44. Management During the Cooling Stage

The Target of Management During the Cooling Stage

The restoration of dying neurons and neuroprotection against secondary brain damage are the main goals of intensive care unit (ICU) management during the cooling stage of brain hypothermia treatment [22,24]. Management of neuroprotection against the progression of brain edema, ischemia, intracranial pressure (ICP) elevation, free radical attack, and neuroexcitation is not sufficient for severely brain-injured patients. Prior to neuroprotection management, restoration therapy should be considered for severely brain-injured patients affected by trauma, stroke, hypoxia, or cardiac arrest.

The administration of sufficient oxygen and suitable metabolic substrates such as glucose and phosphate are fundamental for neuronal restoration in injured brain tissue [1,12,33,36,41]. For the success of this treatment, stable systemic circulation, control of hemoglobin dysfunction [13,21,22,24], management of insulin-resistant hyperglycemia [23,24,27], control of blood–brain barrier (BBB) function [11], prevention of neurotoxic glutamate release [3,5], and care management of hypothalamus–pituitary–adrenal (HPA) axis neurohormonal abnormality [4,10,17,24,29] under brain hypothermia are all required at the start of treatment.

The next step of neuroprotection, such as management of ICP elevation [37], brain edema [41], BBB dysfunction [35], disturbance of microcirculation [33], free radical reactions [18,20,23], and elevation of brain tissue temperature by brain thermo-pooling [23,25,26] must be achieved with the prevention of hypothermia-associated complications [2,14,35,43]. In the management of severely brain-injured patients, special consideration of memory disturbance, emotional dysfunction, and vegetation is required, even at the acute stage [20–22,24].

The management targets at the initial cooling stage are:

Systolic blood pressure >100 mmHg
$PaO_2/FiO_2 > 300$
Serum glucose 120–140 mg/dl
Oxygen delivery >700–800 ml/min (Other monitor markers $ETCO_2$ 32–38 mmHg, $PaCO_2$ 34–38 mmHg, Hb > 11 g/dl, SaO_2 > 98%)
O_2ER 22%–25%
Serum pH 7.3–7.4
Serum phosphate 3–5 mg/dl
Serum potassium 4–5 mg/dl
Serum magnesium 1.5–2.0 mEq/l
Serum albumin >3.0–3.5 mg/dl
Antithrombin-III (AT-III) >100%
Ht < 35%
ICP < 15 mmHg
SjO2 60%–80%
Brain tissue temperature 32°–34°C intermittent control
Vitamin A >50 μg/dl
Abdominal pressure <15 mmHg
Gastric juice pH < 3.5
QT interval <450 mm/s and no arrthythmia

Time Schedule for Management of Brain Tissue Temperature

The time schedules for mild (34°C) and moderate (32°–33°C) brain hypothermia are different during the cooling stage (Fig. 43, Chap. 34). This is because at brain temperature of 34°–37°C, pituitary hormonal release is not severely suppressed and a low incidence of immune dysfunction is associated with a reduction in growth hormone level [9]. Also, glucose metabolism is dominant over lipid metabolism until the brain tissue temperature reaches 34°C [20,24]. However, below 34°C, there are dramatic changes in systemic circulation, metabolism, and immune function that are caused by reduced serum catecholamines, increased brain tissue glucose caused by hyperglycemia associated with a metabolic shift from glucose to lipid, and a reduced growth hormone level, respectively [22,24]. Therefore, in the management of moderate brain hypothermia, special consideration must be given to prevent these complications.

N. Hayashi et al., *Brain Hypothermia Treatment*

Mild Brain Hypothermia

Mild brain hypothermia treatment is indicated for cases in which Glasgow Coma Scale score (GCS) is less than 8, and there are no signs of herniation or cardiopulmonary dysfunction, as described in Chaps 28 and 29. If a full medical team is not available, induction of mild brain hypothermia treatment is also recommended.

Brain tissue temperature should be controlled at about 34°C for 3–7 days until evidence of recovery or partial recovery of the brain injury is observed (Figs. 39, Chap. 32; 43, Chap. 34). Therefore, the cooling duration depends on the severity of brain injury or stroke. The most important ICU requirements are the prevention of pulmonary infection and cytokine encephalitis, with neuro-protection against brain edema, cerebral blood flow (CBF) disturbances, brain hypoxia, metabolic imbalance, and ICP elevation [24]. The technique for the prevention of infection during mild brain hypothermia is not difficult. The required management criteria are the control of serum albumin level above 3.5 g/dl, cerebrospiral fluid (CSF)/serum albumin ratio to less than 0.01, serum glucose level to 120–140 mg/dl, replacement of vitamin A to greater than 50 mg/dl, hemoglobin (Hb) greater than 12 g/dl, 2,3-diphosphoglycerate (DPG) greater than 10 mmol/gHb, AT-III greater than 100%, platelet count 50 000–80 000/cu mm, digastrics decontamination, muscle massage, abdominal pressure less than 10 mmHg during the cooling stage and before the rewarming preconditioning stage [22,24]. The detailed ICU management technique is discussed later in this section. Such ICU management is very useful for preventing worsening of rewarming stage infections.

Moderate Brain Hypothermia

Moderate brain hypothermia is indicated as a second stage treatment in cases that show no effects from mild brain hypothermia treatment. Two-step variable speed induction is very safe and effective as restoration therapy for neuronal recovery in injured brain tissue [22,24]. Rapid induction of brain hypothermia to 34°C is scheduled initially. ICU management then focuses on stabilization of systemic circulation, control of serum glucose at 120–140 mg/dl (at least lower than 180 mg/dl), management of cardiopulmonary dysfunction such as arrhythmia and elongation of the QT interval to greater than 450 mm/s on the electrocardiogram (ECG), and treatment of hypopotassemia. After stabilizing these clinical issues, the brain tissue temperature is then reduced to 32°–33°C for periods of 5–6 h, as shown in Fig. 39 (Chap. 32).

Prolonged moderate brain hypothermia is very successful for the prevention of free radical reactions (Fig. 77, Chap. 42), neurotoxic neurotransmitter release (Fig. 76, Chap. 42) [5,21,24,27], vascular engorgement, and the progression of brain edema; however, it is very stressful to the systemic circulation and immune function because of reduced HPA axis neurohormone function [22,24]. Prolonged continuous control of brain tissue temperature at 32°C is not recommended because of diminished pituitary hormonal release. The reduction of growth hormone (GH) produces diminished CD4 activity, lymphocytopenia, reduces lypolytic action, and results in immune crisis (Fig. 42, Chap. 33) [20,24].

To prevent these complications, the use of intermittent moderate brain hypothermia is useful [24]. Temporary brain tissue temperature elevation from 32°–33°C to 34°C for a short duration prevents the excessive reduction in pituitary hormones. In this management, the timing of temporary brain tissue temperature elevation is also important. Because the physiological release of GH occurs in the early evening and into the night, the temporary elevation of brain tissue temperature should be scheduled at 18:00–22:00 hours to prevent immune crisis and pituitary dysfunction (Fig. 39, Chap. 32).

This intermittent control of brain tissue temperature during moderate brain hypothermia produces lower incidence of GH replacement, GH-associated hyperglycemia, immune crisis, and complications of pulmonary infection. The time schedule for the management of cooling at 32°–33°C is provided in Fig. 43 (Chap. 34).

Restoration Therapy for Injured Neurons

For a long time, neuroprotection therapy has been considered to be the main goal of management in brain-injured patients because it is difficult for injured neurons to make a recovery. Prevention of further secondary damage was the main purpose in ICU management. However, recent clinical studies in ICU management demonstrated the presence of new brain injury mechanisms that were not observed in anesthetized experimental animal models [23,25,26]. Slow release of bound oxygen from hemoglobin in the brain, systemic bloodstream shifts to the intestinal organs, increasing brain tissue glucose and lactate levels caused by insulin-resistant hyperglycemia, and reduced neuronal activity occur due to stress to the HPA axis neurohormonal immune system following

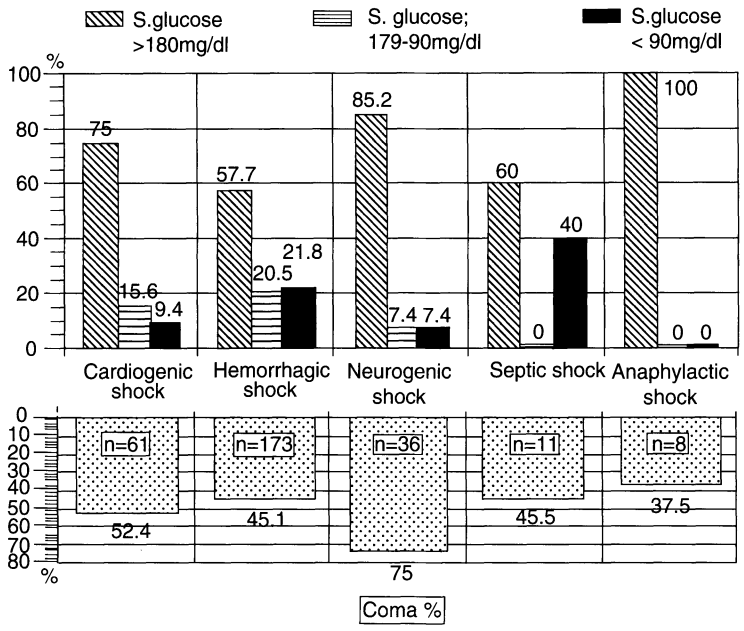


Fig. 82. The incidence of stress-associated hyperglycemia and coma in various shock patients

severe brain injury [23]. Changes in management to accommodate these new findings of brain injury mechanisms have produced unexpectedly excellent clinical results in cases of injury that were considered to be difficult to survive or would provide little neuronal recovery. Put simply, correct management for severely brain-injured patients has not been performed using previously accepted hypothermia treatment. The neuron is in fact stronger than was previously thought.

Management of Systemic Circulation and Metabolism

In the cooling stage of brain hypothermia treatment, unstable systemic circulation is produced by two main reasons. One is cardiac dysfunction produced by cardiac ischemia and hypoxia by the excess release of catecholamines and hemoglobin dysfunction [5,24]. The other is poor management of the hypothermia technique, in particular rapid induction of hypothermia without management of dehydration [7].

Harmful stress stimulates the HPA axis and produces an excess release of catecholamines, epinephrine, norepinephrine, and dopamine in the bloodstream [23]. The severity of these catecholamine surges is correlated to changes in rapid stress, severity, and the type of disease [8]. In our clinical studies, anaphylactic shock, cardiac arrest caused by heart infarction, diffuse brain injury and acute subdural hematoma, subarachnoid hemorrhage, and neurogenic shock produced the most severe excess releases of catecholamines and produced hyperglycemia (Fig. 82).

Delayed induction of hypothermia produces catecholamine surge-associated cardiac dysfunction because of coronary vasoconstriction and contraction myocytolisis of cardiac muscles. This means persistent cardiac contraction, difficult cardiac muscle relaxation, and cardiac ischemia [23]. To escape these cardiac hazards, early induction of hypothermia is successful; however, overly rapid induction of hypothermia and cooling below 34°C produces an excessive reduction in serum catecholamines. Therefore, the management of brain temperature must be conducted carefully with step-by-step monitoring of the ECG, vital signs, PaO_2, and serum glucose level.

Another cause of unstable systemic circulation during brain hypothermia treatment is early administration of hyperosmotic solution. At a brain tissue temperature of 34°C, serum dopamine is reduced to very low levels and epinephrine and norepinephrine are reduced by about 50%. Early administration of manitol during the cooling stage causes a volume deficit for the maintenance of microcirculation combined with reduced cardiac output. The intestinal organs and renal flow are very sensitive to ischemia caused by severe hypothermia. The complication of AT-III lower than 80% and dehydration by manitol administration produces a high risk of intestinal ischemia and renal ischemia. These complications can easily cause systemic infections, liver dysfunction, malnutrition, immune dysfunction, and severe pulmonary infection [14,24].

Basic management of systemic circulation and metabolism at the initial cooling stage of brain hypothermia requires normovolemic fluid resuscitation, maintenance of cardiac function by sufficient administration of oxygen, and adequate control of potassium phosphate, magnesium, and serum glucose (Fig. 30, Chap. 26) [20,22,24]. The application of elastic bandages to the extremities to prevent excess fluid resuscitation, and the use of the abdominal balloon catheter technique are also successful for maintaining stable cardiopulmonary–brain circulation (Figs. 31, Chap. 26; 59, Chap. 42).

As a pharmacological treatment, administration of phosphodiesterase inhibitors with adrenergic agents doputamine (selective β1-adrenergic effects; Doptorex) is recommended to maintain cardiac output. However, early administration of dopamine is not recommended for two reasons. One is the activation of the blood shift to the intestinal organs and promotion of masking brain hypoxia even with normal cerebral perfusion pressure (CPP), the other is the possibility of hydroperoxide radical formation in injured brain tissue [3,40] by chemical reaction of dopamine with oxygen under the conditions of severe damage to the BBB. This is because serum dopamine may be permeable to the damaged BBB and diffuse into the injured brain tissue. As another pharmacological treatment for maintaining systemic circulation, the administration of AT-III is useful for maintaining microcirculation in the brain and intestinal organs [24,33].

Hypertonic crystalloid solutions of 7% ascorbic Ringer solution (limit of 1000 ml) combined with colloids and 5% albumin is our initial choice for fluid resuscitation to prevent the various complications of catecholamine surge-associated hyperglycemia. After stabilizing the systemic circulation, normovolemic and isotonic fluid is used with balanced Na^+, K^+, Cl^-, magnesium chloride, and potassium phosphate.

The severe brain trauma patient often suffers other hemorrhagic trauma at the same time. It is very difficult to maintain cerebral circulation and coronary circulation in such cases. The insertion of a balloon catheter into the abdominal aorta produces some chance of survival. Temporary and incomplete occlusion of abdominal blood flow by the balloon catheter (Fig. 31, Chap. 26) is sometimes very successful in maintaining stable cardiopulmonary function and aiding neuronal restoration of dying neurons in cases of multiple trauma. Control of serum hypophosphatemia to 3–4 mg/dl, serum pH higher than 7.3, PaO_2/FiO_2 greater than 300, serum glucose at 120–140 mg/dl, management of AT-III higher than 100%, and replacement of serum albumin to greater than 3.0 mg/dl are also very successful measures for the maintenance of systemic circulation and oxygen metabolism.

Management of Hemoglobin Dysfunction

Hemoglobin is a very strong carrier of oxygen into the brain. However, without the hemoglobin enzyme 2,3-diphosphoglycerate (DPG), bound oxygen cannot be released from hemoglobin in the brain. This complication has already been reported in the replacement of preserved blood and hemofiltration therapy [13]. This means that oxygen inhalation with normal PaO_2 is not adequate care management. Normal oxygen delivery into the brain with no administration of oxygen for dying neurons is a serious situation in attempts to restore injured brain tissue. Recent chemical research initiated the technique of direct measurement of serum DPG and hemoglobin-binding DPG. The simultaneous measurement of hemoglobin-binding DPG in arterial blood and in internal jugular venous blood gives very useful information about neuronal hypoxia. In severe brain trauma patients (GCS less than 6), hemoglobin-binding DPG in jugular venous blood was reduced in 47% of patients and was at seriously low levels in 24% of patients [23]. Severe hyperglycemia, severe acidosis ($pH < 7.2$), reduced potassium phosphate, and loss of magnesium are known causes of DPG reduction [23,27].

The management of hemoglobin dysfunction requires the replacement of potassium phosphate and control of serum phosphate at 3–5 mg/dl, replacement of magnesium chloride and control of serum magnesium to about 1.6 ± 0.20 mEq/l, maintenance of serum pH above 7.3, control of serum glucose at 120–140 mg/dl, and prevention of red blood cell aggregation by maintaining serum AT-III higher than 100% [24].

An alternate management strategy for neuronal hypoxia that is produced by hemoglobin dysfunction is the perfusion of a fluorocarbon oxygen carrier (F44E emulsion-Revoxyn) as part of the CSF technique, and has been developed in experimental studies by Triolo et al. [42]. This management strategy is still undergoing clinical research; however, this method may become a new ICU method for critical brain-injured patients affected by trauma, cardiac arrest, or stroke.

Control of Insulin-Resistant Hyperglycemia

The considerations and care management methods for hyperglycemia are presented in the description of induction care management (Fig. 81, Chap. 43). At the cooling stage, management of hyperglycemia is important. Serum glucose is maintained at 120–140 mg/dl by

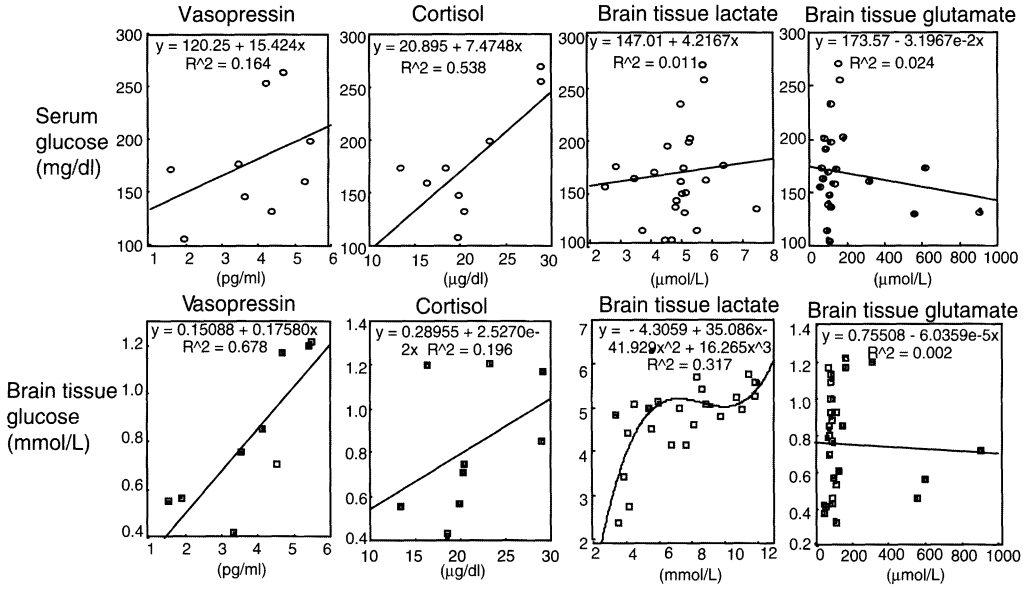


Fig. 83. The effects of hyperglycemia increasing brain tissue glucose on changes of brain tissue lactate and neuronal hormones

Table 19. The effect of neuronal hormones on the metabolism of macronutrients

Neuronal hormones	Insulin release	Muscle glucose uptake	Hepatic glucogenesis	Proteolysis	Lipolysis	Ketogenesis
Catecholamines	↓	↓	↑	↑	↑	↑
Glucagon			↑			↑
Growth hormone	↓	↓		↓	↑	↑
Glucocorticoids		↓	↑	↑	↑	↑
Thyroid hormones			↑	↑	↑	↑

↓, Decrease; ↑, increase

a continuous drip of insulin included with saline (Humarin-R 50 U + saline 100 ml). There are many causes of unsuccessful management of hyperglycemia. Excessive lowering of the body temperature produces a shift from glucose to lipid metabolism and reduces the glucose expenditure. The control of hyperglycemia then becomes very difficult by ordinary administration of insulin. Further administration of insulin or elevation of body temperature by about 0.5°–1.0°C is advised. At the same time, prolonged hypothermia reduces liver and skeletal muscle metabolism and glucose consumption, reduces dramatically and produces insulin-resistant hyperglycemia [23,24]. The ability of the body to metabolize many pharmacological medicines such as antibiotics and radical scavengers also decreases during prolonged brain hypothermia treatment. Therefore, overdoses of pharmacological medicines can occur very easily and can also reduce the liver function. This poor iatrogenic management also promotes insulin-resistant hyperglycemia during brain hypothermia treatment. Stabilized albumin-binding antibiotics complicate liver dysfunction because serum hypo-albuminemia may easily occur with reduced liver function during prolonged hypothermia. Selection of non-albumin-binding antibiotics, low dosages of antibiotics, replacement of serum albumin, and liver protection are required. The effects of hyperglycemia and increased brain tissue glucose on brain tissue lactate levels and neurohormonal changes are presented in Fig. 83. The critical concentration of serum glucose to produce increases in brain tissue lactate is 180–200 mg/dl.

Management of HPA Axis Neurohormone Dysfunction

After severe brain injury, HPA axis neurohormonal function is stimulated and releases vasopressin, GH, adrenocorticotropic hormone (ACTH), and catecholamines into the bloodstream (Table 19) [6,17,30,31]. All of these reactions are defense mechanisms against brain stress and brain damage. However, excess release

of these neurohormones produces further hazard to the injured brain by the occurrence of hemoglobin dysfunction, insulin-resistant hyperglycemia, promotion of BBB dysfunction, and neuronal hypoxia [23]. No management of these defense responses is also a dangerous condition in the injured brain [8,9,17]. How to suitably manage and control these defense reactions is very important for the preservation of injured neurons at the cooling stage. The neurohormone reactions is nonanesthetized patients could be prevented by early induction of brain hypothermia to less than 34°C. However, prolonged treatment at lower than 34°C produces an excessive reduction in neurohomone release and causes immune dysfunction and loss of animation activity [10,21–23]. In the management of critical brain-injured patients, prolonged moderate brain hypothermia management must be used to prevent brain edema, free radical neuronal damage, and ICP elevation [20,24,27]. To prevent the loss of animate activity associated with prolonged hypothermia, intermittent control of brain tissue temperature between 32° and 34°C with neurohormone replacement therapy is successful [24].

Hypothalamus Dysfunction

The direct damage of the hypothalamus produces a reduction in vasopressin release. As complications, hypoosmotic urinalysis, dehydration, reduction of systemic circulation, hyponatremia, and diabetes mellitus can occur. The excessive administration of manitol during hypothalamus dysfunction produces severe dehydration and worsens the microcirculation of major organs, the brain, heart, lungs, and intestinal organs [7,24].

