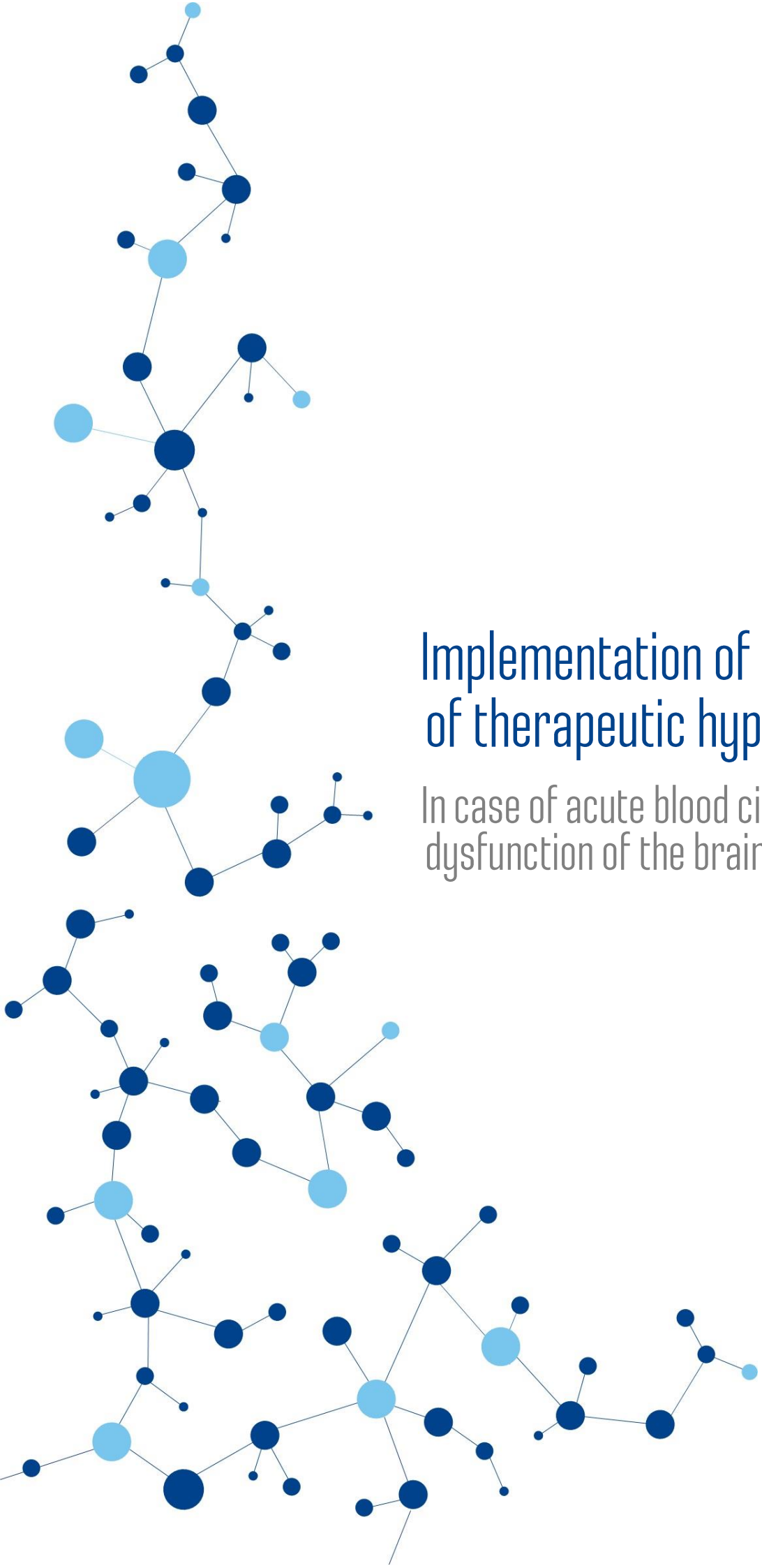

Implementation of technology of therapeutic hypothermia

In case of acute blood circulation dysfunction of the brain

Implementation of technology of therapeutic hypothermia

(In case of acute blood circulation dysfunction of the brain)

Terms and abbreviations:

TH – therapeutic hypothermia;

ABCDB – acute blood circulation dysfunction in the brain;

EAA – excitatory amino acids;

LP – lipid peroxidation;

IP – intracranial pressure;

CPR – cardiopulmonary resuscitation;

ABE – acid-base equilibrium;

GTH – general therapeutic hypothermia;

ALV – artificial lung ventilation;

NRP – no-reflow phenomenon;

CCH – cranio cerebral hypothermia;

BBC – brain blood circulation;

RTB – radio thermometry of the brain;

BAS – biologically active substances;

THE – Therapeutic hypothermia equipment;

1. TH effects mechanisms during central nervous system dysfunction.

Modern research allowed to identify dynamics and chain of development of the molecular and biochemical pathogenesis mechanisms, which develop after trauma, global and acute focal brain ischemia as well as reperfusion processes[1]. Standard type of formation of secondary cerebral injuries, which determine clinical outcome outline therapy strategy, which is based on principle «the earlier the better», which means that the earlier treatment starts, the better is the result[2]. It is necessary to use multifactor approach, which takes into account therapy of basic life support system and vital functions of the organism, and pathogenetic therapy - neuroprotective and restoring perfusion, restriction of glutamate cascade, reduction of oxidant stress and calcium overload of neurons, reduction of local inflammation and apoptosis[3].

Search for means of neuroprotection launched wide research of the TH effects when used during global ischemia, neurotrauma and ABCDB[4] during the last 20 years.

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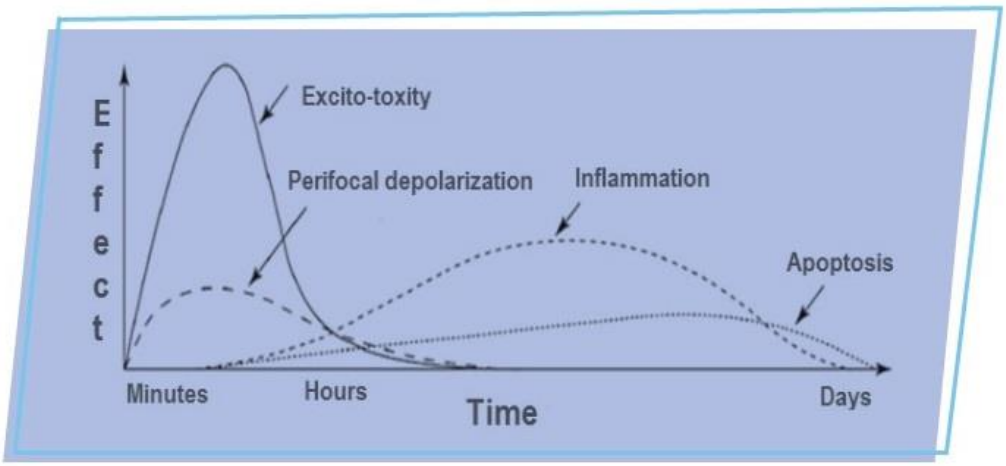
1.1. Main mechanisms of pathogenesis of neuron stroke during brain ischemia.

Directly from the moment of ABCDB or neurotrauma development, which form primary lesion area extremely fast, energy deficit of neurons rises sharply[5], and is followed by massive discharge of excitatory amino acids (glutamate and aspartate)[6].

Hypoxia and substratum deficiency lead to transmembrane potential dysfunction, synaptic transmission, axoplasmic transport and action potential[7]. Stimulation aggravates energy deficit, which intensifies excitotoxicity effects and is followed by sharp discharge of EAA[8], calcium neuron homeostasis dysfunction[9], development of lactic acidosis[10], accumulation of free-radical compounds and LP[11] activation.

Oxidative stress and local inflammation[12] start to appear in the first 2-3 hours of ABCDB, which will reach maximum level after 12-36 hours, providing basis for ischemia consequences, which are formed by 2nd -3rd day. Activation of apoptotic death of neurons[13,14] also contributes to this. On the Picture 1 is shown sequence and length of pathogenesis of neuron damage mechanism[15] is shown.



Picture 1. Main mechanisms of neuron damage in the penumbra area and periods of development.

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Brain areas in the ischemia zone are damaged irreversibly during 6-8 minutes and form «core» zone of the stroke which is surrounded by «ischemic penumbra» or penumbra. In the area of penumbra metabolic activity is maintained for several hours and only functional changes of neuron remain. Safety of neurons is identified by the perfusion level in this area of the brain. Some parts of the brain are particularly sensitive to the ischemia (hippocampus, neocortex, cerebellum, thalamus)[16].

Recovery of adequate perfusion and effective neuroprotection which aim to protect «penumbrae» neurons, are main tasks of stroke therapy from the first hours of the injury/disease.

