



# The Lund Therapy: A Physiological Approach

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Per-Olof Grände and Peter Reinstrup

## Recommendations

### Level I

There have been no level I studies performed to evaluate the Lund guidelines relative to any alternative guidelines.

### Level II

There are no level II randomized studies that support any specific TBI guideline.

### Level III

There have been several level III studies including two smaller randomized studies giving some support for the Lund therapy.

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P.-O. Grände (✉)  
Department of Anaesthesia and Intensive Care,  
Lund University and Lund University Hospital,  
Lund, Sweden  
e-mail: [per-olof.grande@med.lu.se](mailto:per-olof.grande@med.lu.se)

P. Reinstrup  
Department of Anaesthesia and Intensive Care,  
Lund University and Lund University Hospital,  
Lund, Sweden

Department of Intensive and Perioperative Care,  
Skånes University Hospital, Lund, Sweden  
e-mail: [peter.reinstrup@med.lu.se](mailto:peter.reinstrup@med.lu.se)

## 55.1 Overview of the Lund Guidelines

1. A vasogenic brain oedema is a consequence of an unbalance of the hydrostatic and the colloid osmotic pressure in the Starling fluid equilibrium, providing a disrupted blood-brain barrier (BBB). The intracranial pressure will however increase more than an increase in hydrostatic capillary pressure or decrease in colloid osmotic pressure, as the brain is enclosed in the rigid cranium. Details of this mechanism have been described previously (see Grände 2017). Vasogenic brain oedema may be confined by counteracting a raised hydrostatic capillary pressure, which can be accomplished by antihypertensive treatment (see (2) below). It may also be confined by avoiding low colloid osmotic pressures (see (3) below). A CPP of 60–65 mmHg should be aimed at in most cases for the adult, but somewhat lower values may be necessary to reduce a significantly raised ICP. The ICP-reducing therapy should be started early after arrival to the intensive care, and normovolaemia is assured independent of prevailing ICP.
2. An ICP measuring device should be installed. Zero baseline for ICP should be set in the ear level (midlevel of the brain). Brain oedema can be reduced by normalization of the normally raised arterial blood pressure (providing normovolaemia) by antihypertensive