The management of serum vasopressin is not simple during the cooling stage of brain hypothermia. The release of vasopressin is accelerated by serum hyperosmotic pressure and the feedback mechanism of neural control of macronutrient intake such as hyperglycemia [23,30,31]. The management of vasopressin release is very important to determine the prognosis. Overly rapid induction of moderate brain hypothermia reduces vasopressin release and complicates diabetes mellitus. Dehydration under brain hypothermia is very dangerous, and promotes ischemia in the intestinal organs with immune crisis and CBF disturbances by reason of reduced serum catecholamines and circulation blood volume [24,27]. Therefore, before the administration of manitol, stabilization of the systemic circulation by normovolemic fluid resuscitation is important. Excessive reduction of serum catecholamines during the cooling stage is prevented by intermittent control between moderate (32°–33°C) and mild (34°–35°C) brain hypothermia, as shown in Fig. 43 (Chap. 35). The pharmacological administration of phosphodiesterase inhibitors combined with adrenergic agents such as dopamine is an additional care method. On the other hand, excessive release of vasopressin occurs because of unsuitable management of hyperglycemia during brain hypothermia at 33°–34°C [24]. The activation of BBB dysfunction, induction of proinflammatory cytokines, and induction of cytokine encephalitis with combination of systemic or severe pulmonary infection were recorded in our clinical studies using microdialysis [23,24]. Hyperglycemia with glucose serum levels higher than 230 mg/dl, with severe BBB dysfunction (evaluated by CSF/serum albumin >0.02), serum albumin less than 2.5 g/dl, and pulmonary infection is a very dangerous situation at the cooling stage [24]. The excessive reduction or release of vasopressin during cooling stage of brain hypothermia are also clinical issues.

Hypopituitarism

Pituitary gland hypothermia is unavoidable during brain hypothermia treatment. ACTH is the most sensitive of the pituitary hormones to hypothermia (Fig. 24, Chap. 23). ACTH is a regulator of neutrophil; therefore, the control of brain hypothermia below 34°C is an interesting technique to prevent neutrophil-associated inflammatory reactions [10]. Brain hypothermia at temperatures below 32°–33°C reduces levels of thyroid stimulating hormone (TSH) and GH. Recent clinical studies demonstrated that GH not only activates human growth, but also regulates the immune functions. Our preliminary studies suggested that GH stimulates the CD4 immune system and suppresses the CD8 immune system [20,23,24]. In addition, the number of lymphocytes is strictly correlated to changes of GH under brain hypothermia [9]. From these clinical studies, GH appears to activate the cellular immune functions such as interleukin I (IL1) and IL6; however, anti-inflammatory immune function such as IL8 and IL10 may be suppressed [20]. An indirect indicator of reduced GH level is lymphocytopenia, lower than 1000/mm^3. The replacement of GH is very useful to provide recovery from immune dysfunction during brain hypothermia treatment. However, replacement of GH produces clinical issues; one is the high cost and the other is hyperglycemia [24]. To prevent immune dysfunction associated with reduced GH, there are two choices. One is to temporarily elevate the brain tissue temperature from 32°–33°C to around 34°C from 18:00 to 22:00 hours. The other is pharmacological stimulation for the production of GH. Administration of L-arginine and IGF-1 is successful in providing recovery of immune function during brain hypothermia treatment [24]. However, before this pharmacological treatment, careful management of hyperglycemia is recommended

because GH reduces the glucose uptake from skeletal muscles.

Neuroprotection Therapy

Neuroprotection therapy is not directly effective in providing neuronal recovery. However, without such management, neuronal restoration in injured brain tissue is difficult.

Prevention of Brain Thermo-pooling and Vascular Engorgement

The elevation of brain tissue temperature by brain thermo-pooling occurs when the body temperature is greater than 38°C, systolic blood pressure is lower than 90–100 mmHg, and during reperfusion of CBF [23,25,26]. Figure 84 shows a typical case of brain thermo-pooling after ischemic reperfusion. These specific conditions occur during the acute stage and the induction stage of brain hypothermia treatment. Unsuccessful management of brain thermo-pooling suggests poor prognosis even with normal control of ICP. The brain thermo-pooling phenomenon is not recorded under the management of brain hypothermia. However, rapid elevation of brain tissue temperature of 1°–2°C produces acute brain swelling by vascular engorgement at the early cooling stage. This is because the pathophysiology of the brain thermo-pooling phenomenon includes elevation of brain tissue temperature, increased metabolic demand, and disturbance of autoregulation of CBF.

To prevent pituitary hormonal dysfunction, immune dysfunction, and liver dysfunction, control of brain tissue temperature between mild and moderate brain hypothermia must be carried out very carefully (Figs. 39, Chap. 32, 43, Chap. 34) [20,22,24]. As a technique for intermittent elevation of brain tissue temperature from 32°–33°C to 34°C, the removal of the cooling blanket

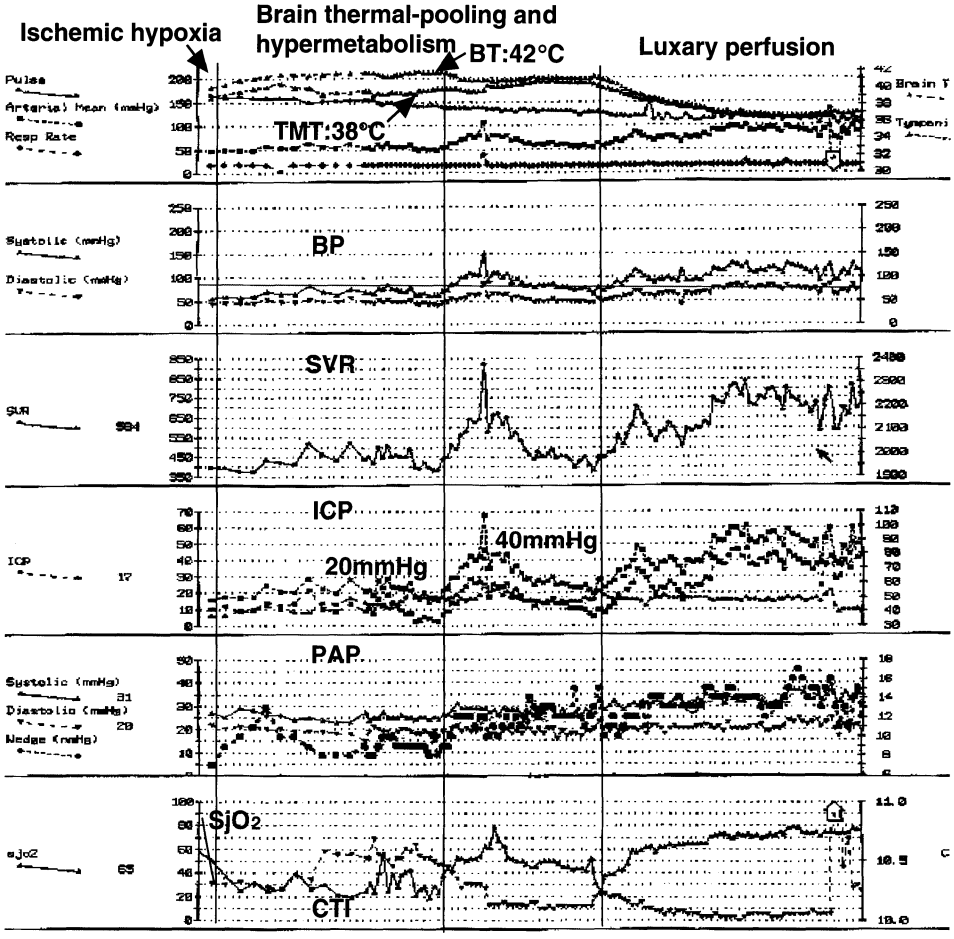


Fig. 84. Typical cases of brain thermo-pooling and ischemic hypermetabolism after reperfusion of severe brain ischemia. *TMT*, Tympanic membrane temperature; *BT*, brain tissue temperature; *BP*, blood pressure; *SVR*, systemic vascular resistance; *ICP*, intracranial pressure; *PAP*, pulmonary arterial pressure; *CTI*, cerebral theramal index; SjO_2; jugular venous oxygen

from the patient's body, little by little, is recommended. The careful elevation of cooling blanket water temperature is not recommended because it is very difficult to reduce the brain tissue temperature rapidly if the brain tissue temperature is elevated by more than 1°C. The technique of reducing the cooling area without changing the cooling blanket temperature is safe and is much easier for the control of intermittent elevation of brain tissue temperature.

Prevention of Excess Release of Cerebral Dopamine and Free Radical Reactions

A number of compounds with free radical scavenging properties have been studied with the hope that they will reduce the toxic effects of free radicals. Many effective radical scavengers have been reported; however, in clinical studies, successful pharmacological scavengers have not yet been identified. Recent phase II clinical studies of the effectiveness of tirilazad (U-74006F), a 21-aminosteroid, suggested no clinical improvement in overall functional outcome of stroke patients [12,33].

As metabolic substrates of ·NO radicals, the NO_2/NO_3 ratio is a good indicator of ·NO radical reactions (Fig. 78, Chap. 42) [27]. Our clinical studies suggested that low NO_2/NO_3 in serum was very sensitive to the hemoglobin content. The critical level of hemoglobin for increasing NO_2/NO_3 was less than 10–11 mg/dl. Hemoglobin is a very useful physiological radical scavenger in systemic circulation. To prevent various complications that are associated with free radicals, such as pneumonia, liver dysfunction, intestinal dysfunction, and many other organic disturbances, the management of hemoglobin above 11 mg/dl is favored by reasons of maintaining oxygen delivery and also for radical scavenging. Hemoglobin is a powerful physiological scavenger in severely brain-injured patients. The management of hemoglobin above 11 mg/dl is effective in maintaining of sufficient oxygen delivery and prevents free radical reactions in the brain, lungs, and intestinal digestive organs.

In the management of severe brain damage caused by trauma, stroke, or cardiac arrest, the prevention of vegetation and memory disturbances are very important. In our recent clinical studies, selective radical attack of the dopamine A10 nervous system has been pointed out as a mechanism of emotion–memory disturbances in severely brain-injured patients. The dopamine A10 nervous system is the center of neuronal function for memory, emotion, volition, love, and anxiety (Fig. 34, Chap. 26). Therefore, damage to the A10 nervous system can easily result in vegetation. The precise damage mechanism of the dopamine nerve system has been clarified by experimental animal studies [3]. The brain ischemic stroke produces the release of dopamine. In the brain, this released dopamine reacts with oxygen and produces quinine and hydrogen peroxide. Hydrogen peroxide is then easily converted to the neurotoxic $\cdot OH^-$ radical [40]. These chemical reactions in severely injured brain tissue are thought to produce the selective radical damage to the dopamine nervous system (Fig. 33, Chap. 26).

For the management of selective radical damage to the dopamine A10 nervous system, the administration of a radical scavenger and prevention of dopamine release from the dopamine A10 nervous system may be considered. The administration of a pharmacological radical scavenger such as Radicut, vitamins E and C, and control of hemoglobin above 11 g/dl are basic techniques to prevent selective radical attack to the dopamine A10 nervous system. The prevention of dopamine release in the injured brain by early induction of brain hypothermia to below 34°C, and pharmacological treatment with metoclopramide at the acute stage are another treatment (Fig. 30, Chap. 26).

Prevention of Excess Release of Cerebral Glutamate

The management of brain tissue hypothermia is very successful for the prevention of neurotoxic glutamate release [16] in injured brain tissue [24]. This neuroprotection effect is correlated to lowering of brain tissue temperature. Our clinical studies using microdialysis suggest that the release of brain tissue glutamate can be reduced to 5%–15% of normal levels under moderate brain hypothermia and about 40% under mild brain hypothermia, as shown in Fig. 78 (Chap. 42).

The effect of hypothermia to prevent glutamate release is not simple. The toxicity of brain tissue glutamate increases in the presence of lactate as shown by increased neuronal cell membrane damage indicated by the marker glycerol (Fig. 85). The severity of BBB dysfunction combined with systemic infection also affect the responsiveness of glutamate release during the cooling stage of brain hypothermia. Severe systemic infection produces increases of proinflammatory cytokines in the bloodstream. These cytokines may go into the injured brain tissue via the damaged BBB. The increased CSF IL6 correlated with the severity of BBB damage in some patients (Fig. 23, Chap. 22). The critical level of BBB dysfunction to produce cytokine encephalitis is a CSF/serum albumin ratio higher than 0.01 (Fig. 55, Chap. 39). In this patient, management of brain tissue hypothermia was not effective in reducing

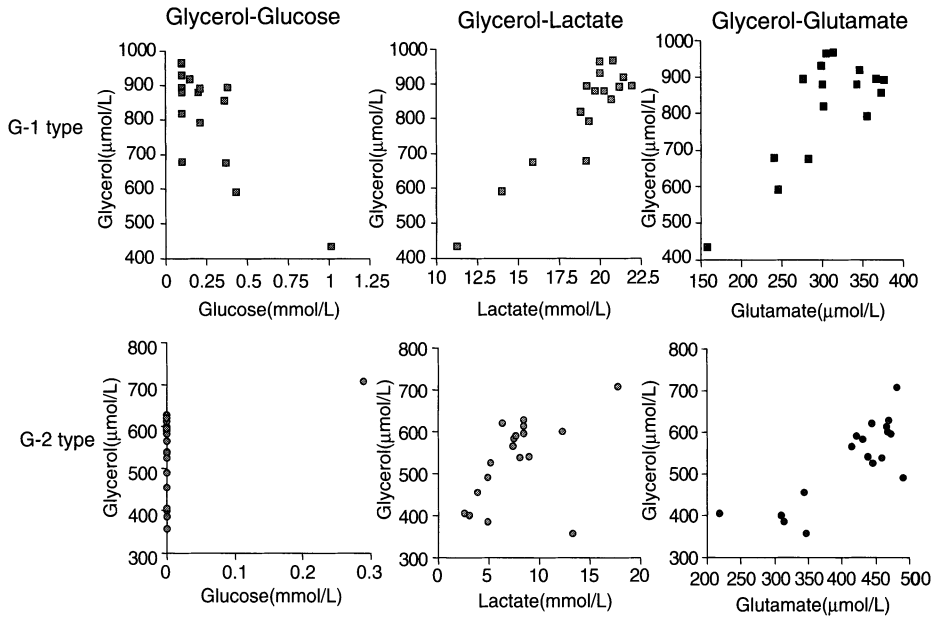


Fig. 85. The neuronal toxicity of brain tissue glutamate correlated to increasing brain tissue lactate

the glutamate release even with management of brain hypothermia at 32°C. The serum proinflammatory cytokines are produced, not only by severe brain tissue damage, but also, by damage of the lungs and intestinal organs. From these results, management of extracerebral organs and prevention of severe infection must be taken with the same level of care as the management of brain injury. Therefore, in the ICU management of the cooling stage, careful management of the injured brain and extracerebral major organs, and prevention of pneumonia are required. The complications of severe or prolonged pulmonary infection and inappropriate management of the BBB during brain hypothermia treatment suggest unsuccessful treatment. These concepts must be considered for the success of brain hypothermia treatment.

Management of BBB Dysfunction

Damage to the BBB has, for a long time, been considered to be a result of brain ischemia and direct brain tissue destruction. Recent basic studies demonstrated that induction of serum cytokines associated with disturbances of microcirculation also cause damage of the vascular intimae, and, possibly, the changes in the BBB. These proinflammatory cytokines in injured tissue may be produced by a number of factors, including injured vascular endothelium, proliferation of macrophages, and infiltration of microglias. The proinflammatory cytokines, such as IL1, IL6, and tumor necrosis factor (TNF), activate the coagulation factor thrombin, reduce tissue plasminogen activator, stimulate micro-embolus formation, and change the vascular permeability. However, recent clinical studies suggested that stress-associated neurohormone vascular reactive hormones and vasopressin also stimulate IL1 and IL6 production and change the BBB function. The precise mechanism of the central neurohormone influence on BBB function is not yet clarified.

In the management of BBB dysfunction, steroids have long been used. The effectiveness of anti-edema is still controversial. In experimental animal studies with anti-edema, the effect of the steroid is positive; however, in clinical studies, negative results have been reported in the acute stage of severe brain injury. However, steroid is very effective for brain edema produced by metastatic brain edema.

The recent clinical studies provided similar answers about this discrepancy of the anti-effect of brain edema. The harmful stress-associated hyperglycemia following severe brain damage is not serious in anesthetized experimental animals; however, stress-associated hyperglycemia is a very serious condition in nonanesthetized clinical brain-injured patients. This severe hyperglycemia stimulates neuropeptide Y receptors in the hypothalamus appetite center and produces vasopressin release as a mechanism of neural control of the macronutrient feedback mechanism [30,31]. Steroid also stimulates the neuropeptide Y receptor, because these receptors include the glucocorticoid type II receptors. The administration of steroid under the conditions of hyperglycemia produces further stimulation of vasopressin release. Vasopressin is not only a

vasoconstrictor, but also stimulates the induction of proinflammatory cytokines IL1 and IL6. Steroid is not recommended in cases of stress-associated hyperglycemia to prevent brain edema in the acute stage.

Animal studies suggested that vasopressin release could be prevented by moderate hypothermia [9]. However, in clinical studies, vasopressin release could not be prevented by moderate brain hypothermia (32°–33°C) under the conditions of hyperglycemia with serum glucose level above 230 mg/dl.

For management of BBB dysfunction during the cooling stage of brain hypothermia, the control of serum glucose at 120–140 mg/dl is fundamental. Early control of brain tissue temperature at 34°C prevents catecholamine surge and the release of vasopressin. For pharmacological management of BBB dysfunction, administration of AT-III is effective in preventing endothelial vascular reaction and micro-embolus formation. During brain hypothermia treatment, AT-III level higher than 100% is recommended. Combination therapy of AT-III with low molecular weight heparin is recommended for severely damaged BBB function, such as in cases with CSF/serum albumin ratio greater than 0.01. After management of endovascular inflammatory reactions, replacement of serum albumin to a level higher than 3.0 g/dl is useful [24]. The high osmotic pressure reduces the permeability of the BBB and stabilizing of anti-inflammatory cytokines justifies replacement of serum albumin. The management of serum albumin is also very important to prevent intestinal mucous edema.

The management of serum glucose, serum albumin, and AT-III are important for management of BBB dysfunction and brain edema at the cooling stage of brain hypothermia treatment. These combined treatments for BBB dysfunction strongly affect the prognosis of children.

Prevention of Brain Edema

Brain edema can have multiple causes; cellular edema is caused by dysfunction of cell membrane functions and intracellular homeostasis in glia and neuron cells; vasogenic edema results from impairment of the BBB; hydrostatic edema occurs after disruption of autoregulation, most often after rapid decompression of acute subdural hematoma; and osmotic edema results from serum hypo-osmolarity associated with hypoalbuminemia and hyponatremia [41]. In the ICU management of severely brain-injured patients, these multiple causes of brain edema can be observed simultaneously. Combination of various types of brain edema will change with each cases and over time. The early selection and implementation of the management procedure for the various types of brain edema are important for the success of the cooling stage of brain hypothermia treatment.

The initial target of brain edema treatment is the prevention of cellular swelling of glia and neurons. The management of brain hypoxia and adequate administration of metabolic substrates without disturbances of microcirculation are important for management of cellular swelling. To prevent cytotoxic brain edema, essential management criteria include systolic blood pressure greater than 100 mmHg, PaO_2/FiO_2 greater than 300, serum glucose 120–140 mg/dl, oxygen delivery greater than 700–800 ml/min, Hb greater than 11 mg/dl, SaO_2 greater than 98%, serum pH 7.3–7.4, serum phosphate 3–5 mg/dl, serum magnesium 1.2–2.0 mEq/l, serum albumin greater than 3.0 mg/dl, AT-III greater than 100%, and ICP less than 15 mmHg. The head position should be kept flat to maintain sufficient CBF [39]. Early administration of hyperosmotic agents, manitol and glycerol, is not recommended during brain hypothermia treatment. This is because unstable systemic circulation will be activated very easily because of reduced circulation volume under the conditions of reduced serum catecholamines and hypothermia. In addition, glycerol could produce more brain tissue lactate with hyperglycemia. Therefore, glycerol is not the first choice for hyperosmotic therapy in the cooling stage in cases of stress-associated hyperglycemia.

After 6–12 h from brain damage, vasogenic edema becomes a major target of ICU management. The management of BBB dysfunction by control of serum glucose at 120–140 mg/dl, serum albumin greater than 3.0 g/dl, and AT-III greater than 100% are useful to stabilize vasogenic edema. Hyperosmotic agents, manitol and glycerol, are very successful in removing the interstitial edema at the stabilized condition of systemic circulation. After normovolemic fluid resuscitation, the combination therapy of manitol 500–1000 ml/day with frusemide (20–100 mg/day) is successful for the temporary recovery from severe brain edema and pulmonary edema. The administration of manitol under the condition of hypo-albuminemia (albumin lower than 2.5 g/dl) cannot expect an osmotic anti-edema effect. After 6–12 h of brain damage and with controlled stable systemic circulation, the head-up position (5°–10°) is recommended to maintain an easy venous outflow circulation. The head-up position helps reduce brain edema and prevent venous stasis.

Control of ICP

The development of intracranial hypertension is accompanied by rebleeding from injured brain tissue,

neurological deterioration caused by brain edema and hydrocephalus, venous stasis with elevation of mediastinal pressure, and intestinal organ dysfunction with abdominal hypertension during the cooling stage of brain hypothermia treatment. As results of these complications, elevation of ICP can produce a reduction of CPP, brain ischemia, neuronal hypoxia, acceleration of brain swelling, and herniation at the final stage. The relationships between ICP elevation and pathophysiological changes in the brain tissue are described earlier in Chap. 20. Therefore, this discussion will describe the management of ICP elevation during brain hypothermia treatment.

To control ICP during brain hypothermia treatment, the sources of accompanying complications such as rebleeding, hydrocephalus, development of brain edema, pulmonary obstructions, and abdominal hypertension should be dealt with initially. The management of normovolemic fluid resuscitation, sufficient oxygen delivery (>700–800 ml/min), and adequate serum glucose (120–140 mg/dl) are fundamental before the control of ICP.

Head Position

Slight head-up position of 5°–8° helps to keep cerebral venous outflow. Therefore, the head-up position is recommended for control of ICP elevation. However, in severely brain-injured patients, most cases suffer unstable systemic circulation. The reduced cardiac output caused by cardiac ischemia and changed peripheral vascular resistance due to excess release of catecholamines are causes of unstable systemic circulation. Furthermore, injured neurons need sufficient oxygen and adequate metabolic substrates for neuronal restoration through the stabilized systemic circulation. Brain edema and ICP elevation progress as results of insufficient care. To avoid these consequences, head position should be kept flat until stabilized systemic circulation is obtained at the initial time of the cooling stage [24]. These management techniques are especially important for the induction of the cooling stage of brain hypothermia treatment.

