The Lund Concept for the Treatment of Patients With Severe Traumatic Brain Injury

Per-Olof Grände, MD, PhD

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Abstract: Two different main concepts for the treatment of a severe traumatic brain injury have been established during the last 15 years, namely the more conventional concept recommended in well-established guidelines (eg, U.S. Guideline, European Guideline, Addelbrook's Guideline from Cambridge), on the one hand, and the Lund concept from the University Hospital of Lund, Sweden, on the other. Owing to the lack of well-controlled randomized outcome studies comparing these 2 main therapeutic approaches, we cannot conclude that one is better than the other. This paper is the PRO part in a PRO-CON debate in this journal on the Lund concept. Although the Lund concept is based on a physiology-oriented approach dealing with the hemodynamic principles of brain volume and brain perfusion regulation, traditional treatments are primarily based on a meta-analytic approach from clinical studies. High cerebral perfusion pressure has been an essential goal in the conventional treatments (the cerebral perfusion pressure-guided approach), even though it has been modified in a recent up date of U.S. guidelines. The Lund concept has instead concentrated on management of brain edema and intracranial pressure, along with improvement of cerebral perfusion and oxygenation (the intracranial pressure and perfusion-guided approach). Although conventional guidelines are restricted to clinical data from meta-analytic surveys, the physiological approach of Lund therapy finds support in both experimental and clinical studies. It offers a wider base and can also provide recommendations regarding fluid therapy, lung protection, optimal hemoglobin concentration, temperature control, the use of decompressive craniotomy, and ventricular drainage. This paper puts forward arguments in support of Lund therapy.

Key Words: Lund concept, brain edema, cerebral perfusion pressure, intracranial pressure, positive endexpiratory pressure, arterial blood pressure, bloodbrain barrier, traumatic head injury, U.S. Trauma Foundation guideline

The Lund concept for the treatment of severe head injury was introduced in 1990 to 1991 at the University Hospital of Lund, Sweden. (For detailed information on its principles and the formal guide to its clinical application, see Ref.[1]). It was initiated because of the high mortality rate of these patients at that time, and because of the weak physiological and clinical support of the standard therapies used. Somewhat later, the traditional therapies became more strictly defined in conventional guidelines such as the U.S. Guidelines,[2] the European Guidelines,[3] and Addenbrookés Guidelines.[4] Lund therapy differs markedly from these therapies, both from a theoretical and from a clinical point of view.

The conventional guidelines are based on meta-analytic surveys from clinical studies, and can be characterized by the maintenance of a relatively high cerebral perfusion pressure (the CPP-guided approach). Lund therapy is a theoretical approach mainly based on physiological and pathophysiological hemodynamic principles of brain volume and brain perfusion regulation, and is characterized by the treatment of intracranial pressure (ICP) and maintenance of cerebral perfusion (the ICP and perfusion-guided approach). In contrast to conventional guidelines, it also provides relatively strict recommendations regarding fluid therapy, optimal hemoglobin concentration, lung protection and temperature control, and the risks and values of cerebrospinal fluid (CSF) drainage and of decompressive craniotomy. As can be seen from studies in the reference list, most components of Lund therapy find support from clinical and experimental studies, and outcome studies using the Lund concept have shown promising results both for adults and for children.[1] Lund therapy has also been used for the treatment of brain edema in meningitis.[5] Unfortunately, evidence-based clinical support for both the Lund concept and the more traditional guidelines is weak,[6] but Lund therapy has the advantage of a solid foundation in physiological hemodynamics. A first study comparing Lund therapy (n = 30) and conventional treatment (n = 38) regarding outcome in severely head-injured patients was published recently, presenting a mortality rate with Lund therapy almost half of that with conventional treatment.[7]

Doubts about the effectiveness of the traditional treatments were raised by a survey study from England

From the Department of Anesthesia and Intensive Care, Lund University and Lund University Hospital, Sweden.
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Reprints: Per Olof Grände, MD, PhD, Department of Anesthesia and Intensive Care, Lund University Hospital, Lund SE-22185, Sweden (e-mail: per-olof.grande@med.lu.se).

