The “Lund Concept” for the treatment of severe head trauma – physiological principles and its clinical application

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Abstract

The Lund Concept is an approach for the treatment of severe brain trauma that is mainly based on hypotheses originating from basic physiological principles regarding brain volume and cerebral perfusion regulation. Its main attributes have found support in experimental and clinical studies. This review explains the principles of the Lund Concept, and shall serve as the actual guide for its clinical application. The therapy has two main goals: 1) to reduce or prevent an increase in ICP (ICP-targeted goal) and, 2) to improve perfusion and oxygenation around contusions (perfusion-targeted goal). The Lund therapy considers the consequences of a disrupted BBB for development of brain oedema and the specific consequences of a rigid dura/cranium for general cerebral haemodynamics. It calls attention to the importance of improving perfusion and oxygenation of the injured areas of the brain. This is achieved by normal blood oxygenation, by maintaining normovolemia with normal haematocrit and plasma protein concentrations, and by antagonizing vasoconstriction through reduction of catecholamine concentration in plasma and sympathetic discharge (minimizing stress and by refraining from vasoconstrictors and active cooling). The therapeutic measures mean normalization of all essential haemodynamic parameters (blood pressure, plasma oncotic pressure, plasma and erythrocyte volumes, PaO_2, $PaCO_2$), the use of enteral nutrition, and avoidance of overnutrition. To date, clinical outcome studies using the Lund Concept have shown favourable results.

Introduction

The Lund Concept for treatment of severe head trauma, developed at Lund University Hospital in Sweden, was introduced between 1992 and1994 [1,2]. Its main characteristics are based on hypotheses originating from basic physiological principles regarding control of brain volume and cerebral perfusion. The present review is aimed at explaining the principles of the Lund Concept and to serve as the formal guide to its clinical application. A short presentation of this review was given at the Twenty-Fourth International Symposium on Intensive Care and Emergency Medicine, Brussels, March 2004 [3].

In spite of improved intensive care during the last few decades, mortality and permanent disability rates after head injury are still high [4,5]. A recent database survey from England and Wales showed that there has been no overall improvement in outcome in the last decade [5]. Outcome is a consequence of the initial impact, and secondary injury mechanisms. Secondary injuries develop over a period of hours and days after the primary injury, and contribute to brain swelling and further loss of potentially salvageable cells. A main goal of modern therapeutic interventions is to reduce secondary injuries [6]. However, we still lack scientific support for most components used for treatment of severe head injury [7,8].

Various guidelines or protocols used for the treatment of severe head injury have been introduced during the last decade. Those of the US Brain Trauma Foundation [9], those of the European Brain Injury Consortium (EBIC) [10], and the Addenbrooke protocol from Cambridge [11] are mainly based on comprehensive meta-analytic overviews combined with consensus and expert opinions. The specific Rosner protocol favours the hypothesis that an increase in arterial blood pressure will improve outcome by reducing intracranial blood volume due to autoregulatory vasoconstriction, and by improving cerebral perfusion [12].

An essential goal of these guidelines is to maintain CPP above a certain level, to squeeze enough oxygenated blood through the swollen brain (CPP-targeted therapy) [7,9,10,13,14]. It is suggested that mean arterial pressure should be maintained above 90 mmHg with a minimal CPP of 60–70 mmHg, if necessary with the aid of vasopressors [9-12,15]. Osmotherapy (e.g. mannitol) and high-dose barbiturate therapy are common treatments aimed at reducing ICP. Traditional guidelines do not specify which fluid therapy should be used, but crystalloid solutions are the main plasma volume expander recommended in most reviews [7,11,13,14].

The Lund Concept is an alternative approach to the treatment of severe brain injury, and originates from hypotheses based on basic physiological principles regarding brain volume control and cerebral perfusion. It covers how to deal with components such as blood pressure, ventilation, nutrition, sedation, volume substitution and body temperature [3,16]. Its main principles have found some evidence in experimental studies [17-19], and clinical outcome studies from 4 different neurotrauma centre using the principles of the Lund therapy have so far shown favourable results in adults [20-24] and children [25]. It has also been used for the treatment of raised ICP in meningitis [26].

