■ CLINICAL INVESTIGATIONS

Assessment of the Lower Limit for Cerebral Perfusion Pressure in Severe Head Injuries by Bedside Monitoring of Regional Energy Metabolism

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Background: In patients with severe traumatic brain lesions, the lower limit for cerebral perfusion pressure (CPP) is controversial. The aim of this prospective study was to assess this limit from bedside measurements of cerebral energy metabolism and to clarify whether the penumbra zone surrounding a focal lesion is more sensitive to a decrease in CPP than less-injured areas.

Methods: Fifty patients with severe head injury were included after evacuation of an intracranial hematoma and/or focal brain contusion. They were treated according to intensive care routine (Lund concept), including continuous monitoring of intracranial pressure. One microdialysis catheter was inserted in less-injured brain tissue ("better" position), and one or two catheters were inserted into the boundary of injured cerebral cortex ("worse" position). Concentrations of glucose, pyruvate, and lactate were analyzed and displayed bedside and were related to CPP (n = 29,495).

Results: Mean interstitial glucose concentration was unaffected by the level of the CPP within the studied ranges. Increases in lactate concentration ($P = 0.0008$) and lactate–pyruvate ratio ($P = 0.01$) were obtained in the "worse" but not in the "better" position at CPP less than 50 mmHg compared with the same positions at CPP greater than 50 mmHg.

Conclusions: The study results support the view that CPP may be reduced to 50 mmHg in patients with severe traumatic brain lesions, provided that the physiologic and pharmacologic principles of the Lund concept are recognized. In the individual patient, preservation of normal concentrations of energy metabolites within cerebral areas at risk can be guaranteed by intracerebral microdialysis and bedside biochemical analyses.

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IN patients with severe traumatic brain injuries, death is usually caused by an intractable increase in intracranial pressure (ICP). ICP is monitored continuously in most neurosurgical centers, and there is consensus concerning most aspects of initial management (controlled ventilation, avoidance of hypovolemia and arterial hypotension, blood volume substitution, early evacuation of focal intracranial mass lesions). However, in the treatment protocols for sustained increase in ICP, the strategies differ widely.[1] In recent years, the varying views have been polarized into two groups. One group focuses on cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) and includes pharmacologically induced increases in mean arterial blood pressure (MAP) and CPP to improve CBF.[2–6] In these treatment protocols, MAP and CPP are increased by intravenous infusion of inotropic drugs and/or vasopressors (norepinephrine, phenylephrine), and the treatments are considered to be CPP targeted or CBF targeted.[1–6] The second group focuses on reduction of ICP by decreasing one or more of the intracranial volumes (volume targeted, Lund concept). According to the Lund concept, an increased reabsorption of intracerebral water is accomplished by maintaining a normal colloid osmotic pressure (with blood transfusion and albumin infusion) in combination with a reduction in intracapillary hydrostatic pressure.[7–9]

The physiologic and pharmacologic principles behind the two therapeutic concepts are incompatible. For the CPP-targeted therapy, the lower acceptable limit for CPP has often been set at 70 mmHg,[1,3–6] but considerably higher CPP has also been recommended.[10] For the Lund concept, the lower limit has been set at 50 mmHg.[7,8] Intracerebral microdialysis with bedside monitoring of metabolites reflecting cerebral energy metabolism may offer a possibility to evaluate the lowest acceptable CPP in the individual patient.[11] In the present study, microdialysis catheters were inserted into less-injured ("better"), as well as more-injured ("worse"), parts of the brain in patients with severe head injuries. The objectives of the study were to investigate whether cerebral energy metabolism was more at risk in the worse position than in the better position during a decrease in CPP and to assess the lower acceptable limit for CPP for the two regions. We report the results of 29,495 bedside biochemical analyses (glucose, pyruvate, lactate) in relation to CPP in 50 patients with severe head injuries.