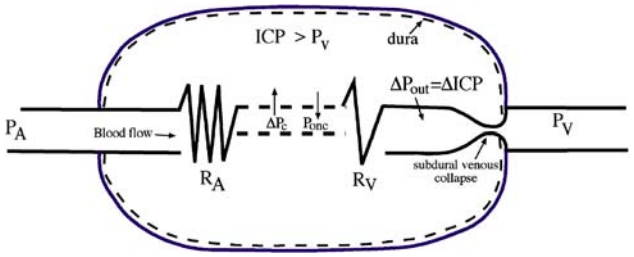

FIGURE 1. Schematic illustration of the brain surrounded by the dura/cranium. As intracranial pressure (ICP) is above the venous pressure outside the dura (P_V), a passive venous collapse (resistance) is developed just inside the dura, related to the difference between ICP and P_V. This variable collapse protects the brain from change in P_V as induced, for example, by head elevation or by positive endexpiratory pressure in the ventilator, as a change in P_V will be compensated for by a corresponding change in the venous collapse. An increase in ICP induced by filtration (disrupted blood-brain barrier) due to an increase in hydrostatic capillary pressure (P_c) and a decrease in oncotic pressure (P_{onc}) will increase venous pressure just before the venous collapse (P_{out}). This increase will be partly transferred back to the capillaries with a further increase in P_c and further filtration, and so on, finally reaching a new steady state. This mechanism explains why ICP increases much more than the initial increase in P_c or decrease in plasma oncotic pressure that started the filtration. P_A indicates arterial pressure; R_A, precapillary resistance; R_V, postcapillary resistance. Reproduced with permission from Ref.[1]

and Wales showing that there had been no overall improvement in outcome in severe head injuries between 1995 and 2003, despite improved general intensive care.[8] Moreover, a recent study found that monitoring of ICP resulted in reduced survival,[9] most likely due to the adverse effects of the ICP-reducing therapy provided to patients after an elevated ICP was recorded.

Conventional guidelines recommend that the ICP-reducing therapy should start first when ICP is above 20 to 25 mm Hg.[3,10,11] Owing to the lack of apparent side effects of its different components, Lund therapy can be started early before ICP is increased, counteracting the development of brain edema from the start.

From having been strongly controversial and widely criticized, the Lund concept has become more accepted during the past few years, which is not least reflected in the fact that the U.S. guidelines have moved closer to Lund therapy concerning CPP, the use of vasopressors, and hyperventilation.[10] In this paper, I put forward theoretical and clinical arguments in support of Lund therapy.

TREATMENT OF ICP

It has been suggested that a high CPP improves oxygenation of the injured brain by squeezing blood through the swollen brain, and that it reduces intracranial blood volume through an autoregulatory vasoconstrictor response.[4,12] The improved oxygenation may, however, be transient in the injured brain, with capillaries passively permeable to small solutes, as the high perfusion pressure will induce transcapillary filtration and exacerebate edema,[13–15] and the autoregulatory response is weak after a brain injury. Figure 1 explains why the filtration results in a much larger increase in ICP than the increase in hydrostatic capillary pressure or decrease in plasma oncotic pressure triggering the filtration.[14–16] Consequently, the decrease in ICP will be much larger than an induced decrease in hydrostatic capillary pressure and increase in oncotic pressure triggering ICP reduction. Note that this is a slow process taking several hours before any absorption-induced decrease in ICP can be observed. Vasoconstrictors to increase arterial pressure may also have extracranial side effects, such as acute respiratory distress syndrome (ARDS).[17] Vasoconstrictors may also cause increased general leakage of plasma resulting in hypovolemia and general tissue edema as shown in rats[18] and humans.[19]

These side effects are reduced with Lund therapy, by accepting a lower CPP than the initially recommended 70 mm Hg and by avoiding vasopressors. The Lund concept even advocates the use of antihypertensive treatment in terms of β-1 blockade, α-2 agonists, and angiotensin II antagonists to counteract the development of edema. From the fluid therapy given in the Lund concept, CPP will remain within acceptable levels despite antihypertensive therapy (see below). Furthermore, normalization of a reduced plasma oncotic pressure may counteract filtration in the brain according to the Starling fluid equilibrium equation,[1,20] which also means that a higher CPP can be accepted without inducing transcapillary filtration. This can be achieved by using albumin as the main plasma volume expander (see below).

Dihydroergotamine was used in the initial guidelines of the Lund concept to reduce venous intracranial blood volume at a significantly elevated ICP.[1] As craniotomy has become a more effective alternative to break off an uncontrolled increase in ICP, and due to the fact that dihydroergotamine as a vasoconstrictor is associated with adverse compromised circulation of various tissues of the body, this drug is no longer recommended in Lund therapy.

