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The Lund concept: Is this logical?

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Summary

The optimal therapy of sustained increase in intracranial pressure (ICP) is still controversial. The “Lund concept” is based on the physiological volume regulation of the intracranial compartments. In addition to its other functions the blood-brain barrier (BBB) is the most important regulator of brain volume. Water exchange across the intact BBB is counteracted by the low permeability to crystalloids (mainly Na⁺ and Cl⁻) combined with the high osmotic pressure (5,700 mm Hg) on both sides of the BBB. If the BBB is disrupted transcapillary water transport will be determined by the differences in hydrostatic and colloid osmotic pressure between the intra- and extracapillary compartments. Under pathological conditions pressure autoregulation of cerebral blood flow is often impaired and intracapillary hydrostatic pressure will depend on variations in systemic blood pressure.

The “Lund concept” can be summarized in four paragraphs: I. Reduction of stress response and cerebral energy metabolism; II. Reduction of capillary hydrostatic pressure; III. Maintenance of colloid osmotic pressure and control of fluid balance; IV. Reduction of cerebral blood volume. The efficacy of the treatment protocol has been evaluated in experimental and clinical studies regarding the physiological and biochemical (utilizing intracerebral microdialysis) effects. The clinical experiences have been favourable.

Key-words: Brain oedema, blood-brain barrier, microdialysis

Except for decompressive craniectomy all treatments of increased intracranial pressure (ICP) are directed towards decreasing the volume of one or more of the intracranial components:

$$V_{\text{intracran}} = V_{\text{blood}} + V_{\text{brain}} + V_{\text{CSF}} + V_{\text{mass lesion}} \quad (\text{Eq. 1})$$

Surgical treatments include evacuation of mass lesions ($V_{\text{mass lesion}}$) and, in some cases, drainage of CSF (V_{CSF}). The importance of early and adequate surgical evacuation of focal mass lesions is well documented and will not be discussed further in this presentation. The regulation of the remaining two volumes (V_{blood} and V_{brain}) is in focus for the (non-surgical) intensive care. However, the surgical and non-surgical treatments are closely connected since all surgical therapies have one consequence in common: they all reduce tissue interstitial pressure. As discussed below, in a situation with increased permeability of the blood-brain barrier (BBB), a decrease in tissue pressure will lead to increased transcapillary water filtration. The consequences are well known to all neurosurgeons: the gradual

increase in ICP almost always observed after evacuation of focal lesions; the collapse of the ventricles often induced by ventricular drainage; the bulging of cerebral tissue through the bone defect after craniectomy. The rapid change in volume obtained by surgical treatment should accordingly always be combined with a non-surgical therapy aiming primarily at a slow and lasting reduction in brain water content.

Blood-brain barrier permeability

Like other organs the volume regulation of the brain is primarily determined by mechanisms controlling the water exchange across the capillaries. Regarding these mechanisms the brain differs from other organs in its highly sophisticated capillary membrane function – the BBB. In addition to its other physiological functions the BBB is the most important regulator of cerebral volume (8).

The flux of water across a membrane or microvascular bed (J_v) is described by the equation

$$J_v = L_p \times A \times [\Delta P - \sum \sigma_s \times \Delta \Pi_s] \quad (\text{Eq. 2})$$

where L_p is hydraulic conductivity, A is the surface area available for fluid exchange, ΔP is the transcapillary hydrostatic pressure difference, $\Delta \Pi_s$ the transcapillary osmotic pressure difference and σ_s the reflection coefficient of each solute (s) of the system. The transcapillary water transport is accordingly defined by the difference in hydrostatic pressure (ΔP), the osmotic pressure gradient ($\Delta \Pi_s$), the endothelial component which will determine which solutes are reflected and will contribute to the osmotic pressure gradient (σ_s), and the hydraulic conductance of the capillary wall ($L_p \times A$). The two major solutes of biological fluids (Na^+ and Cl^-) have a blood-brain barrier reflection coefficient of 1.0. Water passing the BBB in any direction will thus be virtually devoid of crystalloids and an opposing osmotic gradient, which counteracts further fluid transport, will immediately be created.