To date there has been no comprehensive overview of the “Lund Concept”, including its basis in fundamental physiology and guidelines for its clinical application. The aim of the present review is to fill this need.

Volume regulation of the brain

Intact blood-brain barrier

Because of the limited space for volume expansion and to maintain ICP at its normal level of 8–13 mmHg, the volume of the brain is more effectively controlled than that of other organs. Control of brain volume is based on the intact blood-brain barrier (BBB), which means that passive transport of even the smallest solutes - such as sodium and chloride ions - across the cerebral capillaries is highly restricted. Only water passes the semi-permeable capillary membrane passively [27]. Active transfer by carrier transport systems is essential for brain nutrition and for the interstitial milieu, but is not involved in brain volume regulation, and the brain also lacks a compensatory lymphatic drainage system [27].

Fig. 1a illustrates the intact semi-permeable cerebral capillary. At steady state, forces for fluid exchange between the intravascular, the interstitial and the intracellular spaces are in balance, and there is no net fluid exchange across the capillary or cellular membranes. The crystalloid osmotic pressure is equally large (≈ 5,600 mmHg) in the 3 compartments. The transcapillary hydrostatic capillary pressure of 20–25 mmHg is roughly balanced by a similar large plasma oncotic pressure. Filtration of water across the capillary membrane triggered by imbalance between the hydrostatic and oncotic transcapillary pressures will create an opposing osmotic gradient due to the dilution of the interstitium, and effectively halt further filtration. By this mechanism, the normal brain is protected from variations in brain volume following alterations in intracapillary hydrostatic or oncotic pressures.

Disrupted blood-brain barrier

If the capillary membrane permeability for small solutes is increased (Fig. 1b), the condition will approach that described as “small pore permeability” in other organs of the body [28].

Transcapillary filtration following imbalance between the hydrostatic and oncotic pressures will be counteracted less by interstitial dilution, and will continue until antagonized by the increase in ICP.

While some studies indicate short-lasting damage of the BBB after a brain trauma [29], other studies suggest more long-term damage [30,31,32]. The development of oedema seen after an increase in arterial pressure [19, 33], or that related to a low oncotic pressure [34, 35], and that developed in the cranial opening after craniotomy (see below), however, must be associated with permeability for small solutes, as it is triggered by imbalance between the transcapillary hydrostatic and oncotic pressures. MRI has shown that intracellular oedema is an important part of posttraumatic brain swelling, and mainly occurs around contusions [31,36], while oedema in non-hypoxic areas is more of the interstitial vasogenic type related to disruption of the BBB [37]. An increased osmotic interstitial pressure from the metabolic production of osmolarity and disintegration of molecules and cell membranes may also contribute to the post-traumatic brain oedema [38]. Even though the mechanisms and the events behind a disrupted BBB are still poorly understood [39], there are strong indirect and direct supports for the hypothesis that disturbance of capillary permeability for small solutes is one essential triggering mechanism behind development of brain oedema.

Haemodynamic effects of a rigid cranium

Fig. 2 is a schematic illustration of the cerebral vascular bed enclosed in the rigid dura/cranium. The normal tissue pressure of the brain (ICP) of 8–13 mmHg is higher than the venous pressure outside the dura (0–5 mmHg). According to elementary principles of fluid mechanics, collapse of a passive elastic vessel must occur before it leaves a high-pressure

space for a space with lower pressure [40]. The degree of subdural collapse is related to the difference between ICP and extradural venous pressure and the passive collapse acts functionally as a variable venous outflow resistance (R_{out}) [3,17,18,41,42]. This means that the venous pressure just upstream of the collapse (P_{out} in Fig. 2) always equals ICP and that CPP is independent of extradural venous pressure. The fact that CPP can be calculated as the difference between arterial pressure and ICP is based on the existence of a passive subdural collapse [16,18]. The subdural collapse also means that alterations of extradural venous pressure will not be transferred to the brain circulation, as a change in venous pressure will cause an immediate compensatory change in degree of collapse [3,17,18].

