Monitoring Cerebral Blood Flow in Neurosurgical Intensive Care

a report by

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Therapeutic concepts in neurosurgical intensive care require sophisticated and refined neuromonitoring applications, because the individualised approach to the treatment of head-injured patients relies on the assessment and interpretation of the key parameters of brain tissue viability and function. Monitoring of regional cerebral blood flow (rCBF) in particular has been a long-term problem due to a lack of devices available for continuous bedside online monitoring. A novel thermal diffusion (TD) microprobe was introduced recently for continuous bedside monitoring of rCBF (TD-rCBF). The following article provides a description of the technique and describes the clinical application and the potential of this novel microprobe to assess CBF in patients suffering from subarachnoid haemorrhage (SAH) or traumatic brain injury (TBI).

In neurosurgical practice, monitoring of CBF plays an important role, as the brain depends on continuous blood supply due to its inability to store glucose or oxygen. During pathological conditions such as SAH or TBI, the patient – and consequently the functions of the brain – cannot be supervised clinically. Furthermore, secondary insults in SAH or TBI represent dangerous and often lethal complications, making continuous neuromonitoring essential for neurosurgical intensive care. Under these conditions, rCBF is considered an important upstream monitoring parameter that is indicative of tissue viability. In order to be able to establish new therapeutic approaches that focus on the pathophysiological basis of the secondary insult, neuromonitoring strategies need further refinement, as continuous monitoring of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) has failed to adequately identify malperfusion in the brain-injured patient.[1] In this scenario, continuous monitoring of rCBF could provide the opportunity to diagnose and to correct insufficient rCBF before deficits in tissue oxygenation and metabolism are recognised.[2] There are a variety of CBF measurement techniques available, such as stable xenon-enhanced computed tomography (sXe-CT), single-photon-emission computed tomography (SPECT), magnetic resonance imaging (MRI) and positron emission tomography (PET); however, these methods are hampered by several clinical and practical drawbacks.

Monitoring of rCBF in neurosurgical intensive care should ideally be performed in a continuous way at the bedside, providing quantitative rCBF values with high temporal and spatial resolution. Although laser-Doppler flowmetry (LDF)- and thermal diffusion flowmetry (TDF)-based measurement techniques provide continuous bedside monitoring of CBF, their clinical acceptance has been very low due to enduring technical drawbacks. Since LDF detects and measures erythrocyte flux, definite conclusions about nutritive perfusion and quantitative CBF cannot be drawn by means of this method.[3] Furthermore, TDF-based measurement techniques, such as cortically placed probes, were hampered by difficulties regarding the reliability and validity of the readings obtained.[3] Recently, however, the TD-rCBF microprobe, which is implanted intra-parenchymally and therefore circumvents the major drawbacks of the old systems that have been in use so far, has been introduced in clinical practice. It enables the quantitative, continuous bedside assessment of rCBF, which guarantees high reliability due to advanced mathematical modelling systems.[4] This article illustrates the technique of the TD-rCBF microprobe and introduces its clinical application in patients with SAH and TBI.

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Intra-parenchymal Thermal Diffusion Flowmetry of Regional Cerebral Blood Flow

Thermal Diffusion Flowmetry – Probe Design

The TD-microprobe consists of a flexible, medical-grade polyurethane catheter of 0.9mm diameter with two thermistors (a proximal and a distal thermistor, 5mm apart) embedded within the catheter. The distal thermistor is heated to approximately 2°C above the tissue temperature, thereby generating a constant spherical temperature field with a diameter of approximately 4mm. By positioning the thermistors 5mm apart, the proximal thermosensor is located outside the thermal field, thereby allowing continuous monitoring of tissue temperature and compensation of baseline fluctuations. The power dissipated by the heated thermistor (0.005–0.01W) provides a direct measure of the tissue's ability to transport heat. However, thermal transfer includes both intrinsic conductive properties of the tissue and convective effects induced by blood perfusion. Therefore, it is necessary to separate thermal conduction and convection components in order to achieve an adequate and reliable measurement of CBF in quantitative and absolute

