Simultaneous Bedside Assessment of Global Cerebral Blood Flow and Effective Cerebral Perfusion Pressure in Patients with Intracranial Hypertension

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Abstract

Background We examined a bedside technique transcerebral double-indicator dilution (TCID) for global cerebral blood flow (CBF) as well as the concept of effective cerebral perfusion pressure (CPP_{eff}) during different treatment options for intracranial hypertension, and compared global CBF and CPP_{eff} with simultaneously obtained conventional parameters.

Methods Twenty-six patients developing intracranial hypertension in the course of traumatic brain injury or subarachnoid hemorrhage were prospectively analyzed using a combined assessment during elevated ventilation (n = 15) or osmo-therapy (hypertonic saline or mannitol). For calculation of global CBF, injections of ice-cold indocyanine green boluses were performed and temperature and dye concentration changes were monitored in the thoracic aorta and the jugular bulb. CBF was then calculated according to the mean transit time principle. Estimation of CCP, the arterial pressure at which cerebral blood flow becomes zero, was performed by synchronized registration of corresponding values of blood flow velocity in the middle cerebral artery and arterial pressure and extrapolation to zero-flow velocity. CPP_{eff} was calculated as mean arterial pressure minus critical closing pressure (CPP_{eff} = MAP_c - CCP).

Results Elevated ventilation causes a decrease in both ICP (P < 0.001) and CBF (P < 0.001). While CPP_{conv} increased (P < 0.001), CPP_{eff} decreased during this observation (P = 0.002). Administration of osmotherapeutic agents resulted in a decrease of ICP (P < 0.001) and a temporary increase of CBF (P = 0.052). CPP_{conv} and CPP_{eff} showed no striking difference under osmotherapy.

Conclusion TCID allows repeated measurements of global CBF at the bedside. Elevated ventilation lowered and osmotherapy temporarily raised global CBF. In situations of increased vasotonus, CPP_{eff} is a better indicator of blood flow changes than conventional CPP.

Keywords Transcerebral double-indicator dilution technique · Global cerebral blood flow · Effective cerebral perfusion pressure · Critical closing pressure · Intracranial hypertension · Mannitol · Hypertonic saline

Introduction

Insufficient cerebral blood flow (CBF) is associated with poor outcome in patients suffering from intracranial hypertension higher than 20 mmHg. Therefore, it is a general practice in neurointensive care units to monitor and assure a correct cerebral perfusion pressure (CPP) to ensure sufficient blood flow in these patients [1]. Conventionally, CPP is calculated as cerebral mean arterial blood pressure (MAP_c) minus intracranial pressure (ICP) (CPP_{conv} = MAP_c - ICP). Therapeutic interventions such as elevated ventilation or administration of osmotic agents in patients with intracranial hypertension are recommended to reduce ICP and in turn increase CPP [1]. However, this equation
does not include all factors that affect CPP, e.g., vasomotor tone and venous pressure [2]. From a physiological point of view, the effective CPP is the difference between momentary arterial pressure and the pressure at which cerebral blood flow in the precapillary bed suspends [3]. Determining this particular pressure, called critical closing pressure (CCP) (CPP_{eff} = MAP_{c} - CCP) [3–5] and obtainable with help of transcranial Doppler, can be used to monitor CPP.

In addition to mere observation of perfusion pressure (CPP) there is a strong interest in direct measurement of perfusion itself (CBF). Invasive probes, however, can only indicate regional blood flow conditions, and patient transfer from the neurointensive care unit to radiological units to assess global CBF provides only momentary values and presents a high risk for critically unstable patients. In order to overcome these disadvantages a new method has been introduced for the bedside monitoring of global CBF in intensive care patients that refers to the mean transit time principle [6], the transcerebral double-indicator dilution technique (TCID) which has shown a good correlation of CBF values in comparison to the Kety–Schmidt method, as well as good reliability [7–10].

In this study, we assessed global CBF by means of the TCID technique and calculated CPP_{eff} and CPP_{conv} in patients with intracranial hypertension in the course of two medical therapy options, elevated mechanical ventilation or osmotherapy. Our aim is to test the two methods for determination of global CBF and CPP_{eff} in clinical practice and to find out whether CPP_{eff} could be superior to CPP_{conv} in indicating cerebral blood flow changes.

