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THERAPEUTIC HYPOTHERMIA

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Living organisms according to the regulation of their body temperature are divided into two main groups, homoiotherms and poikilotherms. Homoiotherms are able to maintain constant their body temperature inspite of substantial changes of the environmental temperature. This is connected with all the time engagement of body metabolism and specific regulatory mechanisms. The body temperature of poikilotherms is closely dependent on the ambient temperature. In very low temperatures especially during winter the animals can survive by multiday hibernation which is realized by drop of their body temperature and torpor. The nature thus enbles survival by means of pronounced reduction of energy expenditure, water loss and other physiological functions. In daily poikolitherms hypothermia and torpor lasting for several hours is used by diverse species in all climate zones.

Animals regulate their body temperature by means of hippothalamic thermoregulatory centre which coordinates the production and the release of the heat. Subcutaneous and mucosal thermoreceptors mediate peripheral thermoinformation. Heat production is influenced by metabolic processes which are hormonally modified and by shivering. In newborns nonshivering thermogenesis of the brown fat is used. Important role play vasomotoric reactins as vasoconstriction or vasodilatation. Mechanisms by which the organism gains or loosis temperature are dependent on the environmental temperature. Heat loss occurs via following mechanisms: radiation-emitation of heat in temperature lower than 37 °C, conduction – loss or gain of heat by the contact with cold or warm subjects inclusive of water, convection – due to the flow of air or water and evaporation – release of heat from the skin and the respiratory system (3, 15, 38, 66). The much higher thermal and ischemic tolerance of tissues of hibernators than those of homoiotherms led to the meditation about the use of hypothermia in medicine. Many animal and human studies setteld now recognized term therapeutic hypothermia, with its positive effects on metabolic, neurologic, cardiovascular and respiratory disturbances which are summarized in contemporary reviews (49, 55, 68).

At present there are many currently avaiable methods and devices for inducing and maintaining hypothermia (32, 41, 44). Principally they are divided to surface and core cooling. Surface cooling is realized by cold air exposure of skin with fans, air-circulating cooling blankets, fluid ice packs, prerefrigerated cooling pads, water-circulating cooling blankets, selective head cooling etc. Core cooling is performed by intravenous catheters, infusion of ice-cold fluids, extracorporal circulation, peritoneal lavage (tested in animals) antipyretic agents (with low efficacy). According to the dept following ranges of hypothermia are used: mild 35.9–34 °C, moderate 33.9–32 °C, moderate deep 31.9–30 °C and deep under 30 °C.

As to the course important is the speed of induction of hypothermia with better results when cooling is initiated rapidly. Duration of cooling depends on the severity of injury. Speed of rewarming should be slow with proper management and prevention of side effects (39). Induction of hypothermia is easier in old patients due to a slower counter-regulatory response and worse in obese patients due to the insulating properties of fat tissue. Eventual initial complication as fever can be suppressed by medication as well as shivering where skin counterwarming is also possible (12, 13, 14, 67). The key beneficial of therapeutic hypothermia is the reduction of the whole body metabolism. Basal and cerebral metabolic rates decrease by about 7% for every 1 °C reduction in core temperature. Decreased utilization of glucose, oxygen and high-energy phosphates mitigates secondary energy failure (61). Insulin release and secretion are decreased, glucagon secretion increases (10). Processes that are induced by anaerobic respiration are all ameliorated. During cooling are altered pharmacocinetics and pharmacodynamic of drugs (60).

Cardiovascular effects appear as decrease of heart rate, cardiac output and arterial pressure (35). Heart rate is reduced by about 10 °C reduction in body core temperature. Also cardiac output decreases linearly with variable effects on stroke volume. Slowing diastolic repolarization increases both myocardial conduction time and absolute refractory period concomitantly with the depression of sympathetic autonomic nervous system (19). ECG changes include prolonged PR, QRS and QT intervals and in adults positive deflection between the QRS and ST segments- Osborne or J wave (12). The decrease of cardiac output is compensated by total peripheral resistence. This and the hypoxia induced loss of cerebral autoregulation maintains the cerebral perfusion. Mild hyperthermia may increase membrane stability, therby decreasing the risk of arrhytmias in contrast to deep hypothermia (40).

Hypothermia suppresses nonconvulsive and convulsive status epilepticus as well as spreading depression. There is a linear relationship between body temperature and EEG voltage. Deep hypothermia below 23 °C results in an isoelectric EEG. Nevertheless during this condition it is possible in rats and dogs to provoke epileptogenic discharges after local application of strychnine and acetylcholine to the brain cortex. Thus EEG is not a reliable indicator in the prognosis of outcome of brain ischemia (54). Hypothermia inhibits harmfull excitatory processes occuring in brain cells during ischemia reperfusion, suppresses inflammatory reactions and release of inflammatory cytokines, reduces generation of free radicales, decreases intracranial pressure which ameliorates cytotoxic edema (7).