Neuron life span in the area of penumbra determines the length of «therapeutic window» - period, when treatment procedures are the most effective.

Thrombolytic therapy with usage of recombinant tissue plasminogen activator (tPA) is the most effective method for recovery and prevention of irreversible damage of brain tissue[17] at the present moment. However, time for therapeutic effectiveness does not exceed 4-6 hours from the beginning of the ABCDB and dangers of development of hemorrhagic complications do not allow to use thrombolysis in more than 10% of cases[18].

It is significant, that restoration of blood flow (reperfusion) also provokes development of cascade of pathological reactions[19]. At first postishemic hyperperfusion is developed, oxidant stress intensifies sharply as a result of endogenous antioxidant systems exhaustions, neurotoxity effects increase. After that postischemic hypoperfusion with microcirculation dysfunction and NRP[20] can develop, which can significantly worsen results of therapy.

Main complex of damaging cascades during reperfusion initiates free radical oxidation, and neuron membrane damage begins after several minutes after blood flow recovery. Damage rate is highly active in the first hours and can last for several days[21]. Development of the inflammation is activated with anti-inflammatory cytokine and entails brain tissue infiltration with leucocytes[22]. Pharmacological neuroprotection aims to influence pathogenesis mechanisms and requires wide range of medications. Antagonists of NMDA-receptors (for example: magnum) are used. Limitation of excitatory neurotransmissions can be achieved to some extent with inhibitory amino acid (glycine, gamma aminobutyric acid, (GABA).

In order to suppress pathogenic reactions, the following medicine is used: medicine which has antioxidant effects, medicine which aid reduction of local inflammatory reaction (antagonists of anti-inflammatory cytokines and cell adhesion molecules),

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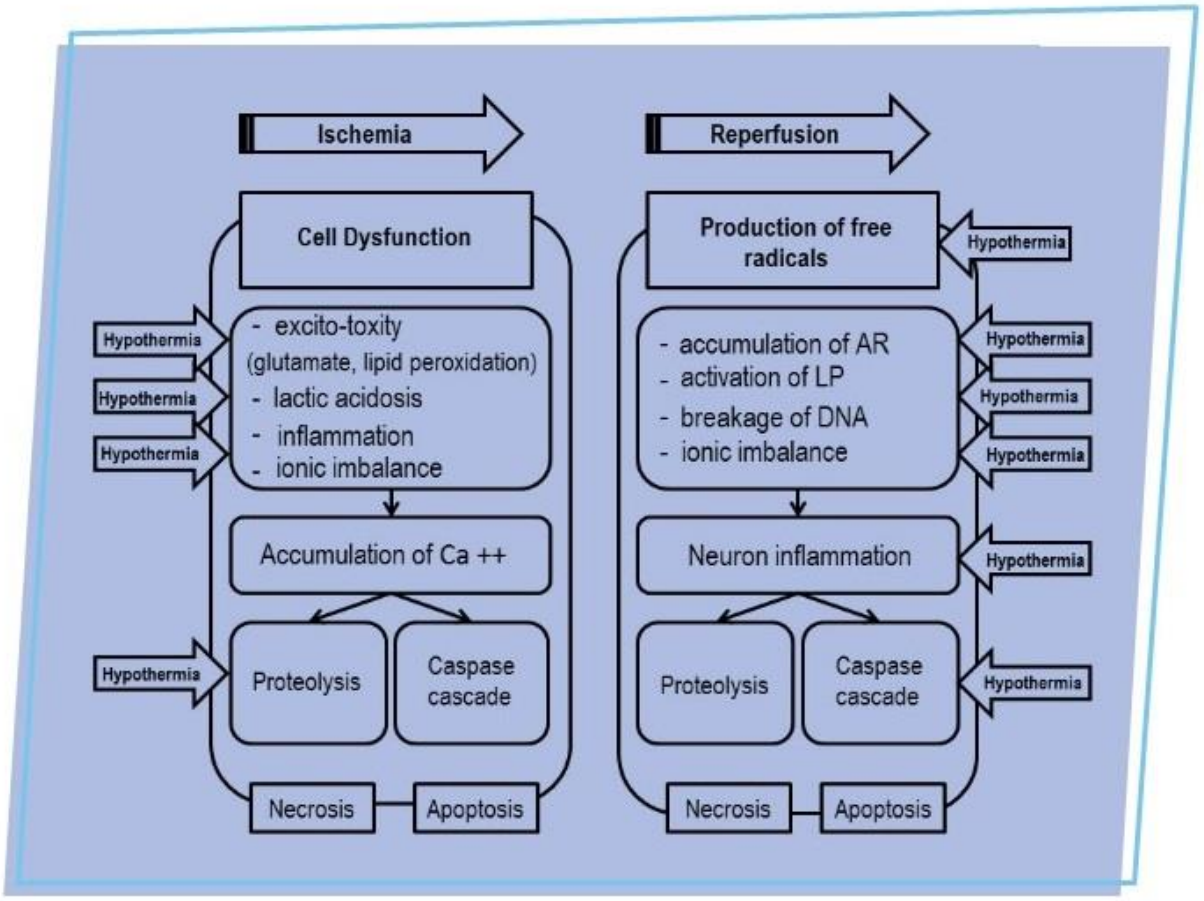
neuroimmunomodulators (neuropeptides) and regulators of receptor structures (gangliosides) are used. Dehydration therapy of brain edema and correction of feverishness conditions are also important part of neuroprotective therapy[23].

Consequently, pathogenic neuroprotective therapy of ABCDB requires usage of wide range of medicine of different effect.

1.2. TH – neuroprotection method.

Quite recently Lampe JW. и Becker LB. (2011) offered scheme of mechanisms of work of TH[24]. It is represented on the Picture 2, it allows to create overall map of influence of brain temperature reduction processes on pathogenic mechanisms of neuron damage during total ischemia and reperfusion.



Picture 2. Scheme of therapeutic action of TH (according to JW. и Becker LB., 2011)

Big volume of completed experimental and clinical research allows to consider TH as effective method of protection, which positively influences the majority of key mechanisms of the secondary neuron damage.

Depression of metabolism in the cells during temperature decrease is traditionally considered as important part of the neuroprotection characteristic of hypothermia[25]. Decrease in need for oxygen, substratum and adenosine triphosphate (ATP) contributes for decrease in neuron reactions on ischemia, prologues their lifespan during

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hypoperfusion. Discharge of EAA, cellular respiration and production of free radicals, transmembrane permeability which are provoked by ischemic cascade decrease[26].

Limitation of local inflammation during ischemia and neurotrauma with TH[27] is accompanied with decrease of leucocyte migration and their infiltration to brain tissue[28], edema is reduced and IP decreases[29]. Volume of neural tissue damage and neuron loss is reduced when using hypothermia by both necrobiotic type and by apoptosis[30]. Importantly, TH effects on pathogenic reactions development are shown in both ischemic phase and during reperfusion period.

Major experimental research and testing of TH effects during CPR has shown that mild hypothermia, +32-34°C increases neuron protection of the subcortical structures and cerebral cortex after 10 minute cardiac arrest among cats and increases regeneration of major homeostasis indexes (glycohemia, ABE) and increases survival rate by 18-20% in comparison to CPR among animals with nornothermia[31].

Experiment also identified that usage of TH has high risk of fibrillation development, but improves neurological status among dogs[32] after CPR and reperfusion during cardiac infarction and moderate general hypothermia +29-32°C.

Experimental works confirm significant limitations of morphological consequences of secondary injuries during acute brain ischemia and general cooling. TH influence on the pathogenic cascades, which are initiated by reperfusion are observed and conclusion is drawn that therapeutic window can be expanded for pharmacotherapy, including thrombolysis during early cooling[33,34].

European scientific group (Hypothermia After Cardiac Arrest – HACA) published multi-central random research in 1993, which consisted of 275 patients, older than 18 years (9 centers in 5 countries) with standard mild hypothermia (+32-34°C) after cardiac arrest, fibrillation and restoration of spontaneous blood circulation but not later than after 60 minutes. GTH was used for 24 hours with subsequent spontaneous warming. Positive neurological outcomes are registered using meta analysis after 6 months among 55% of

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patients after TH and among 39% of patients without TH[35]. These results coincide with «Nagao K. e.a.» (2002) data, which mark positive neurological status of patients after CPR and standard TH in 57% of all cases[36].

Australian group of TH study gives data with positive neurological rehabilitation among 49% of patients, who survived after CPR, using TH and among 26 of patients, without TH[37].

Risk of cardiac arrest in conditions outside of hospital among patients decreases by 20% if cooling is initiated in the first hour after restoration of heart activity[38].

