Assessment of critical thresholds for cerebral perfusion pressure by performing bedside monitoring of cerebral energy metabolism

CARL-HENRIK NORDSTRÖM, M.D., PH.D.

Department of Neurosurgery, Lund University Hospital, Lund Sweden

An intractable increase in intracranial pressure (ICP) leading to a progressive decrease in cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) is the dominating cause of death in patients with severe brain trauma. Arterial hypotension may further compromise CPP (and CBF) and significantly contributes to death. In addition, the injured brain is sensitive to raised CPP due to an increased permeability of the blood–brain barrier (BBB) to crystalloids and an impaired pressure autoregulation of the CBF. Given these circumstances, an increase in CPP will cause a net transport of water across the BBB and a further elevation in ICP. Accordingly, the assessment of the lower critical threshold for CPP is important for neurological intensive care. This level varies among different patients and different areas of the brain. In fact, the penumbral zones surrounding focal brain lesions appear to be the most sensitive. In the individual patient, preservation of normal cerebral energy metabolism within areas at risk during a decrease in CPP can be guaranteed by performing intracerebral microdialysis and bedside biochemical analyses.

KEY WORDS • blood–brain barrier • brain edema • brain trauma • cerebral perfusion pressure • intracranial pressure • microdialysis

An intractable increase in ICP leading to a progressive decrease in CPP and CBF is the dominant cause of death in patients with severe brain trauma. Arterial hypotension may further compromise CPP (and CBF), and hemorrhagic shock is a common complicating factor that significantly contributes to death.³¹ In addition, hypotensive episodes unrelated to hemorrhagic hypovolemia have been reported to be relatively frequent and associated with an unfavorable patient outcome.⁵ Furthermore, CBF is often variable in severe brain trauma, and regional CBF is frequently very low in pericontusional areas.¹⁵ Based on these experiences, it might seem logical both to restore circulating blood volume and to use vasopressors liberally to achieve a further increase in CPP. This idea has gained additional support from the (previously) generally accepted hypothesis that a pharmacologically induced increase in MABP effectively decreases ICP.^{35,36} In one study, Rosner, et al.,³⁶ asserted that the minimal level of CPP should be greater than 70 mm Hg and that certain patients might require a level of 100 mm Hg or more. Nonetheless, if the traumatized brain always benefits from increasing the CPP, what then is the point of assessing a minimal acceptable level? Perhaps an increased blood

pressure is harmful to the injured brain, which implies that many patients might benefit from a pharmacological reduction in CPP. In an effort to respond to these issues, I will first briefly review the regulation of brain volume under physiological and pathophysiological conditions.

REGULATION OF BRAIN VOLUME

All treatments for increased ICP are directed toward decreasing the volume of one or more of the following intracranial components (or, in selected cases, by increasing the total intracranial volume by craniectomy): volume of intracranial blood (V_{blood}), volume of brain tissue (V_{brain}), volume of intracranial CSF (V_{CSF}), and volume of intracranial focal mass lesion ($V_{\text{mass lesion}}$). The relationship of these components is expressed in the following equation:

$$V_{\text{intracranial}} = V_{\text{blood}} + V_{\text{brain}} + V_{\text{CSF}} + V_{\text{mass lesion}}$$

Nonsurgical treatments are directed toward the volume of blood and the volume of brain tissue. A rapid but relatively short-lasting decrease in ICP is conventionally obtained by controlled hyperventilation therapy, which reduces the volume of intracranial blood. A more lasting decrease in intracranial blood volume may be achieved pharmacologically by precapillary vasoconstriction or by reducing blood volume within the venous compartment.^{12,27} The most effective, long-term nonsurgical treatment is to decrease the volume of the brain tissue, however.

Abbreviations used in this paper: BBB = blood–brain barrier; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; MABP = mean arterial blood pressure; SD = standard deviation.