BLOOD VOLUME EXPANDERS

A subnormal blood volume means that the low CPP values accepted and recommended in the Lund concept, and nowadays also in the U.S. guidelines, may be too low to maintain an adequate cerebral perfusion, especially in the penumbra zone.[21] In the Lund concept, strong emphasis is therefore placed on the importance of avoiding hypovolemia-induced activation of the baroreceptor reflex by providing strict recommendations regarding the type of blood volume-expanding treatment and how to minimize any side effects of the fluid therapy. Conventional guidelines provide no directives on how to maintain normovolemia, with the risk that the patients will suffer from concealed hypovolemia.

Crystalloids are not used as a plasma volume expander in Lund therapy, as they are associated with general tissue edema, which also involves the injured

brain with a disrupted blood-brain barrier.[1,20,22] To maintain a normal general fluid balance, however, a crystalloid solution up to about 1 L/d for the adult may be necessary. In the Lund concept, albumin is recommended as the main plasma volume expander—preferably a 20% solution due to its more effective absorbing effect, an effect that is beneficial to reduce interstitial volume not only for the injured brain but also for the rest of the body. In contrast to crystalloid solutions, albumin is not distributed to the interstitium of the injured brain, resulting in less brain edema.[20,22] A slow infusion rate of a colloid results in a more long-lasting plasma volume expansion compared with when given at a fast infusion rate (unpublished data). This, in combination with relatively low arterial pressures, the avoidance of vasopressors, and maintenance of relatively normal hemoglobin concentrations (see below), and adequate physiotherapy to stimulate the lymphatic drainage system, reduces plasma leakage and the need for plasma volume expanders. The side effects associated with interstitial accumulation of albumin will also be reduced. The worse outcome in head-injured patients with albumin compared with saline in the Saline vs Albumin Fluid Evaluation-traumatic brain injury study may be explained by increased plasma leakage of albumin due to extensive use of vasopressors.[23]

In the Lund concept, blood transfusions (only leukocyte-depleted blood) up to a hemoglobin concentration above 12 g/dL are recommended, as the red blood cells are not only essential for oxygenation of the brain but also for maintenance of normal blood volume.[1] Conventional guidelines provide no directives regarding blood transfusions, and hemoglobin concentrations down to 8 g/dL are normally accepted.

TREATMENT TO IMPROVE PERFUSION

Perfusion of a tissue depends on perfusion pressure and vascular resistance. Regarding perfusion and oxygenation of the brain, a relatively low CPP can be compensated by an optimal fluid therapy. This was confirmed by a microdialysis study on head-injured patients treated according to the Lund concept.[24] This study showed improved oxygenation, greater blood flow, and less tissue degradation despite reduced arterial pressure with antihypertensive therapy, by measurement of interstitial lactate/puruvate ratio, glycerol, glucose, and glutamate in the penumbra zone. The results can be explained by avoidance of noradrenalin-induced vasoconstriction and plasma leakage and by avoidance of low hemoglobin concentrations. These data support the view that an adequate blood volume is more important for oxygenation of the penumbra zone than a high CPP.

CPP remains in the range of 60 to 70 mm Hg in most adult patients treated with Lund therapy.[1,24] If necessary to counteract a significantly elevated ICP, a minimum CPP of 50 mm Hg has been accepted in adult patients in the Lund concept, providing an otherwise optimal fluid therapy—a view supported by a microdialysis study.[25] CPP values down to 40 mm Hg are accepted in small children. These CPP values are also recommended in the latest update of the U.S. Guidelines for the adults[10] and for children. Once again, such low CPP values can only be accepted if the hemodynamic and blood volume principles of Lund therapy are recognized.

OSMOTHERAPY

Osmotherapy, and mannitol in particular, has been used worldwide since the 1960s to reduce an elevated ICP, and it is a cornerstone component in conventional guidelines.[2–4,10] There is still a lack of reliable studies showing improved outcome with this therapy. A few outcome studies concluded on a beneficial effect with high-dose mannitol, but due to questions about the integrity of these studies, they cannot be used as support for mannitol.[26]

Osmotherapy is not used in Lund therapy due to the lack of scientific and physiological support and due to documented side effects. Its ICP-reducing effect is transient and, at least for mannitol and urea, is followed by a rebound increase in ICP some hours after the infusion, aggravating the brain edema. Mannitol may also be associated with renal insufficiency and severe electrolyte disturbances. Osmotherapy, especially hypertonic saline,[27] may play a role in the reduction of ICP in an acute situation in the ambulance or under transportation to the operating room to release a menacing brain stem herniation.