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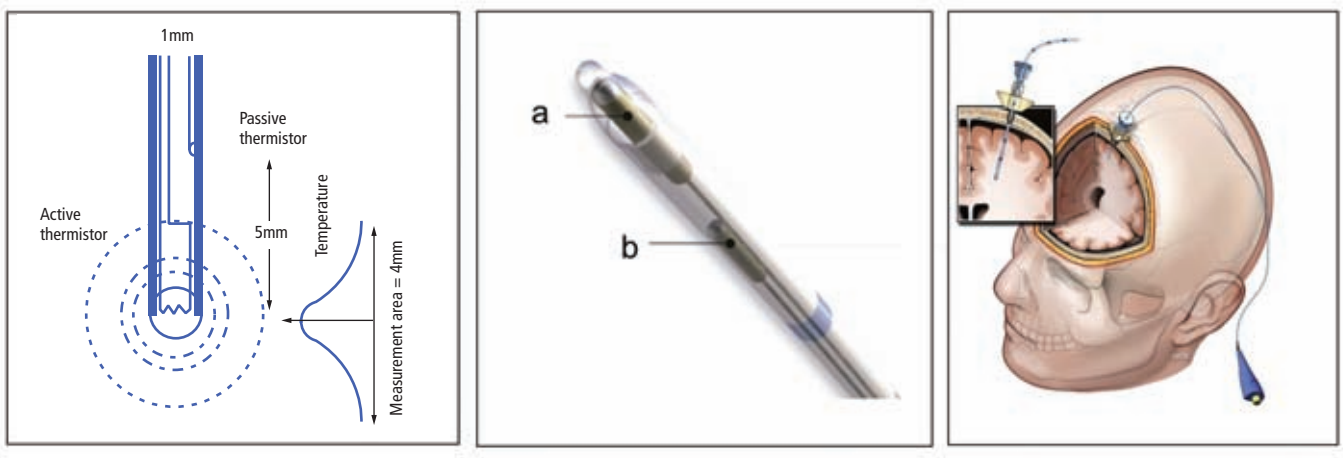
Figure 1: Illustration of the Usage and Technical Settings of the Thermal Diffusion Flowmetry of Regional Cerebral Blood Flow Microprobe



Left and middle image: schematic illustration of the technical principle of the rCBF-TD microprobe and demonstration of arrangement of the two thermistors required for determination of thermal conductivity and convection; a = active thermistor, b = passive thermistor.
Right image: demonstration of in situ *placement of rCBF-TD microprobe.*

physiological data. This was usually achieved by no-flow calibration with earlier heated probes, making heated probes impractical for daily clinical use in neurosurgical intensive care. The TD-rCBF microprobe discussed in this article permits reliable quantification of tissue perfusion by determining the conductive properties of the tissue from the initial rate of propagation of the thermal field and by separating this component from the total heat transfer as the determinant of the thermal convection component. Using a series of data-reduction algorithms, convection and conduction components are acquired separately, making no-flow calibration unnecessary. The volume of the generated temperature field is approximately 27mm^3 and therefore allows analysis of rCBF in this area. Usually, CBF values are recorded at a rate of 1Hz during clinical application. Illustrations of the TD-rCBF microprobe usage and technical settings are depicted in *Figure 1*.

Thermal Diffusion Flowmetry – Probe Placement and Use

According to evidence obtained in experimental and clinical validation studies of the TD-rCBF microprobe, the TDF probe is best placed 20–25mm below the cortical surface via a small burr hole and secured by tightening a metal bolt. Under these conditions, white-matter perfusion is obtained. As a general rule, mean TD-rCBF values range between 18 and 25ml/100g/min using this application form. At this point, it is important to stress that CBF values measured by TD-rCBF vary depending on the placement of the probe. Therefore, control of microprobe placement is important for interpreting CBF data acquired by TD-rCBF.