Pharmacological Sedation and Muscle Relaxation

The negative effects of excess neurohormone reactions that cause harmful stress to the HPA axis have been described previously. However, induced hypothermia as management of severe brain injury is also stressful to the human body. Pharmacological sedation, muscle relaxation, and neuroleptanalgesia are necessary to avoid hypothermia stress even with coma patients. However, the sedative pharmacology and analgesia must be chosen carefully because these drugs also effect changes of CBF, brain metabolism, and ICP elevation. Table 13 (Chap. 41) summarizes the physiological characteristics of sedative and analgesic agents. For the pharmacological management to maintain sedation during brain hypothermia treatment, the combination of midazolam, fentanyl, and pancuronium is recommended. Midazolam is the first choice for prolonged anesthesia without major complications of cardiovascular and renal dysfunction. Midazolam is not only effective for sedation, but is also effective in preventing traumatic convulsions and ischemia seizures. Propofol can be used with hypertensive patients at the acute stage with normovolemic fluid resuscitation.

Osmotic Management

Increasing the serum osmotic pressure is a simple mechanical method to remove interstitial brain edema. As a pharmacological drug, manitol is the first choice. Glycerol is not indicated in cases of harmful stress-associated hyperglycemia because of increasing brain tissue lactate. However, in hypo-albuminemia, the hyperosmotic effects for reducing brain edema will expire. Therefore, hyperosmotic management must be scheduled in the absence of hypo-albuminemia. The early administration of manitol is not indicated at the induction of brain hypothermia treatment where there is unstable systemic circulation with reduced circulation volume. At the cooling stage, osmotic management must occur with stabilized systemic circulation.

CSF Drainage

The retention of CSF in severe brain injury increases ICP and reduces the absorption of interstitial edema and neurotoxic substrates throughout the ventricular CSF circulation. In the acute stage, the release of neurotoxic neurotransmitters, such as glutamate and dopamine, are major targets of treatment. Brain hypothermia treatment is very successful in preventing the release of these neuronal transmitters; however, brain hypothermia management is not useful for removing previously released neurotoxic glutamate and dopamine. CSF drainage in the acute stage is the only effective means of removing these neurotoxic neurotransmitters. Prolonged retention of these neurotransmitters may produce synaptic dysfunction. CSF drainage can be expected to reduce the prolonged retention of these neurotoxic neurotransmitters with or without ICP elevated hydrocephalus. The three major purposes of CSF drainage are reduction of ICP elevation, the recovery of interstitial edema, and removal of neurotoxic neurotransmitters. For these reasons, we prefer CSF drainage, if possible, in the acute stage even with normal ICP.

Prevention of Pulmonary Obstruction and High Mediastinal Pressure

Airway obstruction during the management of severe brain injury with brain hypothermia treatment is a serious complication. Brain hypoxia and cerebral venous stasis are clinical issues of airway obstruction. When the cerebral venous pressure is about 15 mmHg and the saggital sinus pressure is 5 mmHg, a mediastinal pressure higher than 15–20 mmHg will produce ICP elevation. We control the ventilator with an airway pressure at 17–20 mmHg, and keep PEEP pressure lower than about 10 mmHg during brain hypothermia treatment.

An airway pressure higher than 25 mmHg, can produce increased cerebral venous pressure, portal venous stasis, and congestion of intestinal organs. However, with the complication of severe pulmonary infection with pulmonary congestion, the airway pressure should be controlled at 20–25 mmHg for short durations with PaO_2/FiO_2 higher than 300.

Control of Abdominal Hypertension

Abdominal pressure is lower than 5 mmHg under normal physiological conditions. Abdominal hypertension produces dysfunction in various intestinal organs. Urinary obstruction, paralytic ileuses, and the complication of abdominal bleeding are causes of abdominal hypertension. Mild abdominal hypertension, 10–15 mmHg, reduces the disturbance of microcirculation in digestive intestinal organs. Venous congestion of the liver and lungs develop at abdominal pressures higher than 17–20 mmHg. ICP elevation with venous stasis and cardiac congestion develop at abdominal pressures higher than 25 mmHg. To prevent abdominal hypertension, urinary drainage and insertion of an ileum catheter is fundamental. Gastric lavage on the first day, followed by insertion of an ileum catheter into the ileum beyond the Trize ligament on the second day is an ideal schedule for control of abdominal hypertension, ischemia of digestive organs, and early enteral nutrition [24].

Other Treatment

The basic pathophysiology of cytotoxic and vasogenic brain edema is the destruction of cell membrane function complicated with disturbances of intracellular homeostasis in neurons, glia, and vascular intimae. The stabilization of ion channels and morphological reconstitution of cell membranes in these neuronal and vascular cells are fundamental management strategies. Sufficient oxygenation, adequate administration of glucose, replacement of phosphate with vitamin A, replacement of magnesium, and inhibition of lipid peroxidation are required to stabilize cell membrane functions and prevent brain edema. The management criteria required to prevent cellular swelling are oxygen delivery greater than 700–800 ml/min, Hb greater than 11 mg/dl, SaO_2 greater than 98%, serum pH 7.3–7.4, serum phosphate 3–5 mg/dl, serum magnesium 1.6 ± 0.2 mEq/l, serum albumin greater than 3.0 g/dl, and AT-III greater than 100%.

To inhibit lipid peroxidation, lipid soluble seleno–organic compound (Ebselen) and glutathione peroxides are introduced in clinical treatment. Recent clinical studies in which 300 patients were randomized within 48 h of ischemic stroke to either Ebselen or placebo showed that Ebselen-treated patients had a significantly better outcome, especially if treated within 24 h of onset.

Sodium channel antagonists, anticonvulsants, phenytoin and its water-soluble derivative fosphenytoin, and lamotrigine and related compounds BW-1003C87 and sipatrigine (BW-619C89) are all sodium channel antagonists with cytoprotective properties are being developed. Phenytoin and fosphenytoin have demonstrated neuroprotective ability in animal studies of cerebral ischemia. A multicentre placebo-controlled clinical study of fosphenytoin, lamotrigine, BW-1003C87, sipatrigine (BW-619C89), lubeluzole which acts as a sodium channel blocker and inhibits glutamate release and nitrite oxide-medicated toxicity, and lifarizine which possesses both sodium and calcium channel modulating properties, is in progress.

Pitfalls of ICP Management During Brain Hypothermia

Early administration of manitol and dopamine at the acute stage is dangerous in a condition of unstable systemic circulation with BBB dysfunction. To prevent the progression of brain edema, rapid administration of manitol and glycerol in the acute stage produces dehydration, circulating volume reduction, and intravascular slugging in microcirculation. Furthermore, during brain hypothermia treatment at 32°–34°C, serum catecholamines will be reduced to less than 50% of normal levels [20,24,27]. Therefore, early administration of manitol without suitable fluid resuscitation causes unstable systemic circulation and disturbance of cerebral microcirculation. Before starting anti-edema therapy, maintenance of cerebral circulation with administration of sufficient oxygen and adequate glucose is important. Brain edema develops with unsatisfactory management of cerebral circulation, neuronal oxygenation, and brain metabolism. The early administration of dopamine to maintain systolic blood pressure above 100 mmHg is not recommended for two reasons. The administration of dopamine in cases of severely

damaged BBB function with a CSF/serum albumin ratio of more than 0.01 causes an increase of serum dopamine penetration into the injured brain tissue [24]. Increased cerebral dopamine in the injured brain tissue produces neurotoxic radical formation. The other argument against dopamine administration is the shift of the systemic circulation into the intestinal organs caused by pharmacological vasodilatation of the kidneys and intestinal digestive organs. Normovolemic fluid resuscitation with good cerebral oxygenation and careful management of harmful stress-associated hyperglycemia are very important at the cooling stage.

Prevention of Convulsion

The exact incidence of posttraumatic epilepsy after severe brain injury is difficult to evaluate because of prophylactic administration of phenytoin and inconsistency in injury severity and treatment. However, posttraumatic epilepsy during brain hypothermia treatment is a serious complication. Hyperemia, release of excitatory neurotransmitters, consumption of residual brain energy, and brain ischemia after convulsions all worsen brain damage. The critical persistent time of epilepsy for the development of neuronal necrosis is about 20–30 min. Therefore, prophylactic treatment against epileptic seizure is very important during the cooling stage.

The key points for management of posttraumatic epilepsy are:

1. Type is divided into early epilepsy (≤7 days) and late epilepsy (>7 days) after head trauma.
2. Prophylactic anticonvulsant does not reduce the frequency of late seizures.
3. Anticonvulsants should be used to prevent early seizures in high risk patients such as those with GCS ≤ 8 on admission.
4. Cases with acute subdural, epidural, or intracerebral hematoma, open depressed skull fracture with parenchyma injury, cortical injury, or penetrating injury, and history of significant alcoholic abuse are recorded in high incidence.
5. Discontinue anticonvulsants after 1 week in most uncomplicated cases.

To understand indications and select anticonvulsant medicines, modes of action, metabolism, dosage, and side effects are summarized in Table 20.

Table 20. The pharmacological characteristics of various anti-epieptic medicines

	Benzodiazepines	Midazolam	Phenytoin	Valproate	Phenobarbital
Mode of action	Postsynaptic Bz1 (anti-convulsant, anxiolytic effects) Presynaptic Bz2 (sedation, and hypnotic) receptor mediated	Activate GABA neurons with binding of post synaptic Bz1 receptors	Membrane stabilizer Prevent Na^+ influx	Inhibitor of GABA transaminase and glutamate decarboxylase	Depressant effect on neuronal membranes
Metabolism	Receptor binding. The highest density of receptors in cerebral cortex, with low density in cerebellum, basal ganglia, limbic system, and brain stem	Liver and intestine	Liver Can saturate enzyme systems Long half life	Liver Protein bound Short variable half life	Liver or excreted in urine unchanged Long half life
Dosage	5–10 mg i.v. Peak effects are seen in 5–10 min	0.15–0.3 mg/kg (i.v.) Maintenance: half or same dosase of 0.15–0.3 mg/kg	Can be given as single dosage e.g., 150–400 mg at night	2–3 × daily 600 mg to 3 g total daily dosage	Can be given as single dosage, e.g., 90 mg at night
Side effects	Allergic reaction Memory impairment	Low incidence of arrythmia and hypotension	Gum hypertrophy Cerebellar dysfunction at toxic levels	Gastrointestinal upset Thrombocytoprnia Drug-induced hepatitis Hair loss Tremor/chorea	Sedation Depression Behavioural disturbances in children Skin rashes Withdrawal seisures

The initiation of antiepileptic medicine such as benzodiazepines for cortical damage, midazolam for damage of the basal ganglia, and followed by phenytoin for neuroprotection of cerebellum are recommend within 3–6 h after severe brain damage. Phenytoin is also effective for the prevention of cytotoxic brain edema by acting as a membrane stabilizer, and prevents Na^+ influx in severely brain-injured patients. Vitamin B is nesessary to prevent epileptic seizure after severe brain injury.

Phenobarbital has been utilized to control seizures and ICP elevation for a long time; however, phenobarbital blocks the hydrogen transport system in mitochondria and causes severe reduction of adenosine triphosphate (ATP) production. This negative effect is a serious condition for neuronal restoration in severely brain-injured patients, especially under the conditions of brain hypothermia. For the success of neuronal restoration, dying neurons require ATP production even under the conditions of brain hypothermia. The administration of phenobarbital is not recommended for the restoration of dying neurons except under special conditions such as prolonged epilepsy and uncontrolled ICP elevation despite the use of various treatments.

The combination of phenobarbital and brain hypothermia is very powerful for reducing ICP elevation; however, reduction of brain tissue ATP is a very dangerous condition for dying neurons in injured brain tissue. Our preliminary clinical studies of the combination of brain hypothermia and phenobarbital administration suggested poor prognosis even with normalization of ICP elevation.

Other ICU Management Issues

Control of $PaCO_2$

Animal studies have suggested the use of a closed circulation system to measure oxygen consumption and carbon dioxide production. During brain hypothermia with low blood temperature, the production of carbon dioxide will be low. For moderate brain hypothermia, $PaCO_2$ will be 2–4 mmHg lower than that at 37°C. Therefore, $PaCO_2$ greater than 40 mmHg during brain hypothermia treatment suggests the possibility of trouble within the respiratory system. On the other hand, hyperventilation during brain hypothermia treatment can cause a large reduction in $PaCO_2$ with disturbance of the systemic microcirculation. The control of $PaCO_2$ at 32–36 mmHg during brain hypothermia treatment is recommended.

Fluid Selection

The basic choice for fluid selection requires normal osmotic pressure, low glucose content, adequate phosphate and magnesium, and the normal valance electrolytes sodium, potassium, and chloride. Prevention of harmful stress-associated hyperglycemia is important to avoid hemoglobin dysfunction, excess release of vasopressin, increased brain tissue lactate, and activation of proinflamatory cytokines [23,24].

The early management of BBB dysfunction is also as important as early fluid resuscitation. The replacement of AT-III to prevent endovascular inflammatory reactions, followed by 5% albumin is useful for the management of BBB dysfunction. The management of AT-III at higher than 100% under brain hypothermia (32°–34°C) is successful for the prevention of endovascular damage and micro-embolus formation in the systemic circulation [20,22,24]. Hypo-albuminemia after severe brain injury is a common complication [34]. The replacement of albumin and maintenance of serum albumin higher than 3.0 g/dl is very successful for the prevention of brain edema with normalization of BBB dysfunction, and also prevents infection during the cooling stage of brain hypothermia [20,22,24]. The effect of albumin in preventing infection is discussed later in this section.

The use of magnesium chloride with potassium phosphate is also important to prevent respiratory muscle weakness. Respiratory muscle weakness is a very dangerous complication because of activated immune crisis, reduced adaptation to prolonged hypoxia, induction of pulmonary atelectasis, and susceptibility to severe pulmonary infection. The management of protein synthesis of respiratory muscle is helpful in avoiding these complications.

Management of Digestive Organs

The major targets for the management of the digestive organs during the cooling stage are:

Prevention of abdominal hypertension
Control of intestinal mucous edema
Maintenance of microcirculation to intestinal organs
Prevention of pulmonary hypertension
Removal of the contents of a full stomach
Control of gastric juice pH
Control of intra-ileum lumina pressure
Control of macronutrient intake feedback reaction
Prevention of bacterial translocation
Management of digastrics decontamination
Enteral nutrition
Maintenance of energy source to intestinal immune cells

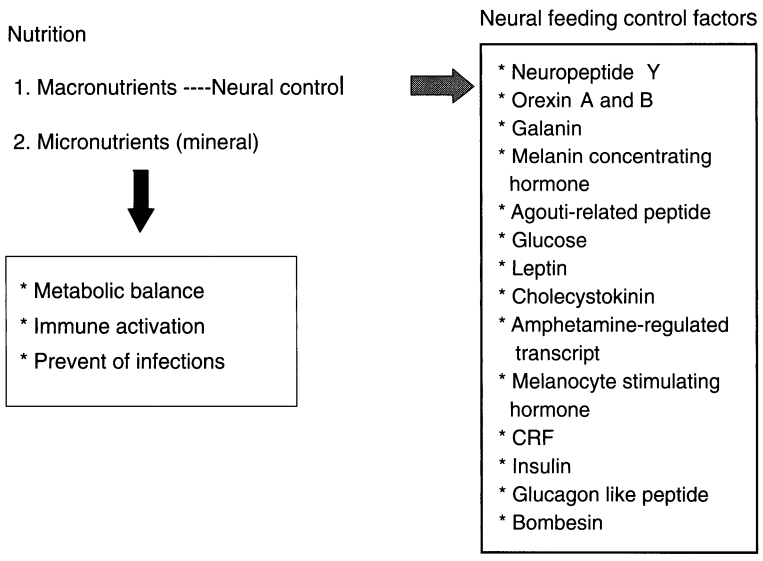


Fig. 86. Basic nutritional consideration in severely brain-injured patients. CRF, corticotropin releasing factor

The abdominal pressure can be controlled to less than 10 mmHg to prevent ischemia of the intestinal organs, portal venous stasis, and ICP elevation, by insertion of an ileum tube. The management of hypo-albuminemia (higher than 3.0 mg/dl of serum albumin), replacement of AT-III (higher than 100%,) and prevention of abdominal hypertension are important to prevent intestinal mucous edema and for the management of the digestive organs. Unsuccessful management of intestinal mucous edema produces various complications such as diarrhea during enteral nutritional administration, pancreatic dysfunction because of pancreatic duct obstruction, immune dysfunction, and activation of bacterial translocation [24].

Pulmonary hypertension can also produce congestion of the portal vein, venous stasis of the digestive organs, and intestinal mucous edema. We prefer the use of a ventilator with low tidal volume and PEEP pressure lower than 15 mmHg. The critical airway pressure to produce intestinal dysfunction is 35 mmHg. Gastric lavage after cranial surgery is important to prevent abdominal hypertension and pneumonia (Mendelson's syndrome). Washing of the stomach with normothermic saline and control of gastric juice pH lower than 3.5 are very useful for the prevention of intestinal bacterial translocation thoughout the mouth and trachea. Gastric juice pH greater than 4.0 sees the breakdown of the chemical acid barrier to intestinal bacteria. The insertion of an ileum tube distal to the Traiz ligament is useful for the control of intestinal ischemia by reducing intra-luminal pressure. The management of digastrics decontamination with nonabsorbable and hypothermia-active antibiotics (combination of levofloxacin (Cravit, 200 mg) + amphotericin B 100–300 mg) and early administration of enteral nutrition are useful to prevent systemic infections. The energy source of intestinal immune cells is glutamine that is produced in the lungs and skeletal muscles. Therefore, management of pulmonary infection and muscle weakness is also important to prevent immune crisis during brain hypothermia treatment.

Nutritional Management

Nutritional considerations are divided between the use of macronutrients and micronutrients (Fig. 86). The metabolic nutritional phase is divided into the metabolic ebb phase and metabolic flow phase (Fig. 87). In the ICU management of critically ill patients, early administration of parenteral and enteral nutrition is recommended. However, enteral and parenteral nutrition that is too early can increase neurotoxic glutamate in injured brain tissue because serum glutamate is approximately doubled by enteral and parenteral nutrition (Table 10, Chap. 33). Neurotoxic serum glutamate can be permeable to the damaged BBB and worsen the condition. Before deciding upon enteral nutrition, the severity of BBB dysfunction (determined by CSF/serum albumin ratio) and the level of hypo-albuminemia must be determined. During brain hypothermia treatment, serum glucose rapidly increases because of reduced glucose expenditure after the brain temperature falls below 33°C. Hyperglycemia with serum glucose greater than 230 mg/dl activates vasopressin release and changes BBB function (Fig. 88). Hypo-albuminemia also produces increased permeability of the BBB by an osmotic mechanism. Early enteral nutrition is very effective for the prevention of infection by maintaining glutamine and providing energy to immune cells.

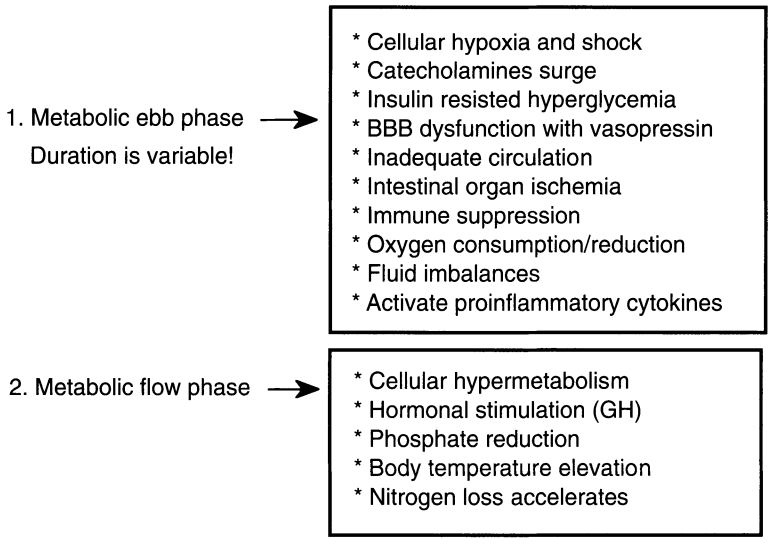


Fig. 87. Two metabolic nutritional phases and related pathophysiology

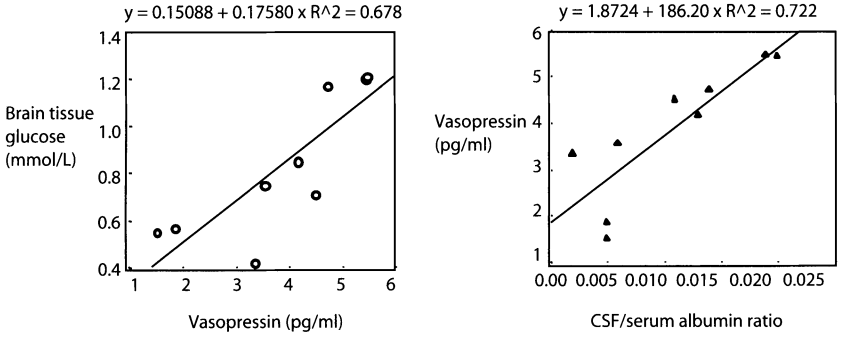


Fig. 88. The relationships between changes of brain tissue glucose, cerebrospinal fluid (CSF) vasopressin and CSF/serum albumin ratio [blood–brain barrier (BBB) dysfunction marker]. Increasing brain tissue glucose promotes excess release of vasopressin by macronutrient neural feed back mechanism and changes of BBB dysfunction

However, glutamine is a very neurotoxic substrate. The serum glutamine concentration increases twofold after enteral and parenteral nutrition. Therefore, early enteral nutrition under the conditions of severe BBB dysfunction (CSF/serum albumin ratio ≥0.01) can promote the progression of delayed neuronal death by increasing the brain tissue glutamate level. Because the peak time of BBB dysfunction will be about 3–4 days after brain injury, glutamine-free enteral nutrition is recommended for this period. However, there is no correct answer regarding enteral nutrition during brain hypothermia treatment. Increasing brain tissue glutamate was not recorded with the following strategy of nutritional management during brain hypothermia.

