SEVERE BRAIN INJURY MANAGEMENT

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ABSTRACT

Management of severe brain injury, the main cause of death in young population, has now standardized principles that lead to the improving of the outcome. The treatment of this traumatic illness is direcly connected to cerebral physiopathology. After the impact, there are some cerebral mechanisms that are modified and are responsible for the appearance of the secondary injury: damaging of the cerebral metabolism, which has characteristic a very high metabolic rate compared to other tissues, altering the cerebral blood flow responsible for the cerebral oxygenation, altering the blood brain barrier with direct consequences on cerebral edema. Therefore, therapeutic aspects are connected to monitoring and will address to ensuring the hemodynamic stability, accurate oxygenation and correction of the factors that may worsen secondary injury (temperature, glycemia, osmolarity).

Key words: brain injury, cerebral metabolism, cerebral perfusion pressure, vasogenic edema, hypothermia, glycemia, sodemia

Brain injury is one of the most frequent causes for long term mortality, involving high cost for society. Usage of the new monitoring and diagnostic techniques for the primary and secondary injury has contributed to the improvement of the intensive care and the neurological outcome.

NEUROPHYSIOPATHOLOGY

The treatment of the patients with severe brain injury in the intensive care unit requires the understanding of the cerebral metabolism, the intracranial pressure (ICP), of the cerebral autoregulation mechanism, of the fluid and electrolyte balance, for correction of these parameters after brain injuries.

The skull is a solid box in which the volume of his components (brain tissue 80%, cerebro-spinal fluid CSF 8%, blood 12%) has to remain constant. Any increase in the volume of one of these components must determine the decrease in the volume of the others for maintaining a normal ICP.

Cerebral vasculature has an autoregulation mechanism for maintaining a constant cerebral blood flow (CBF). The energy required for the brain is provided by glucose in an amount of 90% by aerobe metabolism and represents 20% of total body oxygen consumption. These three mechanisms (ICP, cerebral autoregulation and cerebral metabolism) represent the intrinsic factors responsible for the regulation of CBF.

There are, also, extrinsic mechanisms, mainly CO_2 arterial pressure ($PaCO_2$) and temperature, which significantly modify CBF and major interfere in cerebral physiology.

The unique structure of cerebral vessels has determined the concept of blood-brain barrier (BBB), with major consequences in water and electrolytes passing.

In trauma situations, the major feature of the BBB, the lack of permeability, is lost, and so, the brain water volume will increase.

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In the following, we will present the essential aspects of the mechanisms that modify the cerebral homeostasis in severe brain injury, more exactly, his major determinant, that is CBF.

Total CBF rate is 50 ml/100g/min, the medium being calculated between flow in gray matter of about 80ml/100g/min and the flow in white matter of about 20ml/100g/min. So, CBF averages 750ml/min in adults (15-20% of cerebral output).

A. Cerebral metabolism

The brain requires 20% of total body oxygen consumption. The cerebral metabolic rate ($CMRO_2$) is about 50ml O_2/min and is maximum in the gray matter.

Neuronal cells normally utilize glucose as their primary energy source. Brain glucose consumption averages 5mg/100g/min, of which over 90% is metabolized aerobically. $CMRO_2$ is therefore parallel with glucose consumption, excepting starvation periods when ketone bodies also become major energy substrates. It's to mention that paradoxically hyperglycemia can exacerbate global hypoxic brain injury by accelerating cerebral acidosis and therefore producing cellular injury. This mechanism is less proved in focal cerebral ischemia.

Releasing of catecholamine and hyperglycemia are components of the stress response after brain injury. Patients with severe brain injury have higher levels of glucose compared to those with medium or minor injury. Hyperglycemia must be treated aggressively when global cerebral ischemia is present.

Interruption of blood flow is followed by consumption of the glucose and glycogen stores in the brain in 4 minutes. Severe sustained hypoglycemia is as much devastating as hypoxia.

ATP stores are depleted and irreversible cerebral injury occurs. Hippocampus and cerebellum appears to be most sensitive to hypoxic injury. Values of CBF below 20-25ml/100g/min are usually associated with severe cerebral impairment (slow waveforms on the EEG). Anaerobe metabolism is activated and lactic acid accumulate producing local pH dropping with mitochondrial damage, vasodilatation, failure of Na-K andenosinetriphosphatase (ATPase) pumps, followed by Na, Cl influx and then water influx. This is the mechanism of cytotoxic edema, the most frequent type of edema after brain injury. In area contiguous with ischemia, there is an acceleration of cerebral metabolism for providing supernormal levels of oxygen to prevent the ischemic penumbra from infracting. This can lead to the rising of the local cerebral temperature.