In spite of positive neurological prognosis among patients after global ischemia, TH results are significantly dependent on type of warming[39]. It is shown, that high rate of body temperature increase after mild GTH over 1°C/hour (from +32 to +37°C) particularly after moderate GTH can provoke gross violations of heart rate[40].

Majority of clinical results of positive neuroprotection application of TH are acquired after CPR and heavy neuroinjury[41], because general cooling method was used as medical maintenance which corresponds with patients condition and GTH (ataraxia, intubation, ALV, miorelaxation).

Clinical practice among only several patients after ischemic stroke requires intubation of trachea and ventilation. Proved neuroprotective effects of hypothermia assume the most efficient usage of method among conscious patients in moderately grave condition. And there will be significantly more indications for hypothermia application if it is possible to avoid intubation and additional sedation of patients[42].

This prerequisite is basis for really mild hypothermia method development with decrease of the temperature of the caloric centre of the organism within +35-36°C, which does not require pharmacological neutralization of muscle shivering, ALV and general anesthesia[43]. However, it is established, that neuroprotection is more effective when using lower temperatures.

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[43] – Kammersgaard LP, Rasmussen BH, et al. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study: the Copenhagen Stroke Study. Stroke 2000;31(9):2251–6.

After modeling of ischemic stroke among rats, it has been identified that neuroprotective properties of therapeutic hypothermia appear at temperature below +35°C, and result in decrease of stroke by 44% in comparison to animals with higher temperature[44], and it is enough to cool down only for 3-4 hours in order to significantly reduce brain stroke volume[45]. Estimation of clinical results of TH application during ischemic stroke is often difficult due to the variety of available techniques where the beginning of cooling, surface and transvenous general cooling of different length and depth is different for each method. Similarly in combined research the archive analysis of GTH application among 423 patients has been undertaken. It did not identify significant differences in control and main groups in death rate and successful therapy rate after 1 and 3 months after stroke[46].

However, positive effect of TH and potential of general cooling method in combination with thrombolytic therapy[47] after ischemic stroke is established. Also, high neuroprotective potential of TH allows to achieve good clinical results, but it is statistically insignificant in multi-central research due to heterogeneity of sample, difference and high dispersal of results. Perspectives for method development are dependant on combination of TH and pharmacology as well as development of standard methods and their applications for ischemic stroke[48].

Importance of systematic implementation of TH after stroke is outlined in many works. In «Krieger» (2001)[49] paper it is shown that quick warming after hypothermia can lead to reactive brain edema development. In the experimental work it has been identified that delay in TH application for longer than 3 hours from the moment of brain ischemia modeling, significantly decreases effectiveness of hypothermia session[50]. According to «Colbourne e.a.» (1993) clinical research, cooling during 24 hours allows to achieve clear neuroprotective effects, even if treatment was delayed by up to 6 hours after beginning of ischemic stroke[51]. Moreover, it is very important to provide adequate to the patient's condition length of the cooling, as short period of temperature decrease might not provide for sufficient level of neuron protection. Also, development of vascular reactions during early warming can provoke opposite result. It is important to note that TH reduces risk of NRP after CPR[52].

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Clinical data is accumulated about successful combination of TH with adopted protocols of pharmaceutical therapy after ischemic stroke[53], including reperfusion therapy[54], magnesium medicine and antioxidants[55].

Therapeutic Hypothermia effects start to reveal only with sufficient level of brain temperature decrease and continue during the period of effective hypothermia. These effects show significant impact on pathologic process flow, provided that cooling is included in complex therapy, taking into consideration therapeutic window, in other words, during 24 hours from the beginning of the disease[56].

At present moment major approaches to TH application during CPR, neurotrauma and ABCDB are formed. GTH can be applied to seriously ill patients in accordance with «Methodical recommendations of European Reanimation Union» (2010). In order to run temperature management and prevent unwanted effects of neurogenic fever as well as potentiation of neuroprotective therapy, really mild hypothermia is advised[57]. Moreover, positive experience of craniocerebral cooling should be noted[58], which allows to induce not only CCH but mild GTH.

Depth and focality of hypothermia development must be thoroughly controlled disregarding choice of method, which assumes usage of TH.

2. Modern methods of TH.

Clinical results, which are collected after TH among emergency care patients, stimulated development of various types of equipment for decrease of overall and local temperature. At present moment over 15 types of various equipment for emergency care are produced which can be divided into the following groups according to main cooling principles:

- Equipment for reduction of temperature of the main heat carrier of the organism – of the blood;
- Equipment for reduction of temperature from wide areas of the patient's body;
- Equipment for cooling of hairy part of the scalp.

2.1. Reduction of blood temperature.

This group of equipment reduces temperature by cooling of blood, using special heat-exchanging catheters, which circulate +20°C water in closed circuit. Heat-exchanging catheter is injected in great veins (clavicular artery vein or femoral vein), where it is fixated for up to 72 hours (Picture 3). In addition to heat-exchanging port, which is connected to hypothermia equipment, catheter is equipped with infusion ports, which

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increase it's functionality.

Picture 3. Scheme of the equipment for internal blood cooling (equipment "CoolGuard" and "Zoll") heat-exchanging internal catheter.

Considering high effectiveness of the convection regulation of the thermal balance of the organism using blood flow, this method allows to provide quick GTH and reduce temperature of the body to +32-35°C for 45-60 minutes. Availability of controlled feedback which is provided by measurements of the temperature of the thermoregulation center (esophagus, rectum, urinary bladder) allows to support set body temperature level with high precision.

Currently, this is the most precise method for temperature management, which allows not only to reduce basal temperature with necessary speed and to maintain it on the set level, but also provides for necessary speed of warming of patients during unwanted hypothermia and brings patients out of GTH session.

Main disadvantages of the method are invasive application, danger of infection and dislocation of catheter, thrombosis, limitation of application as it is aimed at GTH induction and not decrease of brain temperature, which is particularly important for neuron function improvement in the area of penumbra.

2.2. Removal of heat from large areas of patient's body surface.

This methods are based on the surface removal of heat using mattresses, blankets, collars, cuffs, head bandages, big size applicators, which provide cooling of limbs and projection of great vessels. Applicators can be described as closed voids with tubes through which water (~ +5°C) runs in the form of assisted circulation (Picture 4).

Picture 4. Induction equipment GTH during surface removal of heat ("Blankentrol" – on the left and "ArcticSun" – on the right).

Applicator contacts with wide area of the skin surface, including area of projection of great vessels, allows to remove heat fast and reach desired level of temperature reduction of heat centre in 45-60 minutes.

Equipment for this method also includes controlled feedback by temperature monitoring of the thermoregulation center of the organism, which allows to maintain body temperature precisely in the set parameters.

Among advantages of such method is simplicity of operation. Yet, it is intended only for GTH induction, although some modifications have accessories for scalp surface cooling

(applicators designed in the form of head bandages) and neck (collar-applicators) for cooling of vertebrobasilar and carotid vessels.

Methods of GTH (sections 2.1 and 2.2) require compulsory and strong sedation, usage of ALV and medicine, which blocks endogenous mechanisms of thermoregulation and muscle shivering. Decrease of patients body temperature is restricted to only mild hypothermia level (+32-35°C) in order to reduce risk of complications development.

The following qualitative characteristics of method significantly limit range of application and decrease potential neuroprotection functions, which can be achieved with decrease of brain temperature. The following arguments support previous statement:

1) Instrumental and pharmacological characteristics of GTH make it inapplicable during ischemic stroke of moderate severity, when patient is conscious and strong sedation makes the control of neurological status of the patient impossible. And it is very big group of patients, which requires neuroprotection therapy and what is the most significant, the most perspective if the field of positive neurological prognosis of the disease.

2) Permissible level of body temperature decrease is limited to +32-35°C diapason, due to risks of complications in cardiovascular system, while permissible level of brain temperature decrease is significantly lower. At temperature of +25-27°C reverse metabolism depression can develop, which is accompanied with pronounced suppression of signal interaction in the brain. As a result bioelectrical activity in the brain decreases (according to EEG) together with autoregulation capabilities of the brain blood flow. Those can be easily recovered with temperature increase[59].

   Moreover, we previously provided you with data about neuroprotection effects which gradually grow with the decrease of brain temperature. Also, decrease of the temperature by 1°C provides for neuron stability to the hypoxia and reduces consumption of oxygen by 5-7%. During GTH brain temperature can be reduced no lower than basal temperature (in other words no lower than 3-5°C), while local temperature reduction of the brain can be reduced up to 10-12°C, which could increase TH effectiveness.

3) In case of stroke, in the area of «penumbra» happens disturbance of microcirculation and develops edema. This leads to compression of small, medium and great vessels. As a result, cold blood circulation is hindered to those areas, which need temperature reduction the most.