Clinical Application

Thermal Diffusion Flowmetry of Regional Cerebral Blood-flow Monitoring in the Management of Subarachnoid Haemorrhage

Among the major goals in the management of patients with SAH are the reliable and early detection of symptomatic vasospasm and the early prevention of vasospasm-induced ischaemia, which carries a considerable risk for secondary morbidity. As many as 50–70% of SAH patients develop angiographic vasospasm and 19–46% of SAH patients develop clinically symptomatic vasospasm leading to a delayed ischaemic neurological deficit (DIND).[5–7] Among the latter, 64% develop cerebral infarction.[8,9] These data emphasise the importance of the early and reliable detection of haemodynamically relevant vasospasm in order to start specific therapeutic interventions such as triple-H therapy. In awake patients, clinical examination remains the gold standard and best surveillance tool for detecting neurological deterioration. However, comatose and ventilated patients are not amenable to neurological examination. Therefore, clinicians have to rely on various direct and indirect techniques aiming to detect critical changes in rCBF in order to diagnose haemodynamically relevant vasospasm.

Cerebral angiography remains the gold standard in the diagnosis of cerebral vasospasm. However, the specificity of angiography in the diagnosis of symptomatic or haemodynamically relevant vasospasm has recently been calculated to be only 50%, indicating that the haemodynamic relevance of angiographic vasospasm cannot be assessed adequately.[10] Based on this significant disadvantage, transcranial Doppler (TCD) ultrasonography is often used in combination with cerebral angiography to detect haemodynamic changes in major cerebral arteries. Since its introduction, TCD has found widespread acceptance as an elegant, non-invasive and inexpensive bedside method for detecting blood-flow changes indicative of cerebral vasospasm in major cerebral arteries. However, TCD ultrasonography has been demonstrated to be a non-specific tool in the diagnosis of cerebral vasospasm, and it does not provide quantitative and direct data about cerebral blood flow.[11] In angiographic vasospasm, elevated blood-flow velocities fail to improve diagnostic safety because they do not correlate with cerebral perfusion. Therefore, combined angiography and TCD ultrasonography lack high specificity for reliable diagnosis of symptomatic vasospasm.[10,11] In consequence, the assessment of rCBF as a

> …combined angiography and transcranial Doppler ultrasonography lack high specificity for reliable diagnosis of symptomatic vasospasm.

central parameter of cerebral oxygen and nutrient supply represents the ideal goal parameter to detect haemodynamic vasospasm.

Three diagnostic modalities are used clinically to assess CBF directly: SPECT, sXe-CT and PET-CT. All three methods have been demonstrated to assess CBF directly and to confirm symptomatic vasospasm.[11,12] However, these methods are characterised by significant clinical drawbacks. First, rCBF status as determined by these methods cannot be performed at the bedside and requires patient transfer, which often carries a high risk of secondary insults in severely brain-injured patients. Second, all of these techniques provide a 'snap-shot' impression of the rCBF status only and do not allow continuous monitoring. Third, all of these techniques require the use of radioactive or expensive tracers, making them impractical procedures for daily use in intensive care patients.

> …thermal diffusion regional cerebral blood flow (CBF) monitoring represents a useful and effective tool for monitoring CBF in subarachnoid haemorrhage patients…

TDF represents an effective method for direct and bedside monitoring of CBF. Since its introduction in 1973, technical progress has led to the development of the above-described TDF microprobe (TD-rCBF). This novel TD microprobe has been validated in an experimental and clinical setting, demonstrating reliable, continuous and high temporal resolution even in the case of minor flow changes.[4] CBF values obtained by TD-rCBF are in total agreement with rCBF values obtained in sXe-CT studies.[4] An additional strength of the method is its ability to integrate the obtained online values in extended monitoring settings. Thus, TD-rCBF monitoring allows the introduction of cerebrovascular resistance (CVR) as a calculated monitoring parameter (CVR = CPP/TD-rCBF).[4] Using this approach, the reliable detection of vasospasm-induced cerebral hypoperfusion has been demonstrated with a sensitivity of 90% and specificity of 75%. A TD-rCBF cut-off value of 15ml/100g/min and a CVR value of 10 have been demonstrated to be the best diagnostic threshold values in this regard. Consequently, the rCBF measurements and CVR calculations enable the early identification of patients at risk of developing a DIND.[2] Additionally, direct rCBF monitoring allows validation and surveillance of therapeutic interventions aiming at improving CBF. Therefore, goal-directed and targeted therapy can be achieved by TD-rCBF monitoring.