Volume regulation of all tissues is determined by the fluid exchange across the capillaries. Water transport across a microvascular bed (J_v) is described in the following equation:

$$J_v = L_p \times A \times (\Delta P - \sum \sigma_s \times \Delta \Pi_s)$$

where L_p represents the specific permeability for water (hydraulic conductivity) and A is the surface area available for fluid exchange. The product of L_p and A is denoted as the hydraulic conductance and reflects the total capacity for fluid exchange. Furthermore, ΔP is the transcapillary hydrostatic pressure difference; $\Delta \Pi_s$, the transcapillary osmotic pressure difference; and σ_s , the reflection coefficient of each solute (s) of the system. Water exchange across the capillary wall is thus determined by the hydraulic conductance of the capillary wall ($L_p \times A$), the differences in hydrostatic pressure (ΔP) and osmotic pressure gradient ($\Delta \Pi_s$) across the capillary wall, and the endothelial component determining which solutes are reflected and will contribute to the osmotic pressure gradient (σ_s). The value of σ depends on the relative permeabilities of the membrane to water and to solute: if the membrane is impermeable to the solute but not to water, σ equals 1; and if the permeability of the solute is identical to the diffusion coefficient in water, σ equals 0.

Volume control in the brain differs from that in other organs because of the BBB. In addition to its other vital functions, the BBB is the most important regulator of cerebral volume.¹⁰ In other tissues, the osmotic force is mainly derived from the difference between plasma and interstitial colloid osmotic pressure, which approximately balance the transcapillary hydrostatic pressure (~20–25 mm Hg). The situation across the BBB is quite different. Sodium and chloride, which are the two major solutes in biological fluids, have BBB reflection coefficients of 1. Transcapillary fluid exchange across the BBB is thus effectively counteracted by the low permeability to crystalloids combined with their high osmotic pressure (~5700 mm Hg) on both sides of the capillary wall.¹⁰ Water passing across the BBB in any direction will accordingly not be accompanied by crystalloids. If, due to a difference in hydrostatic pressure, water crosses the BBB, an opposing osmotic gradient will immediately be created. Thus, brain volume operates within physiological conditions relatively independent of variations in intracapillary hydrostatic and colloid osmotic pressure. In addition, because of the pressure autoregulation of CBF, intracerebral capillary hydrostatic pressure functions within physiological conditions unaffected by variations in MABP.^{12,27}

In patients with severe head injuries, autoregulation of CBF is often impaired, and variations in MABP will be directly reflected in the intracapillary hydrostatic pressure.⁷ Opinions vary regarding the permeability of the BBB in these patients. Data from experimental studies of brain trauma have shown that edema formation does not correspond with BBB opening and that this is not required for edema formation.³ In these studies only the permeability of large molecules was investigated, however, and it is reasonable to assume that given various pathological conditions, the BBB may have a significantly reduced reflection coefficient for crystalloids. As in other tissues, tran-

scapillary fluid exchange will then be controlled according to the Starling equilibrium: water exchange across the capillary wall is determined by the differences in hydrostatic and colloid osmotic pressure between the intra- and extracapillary compartments.²¹ These pathophysiological conditions are probably valid in patients with severe brain trauma and should have a fundamental influence on neurological intensive care. According to these physiological principles, it is important not only to restore a normal circulating blood volume and a sufficient CPP, but also to normalize the colloidal osmotic pressure and to keep MABP (and hence intracapillary hydrostatic pressure) as low as possible. These physiological considerations constitute the basis for the volume-targeted therapy of high ICP (sometimes referred to as the "Lund concept").^{1,9,12,27} Obviously, a reduction in MABP (and CPP) might jeopardize cerebral energy metabolism in these patients, especially in vulnerable regions such as the penumbral zones surrounding focal mass lesions. To eliminate these risks and to establish the critical thresholds for CPP, patients with severe brain trauma are, in our intensive care unit, monitored with the aid of intracerebral microdialysis. Bedside analyses of variables reflecting cerebral energy metabolism have been conducted as a clinical routine since 1995.