Imbalance between hydrostatic and oncotic transcapillary pressures creating filtration will successively increase ICP. The simultaneous increase in P_{out} will be transferred in a retrograde manner, resulting in an increase in capillary pressure which will cause further filtration and further increase in ICP, and so on. Due to the fall in pressure across the venous resistance (R_V), a new steady state at a raised ICP will finally be established [3,16,19]. If, as suggested, about 80% of the increase in ICP will be transferred to the capillaries, it can be calculated that the highest increase in ICP will be 8 times larger than the initial imbalance between hydrostatic and oncotic pressures [16,17], which also finds support experimentally [19].

Effects of arterial and oncotic pressure variations on ICP

While the brain is protected from variations in venous pressure by the passive subdural venous collapse, it is protected from arterial pressure variations by an active autoregulatory mechanism. Autoregulation counteracts changes in blood flow and hydrostatic capillary

pressure in the brain following variations in arterial pressure [43], e.g. from those that occur in the brain because of changes in body position. While a change in hydrostatic or oncotic capillary pressure cannot influence brain volume when the BBB is intact (see above), a change in these pressures may trigger a slow filtration or absorption at a disrupted BBB [16,31]. As the autoregulatory capacity is not perfect even under normal circumstances and is most likely reduced after a head injury [33], a change in arterial pressure will influence the brain volume at a disrupted BBB [19,44] and, consequently, anti-hypertensive treatment will reduce brain oedema.

The hypothesis that a raised oncotic pressure reduces ICP after trauma has still not been confirmed experimentally [30,45]. Clinical and experimental studies, however, have shown that ICP after brain trauma is greater at low rather than high oncotic pressures [34, 35]. The oncotic absorbing effect is independent of the autoregulatory capacity.

The use of head elevation and PEEP

If the brain is protected from venous pressure variations by a variable subdural venous collapse [16-18], there will be no increase in ICP from the venous side by PEEP as suggested [c.f. 46], and no increased venous drainage following head elevation [c.f. 14,47,48]. This hypothesis means that PEEP can be used safely to prevent atelectasis after a head trauma (Table, point 2) [49]. The immediate decrease in ICP observed after head elevation may be explained by reduced blood volume rather than increased venous drainage [50,51]. Head elevation may slowly decrease a raised ICP by reducing hydrostatic capillary pressure when CPP is reduced, by analogy with anti-hypertensive treatment as discussed above. However, except for the risk of inducing too low a CPP, there may be limitations in the use of head

elevation by the simultaneous reduction in venous return to the heart, an effect especially pronounced in deeply sedated patients with impaired motor tone (Table, point 8).

Decompressive craniotomy and other surgical measures

Evacuation of haematomas and focal lesions, CSF drainage and craniotomy all mean loss of transcapillary counter-pressure and increased transcapillary pressure. It is reasonable to assume that this effect explains the brain herniation seen in the cranial opening after craniotomy, the slow recovery in ICP from a lowered value after the operation, and the ventricular collapse sometimes observed following CSF drainage.

Interest in decompressive craniotomy as a means of improving outcome has increased in the past decade [13,52,53]. The decrease in arterial pressure often seen after craniotomy, most likely an effect of reduced pressure influence on the vasomotor centre, may be beneficial by reducing development of brain oedema and the degree of herniation in the cranial opening according to the principles discussed above. From that point of view, vasopressor therapy with the purpose of preserving a high arterial pressure after craniotomy can be questioned (Table, point 11).

Hyperosmotic therapy

Hyperosmotic substances such as urea, glycerol, hypertonic saline and especially mannitol are used worldwide to treat brain oedema. The effectiveness of hyperosmotic therapy, however, can be questioned as the ICP-reduction is a transient effect. It may also be associated with adverse rebound and renal effects [7,14,54,55], and the long-term beneficial effects are poorly documented [7,15].

