopic surgery very significant intracranial pressure changes occur that are much greater than anticipated. Even more, neurosurgeons assert that the most complicated neurosurgical interventions are only possible in a minimally invasive way if neurosurgical induction of high rinsing pressure is performed. Because these
in intracranial pressure changes can occur extremely fast, and can have detrimental consequences, a reliable perioperative intracranial pressure monitoring is essential. In this thesis, we describe the development of this new monitoring methodology.

In our ongoing work, we are optimizing the architecture of a practical, disposable pressure monitoring device for application during endoscopic surgery in routine practice.

Secondly, a prospective interventional study is being performed to confirm the improved diagnostic value of this transcendoscopic intracranial pressure monitoring system.

In parallel to this research line focusing on intracranial pressure monitoring, other animal research is being planned on differential suppression by various anaesthetic drugs of metabolism in different brain regions. The final aim is to optimize the local cerebral metabolism during surgical procedures in order to minimize ischaemic damage and to improve cognitive outcome.

In a third research line, we aim to investigate the degree of neuro-inflammation during surgical procedures involving cardiopulmonary bypass, its involvement in postoperative cognitive disorders and possible strategies to modulate this process. In a first number of studies in rats, a novel PET tracer $^{11}$C-PK11195 will be examined for its ability to quantify the degree of neuro-inflammation in different brain regions. Depending on the results of these initial studies, several preventive interventional strategies will be examined in animal research, and the tracer will be used in prospective studies in patients undergoing surgery requiring cardiopulmonary bypass.