Cortical brain microdialysis and temperature monitoring during hypothermic circulatory arrest in humans

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Abstract

Objectives—Critical vascular surgery of the brain or the heart occasionally requires total cessation of the circulatory system. Profound hypothermia is used to protect the brain from ischaemic injury. This study explores the use of microdialysis to measure metabolic indices of ischaemia: glutamate, lactate, and pH, and cerebral temperature during profound hypothermia and circulatory arrest.

Methods—Effluent from a microdialysis catheter placed in the cerebral cortex of three patients undergoing complete circulatory arrest was continuously sampled. Samples were pooled over 10 minute periods and glutamate and lactate concentrations were measured postoperatively. Brain temperature and pH were measured on line intraoperatively. Electroencephalography and monitoring of somatosensory evoked potentials and brainstem auditory evoked potentials were simultaneously carried out.

Results—Patient 1 had normal glutamate and lactate. PH was 6.75 to 6.85 and increased to 6.9 after warming ensued. Patient 2 had raised glutamate and lactate during most measurements. The glutamate concentrations peaked at 305 $\mu\text{M/l}$ at the start of the measurements and fell below 20 $\mu\text{M/l}$ after warming. The lactate concentrations peaked at 680 $\mu\text{M/l}$ before cooling, rose to 1040 $\mu\text{M/l}$ during the cooling process, decreased to 212 $\mu\text{M/l}$ during circulatory arrest, and rose again to 620 $\mu\text{M/l}$ after warming. The pH started at 7.06 and continued a downward course until stabilising at a pH of 6.5 after circulatory arrest. Patient 3 had a transient, mild increase in glutamate and lactate during the cooling and warming period. pH was stable throughout.

Conclusion—Microdialysis combined with temperature and pH measurements of the cerebral cortex promises to be an important tool in detecting cerebral ischaemia. Further studies are needed to validate our findings and test the feasibility of modifying ischaemic changes.

Recent advances in cardiac surgery have fueled interest in the technique of hypothermic circulatory arrest for the treatment of giant and complex intracranial aneurysms.^{1 2} The therapeutic benefit of profound hypothermia is due in part to the reduced metabolic demand.^{3 4} Other beneficial effects of deep hypothermia contributing to its neuroprotective efficacy include the decreased release of excitatory amino acids and the lessening of various detrimental enzymatic reactions.^{5 6} The duration of safe cardiac arrest at a given brain temperature is unknown.⁷ The few reports that have measured brain temperature in humans have shown that it cannot be accurately deduced from other body temperature sites.⁸⁻¹⁰ The temperature gradient depends on the metabolic rate of the brain, the blood flow to the brain, and the temperature of the blood. Neurophysiological monitoring, especially somatosensory evoked potentials (SSEPs),¹¹ are often used during surgery to detect dysfunction of the nervous tissue. SSEPs become isoelectric during cooling and therefore may be unable to detect ischaemia while the brain is cooling.

We describe in vivo microdialysis for the detection of potential ischaemia with promising results. Microdialysis allows the sampling of small molecules present in extracellular fluid from a selected area of the brain. The basic principle consists of a semipermeable membrane at the end of a double lumen probe which allows free diffusion of water and solutes from the extracellular space to the perfusion medium (normal saline) on the other side of the membrane. This perfusion medium is constantly renewed via a pump and the effluent is sampled for analysis.^{12 13} The pore size of the dialysis membrane cuts off molecules above a molecular weight of 20 000. In vivo microdialysis has recently been used in patients with subarachnoid haemorrhage,¹⁴⁻¹⁶ trauma models of simulated ischaemia,¹⁷ and surgery for epilepsy.^{18 19} This is the first report of in vivo microdialysis measurements of the extracellular amino acid glutamate and lactate, and on line pH in three patients whose circulation was arrested to clip a large basilar tip aneurysm. Brain temperature was monitored in two of the three patients.

Patients and methods

Three patients were entered into the protocol, which was approved by the Institutional Review Board (human research committee of the George Washington University Medical Center). All patients signed the approved informed consent form.

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Received 6 November 1996
and in final revised form
2 October 1997
Accepted 20 October 1997

(J Neurol Neurosurg Psychiatry 1998;64:611-618)

Keywords: brain temperature; circulatory arrest; hypothermia; microdialysis

Figure 1 Time course of glutamate, lactate, pH, and oesophageal temperature in cerebral dialysate before, during, and after hypothermic circulatory arrest in patient 1. LBF = low bypass flow; CA = circulatory arrest.