- therapy in terms of  $\beta_1$  antagonist (e.g. metoprolol 1 mg/mL, 1–2 mL/h i.v., or 50 mg  $\times$  1–2 per os for an adult) and  $\alpha_2$  agonist (clonidine diluted to 15  $\mu$ g/mL, 0.5–1 mL/h i.v., or 150  $\mu$ g  $\times$  1–2 per os for an adult or dexmedetomidine 0.2–1.0  $\mu$ g/kg/h i.v.). If blood pressure is still too high, use also angiotensin II antagonist (e.g. losartan 50 mg  $\times$  1–2 per os for an adult). If necessary, head elevation (max 15–20°) can be used to reduce cerebral perfusion pressure (CPP). In children and adolescents, the doses should be adapted to their age. An arterial blood pressure resulting in too low CPP (CPP below 55 mmHg in adults and below 40 mmHg in small children) may be an indication of a concealed hypovolaemia to be treated with extra fluid substitution before the start of the antihypertensive treatment (see (4) below and Chap. 63). If CPP is still too low, the antihypertensive treatment should be reduced. If there is a need of vasoconstrictors to maintain an adequate CPP, use lowest possible dose. It is important that baseline levels for ICP and blood pressure are the same to get correct CPP values.
3. Normalization of the plasma oncotic pressure with a colloid solution with the purpose to reduce brain oedema by improving transcapillary absorption and to improve perfusion of the brain. Preferably use 20% albumin solutions up to a plasma albumin concentration of 32–36 g/L.
  4. A blood volume expanding therapy aimed at preservation of normovolaemia by infusion of albumin (preferably 20% solutions) to normal albumin concentrations (32–36 g/L) and by maintenance of a haemoglobin concentration above 110 g/L (always leucocyte-depleted blood). A crystalloid (normal saline 1.0–1.5 L/day for an adult and correspondingly lower volumes for children) can be given to obtain an adequate general fluid balance and urine production. The blood pressure response from additional volumes of blood and albumin or passive leg elevation will show if a low blood pressure can be explained by hypovolaemia. The volaemic state can also be checked with pulse pressure variations (PPV) (PPV > 10% may indicate hypovolaemia). The need for vasopressors is small when following this therapy and should be avoided. If still used to obtain an adequate blood pressure, it should be used in lowest possible doses. Diuretics can be used (not mannitol).
  5. Anti-stress therapy in terms of midazolam 5 mg/mL (0–3 mL/h for an adult) and fentanyl 0.05 mg/mL (0–3 mL/h for the adult). The hypotensive drugs  $\alpha_2$  agonist and  $\beta_1$  antagonist (see under (1) above) also act as sedatives and reduce catecholamine concentration in plasma. Catecholamine concentration in plasma is also kept low by avoiding noradrenalin and by not using active cooling. Wake-up tests should not be used until start of the weaning procedure, and do not extubate until ICP has stabilized at a relatively normal level.
  6. If there are problems with persistent high ICP (above 25 mmHg), the following measures can be taken: (1) surgical removal of available haematomas and contusions, (2) start of thiopental (pentothal, 50 mg/mL) initiated by treatment with a bolus dose of 1–3 mL followed by a continuous infusion of 1–3 mg/kg/h for the adult for at most 2 days (be aware of the risk with respiratory insufficiency with a more long-term use of this drug), or (3) decompressive craniectomy. Osmotherapy to reduce ICP has side effects in terms of renal and electrolyte disturbances and adverse rebound effects at its discontinuation and should be used only for acute prevention of brainstem herniation or to give space during brain surgery. Drainage of CSF—see under (9) below. The therapy may be guided by data from a microdialysis catheter placed in the penumbra zone.
  7. Use low-energy nutrition (15–20 kcal/kg/day from days 2–3 for an adult, but relatively more energy for children). An energy supply of 1200–1400 kcal/day to the adult is enough to cover the basal metabolism under sedation and ventilatory support. If possible, use mainly enteral nutrition (high doses of parenteral fat nutrition may cause fever). Avoid over-nutrition. Keep blood glucose in the range of 6–10 mmol/L, and electrolytes should be normal. If there are difficulties to

achieve enough energy supply with enteral nutrition, add glucose (5–10%) with electrolytes i.v. As a last measure, low doses of parenteral nutrition of fat and amino acids can be added.

8. Mechanical ventilation (preferably volume-controlled), keeping a normal PaO<sub>2</sub> and a normal PaCO<sub>2</sub>. A temporary moderate hyperventilation can be accepted for a short time period to prevent an acute brainstem herniation. PEEP (6–9 cm H<sub>2</sub>O) is mandatory to prevent atelectasis. Inhalation of a  $\beta_2$  agonist may help to clean the lung, but the doses should be reduced if there is a blood pressure fall and increase in ICP by a general  $\beta_2$ -induced vasodilation.
9. Drainage of CSF can be performed via a ventricular catheter (not by lumbar puncture) and should be performed from a relatively high ICP pressure level to reduce the risk of ventricular collapse and brainstem herniation. A CT scan can show if the drainage causes a tendency of ventricular collapse.

#### Tips, Tricks, and Pitfalls

- Use the therapy within the framework of the guidelines.
- Start the therapy early after arrival to the intensive care unit to counteract the development of brain oedema and an increase in ICP prophylactically.
- A not too low haemoglobin concentration helps to avoid hypovolaemia and optimize oxygenation of the penumbra zone (only leucocyte-depleted blood should be used).
- Osmotherapy should be avoided due to the risk of a rebound effect and adverse renal effects and electrolyte disturbances. It can still be used to prevent acute brainstem herniation, e.g. during transportation, and to allow space during brain surgery.
- Decompressive craniectomy can be used to reduce ICP and prevent brainstem herniation.

- Normality of most physiological parameters is worth aiming at.
- Peep is mandatory to counteract atelectasis.