For cases in which BBB dysfunction is not severe (CSF/serum albumin ratio <0.01), early enteral nutrition, that includes 1% $ZnCl_2$, glutamine (Glumin-S, Kyowa Hakko, Tokyo, Japan), arginine (arginine hydrochloride, Ajinomoto-pharuma, Tokyo, Japan), and amino acid for activation of immune function, should start from 2 days after trauma. However, in cases in which the CSF/serum albumin ratio is higher than 0.02, initial enteral nutrition is limited to saline with $ZnCl_2$ initially and is then followed by ω-3 unsaturated fatty acid enteral nutrition (Fibren-HY, Meiji, Tokyo, Japan) (Fig. 89). During brain hypothermia treatment, glucose metabolism shifts to lipid metabolism. At 34°C during mild brain hypothermia, the division between glucose and lipid metabolism is about equal. However, at 32°C lipid metabolism becomes dominant (about 82%) over glucose metabolism (about 18%). The ω-3 unsaturated fatty acid enteral nutrition is reasonable as nutrition during brain hypothermia treatment. The enteral nutrition of Fibren-HY is very successful for the prevention of activation of harmful stress-associated hyperglycemia even at the early stage. After stabilizing BBB function amino acid nutrition with glutamine can begin about 3–4 days after brain damage with monitoring of serum glutamate. Enteral nutrition is very useful for preventing severe systemic infections and for the management of immune crisis during brain hypothermia treatment.

Prevention of Immune Crisis

The mechanism of immune dysfunction under hypothermia has not been elucidated previously. Our recent clinical study suggested that GH is a regulator of

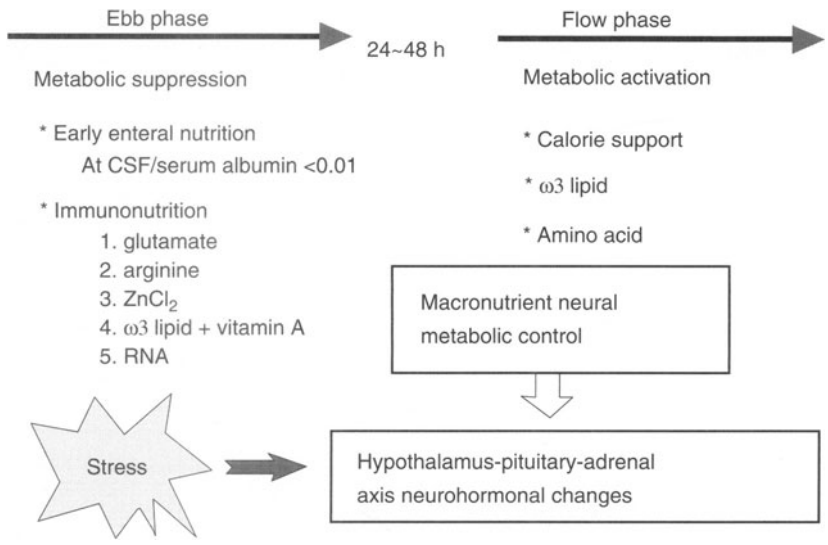
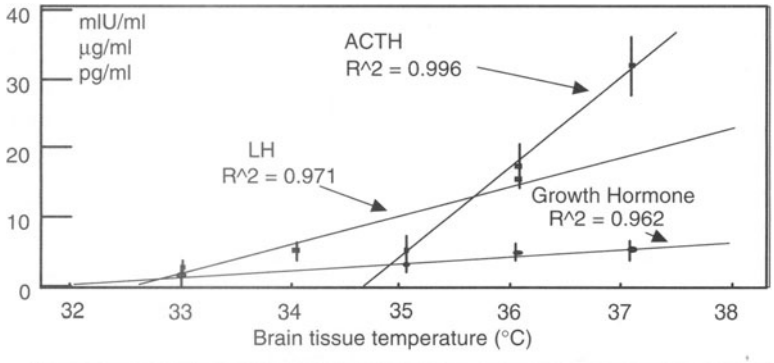


Fig. 89. Nutritional considerations for severely brain-injured patients



Hormone	Immunologic Function
ACTH	Stimulates NK-cell activity, Stimulates B-cell proliferation Suppression of IFN-γ synthesis Suppress MHC class II expression by macrophage
GH	Enhances the generation of cytotoxic T cells (IL2,IL5,IL6) Suppress the antiinflamatory cytokines Stimulates the production of O_2 by macrophages

Fig. 90. Brain hypothermia produces pituitary hypo-function and immune dysfunction. *ACTH*, adrenocorticotropic hormone; *GH*, growth hormore; *LH*, luteinizing hormone

the immune response (Fig. 90) [24]. The use of brain hypothermia cannot avoid subjecting the pituitary gland to low temperature and results in a reduction of serum GH level. GH activates CD4 and cellular immune function and produces increased levels of proinflammatory cytokines IL1 and IL6 [9,20]. However, CD8 associated with anti-inflammatory cytokine IL10 and fluid immune function will be suppressed (Fig. 37, Chap. 27). Therefore, we believe that excessive release of GH causes the activation of proinflammatory cytokines and worsening of systemic infections. On the other hand, excessive reduction of GH caused by brain hypothermia causes cellular immune suppression and susceptibility to infection. The number of lymphocytes strongly correlates to the release of serum GH during brain hypothermia treatment as shown in Fig. 42 (Chap. 33). Lymphocytopenia lower than 1000 mm^3 is an indirect critical measure of immune dysfunction during brain hypothermia treatment. Glutamic acid is an energy source for lymphocytes and is produced in the lungs and skeletal organs. Therefore, prevention of pulmonary infection and administration of glutamine, alanine, potassium phosphate, and magnesium chloride are also important to prevent immune crisis during brain hypothermia treatment. Administration of growth hormone and arginine is a direct treatment to prevent immune crisis. However, it is difficult to prevent immune crisis by these replacement therapies alone. The use of inter-

mittent brain hypothermia and prevention of pituitary hormonal crisis is a novel technique for the prevention of infection during prolonged brain hypothermia treatment [20,22,24].

In the use of intermittent brain hypothermia, the brain tissue temperature is elevated slightly from 32°–33°C to 34°C during the evening period of 1800–2000 hours which is the time of physiological GH increase without the complication of hyperglycemia. In cases of severe infection with reduced immune function, we controlled brain tissue temperature at 34°C using various treatments as described previously.

The management of immune crisis during brain hypothermia treatment requires:

Prevention of pulmonary infection
Management of respiratory muscle metabolism
Management of skeletal muscle (massage and prevention of venous stasis)
Replacement of phosphate, magnesium, alanine, and glutamine
Administration of arginine with normal levels of hemoglobin (>11 g/dl)
Intermittent brain hypothermia control
Early enteral nutrition that includes glutamine

Special Consideration for Prevention of Infection During Hypothermia

During the management of brain hypothermia treatment, control of infection is very important and directly affects the prognosis [14]. Increasing serum cytokines under the condition of severe BBB damage results in cytokine encephalitis. The complication of cytokine encephalitis in severe brain injury produces brain edema and release of neurotoxic glutamate that is difficult to control even with 32°–34°C brain hypothermia. Therefore, the complication of pneumonia and systemic infection during brain hypothermia means unsuccessful treatment. The major causes of infection during brain hypothermia treatment are HPA axis neurohormone dysfunction, suppression of immune function, energy crisis in immune cells, hypo-albuminemia, metabolic suppression of skeletal muscles, enteral bacterial translocation, and inadequate parenteral and enteral nutrition (Table 21) [24].

Fundamental Management for Prevention of Infection During Brain Hypothermia

All severely brain-damaged patients affected by trauma, stroke, hypoxia, or cardiac arrest produce stress neurohormonal reactions and release excess HPA axis hormones [8,23]. These stress reactions are not severe in anesthetized animal models. However, specific HPA axis neurohormonal reactions of clinical patients produces insulin-resistant hyperglycemia, activation of cytokines, hypo-albuminemia, pulmonary edema, and immune dysfunction [23].

Table 21. The causes of severe infection during brain hypothermia treatment

Unsuitable management of hypothalamus-pituitary-adrenal axis neuroendocrinological dysfunction
Hyperglycemia caused by catecholamine surge
Excess stimulation of neuropeptide Y receptors
Respiratory muscle weakness caused by reduced insulin
Immunological dysfunction caused by muscle weakness
Hypo-albuminemia
Reduced release of growth hormone caused by hypothermia
Cellular immune dysfunction
Lymphocytopenia
Poor enteral care management
Gastric mucous edema caused by hypo-albuminemia
Abdominal hypertension
Unsuitable nutritional care management
Increase of serum glutamate and brain tissue glutamate caused by early nutrition: if CSF/serum albumin > 0.02

CSF, cerebrospinal fluid

Delayed induction of brain hypothermia produces an excess release of catecholamines and severe hyperglycemia [23]. Severe hyperglycemia (serum glucose >230 mg/dl) stimulates the release of vasopressin [30,31], and activates proinflammatory cytokines, BBB dysfunction, hemoglobin dysfunction, and disturbances of microcirculation in the brain, lungs, and heart [23,24]. Excessive stimulation of cytokines results in damage during DNA synthesis of albumin. Of these factors, hypo-albuminemia (serum albumin <2.5 mg/dl) is a big issue for the management of infections because of intestinal mucous edema, pancreatic duct obstruction, inaction of albumin-binding antibiotics, and BBB dysfunction. The intestinal mucous edema can easily reduce digestive immune function and hinders early enteral nutrition because of diarrhea. Therefore, hyperglycemia and hypo-albuminemia combined is a very dangerous condition for worsening systemic infections.

On the other hand, overly prolonged suppression of the HPA axis neurohormonal reaction also results in susceptibility to infection. Brain tissue temperature lower than 34°C reduces the levels of GH and ACTH. GH is a very important regulator of immune function of CD4 and lymphocytes. The critical brain tissue temperature for maintaining immune function and lymphocytes activity is about 32°C as shown in Fig. 4 (Chap. 20). Therefore, in moderate brain hypothermia below 34°C, immune dysfunction can easily complicate systemic infection. The early induction of brain

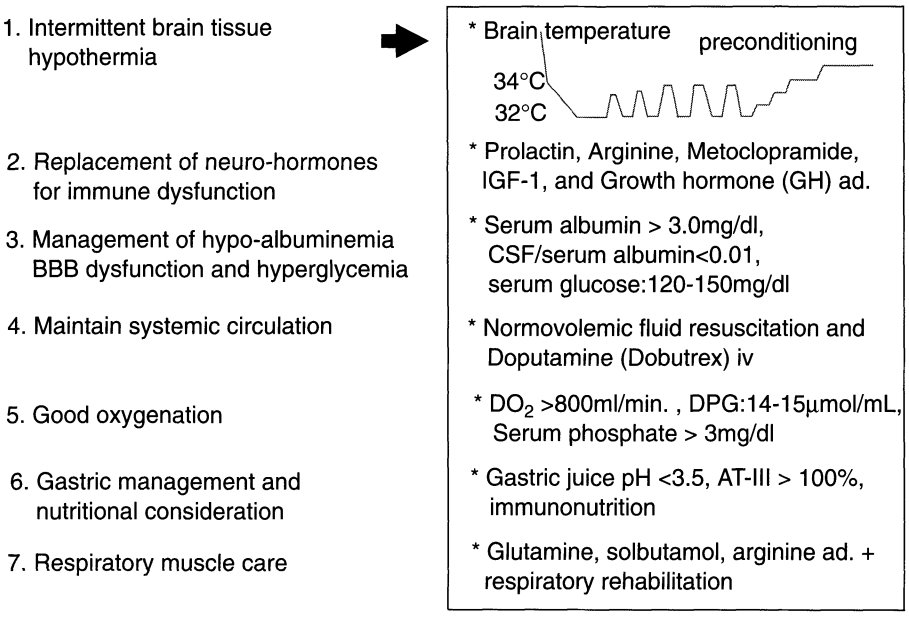


Fig. 91. Basic infectious control management during brain hypothermia treatment. BBB, blood–brain barrier; IGF-1, insulin like growth factor; CSF, cerebrospinal fluid; DPG, 2,3-diphosphoglycerate

hypothermia and intermittent brain hypothermia management with well-organized hyperglycemia and hypoalbuminemia is most important to prevent easy infection. The fundamentals of infectious care management during brain hypothermia are summarized in Fig. 91 and are different to previous antibacterial infection management criteria.

Early Management of Pulmonary Infection

Gastric lavage using normothermic saline is fundamental for the prevention of Mendelson's syndrome pneumonia. This management is also effective in preventing abdominal hypertension and bacterial translocation when combined with control of gastric juice pH at about 3.0–3.5. Iced saline is useful for early induction of hypothermia; however, at the cooling stage, gastric lavage with too much cooled saline can easily cause arrhythmia and AV block, especially in cases showing dehydration, hypokalemia, or cardiac disease.

The high incidence of infection during brain hypothermia treatment is mainly produced by bacterial translocation of intestinal bacteria and immune suppression (Table 22). The early management of intestinal bacterial translocation and immune dysfunction is very successful for the prevention of infection during brain hypothermia treatment. Pseudomonas and gram-negative enteral bacteria are most common bacteria that cause pneumonia. Immipenem cilastain sodium (Tienam 1–2 g/day ×3) or meropenem trihydrate (Meropn, 1–2 g/day ×4) are recommended as first choice antibiotics for gram-negative bacteria and Pseudomonas at the cooling stage.

Early nutrition is very successful in preventing infection, as previously described. However, before starting enteral nutrition, intestinal organ ischemia must be controlled. Intestinal ischemia is produced by microembolus formation associated with reduced AT-III (≤80%), abdominal hypertension (≥15 mmHg), and mucous membrane edema caused by severe hypoalbuminemia (≤2.5 mg/dl). The presence of severe BBB damage with a CSF/serum albumin ratio of more than 0.01 is also a negative factor for early enteral nutrition. For early nutrition, the CSF/serum albumin ratio must be higher than 0.01.

To prevent complications, two-step enteral nutrition is preferred. Initially, no glutamine should be included in enteral nutrition (such as Ensure) that combines with replacement of AT-III and serum albumin for 3–4 days after brain injury. Glutamine can then be included in enteral nutrition as shown in Fig. 89.

Table 22. Bacterial infection and the immunocompromised host

Microorganisms	Immunocompromised host
Pseudomonas	Insufficiency of macrophages
Staphylococcus	
Enterobacter	
Candida	
Aspergillus	
Herpes	Abnormal T-cells
Cytomegalo virus	
Toxoplasma	
Legionella	
Mycobacteria	
Histoplasma	
Pseudomonas	Abnormal B-cells
Pneumocytis carini	
Streptococcus pneumoniae	
Streptococcus pneumoniae	Insufficiency of compliments
Nisseria	

Control of hyperglycemia prevents the excess release of vasopressin, induction of IL1 and IL6, and BBB dysfunction through the reduction of macronutrient responses. These increased serum cytokines, such as IL1 and IL6, can easily permeate the damaged BBB and cause severe brain edema. Additional cytokine encephalitis with infection during brain hypothermia is a very dangerous complication.

ICU Care for Prevention of Systemic Infection

The basic steps of ICU care to prevent infection are:

1. Intermittent elevation of brain tissue temperature from 32°C to 34°C during the evening
2. Naso–oral cavity cleaning
3. Gastric juice pH < 3.5
4. Prevent abdominal hypertension <10 mmHg
5. Digestive decontamination antibiotics
6. AT-III > 80% to 100% and gastric pHi > 7.3
7. Serum albumin >3.5 mg/dl
8. Replacement of $ZnCl_2$, arginine, and Hb > 11 g/dl
9. Gastric immune nutrition replacement followed by nutritional care
10. Ventilator care and urinary care
11. Breathing rehabilitation
12. Management of lymphocytopenia (34°C brain hypothermia, GH, γ-globulin)
13. Low dosage of antibiotics and nonprotein-binding antibiotics
14. O_2ER 23%–25%; DPG 12–15 mmol/gHb
15. Muscle rehabilitation

Management of Severe Pulmonary Infection

If severe infection occurs during brain hypothermia treatment, steps must be taken to:

Isolate the infectious source
Prevent systemic inflammatory reactions
Administer hypothermia-effective antibiotics
Recover immune function
Manage intestinal ischemia
Prevent intestinal bacterial translocation
Replace albumin
Control hyperglycemia

To minimize the effect of infection on brain damage, the management of BBB dysfunction is also important.

Removal of Infectious Source. In most cases, enteral bacteria from the patient are the infectious source. The enteral administration of amphotericin B, vancomycin, or albekacin in combination with intravenous injection of hypothermia-effective antibiotics such as cefmetazole, flomoxef, or arbekacin or bacteria-sensitive antibiotics is basic treatment. The management of gastric juice pH to less than 3.5 provides a barrier to the enteral bacteria translocation through the mouth and trachea.

Direct Management and Anti-inflammatory Treatment for Infected Organs. The administration of hypothermia-effective antibiotics, delivery of sufficient oxygen (≥700–800 ml/min), and stabilization of vital signs are effective in the management of infected organs. The sensitivity of antibiotics under the conditions of brain hypothermia has not been studied. Our recent clinical studies suggested that cefmetazole, flomoxef, and arbekacin were effective even under the conditions of hypothermia. However, further studies of the effects of hypothermia on the action of antibiotics are required.

Prevention of Systemic Inflammatory Reactions. Anti-inflammatory medicine such as aspirin, AT-III, or AT-III combined with low molecular weight heparin are treatments of choice. AT-III is very sensitive for the prevention of vascular inflammation. Steroid pulse therapy for the prevention of inflammatory reactions is not recommended during brain hypothermia treatment. Under the condition of hyperglycemia the steroid may overstimulate the neuropeptide Y receptor in the vascular wall of the lungs, brain, and heart. The stimulation of the hypothalamus neuropeptide Y receptor by steroid and hyperglycemia also produces the release of vasopressin. These pathophysiological reactions produce increased vascular permeability and disturbances of microcirculation. During brain hypothermia treatment, serum glucose increases because of reduced glucose expenditure. Therefore, steroid is not recommended for the prevention of systemic inflammatory reactions during brain hypothermia treatment. The management of hyperglycemia is also effective in preventing cytokine reactions, indirectly associated with preventing the excess release of vasopressin.

Recovery of Immune Function. The intravenous administration of GH and/or L-arginine is very powerful in boosting immune functions (Fig. 92). Although GH is very useful for increasing the immune activity and lymphocyte action, GH is very expensive and is difficult to use for a prolonged period. As an alternate medication, L-arginine is much easier to use in ICU management.

Control of Intestinal Bacteria and Prevention of Bacterial Translocation. Digastrics decontamination with enteral administration of nonabsorbable antibiotics, early enteral nutrition for immune cells, control of abdominal hypertension, prevention of intestinal mucous edema, and management of AT-III to prevent disturbances of intestinal microcirculation are effective management steps for the control of bacterial translocation.

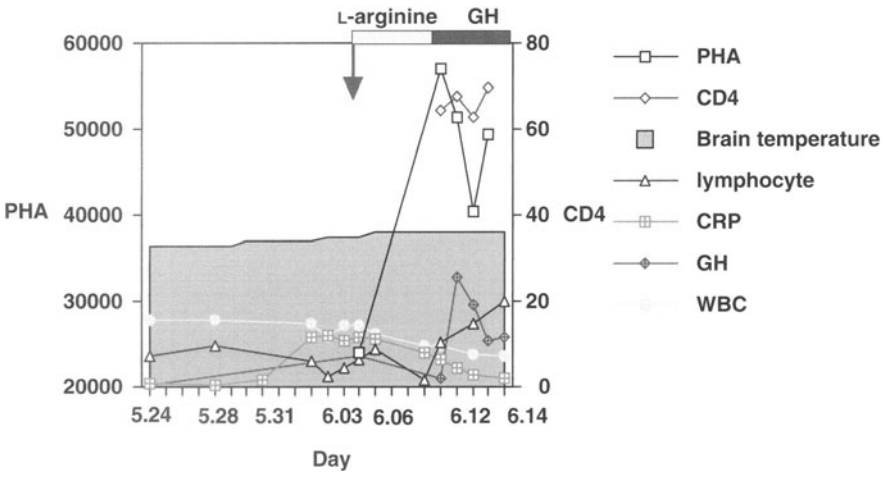


Fig. 92. The successful recovery of immune function by administration of L-arginine and growth hormone (*GH*) in severe pneumonia. PHA, phytohemagglutinin; CD4, CD4-T cell; CRP, C-reactive protein; GH, growth hormone; WBC, white blood cell

Protection of BBB. It is difficult to prevent cytokine chemical encephalitis without management of BBB. Proinflammatory cytokines in the bloodstream may easily permeate the damaged BBB in cases of systemic infection. Cytokine encephalitis produces an uncontrollable increase of neurotoxic glutamate in injured brain tissue even with moderate brain hypothermia. The critical level of BBB dysfunction is evaluated with a CSF/serum albumin ratio higher than 0.01. For treatment of BBB dysfunction, administration of AT-III combined with low molecular weight heparin to prevent vascular inflammation and micro-embolus formation is used initially. After that, replacement of serum albumin to more than 3.0–3.5 mg/dl is basic management for injured BBB. The use of steroid is not recommended under the presence of stress-associated hyperglycemia.

Antimicrobial Therapy. The choice of antibiotics is determined by a culture study of antimicrobial sensitivity. In our clinical studies of pneumonia bacteria, 46.8% were gram-negative, 35.9% were gram-positive, and fungal infection accounted for 14.5%. In these bacteria, methicillin resistant *staphylococcus aureus* (MRSA) was most common at 15.8%, and followed *Pseudomonas aeruginosa* 9.7%, *Klebsiella pneumoniae* 7.6%, *Eenterococcus faecalis* 6.9%, *Escherichia coli* 4.1%, and *Streptococcus pneumoniae* 2.1%. The antimicrobial effects of antibiotics are influenced by body temperature, serum albumin level, and liver and renal function. Before starting antimicrobial therapy, diagnosis of the antibiotic sensitivity, the presence of hypo-albuminemia, and the hepatic–renal functions are important. However, information concerning the antimicrobial effects toward bacteria under hypothermia is limited. Our clinical studies suggested that the antimicrobial effects of cefoperazone, which is metabolized in the liver, was much more effective than the renally eliminated antibiotics cefmetazole, flomoxef, and arbekacin under hypothermia. The antimicrobial effects of arbekacin, vancomycin, amino glycosides, and β-lactams, which are almost totally eliminated by the kidneys, are not effective with the conditions of mild brain hypothermia without renal dysfunction. If hepatic–renal function is reduced by about 50%, the required dose of these antibiotics is about 50% of a normal dose. Multi bacteria infections occur in many cases during brain hypothermia, and therefore, double-drug therapy is recommended. In brain hypothermia treatment, compromised host patients with immune dysfunction and enteral ischemia with unsuitable neurohormone management are commonly infected. Intravenous administration of antipseudomonal penicillin with amino glycoside and/or vancomycin is the medication of first choice for severe pulmonary infections. Prophylactic enteral administration of amphotericin B, vancomycin, or albekasin is very successful to prevent the occurrence of severe pulmonary infections. Antibiotic therapy should not be continued for more than 2 weeks.