LUNG FUNCTION

It is well known that extracranial complications such as pulmonary insufficiency contribute to a poor outcome after a severe head injury.[17] The Lund concept includes some specific lung-protective measures, which may explain the low frequency of severe ARDS with this therapy.

Vasoconstrictors and high-dose barbiturate therapy, which still belong to the standard treatments of severe head injury,[3,4,11] are associated with the development of pulmonary complications in terms of ARDS, pneumonia, and high fever.[17,28] Pulmonary complications are reduced with Lund therapy by not using these components and by strongly advocating positive endexpiratory pressure (PEEP).[1] PEEP is an important measure to reduce atelectasis, but has been controversial in head-injured patients due to the potential risk of increasing ICP by an increase in venous pressure. Conventional guidelines provide no specific recommendations regarding PEEP. We have shown experimentally that a tissue enclosed in a rigid shell, like the brain, is protected from venous pressure variations by a variable passive venous outflow resistance, provided that the tissue pressure is above the venous pressure outside the shell (Figure 1).[13–16] Such a mechanism means that the use of moderate PEEP (5 to 8 cm H_2O) is safe. Inhalations and moderate bagging (under ICP control) are other lung-protective measures recommended in Lund therapy. Avoidance of crystalloids as plasma volume expanders

may also reduce the risk of development of lung edema. All these measures taken together may explain why severe ARDS is very rare in patients with an isolated head injury who are treated according to the Lund concept.

Hyperventilation is not used in Lund therapy, as it may aggravate the hypoxia in the penumbra zone. This view is in agreement with recent updates of the U.S. Guidelines,[10] whereas other guidelines still accept moderate hyperventilation.[3,4,11]

ANTISTRESS THERAPY

Wake-up tests are accepted in many neurointensive care units to evaluate the status of the patient, which also implies the use of mainly short-acting sedatives such as propofol. Wake-up tests are not a component of Lund therapy due to stress effects, which result in an increase in ICP and the release of catecholamines in plasma, with the risk of reduced perfusion of the brain. The fact that propofol may have serious side effects with more long-term use both in children and in adults is an additional argument against the use of wake-up tests. Instead, patients are rather heavily sedated with midazolam and analgetics in combination with clonidine, and this sometimes involves a short-term treatment with a low dose of pentobarbital.[1] Sedatives are not discontinued until ICP has been stabilized at a normal level and until weaning from the ventilator will be successful. A beneficial side effect of this sedation regime is the lack of epileptic seizures,[29] which means that there is no indication of prophylactic anticonvulsary treatment.

TEMPERATURE

Owing to the well-known neuroprotective effect of hypothermia, active cooling is used in many neurotruama centers today and is an option in some conventional guidelines.[4] Active cooling has never been a component of the Lund concept, due to the potential side effects inherent in the significant stress and catecholamine release initiated by the difference between body temperature and the temperature value set by the thermostat, with the risk of reducing cerebral circulation of the penumbra zone. Recent randomized studies have also indicated worsening of outcome with active cooling in patients with traumatic brain injury.[30] Lund therapy involves the treatment of high fever pharmacologically instead.[1]

DRAINAGE OF CSF AND DECOMPRESSIVE SURGERY

Drainage of CSF increases transcapillary pressure in the brain due to reduced tissue pressure inducing filtration. Loss of CSF volume will be replaced by more edema with a risk of ventricular collapse. The risk can be reduced if the drainage is performed from a relatively high-pressure level and if ventricular volumes are evaluated by computed tomography controls. Under such circumstances, CSF drainage is accepted in the Lund concept to control an elevated ICP (only through ventricular drainage), especially if there are signs of hydrocephalus.[1]

Decompressive surgery in terms of craniotomy and evacuation of hematomas and available contusions are options in Lund therapy. Owing to the lack of studies showing beneficial effects on outcome, decompressive craniotomy is a controversial measure. An important side effect with craniotomy is strangulation in the cranial opening due to herniation. As the protuberance can at least partly be explained by transcapillary filtration due to loss of counter pressure in the cranial opening, antihypertensive treatment and a relatively low CPP, in combination with normal plasma oncotic pressure, as favored in the Lund concept, may reduce the adverse effects of craniotomy. Decompressive craniotomy is the last therapeutic measure to prevent brain stem herniation in Lund therapy.[1]

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