B. Cerebral perfusion pressure (CPP) and intracranial pressure (ICP)

CPP represents the blood pressure gradient through cerebral vessels and equals the difference between mean arterial pressure (MAP) and intracranial pressure (ICP).

CPP = MAP-ICP

Normal values range between 70-100 mmHg. Since intracranial pressure is normally less than 10 mmHg, CPP is mainly dependent on MAP.

Medium or high levels of ICP (>30 mmHg) can significantly compromise CPP and CBF, even in the presence of a normal MAP. Compensatory mechanisms of maintaining the ICP between normal values (intracranial compliance) include:

- an initial displacement of CSF from the cranial to the spinal compartment;
- an increase in CSF absorption;
- a decrease in CSF production;
- a decrease in total cerebral blood volume (primary venous).

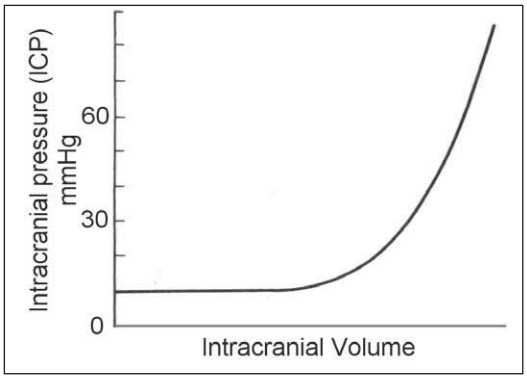

FIGURE 1. *The intracranial compliance*

Intracranial compliance can be increased in patients with brain injury by injecting sterile saline in the intraventricular catheter that monitors ICP. An increase in ICP>4mmHg following injection of 1 ml of saline indicates a low compliance. At that point, compensatory mechanisms have been exhausted and CBF will drop (normal values are 50-75ml/100g/min, approx. 20% of cardiac output). Sustained elevations in ICP can lead to catastrophic herniation of the brain through one of the following 4 sites:

- the cingulated gyrus under falx cerebry;
- the uncinate gyrus through the tentorium cerebelli;

- the cerebellar tonsils through the foramen magnum;
- any area beneath a defect in the skull (transcalvarial).

Clinical studies have shown a decreasing mortality to 30-40% at the patient with severe brain injury when CBP was maintained above 80 mmHg. Decreased CBP under 60 mmHg yielded the rising of mortality to 95%.

C. Cerebral autoregulation mechanism

The brain, like the heart and kidneys, tolerates wide variations in blood pressure without changes in CBF. Cerebral vessels rapidly adapt to changes in CPP.

Decreases in CPP result in cerebral vasodilatation, while elevations yield vasoconstriction, therefore CBF remains nearly constant between MAP of about 60 and 160 mmHg.

Beyond these limits, CBP becomes pressure-dependent. In the normotensive patient, values of MAP>150-160 mmHg can disrupt blood brain barrier, yielding cerebral edema and hemorrhage.

It's important to mention that in the patients with chronic arterial hypertension, the cerebral autoregulation curve is shifted to the right.

D. The most important extrinsic mechanism that influences CBF is respiratory gas tensions, especially $PaCO_2$. CBF is directly proportional to $PaCO_2$, between tensions of 20-80 mmHg. This effect is almost immediate (a CBF rise of 1-2ml/100g/min per

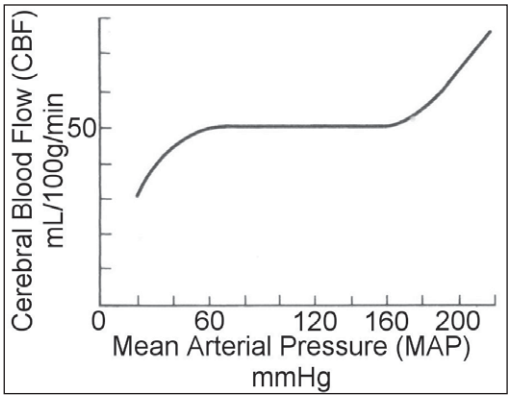

FIGURE 2. *Cerebral autoregulation*

mmHg change in $PaCO_2$) and is due to the changes in the pH of CSF and cerebral tissue. BBB is not permeable to the passing of ions, but CO_2 can cross it, therefore acute changes in $PaCO_2$ but not HCO_3^- concentration adjusts to compensate for the change in $PaCO_2$, so that the effects of hypocapnia or hypercapnia are diminished. Marked hyperventilation ($PaCO_2$ < 20 mmHg) may produce decreases in CBF with electroencephalographic changes suggestive for cerebral impairment even in normal individuals.