Materials and Methods

Patients

A total of 50 consecutively presenting patients with severe traumatic brain lesions (posttraumatic coma > 6 h) were included in this prospective study. The mean age of the patients was 43 ± 18 yr (range, 2–75 yr). All patients were treated surgically with evacuation of focal, intracranial mass lesions. Thirty-one patients had an acute subdural hematoma (2 combined with an extradural hematoma, 15 combined with focal cerebral contusions), 3 patients had a combination of focal contusion and extradural hematoma, 15 patients had pure focal hemorrhagic contusions, and 1 patient had a pure epidural hematoma. The clinical decision to evacuate the focal lesion was always based on computed tomography scan, neurologic state on admission, and, in many cases, repeated neurologic evaluation. All patients received an intraventricular catheter for continuous ICP monitoring. Seven patients died during the intensive care period—all because of increased ICP (mean age, 45 ± 25 yr; range, 15–75 yr).

All treatment was in accordance with clinical routine in our department, and the ethical committee of Lund University Medical Faculty (Lund, Sweden) has approved the use of microdialysis with multiple intracerebral catheters as a routine procedure in patients with severe traumatic brain injuries. Informed consent was obtained from relatives of all patients.

Microdialysis Technique

The technique for intracerebral microdialysis and bedside biochemical monitoring has been described in detail elsewhere.[12,13] Briefly, during surgery, one or two microdialysis probes (CMA 70, molecular cutoff of 20 kd; CMA Microdialysis, Stockholm, Sweden) were inserted into the brain tissue surrounding the evacuated focal mass lesion (worse position).[11,13] In addition, one microdialysis catheter was inserted into the cerebral cortex *via* a separate burr hole close to that used for ICP recording (better position).[11-13]

Figure 1 shows the positioning of the intracerebral microdialysis probes in a typical case. A large, hemorrhagic frontal contusion (fig. 1A) was evacuated, and two microdialysis probes were positioned in the surrounding (worse position) brain tissue (fig. 1B). The ventricular catheter used for ICP monitoring is shown in figures 1B and 1C. Figure 1C also shows the position of the third intracerebral probe (better position) in relation to the ventricular catheter.

The catheters were perfused (Perfusion Fluid; CMA Microdialysis, Stockholm, Sweden) at 0.3 μl/min from a microinfusion pump (CMA 106; CMA Microdialysis, Stockholm, Sweden), and samples (median number per patient, 114; range, 12–532) were collected every 60 min for bedside analyses of glucose, pyruvate, and lac-
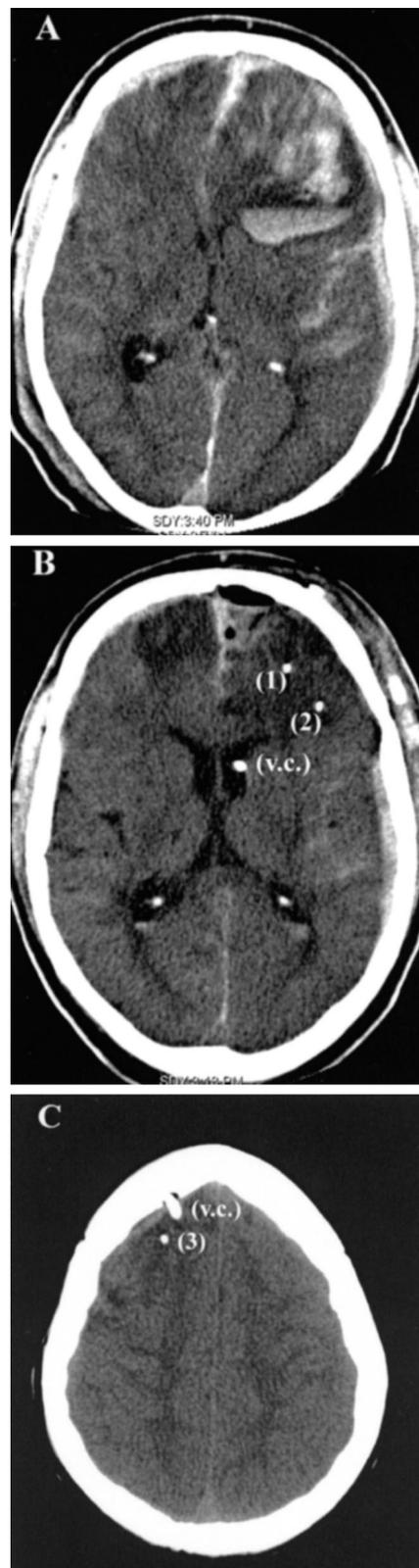