4) In case of ischemic stroke, in the area of stroke center and «penumbra», inflammation is developed, and critically high heat production areas are formed. They are called locuses of «metabolic processes» or local hyperthermia. As a result, temperature of some brain areas can reach critical values – +41°C and higher and almost always exceed basal temperature[60,61]. In such conditions, insufficient local blood flow can not provide for effective convection and removal of heat from warmed up brain areas. Decrease of temperature is done by heat removal, in other words heat energy is transmitted from relatively warm parts of the brain – to colder parts. This type of heat transmission is significantly less effective, than convection and heat flow depends from heat capacity and conductivity of tissues, level of metabolic activity in the nidus

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and Δt°C warm/cold, which in not high during GTH.

2.3. CCH which is induced on the equipment.

Disadvantages of the described methods of the GTH procedure are compensated by CCH induction, which is based on the surface heat removal from cranial part of the scalp (hairy, part of the head/scalp)[62].

In the western medicine CCH application among adults remains rare at the moment due to dominating assumption, that in order to reduce brain temperature, cooling of whole body is required. In case when blood temperature is reduced to +32-35°C, it flows from heat center of scalp and provides for convection heat removal while reducing temperature in the brain. Opinion that it is impossible to reduce central heat flows of blood towards brain, using only cooling of the surface of the scalp, held usage of CCH back.

3. Project technology.

3.1. Controlled CCH.

Domestic experience, which was accumulated in XX century and modern research of the brain temperature variations among healthy population and patients with ABCDB and Traumatic brain injury (TBI)[63] patients allowed to clearly show, that cooling of scalp surface can induce hypothermia of brain at different levels[64], depending on level of intensiveness of heat removal and cold effect exposition.

It was also shown that using CCH allows to provide for effective intraoperative protection of the brain during temporary occlusion of the internal carotid artery in case of carotid endarterectomy[65].

Craniocerebral cooling to the +33-34°C temperature level in the nasopharynx among patients with one- and two-sided arthrosclerosis lesion of carotid arteries under multi-component general anesthesia allowed to safely carry out long (occlusion up to 60 minutes) surgical reconstruction of internal carotid artery. It is important to note, that according to Deryagin M.N. (2004) CCH was induced using cloth hat, which was filled with comminuted ice. And during the whole surgery it was possible to induce not only brain hypothermia, but also mild GTH.

Works which allowed to find detailed features of hypothermia development during isolated cooling of scalp area have been undertaken during the research of modern technology and equipment for CCH [66,67,68,69,70,71].

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[62] – от англ/лат.- *scalp* от лат. *scalpere* — резать или Skin, Connective tissue, Aponeurosis, Loose areolar connective tissue, Pericranium- periosteum, волосистая часть головы

[63] – Колесов С.Н. Диагностические возможности тепловидения в нейрохирургии, Автореф. дис. канд. мед. наук.-М.,1980.-28 с.

[64] – Obdulia Ley, Yildiz Bayazitoglu Effect of physiology on the temperature distribution of a layered head with external convection//International Journal of Heat and Mass Transfer, 46, 2003, 3233–3241

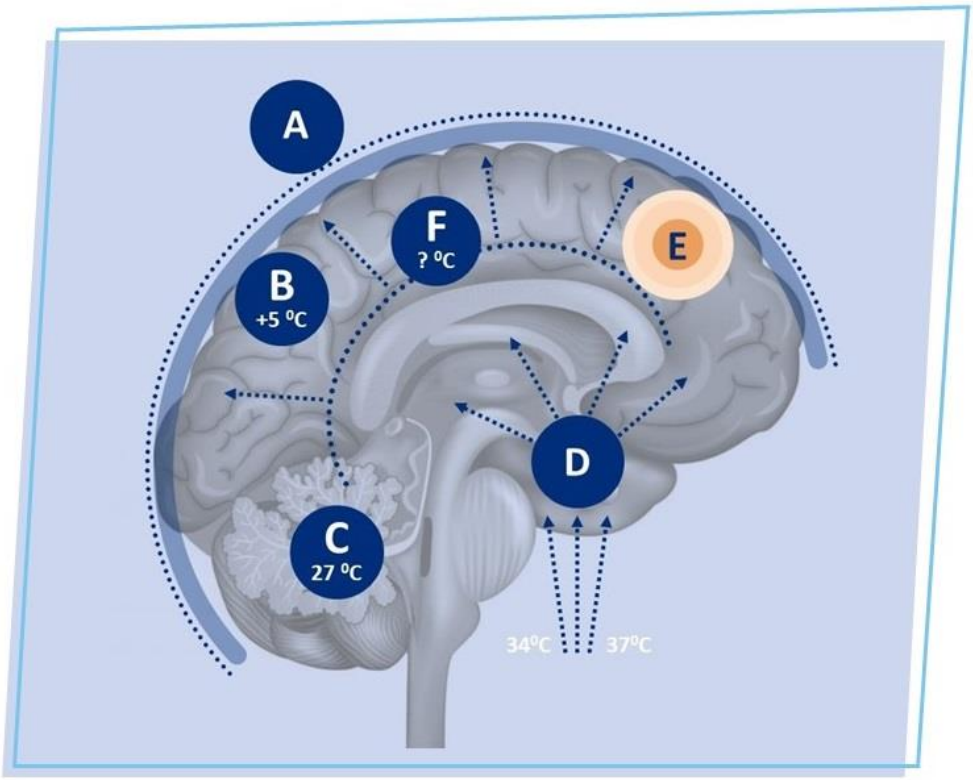
[65] – Дерягин М.Н. Краниоцеребральная гипотермия в хирургии сонных артерий, Дисс. канд. мед. наук, Новосибирск, 2004

[66] – Шевелев О.А., Бутров А.В., Евдокимов Е.А. и др. Краниоцеребральная гипотермия – методика защиты мозга в неотложных состояниях// Новости анестезиологии и реаниматологии, №1, Москва, 2009, С.15-19

[67] – Шевелев О.А. Криотерапия в России В сб. Национальные приоритеты развития России: образование, наука, инновации,М., Инноватика, 2009, С.337-340

When using CCH (Picture 5), cooling of scalp with helmet (A) allows to form hypothermia of skin and hypodermic tissues as well as scalp bones (B).

Temperature monitoring demonstrates decrease of temperature by -4°C in the ear canal (C). Anatomically this area is close to temporal lobe.



Picture 5. CCH

Central heat inflows (D) aggravate formation of hypothermia in the brain.

It is very important to note, that during the formation of the core of the injury and during brain edema (E), blood flow in the damaged hemisphere is deeply aggravated. Cold blood during general hypothermia (B) can not cool area of injury.

It is also important to note, that development of GTH improves and enhances conditions for even cooling of the brain.

Intensive heat removal process takes place in the area of tight contact of the helmet with the surface of the head. This allows to decrease temperature in the vast areas of brain in only 1 hour by 2-4°C.

Temperature difference between brain surface and scalp skin is approximately Δt=30°C (5ºC – temperature of scalp, 36ºC – temperature of cerebral cortex), which allows CCH

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[68] - Шевелев О.А., Бутров А.В. Технологии лечебной гипотермии в интенсивной терапии и реаниматологии// Неотложная медицина. №3, 2010, С.45-49

[69] - Шевелев О.А., Бутров А.В. Технологии лечебной гипотермии в интенсивной терапии и реаниматологии// Неотложная медицина. №3, 2010, С.45-49

[70] - Шевелев О.А., Бутров А.В., Каленова И.Е., Шаринова И.А. Краниоцеребральная гипотермия в терапии ишемического инсульта//Укр. ж-л Боль, обезболивание и интенсивная терапия , №1, 2012, С.605-608

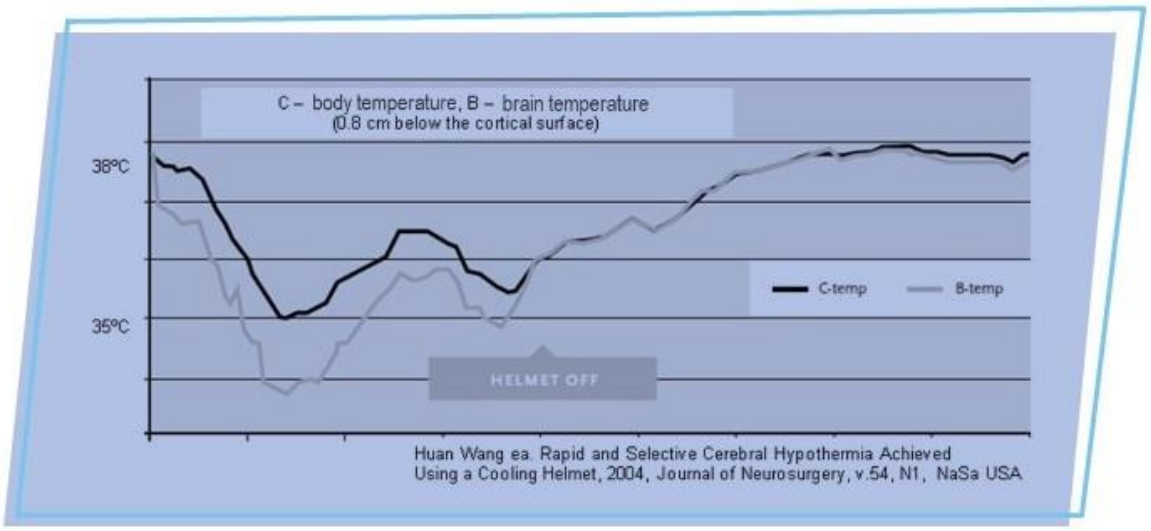
[71] - Шевелев О.А., Бутров А.В., Каленова И.Е., Шаринова И.А. Коррекция неврологического статуса у больных в острейшем периоде ишемического инсульта методом терапевтической гипотермии// Российский нейрохирургический журнал, Том IV, Балтийский форум, 2012, С. 69-70

to provide for heat removal at the intensity level of up to 60 W (overall value of the organism heating productivity – 100 W). Also, it allows to reduce temperature of the brain surface and induce conditions of general mild hypothermia development.