Compared with $PaCO_2$, only extreme changes in PaO_2 can alter CBF. Hyperoxia may be associated with minimal decreases (-10%) in CBF, while severe hypoxemia (PaO_2 <50 mmHg) profoundly increases CBF.

E. Temperature

Hypothermia decreases CBF and cerebral metabolic rate, while pyrexia raises CBF with 5-7% perºC. At 20ºC, electroencephalogram is isoelectric. Above 42ºC, metabolic rate produce altering of cellular oxygenation, with cell damage. In the brain injury, spontaneous swings in the body temperature (hypothermia or hyperthermia) are due to the damage of hypothalamus.

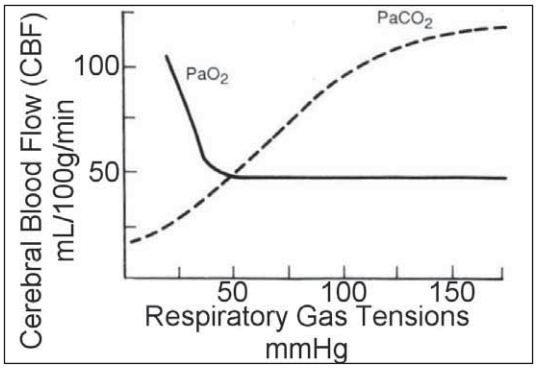

FIGURE 3. *The relation between CBF and respiratory gas tensions*

F. Other extrinsic factors that alter CBF

Elevated blood viscosity, as may be seen with marked polycytemia can reduce CBF. Hematocrit, as major determinant for blood viscosity, is also essential for oxygen carrying capacity. Therefore, a reduction in hematocrit improves viscosity and CBF, but, unfortunately can impair oxygen delivery. Clinical studies suggest that optimal hematocrit for cerebral oxygen delivery has values between 30-34%.

Big cerebral vessels are innervated by sympathetic fibers originating in the superior cervical

sympathetic ganglion. Intense sympathetic stimulation induces cerebral vasoconstriction, which can limit CBF.

BLOOD BRAIN BARRIER

The structure of the brain capillary is different from the systemic capillary essentially because the junction between vascular endothelia cells are nearly fused (tight gap junction); other features of the brain capillary endothelial cells are the absence of the fenestrations, high mitochondrial content, minimal pinocytic activity, and high electrical impedance.

The paucity of pores and the presence of tight gap junctions are responsible for what is named blood brain barrier (BBB).

The most significant feature of this structure is that it doesn't allow the free passage of electrolytes and molecules with high molecular weights. Plasma proteins are also impeded to cross the BBB because there are only few pinocytic vesicles (transport proteins) in the brain capillary endothelial cells to transport the proteins from plasma into the brain interstitial space.

This lipid barrier, on the other way, allows the passage of lipid-soluble substances, glucose, CO_2 and O_2. The brain capillary endothelial cells require large amounts of energy to allow or restrict these special movements between the brain and the blood circulation, therefore the amount of mitochondria is 3 to 5 times higher compared with systemic capillary.

Because BBB is not permeable to small ions (ex., sodium), rapid changes in plasma electrolyte concentrations produces a transient osmotic gradient between plasma and the brain.

On the other way, water freely pass the BBB as a consequence of bulk flow, thus acute hypertonicity of plasma results in net movement of water out of the brain, while acute hypotonicity causes a net movement of water into the brain, producing cerebral edema.

That's why treating abnormal sodemia and glycemia in patients with severe brain injury must be prompter than in other patients.

BBB is damaged in head injury (and also in other situations: tumors, strokes, meningitis, marked hypercapnia, hypoxia, sustained seizure activity) becomes dependent on hydrostatic pressure rather than osmotic pressure.

At the moment of impact, BBB is damaged, tight gap junctions which provide integrity of the BBB are stretched, so, there is an accumulation of water, electrolytes and proteins, leading to initial vasogenic edema. After that, as we already mentioned, the edema associated with brain injury is cytotoxic.

This initial vasogenic edema appears in the first 30 to 60 minutes from the impact and leads to worse the brain damage, because of mechanical disruption of microvessels, cells, cellular organells, releasing free radicals, accumulation of calcium in the cells. Increased levels of free radicals will affect cellular membrane (lipid peroxidation).

