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SAVE OUR BRAIN

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The brain has a decisive role in the determination of the period of clinical death due to the stop of circulation and respiration. The sensitivity of nervous cells to the lack of oxygen supply limits successful resuscitation to about 5–10 minutes. After unsuccessful resuscitation begins the period of biological death with irreversible extinction of the organism. Improvements of resuscitation methods enable the restoration of the heart activity even after 20 minutes after the expiration of the period of clinical death. Together with artificial ventilation and nourishment it is possible to ensure the blood circulation and this condition maintain for a long time. Thus a complicated situation arises when preserved fundamental life functions are connected with the loss of the brain function. Diagnostic puzzles described with various terms as coma dépassé (61) were solved in 1968 with the acceptance of the diagnosis brain death (20, 78). This diagnosis is anchored in present medical terminology and enables termination of the resuscitation (75, 99). Nevertheless this diagnosis is not acknowledged in some religions. Whereas pope Pius XII declared that in a human being in the state of deep coma with artificial preservation of vital functions his spirit could already leave his body, Islamic and Jewish law Halakah affirm that respiration and heart activity not only represent life but are life as such. Even after irreversible lesion of the brain the life termination is in the hands of the Lord. Artificial ventilation and nourishment must be maintained up to the heart standstill.

The diagnosis of brain death is provided by a commission of experts. Essential are three findings: coma with non-reactivity, absence of trunk reflexes and apnoe. Repeated neurological examination in the extent of 6 hours is suitable. Confirmatory auxiliary diagnostic methods contain angiography with intracranial non-filling at the level of carotic bifurcation, Dopplerometry with absent signals, brain scintigraphy with the lack of isotopic accumulation (the sign of empty cranium), isoelectric EEG and the absence of somatosensoric evoked potentials. The diagnosis of brain death by the commission enables the termination of resuscitation. Simultaneously is thus determined the time of death (78, 80). This can be connected with juridical consequences (21, 58, 77). For instance this is demonstrated by the following casuistic. After car accident the husband was immediately dead. His wife in coma was resuscitated and after the diagnosis of brain death ten days later she was declared dead. According to the matrimonial last will in the case of death of

one member of the family all property will pass to the other. Therefore the inheritance went only to the relatives of the wife.

Circumspection is necessary in the case of diagnosis of brain death in children (48, 81, 94).

Even if the commission confirms the diagnosis of brain death, the resuscitation continues if there is possibility of organ transplantation. The realisation of transplantation is directed by obligatory instructions (5). Anencephalic new-borns are not used for transplantation (47). Persist ethical problems dealing with the possibility to use brain death patients for medical research (56) or for the training of intubation techniques (70). In 2016 a biotechnological company in USA gained a permission for research in 20 clinically dead patients (newspaper information). Resuscitation continues also in a pregnant woman in an advanced stage of pregnancy. In 2015 newspapers and television informed about the case of a pregnant Hungarian women who was after the diagnosis of brain death resuscitated for further 92 days up to the successful delivery of a normal baby.

If the resuscitated comatose patient begins spontaneously to breath he passes into the peristent vegetative state also named as appalic syndrome (15). It is specified by the damage of the brain cortex but with preservation of subcortical structures especially of the reticular formation. There is dissociation between consciousness and wakefulness. Opening of eyes is not connected with fixation of objects or persons, preserved are vegetative functions. Painful and intensive optic or acoustic stimulation leads to primitive motoric patterns and vegetative symptoms. Upper extremities are in flexion, lower extremities in extension. The patient must be artificially nourished. The care of these patients is very demanding personally, materially, financially and psychologically. Important is passive motoric mobilization and postural control for prevention of contractures and decubitus. Requisite is perfect care of hygiene. When the situation continues 4 weeks and later without amelioration the prognosis is unfavourable. Death due to complications can be expected in 2 to 5 years. In the literature there are case studies lasting 10–20 years. 2015 in the Czech Republic died after 5 years in coma Kája Saudek a world known author of comics. The problem of persistent vegetative state is very serious. Only in the USA there are several thousands of patients in this situation.

Fundamental change set in 1983. Medico-ethical commission of New Jersey granted a petition of Karen Ann Quinlan parents to interrupt artificial ventilation of her daughter which was 7 years in coma. Following this case the Supreme Court of USA 1988 settled the petition of Nancy Cruzan parents to interrupt resuscitation after 8 years lasting coma with following conclusion: 1. The case of Cruzan does not brake the law, ethical standards and clinical praxis which enables to terminate resuscitation as evolved in the USA in the case of Quinlan. 2. The competent patient has the right to refuse the resuscitation. In the USA and in some other countries is permitted a written declaration of a competent patient confirmed by a lawyer and witness of following written voluntary: In the case of my terminal state with unfavourable prognosis I refuse therapeutic processes which only prolong the process of dying.