Outcomes. The clinical results of management of systemic infection during brain hypothermia treatment are summarized in Table 23. We experienced a high incidence (64.2%) of severe infection at the initial stage in the period 1991–1993. However, complication of severe infection during brain hypothermia treatment is currently limited to about 5.2% by using the abovementioned infectious control management strategies.

Management of Disseminated Intravascular Coagulopathy and Sepsis

The activation of intravascular coagulation during the cooling stage and activation of fibrinolysis at the rewarming stage is the major target of management

Table 23. The advances in management of pulmonary infection during brain hypothermia treatment

Period	Treatment	Cases	Percentage
1991–1993	Antibiotics	9/14	64.2%
	γ-Globulin		
	Physiological rehabilitation		
	Prevention of hypoproteinemia		
1994–1995	GL-washing	16/50	32.0%
	O_2ER control at 23%–25%		
	Kinetic therapy		
	Early intestinal nutrition		
	Electrical muscle stimulation		
1996–1998	Replacement of growth hormone	21/16	12.5%
	L-Arginine, glutamine, Zn immune		
	Hemoglobin > 12 mg/dl		
	Vitamin A and lipid nutrition at rewarming stage		
1999–2001	Intermittent hypothermia	1/19	5.2%
	Serum glucose 120–140 mg/dl		
	Serum albumin > 3.5 mg/dl		
	Two-step enteral nutrition		
	Digestive decontamination		
	Immune care management		

GL, gastric lavage

Table 24. The changes of coagulation and fibrinolysis markers between disseminated intravascular coagulation (DIC) and non-DIC during cooling stage and at rewarming stage

	Day 0		Day 1		Day 2	
	DIC	non-DIC	DIC	non-DIC	DIC	non-DIC
Cooling phase						
PLT (/mm^3)	7.6 ± 4.2**	23.3 ± 7.9	6.4 ± 3.7**	16.9 ± 4.7	5.8 ± 3.4**	14.9 ± 5.7
FPA (ng/ml)	48.4 ± 18.8*	23.1 ± 10.1	22.2 ± 9.7*	11.5 ± 5.2	24.4 ± 9.8**	6.6 ± 3.4
D-dimer (μg/ml)	33.1 ± 16.4*	4.1 ± 2.5	21.2 ± 19.8*	5.0 ± 3.4	9.6 ± 3.4**	1.8 ± 0.8
Rewarming phase						
PLT (/mm^3)	6.9 ± 1.2**	12.1 ± 4.7	4.8 ± 1.5**	12.8 ± 6.6	6.1 ± 1.4*	12.6 ± 8.5
FPA (ng/ml)	35.5 ± 5.4*	5.0 ± 2.0	57.2 ± 8.8*	4.5 ± 1.4	59.3 ± 8.1*	4.9 ± 1.9
D-dimer (μg/ml)	7.5 ± 3.3*	1.8 ± 0.3	10.5 ± 6.8*	1.9 ± 0.6	13.3 ± 6.4*	2.7 ± 1.1

Entries given as mean ± SD. $n = 24$
PLT, platelet; FPA, fibrino-peptide A
* $P < 0.05$
** $P < 0.01$

in disseminated intravascular coagulopathy (DIC) (Table 24). The background of these pathophysiological changes includes activation of leukocytes and endothelial injury, tissue factor generation, activation of extrinsic pathway of coagulation, systemic microembolus formation, and organ failures. Ventilator respiratory management, pharmacological management for increased coagulopathy, improving oxygen delivery to major organs, antimicrobial therapy for enterobacteria, activation of immune function, fluid resuscitation for maintaining microcirculation, metabolic and nutritional support, prevention of acute renal failure, and management for acute lung injury are major targets of DIC management in the ICU. The management of sepsis and DIC based on a care map is useful (Fig. 93).

Sepsis-associated respiratory failure is one of the most difficult ICU management issues during brain hypothermia treatment. Inadequate ventilation management of air pressure, pressure pattern, tidal volume (V_T), and ventilatory rate can markedly worsen lung injury. The use of low tidal volume (10–15 ml/kg → 5–9 ml/kg), moving away from normal gas-exchange blood values ($PaO_2 > 75$ mmHg → SaO_2 90% ± 5%, $PaCO_2$ 40 ± 5 mmHg → accept 40–50 mmHg, if other parameters do not achieve normal values, pH 7.4 ± 0.05 → accept ≥37.3), low airway pressure (maintain plateau pressure

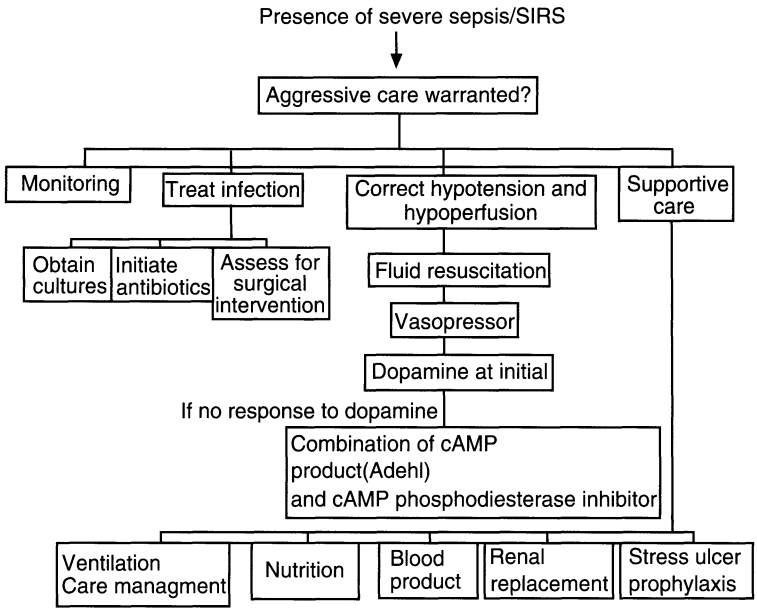


Fig. 93. The care map for sepsis and disseminated intravascular coagulability (DIC)

≤35 cmH_2O), PEEP at about 10–15 cmH_2O with constant $PaCO_2$, and inspiratory/expiratory (I/E) ratio greater than 1, and the new ventilatory and oxygenation technique with management of hemoglobin enzyme are fundamental ventilation management steps. A high airway pressure can easily complicate baro-trauma in infected lungs. The use of effective airway management and respiratory rehabilitation support the ventilation therapy.

Pharmacological management for reduced perfusion pressure is fluid resuscitation (crystalloid and colloids) combined with dopamine administration. If this management is unsuccessful in maintaining stable systemic circulation, combined administration of adehl (cyclic adenosine monophosphate production) and or amurinon (cyclic adenosine monophosphate phosphodiesterase inhibitors), followed by doputamine is recommended. Insulin-resistant hyperglycemia is not activated by this pharmacological blood pressure management.

Based on the known pathogenetic mechanism of DIC, three major treatment strategies can be distinguished: inhibition of systemic activation of coagulation, enhancement of fibrinolysis, and restoration of the relative or absolute deficiencies of natural inhibitors of coagulation. AT-III combined with low molecular weight heparin (danaparoid sodium), tissue factor pathway inhibitor (TFPI), and protein C are effective in preventing the systemic activation of coagulation as well as the proinflammatory response and lethal effects of *E. coli* bacteria.

Adequate tissue oxygenation requires management of oxygen delivery, and oxygen transport with good circulation of the bloodstream. $PaO_2/FiO_2 \geq 300$, $SaO_2 \geq$ 99%, oxygen delivery >700–800 ml/min, Hb ≥ 11 g/dl, DPG 12–15 µg/dl, phosphate 3–5 mg/dl, pH ≥ 7.3, $PaCO_2$ 32–38 mmHg, $ETCO_2$ 24–28 mmHg, AT-III > 100%, and serum albumin ≥ 3.0 mg/dl are indication parameters of oxygenation therapy.

Staphylococcus aureus, fungemia, *E. coli*, *Klebsiella sp.*, *Pseudomonas aeruginosa* and their complications are major causes of sepsis. To determine the choice of antibiotics, the end toxin potentials of antibiotics must be considered for the treatment of DIC and sepsis. For antibiotics that enhance end toxin release, cefataxime, cefazidime, aztreonam, and quinolones are nominated. On the other hand, as inhibitors of end toxin release, the action of aminoglycoside, polymixin, tetracycline, teichoplanin, meropenam, and chloramphenicol has been demonstrated. Aminoglycoside, amphotericin B, arbekacin and vancomycin are easy to use for the management of sepsis without severe renal dysfunction. If renal dysfunction is a complication, the use of cefoperazone, which is metabolized in the liver, is one of the methods of choice. However, these antibiotics do not work under the conditions of severe hypo-albuminemia (serum albumin < 2.5 mg/dl) because of unstable antibiotics in the bloodstream, complication of free bacteria, diarrhea caused by enteral mucous edema and ischemia, and activation of proinflammatory cytokines. Before antimicrobial therapy, care should be taken to ensure that serum albumin is higher than 3.0 g/dl, AT-III is greater than 100%, serum phosphate is 3.0–5.0 mg/dl, serum glucose is 120–140 mg/dl, and there is sufficient oxygen delivery.

Metabolic and nutritional support is also important in the management of DIC and sepsis. After stabilizing

BBB dysfunction and the replacement of serum albumin, ω-3 unsaturated fatty acid enteral nutrition (fibren-HY) can begin, combined with 1%$ZnCl_2$ and glutamine for 3–4 days in cases of CSF/serum albumin ratio lower than 0.01. After the peak time of cytokine production or clinical signs of the disappearance of vascular reaction of conjunctives, amino acid enteral nutrition is recommended. Early enteral nutrition is very successful for the prevention of immune crisis and immunological dysfunction.

Prevention of Hypokalemia

During brain hypothermia, hypopotassemia is one of the common complications in serum electrolytes. The consumption of potassium in the metabolic shift from glucose to lipid metabolism, elimination from intestinal organs, and reduced vasopressin are considered to be causes of hypopotassemia. However, the detailed mechanism of hypopotassemia during brain hypothermia treatment is not get elucidated. Hypopotassemia with potassium levels lower than 3.0 mg/dl can easily introduce cardiac dysfunction, such as arrhythmia, AV block, and elongation of the QT interval. The paresis of intestinal peristalsis is also a serious complication during brain hypothermia treatment. The replacement of potassium by infusion drip is recommended for serum potassium levels lower than 3.0 mg/dl.

Indications to Stop Hypothermia

Indications to halt advanced brain hypothermia include cardiac arrhythmia, elongation of the QT interval to greater than 450 mm/s, hypopotassemia with potassium level lower than 3 mEq/dl, hypo-albuminemia with serum albumin lower than 3.0 g/dl, lymphocytopenia lower than 1000 mm^3, and oxygen delivery less than 500 ml/min. After replacement therapy or stabilization of these pathophysiological changes, advanced brain hypothermia treatment can be restarted. If these abnormal parameters cannot be controlled, brain temperature should be rewarmed by 0.5°–1.0°C and maintained at about 34°–34.5°C. In most cases, the complications associated with hypothermia are recorded at brain tissue temperatures lower than 33°C.

The observation of a J wave on the ECG, which increases at lower body temperature, does not mean the occurrence of cardiac dysfunction. The environment of electrical conduction in cardiac muscle is changed according to the J wave appearance. However, the precise mechanism of the J wave is not known. The cardiac output begins to reduce as the brain tissue temperature falls below 33°C. The other complications of immune crisis, including lymphocytopenia, metabolic imbalanced hyperglycemia, elongation of the QT interval, and muscle metabolic reduction, also progress more rapidly at brain tissue temperatures below 33°C. Therefore, the risk of hypothermia-associated complications is markedly different between mild (34°C) and moderate (32°–33°C) brain hypothermia. This is why brain tissue temperature at 34°C is known as mild brain hypothermia, and brain tissue temperature at 32°–33°C is known as moderate brain hypothermia.

Other complications of hypothermia, such as ventricular fibrillation, hypercalcemia, hyperglycemia, consumption of vitamin A with unstable membrane phosphate metabolism, prolonged muscle relaxation, shivering, and prolonged coagulation time, are recorded as a physiological reactions of brain hypothermia treatment.

The indications and contraindications of brain hypothermia treatment are listed in Table 5 (Chap. 29). If various contraindicated factors, such as shock, arrhythmia, severe hyperglycemia, and cardiac insufficiency, can be managed within 6 h, brain hypothermia treatment can be started with care. In these cases, mild brain hypothermia is recommended initially. After maintenance or stabilization of vital signs and ensuring that oxygen delivery is more than 700–800 ml/min, serum glucose is lower than 180 mg/dl, serum potassium is higher than 3 mEq/dl, there is no arrhythmia, and the QT interval is less than 450 mm/s, more advanced moderate brain hypothermia treatment can progress. The two-step induction is very successful in avoiding the complications of brain hypothermia treatment. The clinical result of the two-step induction is better than that for rapid induction of moderate brain hypothermia.

The Computed Algorithm Management System

In the ICU, severely brain-injured patients are managed with an understanding of the mechanism of brain damage, the systemic responses of cardiopulmonary function, excess release of HPA axis neurohormones, changes of immune function, administration of neuronal oxygenation, and imbalance of glucose metabolism. These management targets are diagnosed by monitoring of cardiopulmonary function using the Swan Ganz catheter, blood gases, laboratory examinations, monitoring of intracranial pathophysiological changes such as ICP, SjO_2, brain tissue oxygen tension, jugular venous temperature, brain tissue temperature, tympanic membrane temperature, and CBF, neuronal function by

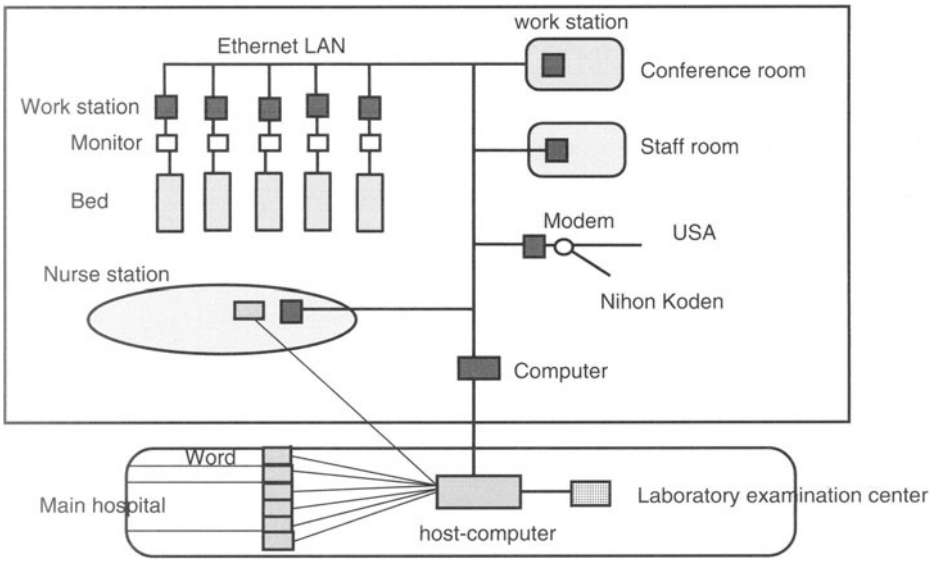


Fig. 94. The block diagram of the computer care management system in the medical center

electroencephalogram (EEG) and brain stem auditory evoked potential, and morphological changes of the brain by computed tomography or magnetic resonance imaging. However, successful treatment of severe brain damage can be obtained by not only understanding the relationships between each brain injury mechanism, but also by a total diagnosis approach to brain damage. The computed total care management system is very useful for understanding the relationships between each brain injury mechanism and total diagnosis of brain damage.

In the ICU management of critically ill patients, team management is the accepted standard. For the success of team care management, real time monitors should be present at the bedside, in the conference room, and also in the staff office. It is preferable that a senior doctor should contribute toward team management and maintain a very high level of medical input throughout the computed care management system. The block diagram of our computed ICU care management system is described in Fig. 94.

The computed ICU care management system opened a new concept for monitoring severely brain-injured patients. The cerebral thermal index with monitoring of SjO_2 is very successful for monitoring changes of CBF and brain metabolism. The computed monitoring of alveolar capillary CO_2 permeability index (end tidal CO_2/(cardiac output × $PvCO_2$) is also useful to diagnose the alveolar permeability.

One of the difficult points of the computed monitoring system is the inclusion of the algorithm care management system. The medical team cannot be at full strength for the entire day, and especially so at midnight. This is because senior medical staff doctor cannot always work at this time. Therefore, the question of how to take perfect care of the patient, even at midnight, is important. Without establishing the management care system, it is difficult to support patients with the most advanced medical management.

Concept of Computed Algorithm Management

Abnormal data, that are recorded by the computer monitoring system, can be identified by automatic flashing on the bedside display. The selection of abnormal flashing data on the computer display brings up seven cards that describe the algorithm management. In this section, the most popular algorithm management cards for brain hypothermia treatment are discussed.

Algorithm for Unstable Brain Tissue Temperature

The contents of the seven algorithm cards contain information about brain tissue temperature, the effect of brain temperature on brain damage, fundamental management of brain tissue temperature, pharmacological treatment to control brain tissue temperature, management of complications that are associated with brain tissue temperature, and recommendations for management of brain tissue temperature. Each of the cards for algorithm management of brain tissue temperature are described in Table 25–33.

Table 25. Algorithm management of brain tissue temperature: information

- Brain temperature (BT) changes by 4 factors
  - Blood temperature (core temperature)
    - Main basic factor of brain temperature
  - BP (CPP)
    - Carrier of core temperature into the brain
  - Brain metabolism (0.5°C)
    - Small factor
  - CBF
    - Carrier and washout factor of brain temperature
- Brain temperature is regulated by CBF washout mechanism
  - Brain thermal pooling (SBP < 90–100 mmHg, reperfusion and >38°C body temperature)
  - BT = jugular venous blood temperature
- Cooling of brain temperature method
  - Cooling blanket method: lower blanket water temperature and change cooling body surface
  - Direct blood cooling method
  - Chilled saline gastric lavage
  - Cooling body by alcohol or steamed water evaporation
  - Cooling CSF
- Unsuccessful cooling of brain tissue temperature
  - Blood temperature is not low enough
  - Blanket is too small
  - Blanket water flow is slow
  - Obese patient (fatty tissue is slow conductor of heat), two-machine cooling method is recommended
  - Body wrapping is not complete
  - Room temperature is high
  - Many heat-generating machines around the bed
  - Bed making is not suitable
  - Infections and high fever
  - Malignant hyperthermia
  - Dehydration

BP, Blood pressure; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; SBP, systolic blood pressure; CSF, cerebrospinal fluid

Table 26. Algorithm management of brain tissue temperature: diagnosis of CBF disturbances and brain metabolism by monitoring of brain tissue temperature, internal jugular venous blood temperature, tympanic membrane temperature, and internal jugular venous O_2 saturation

	CTI	$SjvO_2$
Hypermetabolism	→	↘
Hypometabolism	→	↗
Ischemia	↗	↘
Ischemic hypermetabolism	↑	→ ↗
Ischemic hypermetabolism	↗	→ ↘
Nonfilling	<1	↗ ↘
Luxury perfusion	↘	↗
Recovery	↘	↘

CTI, Cerebral thermal index (brain tissue temperature ÷ tympanic membrane temperature or internal jugular venous blood temperature ÷ tympanic membrane temperature); $SjvO_2$, internal jugular venous blood saturation

Table 27. Algorithm management of brain tissue temperature: pathophysiology

- Mild brain hypothermia (~>34°C of brain tissue temperature)
  - 50% prevention of NO radicals
  - Reduction of catecholamine surge is about 50%. This effect is diagnosed by monitoring of serum hyperglycemia, lactate and 2,3 DPG

Catecholamine surge
↓
ATP↓→cAMP
↓
ATP + glycogen → hyperglycemia (>230 mg/dl)
↓
Lactate production and DPG reduction

  - Increase anaerobic metabolism by imbalance of cerebral oxygenation and glucose metabolism
  - Unsuccessful neuroprotection of A10 nervous system
- Rapid or unstable changes between mild and moderate brain hypothermia
  - Difficult to maintain stable $\bar{D}O_2 > 700$ ml/min
  - Unstable brain metabolism
    - >34°C: glucose-dominant metabolism
    - <34°C: lipid-dominant metabolism
  - Unstable immune function
  - Difficult prevention of selective radical attack to the dopamine nervous system
  - No recovery of injured brain and stop progress of secondary brain damage
  - Brain damage will be much worse at rewarming stage

DPG, diphosphoglycerate

Table 28. Algorithm management of brain tissue temperature: basic management

- Stabilize cardiopulmonary functions
  - SPB > 100 mmHg
  - Hb > 12 mg/dl
  - DPG > 14 μmol/ml
  - $\bar{D}O_2 > 700$–800 ml/min
  - $K^+ > 3$ mEq/dl
- Stabilize autonomic nerve reactions
  - Anesthesia
  - Analgesia
- Increase neuroimmune functions
  - Increase IGF-1, L-arginin infusion
  - Replacement hormone, growth hormone
  - Activate skeletal muscle protein synthesis
- Antipyretics medication
- Technical considerations
  - Alcohol heat evaporation
  - Chilled saline gastric lavage
  - Complete body wrapping and prevent heat conductance to room air
  - Reduce room temperature to 18°C
  - Maintain room air outflow circulation
  - Two cooling machines
  - Direct blood cooling method
  - Ventilator drive with air compressor
  - Limited use of heat-generating medical devices around the bed
  - Combination of isolated cooling of CSF circulation

SBP, Systolic blood pressure; Hb, hemoglobin

Table 29. Algorithm management of brain tissue temperature: medication

Stabilize cardiopulmonary functions
  BP > 100 mmHg, E + dopamine or E + vasopressin
    E, 8 mg/250 mlD5W (bronchodilatation and increase CO)
    D, 400 mg/250 mlD5W (increase CO and maintain renal flow)
    V, 0.1–0.4 U/min (increase CO without ATP consumption)
  $\bar{D}O_2$ > 700–800 ml/min, Doputrex 500 mg/250 mlD5W (increase CO)
Stabilize autonomic nerve reactions
  Anesthesia, midazolam (Dormicum) 10 A (200 mg) + K-free maintenance solution, solita T4-200 ml, 10–20 ml/h drip infusion
  Analgesia, [Fetanest 0.1–0.2 ml/kg/2–3 h + vecuronium (0.02–0.2 mg/kg)] 1–2 day followed by buprenorphine HCl (Lepetan) 0.8 mg(4 A)/day, adult i.v. drip
Prevent hypothalamus edema and increase neuroimmune functions
  Increase IGF-1, L-arginine infusion (one bottle infusion drip/h)
  Steroid hormone, methylpredonisolone 5–30 mg/kg loading followed by a tapering dose
Antipyretics medication
  Aspirin 320–650 mg by rectal suppository every 4–6 h, not to exceed a total daily dose of 3.6 g[a]
  Acetaminophen 325–365 mg po tubing every 4–6 h in adult, or 10 mg/kg every 4 h in children