Increase in length of exposition by up to 4 hours leads to significant decrease of temperature of the brain without changes in basal temperature.

CCH procedures which last more than 8 hours among conscious patients provides for the development of very mild GTH (+35-36°C) without muscle shivering and does not require additional sedation.

Application of CCH on patients which are in coma, medical anesthesia during intubation and ALV or, in other words, during suppression of thermoregulation and thermogenesis reactions, results in mild hypothermia (+32-33°C) development during 4-8 hours of scalp cooling. Even so, tympanic temperature is always lower than basal by 2-4°C (Picture 6). Induced hypothermia parameters fully complies with «European Union Reanimation Recommendations – 2010».



Picture 6. Graphs of temperature of body and brain during CCH.

CCH in comparison GTH has number of significant advantages:

- CCH can be applied in any conditions.

  GTH is not applicable among conscious patients, as it requires instrumental and pharmacological assistance (sedation, muscle relaxation, ALV).
- Permissible level of body temperature decrease during hypothermia is 32°C, which does not allow to achieve required cooling of the brain (25-27°C) when using GTH in comparison to CCH.
- During CCH, neuroprotection is more effective, because effects of neuroprotection increase cogradiently as tissue temperature decreases.
- When GTH is applied, brain edema during cerebral injuries aggravates delivery of cooled blood to the centers of the injuries.
- Also, there are complications when GTH is applied, which were main causes for method rejection in 70s – 80s f the XX century:
  - Cardiovascular system depression (decrease of blood pressure, decrease of cardiac output, atrioventricular transmission slowdown, fibrillation, asystole).
  - Increase in bleeding.

  - Depression of metabolism and of functions of internal organs of the organism.
  - Increase in suppurating-septic complications.
- CCH allows to undertake mild GTH (no lower than 32ºC) for patients in medical anesthesia and coma.
- CCH initiates fast regress of neurological deficit among patients with ischemic stroke during the first/second day after beginning of the pathology.
- CCH effectively stops neurogenic fever and stabilizes temperature in the nidus of cerebral cortex hyperthermia.

Based on the results of the research, Therapeutic Hypothermia Equipment «THE-01» has been created, which provide for controlled CCH – surface heat removal from hairy scalp using helmets with channels of coolant circulation which circulate at regulated temperature. The equipment is protected by RF Patents[72,73,74,75,76].

Equipment has properties of feedback and provides monitoring data of skin temperature under helmet and tympanic temperature. This allows to maintain heat removal level precisely in the set parameters.

Among advantages of this method, there are simple operation procedures, function of brain hypothermia induction for conscious patients and reduction of cold bearing on the organism, which prevents GTH complications development.

3.2. TH induction among healthy population characteristics.

One of the main problems of clinical application of CCH during the acute period of ischemic stroke is monitoring of the temperature of the brain during hypothermia induction. It is necessary for identification of permissible and safe levels of brain temperature reduction as well as effectiveness of hypothermia induction in the acute period of ischemia, which is followed by significant vascular and metabolism disorders.

General BBC of human at rest is approximately 55ml/100 g per minute, which is 15-20% of overall cardiac output. Dynamic variations of BBC are dependent on fulfillment of general and local metabolic needs and are identified by level of system blood pressure, which represents main tendencies in BBC autoregulation.

Brain metabolism is significantly high and is accompanied with release of heat (20% of overall heat output of the organism at rest), while mass of the brain is approximately 1,5% of overall body mass[77].

Surplus of the heat output is removed due to convection. Change of Δt of inflowing arterial and outflowing venous blood is normally insignificant and is equal to 0,2 – 0,27°C, and provides heat removal at 12-13 cal/hour level. Role of thermal conductivity in the thermoregulation processes should not be underestimated. During change of temperature between brain surface (+37°C) and scalp skin (+32°C) which is equal to 4,7-

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[72] – Усышкин И.М., Шевелев О.А. Аппликатор для гипотермии, Патент РФ № 74563 от 15.02.2008

[73] – Усышкин И.М., Шевелев О.А. Устройство для локального охлаждения и/или согревания тела человека, Патент РФ №94149 от 20.03.2010

[74] – Усышкин И.М., Шевелев О.А. Устройство для охлаждения наружных покровов головы и головного мозга человека, Патент РФ №96762 от 20.08.2010

[75] – Галкин И.И., Агишев С.А., Костенко А.Ю. и др. Теплообменник для систем локального охлаждения тела человека, Патент РФ №97504 от 10.09.2010

[76] – Усышкин И.М., Шевелев О.А. Устройство для локального охлаждения тела человека Патент РФ (пром. образец) №83369 от 16.10.2012

[77] – Физиология терморегуляции. Л., Наука, 1984, С.470.

5°C, outside heat flow will also be equal to approximately 12,4 cal/hour или 14,4 W[78]. Considering that heat productivity of the brain is normally equal to 20 W, convection and heat productivity can fully provide temperature homeostasis of the brain and prevent it from overheating. Central convection heat inflows prevent brain from hypothermia.

Craniocerebral heat removal should be aimed at reduction of high brain heat production and disabling of central heat inflows. Obviously, this task is more complicated for patients with fever.

Efficient surface heat removal with heat conductivity at high values of Δt will contribute to temperature gradients formation on the various levels: scalp skin/surface of brain cortex/subcortical structures/base of the brain in the area of central heat flows. Fast and even reduction of temperature in the brain can not be expected at such conditions.

However, when temperature was changed directly during CCH, local hypothermia existence has been proven. Paper written by William Olivero[79] shows that temperature of neurosurgery patients was by 2,4°C lower than basal temperature after 3-4 hours of CCH achieved effect of mild hypothermia. This was possible due to cooling of carotid areas and brain temperature, which is measured with sensor and implanted 0,8 cm deep in brain parenchyma. Scalp skin and carotid areas were cooled with tube helmet and cryoapplicator-collar, in which cold water (approximately +5°C) was circulating as part of this method.

Invasive measurement of the brain temperature among patients with the stroke is not possible. However, methods of radiothermometry, which allow to measure temperature level 5 cm deep from the surface of the brain cortex, which corresponds with level of surface layers of the brain cortex[80]. Capacity of the electromagnetic radiation in the decametric diapason is proportionate to metabolic activity of deep tissues level and level of their temperature[81].

Application of RTT of the brain allowed to identify temperature heterogeneity of the cortex of the brain hemisphere at rest and during functional loads, which are accompanied by creation of areas with temperature gradient of 1-1,5°C[82]. RTT method is used during functional brain research[83] and for diagnosis of the vascular disorders[84].

In order to research hypothermia induction specifics during craniocerebral cooling, we have initiated temperature mapping of the brain using RRT with «PTM-01»[85] equipment.

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[78] – Гомеостаз на разных уровнях организации биосистем. Наука, Сибирское отделение, 1991, С. 233.

[79] – William Olivero Patients were randomly assigned to groups receiving either the cooling helmet or no cooling, and brain temperatures// J of Neurosurgery, 4(4), 2004, 232-39

[80] – Будякин Г.И., Кривонос М.А, Вологодин М.У. Первый опыт тепловизионного исследования в динамике острых травматических внутричерепных гематом и очагов ушиба. // Черепномозговая травма и ее осложнения.-Л.,1981.-с. 33-25.

[81] – Густов А. В., Цейтлина В.Н. Дециметровая радиотермометрия в дифференциальной диагностике опухолей и сосудистых заболеваний головного мозга // Тепловидение в медицине.-Киев,1984.-С.19.

[82] – Густов А.В., Троицкий В.С., Горбачев В.П. Исследование кранио-церебральной температуры методом дециметровой радиотермометрии // Физиология человека,1985.-Т.11,N.1.-С.151-154.