Fig. 1. (*A*) A large, hemorrhagic frontal contusion was evacuated. (*B*) Two microdialysis probes, (1) and (2), were positioned in surrounding ("worse") brain tissue, and a ventricular catheter (v.c.) was inserted. (*C*) A third microdialysis probe (3) was placed in the opposite ("better") hemisphere.

tate using a CMA 600 Microdialysis Analyzer (CMA Microdialysis, Stockholm, Sweden).[12] Since the analytical techniques were partly developed during the study, it was possible to measure pyruvate bedside in only 33 of the patients. All biochemical data were compared with the reference concentrations in normal human brain obtained using identical microdialysis and analytical techniques.[12]

Treatment during Intensive Care

All patients were sedated and intubated with controlled ventilation. Neuromuscular blockade was not used. Stress response was reduced by liberal use of midazolam (5–20 mg/h) and fentanyl (2–5 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and continuous infusion of low-dose thiopental (0.5–3 mg $\cdot kg^{-1} \cdot h^{-1}$) was also used in most patients. Increased ICP was treated according to the protocol (Lund concept) in our department.[7–9] The protocol includes antihypertensive and antistress treatment with a combination of the β_1-antagonist metoprolol (0.2–0.3 mg $\cdot kg^{-1} \cdot 24 h^{-1}$ intravenously) and the α_2-agonist clonidine (0.4–0.8 $\mu g/kg$ every 4–6 h intravenously)[14] and was initiated when the patient was clearly normovolemic, as determined by erythrocyte and albumin–plasma transfusions to normal albumin and hemoglobin values and to a normal central venous pressure. A CPP of 60–70 mmHg was considered optimal, but, if necessary to control ICP, a CPP of 50 mmHg was accepted in adults. During episodes of high ICP and low CPP, intravenous infusion of dihydroergotamine was used in 11 patients but always at a lower dose and for a shorter duration than in previous studies.[7–9,15,16] Diuretics (furosemide) and albumin infusion were used to achieve a balanced or moderately negative fluid balance. During the first 24 h, patients were given parenteral fluid, including glucose-containing solutions. All patients were later given low-calorie enteral nutrition (maximum energy supply, 15–20 kcal $\cdot kg^{-1} \cdot 24 h^{-1}$). Insulin was administered intravenously to achieve a blood glucose concentration less than 8 mM (144 mg/dl).

Statistics

The statistical evaluation was performed in collaboration with Jan-Åke Nilsson, B.Sc., consulting statistician at the Department of Internal Medicine, Malmö University Hospital, Malmö, Sweden. Four ranges of CPP were chosen arbitrarily: less than 50 mmHg, 50–60 mmHg, 61–70 mmHg, and greater than 70 mmHg. Within each CPP range, the median concentrations of the biochemical variables obtained by intracerebral microdialysis, as well as the lactate–pyruvate ratio, were calculated for each patient. For each variable, five hypotheses were tested using the Wilcoxon matched pairs test for pairs of variables in the worse and better parts of the brain in relation to the CPP levels: worse part greater than 70 mmHg *versus* better part greater than 70 mmHg,
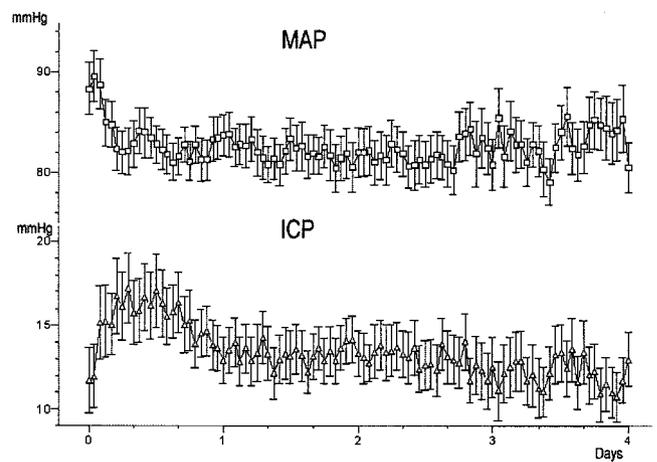