Methods

Patient Characteristics and Intensive Care Management

This prospective clinical study was approved by the University of Bonn Institutional Review Board and written consent was obtained from all the patients or their closest relatives.

All the patients underwent simultaneous bedside assessment of global CBF, ICP, CPP_{conv}, CCP, and CPP_{eff} together with basic hemodynamic parameters such as heart rate (HR), continuous cerebral arterial pressure (AP_{c}), mean cerebral arterial pressure (MAP_{c}), and arterial and cerebrovenous blood gas samples. All the patients were kept under sedation, analgesia, and mechanical ventilation according to the local intensive care unit regimen for patients with intracranial hypertension.

Patient Groups

Patients admitted to the University of Bonn Medical Center are addressed either to the Anaesthesiology or to the Neurosurgery intensive care unit, depending on the severity of the brain lesions.

Group 1 (Elevated Ventilation)

Group 1 included 15 consecutive patients treated in the intensive care unit of the Department of Anaesthesiology, for initially mild traumatic brain injuries (MTBI). Traumatic CT findings were present in all these patients. The injuries were judged mild due to clinical impact and radiologic extension and were graded according to the initial Marshall CT Sore [11, 12]. The patients developed intracranial hypertension during their hospitalization in the course of systemic inflammatory response syndromes (SIRS) [13, 14] and were treated by an elevation of mechanical ventilation in reference to their baseline settings to lower arterial carbon dioxide tension (PaCO_{2}) by 7 mmHg. Measurements were performed under baseline ventilation conditions (T_{0}) and after undergoing elevated ventilation for approximately 30 min (T_{ElevVent}) (Fig. 1).

Group 2 (Osmotherapy)

Group 2 included a consecutive group of 11 patients with intracranial hypertension due to aneurysmal subarachnoid hemorrhage (SAH) or severe traumatic brain injury (TBI), hospitalized in the Department of Neurosurgery. As for Group 1, the Marshall CT Score was applied for TBI patients and the WFNS Scale for SAH patients [11, 12, 15]. Patients in Group 2 were treated by intravenous administration of the hypertonic saline HyperHES® 7.2% (n = 8) or, if baseline sodium serum levels were too high, by mannitol 20% (n = 3). As in group 1, the baseline measurement T_{0} was performed immediately prior to therapy. Then, the respective infusions of 150 mg/kg b.w. as for HyperHES® and 0.5 g/kg b.w. as for mannitol (=usual amount for a single adult application), were administered within 15 min. Measurements were repeated 15 (T_{15}) and 60 min (T_{60}) after administration (Fig. 1).

Measurement of Global CBF via TCID Technique

CBF was measured with the TCID technique [10]. The underlying theory to this method is the mean transit time principle according to which blood flow through the brain can be calculated when the transcerebral mean transit time of a diffusible indicator from the organ’s arterial inlet to its venous outlet as well as the partition coefficient λ between brain and blood for the respective indicator are known (CBF = λ/mtt [ml/s/g]) [16]. The transcerebral mean transit time in turn consists of an intravascular and an extravascular part (mtt = mtt_{iv} + mtt_{ev}) [17, 18]. The TCID technique makes use of two simultaneously
administered indicators: negative heat (ice-cold isotonic saline bolus injections), serving as a highly diffusible indicator, and dye concentration (indocyanine green in the bolus liquid) serving as a strictly intravascular indicator. If after indicator injection their concentration changes over time at the arterial inlet and venous outlet of the brain are continuously recorded, then the mean transit time can be calculated using computer-assisted via a transport function [16]. Negative heat is sufficient for calculation of CBF, but indocyanine green in addition allows to verify the intravascular part of the transport function [17–19]. The partition coefficient for the highly diffusible heat can be assumed to be 1 ml/g [20] (CBF = 1/mtt [ml/g/s]) and the formula can be modified to the standard unit for CBF (CBF = 60 × 100/mtt [ml/100 g/min]) [10].

Technically, the method requires simultaneous registration of thermo- and dye-dilution curves via two intravascular fiberoptic thermistor catheters at the arterial inflow and venous outflow of the brain as well as a central venous line for the indicator injection (Fig. 2). CBF was then calculated offline with a portable computer by curve analysis software written in Pascal [10].