CO, Cardiac output
[a]Aspirin + acetaminophen every 6 h may be tried if failed at low temperature

Table 30. Algorithm management of brain tissue temperature: complications

Unstable cardiac output and cardiac dysfunction
Unstable metabolic conditions
  Glucose metabolism dominant at ~34°C
  Lipid metabolism dominant at lower than 34°C of brain hypothermia
    Rapid induction of 32°–33°C brain hypothermia produces hyperglycemia and increases brain tissue glucose and lactate more than 34°C brain hypothermia management. Therefore, 32°–33°C brain hypothermia without correct management of hyperglycemia is much worse than 34°C mild brain hypothermia management
Unstable immune functions
  Rapid reduction of growth hormone below 33°C brain tissue temperature
  ↓
  Reduce CD4 and lymphocytes
Reduce the neuronal protection mechanism of brain hypothermia with ICP elevation, brain edema, glutamate neuroexcitation, dopamine radical attack
No recovery of brain damage and restart brain damage at the rewarming stage
  ↓
Much worse brain damage

Table 31. Algorithm management of brain tissue temperature: special considerations

Before lowering temperature of blanket water
  Two checks ↓
    Cardiopulmonary function is stabilized
    Is brain temperature controllable?
    ↓
Remove the negative factors and keep cerebral oxygenation
    ↓
Start basic nursing care plan of algorithm for uncontrolled brain temperature

Table 32. Algorithm management of brain tissue temperature: keywords

Brain tissue temperature
Cooling
Hypothermia

Table 33. Algorithm management of brain tissue temperature: references

1. Iatrou CC, Domaingue CM, Thomas RD, Nye DH (2002) The effect of selective brain cooling on intracerebral temperature during craniotomy. Anaesth Intensive Care 30:167–170
2. Safar P, Behringer W, Bottiger BW, Sterz F (2002) Cerebral resuscitation potentials for cardiac arrest. Crit Care Med 30(4 Suppl):S140–144
3. al-Alousi LM, Anderson RA, Worster DM, Land DV (2002) Factors influencing the precision of estimating the postmortem interval using the triple-exponential formulae (TEF). Part II. A study of the effect of body temperature at the moment of death on the postmortem brain, liver and rectal cooling in 117 forensic cases. Forensic Sci Int 125:231–236
4. Callaway CW, Tadler SC, Katz LM, Lipinski CL, Brader E (2002) Feasibility of external cranial cooling during out-of-hospital cardiac arrest. Resuscitation 52:159–165
5. Yan Y, Tang W (2001) Changes of evoked potentials and evaluation of mild hypothermia for treatment of severe brain injury. Chin J Traumatol 4:8–13
6. Zhu L, Diao C (2001) Theoretical simulation of temperature distribution in the brain during mild hypothermia treatment for brain injury. Med Biol Eng Comput 39:681–687
7. Mustafa S, Thulesius O (2002) Cooling-induced carotid artery dilatation: an experimental study in isolated vessels. Stroke 33:256–260
8. Taylor DL, Mehmet H, Cady EB, Edwards AD (2002) Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat. Pediatr Res 51:13–19
9. Laptook AR, Shalak L, Corbett RJ (2001) Differences in brain temperature and cerebral blood flow during selective head versus whole-body cooling. Pediatrics 108:1103–1110
10. Felberg RA, Krieger DW, Chuang R, Persse DE, Burgin WS, Hickenbottom SL, Morgenstern LB, Rosales O, Grotta JC (2001) Circulation 104:1799–1804

Table 34. Algorithm management of hypotension: information

Shock: SBP < 90 mmHg Shock index (SI) = pulse ÷ SBP	Bleeding volume →	SI = 1; 1000 ± 250 ml SI = 2; 2000 ± 250 ml SI = 3; 3000 ± 250 ml

Mean BP = [diastolic BP + (SBP – diastolic BP)] ÷ 3
Mean BP = (cardiac output × peripheral resistance) ÷ 80 + central venous pressure
Peripheral resistance = [(Mean BP – central venous pressure) × 80] ÷ cardiac output
CBF autoregulation works under the SBP at 70–170 mmHg, and mean BP at 50–150 mmHg
Brain thermo-pooling occur at BT > 38°C, after reperfusion, SBP < 90–100 mmHg
Catecholamine surges
NE (~1 h) > vasopressin (~2 h) > E (~3 h) > dopamine (more ~3 h)
Masking brain hypoxia—neuronal hypoxia even with normal PaO_2, CBF, CPP, and oxygen delivery
Causes: hemoglobin DPG reduction, brain thermo-pooling, hyperglycemia acidosis (pH < 7.2), blood shift for intestinal organ by dopamine dominant circulation

SBP, Systolic blood pressure; BP, blood pressure; NE, norepinephrine; E, epinephrine

Table 35. Algorithm management of hypotension: diagnosis

	Adult	Children
• Blood volume	65 ml/kg	80 ml/kg
• Pulse	60–90/min	Nursing 120–160/min Infancy 90–140/min School children 75–100/min
• Blood pressure	94–140/62–80 mmHg	New born 60–90/20–60 mmHg Nursing 74–100/50–70 mmHg Infancy 82–100/50–78 mmHg School children 84–120/54–80 mmHg
• Stroke volume	50–120 ml/beat	Newborn 5 ml/beat Infancy 15 ml/beat School children 35 ml/beat
• Cardiac index	2.5–4 l/min m^{-2}	3.5–4 l/min m^{-2}
• SVR	800–1600	800–1600
• PVR	80–240	80–240
• Right atrial pressure	5 mmHg	3 mmHg
• PCWP/LAP	10 mmHg	8 mmHg
• Left atrial pressure	120/10 mmHg	100/6 mmHg
• Aortic pressure	120/80 mmHg	100/6 mmHg

SVR, Systemic vascular resistance; PVR, pulmonary vascular resistance; PCWP/LAP, pulmonaly capillary wedge pressure/left atrium pressure

Algorithm for Low Blood Pressure

The maintenance of blood pressure is very important during brain hypothermia treatment. Dehydration therapy using manitol, reduced serum catecholamines, hyperventilation to reduce brain swelling, AV block by hypothermia, and occult bleeding with multiple trauma are major causes of low blood pressure at the cooling stage. The algorithm management cards for the management of blood pressure are shown in Tables 34–42.

Algorithm for ICP Elevation

The management of ICP is focused on maintaining a pressure lower than 15 mmHg at the cooling stage, although elevation to 20 mmHg is permissible under ICU management. However, ICP elevation can occur as a result of unsuccessful management of brain ischemia, hypoxia, edema, brain thermo-pooling, and vascular engorgement. The prevention or restoration of brain ischemia, hypoxia, brain swelling, and brain thermo-pooling are initial targets of management, and brain hypothermia is one of the methods used to treat these pathophysiological changes. The management of brain hypothermia for the control of ICP does not provide a useful restoration effect. The algorithm management cards for ICP elevation are shown in Tables 43–51.

Algorithm for Pulmonary Infections

The complication of severe pulmonary infection during the cooling stage is a very serious condition for the management of patients. Inadequate oxygen uptake, reduced immune function, cardiac dysfunction, and

Table 36. Algorithm management of hypotension: pathophysiology

1. The maintaining force to CBF
2. Washout the brain temperature (BT)
3. Promote acute brain swelling

- Cerebral perfusion pressure (CPP)
- Lower CPP = MAP – ICP < 80 mmHg
- Tympanic membrane temperature ÷ core temperature < 1.0

↓

Brain ischemia

- ICP 20–25 mmHg: venous stasis
- ICP 25–35 mmHg: CBF disturbances
- ICP 35–45 mmHg: brain swelling
- ICP > 45 mmHg: non or poor filling

Acute brain swelling
  Disturbed autoreguration to CBF: SBP < 70 mmHg, >180 mmHg; $PaCO_2$ > 45 mmHg
Brain thermo-pooling (elevation of brain tissue temperature >40°C)
  Body temperature >38°C, BP < 90–100 mmHg after reperfusion
Non effect of oxygen inhalation
  Low Hb-DPG

Table 37. Algorithm management of hypotension: basic management

Elastic bandaging of extremities
Normal volume replacement
Medication
  Stage 1 (brain temperature ~34°C) E → E + vasopressin (within 3 h)
  Stage 2 (brain temperature 32°–33°C) E + vasopressin + dobutrex → vasopressin + dobutrex
SBP maintain > 100 mmHg
CPP > 80 mmHg
Hb > 12 mg/dl
Oxygen delivery > 700 ml/min
2,3-DPG > 13 mmol/ml
Serum K^+ > 3 mEq/dl
Serum glucose 120–160 mg/dl

Table 38. Algorithm management of hypotension: medication to increase cardiac output and vascular resistance and provide volume replacement

Dosage	Compatible solution	Incompatible drugs
NE 8 mg/250 ml D5W	Aminophyline	Insulin
Low systemic vascular resistence	Amphotericine B	Lidocaine HCl
	Azathioprine Na	Pentobarbital Na
	Folic acid	Phenobarbital Na
	Furosemide	Sodium bicarbonate
E 2 mg/250 ml D5W or NS	Aminophyline	Pentobarbital Na
Bronchiospasm, anaphylactic, septic, or cardiogenic shock	Amphotericine B	Phenobarbital Na
	Imperiling Na	Propofol
	Azathioprine Na	Sodium bicarbonate
	Lidocaine HCl	Warfarin sodium
D 400 mg/250 ml D5W	Acyclovir Na	Cefoperazone Na
3–10 μg/kg min^{-1} β1 and D effects 10–40 μg/kg min^{-1} via α1 sepsis, cardiogenic shock, renal insufficiency	Alteplase	Chloramphenicol Na succinate
	Amphotericine B	
	Imperiling Na	Ganciclovir Na
	Azathioprine Na	Gentamicin sulfate
	Cefazolin Na	Propofol
	Cefepime HCl	Sodium bicarbonate
Dobutrex	Acyclovir Na	Cefuroxine
500 mg/250 mlD5W	Alteplase	Chroramphenicol
Low cardiac output, cardiogenic shock, congestive heart failure, cardiomyopathy	Aminophyline	Digoxin
	Amphotericine B	Folic acid
	Imperiling Na	Furosemide
	Azathioprine Na	Heparine sodium
	Bumetanide	Penicillin G
	Cefazolin Na	Phenobarbital
	Cefepime HCl	Propofol

D5W, Dextrose 5% in water; NS, NaCl 0.9%; D, dopamine

Table 39. Algorithm management of hypotension: complications

Brain ischemia caused by prolonged hypotension
Worsening at rewarming stage with short duration of hypothermia treatment. Short-duration brain hypothermia stops progression of secondary brain damage. The primary brain damage, with not enough recovered neurons, reprogresses at rewarming stage. The rapid pathophysiological changes by rewarming worsen reprogression of primary brain damage
Difficult moderate brain hypothermia treatment (32°–33°C) caused by unstable cardiac function associated with reduced serum catecholamines. The cardiac output is reduced below brain tissue temperature of 33°C
Easy to reduce the platelets and fall in disseminated intravascular coagulopathy by suppression of liver function

DIC, Disseminated intravascular coagulation

Table 40. Alorithm management of hypotension: special considerations

1. Hypotension is major cause of unsuccessful brain hypothermia treatment and elevation of ICP at rewarming stage
2. Main cause of hypotension is different time window and level of lower brain temperature 3–6 h → time

Catecholamine induced cardiomyocontraction and coronary spasm	Blood shift to intestine (bladder temperature > tympanic membrane temperature)
Reduced circulation volume	Reduced CO by moderate brain hypothermia

Management: control BP > 90 mmHg and combination of oxygen management to prevent brain hypoxia

1. Mild brain hypothermia 2. No dehydration therapy 3. Bronchial dilatation with no ATP consumption, intestinal vasodilatation, hypertensive drugs 4. Intermittent elastic bandaging of extremities 5. Flat position	→	1. Moderate hypothermia 2. Increase cardiac output 3. No intestinal vasodilatation hypertensive drugs 4. Increase SVR by elastic bandaging of extremities 5. Flat position depends on ICP elevation

1. Hb > 11–12 mg/dl
2. 2,3-DPG > 14 mmol/ml
3. $\bar{D}O_2$ > 700–800 ml/min
4. Serum glucose 120–150 mg/dl
5. O_2ER 23%–25%
6. Serum K^+ > 3 mEq/dl

CO, Cardiac output; ATP, Adenosine triphosphate; SVR, systemic vascular resistance

Table 41. Algorithm management of hypotension: keywords

Hypothermia
Hypotension
Blood pressure

Table 42. Algorithm management of hypotension: references

1. Kitagawa H, Akiyama T, Yamazaki Mori H, Sunagawa H (2002) Effects of moderate hypothermia on in situ cardiac sympathetic nerve endings. Neurochem Int 40:235–242
2. Laussen PC, Murphy JA, Zurakowski D, Sullivan LJ, McGowan FX Jr, Demaso DR (2001) Bispectral index monitoring in children undergoing mild hypothermic cardiopulmonary bypass. Paediatr Anaesth 11:567–573
3. Mori K, Itoh Y, Saito J, Takeyama Y, Kurata Y, Kaneko M, Asai Y, Torigoe T, Dickson EW (2001) Post-resuscitative hypothermic bypass reduces ischemic brain injury in swine. Acad Emerg Med 8:937–945
4. Nakae Y, Fujita S, Namiki A (2001) Isoproterenol enhances myofilament Ca(2+) sensitivity during hypothermia in isolated guinea pig beating hearts. Anesth Analg 93:846–852
5. Chi OZ, Choi YK, Lee DI, Kim YS, Lee I (2001) Intraoperative mild hypothermia does not increase the plasma concentration of stress hormones during neurosurgery. Can J Anaesth 48:815–818
6. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A (2001) Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. Hepatology 34:50–54
7. Ozaki H, Nagai Y, Tochihara Y (2001) Physiological responses and manual performance in humans following repeated exposure to severe cold at night. Eur J Appl Physiol 84:343–349
8. Xu H, Aibiki M, Seki K, Ogura S, Yokono S, Ogli K (2000) Effects of induced hypothermia on renal sympathetic nerve activity and baroreceptor reflex in urethane-anesthetized rabbits. Crit Care Med 28:3854–3860
9. Weis SJ, Muniz A, Ernst AA, Lippton HL, Nick TG (2000) The effect of prior hypothermia on the physiological response to norepinephrine. Resuscitation 45:201–207
10. Himmelseher S, Pfenninger E (2000) Neuroprotection in neuroanesthesia: current practices in Germany. Anaesthesist 49:412–419
11. Krismer AC, Lindner KH, Kornberger R, Wenzel V, Mueller G, Hund W, Oroszy S, Lurie KG, Mair P (2000) Cardiopulmonary resuscitation during severe hypothermia in pigs: does epinephrine or vasopressin increase coronary perfusion pressure? Anesth Analg 90:69–73
12. Kanstrup IL, Poulsen TD, Hansen JM, Andersen LJ, Bestle MH, Christensen NJ, Olsen NV (1999) Blood pressure and plasma catecholamines in acute and prolonged hypoxia: effects of local hypothermia. J Appl Physiol 87:2053–2058
13. Lesser JB, Koorn R, Vloka JD, Kuroda MM, Thys DM (1999) The interaction of temperature with thiopental and etomidate on extracellular dopamine and glutamate levels in Wistar-Kyoto rats subjected to forebrain ischemia. Acta Anaesthesiol Scand 43:989–998
14. Roscher R, Ingemansson R, Algotsson L, Sjoberg T, Steen S (1999) Effects of dopamine in lung-transplanted pigs at 32 degrees C. Acta Anaesthesiol Scand 43:715–721
15. Weiss SJ, Muniz A, Ernst AA, Lippton HL (1998) The physiological response to norepinephrine during hypothermia and rewarming. Resuscitation 39:189–195
16. Azzam FJ, Fiore AC (1998) Postoperative junctional ectopic tachycardia. Can J Anaesth 45:898–902
17. Sellden E, Lindahl SG (1998) Amino acid-induced thermogenesis to prevent hypothermia during anesthesia is not associated with increased stress response. Anesth Analg 87:637–640
18. De Riva C (1997) Hypoglycaemia unawareness in a young boy with insulin-dependent diabetes mellitus and anti-adrenal medullary antibodies. Diabetes Metab 23:528–532
19. Sellke FW, Tofukuji M, Stamler A, Li J, Wang SY (1997) Beta-adrenergic regulation of the cerebral microcirculation after hypothermic cardiopulmonary bypass. Circulation 96(9 Suppl):II-304–310
20. Roscher R, Ingemansson R, Wetterberg T, Algotsson L, Sjoberg T, Steen S (1997) Contradictory effects of dopamine at 32 degrees C in pigs anesthetized with ketamine. Acta Anaesthesiol Scand 41:1213–1217

Table 43. Algorithm management of ICP elevation: information

- $ICP = \frac{\text{brain volume} + \text{CSF} + \text{Blood dume} + \text{mass lesion}}{\text{volume of cranial cavity}}$
- CPP = MABP – ICP
- Normal value: ICP 10–12 mmHg, CPP > 65–75 mmHg
- Brain edema
  - Cytotoxic edema (brain hypoxia)
  - Vasogenic edema (vascular engorgement)
  - Interstitial edema (BBB destruction)
  - Osmotic edema (hypo-albuminemia <2.5 g/dl)

Brain hypoxia: PaO_2 < 60 mmHg, DPG < 10 mmol/gHb,
Vascular engorgement: disturbed auto regulation + BP elevation, $PaCO_2$ 45–50 mmHg, and SBP > 180 mmHg are trigger factors
BBB destruction: CSF/serum albumin ratio (CSAR) > 0.01,
CSAR > 0.02 severe BBB dysfunction
Osmotic edema: severe hypo-albuminemia (serum albumin < 2.5 g/dl)

- Water filtration (WF) rate in the brain capillary

WF = K [(vascular pressure-tissue pressure) – (serum osmotic pressure-tissue osmotic pressure)]

Arterial side capillary pressure = 35–40 mmHg
Venous side capillary pressure = 12–20 mmHg
Brain tissue pressure = 8 mmHg
Serum osmotic pressure = 25 mmHg
Tissue osmotic pressure = 5 mmHg
→ Interstitial water is removed to venous root by –7 mmHg pressure

- ICP elevation occurs with brain edema, hydrocephalus, vascular engorgement, mass lesion such as hematoma, and cranial decompression

MABP, Mean arterial blood pressure

Table 44. Algorithm management of ICP elevation: diagnosis

Clinical signs and symptom of ICP elevation	
Headache	
Vomiting	
Disappearance of venous pulsation of eye base → choked disc	
Tympanic membrane temperature is lower than core temperature	
ICP monitor	
CSF ventricular pressure	
Epidural pressure	
Brain tissue pressure	
Calibration of zero point of ICP	
Closed skull	height of III ventricle
Semi closed decompressed external skull bone	height of heart
ICP elevation	more than 20 mmHg
Evaluation of ICP	
Closed skull	all kinds of ICP monitoring are useful
Semi-closed skull bone	CSF ventricular pressure is only available
Effect of atmospheric air pressure	
More than 1010 hPa produces compression of brain	
Less than 1010 hPa activates brain explosion through skull cavity	

Table 45. Algorithm management of ICP elevation: pathophysiology

ICP elevation and pathophysiological changes	
ICP	Pathophysiological changes
20–25 mmHg	Venous stasis, plasma skimming, heterogeneous hypoxia
25–30 mmHg	Disturbances of microcirculation, plasma skimming brain hypoxia, intercompartment pressure difference
30–45 mmHg	CBF disturbances, disturbances of autoregulation herniation
>45 mmHg	Poor filling and nonfilling
Time course	
Acute brain swelling (few seconds)	
Brain edema (peak 24–48 h)	
Severe BBB damage: (CSF albumin/serum albumin ratio > 0.02)	
Serum cytokines (proinflammatory cytokines, helper T-cell induced cytokines, and anti-inflammatory cytokines) directly affect the injured brain tissue	
Herniation	
Brain stem death	
Effect of pathophysiology by original diseases	

Table 46. Algorithm management of ICP elevation: basic management

Direct management of ICP elevation
Remove hematoma and large external decompression that includes lower temporal lobe
Head-up position (CPP > 80 mmHg)
Management of hypo-albuminemia (serum albumin > 3.5 g/dl)
Hyperosmotic, diuretic therapy
Manitol > glycerol (not indicated at hyperglycemia)
Suppress the CSF production
Furosemide, lasix
Management of promoting factors
Prevent bronchial obstruction
Lower PEEP (<7 cmH_2O)
Lower mediastinal pressure (<15 mmHg)
Prevent abdominal hypertension (<15 mmHg)
Urinary catheter, gastric tube, and ileum tube
$PaCO_2$ 25–35 mmHg
Maintain adequate CPP (80–100 mmHg)
Elastic bandaging of extremities
Abdominal aorta balloon catheter
Management of masking brain hypoxia
SaO_2 > 98%, FiO_2/PaO_2 > 350
$\bar{D}O_2$ > 700–800 ml/min, DO_2I > 600 ml/min
pH > 7.3
DPG 10–15 mmol/gHb
Gastric pHi > 7.3
Hb > 11–12 mg/dl
AT-III > 100%
$ETCO_2$ 32%–38%

PEEP, Positive endo-expiratory pressure

Table 47. Algorithm management of ICP elevation: medication

Direct pharmacological management of ICP elevation	
Hyperosmotic, diuretic fluid administration	
Manitol and glycerol	
Suppression of CSF production	
Furosemide and lasix	
Anti-edema	Albumin infusion
Prevent IL1, TNF cytokines	
Steroid	Not indicated at hyperglycemia (>180 mg/dl)
Stabilization of ICP	
Anesthesia combination with analgesia	
Midazolum (use at serum albumin > 3.5 g/dl)	
Propofol	
Muscle relaxation	
Maintaine adequate CPP (80–100 mmHg)	
Prevent excess blood shunt to intestine	
Vasopressin > NE	
Management of masking brain hypoxia	
$\bar{D}O_2$ > 800 ml/min	Doptorex + NE
pH > 7.3	$NaHCO_3$
DPG 10–15 µmol/gHb	K_2HPO_4, inosin IV
Gastric pHi > 7.3	AT-III > 100%
Hb > 11–12 mg/dl	Reserved blood (check the DPG and temperature > 32°C)
SBP > 100 mmHg	NE > D > vasopressin > E

