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Comprehensive Study And Prognostic Criteria Of The Main Systemic Mechanisms Of Secondary Brain Damage In Combined Craniocerebral Injury During The Acute Period

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ABSTRACT

Background: Secondary systemic mechanisms of brain damage significantly influence outcomes in patients with severe combined craniocerebral injury (SCTBI). Despite progress in neurocritical care, mortality remains high due to impaired cerebral perfusion regulation and systemic homeostatic disturbances.

Objective: This study aimed to investigate the main systemic mechanisms contributing to secondary brain injury in SCTBI and identify prognostic factors associated with poor outcomes.

Methods: A total of 270 patients with severe SCTBI treated from 2022 to 2024 were analyzed. Clinical, neurological, and laboratory parameters—including hemodynamics, oxygenation, and sodium balance—were evaluated. The relationships between arterial hypotension, hypoxemia, sodium and osmotic disturbances, and clinical outcomes were statistically assessed.

Results: Early arterial hypotension occurred in 81% of cases and was a strong independent predictor of mortality and vegetative outcomes. Combined arterial hypotension and hypoxemia significantly worsened prognosis, particularly in diffuse and compressive brain injuries. Sodium imbalance, including both hyponatremia (<125 mmol/L) and hypernatremia (>155 mmol/L), increased mortality by 36–64%. Lymphotropic antibiotic therapy demonstrated beneficial effects by improving perfusion and reducing cerebral edema.

Conclusion: Secondary systemic factors such as arterial hypotension, hypoxemia, and sodium imbalance play a decisive role in the pathogenesis of secondary ischemic brain injury. Early detection and correction of these factors are essential to improve survival and neurological recovery in patients with severe combined traumatic brain injury.

KEYWORDS: Severe traumatic brain injury; Craniocerebral trauma; Arterial hypotension; Hypoxemia; Sodium imbalance; Osmotic homeostasis; Brain edema; Perfusion pressure; Lymphotropic therapy; Prognostic markers.

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INTRODUCTION

Clinical and experimental studies have shown that after combined craniocerebral injury, the physiological mechanisms maintaining perfusion pressure are damaged. The autoregulation of cerebral blood flow is partially or completely impaired. Under these conditions, following a traumatic brain injury, the brain is unable to adequately respond to systemic disturbances of homeostasis. As a result, various secondary lesions develop in the brain tissue, predominantly of an ischemic nature, which are found in 80–90% of deceased patients. At present, among systemic disturbances of homeostasis, the following are most frequently described as secondary damaging mechanisms of the brain: hypotension, hypoxemia, disturbances of sodium metabolism and osmotic homeostasis, hypocapnia and hypercapnia, hyperthermia, extracranial inflammatory complications, and others.

Arterial Hypotension in Combined Traumatic Brain Injury during the Acute Period

In our study, to investigate the prognostic significance of arterial hypotension, 187 patients with severe combined craniocerebral trauma who were treated at the Republican Scientific Center for Emergency Medical Care (RSCEMP) during the period of 2022–2024 were selected. Data obtained from patients in a terminal state were excluded from the study. Heart rate and arterial pressure were continuously monitored. The dependence of systemic circulation parameters on the kinetics of biogenic amines, as well as clinical, neurological, and radiological data, was analyzed.

An analysis of selected systemic hemodynamic parameters during days 1–21 after combined craniocerebral trauma revealed that arterial hypotension (at admission and within the first 14 days) was observed in 81% of cases (early hypotension). This slightly exceeds the incidence rate of arterial hypotension reported in the traumatic coma database—34.6% of cases. The proportion of patients with associated injuries among those with arterial hypotension was 88%, compared to 27% among patients without arterial hypotension. This indicates that arterial hypotension upon admission is associated with multiple injuries and results from blood loss.

Arterial hypotension was most frequently observed in patients with diffuse injuries (51%) and much less often in those with focal lesions (30%). Patients with early arterial hypotension had worse outcomes (85%—fatal outcomes and vegetative states). In the group of patients without arterial hypotension, the proportion of fatal outcomes and vegetative states was 15% of cases.

According to our data, in patients with severe craniocerebral trauma, there are two critical levels of systolic blood pressure reduction. The first is when the mean arterial pressure decreases within the range of **70–89 mmHg**, where fatal outcomes were observed in only 20% of cases; the second is when the mean arterial pressure falls **below 70 mmHg**, where fatal outcomes were recorded in **61% of cases**.

