OXYGEN THERAPY IN THE RECOVERY PERIOD FOLLOWING CLINICAL DEATH

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Management of the recovery period following clinical death is one of the least investigated phases of pathological physiology and therapy in terminal conditions.

In the process of dying, in clinical death and in the recovery period following, one can observe intense hypoxia of various types, as shown by the work of V. A. Negovskii [10], M. S. Gaevskaia [5], E. M. Smirenskaia and E. S. Zolotokrylinaia [16], O. N. Bulanovaia [3]. It is only natural that the matter of abolishing the hypoxia by administration of oxygen presents a fundamental therapeutic problem during the recovery period.

The literature contains a variety of opinions on the subject of administration of oxygen in hypoxia. A number of investigators [4, 19, 23 and others] are of the opinion that administration of 100% oxygen is indicated in hypoxia; the majority of authors [2, 9, 13, 14, 18, 20-22] point out the hypersensitivity of the organism in intense hypoxia to oxygen and the possibility of producing the paradoxical action of oxygen – hyperoxia.

This makes it imperative to investigate the possibility and effectiveness of the use of oxygen in the recovery period following clinical death. The following experiments were carried out in investigating this problem.

EXPERIMENTAL METHODS

We carried out experiments upon 40 adult dogs. A state of clinical death was produced in animals, anesthetized with pantopon and ether, by massive bleeding from the femoral artery. The period of dying lasted from 7 to 20 minutes, clinical death lasted 5 minutes. Vital functions were restored by the method developed by V. A. Negovskii and co-workers. Oxygen therapy was begun at different stages of the recovery period following clinical death and was administered by methods used in clinical medicine: artificial respiration during resuscitation, oxygen inhalation from a bag or in an oxygen tent after restoration of spontaneous respiration. Depending on the method employed the experiments were divided into three groups. In group III determinations of the gaseous content of blood flowing to and from the brain and of the rate of blood flow were made by Komissarenko's method.

The effectiveness of oxygen therapy was determined by estimating the general condition of the animals (pulse, respiration, temperature, blood oxygen saturation, pulmonary ventilation, rate of blood flow, etc.), the survival period following clinical death and the morphological changes. Viability of the animals after clinical death was determined by the time it took to re-establish respiration. According to V. A. Negovskii's data, complete restoration of vital functions takes place in 1-3 days in animals which were denied oxygen therapy and in which respiration was re-established in $1\frac{1}{2}$-2 minutes following clinical death of 5 minutes duration; in animals in which respiration was re-established in 4-5 minutes complete restoration of vital functions occurred in 4-6 days and only in 60% of the cases, and in animals in which re-establishment of respiration took 7-9 minutes the mortality rate in the first day was 98-100%.

Histological examination of the brain and viscera was performed on 20 dogs in group III. Fourteen of the 20 died in 1-5 days, one on the 30th day and 5 were sacrificed on the 14th, 47th, 67th, 75th and 97th day, respectively, following the experiment. The brain was stained by the method of Nissl, Snesarev (for astrocytic glia, argyrophilic granules and connective tissue), Miiagav (as modified by Alexandrovskaia) and Bil'shovski. The viscera was stained for fat with hemotaxylin-eosin according to the method of Van Gieson.

EXPERIMENTAL RESULTS

In the 9 dogs of group I in which artificial respiration using 100% oxygen was administered at the rate of 24-28 per minute, it took 2-2½ times as long to re-establish spontaneous respiration. When apparatus inducing active inspiration and expiration was employed, spontaneous respiration was re-established in 4-5 minutes and in control animals in 1½ -2 minutes; only in one dog was respiration re-established rapidly – in 2 minutes, as in the controls. When apparatus for inducing artificial respiration was used only during active inspiration, respiration was re-established in 5-8 minutes and in the controls 2-4 minutes. The delay in re-establishing respiration in these experiments was due, according to the data in the literature ([24] and others), to central nervous system depression, particularly the respiratory center, by oxygen. The delay was not great because superimposed on the depression of the respiratory center was the sensitivity of the center to reflex stimulation brought about in our experiment by means of artificial respiration. Most of the experimental animals in this group (7 of the 9), including the dog in which there was no delay in re-establishing of respiration, perished. In the remaining 2 animals artificial respiration with oxygen had no effect; in them complete re-establishment of vital functions was observed after an interval typical for controls (see Table).

TABLE

Results of Oxygen Therapy Following Clinical Death from Blood Loss

Experiment group	Type of oxygen therapy	No. of experiments and oxygen dosage	Results			
			animals died in 1-5 days	no effect	Prolongation of life	complete re-establishment of respiration
I	Artificial respiration with oxygen	9 expts. 100% oxygen	7 (2-8 min)	2 (3-4 min)	—	—
II	Inhalation of oxygen from a bag	9 expts. 100% oxygen:	3 (3-3½ min)	—	—	—
		3 expts.–5 min. every 20 min.	—	1 (10 min)	4 (5—7 min)	1 (5½ min)
		6 expts.–3 min. every 30 min.			8—47 days	46 hrs
III	Inhalation of oxygen in tent	22 expts.				
		3 expts.–70% oxygen, 2 hrs	3 (1½—2 min)	—	—	—
		12 expts.–40-50% oxygen, 2 hrs.	—	12 (2—10 min)	—	—
		7 expts.–40-50% oxygen, 4 hrs.	—	—	4 (6½—9½ min)	3 (4½—7 min)
					8—97 days	2—3 days
total (40 dogs)			13	15	8	4

Note: The time consumed in re-establishing respiration is shown in parentheses.