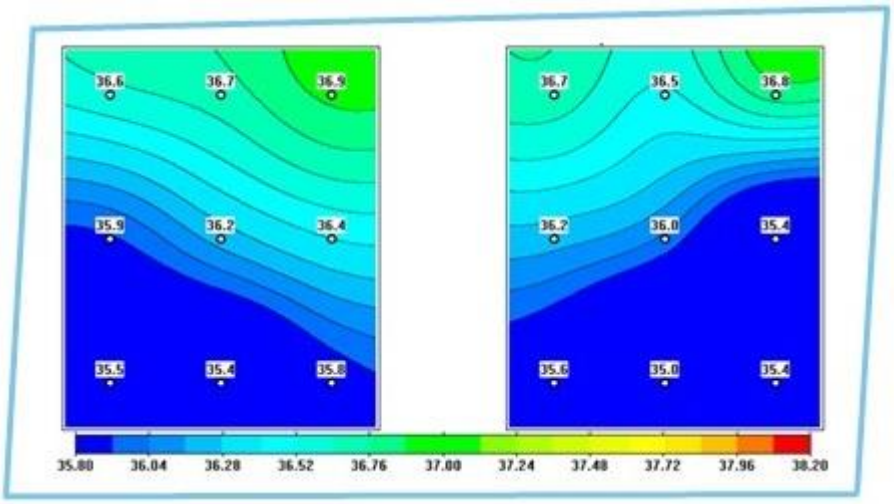
[83] – В.Л. Анзимиров, Н.А.Архипова и др. Динамическое терморадиокартирование коры головного мозга при функциональных нагрузках.- Радиотехника, 1991, 8, с.74.

[84] – Е.В. Петрова, Н.Б. Холодова, А.Г. Сельский, В.И. Пасечник, А.В. Янович. Динамическое исследование температурных полей головного мозга человека.- Физиология человека, 2001, т.27, №1, с.23 - 30.

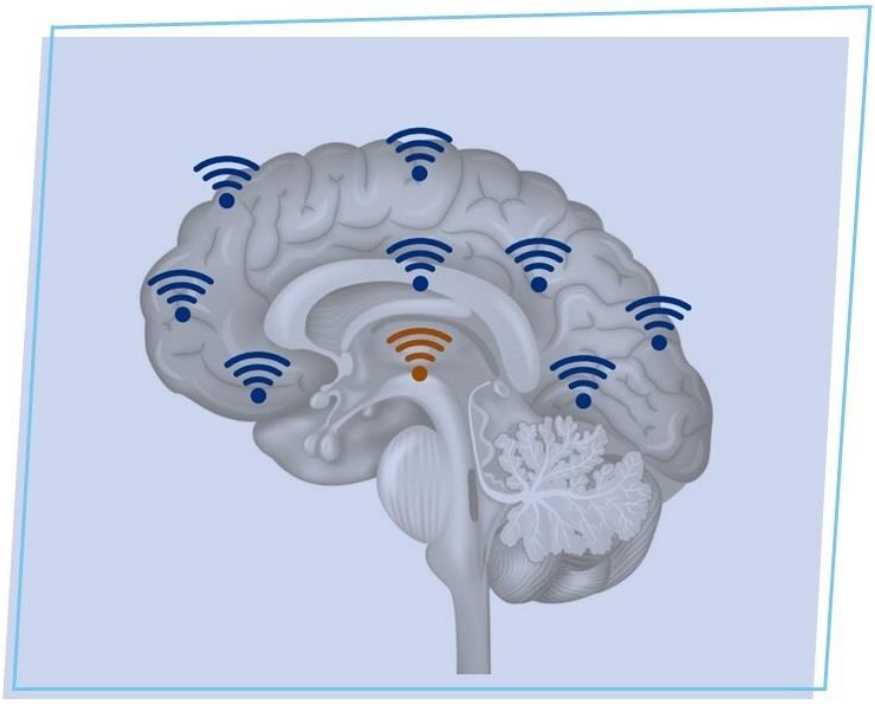
[85] – Шевелев О.А., Бутров А.В., Чебоксаров Д.В., Ходорович Н.А. Неинвазивное суточное термокартирование головного мозга в динамике ишемического инсульта при краниоцеребральной гипотермии//Вестник РУДН, серия Медицина, 2012, №7, С. 62-64

After preliminary temperature mapping CCH was induced on 20 healthy individuals using «THE-01» for 4 hours, stabilizing temperature of the skin of the surface of the whole scalp on the +3-5°C level. During the temperature mapping of the brain surface maximum temperature gradient of the various areas of the brain cortex was 1,9°C. Distribution of temperature fields of the left (А) and right (Б) hemisphere is symmetrical (Picture 5). Measurements have been taken from 9 spots of the right and left hemisphere as it is shown on the Picture 6.

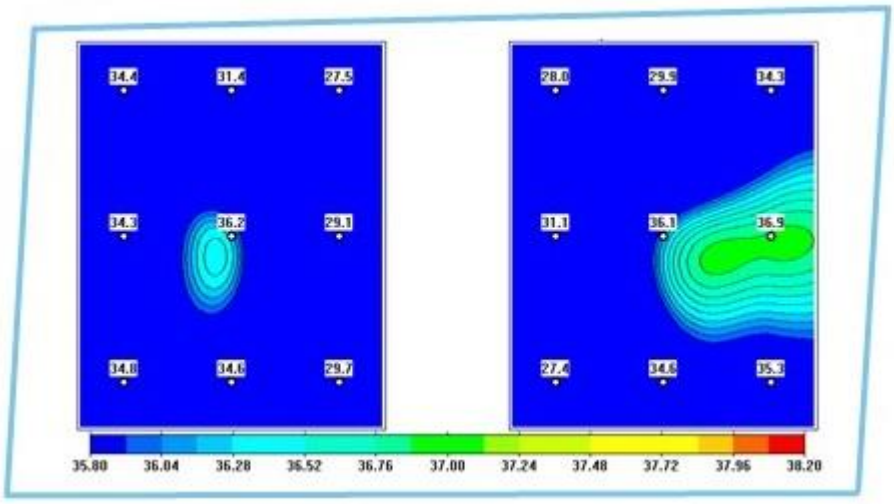
Average temperature of the left and right hemisphere were almost the same (А -36,74 ± 0,37, Б - 36,64 ± 0,32°C). After 4 hours of CCH induction, temperature distribution in the cortex of the brain changed significantly (pic. 11). Maximum gradient of the temperature in various parts of the brain reached 9,4°C. Overall, average temperature of left (А) and right (Б) hemispheres were not different (А – 32,4 ± 0,83, Б – 32,6 ± 0,91), demonstrating effect of temperature reduction of the surface of the brain in both hemispheres after CCH by more than 4°C. Temperature reduced in various areas of brain up to +27,4°C. Such deep local cooling did not provoke any unpleasant sensations and was tolerated without problems. After procedure sleepiness was recorded between 3 patients. There were no changes in cardio-vascular system and respiratory system.



Picture 7. Thermographic map of the brain of the healthy patient.



Picture 8. Areas of the measurements of creation of temperature map of the brain cortex.



Picture 9. Thermographic brain map of the healthy individual after 4 hours of CCH induction (left hemisphere and right hemisphere).

This research not only shows that CCH can be induced with this method but also confirms competence of using tympanic temperature to control brain hypothermia induction. Average tympanic temperature (left and right acoustic duct) before CCH was +36,5 ± 0,79°C, and after 4 hour session of CCH - +32,2 ± 0,67°C, demonstrating reduction of temperature by 4,3°C. Average temperature in areas (Picture 7), which are located in projection of temporal lobes and closest to areas of tympanic temperature measurements points was +36,6 ± 0,47°C before CCH, and +32,9 ± 0,76°C – after. There were no proved differences of temperature measurements, recorded in the internal area of the ear canal.

Results given below demonstrate trustworthy descriptiveness of the RRT-diagnostics which, what is significantly important, prove competence of solution to measure tympanic temperature with aim to estimate integral dynamics of hypothermia development during CCH. Registration of tympanic temperature allows not only to

simplify method of measurement of development of local hypothermia dynamics, but also to use this parameter as operating signal for feedback during CCH.

Papers about heat-mass-exchange based on the heat models of the brain show that increase in the heat flow by increase in Δt°C of the scalp/ brain surface and increase in length of cold exposition, will provide for reduction of temperature of the deep tissues of the brain. In particular, by the 4th hour of the CCH procedure, temperature of the brain conrtex is reduced by Δt°C according to our data. This forms heat flow to the outside, which reduce temperature of the subcortical structures due to the new gradient of temperature formation – cooling of cortex/subcortical structures. As a result, heat center of the brain shifts to it's base, in other words - to areas of central heat influxes. Still, depth of hypothermia penetration or shift in heat center can occur at the speed of 0,9 cm/hour[86]. With the appropriate volume and length of the heat removal, local cerebral hypothermia is formed. Cooled blood, which outflows from the brain during relatively large exposition of the hypothermia, and which is even more noticeable during thermogenesis reactions suppression, can induce mild general hypothermia.