In addition, in patients with arterial hypotension, despite the fact that the severity of condition at admission was approximately the same, the admission scores did not differ significantly between patients with arterial hypotension (5.1 ± 0.6) and those without it (5.7 ± 0.4; $p > 0.05$). The average duration of the comatose state was significantly longer in patients who experienced arterial hypotension (10.2 ± 2.1 days) compared to patients without arterial hypotension (4.9 ± 1.6 days; $p < 0.05$).

The genesis of early arterial hypotension was associated with an absolute or relative decrease in circulating blood volume due to various causes, observed in 72% of cases. In 37.2% of cases, the reduction in circulating blood volume was pronounced, indicating acute hypovolemia. Hypovolemic disorders led to a decrease in stroke volume in 52% of cases, which was compensated by cardiac output through an increased heart rate in only 15.1% of observations. A significant correlation was observed between the cardiac index and circulating blood volume ($r = 0.56$; $p < 0.05$) on one hand, and between circulating blood volume and stroke index on the other ($r = 0.57$; $p > 0.01$).

Regression analysis of cardiac index, stroke index, and circulating blood volume parameters in the acute period of severe combined craniocerebral trauma indicated a strict statistical dependence of cardiac output changes on the severity of hypovolemic disorders. A weak linear relationship between systolic arterial pressure and stroke index with heart rate indicated a reduction in the strength of adaptive-compensatory reactions aimed at maintaining systemic arterial pressure and cardiac output.

These findings partly coincide with the opinions of Chesnut R.M. et al., 1993; Gaitur E.I., 1999; Amcheslavsky V.G., 2002, who argued that the outcome of acute hypovolemia in traumatic brain injury does not depend on age, depth of consciousness depression at admission, or the presence of combined injuries. The authors suggest that the effect of multiple systemic trauma is mediated through systemic arterial hypotension (156). Indeed, a correlation between circulating blood volume and the patient's condition, as ranked by the Glasgow Coma Scale, was noted as weak (HU2, $p < 0.05$).

In the group of patients with hypovolemia, certain features of the humoral regulation of circulation were identified. These included a short-term activation of the sympatho-adrenal system during the first to third days after injury, manifested as a tenfold increase in catecholamine levels.

In the group of patients with fatal outcomes and hemodynamic disorders, significant changes in the mechanisms maintaining fluid volume and electrolyte concentrations were observed, correlating with the identified hypovolemic disturbances. During the first three days, in patients with severe traumatic brain injury accompanied by hypovolemia and arterial hypotension, the levels of antidiuretic hormone secretion remained within normal ranges (4.8 ± 0.9 pmol/L), although it is known that a 15% reduction in circulating blood volume should trigger ADH secretion complications (Gaitur E.I., 1999).

In addition, activation of the renin-angiotensin-aldosterone system was reflected in the observed correlations: plasma renin activity – circulating blood volume ($r = -0.54$; $p > 0.05$), aldosterone – circulating blood volume ($r = -0.56$; $p < 0.05$), aldosterone – mean arterial pressure ($r = -0.57$; $p < 0.05$), indicating activation of this humoral system as hypovolemia and hypotension increased. A twofold increase in angiotensin concentration typically led to increased blood flow in the arterio-venous shunts of the brain.

In the group of patients with early prolonged systemic hypotension (mean arterial pressure = 81 ± 1.2 mmHg), a moderate decrease in the mean linear blood flow velocity was noted. By days 2–3, in the middle cerebral artery, the linear blood flow velocity

decreased to 40.1 ± 2.1 cm/s. This was accompanied by a predominant reduction in diastolic blood flow velocity, while systolic velocity values remained preserved. These findings indicated an increase in peripheral vascular resistance due to elevated intracranial pressure, resulting in reduced cerebral perfusion.

One of the mechanisms for the rise in intracranial pressure in systemic arterial hypotension in patients with severe traumatic brain injury is an increase in central venous pressure. Central venous pressure elevation usually accompanies resuscitation procedures in hypovolemic shock. As a result of increased intracranial pressure with decreased mean arterial pressure, cerebral perfusion pressure falls, leading to hypoxic brain injury. According to cerebral oximetry data (Fig. 8), patients in this group exhibited decreased brain tissue oxygen saturation (rSCb). Figure 9 presents data on changes in mean arterial pressure, intracranial pressure, mean linear blood flow velocity, and brain tissue oxygen saturation during an episode of arterial hypotension. Our findings correspond with data reported by Konovalov A.N., 2001–2004, and Amcheslavsky V.G., 2002.