Fig. 2. Mean values ± SEM (mmHg) for mean arterial blood pressure (MAP; *top*) and intracranial pressure (ICP; *bottom*) during the initial four postoperative days after evacuation of intracranial focal mass lesions in 50 patients with severe traumatic brain lesions. The data have been clustered to one value each hour.

worse part less than 50 *versus* better part less than 50, worse part less than 50 *versus* worse part greater than 70, worse part less than 50 *versus* worse part greater than 50, and better part less than 50 *versus* better part greater than 50. Due to repeated comparisons $P \leq 0.01$ was considered statistically significant.

Results

For the entire group of 50 patients, MAP was 82 ± 15 mmHg (mean ± SD), and ICP was 14 ± 10 mmHg (mean ± SD) during the first 4 days after surgical evacuation of the focal mass lesions. The changes over time (mean ± SEM) for both parameters are shown in figure 2. During the first 6 h after surgery, ICP increased from
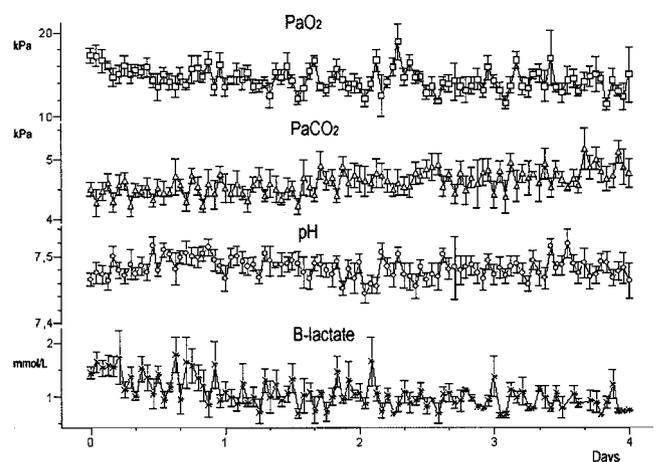

Fig. 3. Mean values ± SEM for arterial Po_2 (kPa), Pco_2 (kPa), pH, and lactate concentration (mM) during the initial four postoperative days after evacuation of intracranial focal mass lesions in patients with severe traumatic brain lesions. The data have been clustered to one value each hour.
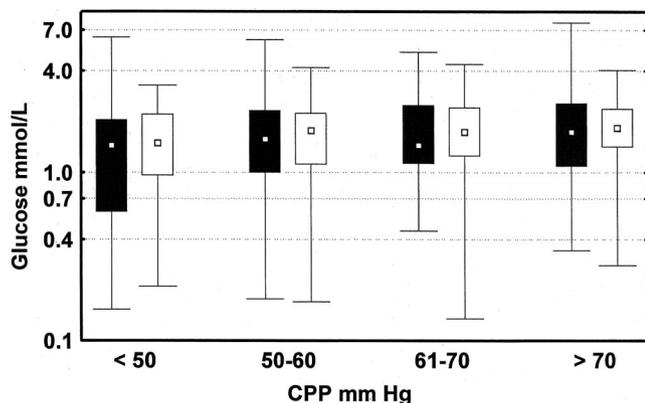
Fig. 4. Median level (central square) for glucose (n = 10,253; logarithmic scale) in the "better" and "worse" positions in relation to four ranges of cerebral perfusion pressure (CPP). The boxes (solid = better; open = worse) represent the lower and the upper quartiles, and the whiskers represent the range. The results of the statistical evaluation (pairs of data) are shown in table 1.