Ornithine decarboxylase is also released in high levels, producing putresceine that induces water extravasation from cerebral microvessels and increases vasogenic edema.

PRIMARY INJURY AND SECONDARY INJURY

Primary injury is the neurological damage that occurs at the time of impact.

The most probable primary injury is cerebral contusion and the patient is usually comatose without signs of localizing neurological deficits. This is due to a diffuse or multifocal process that produce disruption of BBB with brain swelling (edema). Focal injuries are represented by intracerebral hematoma, epidural hematoma and subdural hematoma.

The clinical hallmark signifying a mass lesion is the rising of ICP associated with focal deficits. Most of the patients are conscious, but after a while, their general condition deteriorates into coma, requiring quick diagnose of the hematoma with computed tomography.

Usually, epidural hematomas are caused by a skull fracture and frequently occur in the temporoparietal region, as skull fractures in this area cross the path of the middle meningeal artery.

Epidural hematoma can rapidly expand inducing coma, fixed dilated pupil ipsilateral to the skull fracture and contralateral hemiparesis. Subdural hematomas are caused by lacerations of the venous sinuses and tend to develop more insidiously.

Epidural and subdural hematomas are indications for surgical evacuation. Intracerebral hematomas are collections of blood ranging from petechial hemorrhages to large collections, usually in the

temporal and frontal lobe. Some lesions are pure hematomas or hemorrhagic contusions. Often, these lesions can be treated medically with follow-up CT scans.

If a rapid mental deterioration occurs, with mass effect and elevation of ICP, surgical evacuation is indicated.

Secondary injury represents the ischemia that occur subsequent and around to the primary injury.

Prevention or reduction of the ischemic area consists in correct management of the head injury, with correction of further hypoxemia and hypotension.

TREATMENT

As a conclusion of the physiopathologic aspects presented and also in introduction of the correct therapeutic management of the severe brain injury in the ICU, the essential parameters that must be achieved to every patient are the following:

- CPP 70-95 mm Hg at normotensive patient;
- ICP 5-15 mm Hg;
- MAP 100 mm Hg at normotensive patient;
- Hemoglobin 10 g/ dl;
- Central temperature 35-37˚C;
- SaO_2>97%;
- PaO_2>115 mm Hg for the first 72 hours, then >100 mmHg;
- Osmolality <320 osm/ l;
- $PaCO_2$ 35-40 mm Hg;
- Na+ 140-145 mEq /l;
- Glucose 80-110 mg/dl;
- PCWP 10-14 mm Hg;
- PAD 12-16 mm Hg;
- PVC 6-8 mm Hg.

Some of the therapeutic considerations for which the achievement of these targets is necessary were presented before.

There are some other aspects with therapeutic visa connected with CPP, ICP, oxygenation, hemodynamics and sodium and osmolality abnormalities.

HEMODYNAMIC STABILITY

Many patients with severe head trauma arrive at the hospital after having episodes of hypotension and hypoxemia. The time between the impact and the arriving at the hospital for correction of these episodes is essential for the improvement in outcome. In most of the cases, severe brain injury is part of a politrauma with hemorrhagic and hypovolemic shock, therefore fluid resuscitation (crystalloids, plasma expanders and blood), oxygenation by intubation and mechanical ventilation are the first steps of the treatment.

The problem with aggressive resuscitation is that excessive crystalloid administration may exacerbate brain edema.

It is important to note that studies demonstrated that isotonic solutions (Ringer lactate and 0.9% saline) have no adverse effect on edema formation, but D5W solutions increase edema, blood glucose and worsen neurological outcome.

Therefore, D5W is to be avoided for the initial resuscitation due to decreased osmolality that appears (administration of free water) and that produces edema.

After initial hemodynamic resuscitation and achievement of the euvolemic status (hemodynamic parameters MAP, PAD, CVP, PCWP), obtaining of an adequate CPP is the mainstay of the treatment.

It must be reminded that in the hypertensive patient, autoregulatory mechanism being shifted to the right, the target values for MAP will be, obviously, higher than 90-110 mm Hg. It's also to keep in mind that most of the episodes of hypotension are due to the direct effect of lowering the ICP: sedation, diuretics. These situations may lead to the use of vasopressive drugs.

On the other hand, a too high MAP responsible for a CPP>95 mm Hg is deleterious because of the risk of damage the BBB, it may exacerbate cerebral edema, rises blood volume and induces pulmonary edema or acute respiratory distress syndrome ARDS.