EPISODES OF ARTERIAL HYPOTENSION AFTER 14 DAYS (DELAYED HYPOTENSION)

Episodes of arterial hypotension after 14 days (delayed hypotension) were often observed against the background of purulent-inflammatory complications in 17% of cases. At the same time, there was no difference in the number of patients with combined injuries between those with delayed hypotension and those without delayed hypotension. In this group, mortality was 14%, and the incidence of vegetative state was 44% of cases. According to other authors, mortality or progression to a vegetative state in patients with delayed arterial hypotension is 66%, compared to 17% in patients who did not have episodes of hypotension (6, 15, 17).

The causes of delayed hypotension in patients with severe traumatic brain injury were septic conditions, iatrogenic factors, and damage to central mechanisms of hemodynamic regulation. In the group of patients with delayed arterial hypotension or episodes of arterial hypotension, periods of systemic arterial pressure changes (Δ ± 25.5 mmHg) were accompanied by reductions in mean linear blood flow velocity in the middle cerebral artery (Δ ± 15.5 ± 2.1 cm/s, $p < 0.05$) and decreases in brain tissue oxygen saturation, indicating severe disturbances of vascular tone autoregulation accompanied by hypoxic disorders.

Thus, early and delayed arterial hypotension is one of the most significant independent adverse prognostic factors in severe combined traumatic brain injury. It is evident that arterial hypotension is a common determinant of secondary ischemic brain injury. The intensive care protocol for patients with severe combined traumatic brain injury should include measures aimed at the mandatory prevention and rapid correction of arterial hypotension of any origin.

ARTERIAL HYPOXEMIA IN ACUTE COMBINED TRAUMATIC BRAIN INJURY

To determine the influence of arterial hypoxemia on the course and outcome of traumatic brain disease, 193 patients with combined craniocerebral trauma were selected. The patients were grouped as follows: 1 group – patients who did not have episodes of hypotension and hypoxemia before admission and during the first 14 days after injury; 2 group – patients who experienced episodes of hypoxemia ($PaO_2 < 60$ mmHg) during this period; 3 group – patients who experienced episodes of both hypoxemia and arterial hypotension (systolic BP < 90 mmHg) during this period. Indicators of hypotension and hypoxemia observed in terminal patients were excluded from the study.

Arterial hypoxemia and hypotension were most frequently observed in the acute period. In patients with severe traumatic brain injury, they were observed in combined cranial injuries. Among patients in group 3, diffuse brain injuries (53 patients) and meningeal hematomas (21 patients) were most common.

As seen in Table 1, patients in groups 2 and 3 sustained more severe injuries than patients in group 1. This is evidenced by the low Glasgow Coma Scale scores at admission in these patients. Patients in groups 2 and 3 had a significantly longer duration of unconsciousness.

Table 1

Relationship between main clinical indicators, outcomes, and study groups

Indicators	**Group 1**	**Group 2**	**Group 3**
Number of patients	121	30	73
Age	25.3 ± 1.7	25.6 ± 3.2	20.9 ± 1.8
GCS score	7.1 ± 0.2	5.9 ± 0.2**	3.9 ± 0.1**
Coma (days)	5.2 ± 0.7	9.6 ± 1.5**	10.5 ± 1.0**
Outcomes (%)			
Good recovery	35	14	8**
Moderate disability	24	15**	10**
Severe disability, vegetative state, and death	20	60**	70**

The significance of differences between Group 1 and the others: *- $p<0.05$; **- $p<0.01$

The presence of hypoxemia led to a significant twofold increase in the number of patients with "unfavorable" outcomes (death, vegetative state, severe disability). The combination of these two factors in a single patient (Group 3) was accompanied by an even greater increase in "unsatisfactory" outcomes.

Among patients with diffuse brain injuries, the presence of only episodes of arterial hypoxemia during the first 14 days after injury did not increase the number of fatal outcomes (see Table 1).