Fig. 5. Median level (central square) for lactate (n = 11,538; logarithmic scale) in the "better" and "worse" positions in relation to four ranges of cerebral perfusion pressure (CPP). The boxes (solid = better; open = worse) represent the lower and the upper quartiles, and the whiskers represent the range. The results of the statistical evaluation (pairs of data) are shown in table 1.

a mean level of 12 to 17 mmHg. The pharmacologic treatment according to the Lund concept started at the beginning of this period, and mean MAP decreased from 89 mmHg to 81 mmHg. During the following 90 h, MAP remained close to the latter level, while ICP slowly decreased. Mean MAP was 84 mmHg, and ICP was 11 mmHg during the last 6 h in figure 2.

Figure 3 shows the simultaneous changes (mean ± SEM) in arterial Po_2, Pco_2, pH, and lactate concentration. Arterial Po_2, Pco_2, and pH were obtained for all 50 patients (n = 952 for each variable). The mean levels of these variables were 108.75 mmHg (14.5 kPa), 34.5 mmHg (4.6 kPa), and 7.48, respectively, during the illustrated period. The lactate concentration of arterial blood (mean concentration, 1.1 mM) was obtained for 24 patients (n = 460).

Figure 4 shows the median concentrations of glucose (n = 10,253) obtained using intracerebral microdialysis of the better and worse positions in relation to four ranges of CPP for all 50 patients. The central squares signify the median concentrations, the boxes (solid = better; open = worse) represent the lower and the upper quartiles, and the whiskers represent the range. In a normal human brain, the intracerebral glucose concentration is 1.7 ± 0.9 mM (mean ± SD) during wakeful-
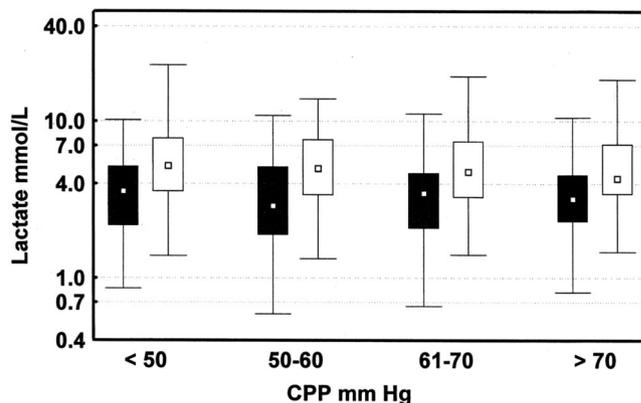
ness.[12] The results of the statistical evaluation according to the five aforementioned hypotheses are shown in table 1. In the statistical evaluation, paired data for each individual patient were included, and the number of patients included in each calculation is given in table 1 (valid N). There were no statistically significant differences in glucose concentration between the better and worse positions or among the different ranges of CPP.

Figure 5 shows the median lactate concentrations (n = 11,538) obtained using intracerebral microdialysis of the better and worse positions in relation to four ranges of CPP for all 50 patients. The central squares signify the median concentrations, the boxes (solid = better; open = worse) represent the lower and the upper quartiles, and the whiskers represent the range. In a normal human brain, the intracerebral lactate concentration is 2.9 ± 0.9 mM (mean ± SD) during wakefulness.[12] The results of the statistical evaluation according to the five aforementioned hypotheses are shown in table 1. In the statistical evaluation, paired data for each individual patient were included, and the number of patients included in each calculation is given in table 1 (valid N). The lactate concentration was significantly higher in the worse position than in the better position for CPP greater than 70 mmHg (P = 0.0015), as well as for CPP

Table 1. Statistical Evaluation of Data Pairs for Glucose, Lactate, and Lactate–pyruvate Ratio in Worse and Better Parts of the Brain and Related to the Level of Cerebral Perfusion Pressure