Arterial and Intracranial Pressure Measurements

Cerebral arterial pressure was continuously monitored and digitally recorded at a sample rate of 50 Hz (for assessment of CPP, see below) by the same intravascular catheter located in the thoracic aorta, with a casual pressure transducer calibrated to the level of the Foramen of Monro. Mean arterial pressure (MAPc) was calculated from these recordings. ICP was monitored by means of conventional intraventricular probes (Duisburger Nadel; Pilling Weck, Karlstein, Germany).

Critical Closing Pressure and CPP<sub>eff</sub>

Estimation of critical closing pressure (CCP) is based on the fact that the regression of cerebral AP of each single heart beat and corresponding flow velocity is linear and, when extrapolated, shows a positive pressure intercept at zero-flow velocity [2]. At this arterial pressure, in the small cerebral resistance vessels the effective downstream pressure becomes zero and vessel flow suspends, consequently causing zero-flow velocity at the arterial observation site, in our study the middle cerebral artery. Continuous monitoring of flow velocity in the middle cerebral artery (V<sub>MCA</sub>) was performed at a depth of 45–55 mm with a 2-MHz transcranial Doppler probe (Multidop T; DWL, Sipplingen, Germany) fixed to the patient’s head using a device-adapted holder apparatus. All Doppler probe adjustments...
were performed by the same investigator (M. Jägersberg). No patient suffered angiographic vasospasm at the moment of assessment. APc was monitored in the aorta as mentioned above. Both curves of APc and V_MCA were simultaneously recorded at a sample rate of 50 Hz (Fig. 3). Offline, the time lag between the two curves was compensated by iterative regression analysis to find corresponding pressure-flow values and CCP was estimated in a heartbeat-to-heartbeat analysis from zero-flow velocity as extrapolated by digital regression analysis of APc–V_MCA plots (Fig. 3). During 30 s, CCPs of each heartbeat were estimated and then averaged to gain an actual CCP independent of respiration artifacts. Hence CPP_{eff} was calculated as MAPc minus CCP [2].

**Statistics**

Data in figures and text are expressed as mean ± standard deviation (SD), in absolute numbers and relative percentage changes to corresponding baseline levels (T_0 = 100%).
for each treatment. Correlation and significance using the Pearson’s correlation coefficient (r) and Student’s t test, respectively, was calculated with help of Microsoft Excel® 2003 SP3.

Results

In total, 63 measurements for CBF, CPP$_{\text{conv}}$ and CPP$_{\text{eff}}$ were obtained in 26 patients during hyperventilation [Group 1, n = 15, aged 54 ± 17 years, 10 men, 5 women; MTBI with initial Marshall CT Scores 2 (×4), 3 (×7) and 6 (×3)] and during osmotherapy [Group 2, n = 11, aged 53 ± 18 years, 6 men, 5 women; SAH n = 6, WFNS Grades 4 and 5, TBI n = 5, Marshall CT Score 3(×1), 4(×2) and 5(×2)]. Relevant results are shown in Fig. 4. No complications were observed in relation to catheterization, indicator injection, or the therapy applied.

Technical Aspects of the TCID Technique

Preparation of the indicator injections took about 5 min and had to be performed 30 min prior to measurement to ensure ice-cold temperature. Retrograde puncture of the internal jugular vein was only performed by trained intensivists. Due to procedure-inherent problems (mainly insufficient indicator injection speed or catheter tip contact with the vessel walls) 28.6% of all measurements had to be repeated. Average injection volume and dye dose per patient was 102.9 ml and 64.3 mg for patients undergoing elevated ventilation, 154.3 ml and 96.4 mg for patients treated with osmotherapy.

Elevated Ventilation

The PaCO$_2$ drop in group 1 during elevated ventilation (PaCO$_2$ at $T_0$ 43.7 ± 3.3 mmHg; PaCO$_2$ at $T_{\text{ElevVent}}$ 36.4 ± 4.2 mmHg, $P < 0.001$) was associated with a significant decrease in ICP ($P < 0.001$) and in CBF ($P < 0.001$) in comparison to baseline ventilation levels. Systemic parameters as HR and MAP remained unchanged. The resulting increase in CPP$_{\text{conv}}$ contrasts the decrease of CPP$_{\text{eff}}$ obtained in the same patients. Correlation between CPP$_{\text{conv}}$ and CBF was −0.29, between CPP$_{\text{eff}}$ and CBF 0.35 without reaching significance (Fig. 4).