According to eq. 2 the magnitude of the hydraulic conductance ($L_p \times A$) describes the rate by which the fluid is transferred across the capillary membrane whenever there is a driving force ($\Delta P - \sum \sigma_s \times \Delta \Pi_s$). Accordingly, the only way of inducing transcapillary filtration or absorption is to disturb the balance between the hydrostatic and osmotic forces across the capillary membrane. For two reasons the magnitude of the cerebral perfusion pressure (CPP) is of less importance for brain volume under normal conditions. Firstly, intracapillary pressure and cerebral blood flow are physiologically tightly autoregulated and variations in systemic blood pressure are generally not transmitted to cerebral

capillaries. Secondly, transcapillary fluid exchange is effectively counteracted by the low permeability to crystalloids combined with the high osmotic pressure of 5,700 mm Hg on both sides of the BBB (8). This contrasts to most other capillary regions where the osmotic pressure force is mainly derived from the difference between plasma and interstitial colloid osmotic pressure approximately balancing the transcapillary hydrostatic pressure (20-25 mmHg). Under pathophysiological conditions the regulation of brain volume may be completely altered. In these conditions pressure autoregulation is often impaired and the BBB may have an increased permeability for crystalloids or even for large molecules. The regulation of brain volume will then depend on the balance between the transcapillary hydrostatic pressure and the transcapillary colloidal osmotic pressure.

Cerebral blood flow and cerebral blood volume

The tight regulation of cerebral blood flow (CBF) primarily secures a continuous and sufficient supply of glucose and oxygen to cover the high cerebral metabolism. Two secondary effects of CBF regulation have important consequences for the regulation of ICP: the intracapillary hydrostatic pressure and the intracerebral blood volume (mainly within the venous compartment). Several important principles within intracranial dynamics can be described in relation to the conventional physiological regulatory mechanisms of the cerebral blood flow: pressure autoregulation, CO₂-regulation, and metabolic regulation.

Pressure autoregulation implies that blood flow remains relatively constant despite variations in CPP within defined limits. The phenomenon is present in many organs and appears to be most prominent in the brain and in the kidneys. In physiological literature autoregulation is usually described as a mechanism, which serves the purpose of keeping intracapillary hydrostatic pressure constant (c.f. above).

A rapid reduction of intracranial blood volume is conventionally obtained by controlled hyperventilation via the CO₂-regulation of CBF. The effect is attained by a pH dependent constriction of precapillary resistance vessels. Prolonged hyperventilation is probably of limited value or may even be harmful since pronounced hyperventilation carries the risk of inducing focal ischemia. Further, the reduction of CBF and CBV during hyperventilation is transient in spite of preserved hypocapnia. Finally, due to impaired cerebrovascular CO₂-reactivity hyperventilation is often not effective in reducing CBV in the most severely brain injured patients (10,21).

A lasting vasoconstriction and reduction of CBV can be achieved through reduction of cerebral energy metabolism e.g. by barbiturates (15). This mechanism appears to be effective only in patients with preserved cerebrovascular CO₂-reactivity (15). In addition, prolonged high-dose barbiturate treatment is associated with pulmonary, cardiovascular and other serious complications (22).

Since in the brain, like in other organs, about 70% of blood volume is located within the venous compartment it might be possible to induce a lasting reduction of CBV with a minimal effect on CBF by inducing a pharmacological constriction of the capacitance vessels. Dihydroergotamine (DHE) is known to primarily constrict venous capacitance vessels within the peripheral circulation and has also been shown to decrease ICP in patients with severe head injuries (9). This effect is obtained although CBF remains unaffected or increases (4,13). DHE has been shown to decrease ICP also in patients with impaired CO₂-reactivity (4) and *in vitro* studies have shown that DHE has a more pronounced constrictor effect on isolated human cortical veins than arteries (14).

Pathophysiological aspects of disturbed brain volume regulation

No techniques are available for quantitative measurements of cerebral intracapillary hydrostatic pressure or the effects of increased hydrostatic pressure on water transport across the BBB. Some aspects may however be studied in a model system utilizing a denervated cat skeletal muscle enclosed in a plethysmograph (1,9). This model simulates the pathophysiological situation in a damaged brain since muscle capillaries are permeable for water and most solutes but much less permeable for proteins ($\sigma \approx 0.8-0.9$). Further, pressure autoregulation of blood flow is impaired in this experimental model.

The clinical implications of the data obtained from these experiments may be summarized as follows. If the injured brain has an impaired pressure autoregulation and a BBB with an increased permeability to crystalloids then transcapillary fluid exchange will be highly dependent on variations in systemic arterial blood pressure. Under conditions with increased BBB permeability to crystalloids a decrease in tissue pressure will cause a net transport of fluid from the capillaries into the interstitial space and, as discussed above, all surgical treatments of increased ICP are associated with a decrease in tissue pressure.

The Lund concept

The “Lund concept” is based on the physiological considerations above and can be summarized in four paragraphs.