Patient 1 was a 48 year old woman with a family history of intracranial aneurysms (mother and sister). She had a large unruptured basilar aneurysm and a smaller right middle cerebral artery aneurysm. She had occasional headaches. Her hypertension was under control.

Patient 2 was a 69 year old man with an acute onset of dysarthria and a worsening pain in the neck and occipital area three days before surgery. He had a history of mild hypertension. Angiography disclosed a large thrombosed upper basilar aneurysm with a broad neck. The left superior cerebellar artery was not seen. Brain MRI showed an infarction of the cerebellum in the distribution of that artery. He was thought to have had a small haemorrhage from the aneurysm, followed by thrombosis of the superior cerebellar artery.

Patient 3 was a 55 year old woman who experienced a syncopal episode three weeks before surgery. She had a history of nausea and visual changes. She was found to have a large

upper basilar aneurysm which was unruptured and involved the left posterior cerebral artery.

Because of the large size and the location of the basilar aneurysms in all three patients it was decided to clip the aneurysms under the protection of hypothermic circulatory arrest. The operations were performed by the senior neurosurgeon, LNS.

ANAESTHESIA AND EXTRACORPOREAL CIRCULATION

All patients had normal echocardiograms without aortic insufficiency.² Before induction we recorded a baseline EEG four channel parasagittal montage of: F4-C4, C4-O2, F3-C3, C3-O1; median nerve SSEPs and brainstem auditory evoked potentials (BAEPs) (Grass equipment and Neuronet software; Computational Diagnostics Inc, Pittsburgh, PA, USA). Anaesthesia was with midazolam, fentanyl, and etomidate for induction. For maintenance we used an infusion of 0.05–0.08 $\mu\text{g/kg/min}$ fentanyl and isoflurane (0.3 % end tidal concentration in 60/40 oxygen/nitrogen). In all patients temperatures were measured in the oesophagus, rectum and bladder. Brain temperature was measured in patients 2 and 3. The chest and abdomen were prepared in a sterile fashion for the femoral artery to femoral vein cardiopulmonary bypass and the optional sternotomy. The patients also received 2 g/kg mannitol, 10 mg dexamethasone, and 1 g phenytoin. Aprotinin was given in accordance with the manufacturer's recommendation (Bayer, Pharmaceutical Division) to decrease excessive bleeding often associated with deep hypothermia.²⁰ Beef lung heparin was administered to maintain an activated coagulation time >750 s and the high thrombin time >300 s. The cardiopulmonary bypass was instituted and patients were cooled. Etomidate was given for additional brain protection before circulatory arrest. Patients 1 and 3 received 1 mg/kg and patient 2 received 1.5 mg/kg. The dosage was based on a burst suppression trial before cooling. Ventricular fibrillation was converted to cardiac standstill with 100 meq potassium chloride in patient 1, 140 meq in patient 2, and 120 meq in patient 3. In patient 1 perfusion was discontinued at an oesophageal temperature of 14°C. Her total circulatory arrest lasted five minutes with 13 minutes of low flow. In patient 2 perfusion was stopped at an oesophageal temperature of 11.5°C and at a cerebral temperature of 15.9°C. His circulatory arrest lasted 24 minutes with six minutes of low flow perfusion (300 ml/min). In patient 3 perfusion was discontinued at an oesophageal temperature of 9.3°C and a cerebral temperature of 15.3°C. Her circulatory arrest lasted 15 minutes with three minutes of low flow perfusion (500 ml/min). The PaCO_2 of all patients was kept between 34–38 mm Hg and was corrected for temperature.²¹ The bypass circuit consisted of a membrane oxygenator (SH-Monolyth) and a centrifugal pump (BIBP80), and was primed with 1600 ml Normosol and 200 ml 25% albumin.

Figure 2 Time course of glutamate, lactate, pH, and brain temperature in the cerebral dialysate before, during, and after hypothermic circulatory arrest in patient 2. LBF = low bypass flow; CA = circulatory arrest.