How to improve microcirculation around contusions

General considerations

Neurotoxic factors, such as excitatory aminoacids and lipid peroxidation (free radicals), and hypoxia have been suggested to trigger secondary insults following a brain trauma [6]. Hypoxic pericontusional areas (penumbra) may expand from impaired oxygenation around haemorrhagic and ischaemic contusions due to vasoconstriction, endothelial cell swelling, blood cell aggregation and wall adhesion [56]. This may cause further release of inflammatory and neurotoxic substances and trigger further cell damage and increase capillary permeability in the rest of the brain by distribution of these substances via the CSF and the interstitium. The hypoxia may also increase brain oedema in the most injured areas by increased interstitial osmotic pressure from cellular and molecular disintegration [38]. Thus, the therapeutic measures have to concentrate on reducing hypoxia in areas with compromised perfusion rather than on a direct inhibition of neurotoxic factors by neuroprotective substances, as we still lack any neuroprotective substance that might improve clinical outcome [6]. Early surgical evacuation of available haematomas and contusions may also prevent brain oedema development by reducing the release of toxic and permeability-increasing substances (Table, point 1).

According to the fourth power relationship in Poiessulle`s law, even small variations in vessel radius may result in large variations in vascular resistance in areas with increased resistance. A relatively small change in the radius of a vessel or in the degree of microcclusion in areas with compromised blood flow will therefore cause a large change in perfusion. Thus, while the perfusion pressure (CPP) in clinical practice can vary by 20-25%,

at most, there may be a much larger variation in perfusion in injured areas through variation in vascular resistance than through variation in CPP. If so, therapeutic measures which reduce vascular resistance are more essential for perfusion and oxygenation in injured areas than those that maintain a high CPP.

Measures to avoid vasoconstriction

Hypovolemia reduces cerebral blood flow via an alpha-mediated effect secondary to baro-receptor reflex activation, an effect shown to be especially pronounced at increased ICP [57]. Prevention of baro-receptor reflex activation and the concomitant catecholamine release by keeping the patient normovolemic is most probably a very important measure for preservation of the microcirculation and to minimize hypoxia in injured areas of the brain. The poor outcome related to hypotension in some previous studies [58] may be better explained by compromised perfusion due to hypovolemia than by the hypotension *per se*.

Vasoconstrictors, such as norepinephrine, phenylephrine, indomethacin [7,9,10,12,59] and dihydroergotamine [60] are used to increase blood pressure and/or to reduce intracranial blood volume. However, by analogy with baroreceptor-reflex activation during hypovolemia, vasoconstrictor therapy may compromise perfusion in the brain and in other organs of the body. A recent clinical study has shown that vasoconstrictor therapy triggers severe ARDS [61]. Dihydroergotamine may be more effective than other vasocontrictors in breaking a high ICP by inducing vasoconstriction also on the venous side with its greater blood volume [60,62]. However, due to the well-known vasoconstrictor-induced circulatory side effects of dihydroergotamine (ergotism), this drug should also be used with greatest caution (Table, point 10) [3,16]. Barbiturates reduce ICP by their metabolically-induced vasoconstrictor

effect simultaneously with their sedative effects. High dose barbiturate therapy has well-known adverse effects in terms of electrolyte, renal and cardiovascular complications, and is associated with severe pulmonary complications with fever; also, no improved outcome has been shown with high dose barbiturate therapy in randomized studies [63,64]. Thus, there are good reasons to avoid high-dose barbiturate therapy and to only use lower doses for a limited period of time (Table, point 5).

In addition, stress-induced increase in sympathetic discharge and catecholamine release may compromise cerebral microcirculation of the pericontusional areas. Stress can be reduced by sedatives and analgesics (Table, point 5), and by the anti-hypertensive therapy discussed below (β-blockade and α_2-agonists) [65,66], and by the avoidance of awaking tests. Beta-blockade may also protect the heart from stress-induced microinfarctions [65].