Nevertheless, TD-rCBF monitoring also has some drawbacks. It is an invasive technique that provides information about blood-flow values only in the area of the implanted microprobe. Even though an incident of acute tissue damage in the form of bleeding, ischaemia or infection in response to probe implantation has so far not been reported, we have to assume that the complication rate of probe implantation is comparable to the complication rate of other intraparenchymal fibre optic microprobes (1–2% risk of bleeding, infection and ischaemia due to impantation). The other drawback involves the focal character of this technique, which mandates an implantation into the vascular territory deemed to be at highest risk of developing vasospasm. For monitoring of CBF in patients with SAH, implantation of the microprobe in the vascular territory of the artery carrying the aneurysm represents the best option. Using this approach, TD monitoring with a cut-off value of 15ml/100g/min and a CVR of 10 showed a sensitivity of 90% and a specificity of 75% for detecting symptomatic vasospasm.[4] Therefore, TD-rCBF monitoring represents a useful and effective tool for monitoring CBF in SAH patients, and provides important information relevant for early detection of delayed cerebral ischaemia. In combination with TCD ultrasonography and angiography, symptomatic vasospasm may be detected early and therefore a targeted and goal-directed therapeutical approach may be performed.[13]

Clinical Application

Thermal Diffusion Flowmetry of Regional Cerebral Blood Flow in the Management of Traumatic Brain Injury

Current management strategies in TBI are directed towards providing an optimal physiological environment in order to minimise secondary insults. Multimodal monitoring techniques assist in identifying or predicting the occurrence of secondary insults, and guide subsequent therapeutic interventions in an attempt to minimise the resulting brain injury. The final extent of brain damage not only is determined by the primary insult itself, but is also significantly influenced by the subsequently developing delayed neuronal death (DND) dependent on rCBF and neurotransmitter release. This secondary brain damage may be initiated or enhanced by episodes of cerebral hypoperfusion, arterial hypotension and hypoxia,[14,15] or by the excessive release of mediator compounds.[16] Although delayed brain ischaemia appears to be the major common pathway of secondary brain damage, an increase of brain perfusion may also develop. This phenomenon, called luxury perfusion,[17] may be accompanied by an increase of intracerebral blood volume[18] and ICP, resulting in a decrease of CPP, impairment of regional CBF and, sometimes, failure of cerebral microcirculation. This pathophysiological mechanism is often referred to as vascular dysfunction after traumatic brain injury, emphasising the central role of CBF in TBI. The importance of CBF monitoring is furthermore underlined by frequently occurring episodes of cerebral hypoperfusion during intensive care[19] and their significant impact on prognosis and patient outcome.[20,21]

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Despite this pathophysiological relevance, current treatment modalities are guided by parameters such as ICP, CPP, tissue oxygenation ($ptiO_2$) and cerebral metabolism (evaluated by microdialysis), which merely represent consequences of rCBF alterations. Therefore, the main parameter of rCBF is assessed only indirectly by these management approaches without sufficient evaluation of rCBF status. As management of TBI patients often involves maintenance of CPP, secondary brain damage may even be aggravated by therapeutic procedures aiming to increase CPP in the scenario of TBI-induced