Osmotherapy

Results of hypertonic saline and mannitol are presented separately due to their different time effects concerning onset and duration.

In the eight patients treated with hypertonic saline a significant decrease in ICP ($P < 0.0001$) during the first 15 min ($T_0$−$T_{15}$) was observed. The further decrease during the next 45 min remained significant ($P < 0.001$) compared to baseline ICP ($T_0$−$T_{60}$). CBF increased significantly after 15 min ($P = 0.024$). However, this effect was no longer present after 60 min with flow values of CBF comparable to baseline level. Both, CPP$_{\text{conv}}$, and CPP$_{\text{eff}}$ had similar trends without statistical significance (r[CPP$_{\text{conv}}$ − CBF] = 0.3; r[CPP$_{\text{eff}}$ − CBF] = 0.59) (Fig. 4).

As for the three patients treated with mannitol, a strong decrease in ICP was accompanied by an important, observation period lasting ($T_0$−$T_{60}$) increase in CBF. CPP$_{\text{conv}}$ and CPP$_{\text{eff}}$ had similar trends to the corresponding CBF (r[CPP$_{\text{conv}}$ − CBF] = −0.42; r[CPP$_{\text{eff}}$ − CBF] = −0.03) (Fig. 4). Due to the small number of patients in this subgroup none of the observations reached significance.

Discussion

In this clinical study, we investigated global CBF at the bedside with the TCID technique in patients with intracranial hypertension in the course of ICP reduction by either elevated ventilation or osmotherapy and evaluated the correlation of global CBF with simultaneously obtained values of CPP$_{\text{conv}}$ and CPP$_{\text{eff}}$. Global CBF significantly decreased under elevated ventilation and increased under osmotherapy. During elevated ventilation, CPP$_{\text{eff}}$ was superior when compared with conventionally obtained CPP in reflecting global CBF changes, while after osmotherapy there was no advantage in assessing CPP$_{\text{eff}}$ when compared with CPP$_{\text{conv}}$. A possible explanation is the strong vasotonic following hypocapnia that is not present to this extent during osmotherapy.

Intracranial Hypertension

The pathologies included in the study, all possibly leading to intracranial hypertension, were MTBI, TBI and SAH. As for SAH and TBI, pathophysiologic pathways have been well examined and we refer to the literature for details [21–26]. Patients with initially MTBI with minor structural CT findings may suffer from delayed intracranial hypertension in the course of a SIRS [13]. The pathogenesis of delayed intracranial hypertension as a “second hit” in these patients is not completely understood. The systemic inflammatory response primarily affects organs other than the blood–brain-barrier-protected central nervous system. However, initial mild brain injury weakening this barrier may expose the brain tissue to the inflammatory process and thus vasogenic and cellular edema [13, 14].

The initial ictus of the diseases mentioned above is different. However, in clinical practice, patients suffering from intracranial hypertension are all treated similarly.
Fig. 4 Results of monitored parameters for patients undergoing elevated ventilation (Group 1) or osmotherapy (Group 2, results for hypertonic saline and mannitol presented separately) in mean ± standard deviation (SD) for absolute numbers and percentage changes to baseline levels ($T_0 = 100\%$). Histogram showing parameter changes in percent. $P$ values calculated with Student’s $t$ test. HR heart rate, MAP, mean arterial pressure calibrated with Foramen of Monro, CI cardiac index, CBF global cerebral blood flow, ICP intracranial pressure, CPP$_{conv}$/CPP$_{eff}$ conventional/effective cerebral perfusion pressure, $S_j$ jugular venous oxygen saturation, NS not statistically significant.
concerning neurointensive care management. Thus, we considered MTBI, TBI, and SAH suitable for evaluation of the two monitoring tools in our study.

TCID Technique

As compared to intracranial CBF probes, which measure blood flow in a small region of interest (regional CBF), TCID provides bedside information about global CBF. As a jugular bulb catheter is needed, this method cannot be called non-invasive. However, complications as hematoma, thrombosis, or infection are rare [27]. Indocyanine green has proved to be a safe indicator that does not cause allergic reactions and is not oncogenic [28]. TCID does not allow for continuous monitoring of blood flow, but can be repeated several times per day. The risk of affection of cerebral metabolism by the ice-cold injections is low since jugular bulb temperature changes are usually less than 0.15°C [8]. Measurement failures (28.6% in our series) have been reported previously (34%) [7], they are easy to detect and hence do not endanger the accuracy of the method. However, as each measurement takes time and a physician, the method demands considerable manpower.