The problems of the persistent vegetative state are here after very complicated. This is confirmed by cases published in the world press and television. For instance in Italy in 2010 the Supreme Court as well as the Parliament permitted to interrupt resuscitation of

Terri Shiavo which was 15 years in coma. Autopsy proved total necrosis of the brain cortex. There persists discrepancy between advocates of termination of resuscitation and those who insist of continuation up to the natural end. One problem that makes the decision particularly hard is the potential for error in the prognosis. An erroneous extension of this reasoning is that there is nothing to loose by continuing but everything to gain. However to unnecessary treat a patient in a quest for absolute certainty may lead to unspeakable suffering.

The interruption of resuscitation coincides with the category of passive euthanasia characterized by terminating or withholding life – sustaining treatments from the patient to let him die. Another approach is the voluntary active euthanasia that is intentionally administering medications or other interventions to cause death at the patient explicit request and with full informed consent. Non-voluntary active euthanasia is when the patient dies without its request, e. g. he may not have been asked. Indirect euthanasia is due to administering of narcotics or other medication to relieve pain with incidental consequence of causing sufficient respiratory depression to result in patient's death. A special form of euthanasia is physician assisted suicide. In Europe every form of euthanasia is illegal and criminal. Legal is euthanasia in Netherland and Belgium, assisted suicide in Switzerland. 1973 Royal Dutch Medical Association declared that euthanasia should remain criminalized but physicians should be permitted to be engaged in euthanasia for dying and suffering patients as a force majeure that is conflict between duties to preserve life and duties to relieve suffering. 1993 Dutch Parliament granted physicians immunity from prosecution if they adhere to 3 conditions: 1. The patient requests euthanasia repeatedly, consciously and freely. 2. The suffering cannot be released by any means except death. 3. The physician must consult it with other physician. In 1999 there were in Netherland presented 9,000 requests for euthanasia, 63% of them due to carcinoma, 3000 were realized. Total mortality in this year included 1.8% of euthanasia, 0.3% of physician assisted suicide and 17.5% interruption or witholding of resuscitation.

In 1986 there was described a new locked in syndrome (100). Its substance is the elimination of the brain stem for instance due to ictus but preservation of the brain cortex. The patient is completely paralyzed with the exception of eye bulbs and eye lids. By closing and opening of eye lids the patient is able to communicate (morse code) or agree with demonstrated concepts or pictures. Up to date several tenths of these cases were described. It is interesting that Alexander Dumas in his book Count of Monte Christo described paralysed Noitier de Villefort who communicated with his family by movements of his eye lids. In the literature diagnosis syndrome Monte Christo can be found. In the chronic stage the patients can continue in social activity and conduct a purposeful life. Locked in syndrome was described also in children (17).

The fundamental knowledge about the vulnerability of the brain to the insufficiency of oxygen supply was gained by huge amount of animal experiments. Mostly were used mice, rats, guinea pigs, gerbils, cats, dogs and monkeys (9, 55, 95). Among different methods mostly used are anoxic anoxia due to the interruption of oxygen supply to the lungs (24, 68), anemic anoxia due to lower capacity of blood to supply tissues with oxygen (28, 48), stagnant anoxia due to the interruption of blood supply to the brain (86) and histotoxic anoxia due to the blockade of cellular oxidoreductive mechanisms (26). Methods in vitro

are also used (28). Next we will be engaged with the model of brain ischemia which best correlates with the situation of the arrest of heart activity. This can be achieved either by occlusion of cerebral vessels or by perfusion of the isolated head which enables its regulation (2, 16, 25, 27, 41, 49, 57, 86, 93, 98). Interruption of the brain circulation leads to immediate EEG changes. It becomes isoelectric already in 15–20 seconds. In experiments with dogs normal EEG could be registered even after 20 minutes lasting complete ischemia. After several hours there could be registered EEG (Fig. 1) and typical epileptogenic discharges after local application of strychnine and acetylcholine to the brain cortex (Fig. 2, 3) as well as the renewal of energetical and structural metabolism (Fig. 4) (80). Further normalized electroretinogram (3, 63, 79), papillary diameter (43, 90) and impedance of the brain cortex (51, 62, 97).