There is a common view that high fever worsens outcome following a severe brain injury, and it is believed that prevention of fever is beneficial [67,68], and that subnormal values may even be neuroprotective [69]. Fever can be avoided or reduced by prevention of pneumonia e.g. by prevention of atelectases and giving general pulmonary support (PEEP, inhalation, bagging) and by avoidance of high-dose barbiturate therapy. The use of enteral instead of parenteral nutrition and avoidance of overnutrition may also counteract fever [70] (Table, point 4). Active cooling induces increased stress and shivering with increased sympathetic discharge and catecholamine release, which may reduce the perfusion in injured areas. In spite of its neuroprotective effects, it is therefore far from granted that active cooling is beneficial for outcome after a brain trauma, a conclusion supported by a randomized multi-centre trial [71]. Thus, until the contrary is proven, there are arguments supporting the view

that active cooling should be avoided in a severely head injured patient. Controlling the thermostat should, from a physiological point of view, be a better alternative to reduce a persistent high fever (Table, point 3). For that purpose, paracetamol and one bolus dose of a steroid (Solu-Medrol) are recommended in the Lund protocol, but be aware of possible side effects with these drugs. For example, besides its liver toxic effects, paracetamol reduces the endogenous production of prostacyclin [72], which may compromise microcirculation of the penumbra zone (see below) and steroids are associated with hyperglycaemia.

Hyperventilation reduces ICP via a pH-dependent vasoconstriction, which may aggravate hypoxia around contusions in spite of the simultaneous reduction in ICP [73,74]. The effect on ICP is transient and the potentially harmful reduction in cerebral blood flow may even persist beyond the duration of the ICP reduction [75]. The general view today is that hyperventilation should be avoided except to prevent brain stem herniation in the acute situation (Table, point 2).

Type of blood volume substitution

Like other patients exposed to trauma, brain trauma patients develop hypovolemia unless given an adequate blood volume substitution, due to increased plasma leakage from blood to tissue in most organs of the body [76]. According to the 2-pore theory for transcapillary fluid exchange [28], the plasma leakage is dependent on the prevailing permeability and the hydrostatic capillary pressure. This means greater transcapillary leakage at a raised arterial pressure than at a normal arterial pressure. No specific recommendations are given in the traditional guidelines regarding type of fluid therapy [9,10], but isotonic crystalloids alone or in combination with colloids are recommended in most reviews [11,30,77].

If the BBB is permeable for small solutes, crystalloids may increase brain oedema when distributed to the interstitium of the brain, by analogy with what occurs in the rest of the body. Colloids have a much greater volume expanding effect per unit infused, and their plasma-expanding effect is more long-lasting than that for crystalloids. Colloids may also be beneficial by maintaining the plasma oncotic pressure according to the principles discussed above. Due to our limited experience in head injured patients with synthetic colloids such as dextran, gelatin and HES solutions, the natural colloid albumin should be the first choice (Table, point 6).

We still lack studies analysing the relationship between Hct and outcome in patients with head injury. A normal Hct compared to a subnormal Hct means a correspondingly smaller plasma volume to be preserved and better oxygen delivery to the brain [78]. In contrast to colloids, the erythrocytes do not pass the capillary membrane, and studies on the dog and rat have shown that the need for plasma expanders to maintain normovolemia is less at normal Hct than at low Hct [79,80]. Thus, there are lines of physiological evidence for the hypothesis that maintenance of a normal haemoglobin and plasma protein concentration may help to achieve the goals of normovolemia and normal plasma oncotic pressure, and to minimize hypoxia in injured areas (Table, point 6). To reduce adverse effects of the transfusion *per se*, only leukocyte-depleted blood should be used [81]. Also the storage time should be as short as possible as the quality of blood is reduced when stored for a long time e.g by decreasing red cell deformability. It seems that these therapeutic principles are also beneficial for perfusion and oxygenation of other organs of the body, as severe ARDS, intestinal ischaemia, and severe renal insufficiency have practically disappeared in our hospital over the past decade in patients with an isolated head injury.

Pharmacologic effects on the microcirculation

By inhibiting platelet aggregation and leukocyte wall adhesion, and by dissolving microvessel-occluding aggregates, the endogenous substance prostacyclin may be beneficial in improving the microcirculation around contusions. A clinical microdialysis study showed reduced interstitial lactate, reduced lactate/pyruvate ratio and glycerol, and increased interstitial glucose following prostacyclin infusion in pericontusional areas, indicating improved microcirculation [82]. Studies in rats have shown that prostacyclin improves microcirculation around contusions and reduces contusion volume in the traumatized brain [83,84]. To date, no side effects have been observed in clinical practice with the low doses recommended [22]. Prostacyclin is an attractive option to improve microcirculation in the pericontusional areas, but further research and clinical experience are necessary before a general recommendation for its use can be made.