I. Reduction of stress response and cerebral energy metabolism

Stress response is reduced by liberal use of sedatives (benzodiazepines) and analgesics (opioids). A further reduction of the stress response and catecholamine release is obtained by a continuous infusion of low-dose thiopental ($0.5\text{-}3\text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) and fentanyl ($2\text{-}5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) but also by treatment with the β_1 -antagonist metoprolol and the α_2 -agonist clonidine (see below). The dose of thiopental is kept low to avoid cardiac inhibition, pulmonary complications and other side effects (22).

II. Reduction of capillary hydrostatic pressure

Mean arterial blood pressure is reduced to the physiological level for the age of the individual patient with a combination of the β_1 -antagonist metoprolol ($0.2\text{-}0.3\text{ mg}\cdot\text{kg}^{-1}\cdot 24\text{h}^{-1}$ *i.v.*) and the α_2 -agonist clonidine ($0.4\text{-}0.8\text{ }\mu\text{g}\cdot\text{kg}^{-1}\times 4\text{-}6$ *i.v.*) (2,3,9). The antihypertensive treatment is initiated after evacuation of focal mass lesions when the patients are clearly normovolemic as obtained by red cell and albumin/plasma transfusions to normal albumin and haemoglobin values and to a normal central venous pressure. A CPP of 60-70 mm Hg is considered optimal but, if necessary to control ICP, a transient decrease in CPP to 50 mm Hg for adults and 40 mm Hg for children is accepted. Thiopental also has a precapillary vasoconstrictor effect, which will contribute to lowering the intracapillary hydrostatic pressure.

III. Maintenance of colloid osmotic pressure and control of fluid balance

Red cell transfusions and albumin are given to achieve normal values (Hb/s 125-140 g/l, alb/s \approx 40 g/l) to ensure normovolemia and to optimise oxygen supply. The albumin/plasma/blood transfusions also serve the purpose of obtaining a normal colloid osmotic pressure favouring transcapillary absorption. A balanced or moderately negative fluid balance is a part of the treatment protocol and is achieved by diuretics (furosemide) and albumin infusion. All patients are given a low calorie enteral nutrition (max energy supply $15\text{-}20\text{ kcal}\cdot\text{kg}^{-1}\cdot 24\text{ h}^{-1}$).

IV. Reduction of cerebral blood volume

Intracranial blood volume may be reduced both on the arterial side with thiopental (15) and on the venous side with DHE (4,9,13,14). DHE is only given when other treatments are insufficient and always at the lowest dose necessary to reduce intracranial pressure. Since the therapy above (paragraph I-III) is usually

successful DHE is rarely used. When given it should not be administered for more than five days in order to minimize the risks of compromising peripheral circulation, in particular in patients with fractures of the extremities or renal insufficiency. The maximum doses of DHE used are: 0.8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ day one, 0.6 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ day two, 0.4 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ day three, 0.2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ day four, and 0.1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ day five.

Cerebral energy metabolism – relation to cerebral perfusion pressure

A reduction of CPP might jeopardize cerebral energy metabolism in patients with increased ICP especially in vulnerable regions such as the penumbra zones surrounding focal mass lesions (7). The intracerebral microdialysis technique permits bedside analyses of compounds reflecting energy metabolism (glucose, pyruvate, lactate) and indicators of excessive concentration of excitatory

Fig 1 transmitters (glutamate) as well as cell degradation (glycerol) (figure 1). The levels obtained during neuro intensive care can be compared to reference levels obtained in the normal human brain (18) and in patients with manifest cerebral ischemia (24). By inserting multiple intracerebral catheters during open surgery it is possible to choose areas of interest *i.e.* the zones surrounding an evacuated focal lesion (7).

Fig 2 Figure 2 summarizes recent data, which support the view that in patients treated according to the “Lund concept” the lactate/pyruvate ratio (cytoplasmatic redox state) is usually not affected in the vulnerable penumbra zone until CPP below 50 mmHg (16). Since cerebral biochemistry is monitored and displayed bedside therapeutic interventions are instituted if in an individual patient CPP is considered to be too low.