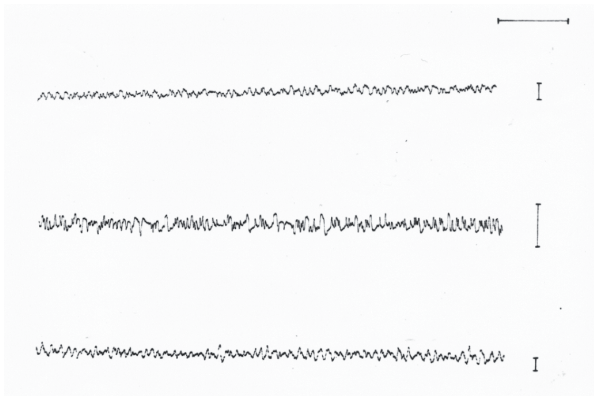

Fig. 1 Spontaneous EEG in 3 experiments with 60 min. lasting ischemia. 1st row-after 4 hours, 2nd row-after 6 hours, 3rd row-after 11 hours of reperfusion. Calibration: seconds, 50 microvolts.

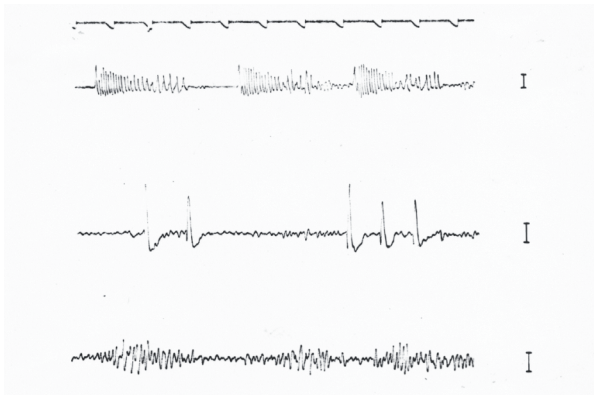

Fig. 2 1st row-seconds, 2nd row-acetylcholine discharges, 200 mV, 3rd row-strychnine discharges – 500 mV, 4th line – spontaneous EEG 200 mV in the 5th hour of resuscitation after 30 min. lasting complete brain ischemia.

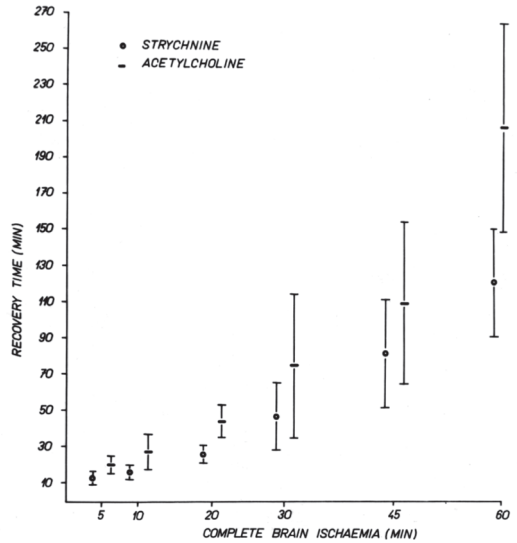

Fig. 3 Renewal of acetylcholine and strychnine discharges depending on the time of complete ischemia.

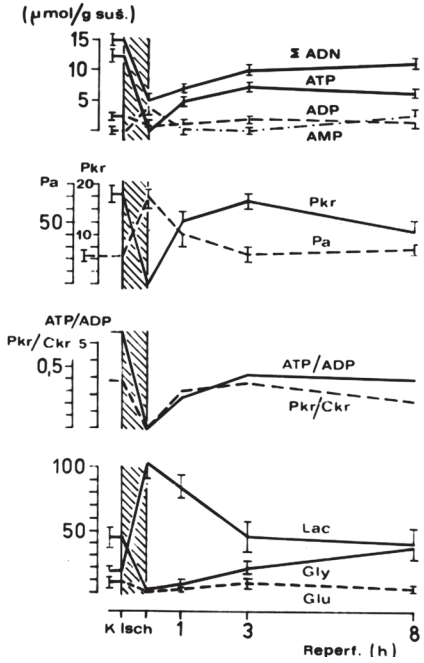

Fig. 4 The level of energetical metabolites in controls (K), after 30 min. lasting ischemia and after reperfusion lasting 1, 3 and 8 hours in micromoles/g of dry substance.