Table 2
Number of patients with fatal outcomes (%) depending on the type of brain injury

Type of brain injury	Group 1	Group 2	Group 3
Diffuse injuries	8%	9%	20%
Intracerebral hematomas	10%	28%	41%
Meningeal hematomas	18%	60%	62%
Overall	12%	32%	32%

The significance of differences between Group 1 and the others: *- p<0.05; **- p<0.01
However, the combination of arterial hypotension and hypoxemia led to an almost significant increase in the number of patients with fatal outcomes among these patients. For focal injuries, a different pattern was observed—both hypoxemia alone and its combination with arterial hypotension increased mortality. Finally, the highest mortality was noted with the combination of the two systemic damaging factors in patients with meningeal hematomas. All of the above indicates that these systemic damaging factors have the most unfavorable impact on the outcomes of traumatic brain injury with brain compression.

When considering the influence of the studied damaging factors on patient outcomes separately, it was found that in the absence of these factors, outcomes did not differ statistically. If hypotension or hypoxemia occurs, the number of patients with "unsatisfactory" outcomes increases almost 1.5 times among adults and almost three times among children (28). The combination of these factors increases the number of patients with unsatisfactory outcomes almost 2 times among adults and almost 4 times among children ($p<0.05$)(28).

Thus, systemic hypoxia is one of the fundamental causes of mortality and poor outcomes in severe combined traumatic brain injury. Patients with acute meningeal hematomas are the most sensitive to these factors.

SODIUM BALANCE DISORDERS IN SEVERE COMBINED TRAUMATIC BRAIN INJURY (SCTBI)

This section presents the results of a study of sodium metabolism disturbances in 175 patients, monitored dynamically during their stay in the intensive care unit in the first 7–10 days after the injury. All patients had severe traumatic brain injury. Depending on the range of fluctuations of individual plasma sodium concentrations and the dynamics of this parameter, the patients were grouped as follows: 1st group – patients whose plasma sodium concentration remained within the normal range of 135–145 mmol/L during the study period. 2nd group – patients with moderate disturbances of plasma sodium concentration from 125 to 155 mmol/L. 3rd group – patients with hyponatremia below 125 mmol/L. 4th group – patients with hypernatremia above 155 mmol/L. 5th group – patients with chaotic alternation of hyponatremia (<125 mmol/L) and hypernatremia (>155 mmol/L).

Group 1 – 73 patients with normal plasma sodium levels during the first 10 days after the injury had less severe trauma and the shortest duration of comatose state. Diffuse brain injuries were more common in this group (34 patients). Outcomes were better than in the other groups.

Group 2 – 103 patients had moderate disturbances of plasma sodium concentration, both decreases and increases, during the study period, but the sodium levels did not exceed 125–155 mmol/L. These moderate disturbances were easily corrected. Diffuse brain injuries also predominated in this group (51 patients). However, the severity of trauma and duration of coma were greater than in the group with normal sodium levels. Outcomes were worse than in Group 1. Twenty-one patients died.

Group 3 – patients with hyponatremia during the first 10 days after the injury. Sodium concentration in these patients dropped to 125 mmol/L or lower. There was no trend toward hypernatremia in this group. Most patients in this group had brain compression (5 patients). The average age was highest in this group. The mean duration of coma was significantly longer than in the other groups. Mortality was higher than among patients with moderate disturbances and normal sodium levels.

Group 4 – 15 patients were characterized by the development of hypernatremia with sodium levels above 155 mmol/L. Most patients in this group had diffuse brain injuries (6 patients) and brain compression (6 patients). The duration of unconsciousness and mortality in this group were higher than in the previous two groups.

Group 5 – 9 patients had chaotic alternations of hypernatremia and hyponatremia. All patients in this group were young, with a mean age of 22.8 years. They suffered the most severe injuries. Brain compression with meningeal hematomas predominated in

this group (4 patients). The mean duration of coma was maximal, similar to Group 3, exceeding 2 weeks. The highest number of deaths was recorded: 5 out of 9 patients.

Thus, the nature of sodium balance disturbances correlated with the outcomes of severe combined traumatic brain injury. Patients with normal plasma sodium levels had the lowest mortality. In the case of moderate sodium balance disturbances (Group 2), mortality increased to 24%. With pronounced disturbances toward hyponatremia (Group 3), as well as toward hypernatremia (Group 4), mortality rose to 36% and 53%, respectively. In patients with severe sodium balance disturbances, when a single patient experienced both hypernatremia and hyponatremia, mortality was highest at 64%.