Clinical results

Ideally all clinical therapies should be based on randomised controlled studies. However, there are virtually no such studies to support any specific treatment for increased ICP (23). The only randomised clinical trial that has compared the consequences of targeting different levels of CPP failed to show a long-term benefit of increasing CPP above 70 mmHg (19). In a recent review on the management of cerebral perfusion pressure after head trauma it was concluded that it seemed likely that a CPP of 60 mmHg provided adequate perfusion for most patients with severe traumatic brain injuries (20). Further, pharmacologically induced hypertension was recently shown to cause a further increase in ICP (17). Clinical outcome of volume-targeted therapy according to the “Lund-concept” has been reported from four Swedish neurosurgical centres (5,6,11,12). All four studies have shown a remarkably low mortality. In the original study, which included a selected group of patients with very severe traumatic brain lesion

and ICP above 25 mmHg in spite of conventional treatment, the decrease in mortality was from 47% to 8% (5). The significant decrease in mortality was associated with significant increases in the groups of “good recovery” and “moderate disability” but did not increase the number of patients in the groups of “severe disability” or “vegetative state”.

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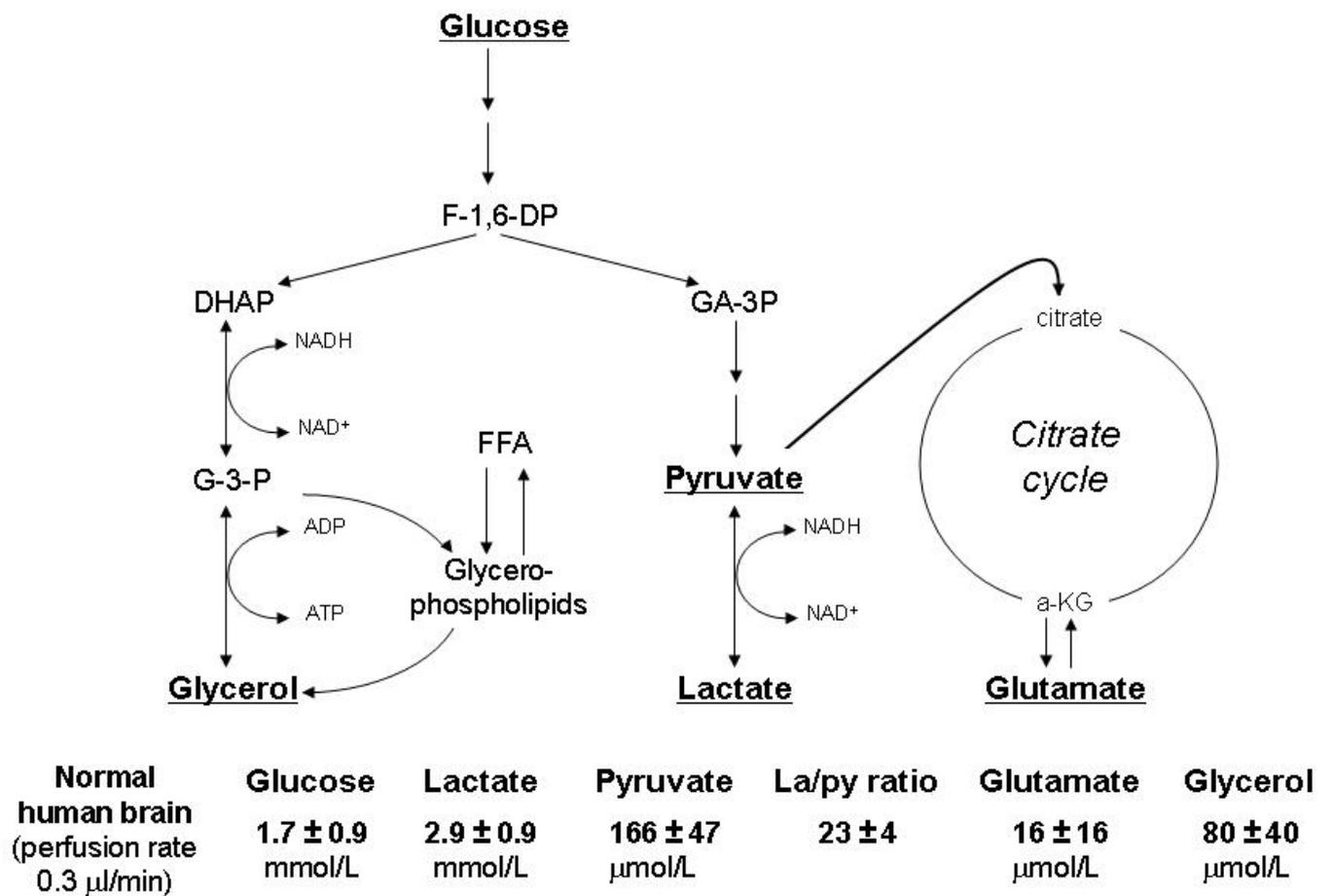


Figure 1. Simplified diagram of intermediary metabolism of the glycolytic chain and its relation to the formation of glycerol and glycerophospholipids and to the citric acid cycle. Abbreviations: Fructose-1,6-diphosphate (F-1,6-DP); Dihydroxyacetone-phosphate (DHAP); Glyceraldehyde-3-phosphate (GA-3P); Glycerol-3-phosphate (G-3-P); Free fatty acids (FFA); α -ketoglutarate (α -KG). Underlined metabolites are measured bedside with enzymatic techniques. Reference levels of the various metabolites for normal human brain obtained from (18).