INTRACEREBRAL MICRODIALYSIS

The technique of microdialysis was introduced more than 25 years ago for monitoring brains in animals^{43,45} and has become a standard procedure in neuroscience, with data from more than 8000 publications supporting its use. The first studies of the brain in humans were published more than 10 years ago.^{13,20} In 1995 CMA Microdialysis (Stockholm, Sweden) introduced microdialysis instruments for clinical use: catheters for peripheral and brain tissue, a microdialysis pump, and a bedside chemical analyzer. The microdialysis catheter designed for use in humans consists of a 60-mm-long shaft and a 10-mm-long dialysis membrane (polyamide, 20,000 molecular weight cutoff) with an outer diameter of 0.62 mm (CMA 70; CMA Microdialysis). The microdialysis catheters are perfused with a Ringer solution (perfusion fluid; CMA Microdialysis) from a microinfusion pump (CMA 106 or CMA 107; CMA Microdialysis) with a flow of 0.3 μ l/minute during clinical routine monitoring. The microdialysis samples are collected in capped microvials (CMA Microdialysis) to prevent evaporation and are analyzed at bedside by using ordinary enzymatic methods on a microdialysis analyzer (CMA 600; CMA Microdialysis). The chemical variables of particular interest during intensive care are those related to glycolysis (glucose, pyruvate, and lactate), degradation of the glycerophospholipids of cell membranes (glycerol), and excessive levels of excitatory transmitters (glutamate). A simplified diagram of intermediary metabolism is featured in Fig. 1.

The measured levels of the chemical substances correspond to their absolute interstitial concentrations only if complete equilibration has occurred over the dialysis membrane. The degree of equilibration for a permeable substance (relative recovery) is mainly dependent on the perfusion rate, the length of the dialysis membrane, and

Fig. 1. Simplified diagram of intermediary metabolism of the glycolytic chain and its relation to the formation of glycerol and glycerophospholipids and to the citric acid cycle. α -KG = α -ketoglutarate; DHAP = dihydroxyacetone-phosphate; F-1,6-DP = fructose-1,6-diphosphate; FFA = free fatty acids; G-3-P = glycerol-3-phosphate; GA-3P = glyceraldehyde-3-phosphate. *Underlining* indicates metabolites that are measured bedside by using enzymatic techniques.

the diffusion of the substance in the tissue. According to the clinical microdialysis equipment, the estimated recovery level for the substances mentioned earlier was approximately 70% of their true interstitial levels at a perfusion rate of 0.3 μ l/minute.¹⁶ Recovery may vary during pathophysiological conditions due to changed conditions of diffusion in the tissue. Note, however, that this variability is relevant mainly when performing studies of absolute concentration levels (for example, pharmacokinetic studies).⁸ During intensive care, the changes caused by the perturbation of energy metabolism are so profound that minor changes in relative recovery are of limited importance. Table 1 features data for these chemical variables in healthy, awake patients³² and in sedated patients with severe brain trauma and cerebral ischemia.⁴⁰ The glycerol level and the lactate/pyruvate ratio are usually of particular interest during intensive care. A marked increase in the glycerol level indicates degradation of the glycerophospholipids of cell membranes.^{14,29,44} The lactate/pyruvate ratio reflects cytoplasmatic redox state, which can be expressed in terms of the lactate dehydrogenase equilibrium where H⁺ stands for ionized hydrogen; NADH, the reduced form of nicotinamide-adenine dinucleotide; NAD⁺, the oxidized form of nicotinamide-adenine dinucleotide; and K_{LDH} the equilibrium constant of the lactate dehydrogenase reaction:³⁷