3.3. Characteristics of TH and CCH induction among stroke patients.

It is known, that neurotrauma and vascular cerebral diseases almost always lead to significant rise of local temperature of the brain and spinal fluid[87,88,89,90]. Yet, temperature of the brain can be higher than body temperature for patients with fever and during normothermia[91].

Local hypothermia of the brain is driven by inflammation development and LP activation[92], significant increase in heat release during increase in neuronal activity and during glutamate activation, ischemia and energy deficit[93]. Inflammation is accompanied with leukocyte brain tissue infiltration, release of BAS and anti-inflammatory cytokine, which are released not only from leukocyte, but also from axon rupture[94]. «Change in metabolism» covers primary and secondary injuries and facilitates of the injury area[95]. Local hypothermia severely disturbs central thermoregulation and results in neurogen

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[86] - Obdulia Ley, Yildiz Bayazitoglu Effect of physiology on the temperature distribution of a layered head with external convection//International Journal of Heat and Mass Transfer, 46, 2003, 3233–3241

[87] - Арутюнов А.И., Семенов Н.В. О температуре мозга и ликвора его полостей в клинике и эксперименте. // Труды Киевского НИИ психоневрологии. -Киев,1949.-Т. 12, с. 150-157.

[88] - Густов А.В., Троицкий В.С., Горбачев В.П. Исследование кранио-церебральной температуры методом дециметровой радиотермометрии // Физиология человека,1985.-Т.11,N.1.-С.151-154

[89] - Ковальзон Â.Ì. Температура мозга // Журн. высшей нервной деятельности. -1969.-Т.19, N 3.-С. 516-524

[90] - Колесов С.Н., Орлов И.Я., Лебедев В.С. Перспективы развития теплорадиотермометрии в нейрохирургии// Травматическое сдавление головного мозга: Тр.Горьковского НИИТО под ред. проф. А.П.Фраермана.- Горький,1990.-с.123-129.

[91] - Busto (Busto R., Deitrich W.D., Globus M.Y., Valdes I., Scheinberg P., Ginsberg M.D. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury//J. Cereb Blood Flow Metab., 1987, 7(6).729-38

[92] - Wong CH., Crack PG Modulation of neuroinflammation and vascular response by oxidative stress following cerebral ischemia-reperfusion injury//Curr Med Chem, 2008, 15, 1-14

[93] - Halliwell B., Free radicals, antioxidants, and human disease: curiosity, cause, or consequence?//Lancet, 1994, 344, 721-4

[94] - Sugawara T., Chan PH., Reactive oxygen radicals and pathogenesis of neuronal death after cerebral ischemia//Antioxid Redox Signal, 2003, 5, 597-607

[95] - Wong CH., Crakc PJ. Modulation of neuroinflammation and vascular response by oxidative stress following cerebral ischemia-reperfusion injury//Curr Med Chem ., 2008, 15, 1-14

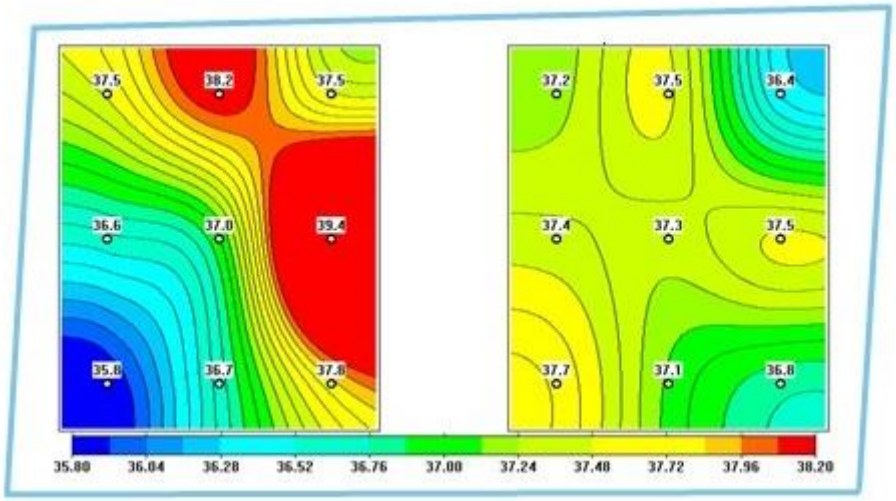
fever development[96].

During local cerebral general hypothermia, CCH induction processes have some specifications.

Among 20 patients with left-side ischemic stroke which happened no more than 24 hours ago, thermal mapping of brain cortex with «PTM-01» has been undertaken, similarly to research among healthy individuals. After that, 4 hour hypothermia was induced, which stabilized surface of the scalp temperature on the +3-5°C level, using hypothermic helmets of «THE-01». All patients were with stroke of medium severity (NIHSS[97] – approximately in the range of 8-15 points), in various degrees of consciousness, without AVL and additional sedation.

Typical picture of temperature fields distribution among patients with the stroke is represented in Picture 8.

The most noticeable thing, is a distinct temperature heterogeneity of the brain cortex, which shows up in appearance of «warmed-up» and relatively «cold» areas of the cortex of the brain.



Picture 10. Representation of temperature fields among patents with ischemic stroke (first hour, 2 centers in the left hemisphere and right hemisphere).

In the injured hemisphere maximum temperature gradient reached 3,5-4°C (among healthy individuals – no more than 1,9°C). In other hemisphere this gradient was significantly lower – approximately 1,5-2°C. Average temperature of the damaged left and right hemispheres were almost the same (А - +38,0 ± 0,45; Б - +37,94 ± 0,28°C). Average rise of the temperature in both hemispheres in comparison to healthy temperature was 1,3°C. In the area of ischemic injury centre and penumbra temperature rise was significantly defined and was equal to +38,7±0,54°C. In one case temperature in the center of injury was +42°C.

This data matches with experimental and clinical results, which are collected during direct measurement of brain temperature change during focal brain ischemia[98,99].

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[96] - Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest//N England J Med., 2002, 346(8), 557-63

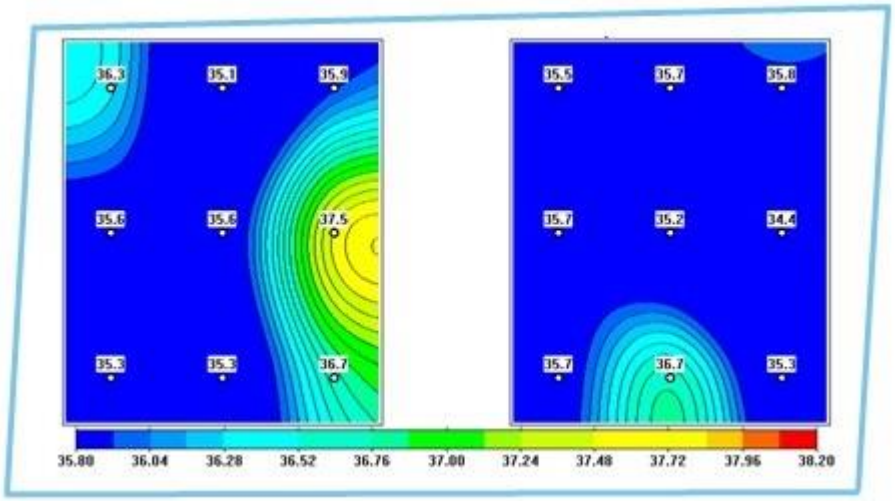
[97] – Шкала инсульта Национального института здоровья, National Institutes of Health Stroke Scale, Brott T., Adams H.P., 1989

[98] - Bartosz Karaszewski, Joanna M. Wardlaw, Ian Marshall Early brain temperature elevation and anaerobic metabolism in human acute ischaemic stroke// Brain 2009: 132; 955–964

After 4 hours of CCH induction, thermal mapping of the cortex of the brain significantly changed (Picture 11).

Temperature decreased in the center if ischemia, outside of lesion in the damaged and intact hemispheres. Average temperature in the left hemisphere reached +36,2 ± 0,27°C, in the right – +36,8 ± 0,18°C. Dynamics of tympanic temperature change had the same tendency: before CCH – +37,8 ± 0,59°C, after CCH – +36,2 ± 0,68°C.

It can be seen, that 4 hour session of CCH among patients with ischemic stroke did not lower brain cortex temperature as much as among healthy individuals. But it is important to note that in «hot» areas of the brain temperature decreased by 2-3°C, reaching almost normal values. Thermal heterogeneity of the surface of the brain significantly evened out.