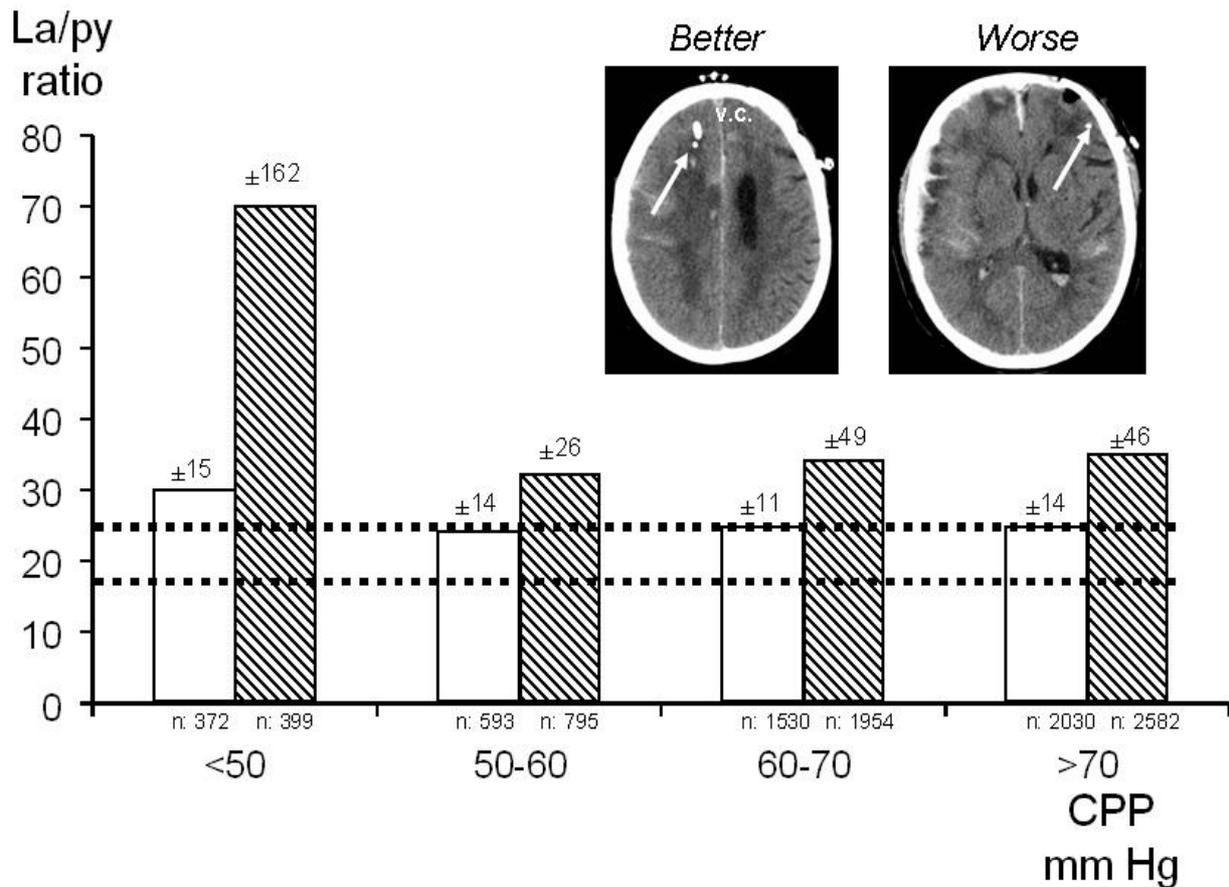


Figure 2. Mean levels \pm S.D. for the lactate/pyruvate (la/py) ratio (n: 7,704 measurements) in the “better” (white) and “worse” (striped) positions in relation to four ranges of CPP. The positioning of the microdialysis catheters in the “worse” (penumbra; surrounding the evacuated haemorrhagic contusion) and the “better” (close to the ventricular catheter – v.c.) areas are shown (arrows). The broken lines indicate the range (mean \pm S.D.; 23 ± 4) in normal human brain during wakefulness. Data from Nordström et al (16).