$$[NADH][H^+]/[NAD^+] = [lactate]/[pyruvate] \times K_{LDH}$$

The time courses of the changes in these variables during transient cerebral ischemia are illustrated in Fig. 2. In this experimental study transient brain ischemia was induced in fetal lambs in utero by occluding the umbilical cord, followed by resuscitation after cardiac standstill (I Amer-Wahlin, et al., unpublished data). The microdialysis technique was identical to that used during clinical conditions, but the perfusion rate was increased (1 μ l/minute) to allow frequent sampling. Induction of ischemia caused an almost instantaneous increase in the lactate/pyruvate ratio shortly thereafter, followed by an increase in the glutamate level. Glucose, pyruvate, and glutamate rapidly recovered after resuscitation, but the levels of lactate and glycerol remained elevated.

Use of the microdialysis technique provides biochemical information concerning only a small volume surrounding the catheter. This may be regarded as an advantage during neurological intensive care given that most adverse events primarily affect the sensitive penumbral zones surrounding focal lesions.⁴¹ Consequently, it is necessary to insert microdialysis catheters into these areas of interest. Figure 3 A and B illustrates the positions of two microdialysis catheters in areas close to superficial contusions following evacuation of an acute subdural hematoma. In addition, a third microdialysis catheter has been introduced close to the ventricular catheter in the opposite, less injured hemisphere (Fig. 3C).

CEREBRAL ENERGY METABOLISM DURING A DECREASE IN CPP

The lower critical limit of CPP for the maintenance of cerebral energy metabolism varies among different individuals (and different species). It also depends on the intra- and extracranial pathophysiological conditions (for example, whether the decrease in CPP was caused by an increase in ICP or a decrease in MABP (hypovolemia, cardiac failure, and so forth). A sudden increase in ICP in normal rats did not cause perturbation of cerebral energy metabolism until CPP had decreased to less than 30 mm Hg.³⁸ An injured brain would be expected to be more sensitive. Furthermore, in a rat model of cranial impact injury, contusion volume was minimized when CPP was kept between 70 and 105 mm Hg and increased at a CPP less than 60 mm Hg or more than 105 mm Hg.¹⁹ These limits, which were obtained under experimental conditions, must not be directly transferred to human conditions, however. In a consecutive series of 50 patients with severe trau-

TABLE 1
Cerebral interstitial concentrations of chemical variables during wakefulness in healthy patients and during ischemia in sedated patients with severe brain trauma*

Patient State	Glucose (mmol/L)	Pyruvate (μ mol/L)	Lactate (mmol/L)	Lactate/Pyruvate Ratio	Glutamate (μ mol/L)	Glycerol (μ mol/L)
healthy, awake	1.7 $\pm$ 0.9	166 $\pm$ 47	2.9 $\pm$ 0.9	23 $\pm$ 4	16 $\pm$ 16	82 $\pm$ 44
ischemic, sedated	0.1 $\pm$ 0.2	31 $\pm$ 47	8.9 $\pm$ 6.5	460 $\pm$ 560	380 $\pm$ 240	570 $\pm$ 430

*Data are given as the means $\pm$ SD from Reinstrup, et al., and Ståhl, et al.⁴⁰

Fig. 2. Graphs demonstrating changes in intracerebral biochemistry in in utero fetal lambs after occlusion of the umbilical cord and resuscitation following cardiac standstill (I Amer-Wahlin, et al., unpublished data). a: Levels of glu-

matic brain injuries, multiple intracerebral microdialysis catheters were inserted to monitor energy metabolism while at a patient's bedside.²⁸ All patients were treated surgically with the evacuation of focal, intracranial mass lesions. Thirty-one patients had an acute subdural hematoma (two were combined with an extradural hematoma and 15 were combined with focal cerebral contusions), three had a combination of focal contusion and extradural hematoma, 15 had pure focal hemorrhagic contusions, and one patient had a pure epidural hematoma. The microdialysis catheters were placed according to the principles in Fig. 3, that is, one or more catheters were positioned in the pericontusional penumbral zone (worse position) and one catheter was placed in the less injured hemisphere close to the ICP recording device (better posi-

tion). All patients were treated according to the Lund concept^{12,27} and the microdialysis samples were analyzed at bedside every 60 minutes.