OPERATIVE PROCEDURES

A frontotemporal craniotomy with an orbitozygomatic osteotomy and extended trans-sylvian approach was performed on all patients in the supine position. A right sided approach was used in patients 1 and 3. The aneurysm of the middle cerebral artery was clipped first without hypothermia in patient 1, and then the basilar aneurysm was explored. In patients 2 and 3 the aneurysms were safely dissected away from the critical perforators and successfully clipped during circulatory low flow or circulatory arrest. Intraoperative angiography showed the aneurysms to be occluded, and the basilar artery and its branches patent. In patient 2 the aneurysm had been partially thrombosed. It was opened to evacuate the clot under circulatory arrest and then clipped. During the operation the superior cerebellar artery was found to be thrombosed. Intraoperative angiography disclosed the occlusion of the aneurysm and the preservation of the previously seen arteries.

MICRODIALYSIS, TEMPERATURE, AND PH MEASUREMENTS

The microdialysis probe (CMA/20; CMA/Microdialysis, Stockholm, Sweden) was 100 mm long and had a membrane of 4 mm length. The outside diameter was 0.5 mm, the volume 1.2 μ l/100 mm, and the flow rate 4 μ l/min. The in vitro recovery rate for glutamate was 11%, for lactate 16%, and the overall recovery under profound hypothermic conditions was reduced by 3%. The probe was previously sterilised at 60°C with ethylene dioxide and was inserted on the operative side into the frontal parasagittal cortex and was secured with two sutures to the dura. This region was selected because it is a watershed area between the middle and the anterior cerebral artery and is very sensitive to ischaemic changes. This is also the highest point in the supine position and therefore at maximum risk for a hypoperfusion injury. Finally this position is out of the surgeon's way. The probe was inserted for more than 80 minutes before heparin was administered. The probe was perfused with sterile 0.9% saline at 4 μ l/min until the dura was closed. All baseline values were obtained 40 minutes after inserting the microdialysis probe. Fractions of 40 μ l were collected every 10 minutes. During surgery the on line pH of the dialysate was recorded with a Hamilton pH electrode.²² Using the same probe, flow rate and perfusion medium, the relative recovery of all indices was measured postoperatively in vitro at 37°C, 30°C, 20°C, 15°C, and 10°C.

A flexible temperature probe (Yellow Springs, series 500) was previously sterilised at 60°C with ethylene dioxide and was inserted in the right frontal cortex of patients 2 and 3, 2 cm from the microdialysis probe.

AMINO ACID AND LACTATE ANALYSIS

The microdialysate was stored at -70°C until measurements were taken. Glutamate in the perfusate was analysed by high performance liquid chromatography (HPLC). We employed electrochemical detection using a modification of the method originating with Donazanti and Yamamoto²³ as was previously described in detail.^{24, 25} Precolumn derivatisation of amino acids with orthophthaldialdehyde (OPA/betamercaptoethanol) was performed before electrochemical detection with a 715 Ultra Wisp sample processor (Nopak C18; 3.9 $\times$ 150 mm; Waters, Toronto, Canada). Due to the inherently unstable nature of amino acids, we employed a fully automated system for the derivatisation procedure. The sample processor dispensed the reagent into the microdialysis perfusate and mixed it thoroughly in a 200 μ l loop. The injection was made precisely two minutes after the reaction time. A baseline 810 Chromatography Work Station (Waters, Toronto, Canada) was used for the data analysis and the calculations of amino acid concentrations. The mobile phase consisted of 0.10 M disodium hydrogen orthophosphate, 0.13 M ethylenediamine tetraacidic acid-sodium salt, and 20% methanol. External standards of 0.625, 1.25, 2.5, 25, 100, 300, and 1300 pM/10 μ l were used for all samples. The lactate

Figure 3 Time course of mean arterial pressure in patient 2 in relation to oesophageal and brain temperature before, during, and after hypothermia. MAP = mean arterial pressure.

was determined by an enzymatic fluorimetric method, in 10–15 μ l samples.²⁶

Results

POSTOPERATIVE COURSE AND OUTCOME

Patient 1 was neurologically intact except for a transient right oculomotor paresis due to the exposure of the aneurysm. She was discharged eight days after surgery and has fully recovered. Patient 2 was responsive and alert the next morning with a mild right hemiparesis. He was extubated after meeting extubation criteria. The patient's neurological status deteriorated several hours later with presumed transient relative hypotension. He became stuporous and the right hemiparesis became dense. An angiogram showed patent vessels. Brain CT showed a small ischaemic zone in the left cerebellum. After treatment with induced hypertension the patient improved to near normal but he had another episode of neurological decline when his blood pressure was normalised. He was treated with an additional course of induced hypertension, but made a very slow recovery. At one month, the patient was abulic and had a severe right hemiparesis. However, three months after his operation he recovered and is now ambulatory and independent. His hemiparesis has been resolved, but he continues to have a dysarthric speech.