## 55.2 Background

While most traditional guidelines for treatment of severe head injury, including the US guidelines, are based on a meta-analytic approach, the Lund concept is in its main parts based on basal haemodynamic physiological principles for control of brain volume and brain perfusion. The Lund concept therefore is presented separately in this chapter. The physiological principles of the Lund concept have later on found support in clinical and experimental studies, including clinical outcome studies involving adults and children. Recent updates of the US guidelines have moved closer to the Lund concept (The Brain Trauma Foundation. The American Association of Neurological Surgeons; Congress of Neurological Surgeons 2007, 2016). The Lund concept has not been changed since its introduction, except that the venous vasoconstrictor dihydroergotamine was deleted from the concept after a few years due to the potential side effects always inherent in vasoconstrictors (Grände 2017).

The Lund concept combines two main goals, namely, halting or treating the development of a vasogenic brain oedema (the “ICP goal”) and a simultaneously intensified support of the perfusion of the penumbra zone (the “perfusion goal”). The purpose of the therapy is to improve outcome by preventing brainstem herniation and by reducing cell death in the vulnerable penumbra zone. A microdialysis study has shown that these goals are reached with the Lund concept in spite of the use of antihypertensive treatment (Ståhl et al. 2001a). Most likely, this can be explained by improved perfusion and oxygenation, especially of the penumbra zone. This effect may be referred to the avoidance of hypovolaemia with albumin and blood transfusions, the avoidance of norepinephrine, the avoidance of active cooling, and the

avoidance of wake-up tests (Skoglund et al. 2012).

The Lund therapy strives towards normalization of essential haemodynamic and biochemical parameters. For an overview of its theoretical background and therapeutic guidelines, see Grände (2006), Koskinen et al. (2014), and Grände (2017). The Lund therapy is applicable to all ages. Outcome studies with the Lund therapy have so far been promising (Eker et al. 1998; Wahlström et al. 2005; Koskinen et al. 2014). No level I and II studies have been performed regarding either the components of the traditional guidelines such as the US guideline and the European guideline in their original versions (Bullock et al. 1996; Maas et al. 1997) or in their updated versions (The Brain Trauma Foundation. The American Association of Neurological Surgeons; Congress of Neurological Surgeons 2007, 2016) or regarding the Lund concept (Grände 2006, 2017; Koskinen et al. 2014). Two smaller randomized studies comparing outcome with a modified version of the Lund concept with that of using conventional treatments, showed a lower mortality rate with the Lund concept (Liu et al. 2010; Dizdarevic et al. 2012). Also US guidelines have found support in a recent study (Gerber et al. 2013).

The “ICP goal” of the therapy is mainly based on the hypothesis that an imbalance between the transcapillary hydrostatic and the oncotic pressures creating filtration will result in a vasogenic brain oedema, provided the blood-brain barrier (BBB) is passively permeable to small solutes. Such a situation can exist in meningitis and after a head trauma. In head trauma patients, the BBB may be disrupted, especially around cerebral contusions. According to this hypothesis, the brain oedema can be counteracted or prevented by reducing a raised hydrostatic capillary pressure, as obtained by the antihypertensive treatment and avoidance of vasopressors, and normalization of a lowered plasma oncotic pressure. As the brain is enclosed in a rigid cranium, the change in ICP by alteration in the vasogenic brain oedema is much larger than the change in hydrostatic capillary pressure initiating the oedema (Grände 2017). It can be calculated that

the change in ICP at most can be 5–6 times larger than the initial change in the hydrostatic capillary pressure.

The “perfusion goal” is aimed at maintaining better perfusion and oxygenation of the penumbra zone. This can be obtained by a low plasma concentration of catecholamines, by preventing hypovolaemia (counteracting baroreceptor reflex activation), if possible by avoiding the use of vasoconstrictors, by avoiding stress, by not using active cooling, and by avoiding low haemoglobin concentrations and hyperventilation (the patient should be normocapnic) and by not using wake-up tests. A more normal haemoglobin concentration will help to give a better oxygenation of the injured parts of the brain and to preserve a normovolaemic state. The cytotoxic brain oedema may also be reduced by a better perfusion and oxygenation. Preservation of normovolaemia is essential to maintain perfusion by reducing activation of the baroreceptor reflex, resulting in less peripheral vasoconstriction and lower catecholamine concentration in plasma.