Figure 4 shows the mean levels of glucose (10,253 measurements), lactate (11,538 measurements), and glycerol (13,244 measurements) and the lactate/pyruvate ratio (7704 measurements), from intracerebral microdialyses of the better and worse catheter positions in relation to four ranges of CPP.²⁸ The interrupted horizontal lines indicate reference values (mean $\pm$ SD) for healthy brains in humans during wakefulness.³² As shown in Fig. 2, changes in glucose and the lactate/pyruvate ratio occurred instantaneously after the induction of brain ischemia, and the levels rapidly normalized after resuscitation. On the other hand, lactate and glycerol levels may remain in-

Fig. 3. Computerized tomography scans (A and B) demonstrating two microdialysis catheters (1 and 2) that have been positioned in areas close to superficial contusions following evacuation of an acute subdural hematoma. C: A computerized tomography scan demonstrating a third microdialysis catheter (3) that has been introduced close to the ventricular catheter (v.c.) in the opposite, less injured hemisphere.

Fig. 4. Bar graphs demonstrating mean ($\pm$ SD) levels of glucose (10,253 measurements; a), lactate (11,538 measurements; b), lactate/pyruvate ratio (la/py) (7704 measurements; c), and glycerol (13,244 measurements; d) in the better (white bar) and worse (gray bar) catheter positions (see text) in relation to four ranges of CPPs in 50 patients with severe traumatic brain lesions. Interrupted lines indicate the range (mean $\pm$ SD) in healthy brains in humans during wakefulness.

creased for hours after transient ischemia (Fig. 2). Accordingly, we would expect the glucose level and the lactate/pyruvate ratio to be the most sensitive and specific indicators of the deterioration of cerebral energy metabolism during a transient decrease in CPP. In the present study, there were no statistically significant differences in glucose concentration when comparing the better and worse catheter positions or the different ranges of CPP. For the lactate/pyruvate ratio, the situation was more complex and a detailed statistical analysis is given in the original report.²⁸ Briefly, no difference in lactate/pyruvate ratio was obtained when comparing the worse and better catheter positions at a CPP higher than 70 mm Hg. The lactate/pyruvate ratio was higher ($p = 0.04$) in the worse than in the better catheter position at a CPP lower than 50 mm Hg. When comparing a CPP less than 50 mm Hg with one greater than 70 mm Hg and a CPP less than 50 mm Hg with one greater than 50 mm Hg, the lactate/pyruvate ratio was higher at the lower CPP in the worse catheter position ($p = 0.04$ and $p = 0.01$, respectively). No difference in lactate/pyruvate ratio was obtained in the better catheter position when comparing a CPP less than 50 mm Hg to one greater than 50 mm Hg. These data support the view that, if necessary, CPP may be reduced to 50 to 60 mm Hg in patients with severe traumatic brain lesions provided that the physiological and pharmacological principles followed in the study (Lund concept) are recognized.

The observation that the glucose concentration was

within normal limits in the worse catheter position at CPP less than 50 mm Hg (indicating a sufficient supply of the substrate [Fig. 4a]) even though the lactate/pyruvate ratio was very high (indicating an insufficient supply of oxygen [Fig. 4c]) is not contradictory. At a normal hemoglobin concentration of 150 g/L and 95% saturation, human arterial blood contains approximately 9 $\mu\text{mol O}_2/\text{ml}$ and the arteriovenous O_2 difference is approximately 3 $\mu\text{mol/ml}$.^{28,37} Thus if CBF is reduced to approximately one third, theoretically all oxygen will be extracted. In practice, however, such a reduction in CBF cannot maintain a normal O_2 supply, because the reduction in PO_2 will also decrease the O_2 diffusion gradient. For glucose, the following approximate levels have been described in humans: arterial concentration 5.1 $\mu\text{mol/ml}$, venous concentration 4.6 $\mu\text{mol/ml}$, arteriovenous glucose difference 0.5 $\mu\text{mol/ml}$.^{28,37} Accordingly, during ischemia induced by a gradual decrease in CBF, O_2 supply to the brain will be insufficient before the supply of substrate is seriously jeopardized.