Arterial, oncotic and cerebral perfusion pressures

According to the principles discussed above, the optimal arterial pressure (or CPP) is the pressure at which the balance in transcapillary hydrostatic and oncotic forces is reached simultaneously with an acceptable perfusion. This means that the higher the oncotic pressure, the higher the CPP – and consequently the better the perfusion – can be achieved without the risk of inducing filtration. Furthermore, the lower the vascular resistance the better the perfusion at a specified CPP and, if necessary to prevent filtration, a lower CPP can be accepted. The latter means that CPP can be lower in unstressed patients and in patients not given any vasoconstrictors, than in stressed patients or in patients given vasoconstrictor therapy. Our experience is that CPP varies between 50 and 80 mmHg in the adult when using

the therapeutical principles described in this review, but in most cases CPP stays in the range of 60–70 mmHg [85]. The lower values (50–60 mmHg) may appear when ICP is markedly raised and can be accepted only if cerebral perfusion is optimized as described above [3,86]. The perfusion can be preserved at a lower CPP in younger individuals than in the adult and ICP values down to 38–42 mmHg have been accepted in small children [3,16], which is in agreement with the US Pediatric Guidelines [87]. An early start of the therapy is recommended as this will prevent the development of high ICP and critically low CPP values.

Provided there is normovolemia and no primary heart failure, head-injured patients are hypertensive or in the upper range of normal pressure and there is a need for anti-hypertensive treatment to normalize arterial blood pressure. $Beta_1$-antagonist, $alpha_2$-agonist and angiotensin II antagonist are recommended, as they reduce arterial pressure without inducing simultaneous cerebral vasodilatation, thereby avoiding a vasodilator-induced increase in blood volume and hydrostatic capillary pressure. These treatments may also have beneficial anti-stress and cardio-protective effects (Table, point 7) [65,66]. The ICP-reducing effect of lowering arterial pressure or of increasing the oncotic pressure is a slow process due to the low filtration coefficient in the brain [27], and it may take hours before a clear reduction in ICP and the subsequent increase in CPP can be observed. Beta-mediated inotropic support increases ICP both by increasing arterial pressure and by the simultaneous cerebral vasodilation.

Conclusion

The present overview describes the principles of the Lund Concept for treatment of a severe head injury, with the two combined main goals (1) to reduce ICP ("ICP-targeted" goal) and (2) to improve microcirculation in the pericontusional areas ("perfusion-targeted" goal). The therapy means normalization of blood pressure, plasma oncotic pressure, plasma and red cell volumes, ventilation, body temperature and electrolytes, and the use of enteral nutrition and avoidance of overnutrition, vasopressors and stress. It can be applied to all patients with severe head injury, independently of age, autoregulatory capacity, other traumatic injuries or multiple organ failures, and should be started early to antagonize increase in ICP and other secondary injuries. So far there are no side effects inherent in the therapy. The therapy also appears to be beneficial for other organs of the body by preventing severe ARDS, intestinal ischaemia and renal failure. Outcome studies using the principles of the Lund Concept have indicated favourable results [20-25]. Guidelines for clinical application are presented in the Table.

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Table. **CLINICAL APPLICATION OF THE "LUND THERAPY" FOR SEVERE HEAD TRAUMA**

1. Surgical evacuation of available haematomas and contusions. Installation of ICP measuring device.

2. Mechanical ventilation to normal P_aCO_2 of 4.6–5.2 kPa (35–39 mmHg) and normal P_aO_2 of 12–14 kPa (90–105 mmHg). Use PEEP (6–8 cm H_2O), intermittent moderate bagging under ICP control, and inhalation to prevent atelectasis. Reduce the doses of beta-stimulating inhalation drugs (e.g. salbutamol) if they increase ICP and decrease blood pressure (vasodilation). Short-term moderate hyperventilation (< 2 min) can break intermittent ICP peaks. Do not extubate until ICP is stabilized at a normal level.