Ischemia leads to serious disturbances of the brain metabolism (82). The main sources of energy from carbohydrates and energetic phosphates are depressed as well as the metabolism of fats which participate on the structure of the nervous tissue, especially on the formation of neuronal myelin sheaths and membranes of nervous cells. Increases cytosolic concentration of calcium which activates proteases participating on the destruction of cellular membranes. The loss of ionic homeostasis together with accumulation of water leads to brain edema which reduces blood circulation. Harmful is the effect of arising oxygen radicals. All these changes substantially impair the brain resuscitation. Experiments with long lasting complete ischemia in dogs proved that immediate and complex resuscitation enables normalization of the metabolism of carbohydrates, energetic phosphates and the brain oxidative capacity up to 30 minutes lasting interruption of blood circulation (35, 69, 87, 88). These results correlated with minimal morphological changes of the brain cortex and with normal structure of the brain stem and cerebellum (52, 59). Bodsch et al. (13) described in monkeys recovery of brain protein synthesis following 1 hour of complete ischemia at various postischemic periods between 1.5 and 24 hours. This correlated with electrophysiological observations and with appearance of cells. Hossmann (39, 40) described recovery of neuronal transmission after 1 hour lasting brain ischemia in cats. Exceptional is 1 year survival of a cat after 1 hour lasting ischemia with recovery of spontaneous respiration and motility.

Striking and fundamental is the difference between successful resuscitation after long lasting experimental brain ischemia and resuscitation after cardiac arrest in clinical praxis. The basic factor is the intensity of blood circulation after the end of ischemia. In experiments with isolated dog head the circulation is at once restored with normal systolic and diastolic pressure. Beside supply of oxygen and energetic resources can be in use the rinse out effect, which removes osmotic active products of anaerobic metabolism from the brain circulation. These metabolites together with the disturbance of ionic homeostasis contribute to brain edema. In our experiments the imminent edema which was indicated by lowering of blood circulation could be eliminated by application of plasma expanders (85, 86). Contemporary level of cardipulmonal resuscitation of the heart activity (89) exceeds the period of clinical death. Critical is the following time when the restoration of heart activity does not correlate with the restoration of brain function. In this connection it is considered a postresuscitation disease which can be connected with other severe complications as acute respiratory distress syndrome (ARDS) or sepsis (66, 67).

In the future it would be desirable to direct the research to the development of new resuscitation methods directed to the restoration of brain activity. Above all it is important to assure sufficient blood circulation already at the beginning of resuscitation when the effectivity of heart contractions gradually increases. This initially limited output could be improved by the use of extracorporeal pump. Isolated brain perfusion is used in patients with brain tumours. The advances in reconstructive surgery of brain vessels are perspective (64). The brain circulation can be improved by application of plasma expanders (14, 29, 42), by cautious use of anticoagulants and removal of acidosis. Universal importance has therapeutic hypothermia. It is necessary to critically evaluate the role of hyperbaric oxygenotherapy. There is a broad spectrum for application of different substances as

reduction agents, for instance iodine compounds, calcium antagonists, growth factors, stem cells etc. It can be presumed that in the future the research and clinical experience will improve the resuscitation methods and thus prolong the period of clinical death.

SUMMARY

The present level of cardiorespiratory resuscitation methods enables the restoration of life exceeding the period of clinical death lasting about 10 minutes. The restoration of heart activity after this period does not correlate with the restoration of the brain functions. Clinical death is thus followed by brain death, persistent vegetative state or locked in syndrome. Animal experiments demonstrate that optimal resuscitation methods can restore electrophysiological and metabolic functions as well as morphology of the brain even after total brain ischemia lasting up to 30 minutes. These results lead to the possibility to prolong the period of clinical death after the development of new effective methods of cerebrocardiorespiratory resuscitation.

Zachraňte náš mozek

SOUHRN

Současná úroveň kardiorespirační resuscitace umožňuje obnovu života v období klinické smrti trvající kolem 10 minut. Obnova srdeční činnosti následující po tomto období nekoreluje s obnovou funkcí mozku. Klinická smrt tak přechází ve smrt mozku, perzistentní vegetativní stav nebo locked in syndrom. Pokusy na zvířatech prokázaly, že při optimalizaci resuscitačních metod lze obnovit elektrofyziologickou a metabolickou funkci mozku i jeho morfologii až po třicetiminutové úplné ischémii. Tyto výsledky potvrzují, že je možné prodloužit období klinické smrti v závislosti na vývoji účinných metod cerebrokardiopulmonální resuscitace.

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