Table 48. Algorithm management of ICP elevation: complications

	ICP elevation	
ICP		
20–25 mmHg		Venous stasis
25–35 mmHg		CBF disturbances
		Intercompartment pressure difference
		Microembolus (plasma skimming)
		AT-III consumption
>35 mmHg	↓	Unconsiousness
	Herniation	
	Brain stem damage	
>45 mmHg		Coma > anisocolia > bilateral pupil dilatation > breathing arrest
	↓	Poor filling
		Non filling
	No recovery	

Table 49. Algorithm management of ICP elevation: special considerations

Surgical considerations
Before surgery: elastic bandage to the legs and, if possible, insert the aorta balloon catheter to prevent brain ischemia
Surgical position: semi-sitting 30–40 degree head-up position
Large external decompression
When brain swelling or not enough brain decompression are observed, other side routine craniotomy should be considered
Low temperature irrigation saline to prevent brain thermo-pooling
Normal oxygen delivery and replacement of DPG
ICU management after surgery
Initial stage (within 3–6 h): prevent masking brain hypoxia and ischemia
After vital signstadization, biochemial examination, and neurological examination (loss of opthalmic venous pulsation), midazolam-combined analgesia and anti-muscle relaxant addition, one-shot corticosteroid addition for prevention of proinflammatory cytokines
No head-up position, prevent airway obstruction, Hb > 11 g/dl, $PaCO_2$ 34–38 mmHg, SaO_2 > 98%, $ETCO_2$ 32%–39%, SjO_2 65%–75% (SjO_2 < 55%)
SBP > 100 mmHg and DPG > 10 mmol/gHb, BT control about at 34°C and CPP > 70% (if BT > 38°C CPP > 80 mmHg), no dehydration fluid resuscitation
After Swan Ganz catheter monitor $\bar{D}O_2I$ > 600 ml/min, O_2ER 23%–25%, O_2ER < 18% replacement of DPG, prevent abdominal hypertension, replacement of magnesium
ICP < 20 mmHg (Camino ICP senser is not available to external decompressed cases, Spiegel berg ICP or ventricular CSF monitor is recommended)
After stabilizing brain oxygenation, BT reduce to 32°C–33°C/5–6 h (if arrythmia and elongation QT > 450 mm/s, BT 34°C)
Second Stage (after 6–12 h)
Serum albumin control at > 3.5 mg/dl (or > 3 mg/dl)
ICP 20–25 mmHg (10–15 degree head-up position > manitol addition > fluosemide addition CSF drainage)
Prolonged 20–25 mmHg requires CT-scan examination
CSF/serum albumin ratio > 0.02 requires high dose of corticosteroid addition and management of systemic cytokine reactions

CT, Computed tomography

Table 50. Algorithm management of ICP elevation: keywords

Hypothermia
ICP
Brain edema

cytokine chemical encephalitis are major clinical issues complicated by severe pneumonia. Cytokine chemical encephalitis is very difficult to manage because this complication involves severe BBB dysfunction, progression of brain edema, and uncontrollable increases in neurotoxic glutamate even with moderate brain hypothermia. Therefore, the complication of pneumonia can cause unsuccessful brain hypothermia management. The management of pneumonia is a key point for the success of brain hypothermia management. In our ICU, the complication of pneumonia was 64% 10 years ago, at the initial stage of brain hypothermia ICU management; however, this complication has reduced to about 5%–8% because of hypothermia-specific infectious management as described in this section. The algorithm management cards for pneumonia are shown in Tables 52–60.

Table 51. Algorithm management of ICP elevation: references

1. Steiner T, Ringleb P, Hacke W (2001) Treatment options for large hemispheric stroke. Neurology 57(5 Suppl 2):S61–68
2. Schneweis S, Grond M, Staub F, Brinker G, Neveling M, Dohmen C, Graf R, Heiss WD (2001) Predictive value of neurochemical monitoring in large middle cerebral artery infarction. Stroke 32:1863–1867
3. Chung C, Gottstein J, Blei AT (2001) Indomethacin prevents the development of experimental ammonia-induced brain edema in rats after portacaval anastomosis. Hepatology 34:249–254
4. Kawai N, Nakamura T, Okauchi M, Nagao S (2000) Effects of hypothermia on intracranial pressure and brain edema formation: studies in a rat acute subdural hematoma model. J Neurotrauma 17:193–202
5. Hayashi N (2000) Brain hypothermia treatment for the management of severe pediatric brain injury. No To Hattatsu 32:122–131
6. Schwab S, Hacke W (1999) Therapy of increased intracranial pressure in space-occupying media infarcts. Z Arztl Fortbild Qualitatssich 93:203–208
7. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W (1998) Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 29:2461–2466
8. Oriot D, Nassimi A (1998) Intracranial hypertension in the infant: from its physiopathology to its therapeutic management. Arch Pediatr 5:773–782
9. Ichai C, Ciais JF, Grimaud D (1997) The internal environment and intracranial hypertension. Ann Fr Anesth Reanim 16:435–444
10. Arkadopoulos N, Chen SC, Khalili TM, Detry O, Hewitt WR, Lilja H, Kamachi H, Petrovic L, Mullon CJ, Demetriou AA, Rozga J (1998) Transplantation of hepatocytes for prevention of intracranial hypertension in pigs with ischemic liver failure. Cell Transplant 7:357–363
11. Shiozaki T, Sugimoto H, Taneda M, Oda J, Tanaka H, Hiraide A, Shimazu T (1998) Selection of severely head injured patients for mild hypothermia therapy. J Neurosurg 89:206–211
12. Hayashi N (1998) The control of brain tissue temperature and stimulation of dopamine-immune system to the severe brain injury patients. Nippon Rinsho 56:1627–1635
13. Gayle MO, Frewen TC, Armstrong RF, Gilbert JJ, Kronick JB, Kissoon N, Lee R, Tiffin N, Brown T (1989) Venous bulb catheterization in infants and children. Crit Care Med 17:385–388
14. Nordby HK, Nesbakken R (1984) The effect of high dose barbiturate decompression after severe head injury. A controlled clinical trial. Acta Neurochir (Wien) 72:157–166
15. Kassell NF, Peerless SJ, Drake CG, Boarini DJ, Adams HP (1980) Treatment of ischemic deficits from cerebral vasospasm with high dose barbiturate therapy. Neurosurgery 7:593–597

Table 52. Algorithm management of pneumonia: information

Pneumonia is acute infection including alveolar space and interstitial tissue. The type is classified by etiology, infectious pattern, and epidemiology
- Etiology
  - Infectious pneumonia
    - Triggered by immune reduction and respiratory weakness
  - Aspiration pneumonia
    - Two causes: acid gastric juice chemical pneumonia and intestinal bacteria pneumonia, triggered by vomiting
- Infectious pattern
  - Lobular pneumonia
  - Segmental or lobular pneumonia
    - X ray observation
  - Bronchoi pneumonia
  - Interstitial pneumonia
- Epidemiology
  - Pneumococcal pneumonia
    - Most common (60%), about 10% mortality
  - Streptococcus pneumonia
    - 10%–15% of nosocomical pneumonia, 35% mortality
  - Pseudomonas pneumonia
    - Common with aspiration pneumonia
  - Other pathogen
    - *Staphylococcus aureus*, *Hemophilus influenzae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*
  - Influenza virus A pneumonia

Table 53. Algorithm management of pneumonia: diagnosis

Diagnosis is based on the characteristic symptoms combined with an infiltrate on chest X-ray. About 30%–50% of patients have no identifiable pathogen despite clinical signs. The bacterial culture studies of sputum and blood are important.
- Lung
  - CRP: C reactive protein (standard; 100)
    - Pneumococcal pneumonia
  - Gram stain, TB stain
    - TB, Chlamydia, Legionella, Mycoplasma
  - Candidia antibody
    - Lactic coagulation reaction <2. Neutropenia is a danger factor
  - Fungal infection
    - Antibacterial therapy, altered host defense mechanism are common causes. Kelatomycosis is common clinical sign
  - Mycoplasma
    - High incidence in hypothermia by reduced CD4 activity and growth hormone. X-ray: patchy bronchio pneumonia in the lower lobes. Pleura effusion and lobular consideration is not common
  - Virus infection
    - Diffuse interstitial infiltration pattern
- Immune function
  - Lymphocytopenia (<1500 mm^3) shows the reduction of immune function
    - Lymphocyte: T-cell (55–80%) and B-cell (5%–20%) normal
    - Immune function: CD_3 58%–88%, CD_4 25%–55%, CD_8 17%–44%, NK-cell 45 ± 5 (M), 30 ± 5 (F)
- Special consideration of brain hypothermia
  - Growth hormone reduction, CD4 immune suppression
  - Effect of albumin-binding type antibiotics reduced by hypo-albuminemia

Table 54. Algorithm management of pneumonia: pathophysiology

Pneumonia	Danger factor	Injured brain
• PaO_2 < 60 mmHg • $\bar{D}O_2$ < 700–800 ml/min • pH < 7.2	Low Hb-DPG →	Neuronal hypoxia
• Elevation of body temperature	SBP < 100 mmHg →	Thermo-pooling
• Increasing of inflammatory cytokines	BBB destruction →	Cytokines encephalitis
	CSF/serum albumin ratio > 0.01	

Danger signs: immature neutrophils, acute renal failure, albumin < 3 g/dl, Ca > 6 mg/dl, creatinine > 5 mg/dl

Table 55. Algorithm management of pneumonia: basic management

Clean nasal-oral cavity, trachea and bronchus. Strong aspiration should be delayed
O_2ER 20%–25%, Hb >11–12 mg/dl, Ht < 40%
Serum albumin > 3.5 mg/dl
Gastric lavage, abdominal pressure < 15 mmHg, gastric juice pH < 3
Gastric wall pHi > 7.3, AT-III > 100%, Ht < 40%
Immune activation: arginine + arginine + IGF1
Antibiotic therapy
Respiratory rehabilitation
Early skeletal muscle massage and activate protein synthesis by sorbutamol and arginine
Enteral immune nutrition (glutamine + Arginine + $ZnCl_2$)
Prevent ventilator associated pneumonia (VAP): high incidence in parasinusitis
- Early onset VAP
  - Pneumococcus and influenza
- Late onset VAP
  - MRSA, Pseudomonas, Enterobactor
- Cuff pressure < 30 cmH_2O

Management of ventilator

Table 56. Algorithm management of pneumonia: medication

Pneumococcal pneumonia (most common, 5%–25% oral ex)
  Penicillin G (PG) 500000 to 2 million U i.v. every 4–6 h > oxacillin 2 g i.v. every 4–6 h (25% P-resisted) > vancomycin 1 g i.v. every 12 h. Alternative drugs: cephalosporin (CP), erythromycin (EM), clindamycin (CM). Oral treatment: CM 300 mg every 6 h. If meningitis is suspected cefotaxime 2 g i.v. every 4 to 6 h + vancomycin 1 g i.v. every 12 h
Streptococcal pneumonia
  PG 500000 to 1 million U i.v. every 4 to 6 h (or CP + CM)
Staphylococcus aureus (after influenza, 30%–40% serious)
  Penicillinase resistant penicillin: oxacillin or nafcillin 2 g i.v. every 4 to 6 h (alternate: cephalothin 2 g i.v. every 4 to 6 h) > vancomycin 1 g i.v. every 12 h (30%–40% Methicillin resistant strains)
Hemophilia influenza (30% b-lactamase resist)
  Trimethoprim-sulfamethoxazole (TMP-SMX) 20 mg/kg per day, cefuroxamine 0.25–1 g i.v. every 6 h
Fungal pneumonia
  Fluconazole 200–800 mg/day > amphotericin B 0.4 mg/kg per day prevent: ketoconazole 200 mg/day + clotrimazole 10 mg every 8 h
Legionairres disease
  EM 1 g i.v. every 6 h start > rifampin 300 mg i.v.
Chlamydia pneumonia
  Tetracycline or EM 10–20 days
Carini pneumonia
  TMP-SMX 20 mg/kg per day

Steroids effective: high IL1/IL10 and IL1/IL2. Colitis: sulfasalazine 1–3 g/day. Immunological replacement: GH, IGF-1, IL10 (iv), early muscle massage, replacement of early enteral globulin

Table 57. Algorithm management of pneumonia: complications

Adult respiratory distress syndrome (ARDS): PaO_2/FiO_2 < 200 mmHg, low lung compliance, bilateral diffuse chest infiltration, PCWP < 18 mmHg
  Treatment: 1. Avoid risk factors 2. Increase FiO_2, PEEP < 5 cmH_2O, keep plateau pressure < 35 mmHg, permissive hypercapnia, adequate fluid management, maximize O_2 delivery, avoid MSOF, nutritional support
  Pleuritis: pancreatitis, subphrenics abscess, lymph obstruction, hypo-albuminemia (serum albumin < 2.5 mg/dl, TP < 3 mg/dl)
Bacterial endocarditis: usually caused by streptococcal infection. Signs: valve dysfunction, hypertrophic cardiomyophathy, arrhythmia
  Treatment: PG 500000 to 1 million U i.v. every 4 to 6 h (or CP + CM). P-resistant streptococci: PG 18–20 million U/day i.v. (ampicillin 12 g/day i.v. every 4 h) + gentamycine 1 mg/kg i.v. every for 4–6 weeks
Liver and intestinal congestion: PEEP >10 cmH_2O
ICP elevation: CVP and abdominal pressure >25 mmHg
Sepsis: SIRS, lactoacidosis, organs dysfunction
  Treatment: 1. Preferable antibiotics 2. Circulation toxins should be neutralized by antibiotics or γ-globulin 3. Circulating cytokines should be neutralized
  Toxic shock: streptococcal toxin is common. Acute renal failure > hypoalbuminemia > hypocalcamia > shock. Clindamycine suppress bacterial toxin. *S. aureus*: flucloxacillin and gentamycin may inhibit toxin product. Intravenous immunoglobulin neutrize toxins in both staphylococcal and streptococcal
Ventilator complications: decrease venous return to the thorax, CO, BP (by high inspiratory pressure, hypovolemia, and muscle weakness)
  Barotraumas: pressure >35 cmH_2O (alveoli pressure) and PEEP is insufficient to collapse lungs

Table 58. Algorithm management of pneumonia: special considerations

Induction stage
Clean nasal-oral cavity
Gastric lavage
Digestive decontamination (levofloxacin (Cravit, 200 mg) + Amphotericin B 100–300 mg) to prevent pseudomonas aspiation pneumonia and enterobacterial translocation
Antibiotics (panipenem betamipron (Carbenin 500 mg × 2/day), or second choice: ceftazidinme (Modasin 1 g ×2/day) or clindamycine (Dalacin, 150–300 mg every 6 h)
$\bar{D}O_2I$ >600 ml/min, $\bar{D}O_2$ > 700 ml/min
Cooling stage
Nasal-oral cavity management
Gastric juice pH < 3.5
Prevent abdominal hypertension < 10 mmHg
Antibiotics: immipenem cilastain sodium (Tienam 1–2 g/day × 3) > meropenem trihydrate (Meropn, 1.0–2.0 g/day × 4) for enterobacteria, gram-negative bacteria and pseudomonas
AT-III > 80%–100% and gastric pHi > 7.3
Gastric immune nutrition replacement > nutrition care
Ventilator care and urinary care
Breathing rehabilitation (alveolar dysfunction, atelectasis)
Intermittent elevation of BT from 32°C to 34°C at evening
Replacement of ZnCl, arginine with Hb > 11 g/dl (if lymph-cytopenia occurred, BT keep at 34°C + GH + γ-globulin addition)
Serum albumin >3.5 mg/dl
Low dosage of antidotes
O_2ER 23%–25%, 2,3-DPG 15-10 mmol/gHb
Prerewarming stage
Preconditioning: no severe infection, serum glucose < 150 mg/dl, vitamin A >50 mg/dl, lymphocyte >1500/mm^3, serum albumin >3.5 mg/dl (prealbumin >20 mg/dl), Hb >12 g/dl, DPG >10 mmol/gHb, AT-III 100%, platelet 50000–80000, GDC, muscle massage, abdominal pressure <10 mmHg
Antibiotics: arbekacin sulfate (Habekacin, 150–200 mg/day × 2) to prevent pseudomonal aerginosa and MRSA infection, + cefozopran hydrochloride (Firstcin 1–2 g/day × 2) for Tienam-resisted acinetobacter and xantomona + fluconazole (Diflucan 100–200 mg/day × 1) for Candida with evidence of β-D-glucan positive reactions)
Digestive decontamination for control of clostridium enteritis and MRSA, enteral administration of levofloxacin (Cravit, 200 mg) and amphotericin B (100–300 mg), combined with vancomycin (2–3 g/day ×4–6 times i.v. drip)
$\bar{D}O_2$ > 700 ml/min, O_2ER 23%–25%
Rewarming stage
Slow step-up rewarming
Prevent rapid shift from lipid to glucose metabolism
Control of serum glucose: 140–170 mg/dl
O_2ER 23%–25%
Management of neuromuscular junction
34–35°C BT keep for 2–3 days and BT > 36°C and then stop muscle relaxant > anesthesia
Nutritional management
Antibiotics: Habekacin, 150–200 mg/day × 2 to prevent pseudomonal aerginosa and MRSA infection, + cefozopran hydrochloride (Firstcin 1–2 g/day × 2) for Tienam-resisted acinetobacter + fluconazole (Diflucan 100–200 mg/day × 1) for Candida with evidence of β-D-glucan positive reactions

The pulmonary care management is variable at each stage of brain hypothermia treatment

Table 59. Algorithm management of pneumonia: keywords

Hypothermia
Pneumonia
Infection
Sepsis

Table 60. Algorithm management of pneumonia: references

1. Saito T, Otsuka A, Kurashima A, Watanabe M, Aoki S, Harada A (2001) Study of lymphocyte and NK cell activity during mild hypothermia therapy. No Shinkei Geka 29:633–639
2. Matthys D, Verhaaren H, Deryck Y (1995) Fatal pneumonia complicating hypothermia for the treatment of postoperative junctional ectopic tachycardia. Pediatr Cardiol 16:294–296
3. Wetterberg T, Steen S (1992) Combined use of hypothermia and buffering in the treatment of critical respiratory failure. Acta Anaesthesiol Scand 36:490–492. PMID: 1632175 [PubMed—indexed for MEDLINE]
4. Okada M, Nishimura F (1990) Respiratory function and acid-base status in accidental hypothermia assessed by arterial blood gas analysis. Jpn J Med 29:500–505. PMID: 2128523 [PubMed—indexed for MEDLINE]
5. Clardy CW, Edwards KM, Gay JC (1985) Increased susceptibility to infection in hypothermic children: possible role of acquired neutrophil dysfunction. Pediatr Infect Dis 4:379–382. PMID: 2991867 [PubMed—indexed for MEDLINE]
6. El-Radhi AS, Jawad MH, Mansor N, Ibrahim M, Jamil II (1983) Infection in neonatal hypothermia. Arch Dis Child 58:143–145. PMID: 6338837 [PubMed—indexed for MEDLINE]
7. Edlich RF, Lande AJ, Goodale RL, Wangensteen OH (1968) Prevention of aspiration pneumonia by continuous esophageal aspiration during esophagogastric tamponade and gastric cooling. Surgery 64:405–408. No abstract available PMID: 5302564 [PubMed—indexed for MEDLINE]
8. Jones RH, Bourdillon RE, Finn R, Martindale K (1966) Hypothemia associated with pneumonia and acidosis. Postgrad Med J 42:273–275. No abstract available. PMID: 5938611 [PubMed—indexed for MEDLINE]

Algorithm for Malnutrition and Diarrhea

The management of digestive organs is important for maintaining immune function, prevention of infections, and to determine pharmacological medication. The intestine is very sensitive to catecholamine surge, disturbances of microcirculation caused by reduced AT-III, osmotic gap, hypo-albuminemia, fecal impaction, and medication. The algorithm management cards for diarrhea and malnutrition are shown in Tables 61–69.