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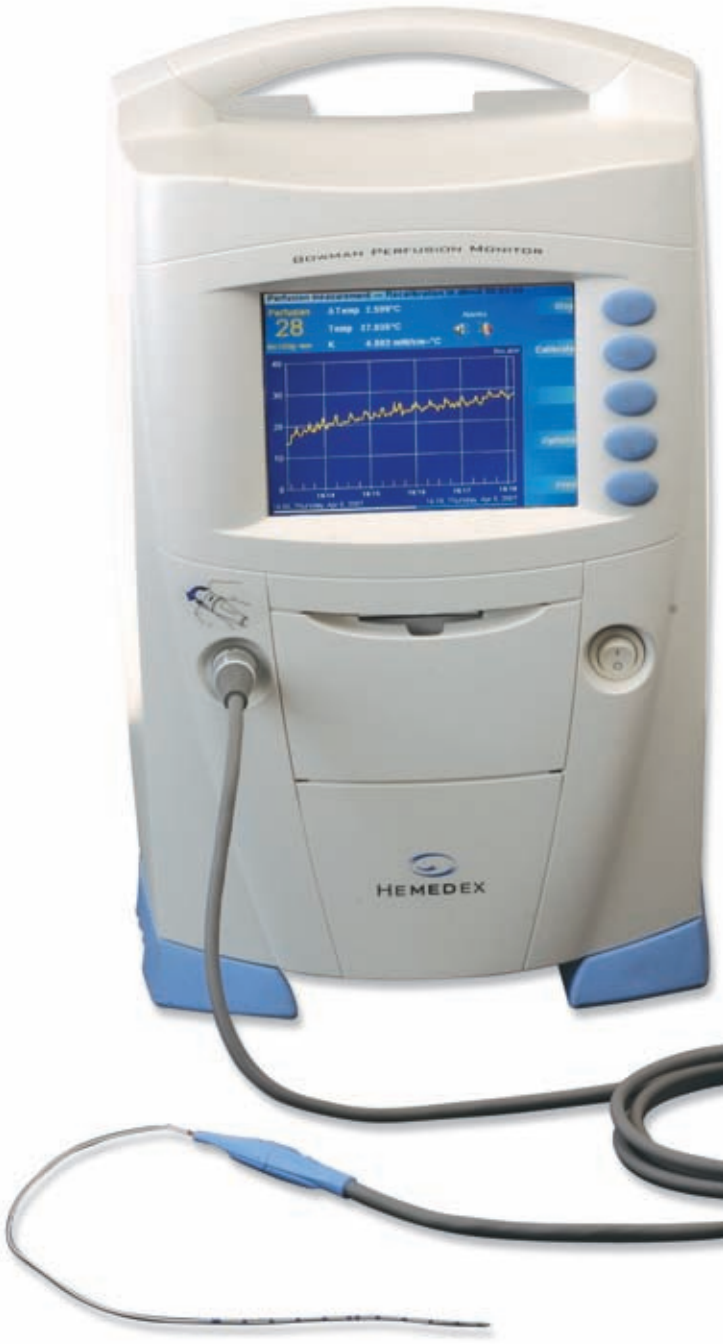

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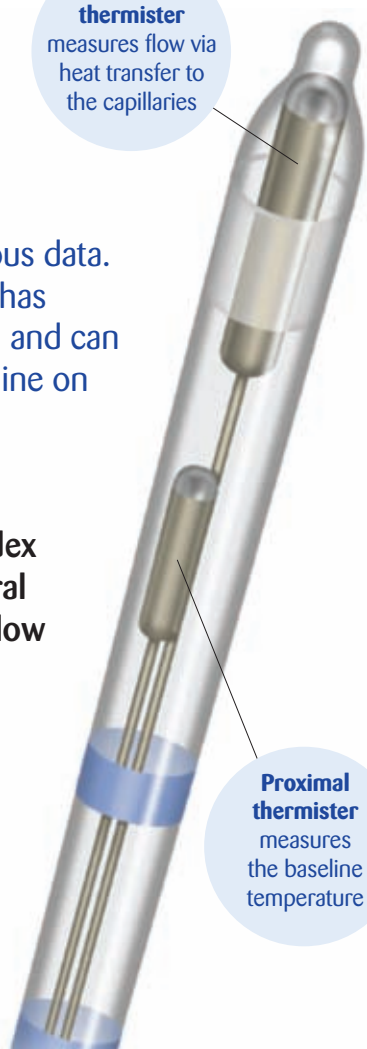

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vasoparalysis with disturbance of cerebral autoregulation. Therefore, direct CBF monitoring seems to become mandatory for the management of TBI patients as none of the current management strategies has shown significant impact on patient outcome.[1,22]