BIOCHEMICAL EVALUATION OF TISSUE OUTCOME

The efficacy of any therapy administered during neurological intensive care is conventionally judged based on clinical outcome. The microdialysis technique offers an additional possibility: restitution of energy metabolism

and intermediary metabolism may be used as an indicator of tissue outcome. It is then important to evaluate the biochemical features not only in less injured parts of the brain, but also in the more vulnerable penumbral zones (Fig. 3).

Figure 5 summarizes physiological and biochemical information in a series of patients treated according to the Lund concept.⁴² The figure graphically shows changes in MABP and CPP (Fig. 5a) as well as intracerebral glycerol levels (Fig. 5b) during the first 72 hours after the start of treatment. In accordance with the Lund concept, CPP decreased from 73 to 62 mm Hg due to the pharmacologically induced reduction in MABP. The gradual decrease in ICP caused a slow increase in CPP back to 65 to 70 mm Hg following the initial decrease. The pharmacologically induced decrease in CPP was associated with a simultaneous decrease in interstitial glycerol in the worse catheter position from a very high level ($> 300 \mu\text{mol/L}$) at the start of treatment to a normal level within 72 hours. These data strongly support the view that the vulnerable penumbral zone may tolerate a controlled decrease in CPP provided that this is achieved according to the physiological principles discussed earlier.

CLINICAL ASPECTS

For two reasons many authors have regarded a substantial increase in CPP, often accomplished by the infusion of vasopressors, as desirable in patients with severe brain trauma. First, the injured brain is exceptionally vulnerable to secondary ischemic insults (in particular, hypotension), which are associated with a poor neurological outcome.^{6,22} Accordingly, it might seem rational to use vasopressors liberally to increase CPP. In a randomized clinical trial, CPP was maintained above 70 mm Hg to improve CBF

and prevent secondary ischemic insults.³⁴ The use of this CBF-targeted therapy successfully reduced the incidence and duration of jugular venous desaturation; however, it also increased the incidence of adult respiratory distress syndrome and failed to improve neurological outcome.³⁴ Consequently, the study data did not support the liberal use of vasopressors, and it was later concluded that a CPP of 60 mm Hg probably provided adequate perfusion for most patients with severe traumatic brain injuries.³³

Second, it has been asserted that a decrease in CPP provokes an increase in ICP (vasodilatory cascade) and, conversely, that an increase in CPP effectively decreases ICP (vasoconstriction cascade).^{35,36} The notion that an increase in CPP would regularly cause a decrease in ICP receives little support from physiological study data. In an experimental study of the injured feline brain, induced arterial hypertension invariably increased ICP.¹⁸ Furthermore, in a recent clinical study of patients with severe brain trauma a titratable phenylephrine infusion used to increase in MABP by 10 to 15 mm Hg significantly increased ICP in almost all studied cases.³⁰

The earlier theoretical physiological discussion strongly supports the view that the injured brain would benefit from maintaining a low intracapillary hydrostatic pressure and a normal colloid osmotic pressure. Data from the clinical microdialysis studies presented earlier document that the injured brain tolerates a controlled decrease in CPP according to the Lund concept. This therapy is focused on a pharmacologically induced reduction in MABP to reduce hydrostatic capillary pressure, colloid infusion to increase plasma oncotic pressure, and antistress therapy and maintenance of a normal circulating blood volume to improve microcirculation.^{1,9,12,27} A reduction of the intracranial blood volume is achieved by reducing cerebral energy metabolism, and a further reduction in blood volume, if