Algorithm for Renal Insufficiency

Acute renal failure can be categorized as prerenal, postrenal, or renal. In the management of brain hypothermia treatment, prerenal and renal failure are

Table 61. Algorithm management of diarrhea and nutrition: information

Causes of diarrhea
Enterocolitis and MOF
Medication-induced diarrhea
Antibiotics; 50% have C. difficile toxins
Additives: sorbitol, manitol, xylitol
Antacids containing magnesium
Asthma medication, e.g., thephyline
Cardiac medication: quinidine, procaineamide, digoxin
Antihypertensive drugs: angiotensin-converting enzyme inhibitors, β-blockers, hydralazine, guanethidine
Diuretics: flosemide, thiazides
Cholesterol medications
Thyroid hormone
Gastrointestinal medications: H2-blockers, metaclopramide, misoprostol
Enteral feeding and osmotic gap diarrhea
Osmotic gap: greater than 100 mOsm/kg and low fecal pH
Hypo-albuminemia
Serum albumin: <2.5 g/dl make subumucosal oncotic pressure reduce and lead to edema of intestinal mucosa (difficult absorption of feeding)
Mesenteric ischemia
Diagnose: gastric pHi < 7.3, AT-III < 70%, leukocytopenia, acidosis, venous thrombosis, hypercoaguable state
Fecal impaction caused by medications
Medications: narcotics, antihypertensives, diuretic, aluminum antacids

Table 62. Algorithm management of diarrhea and nutrition: diagnosis

Nutrition
Metabolic shift occurs from glucose to lipid following brain hypothermia treatment
The balance of glucose to lipid metabolism is equal at 34°C
Lipid metabolism becomes dominant at 32°–33°C
Rapid induction of 33°–34°C produces increasing serum glucose. Unsuccessful care management of catecholamine surge by delayed induction hypothermia also produces stress related-hyperglycemia. Therefore, combination of delayed start of hypothermia and rapid induction of hypothermia produce very dangerous insulin-resistant hyperglycemia
Insulin-resistant hyperglycemia induces vasopressin release and activates BBB dysfunction
The calorie deficit is not a major issue
The lipid metabolism requires vitamin A and growth hormone. The rehabilitation and massage of brown cells are required to maintain energy metabolism during brain hypothermia treatment
The management of serum phosphate (3–5 mg/dl) and magnesium (1.5–1.8 mEq/dl) are also effective to control lipid membrane metabolism
Diagnosis of malnutrition
Muscle degradation, edema of leg, ascitis, hypo-albuminemia (<2.5 g/dl), more than 10 weight loss, intestinal mucous membrane edema, pancreatic duct obstruction and prolonged diarrhea are diagnostic criteria

Table 63. Algorithm management of diarrhea and nutrition: pathophysiology

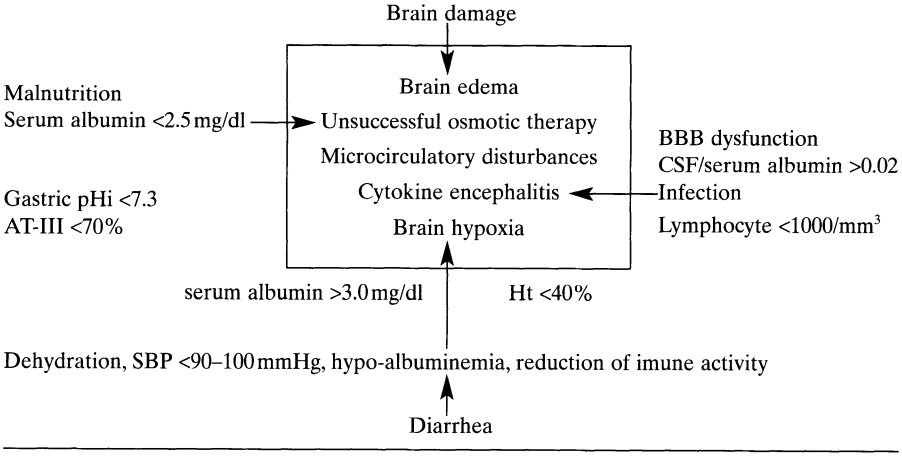


Table 64. Algorithm management of diarrhea and nutrition: basic management

Remove the causes of diarrhea
  Antibiotic-associated diarrhea: stop the antibiotics, metronidazole 250 mg pr qi, (severe cases i.v.) > oral, vancomycin 125 mg qid, because high incidence of C. difficile are complicated
Before feeding care management
  Serum albumin > 3.5 mg/dl, At-III > 100%, Ht 34%–36%
  Preliminary feeding: glutamine with arginine (ET)
  Correct serum electrolytes
  Management of mesenteric ischemia
Feeding care management
  No severe BBB dysfunction (CSF/serum albumin ratio <0.01): early enteral nutrition
  Severe BBB dysfunction (CSF/serum albumin > 0.01): two-step enteral nutrition
    First step: saline feed, control of intestinal pressure, $ZnCl_2$
    Second step (4–5 days later): immune nutrition and then follow with enteral nutrition
  Management of diarrhea: reduce the feeding volume, isotonic fluid infusion
  Control of osmotic gap between serum and stool
    Osmotic gap, → serum Osm–2 (stool Na + K) > 100 mOsm/kg
Fecal impaction
  Gentle enema is usually effective
  DD: diagnose lower anal sphincter pressure

Table 65. Algorithm management of diarrhea and nutrition: medication

Treatment of underlying disorder
  AT-III i.v. infusion
  Replacement of serum albumin
  Metronidazole 250 mg i.v.
  Oral vancomycin 125 mg qid
Symptomatic treatment
  Increase intestinal transit time
    Diphenoxylate 2.5–5 mg tid or qid
    Codeine phosphate 15–30 mg bid or tid
    Loperamide hydrochloride 2–4 mg tid or qid
    Anticholinergics (atropine) can decrease peristalsis
  Electrolyte fluid replacement
    Urgent fluid and electrolyte replacement
    NaCl, KCl, glucose and fluids to counteract acidosis
    Oral glucose electrolyte solutions
Malnutrition
  Immune nutrition
    Glutamine + arginine + ω2 or 3 food (ET)

Table 66. Algorithm management of diarrhea and nutrition: complications

Complication	Clinical index
Dehydration and hemoconcentration	Ht > 45%
Acidosis	pH < 7.2, $PaCO_2$ < 23 mmHg
Disturbances of microcirculation	Gastric pHi < 7.3
	SjO_2 < 55%
Organ ischemia and hypoxia	pH < 7.2
	2,3-DPG < 10 μmol/gHb
	SaO_2 > 85%
	Gastric pHi < 7.3
Immune dysfunction	Serum albumin < 2.5 mg/dl
	Total protein < 4.9 g/dl
	Transferin < 140 μg/dl
	Cholesterol < 90 mg/dl
No effect of hyperosmotic therapy for brain edema	Serum albumin < 2.5 mg/dl

Table 67. Algorithm management of diarrhea and nutrition: special considerations

Prophylactic management for malnutrition and diarrhea
  Maintain circulation of the digestive organs
    Ht: 34%–36%
    AT-III > 100%
    SBP > 100 mmHg
    Gastric pHi > 7.3
    (Serum Osm.) – 2(stool Na + K) < 100 Osm/kg
    Abdominal pressure or bladder pressure < 10 mmHg
    Reduce the intestinal luminar pressure through the ileum tube
    Kinetic therapy
  Enteral nutrition
    Early enteral nutrition for patients of CSF/serum albumin < 0.01
      Saline → immune nutrition (glutamine + arginine + yeast RNA) → honey yogurt
    Two-step enteral nutrition for patients of CSF/serum albumin > 0.01
      First step: saline 50 ml to max 150 ml/4 h, and remove retention fluid → repeat for 3–4 days
      Second stage: honey yogurt
        Administration method: single administration and remove retention enteral food
        Dosage: start from 50 ml to max 150 ml/4 h
  Control of diarrhea
    Antibiotic-associated diarrhea: stop the antibiotics, metronidazole 250 mg pr qi, (severe case i.v.) > oral, vancomycin 125 mg qid, because high incidence of C. difficile are complicated
    Management of osmotic gap diarrhea
    Management of mesenteric ischemia
    Reduce feeding volume and isotonic fluid infusion

Table 68. Algorithm management of diarrhea and nutrition: keywords

Hypothermia
Nutrition
Diarrhea
Bacterial translocation

Table 69. Algorithm management of diarrhea and nutrition: references

1. Lichtenstein A, Onuchic LF, Rocha Ados S (1990) Accidental hypothermia: glycemic, hematologic and blood amylase changes. Rev Hosp Clin Fac Med Sao Paulo. 45: 173–177. Review. Portuguese. PMID: 1726374 [PubMed—indexed for MEDLINE]

Table 70. Algorithm management of acute renal failure: information

Clinical conditions associated with rapid, steadily decreasing renal function (azotemia), with or without oliguria
Classification and etiology
- Prerenal type
  - ECF volume depletion: excessive diuresis, hemorrhage, GI loss, transcellular fluid accumulation
  - Low cardiac output: cardiomyopathy, AMI, pulmonary embolism
  - Lower systemic VR: sepsis, liver failure
  - Increase renal VR: liver failure, renal vein thrombosis, cyclosporine
- Renal type
  - Acute tubular injury: ischemia, toxins (aminoglycosides, β-lactam antibiotics, amphotericin, foscarnet, radiocontrast, cyclosporin-B, myoglobinuria, heavy metal, methotrexate)
  - Acute glomerulonephritis: antineutrophil cytoplasmic antibody-associated (cresentic glomerulonephritis, Wagener's GN)
  - Acute tubulointerstitial nephritis: drug reaction (β-lactams, NSAIDs, sulfonamides, phenytoin, allopurinol), pyelonephritis
- Postrenal type
  - Ureteral obstruction and bladder obstruction

Table 72. Algorithm management of acute renal failure pathophysiology

Prerenal type
- Oliguria (urine < 500 ml/day)
- Normal response to ineffective circulating blood volume

Renal type
- Renal blood flow reduction, reduced glomerular permeability, tubular obstruction, and hypofiltration

Hypocalcemia
Hyperphosphatemia → Reduced calcitriol → Ca deposition in muscle, intestine, and kidneys → Immune dysfunction
Hyperparathyroidism → Brain edema, Multiple small emboli, Malnutrition, Hemoglobin dysfunction and neuronal hypoxia, Easy infection, Multiple major organ failure

Table 71. Algorithm management of acute renal failure: diagnosis

Index	Prerenal	Renal	Post renal	AGN
U/P osmolarity	>1.5	1–1.5	1–1.5	1–1.5
Urine Na (mmol/l)	<20	40>	40>	<30
Fractional excretion of Na (EF_{Na})	<0.01	>0.04	>0.02	<0.01
Renal failure index (Urine Na ÷ U/P creatinine ratio)	<1	>2	>2	<1

Modest daily rise: serum creatinine, 1–2 mg/dl; urea nitrogen, 10–20 mg/dl. Special considerations to cause: serum creatinine >2 mg/dl→rhabdomyolysis EF_{Na}, Urine Na ÷ U/P creatinine; U/P, urine/plasma ratio; AGN, acute glomerulonephritis

Table 73. Algorithm management of acute renal failure: basic management

Proper maintenance of normal fluid balance, blood volume, and BP
Vasopressor drugs
- Dopamine 1–3 μg/kg min^{-1} i.v.
- Furosemide with manitol or dopamine

Avoid dehydration and ECF depletion
Urography and angiography should be avoided
Dialysis
- Hemodialysis is effective for renal insufficiency; however, for the management of severe brain damage, special consideration is required
- Hyperosmotic management is necessary before the induction of hemodialysis by replacement of albumin and manitol
- All renally excreted substances such as digoxin and antibiotics must be adjusted
- To reduce nitrogen loss, administer i.v. essential amino acids
- Management of hyperphosphatemia
- Management of hyperkalemia
- Management of extra cellular volume, osmolality, acid–base balance, and K balance

Table 74. Algorithm management of acute renal failure: medication

Dopamine
- To increase renal blood flow: 1–3 μg/kg min^{-1} i.v.
- To increase urine output: low dosage 0.5–3 μg/kg min^{-1}
- To increase cardiac output: moderate 5–10 μg/kg min^{-1}
- Max: 40 μg/kg min^{-1}
  - Stimulate receptors primarily in the renal, splanchnic, and coronary vascular beds and increase blood flow

Furosemide
- Typically furosemide is initiated as 20–40 mg by direct intravenous injection over 2 min
- A continuous intravenous infusion of 0.25–0.75 mg/kg h^{-1} for no response to direct injection
- Renal dysfunction requires more than 100 mg initial high doses furosemide
- Compatible drugs: gentamicin sulfate heparin sodium, hydrocortisone sodium succinate, meropenem, tobramycin sulfate

Table 75. Algorithm management of acute renal failure: complications

Brain damage caused by renal failure
Brain edema
Multiple small emboli
Malnutrition of neuronal cells
Neuronal hypoxia by hemoglobin dysfunction
Easy brain infection
Brain damage caused by ARF disease
CBF disturbances by hypovolemia
Disturbance of microcirculation
Severe metabolic acidosis
Neuronal dysfunction by hypocalcemia
Systemic complications
Multiple major organ failure
Easy infection
Immune suppression

Table 76. Algorithm management of acute renal failure: special considerations

Care management
Avoid the causes of acute renal failure
Careful administration of prolonged renal toxic medication
Avoid drugs incompatible with renal function
Acute renal failure should be managed without dialysis for severe brain damage under brain hypothermia only when dialysis is unavailable
Dialysis promotes hypo-albuminemia and brain edema
Dialysis needs preconditioning for replacement of albumin
Dialysis causes the loss of DPG and causes neuronal hypoxia even with normal PaO_2 and oxygen delivery

clinical issues in severely brain-injured patients. Rhabdomyolysis caused by extracellular volume depletion, low cardiac output, low systemic vascular resistance, and increased renal vascular resistance are major causes of acute prerenal failure. Stress-associated hyperglycemia and vasopressin release are trigger factors to reduce the glomerular filtration rate in the acute stage of severe brain damage caused by trauma, stroke, or cardiac-arrested brain ischemia. The causes of acute renal failure are categorized as acute tubular injury, acute glomerulonephritis, acute tubulointerstitial nephritis, and acute vascular nephropathy. During brain hypothermia treatment, drug reaction by antibiotics, hypocalcemia, striated muscle trauma, and radio contrast examination are the main causes of acute renal failure. The algorithm management cards for acute renal failure are shown in Tables 70–78.

Table 77. Algorithm management of acute renal failure: keywords

Severe brain damage
Hypothermia
Acute renal failure
Hemodialysis

Table 78. Algorithm management of acute renal failure: references

1. Hekmat K, Abel M, Zimmermann R, Ruskowski H (1994) Diabetic coma with deep hypothermia. Successful resuscitation with hemofiltration. Anaesthesist 43:750–752. German. PMID: 7840404 [PubMed—indexed for MEDLINE]
2. Pignatelli MG, Comelli LF, Costa P, Pession F, Tesselli L, Poletti G, Di Donato R, Giron GP (1981) Acid-base equilibrium changes during deep hypothermia. Minerva Dietol Gastroenterol 27:395–404. Italian. No abstract available. PMID: 7329580 [PubMed—indexed for MEDLINE]
3. Cancio LC, Wortham WG, Zimba F (1994) Peritoneal dialysis to induce hypothermia in a head-injured patient: case report. Surg Neurol 42:303–307. PMID: 7974124 [PubMed—indexed for MEDLINE]

References

1. Almeida A, Delgado-Esteban M, Bolanos JP, Medina JM (2002) Oxygen and glucose deprivation induces mitochondrial dysfunction and oxidative stress in neurones but not in astrocytes in primary culture. Neurochem 81:207–217
2. Ao H, Moon JK, Tashiro M, Terasaki H (2001) Delayed platelet dysfunction in prolonged induced canine hypothermia. Resuscitation 51:83–90
3. Baker AJ, Zornow MH, Scheller MS, Yaksh TL, Skilling SR, Smullin DH, Larson AA, Kuczenski R (1991) Changes in extracellular concentrations of glutamate, aspatate, glycine, dopamine, serotonin, and dopamine metabolites after transient global ischemia in the rat. J Neurochem 57:1370–1379
4. Billiau A, Vankelecom H (1992) Interferon-γ: general biological properties and effects on the neuro-endocrine axis. In: Bartfai T, Ottoson D (eds) Neuro-immunology of fever. Pergamon, Oxford, New York, Seoul, Tokyo, pp 65–77
5. Boels PJ, Verbeuren TJ, Vanhoutte PM (1985) Moderate cooling depresses the accumulation and the release of newly synthesized catecholamines in isolated canine saphenous veins. Experientia 41:1374–1377
6. Chiolero R, Lemarchand TH, Schutz Y, de Tribolet N, Felber JP, Freeman J, Jequier E (1988) Plasma pituitary hormone levels in severe trauma with or without head injury. J Trauma 28:1368–1374
7. Clifton GL, Miller ER, Choi SC, Levin HS (2002) Fluid thresholds and outcome from severe brain injury. Crit Care Med 30:739–745
8. Corte FD, Mancini A, Valle D, Gallizzi F, Carducci P, Mignani V, De Marinis L (1998) Provocative hypothalamopituitary axis tests in severe head injury: correlation with severity and prognosis. Crit Care Med 26:1419–1426
9. Davila DR, Breif S, Simon J, Hammer RE, Brinster RL, Kelley KW (1987) Role of growth hormone in regulating

T-dependant immune events in aged, nude, and transgenic rodents. J Neurosci Res 18:108–116
10. Dempsey IRJ, Combs DJ, Maley ME, Cowen DE, Roy MW, Donaldson DL (1987) Moderate hypothermia reduces postischemic edema development and leukotriene production. Neurosurgery 21:177–181
11. Dietrich WD, Busto R, Halley M, Valdes I (1990) The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia. J Neuropathol Exp Neurol 49:486–497
12. Dorman PJ, Counsell CE, Sanderrock PGA (2000) Recently developed neuroprotective therapies for acute stroke: a qualitative systematic review of clinical trials. In: Prakash A (ed) Acute stroke treatment. Adis, Hong Kong, pp 63–83
13. Dudariev VP, Lanovenko II (1999) Changes in the oxygen-binding properties of the blood in white rats under the influence of hypoxia and its pharmacological correction. *Fiziol Zh* 45:97–103
14. Fedor EJ, Fisher ER, Lee SH, Weitzel WK, Fisher B (1956) Effect of hypothermia upon induced bacteremia. Proc Soc Exp Biol Med 93:510–512
15. Filippi R, Reisch R, Mauer D, Perneczky A (2000) Brain tissue pO_2 related to $SjvO_2$, ICP, and CPP in severe brain injury. Neurosurg Rev 23:94–97
16. Globus MY-T, Busto R, Dietrich WD, Martinez E, Valdes I, Ginsberg MD (1988) Effect on ischemia on the in vivo release of striatal dopamine, glutamate, and γ-aminobutyric acid studied by intracerebral microdialysis. J Neurochem 51:1455–1464
17. Hackl JM, Gottardis M, Wieser C, Rumpl E, Stadler C, Schwarz S, Moukayo R (1991) Endocrine abnormalities in severe traumatic brain injury—a cue to prognosis in severe craniocerebral trauma? Intensive Care Med 17:25–29
18. Han HS, Qiao Y, Karabiyikoglu M, Giffard RG, Yenari MA (2002) Influence of mild hypothermia on inducible nitric oxide synthase expression and reactive nitrogen production in experimental stroke and inflammation. J Neurosci 22:3921–3928
19. Harrington D, Chua TP, Coast AJS (2000) The effect of solbutamol on skeletal muscle in chronic heart failure. Int J Cardiol 73:257–265
20. Hayashi N (1995) Cerebral hypothermia treatment, In: Hayashi N (ed) Cerebral hypothermia treatment. Sogo Igaku, Tokyo, pp 1–105
21. Hayashi N (1997) Combination therapy of cerebral hypothermia, pharmacological activation of the dopamine system, and hormonal replacement in severely brain damaged patients. J Jpn soc Intensive Care Med 4:191–197
22. Hayashi N (1997) Prevention of vegetation after severe head trauma and stroke by combination therapy of cerebral hypothermia and activation of immune-dopaminergic nervous system. Proceedings of the 6th annual meeting of Society for Treatment of Coma 6:133–145
23. Hayashi N (2000) Enhanced neuronal damage in severely brain injured patients by hypothalamus, pituitary, and adrenal axis neuro-hormonal changes. In: Hayashi N (ed) Brain hypothermia. Springer, Berlin Heidelberg New York Tokyo, pp 3–26
24. Hayashi N (2000) The clinical issue and effectiveness of brain hypothermia treatment for severe brain injured patients. In: Hayashi N (ed) Brain hypothermia. Springer, Berlin Heidelberg New York Tokyo, pp 121–151
25. Hayashi N, Hirayama T, Utagawa A (1994) The cerebral thermo-pooling and hypothermia treatment of critical head injury patients. In: Nagai H (ed) Intracranial pressure IX. Springer, Tokyo, pp 589–599
26. Hayashi N, Hirayama T, Utagawa T, Ohata M (1994) Systemic management of cerebral edema based on a new concept in severe head injury patients. Acta Neurochir [Suppl] 60:541–543
27. Hayashi N, Utagawa A, Kinosita K, Izumi T (1999) Application of a novel technique for clinical evaluation of nitric oxide-induced free radiacal reactions in ICU patients. Cell Mol Neurobiol 19:3–17
28. Kagawa M, Nagao S, Bemana I (1996) Arginine vasopressin receptor antagonists for treatment of vasogenic brain edema: an experimental study. J Neurotrauma 13:273–279
29. Kossmann T, Hans V, Lenzlinger PM, Csuka E, Stsahel PF, Trentz O, Morgani-Kossmann MC (1996) Analysis of immune mediator production following traumatic brain injury. In: Schlag G, Redel H, Traber D (eds) Shock, sepsis and organ failure. Springer, Berlin Heidelberg New York pp 263–297
30. Leibowitz SF (1999) Macronutrients and brain peptides: what they do and how they respond. In: Berthoud HR, Seeley RJ (eds) Neural and metabolic control of macronutrient intake. CRC, Boca Raton, pp 389–406
31. Leibowiz SF, Sladek C, Spencer L, Temple D (1988) Neuropeptide Y, epinephrine and norepinephrine in the paraventricular nucleus: stimulation of feeding and the release of corticosterone, vasopressin and glucose. Brain Res Bull 21:905–912
32. Lin TW, Kuo YS (1996) Acute pulmonary oedema following administration of vasopressin for control of massive GI tract haemorrhage in a major burn patient. Burns 22:73–75
33. Lindley RI (2000) Drug therapy for acute ischemic stroke: risks versus benefits. In: Prakash A (ed) Acute stroke treatment. Adis, Hong Kong, pp 53–62
34. MacIntosh TK (1994) Neurological sequele of traumatic brain injury: therapeutic implications. Cerebrovasc Brain Metab Rev 6:109–162
35. McClain CJ, Hennig B, Ott L, Goldblum S, Young AB (1988) Mechanisms and implications of hypoalbuminemia in head-injured patients. J Neurosurg 69:386–392
36. Pasko SA, Volosheniuk TG (1990) Disordered phosphorus metabolism and its correction in the acute period of severe craniocerebral trauma. Zh Vopr Neirokhir Im NN Burdenko 3:14–16
37. Poca MA, Sahuquillo J, Arribas M, Baguena M, Amoros S, Rubio E (2002) Fiberoptic intraparenchymal brain pressure monitoring with the Camino V420 monitor: reflections on our experience in 163 severely head-injured patients. J Neurotrauma 19:439–448

38. Sahuquillo J, Amoros S, Santos A, Poca. MA (2000) Does an increase in cerebral perfusion pressure always mean a better oxygenated brain? A study in head-injured patients. Acta Neurochir [Suppl] 76:457–462
39. Schwarz S, Georgiadis D, Aschoff A, Schwab S (2002) Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. Stroke 33:497–501
40. Silvka A, Coben G (1985) Hydroxyl radical attack on dopamine. J Biol Chem 260:15466–15472
41. Suarez JI (2001) Treatment of acute brain edema. Rev Neurol 32:275–281
42. Triolo AJ, Osterholm JL, Alexander GM, Bell RD, Frazer GD (1990) Local cerebral glucose metabolism after global ischemia: treatment by ventriculocisternal perfusion with a fluorocarbon emulsion. Neurosurgery 26:487–488
43. Valeri CR, Cassidy G, Khuri S, Feingold H, Ragno G, Altschule MD (1987) Hypothermia-induced reversible platelet dysfunction. Ann Surg 205:175–181