Sodium and osmolarity disturbances were most frequently observed in cases of diffuse brain injuries and brain compression—almost in half of the cases—whereas in focal injuries, sodium balance disturbances were observed in only one-third of cases. Therefore, the most significant disruption of osmotic homeostasis regulation mechanisms occurs in diffuse injuries and meningeal hematomas.

It should be noted that patients with hypernatremia and hyperosmolarity more often had fractures of the skull base in the region of the middle cranial fossa, alcohol intoxication, and hemorrhagic shock ($p<0.05$). According to other authors, fractures of the skull base in the region of the sella turcica also more frequently lead to electrolyte disturbances, indirectly indicating primary or secondary damage to the hypothalamic-pituitary region .

A relationship was identified between the severity of brain edema and sodium balance disturbances during the first week after injury. As shown in the table, the number of patients whose brain edema was confined to one or both hemispheres was lowest only in the case of normal sodium levels. In contrast, with hypernatremia and hyponatremia, the number of patients with edema spreading to one or both hemispheres was twice as high. In hyponatremia, intracellular fluid increases, particularly in the brain, leading to increased brain edema. Clinically, this manifests as decreased consciousness and prolonged comatose state.

Table 3
Relationship between the degree of brain edema spread and the degree of sodium balance disturbance

Indicators	Group 1	Group 2	Group 3	Group 4	Group 5
Plasma sodium	135–145	125–155	<125	>155	<125+>155
Local edema	30 (41%)	35 (41%)	2 (18%)	2 (13%)**	—
Within a brain lobe	16 (22%)	14 (14%)	2 (18%)	2 (13%)	3 (33%)
Within 1 or 2 brain hemispheres	27 (37%)	54 (52%)	7 (64%)	11 (74%)*	6 (66%)
Total	73 (100%)	103 (100%)	11 (100%)	15 (100%)	9 (100%)

Significance of differences between Group 1 and the others: * – $p<0.05$; ** – $p<0.01$
The increase in brain edema during prolonged hypernatremia may be associated with excessive accumulation of sodium and chloride in cells, leading to enhanced intracellular edema due to water influx into the intracellular space along the osmotic gradient.

Thus, in patients with severe combined traumatic brain injury (TBI), disturbances of sodium balance and osmotic homeostasis are observed, both towards hypernatremia with associated hyperosmolarity and towards hyponatremia with hypoosmolarity. These changes are most often noted in patients with diffuse injuries and brain compression. They have a significant impact on the clinical course of severe combined TBI and on outcomes, directly or indirectly affecting the severity of brain edema and other processes.

DISCUSSION OF RESULTS

From 2022 to 2024, 270 patients with severe combined TBI were treated. Open TBI was present in 54 patients. Regional lymphotropic therapy according to the method of the Republican Center of Lymphology of the Ministry of Health of the Republic of Uzbekistan was administered to 134 patients without extracranial infectious foci or sepsis. The drugs were administered once daily into the region of the cervical and submandibular lymph nodes on the side of the wound for 2–5 days. Systemic antibiotic therapy was not used.

The method of lymphotropic antibiotic therapy, developed jointly by Andijan and Moscow lymphology scientists, is now widely used in the emergency care system. The essence of the method is the introduction of small doses of antibiotics into tissues and the creation of conditions for temporary, functionally altered microcirculation in the area of antibiotic administration, so that the drug is absorbed into lymphatic, rather than blood, capillaries.

The need to deliver antibiotics into the lymphatic system is explained by the fact that microbes primarily penetrate the lymphatic system, and the main site of action for antibacterial drugs should be the lymphatic vessels and lymph nodes. Unfortunately, traditional methods of antibiotic administration, such as intramuscular, intravenous, intraperitoneal, and others, generally do not provide therapeutic concentrations of antibiotics in the lymphatic system. Moreover, therapeutic concentrations in the blood and tissues are maintained for a very limited time, usually 4–12 hours. This necessitates frequent repeated injections of antibiotics,

which is not without consequences for the body. The lymphotropic antibiotic therapy we used involved a single daily therapeutic dose calculated by body weight and height.