First line antihypertensive drugs are beta- blockers and angiotensin-converting enzyme ACE inhibitors. Antihypertensive drugs containing nitrogen act quickly, but because of the direct vasodilator effect, they increase ICP.

Improving the outcome in patients with severe brain injury was assigned to the concept of "squeezing oxygenated blood into the swollen brain".

Monitoring the ICP is an essential device for the management of severe brain injury, offering not only values of monitoring, but also is a direct way of lowering the ICP by draining CSF when the catheter is placed intraventriculary (intraventriculary

placing has been associated with the potential for infection and parenchyma injury).

Current ICP monitoring utilizes a twist drill for bolt placement in the skull to pass a catheter in the parenchyma or subarachnoidian space.

Some systems allow CSF drainage in which a catheter containing a transducer at the tip is placed into ventricles.

There is now a well-known algorithm in ICU for lowering ICP and improving CPP:

- surgical removing of the mass effect lesion;
- elevate head of the bed to 30 degrees and keep the neck straight to avoid jugular obstruction;
- control of MAP to the optimal value (avoid hypotension and hypertension);
- ventilation to normocarbia and hyperoxia; treat peaks of ICP with mild hyperventilation to PaCO2 of 30-35 mmHg;
- mannitol bolus 0,25-1g /kg over 15 min or hypertonic saline (bolus of 250 ml 3 % saline solution);
- CSF drainage with ventriculostomy;
- light or heavy sedation and paralytics;
- control of pain.

If these measures do not lower ICP below 25 mm Hg, the algorithm will lead to:

- barbiturate coma;
- hypothermia;
- decompressive craniotomy.

One protocol to induce barbiturate coma is the Eisenberg's protocol: a loading dose of pentobarbital at 10mg/kg IV over 60 min, followed by 5 mg/kg every hour for 3 hours, with a maintenance dosage of 1-3 mg/kg/h. It is generally considered that if the induced pentobarbital coma does not lower ICP in 1-4 hours, it is unlikely to succeed without any other therapy. If thiopental is used, the loading dose is 5mg/kg over 10 minutes with an infusion of 3-5 mg/kg/h for 24 hours, and then decreased to 2,5 mg/kg/h.

The advantages of mild hypothermia are:

- lowering the levels of excitatory aminoacids (glutamate);
- improving the reperfusion injury;
- lowering ICP;
- lowering cerebral metabolic rate.

However, hypothermia has a multitude of side effects:

- impeding general oxygenation, including cerebral oxygenation (left shift of the hemoglobin dissociation curve);
- increased peripheral vascular resistance;
- is a direct stimulus for the stress response and lowers the general body resistance to infections;
- may induces shivering with its deleterious effects: raising metabolic rate, inducing acidosis and lowering the SaO_2;
- platelet dysfunction and reversible coagulopathy;
- impaired renal function with water retention;
- cardiac dysrhythmias.

Therefore, current recommendations for using hypothermia in the treatment of severe brain injury are for values not higher than 32˚C and for a period not longer than 48 hours.

Studies have proven no beneficial long-term effect for using hypothermia at patients with severe brain injury compared with normotermic treated patients.

Regarding systemic and cerebral oxygenation, studies have shown that values of PaO_2>150 mm Hg in the first 24-48 hours have improved cerebral oxygenation and long-term neurological status, due to the lowering of lactate level in the brain.

Currently, there are several devices on the market that measure oxygen content. A cerebral oxygen monitor is placed at the bedside, much like a ventriculostomy.

Many studies have shown it to be equally as useful as a jugular bulb catheter for measuring jugular venous oxygen saturation ($SjvO_2$). Cerebral oxygenation monitors may also measure parenchyma temperatures simultaneous to oxygen content.

Brain oxygen tension or partial pressure (PbO_2) is optimal at values greater than 30 mmHg and is not adequate if it drops below a value of 20 mmHg. This monitor yields information that can be used to prevent further ischemia.

There are also systems for measuring CBF which is proportional to metabolic activity. Some detectors placed around the brain measure the rate of radioactive decay of a gamma emitting isotope (133Xe) after systemic injection.

This decay is directly proportionate to CBF. Newer techniques employ positron emission tomography (PET) in conjunction with short-lived

isotopes such as 11C or 15O, for measuring cerebral metabolic rate for glucose and oxygen, respectively.