3. Normothermia is optimal. At persistent high fever (> 38.5 °C), the temperature can be reduced by paracetamol or one bolus dose of Solu-Medrol i.v 5–10 mg/kg. Avoid active cooling.

4. Use low-energy (15–20 kcal/kg/24 hrs for adults, relatively more energy to children), mainly enteral, nutrition. Keep blood glucose normal (5–8 mmol/L), with insulin if necessary. Avoid hyponatraemia.

5. Effective sedation and stress reduction may be obtained by sedatives (midazolam, propofol, thiopental) combined with $alfa_2$-agonist and $beta_1$-blockade (see below). Thiopental should be used only in low doses (2–3 mg/kg bolus + 0.5–3 mg/kg/h i.v.), and for at most 2 days in order to avoid side effects of barbiturates (e.g. pneumonia, ARDS, fever).

6. Normovolemia is mandatory, and accomplished by erythrocyte infusions (leukocyte-depleted blood) to normal S-Hb (125–140 g/L) and albumin transfusions to normal S-alb (35–43g/L), also normalizing plasma oncotic pressure. Albumin is recommended as it is a natural colloid with few side effects, and preferably in high concentrations (20-25%). Our experience of synthetic colloids in these patients is too limited for a general recommendation. Avoid crystalloids as plasma volume expanders. This fluid therapy reduces interstitial brain volume and improves microcirculation generally. Diuretics can be used (not mannitol). Minimize the use of ADH analogue in polyuria.

7. ICP can be controlled by normalizing plasma oncotic pressure (see above) and blood pressure, the latter by anti-hypertensive and catecholamine-reducing therapy with $beta_1$-antagonist (e.g. metoprolol 0.04–0.08 mg/kg × 6–8 i.v., or corresponding doses continuously, or 50–100 mg × 2 p.o.) and $alpha_2$-agonist (e.g clonidine 0.3–1.0 µg/kg × 4–6 i.v., or corresponding doses continuously or *per os*) and angiotensin II inhibitor (e.g. cozaar 50 mg × 1–2 p.o). Clonidine may have adverse $alpha_1$-agonistic effects at high doses, which makes the more specific $alpha_2$-agonist dexmedetomidine a promising alternative. Optimal CPP is individual, in most cases 60–70 mmHg for adults, and 40–55 mmHg depending on age, for children and adolescents. Transient CPP values down to 50 mmHg for adults may be necessary in selected cases to reduce a critically raised ICP. Too low a CPP may be corrected by (a) correcting latent hypovolemia, (b) no extra head elevation, (c) discontinuing thiopental, and (d) reducing the anti-hypertensive therapy. Refrain from using vasopressors.

8. Moderate head elevation (max 20°) can be used to reduce ICP (from the arterial side), providing an acceptable CPP. Additional head elevation may reduce venous return to the heart.

9. Drainage of CSF should be avoided, but drainage via the ventricular catheter may be used to break an incipient Cushing reflex or a critically high ICP. Drainage at a fairly high level may help to control ICP at a later phase of therapy if CSF absorption is insufficient.

10. A prolonged ICP B-wave or incipient high ICP and the Cushing reflex may be broken by a bolus dose of dihydroergotamine (DHE) (Sandoz) (3–4 µg/kg, as most 4 times/day for 2 days). DHE is a last option before craniotomy, and should only be used as that due to serious side effects (ergotism).

11. If ICP increases to life-threatening values despite the interventions described above, a large uni or bilateral partial craniotomy may be life-saving by reducing ICP, breaking a Cushing reflex and reducing

arterial pressure. Optimal ICP-reducing pharmacological and fluid therapy (see points 1–9 above) must be continued in order to reduce brain oedema and strangulation at the border of the craniotomy.

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Legends

Fig. 1. Panel a is a schematic illustration of the cerebral capillary and the forces responsible for transcapillary fluid exchange in the uninjured brain with intact BBB, while panel b shows the cerebral capillary and forces responsible for transcapillary fluid exchange in the injured brain, in which the capillaries are passively permeable for small solutes.