Intravenous administration of colloids such as plasma, blood, albumin, mannitol, gelatinol, and other agents, along with stimulation of lymphatic drainage from affected tissues by introducing tissue lymph drainage stimulants such as trypsin, hyaluronidase, heparin, and "water load" with glucose-novocaine mixture, leads to a pronounced detoxifying effect both at the tissue and systemic levels.

Analysis of extracranial factors causing global ischemic disturbances in the injured brain showed that systemic brain ischemia is one of the main causes of mortality and poor outcomes in traumatic brain injury (TBI). Arterial hypoxemia and hypotension are most frequently observed after combined injuries. Patients with acute subdural hematomas are the most sensitive to these factors, as confirmed by other researchers. According to these data, mortality in patients with brain compression and arterial hypotension can reach 93%. Furthermore, adults and children respond differently to hypotension and hypoxemia; children are more sensitive to these systemic disturbances. Similar results have been obtained by other researchers. There are reports that the combination of arterial hypotension and hypoxemia in the same patient with severe TBI leads to nearly 100% mortality.

Our data partly coincide with the opinion of Chesnut R.M. and colleagues, who believe that the outcome of acute hypovolemia in severe TBI is mediated through systemic arterial hypotension. Our observations also match data from other studies showing that mortality or transition to a vegetative state in patients with delayed arterial hypotension occurs 3.2 times more often compared to patients without hypotensive episodes. A definite correlation was found between changes in $PaCO_2$ and the duration of coma, course, and outcomes of TBI. However, it should be noted that artificial hypocapnia was mainly used to treat the most severe patients, in whom episodes of intracranial hypertension were most often observed. Hypercapnia, on the other hand, usually accompanied hypoxemia and was more often observed after combined TBI with chest trauma, as well as during the development of pneumonia. According to some authors, short-term hypocapnia can be used for emergency reduction of intracranial hypertension until its cause is determined. Other authors note that prolonged use of hypocapnia worsens outcomes.

A pronounced relationship was established between disturbances in sodium balance, osmotic homeostasis, the course of traumatic disease, the severity, and outcomes of traumatic brain injury (TBI). It was found that severe sodium metabolism disorders most often occur in cases of brain compression and diffuse injuries. Prognostic factors for the development of hypernatremia included fractures of the skull base in the middle cranial fossa, pronounced lateral displacement, pre-injury alcohol intoxication, and hemorrhagic shock.

A correlation was identified between the severity of brain edema and the degree of sodium balance and osmotic homeostasis disturbances. Patients with sodium imbalance more frequently exhibited hemispheric or diffuse edema. Both hyperosmolarity and hypoosmolarity were more commonly observed in patients with pronounced brain edema. This indicates that hyponatremia is associated with enhanced intracellular edema, while prolonged hypernatremia leads to increased brain edema, which may be related to the accumulation of various organic substances within neurons. This contributes to an initial reduction in brain cell volume followed by enhanced intracellular edema due to water influx into the intracellular space

Studies of thermoregulation disturbances revealed that hyperthermia occurs most frequently in severe forms of diffuse brain injury and less frequently in meningeal hematomas. A significant correlation was found between thermoregulation disturbances and the presence of open TBI and combined injuries. Thermoregulation disturbances occur significantly more often after skull base fractures, intraventricular hemorrhages, and subarachnoid hemorrhages. Hyperthermia, as a secondary extracranial damaging factor of the brain, depends on the severity of TBI, prolongs the comatose state, and catastrophically worsens outcomes. It was found that purulent-inflammatory complications occur in the majority of patients with severe TBI. Analysis showed that the development of extracranial inflammatory complications is extremely unfavorable from a prognostic standpoint. The source of septicemia was most often exogenous, whereas pulmonary complications and urinary tract infections were more frequently of endogenous origin.

The conducted study demonstrated that primary brain injury is exacerbated by the development of secondary systemic mechanisms of brain damage. In severe TBI, the most significant role is played by impairments in the mechanisms that maintain perfusion pressure (with cerebral blood flow autoregulation being partially or completely disrupted), as under these conditions the brain is unable to adequately "respond" to systemic homeostatic disturbances. As a result, various secondary injuries predominantly of an ischemic nature occur in brain tissue. These ischemic disturbances are caused by secondary systemic mechanisms of brain damage. Therefore, their early detection and interruption are the primary objectives of therapeutic interventions in severe TBI.

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