It is to be reminded that alkalosis (! hyperventilation), hypothermia and lowering 2,3 diphosphoglycerate shift the hemoglobin dissociation curve to the left, increasing hemoglobin's affinity for oxygen and reducing its availability to tissues. Acidosis, hyperthermia, hypercarbia and 2,3-diphosphoglycerate have the opposite effect.

A special attention has to be given to the sodemia values, as the main determinant of serum osmolality, with direct consequences on water movements between body compartments (extracellular and intracellular space), therefore, at the cerebral level, sodium will affect the amount of water in the intracellular space (cerebral edema).

Head injury is usually associated with hypernatremia, caused by the hypovolemia due to losing of free water. The most common conditions that produce hypernatremia associated with head injury are diabetes insipidus (injury of the hypothalamus or pituitary stalk suppresses the release of ADH) and osmotic diuresis (hyperglycemia, mannitol treatment). At levels of Na>160 mEq/l, the consciousness is impaired.

Hipernatremia is treated with hypotonic fluids. If the urinary output is > 250ml/ h for 2 consecutive hours, hormonal replacement with 1-desamino-8-D-arginine vasopressin (DDAVP) is needed. Basilar skull fractures may predispose to the development of diabetes insipidus.

Hyponatremia is frequent in the postoperative period and results usually from the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting (CSW). In SIADH, extracellular volume is increased, but in CSW is decreased because of the high urine output. Severe hyponatremia (Na < 120 mEq/l) produces cerebral edema and seizures.

Correction of hyponatremia can be achieved by giving a loop diuretic to induce water diuresis (ex. furosemid), while replacing urinary sodium loses with isotonic saline. Even more rapid correction can be achieved with intravenous hypertonic saline (3% Na Cl) in markedly symptomatic patients with plasma sodium <110 mEq/l. Plasma sodium should be corrected above 130 mEq/l because lower concentrations may result in significant cerebral edema. On the other side, very rapid correction of hypovolemia has been associated with demyelinating lesions in the pons, resulting in permanent neurological sequelae. Therefore, correction with hypertonic saline must be done slowly.

Other complications associated with head injury are:

- neurogen acute pulmonary edema caused by the releasing of high levels of catecholamine and by the altering of pulmonary capillary permeability from as-yet undescribed neurogenic factors; the treatment is similar as with other cases of pulmonary edema, including PEEP;
- seizures in the first 7 days or later; prophylactic anticonvulsants are recommended for the first 7 days (phenytoin);
- coagulopathy, ranging from abnormalities in the clotting studies to clinically significant bleeding; the most serious bleeding, disseminated intravascular coagulation (CID), is a consequence of releasing of tissue thromboplastins from the cerebral injured area;
- infections: ventilator-related pneumonia, meningitis caused by CSF leaks or by ventriculostomy;
- digestive ulcers (Cushing ulcer).

CONCLUSIONS

Management of severe brain injury improved in the last decades, from the using of mechanical ventilation to ensure an adequate oxygenation and continued with the new techniques of monitoring.

Head injury is currently one example of pathology in ICU in which treatment consists not in administration of different drugs, but monitoring is essential and mandatory for correction, by unspecific means, of the physiopathologic parameters necessary to normalize cerebral homeostasis.

Summarizing, the guidelines for treating severe brain injury will address to:

- hemodynamic stability for ensuring an adequate CBF to decrease secondary injury;
- accurate oxygenation by means of mechanical ventilation, with normocarbia;
- avoiding the factors that rise cerebral metabolic rate: hyperthermia, seizures, pain agitation;
- correction of abnormal values of glycemia, main factor for the cerebral metabolism;
- correction of abnormal values of sodemia, main factor for intracellular water, determinant for cerebral edema.

REFERENCES

1. **Yao F.S.F.** – Problem-oriented patient management 6-th ed., *Lippincot Williams,* 2008; 597-616
2. **Siddiqi J** – Nerosurgical Intensive Care, New York, *Thieme Medical Publishers,* 2008; 174-234
3. **Shapiro H.M., Wyte S.R., Loeser J** – Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension *J Neurosurg.* 1974; 40:90-100
4. **Rovhias A., Kotsan S** – The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery* 200; 46:335-342
5. **Morgan G.E., Mikhail M.S.** – Clinical Anesthesiology 2-nd ed. *Appelton & Lange* 1996; 25:477-481
6. **Irwin R.S., Rippe J.M.** – Manual of Intensive Care Medicine 5th ed *Lippincot Williams* 2009; 117:800-803