Fig. 2. This figure explains the haemodynamic consequences for the brain of being enclosed in the rigid cranium. P_c = hydrostatic capillary pressure, P_{onc} = plasma oncotic pressure, P_A = arterial inflow pressure, Q = cerebral blood flow, R_A = arterial resistance, R_V = venular resistance, P_{out} = pressure retrogradely of the venous collapse, and P_V = venous outflow pressure.

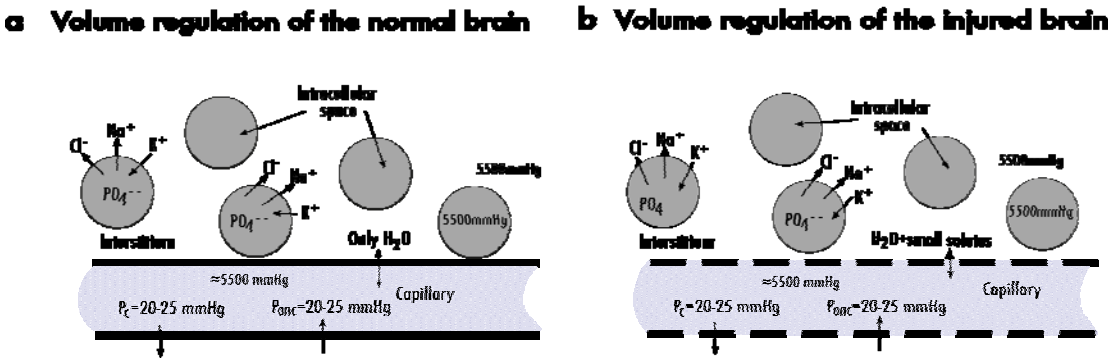
a Volume regulation of the normal brain
b Volume regulation of the injured brain
Intracellular space
Cl⁻
Na⁺
K⁺
PO4⁻⁻
Interstitium
Only H2O
5500mmHg
≈5500 mmHg
Capillary
Pc=20-25 mmHg
Poncc=20-25 mmHg
PO4
H2O+small solutes

Fig. 1

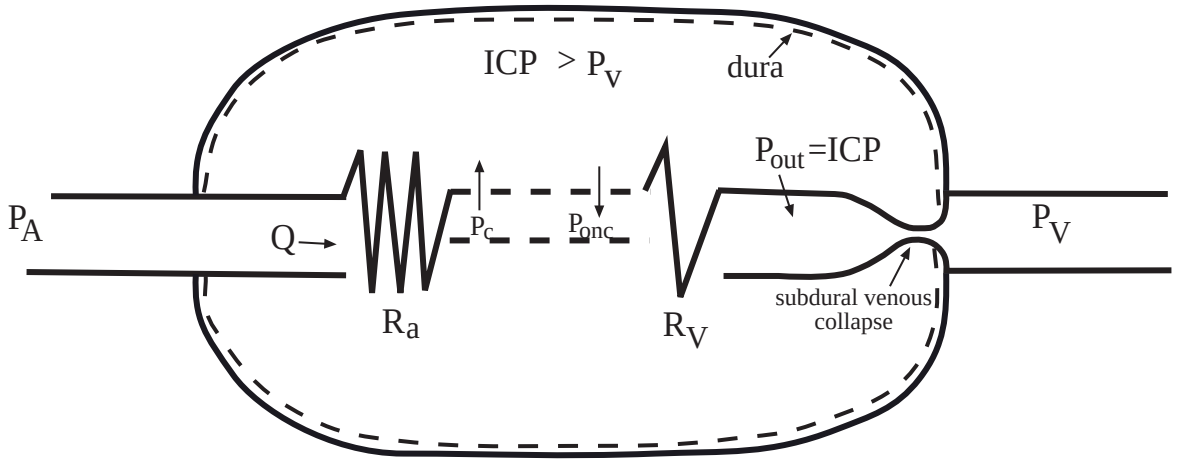
ICP > P_V
dura
P_{out}=ICP
P_A
Q
P_c
P_{onc}
P_V
R_a
R_V
subdural venous collapse

Fig.2