Patient 3 had a transient right oculomotor paresis. She recovered rapidly and was discharged eight days later.

GLUTAMATE

Patient 1 (fig 1)

The glutamate concentrations were low throughout the entire procedure and ranged between 5–14 μ M.

Patient 2 (fig 2)

Before hypothermia the glutamate concentrations ranged from 101 μ M/l to 305 μ M/l and decreased to 60 μ M/l during the cooling

period. During circulatory arrest they increased again to 123 μ M/l. After rewarming the glutamate concentrations gradually decreased from 62 to 16 μ M/l.

Patient 3 (fig 4)

The glutamate concentrations ranged from 11 μ M/l to 26 μ M/l before cooling, rose slightly during cooling (31 to 41 μ M/l), were stable during the circulatory arrest, peaked at 75 μ M/l during the warming phase, and then declined to normal.

LACTATE

Patient 1 (fig 1)

The lactate concentrations were below 400 μ M/l throughout the study with one exception. One spike of 510 μ M/l occurred during the warming phase. The lactate concentration subsequently decreased to 100 μ M/l.

Patient 2 (fig 2)

The lactate concentrations ranged from 360 to 680 μ M/l before cooling. There was a sharp increase to 1040 μ M/l during the early cooling period, with a decline to 212 μ M/l during cardiac arrest. During rewarming the lactate concentrations rose steadily to 640 μ M/l and declined to 440 μ M/l at the time of dural closure.

Patient 3 (fig 4)

The lactate concentrations rose gradually from 248 μ M/l to about 400–500 μ M/l during most of the procedure with a single peak to 750 μ M/l after circulatory arrest.

ON LINE PH

Patient 1 (fig 1)

The pH before and during circulatory arrest ranged from 6.75 to 6.85. During warming it rose rapidly and remained raised above 6.9.

Figure 4 Time course of glutamate, lactate, pH, and brain temperature in the cerebral dialysate before, during, and after hypothermic circulatory arrest in patient 3.

Patient 2 (fig 2)

Before hypothermia the pH ranged from 6.83 to 6.90. During hypothermia and circulatory arrest it fell to 6.55. The lowest value of 6.41 was registered during the early rewarming period. After rewarming the pH remained stable in the range 6.49–6.52.

Patient 3 (fig 4)

The pH ranged from 6.7 to 6.87 during the entire measurement time with the higher values during cooling and circulatory arrest.

TEMPERATURE

Patient 1 (fig 1)

Before cooling the oesophageal temperature decreased from 36°C to 30°C. The patient was cooled to a 14°C oesophageal temperature and was maintained at that temperature for five minutes before the circulation was arrested. Temperature rose slowly to 18°C at the end of the arrest period.

Patient 2 (figs 2 and 3)

The brain and oesophageal temperatures moved in the same direction and changed at equal rates. Brain temperature was 1°C–1.5°C higher than oesophageal temperature before cooling, and 3.9°C–4.5°C higher than oesophageal temperature during circulatory arrest. Lowest brain temperature during circulatory arrest was 15.3°C at an oesophageal temperature of 11.5°C.

Patient 3 (fig 4)

When the oesophageal temperature registered 9.3°C, the brain temperature was 15.5°C, and it remained stable during the circulatory arrest period.

NEUROPHYSIOLOGICAL MONITORING

In all three patients the EEG became isoelectric and the SSEP became unresponsive between 20°C and 23°C oesophageal temperature.