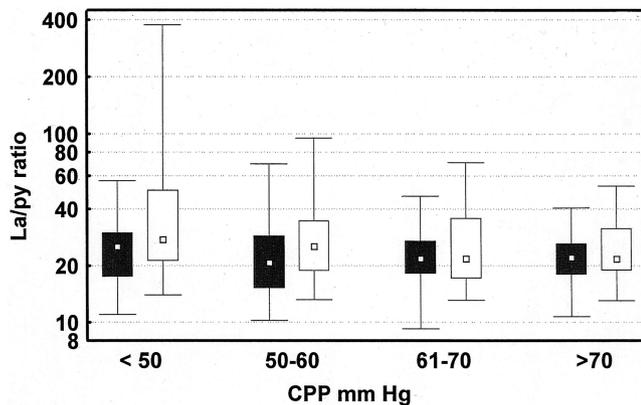| Pair of variables	Glucose		Lactate		LP ratio	
Worse *vs.* Better, CPP mmHg	Valid n	P	Valid n	P	Valid n	P
Worse > 70 *vs.* Better > 70	43	0.86	48	0.0015	30	0.25
Worse < 50 *vs.* Better < 50	23	0.58	28	0.0003	23	0.04
Worse < 50 *vs.* Worse > 70	21	0.36	25	0.26	20	0.04
Worse < 50 *vs.* Worse > 50	21	0.36	28	0.0008	23	0.01
Better < 50 *vs.* Better > 50	25	0.78	35	1.00	24	0.57

CPP = cerebral perfusion pressure; LP = lactate–pyruvate.

Fig. 6. Median level (central square) for the lactate–pyruvate (la/py) ratio (n = 7,704; logarithmic scale) in the "better" and "worse" positions in relation to four ranges of cerebral perfusion pressure (CPP). The boxes (solid = better; open = worse) represent the lower and the upper quartiles, and the whiskers represent the range. The results of the statistical evaluation (pairs of data) are shown in table 1.

less than 50 mmHg ($P = 0.0003$). When comparing CPP less than 50 mmHg with CPP greater than 50 mmHg, the lactate concentration was higher at the low CPP in the worse position ($P = 0.0008$) but was unchanged in the better position.

Figure 6 shows the median lactate-pyruvate ratios (n = 7,704) in the better and worse positions in relation to four ranges of CPP for 33 patients. The central squares signify the median ratios, the boxes (solid = better; open = worse) represent the lower and the upper quartiles, and the whiskers represent the range. In a normal human brain, the intracerebral lactate-pyruvate ratio is 23 ± 4 (mean $\pm$ SD) during wakefulness.[12] The results of the statistical evaluation according to the five aforementioned hypotheses are shown in table 1. In the statistical evaluation, paired data for each individual patient were included, and the number of patients included in each calculation is given in table 1 (valid N). No difference in the lactate-pyruvate ratio was observed when comparing the worse and better positions at CPP greater than 70 mmHg. The lactate-pyruvate ratio was higher ($P = 0.04$) in the worse position than in the better position at CPP less than 50 mmHg. When comparing CPP less than 50 mmHg with CPP greater than 70 mmHg and CPP less than 50 mmHg with CPP greater than 50 mmHg, the lactate-pyruvate ratio was higher at the low CPP in the worse position ($P = 0.04$ and $P = 0.01$, respectively). No difference in the lactate-pyruvate ratio was observed in the better position when comparing CPP less than 50 mmHg with CPP greater than 50 mmHg.

Discussion

According to the Lund concept, a decrease in CPP is not a goal in itself but a measure to decrease brain volume by a slow and continuous transcapillary reab-

sorption of water. During physiologic conditions, regulation of brain volume is mainly determined by the blood–brain barrier (BBB). The intact BBB has a very low permeability for large molecules like colloids but also for crystalloids.[17] Accordingly, the total osmotic pressure is essentially determined by the crystalloids (primarily sodium and chloride) and amounts to approximately 5.700 mmHg. An influx of water across the BBB due to increased intracapillary hydrostatic pressure therefore will not be accompanied by crystalloids, and an osmotic pressure gradient working in the opposite direction will immediately be created, thereby counteracting further water influx. During physiologic conditions, a change in intracapillary hydrostatic pressure or colloidal osmotic pressure therefore will have only minor effects on brain volume. During pathophysiologic conditions with a partial or complete disruption of the BBB, variations in these two variables will, however, be of crucial importance for brain volume and ICP.[9]