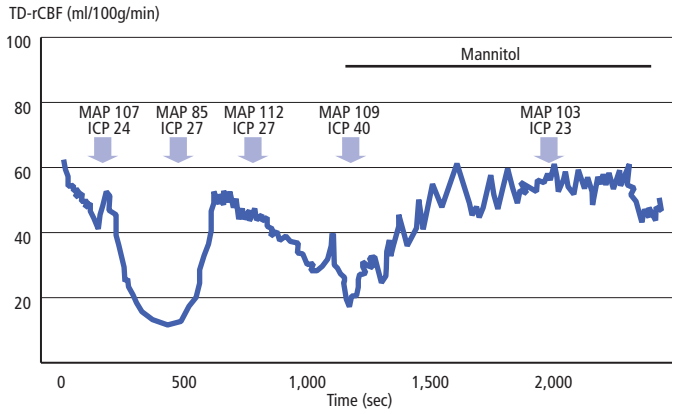
The same direct and indirect monitoring modalities are available for the assessment of rCBF in TBI as have been described for rCBF monitoring in SAH. However, only the TD-rCBF microprobe allows quantitative bedside, high-frequency and continuous analysis of CBF, and therefore represents the best tool for bedside surveillance of CBF in TBI patients.

As the advantages and disadvantages of the different CBF measurement modalities have been discussed above and the principal rationale for monitoring CBF via the TD-rCBF probe in SAH and TBI is the same, we use the following illustrative case to demonstrate the usefulness and reliability of TD-rCBF monitoring in a patient with TBI.

Illustrative Case – Implications of Thermal Diffusion Flowmetry of Regional Cerebral Blood Flow in Clinical Practice

Having undergone TBI, a patient was under multimodal neuromonitoring including assessment of TD-rCBF in our neurosurgical intensive care unit. The patient had suffered intensive left hemispheric cerebral contusion and traumatic SAH after a vehicle accident. As demonstrated in *Figure 2*, initial mean arterial pressure (MAP) was 107mmHg and ICP was 24mmHg with a TD-rCBF value of 50ml/100g/min. After decline of MAP to 85mmHg, a drop in TD-rCBF to 15ml/100g/min was observed. It should be noted that ICP was 27mmHg at this time, resulting in regular CPP of 58mmHg. In order to restore CBF, MAP was increased pharmacologically to 112mmHg with concomitant restoration of TD-rCBF to physiological values. Despite this brief decline in TD-rCBF values (three to four minutes), this episode triggered a permanent increase in ICP up to 40mmHg with consecutive reduction of CBF. This dramatic increase in ICP was counteracted with mannitol application, leading to normalisation of ICP and TD-rCBF values. The increase in ICP was caused by new hypoxic tissue in pericontusional areas, as demonstrated by CT scanning.

Figure 2: Analysis of Regional Cerebral Blood Flow Over a Time Course of 40 Minutes



The chart demonstrates the changes in regional cerebral blood flow (rCBF) and the corresponding values for intracranial pressure (ICP) and mean arterial pressure (MAP). Note the drop in rCBF despite a cerebral perfusion pressure (CPP) of 58mmHg (MAP – ICP = 85mmHg – 27mmHg = 58mmHg) between t=250s and t=500s and the resulting effects on ICP (increase to 40mmHg) and rCBF (decrease to 20ml/100g/min) between t=600s and t=1,200s with a CPP of 69mmHg. After mannitol application, rCBF and ICP are restored to physiological values.

As demonstrated by this case, TD-rCBF monitoring represents an effective and reliable tool to monitor rCBF and thereby also cerebrovascular autoregulation. It provides important information about early alterations of CBF that might ultimately result in significant secondary insults. Furthermore, this illustrative case demonstrates how therapeutic interventions aiming at restoring CBF may be monitored in TBI.

Conclusion

The use of TD-rCBF allows the direct, quantitative assessment of regional cerebral perfusion with high spatial and temporal resolution. Based on its properties, TD-rCBF represents a promising monitoring tool in the management of severely brain-injured patients. The application of this method enables tailored therapies that are based on the pathophysiology of the underlying disease. In addition, the method provides new insights into the pathophysiology of secondary brain injury. ■

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