Normal ICP stays in the range of 8–11 mmHg, which is higher than the venous pressure outside the dura of 0–3 mmHg. This pressure difference will increase, subsequent to an increase in ICP. The pressure fall between the subdural venous pressure and the extradural venous pressure (sometimes called the waterfall phenomenon) will create a subdural passive venous collapse, the resistance of which is directly related to the pressure fall. This means that a change in extradural venous pressure (e.g. a venous pressure increase by PEEP or a venous pressure decrease by head elevation) will not be transferred from the venous side into the brain, as the brain is protected by the variable subdural venous collapse. By this passive mechanism, the brain will not be influenced by venous pressure variations, and PEEP will not increase ICP from the venous side and can be used safely. Moderate PEEP (6–9 cm H<sub>2</sub>O) is therefore an important component in the Lund concept to prevent development of atelectasis. Details of this physiological mechanism have been published previously (see Koskinen et al. 2014; Grände 2017). Consequently, head elevation will not decrease

ICP from the venous side, but head elevation will still decrease ICP due to the simultaneous reduction in arterial pressure.

Our present knowledge regarding the risk of hyperventilation has been discussed in more detail in a special chapter of this book (Chap. 60). Hyperventilation is not a component of the Lund concept.

In contrast to several other studies (e.g. Tomita et al. 1994; Dubois et al. 2006; Chen et al. 2014), the randomized SAFE-TBI study (The SAFE study investigators 2007) showed worse outcome with albumin in TBI patient. The SAFE-TBI study, however, has been strongly criticized and has not changed the recommendations in the Lund concept that isotonic albumin can be used (Grände 2008, 2017). The use of albumin and critical aspects of the SAFE-TBI study have been discussed in the fluid chapter in this book (Chap. 63). To give albumin as plasma volume expander is also justified due to the relatively small volumes of albumin needed to maintain normovolaemia when following the principles of the Lund therapy (Koskinen et al. 2014). See the chapter on fluid therapy.

Vasopressors such as noradrenalin may compromise circulation of the penumbra zone (Brassard et al. 2009) and should therefore be avoided or used in lowest possible doses. It has also been shown that noradrenaline may trigger ARDS (Contant et al. 2001). Low-dose prostacyclin is an option to improve microcirculation and oxygenation of the penumbra zone (Grände et al. 2000; Grände 2017).

Enteral nutrition is to be preferred, and overnutrition should be avoided, especially when using parenteral nutrition. Blood glucose should be kept between 6 and 10 mmol/L, in agreement with the NICE-SUGAR study (Finfer et al. 2015). Especially lower glucose concentrations than 6 mmol/L in the blood should be avoided, as microdialysis studies have shown that the glucose concentrations in the penumbra zone normally are much lower (sometimes even approaching zero) than in less injured tissues, which most likely cannot be fully compensated by a lower metabolism (Grände et al. 2000; Ståhl et al. 2001b).

A CT scan should be performed soon after arrival at the hospital. To counteract the development of an increase in ICP, the therapy should start early. If possible, extensive intracerebral bleedings and available contusions should be surgically evacuated. The Lund therapy is applicable to all ages if doses and physiological parameters are adapted to the patient's age (Eker et al. 1998; Naredi et al. 1998; Wahlström et al. 2005). The Lund therapy is not dependent on the actual autoregulatory capacity, and the benefit of evaluating autoregulatory capacity is small.

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### 55.3 Specific Paediatric Concerns

The principles of the Lund concept are applicable to all ages if doses of nutrition, pharmacological substances, and fluids are adapted to the age. While a lowest CPP of 55 mmHg occasionally can be accepted in the adult, providing an optimal fluid therapy maintaining normovolaemia, relatively lower values can be accepted in adolescents and children and CPP down to 38–40 mmHg in the smallest children, but always providing an optimal fluid therapy.

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