Discussion

Circulatory arrest is a high risk procedure. Indices have not been established which could adequately monitor the early detection of cerebral ischaemia during deep hypothermia. We have used metabolic indices obtained from cortical extracellular fluid by microdialysis for the detection of ischaemia in an area of the brain most susceptible to ischaemia. The indices chosen are established indicators of cerebral ischaemia, but they have not been used in situations of deep hypothermia and circulatory arrest. We chose glutamate, an excitatory neurotransmitter, which has been shown to cause irreversible neuronal injury during ischaemia if excessive amounts are released into the extracellular space or its reuptake is inhibited. Glutamate promotes the entry of calcium and sodium into neuronal cells.^{5 6 27–29} We chose lactate and pH as indicators of the cellular shift towards anaerobic metabolism.³⁰

Glutamate was the best predictor in our patients. Patients 1 and 3 were discharged from the hospital after eight days without neurological deficit. Patient 1 had no increase in glutamate. Patient 3 had a mild increase during cooling and warming, but glutamate concentrations were stable during the circulatory arrest period. Patient 2 had very high concentrations of glutamate and had a hemiparesis. It is not clear whether there was a single ischaemic event and if so when that event occurred or whether there was an ongoing ischaemic process. The patient already had very high concentrations of glutamate when measurements began nearly two hours before cooling started. We can only speculate as to the reason. The patient was symptomatic three days before surgery and had a thrombosis of the superior cerebellar artery with a small infarction. However, the release of glutamate reflects an ongoing process and not an event three days ago. The perfusion pressure may have been inadequate, causing an extension of the infarction and a release of glutamate. General anaesthesia almost always lowers blood pressure by 10% to 20% and if an area of the

brain depends on a critical perfusion pressure this area may have been inadequately perfused. Patient 2 clearly had pressure dependent neurological impairment on the second post-operative day, but this may have been a different aetiology as there is usually more cerebral oedema postoperatively. It is also necessary to consider the small local injury from inserting the probe. We allowed 40 minutes for stabilisation of the probe before measurements were taken. It has been shown in previous studies that a stabilisation period of 30 to 45 min is adequate.^{15 31 32} None of the other patients showed increases in glutamate concentrations after insertion of the probe. We do not think that the high initial glutamate concentration in patient 2 was an insertion artifact as levels of glutamate remained high for two more hours after probe insertion.

With the start of cooling the high glutamate concentrations in patient 2 began to fall rapidly. The decrease in glutamate concentration with the induction of even mild hypothermia has been previously recorded in both animals^{5 33 34} and humans.¹⁵ Mild hypothermia in rats has been shown to provide protection from histopathological injury despite raised lactate concentrations and decreased ATP concentrations. This protective effect was thought to be conferred by the decrease in excitatory neurotransmitters.^{5 33} There were no data found on the effect of profound hypothermia and excitatory neurotransmitters.

Absolute values for glutamate from different publications are difficult to compare and depend on the technique used for microdialysis.^{14 16} Most published values for glutamate are derived from patients with injury. Using the same technique as applied in this paper Shuaib *et al* considered a glutamate concentration of 20 $\mu\text{M/l}$ the upper norm.¹⁵ Mendelowitsch *et al* found glutamate concentrations ranging from 8–25 $\mu\text{M/l}$, which were presumably normal as they were measured in patients before cerebral vascular bypass procedures.³¹ Hillered *et al* reported normal concentrations of 1–2 $\mu\text{M/l}$. These lower concentrations may reflect differences in technique.^{30 32}

The second indicator of ischaemia was lactate. Lactate production has been considered an important indicator of this state.^{35 36} The normal lactate for the human brain obtained by microdialysis has been reported at 200–400 $\mu\text{M/l}$.¹⁶ All patients showed some increase in lactate concentrations. The concentrations in patient 1 spiked after hypothermia, in patient 3 they rose during the warming period, and in patient 2 lactate concentrations were normal at the beginning of microdialysis when glutamate was very high. Lactate rose greatly when glutamate had decreased. It is difficult to see any pattern in lactate concentrations.

Lactate did not correlate well with pH either. We measured pH as another indicator of ischaemia. This poor correlation between lactate and pH has been shown by others. During reversible ischaemia, Paschen *et al* found a significant increase in lactate while pH re-