Fig. 5. a: Graph demonstrating the reductions in MABP and CPP during the first 72 hours after the start of treatment according to the Lund concept (mean $\pm$ standard error of the mean). b: Graph demonstrating glycerol levels (mean $\pm$ standard error of the mean) obtained bedside from microdialysis catheters positioned in the penumbral zone surrounding evacuated focal brain lesions (Glycerol W) as well as from the contralateral hemisphere (Glycerol B). Interrupted lines indicate the range (mean $\pm$ SD) in healthy brains in humans during wakefulness. The intentional decrease in CPP was associated with a normalization of all studied biochemical variables.

TABLE 2
Outcome according to the GOS in patients with severe traumatic brain lesions treated conventionally and according to the Lund concept*

Authors & Year	Study Years	No. of Patients	Treatment Protocol	GOS Score (% of patients)				
				GR	MD	SD	VS	D
Eker, et al., 1998	1982–1986	38	hyperventilation & high-dose barbituate coma	29	13	5	5	47
Eker, et al., 1998	1989–1994	53	Lund concept	38	42	11	2	8
Naredi, et al., 1998	1993–1994	38	Lund concept	42	29	13	3	11
Naredi, et al., 2001	1998	31	Lund concept	61	10	23	3	3

* D = death; GR = good recovery; MD = moderate disability; SD = severe disability; VS = vegetative state.

necessary, can be obtained within the venous compartment by infusing dihydroergotamine.^{2,25,26} The goal of this treatment is to reach a slow and lasting reduction in ICP over hours to days. Detailed accounts of the drugs and dosages used in this treatment protocol have been presented in previous reports.^{1,9,12,27}

Results of randomized controlled studies are used definitively to prove the efficacy of all treatment protocols, and the Lund concept has been criticized for not being proven in this way.¹¹ Currently, there are no such studies to support any specific treatment for increased ICP, however.^{4,39} Until data from such studies are available, the efficacy of the Lund concept may be judged based on the physiological and biochemical studies discussed earlier, and the clinical results compared with historical controls. Clinical outcome following the use of the Lund concept has been reported by investigators from three neurosurgical centers in Sweden.^{9,23,24} The clinical results 6 months after injury, according to the GOS,¹⁷ are listed in Table 2. In the original study, in which were compared two groups of patients with very severe brain trauma, impaired CO₂ reactivity, and an ICP above 25 mm Hg despite conventional treatment, the mortality rate decreased from 47 to 8%.⁹ Significant increases in the groups with a good recovery and moderate disability were obtained, but there was no increase in the number of patients in the groups with severe disability or vegetative state.

CONCLUSIONS

The injured brain is exceptionally vulnerable to secondary ischemic insults (for example, arterial hypotension), but also—due to an increased permeability of the BBB to crystalloids and an impaired pressure autoregulation of CBF—sensitive to increased MABP. An increase in CPP (and a decrease of the colloid osmotic pressure of the blood) will, given these circumstances, lead to a net transport of water across the BBB and an increase in ICP. Accordingly, an assessment of the lower critical threshold for CPP is important for neurological intensive care. This threshold varies among different patients and different areas of the brain, and the penumbral zones surrounding focal brain lesions appear to be the most sensitive.^{15,33,41} Thus, the optimal treatment protocol for patients with severe traumatic brain lesions and increased ICP probably differs among patients. In an individual patient, the preservation of normal cerebral energy metabolism within areas

at risk during a decrease in CPP can be guaranteed by performing intracerebral microdialysis and bedside biochemical analyses.²⁸

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Address reprint requests to: Carl-Henrik Nordström, M.D., Ph.D., Department of Neurosurgery, Lund University Hospital, S-221 85 Lund, Sweden. email: carl-henrik.nordstrom@neurokir.lu.se.