Reliability of Estimation of CCP and CPP\textsubscript{eff}

An essential step to estimate the critical closing pressure (CPP) is the linear extrapolation of a regression line of corresponding values of AP and V\textsubscript{MCA} to zero-flow velocity. Legitimation for this extrapolation was given by Early et al. [29] who reduced AP to zero flow in the monkey and Aaslid et al. [30] who observed pressure-flow velocity correlation to zero-flow velocity in human beings undergoing a short cardiac arrest for cardioversion. Cerebral autoregulation does not interfere with the calculation, as single-heartbeat-derived pressure changes are too fast for the vascular response [31]. An advantage of CPP\textsubscript{eff} is that it does not, unlike CPP\textsubscript{conv}, necessitate placement of an intracranial pressure probe.

Effects of Elevated Ventilation

PaCO\textsubscript{2} induced reduction of cerebral blood volume and hence ICP does not lead to an increase of CBF due to the flow-limiting vasoconstructive response. Our findings are in line with other authors, who observed worsening of CBF under moderate hyperventilation [32–34].

Taking into consideration the elevated vasomotor tone in the small resistance vessels, the resulting perfusion pressure CPP\textsubscript{eff} is physiologically better adapted to real flow conditions. The conventional formula CPP\textsubscript{conv} = MAP\textsubscript{c} − ICP does not respect local vessel reactions. According to our findings CPP\textsubscript{conv} cannot be recommended to monitor blood flow conditions in patients undergoing elevated ventilation.

Osmotherapy—Effects, Duration, Complications

Both mannitol and hypertonic saline are standard osmotherapeutic drugs for intracranial hypertension today. The osmolalities of mannitol 20% and hypertonic saline 7.2% (Hyperhes\textsuperscript{®} 7.2%) are different, with hypertonic saline 7.2% being more than twice as strong (2570 mosm/l) as mannitol 20% (1100 mosm/l). However, equal osmolality is not a methodological demand as the two drugs reduce ICP by partly different pharmacodynamic ways [35, 36]. Hypertonic saline is known to reduce ICP in some cases of mannitol-resistant intracranial hypertension [37, 38], whereas mannitol can be applied in patients in whom high sodium serum levels prohibit hypertonic saline administration.

With regard to statistical significance, our findings underline the effectiveness of hypertonic saline concerning reduction of ICP and temporary increase of CBF as well as the safety of both the drugs (zero adverse effects observed). Furthermore, our findings indicate that mannitol may have stronger and longer lasting effects on CBF than hypertonic saline.

Limitations of the Study

Regional CBF techniques as intraparenchymal probes give information about regions of interest, e.g., the penumbra. Global CBF cannot provide this information. Conversely, regional CBF values are unrepresentative for perfusion of the brain as a whole. A simultaneous observation of CPP—a global parameter—and CBF requires a global CBF technique. TCID presents currently the most handy and repeatable technique of bedside assessment for global CBF. Other methods as Kety–Schmidt or xenon computed tomography, are difficult to apply and limited concerning repeatability. The simultaneous assessment of blood flow and perfusion pressure is important, even if direct correlation between CPP and CBF is methodically incorrect: in clinical practice monitoring at the bedside today is mainly controlled by CPP\textsubscript{conv}—to maintain sufficient cerebral blood flow. However, “real CPP should not be considered a number, but rather a condition for cerebral blood to flow [39]”. Therefore, simultaneous assessment of global CBF and of both CPP\textsubscript{conv} and CPP\textsubscript{eff} is important to define how accurately these surrogate parameters indicate blood flow.

TCID is lacking acuity in very low perfusion rates due to its sensitivity to artifact temperature drifts [9, 10]. In normal or elevated cerebral perfusion the method has proven precision. Additionally, important intensive care parameters such as cardiac output, intrathoracic blood volume, and
lungs and cerebral perfusion. During elevated ventilation, CPP_eff was superior when compared to conventionally obtained CPP in reflecting global CBF changes, while after osmotherapy this correlation was not observed.

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