Hypothermia may affect a broad spectrum of haematological parametres as coagulation and leucocyte function with increased risk of bleeding and infection (4, 22, 28, 30, 43, 65). Therefore application of antibiotics is recommended. Useful is also decontamination of the digestive tract (11). However in asphyxiated children prolonged hypoxia may have already altered the haemostasis before cooling is initiated.

Hypothermia may provide beneficial effects for the abdominal viscera and is hepato – and nephroprotective. It does not increase the risk of necrotising enterocolitis and reduces ischemic – reperfusion injury and microvascular permeability. During cooling it is preferable to witheld enteral feeding to prevent additional stress on intestines.

Prerequsite for sucessful application of hypothermia in the clinical praxis were animal experiments. Many animal species were used – rats, rabbits, cats, dogs, piglets, apes (24, 25, 32, 42, 45, 57). Dogs survived asystole after cooling to 1.5 °C, the heart beeting again upon rewarming the blood without any clinically detectable sequelae during a one month observation period (64). Numerous are experiments with tolerance to anoxoc ischemia in newborn and adult animal models (1, 16, 18, 24, 25, 31). In newborn dogs during profound hypothermia cerebral glucose utilisation was globally depresed but cerebral blood flow remained more than adequate to suport the energy needs of the brain (17). Brain hypothermia protects against ischemic neuronal damage even in the aged animals. Hypothermia may prevent cerebral edema and neuropathologic damage associated with hypoxic-ischemic injury in neonatal rats. Hypothermia after severe transient hypoxia delayed energy filure in newborn piglets and protected the spinal cord from ischemic injury in a chronic porcine model (58, 59). Hypothermic preconditioning increased survival of purkinje cells in rat cerebellar slices after an *in vitro* simulated ischemia (69). But there were described detrimental effects of very prolonged hypothermia in cats and monkeys with and without regional cerebral ischemia. Also in other experiments with rats deep prolonged hypothermia was followed by derangement of peripheral circulation (56).

In clinical disciplines hypothermia is mainly used in internal medicine dealing with acute heart failure, in surgery dealing with complicated operations, in neurology dealing with brain apoplexy, in neonatology dealing with anoxic-ischemic encephalopathy and in reanimatology. Studies with cardiac arrest noted significant improvement with hypothermia implementation (2, 6, 23, 48, 52, 72). It is recommended to cool most cardiac arrest to 32 °C with optimal duration of 24, 48 or 72 hours always with a slow rewarming rate. Questionable is the benefit of hypothermia in prehospital patients with out-of-hospital cardiac arrest (27).

Even patients with nonshockable rhythms should have a chance of full recovery (48). Antegrade and retrograde cerebral perfusion combined with deep hypothermia has protective effect in operations with circulatory arrest (26).

Hypothermia has neuroprotective effect after cardiac arrest (20, 34, 68, 69). Focal cooling suppresses spontaneous epileptiform activity without changing the cortical motor threshold (29), can be used for refractory status epilepticus (9) and ameliorates epileptic brain damage, while hyperthermia agravates it (8, 21b, 33, 37, 53).

Hypothermia is a potential neuroprotective intervention to treat neonatal hypoxic-ischemic encephalopathy. Meta analysis of 13 clinical trials proved reproducible reduction of mortality, neurodevelopmental disability, cerebral palsy, cognitive and psychomotor delay (49). Other publications are more critical (5, 50, 51).

As an extensive independent sphere is the use of hypothermia in cryosurgery (21a). Automated apparatusses and diverse instruments coold by liquid nitrogen (−196 °C) and nitrous oxide (−89.5 °C) are used. Surgical interventions are possible in every tissue and organ inclusive of tumours.

Quite new is cryotherapy using for cooling of the whole body extremely low temperature of 110–160 °C. In the Czech Republic it was introduced in the year 2004 in Čeladná. The procedure in this equippment passes in two steps. Clothed person stays a short time in anteroom with temperature −60 °C. After crossing into the main chambre with temperature −120–130 °C the stay is limited by 3 minutes. The result is a rapid cooling of the body surface with great hyperemia lasting for several hours. The described positive health effects are complex.

SUMMARY

In a review there are described the mechanisms of thermoregulation in homoio – and poikilotherms, the use of hypothermia in animal experiments, in the clinical praxis, in cryosurgery and in cryotherapy.

Terapeutická hypotermie

SOUHRN

V přehledu jsou popsány mechanizmy termoregulace u poikilo- a homoiotermů, využití hypotermie v pokusech na zvířatech, v klinické praxi, v kryochirurgii a v kryoterapii.

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