The lower limit of CPP for maintenance of cerebral energy metabolism varies between individuals and is dependent on intracranial and extracranial pathophysiologic conditions and whether the decrease in CPP is caused by an increase in ICP or by a decrease in MAP (e.g., due to hypovolemia). In experimental studies of normal rat brain, a sudden perturbation of cerebral energy metabolism occurred when CPP decreased to less than 30 mmHg due to increased ICP.[18] The injured brain would be expected to be more sensitive to a decrease in CPP. In a rat model, contusion volume following impact injury was minimized when CPP was maintained between 70 and 105 mmHg and was increased at CPP less than 60 mmHg, as well as at CPP greater than 105 mmHg.[19] However, in the only randomized clinical trial that has examined the consequences of different levels of CPP, the investigators concluded that there is no compelling reason to increase CPP beyond that required to adequately perfuse the brain, and that a CPP of 60 mmHg was probably adequate for most brain trauma patients.[1,20]

Our study supports the view that more-injured brain tissue (worse position) is more sensitive to a decrease in CPP than less-injured brain tissue (better position), as revealed by significant increases in lactate concentration and lactate-pyruvate ratio at CPP less than 50 mmHg. At a normal hemoglobin concentration (150 g/l) and at 95% oxygen saturation, human arterial blood contains approximately 9 micromoles of oxygen per milliliter, and the arteriovenous oxygen difference is approximately 3 μmol/ml.[21] Thus, if CBF is reduced to approximately one third, then, theoretically, all oxygen will be extracted. In practice, such a reduction in CBF cannot maintain the normal oxygen supply since the reduction in Po$_2$ will also decrease the oxygen diffusion gradient. For glucose, the following approximate concentrations have been described for humans: arterial concentration,

5.1 μmol/ml; venous concentration, 4.6 μmol/ml; arteriovenous glucose difference, 0.5 μmol/ml.[21] Accordingly, during a gradual decrease in CBF, the oxygen supply to the brain will be insufficient before the supply of glucose is seriously decreased.

Lactate and pyruvate are considered to be diffusible through cell membranes, and measurements of the extracellular lactate–pyruvate ratio therefore should reflect cytoplasmatic redox changes,[22] which can be expressed in terms of the lactate dehydrogenase equilibrium:

$$\frac{[\text{NADH}][\text{H}^+]}{[\text{NAD}^+]} = \frac{[\text{Lactate}]}{[\text{Pyruvate}]} \times K_{\text{LDH}}$$

Accordingly, the lactate–pyruvate ratio reflects cytoplasmatic pH and regional oxygen availability. We therefore interpret the increases in lactate concentration and lactate–pyruvate ratio in the worse position at CPP less than 50 mmHg (table 1) as indicators of insufficient tissue oxygenation.

In our patients, the lactate level was consistently higher in the worse position than in the better position (table 1). The exact cause for this difference is not known, but compromised regional blood flow is a most plausible explanation. Increasing CPP might then be expected to improve microcirculation and tissue oxygenation in the worse position. However, our biochemical data do not support this assumption: at CPP greater than 70 mmHg, lactate concentration was still significantly higher in the worse position than in the better position, which seems to be in agreement with clinical experiences.[1,14] The data indicate that at CPP less than 50 mmHg, tissue oxygenation may be insufficient in severely injured parts of the brain, as shown by increases in tissue lactate concentration and lactate–pyruvate ratio in the worse, but not in the better, position (table 1).

In conclusion, our study supports the view that, if necessary, CPP may be reduced to 50 mmHg in patients with severe traumatic brain lesions, provided that the physiologic and pharmacologic principles of the Lund concept are recognized. However, it should be recognized that variations among patients might be considerable.[23] In the individual patient, preservation of normal cerebral energy metabolism within areas at risk during a decrease in CPP can be guaranteed by intracerebral microdialysis and bedside biochemical analyses. The optimal treatment protocol for patients with severe traumatic brain lesions and increased ICP probably differs among patients. Therefore, bedside monitoring of biochemical variables may be useful in optimizing the treatment of the individual patient and to evaluate various therapeutic alternatives.

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