Picture 11. Representation of temperature fields among ischemic strokes after 4 hour CCH session (first day, two lesions in the left hemisphere and right hemisphere).

It should be noted that among patients with ischemic stroke, heat production of the brain is substantially increased, which causes significant resistance to the cold loads and accompanied with speed reduction of the temperature decrease. Also, hypothermia induction is restrained by fever. This was particularly noticeable when basal temperature rose higher than 38°C. In this case local hypothermia development is slowed down not only because of local hyperthermia but also increased central heat inflows to the brain. Nevertheless it is possible to stabilize basal temperature among patients with fever, using CCH.

Deep temperature decrease on the surface of the scalp and it's stabilization on the level of +3-5°C provides for relatively high Δt°C on the skin/surface of the brain. This allows to form high level of heat removal and to overcome organism heat production, which requires longer time interval.

It is important to note, that induction of deep local cooling of the skin is safe, does not injure tissues with cold or evoke development of inflammation processes. CCH is applicable to conscious individuals and patients with ischemic stroke without administration of sedative medicine. Also, good individual tolerance of long procedures has been demonstrated.

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[99] - William N. Whiteley, Ralph Thomas,Gordon Lowe Do acute phase markers explain body temperature and brain temperature after ischemic stroke?// Neurology® 2012;79:152–158

3.4. Principle of operation of Therapeutic Hypothermia Equipment «THE-01».

Principle of operation of equipment is based on the technology of controlled CCH – controlled cooling of helmets – cryoapplicatiors, which provide contact heat removal from hairy part of the scalp.

Management of heat removal level is done based on the feedback from set and real temperature of the coolant in the tank, temperature of cryoapplicator, temperature of head skin in the area of cooling and in the internal part of the ear canal (tympanic temperature).

Cooling of refrigerating medium in the tank is implemented by using compression cooling unit with cold production of approximately 350...450 W. Coolant delivery to helmets cryoapplicators is regulated automatically by response of valves with electromagnetic gear. Supply of coolant and termination of circulation (automatic valves response) is achieved when controlled temperature levels reach required parameters.

Equipment is designed as small portable floor machine. On the front panel, six fast quick split joints for equipment and thermosensors connection (2 electric and 4 hydraulic).

Current temperature values are shown on the displays, which are located on the front panel of the machine.

3.5. Technology of procedure of controlled CCH.

Technology of the procedure of controlled CCH is shown based on TH Procedure Implementation Protocol using CCH for patients therapy during acute phase of ischemic stroke. This Protocol is based on the experience of CCH application among ischemic stroke patients in the ABCDB department of Hospital №1 of MPA (Management of President's Affairs) and in anesthesia and resuscitation clinical base of People's Friendship University of Russia, with consideration of international recommendations and known Protocols of GTH American Association of Hypothermia Medicine («American Society of Hypothermic Medicine», «Intensive Cold Emergency Care», http://www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml). Work is based on procedures for 80 patients with ischemic stroke.

THERAPEUTIC CRANIOCEREBRAL HYPOTHERMIA PROTOCOL

- **Estimation of congruence of the patient condition and diagnosis of the illness to the indications and contraindications for method usage, in other words criteria for inclusion and exclusion.**

«Inclusion Criteria»:

- Patients during first 24 hours of ischemic stroke debut after neurovisualisation.
- Preferably with increase of body temperature or tympanic temperature higher than 38°C.
- Among conscious patients without sedation or with impairment of consciousness of various severity during endotracheal intubation and lung ventilation, including comatose patients.
- Protocol can be completed with systolic pressure no lower than 90 mm (of mercury), pulse – no lower than 60/min.

«Exclusion Criteria»:

- Life threatening arrhythmias,
- sepsis,
- terminal diseases,
- external and internal bleeding,
- starting body temperature <34^{0} C.
- Pulmonary edema,
- Pulse lower than 60/min,
- AP-systolic lower than 90 mm of mercury

Diagnostics:

- Main diagnose:
- Collateral diagnosis:
- Competing diagnosis:
- Age:
- Height:
- Weight:
- Allergies:
- Time from the start of the sickness:
- AP:
- Heart rate:
- Level of consciousness according to Glasgo coma scale:
- Estimation of neurological deficit according to NIHSS scale:

- Breathing characteristics (occurrence of spontaneous breathing motions, absence of breathing, irregular or agonal breathing):
- Indications for intubation/ALV:
- Sedation:
- Basic therapy at the beginning of CCH (medicine/dosage):
- CT/MRT data:
- ECG data of cerebral vessels:
- Check for pregnancy for women <50 years (consultation):
- Coagulopathy or uncontrolled bleeding:
- Anti-coagulopathy/thrombolitic therapy:
- Body temperature (area of measurement):
- Tympanic temperature:
- Laboratory research:
  - General blood test + thrombocytes analysis:
  - Glucose:
  - SpO_2, oxygenation index:
  - Estimation of acid-base state and blood gases (pCO_2, pO_2, pH^-, HCO_3^-, BE):
  - FRI, INR, APTT (recommended):
  - Test of main microelements (Ca^{2+}, Na^+, K^+, Cl^-,Mg^{2+}, phosphorus) (recommended):
  - Kidney functions (urea, creatinine, TFR) (recommended):
  - CPK, Myoglobin, Troponin, D-dimer (recommended):
  - Brain natriuretic peptide (recommended):

❑ Taking of the decision about competence of the procedure.

CCH PROCEDURE (time of the procedure):

❑ Hypothermia induction.

- *Preparation for the procedure:*
  - prepare «THE-01» for work,
  - put the helmet on the patient,
  - lock the helmet with external heat insulating helmet,
  - locate temperature sensors on the helmet and in the acoustic duct,
  - register body temperature,
- *Procedure:*
  - Aim: To reduce tympanic temperature below +34, but not lower than 27°C, to maintain basal temperature during whole procedure at the level of no lower than +32°C.
  - ATTENTION! If temperature deviates below recommended, the procedure should be terminated. Patient should be warmed (covered with blanket, hot water bottle should be put to the feet).

- Control over respiratory system (SpO2, Respiratory Rate), maintain saturation at level < 90%, 10≤RR ≤ 30.
- Constant control of hemodynamic parameters (AP, RR). Maintain AP ≥90/40; 250/120≤, RR ≥50; 140≤. If hemodynamic and respiratory system measurements deviate, stop hypothermia.
- If temperature of patients body is ≥ 38°C during 12 hours after termination of the procedure, use antipyretics, repeat CCH.
- If patient has spontaneous blood circulation abnormalities, stop hypothermia.
- Try to begin hypothermia as early as possible.
- Journal of CCH procedure:

Time of the Procedure	Paraeter	Value of the parameter
0,5 hours	Body T	
	Tympanic T	
	AP	
	HR	
1 hour	Body T	
	Tympanic T	
	AP	
	HR	
2 hours	Body T	
	Tympanic T	
	AP	
	HR	
4 hours	Body T	
	Tympanic T	
	AP	
	HR	
8 hours	Body T	
	Tympanic T	
	AP	
	HR	
	NIHSS/Glasgo	
	Infusion volume	
	Medicine	
16 hours	Body T	
	Tympanic T	
	AP	
	HR	
	NIHSS/Glasgo	
	Infusion volume	
	Medicine	
24 hours	Body T	
	Tympanic T	

	AP	
	HR	
	NIHSS/Glasgo	
	Infusion volume	
	Medicine	
Warming for 30 min	Body T	
	Tympanic T	
	AP	
	HR	
Warming for 60 min	Body T	
	Tympanic T	
	AP	
	HR	
	NIHSS/Glasgo	
	Infusion volume	
	Medicine	

Data is written into Journal of CCH procedure in accordance with periods of procedure implementation. However, recommended periodicity of the tympanic and body temperature control is every 30 minutes.

- *Completion of CCH procedure:*
  - Turn off the procedure, control temperature of the helmet for 30 minutes during warming until room temperature (22-25°C), take off the helmet.
  - Control body temperature during 1 hour after completion of CCH.
  - Repeat laboratory analyses after the procedure. Enter data to the Protocol.
  - Repeat Ultrasound imaging. Enter data to the Protocol.
  - Comment on the result:

Current protocol is implemented in such cases, when temperature of patients body corresponds with normal body temperature (no lower than +36°C) or is reduced to +35°C, but not lower. Also, when this condition is not entailed by symptoms of fever or muscle shivering and patient is conscious and remains in contact. If tympanic temperature and body temperature continue to fall, it is important to control automatic switch off of the cooling in the machine for hypothermia induction in accordance with it's manual. If fever starts, the procedure should be terminated.

In cases of deep consciousness depression, intubation and AVL usage necessity, Protocol of the procedure is supplemented with recommendations for GTH procedure.