mained in a physiological range.³⁰ The rise in lactate was accompanied by an alkaline shift in brain tumours.³⁰ Mun-Bryce *et al* found a dissociation between lactate and pH in vasogenic oedema.³⁷ The mechanisms that may influence lactate concentrations are the capacity of the tissue to buffer protons, a change in glucose metabolism,³⁷ impairment of transport mechanisms of lactate from intracellular to extracellular space,¹⁶ and the metabolism of lactate by neuronal tissue. In addition, the availability of substrates and their transport depends on perfusion being present, and during circulatory arrest this does not occur.¹⁶ pH also reflects changes in PaCO_2 .³⁰ The relatively low pH in our patients is probably due to the acid-base management we practised during hypothermia. We kept the PaCO_2 between 34 to 38 mm Hg calculated for the hypothermic temperature. This was accomplished by decreasing total oxygen flow to the oxygenator (pH-stat).³⁰ The pH concentrations before cooling in the three patients ranged from 6.71 to 6.9. The pH values in patient 2 did not fall below the pH of the other two patients before cooling, but did show a persistent downward trend. Although single pH values were not helpful in predicting ischaemia, the long term decreasing trend in patient 2 was an indication that ischaemia took place.

The recovery of molecules by microdialysis can be influenced by many factors. Testing recovery of solutes *in vitro* in a test solution results in a consistent recovery depending on the flow rate of the perfusate.¹² The slower the flow rate the more time there is for solutes to traverse the membrane and the better the recovery. When we tested the effect of profound hypothermia on the rate of recovery *in vitro*, recovery was reduced by only 3%. In a biological system such as the brain, the concentration of solutes in the extracellular space depends on the length of the diffusion pathway, which is a tortuous way between many cells.¹² Uptake and production of solutes within cells and binding to cell membranes and proteins may effect the extracellular concentration. The milieu in the extracellular space changes rapidly.³⁸ Therefore we reported the value of the recovered lactate and glutamate.

Studies on hypothermia are difficult to compare as temperature is usually measured in the rectum or the oesophagus. Temperature has to be measured in the brain to relate cerebral events to cerebral temperature. Our data and those of others indicate that there is not a predictable correlation between brain and body temperature, especially with rapid fluctuations in blood temperature and perfusion,^{8 9 39} and with neuronal injury.^{8 10 40} We do not know the duration of a safe circulatory arrest at a given brain temperature, nor do we know whether too low a temperature may cause the loss of the blood-brain barrier or cause other cerebral injuries.^{41–43} Our circulatory arrest times ranged from 18 minutes to 30 minutes including very low flows of about 300 to 500 ml/min. Cooling is thought to protect the brain from glutamate release, yet in patient 2 at a brain temperature of 15.3°C (oesophageal temperature 11.5°C)

glutamate rose from 60 to 123 $\mu\text{M/l}$. Patient 3 had a mild rise in glutamate with cooling and rewarming; however, with circulatory arrest at a brain temperature of 15.5°C (oesophageal temperature 9.3°C) there was no further increase in glutamate. More information is needed before the duration of a safe circulatory arrest time can be established.

An isoelectric EEG, SSEP, and BAEP may be an indicator that cerebral metabolism is greatly reduced, thereby permitting a safe circulatory arrest. In this study SSEP and BAEP showed a progressive increase in latencies as the temperature declined with no response below about 23°C. However, it has been shown in puppies that during deep hypothermia the EEG did not become isoelectric until the oesophageal temperature reached 13°C or lower.⁴⁴ In that study the EEG was obtained from the epidural space whereas our EEG data was derived from electrodes placed on the outside of the skull. We were unable to detect fine cortical cerebral activity at lower temperatures. More research is necessary before electrophysiological monitoring can be used for detection of ischaemia during cooling. In animals it has been shown that a correlation exists between increases in glutamate and auditory evoked potentials. In cats at a glutamate concentration above 20 $\mu\text{M/l}$ the auditory evoked potentials decreased and above about 60–75 $\mu\text{M/l}$ they were absent. The electrodes were implanted in the cortex.⁴⁵ With electrodes outside the scalp it is unlikely that such a correlation could be established in humans.

In conclusion, we presented for the first time the concentrations of glutamate, lactate, and pH obtained by cortical brain microdialysis combined with brain temperature during profound hypothermia and circulatory arrest. Biochemical monitoring of the brain could provide important information about the relation between ischaemic injury, the degree of cooling, and the safe duration of circulatory arrest if this monitor could be developed on line, as are pH and temperature monitors. It could determine the therapeutic window, when pharmacological or hemodynamic interventions are still possible.

This study was supported in part by Schweizerische National Fonds and the Karger Stiftung; Ciba Geigy Jubiläums-Stiftung; Freiwillige Akademische Gesellschaft Basel; Lichtenstein Stiftung; and the Department of Neurological Surgery, The George Washington University Medical Center.

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