In group II (9 dogs) inhalation of 100% oxygen during the recovery period was administered from a rubberized bag using a mask equipped with inspiration and expiration valves. Inhalation was begun 45-60 minutes following the beginning of resuscitation, when, according to E. M. Smirenskaia [15] and M. S. Gaevskaia [5], the brain begins to consume oxygen more actively, changing from glycolysis to oxidation of carbohydrates. Respiration at this time was spontaneous, 22-28 per minute and arterial blood pressure was 100-130 mm of mercury.

The results obtained in these experiments depended upon the dosage of oxygen. In 3 dogs in which respiration was reestablished in 3-3½ minutes, inhalation of oxygen from the bag for 5 minutes at 20 minute intervals quickly caused deterioration of their condition. After 6-9 such sessions clonic and tonic convulsions of the extremities and a rise of the respiratory rate to 45-54 per minute were observed in the previously quiet animals. When oxygen therapy was continued stronger convulsions extending to the musculature of the trunk and head were observed, the respiratory rate rose to 120-170 per minute and profuse bloody stools were expelled. The dogs died after 10-18 sessions of oxygen therapy over a period of 13-19 hours from the time of resuscitation. The clinical picture and morphological findings corresponded to the symptoms of hyperoxia, described by a number of workers [6, 8, 13, 25-27]. In healthy animals such dosage of oxygen caused no change in their condition. From the data available in the literature one may assume that the most likely mechanism of hyperoxia consists in diminution of ability to accommodate to the hypoxia and in the accumulation in the tissues of carbon dioxide which has a narcotic effect.

As the period of oxygen inhalation was lowered to 3 minutes, the interval increased to 30 minutes and the sessions repeated 8-9 times per day over a period of 5-9 days, oxygen therapy in one dog failed to influence the process of recovery and it died on the first day, as anticipated because of the longer period required to reestablish respiration (10 minutes; see Table). In the remaining 5 dogs there was some clinical evidence of the favorable effect of oxygen therapy. It took the form of prolongation of life to 5-47 days in obviously nonviable dogs with delayed re-establishment of respiration (6-7 minutes). However, complete re-establishment of vital functions was observed in only one of these dogs and took place in 46 hours. Under such conditions controls die within the first day.

In group III (22 dogs) inhalation of air enriched with oxygen to 40-70% was administered in an oxygen tent during the recovery period. The results also depended on the dosage of oxygen and the time when oxygen therapy was started. Three viable dogs with periods of re-establishment of respiration of 1½-2 minutes which were given inhalation of 70% oxygen for 2 hours per day died during the first day with symptoms of hyperoxia. In 2 of these, oxygen therapy was begun 45-60 minutes and in one – 90 minutes after the beginning of resuscitation, when the brain already actively utilizes oxygen. In the case of healthy animals placed in an atmosphere of oxygen of similar concentration for a period 2-3 times greater, no alteration of their condition or harmful effects were noted.

However, in the case of one dog not subjected to clinical death, but in a state of neurosis (established by the method of conditional reflexes), a one hour exposure in an oxygen tent containing 75% oxygen resulted in an abrupt motor excitement and dyspnea (120 respirations per minute) with death following 13 minutes after removal from the tent and due to hyperoxia as was confirmed by morphological examinations.

These experiments indicated the necessity of lowering the oxygen content in the tent, and for the following 12 dogs its content was reduced to 40-50%. That such oxygen dosage is more rational is evident from data in the literature [1, 7, 11, 17, 21, 28, etc.]. Exposure of animals to such a content of oxygen in a tent for 2 hours 40-60 minutes from beginning of resuscitation did not influence the process of subsequent recovery and the outcome of the experiment was determined by the period of re-establishment of respiration (see Table). Oxygen saturation of the blood of these animals rose by 2-4% (from 91-96 to 94-98%) only while they remained in the tent and rapidly fell to initial values when removed from the tent.

Consequently, in the next 7 experiments on animals with longer periods of re-establishment of respiration (4½-9½ minutes) we extended administration of oxygen therapy to 4 hours a day using concentrations of 40-50%; the sessions were instituted 80-112 minutes after beginning resuscitation and were repeated during the following 2-15 days. In 3 animals in which respiration was re-established in 5-7 minutes, complete recovery of vital functions took place; in the remaining dogs life was prolonged to 8-97 days, but significant neurological disturbances were observed.

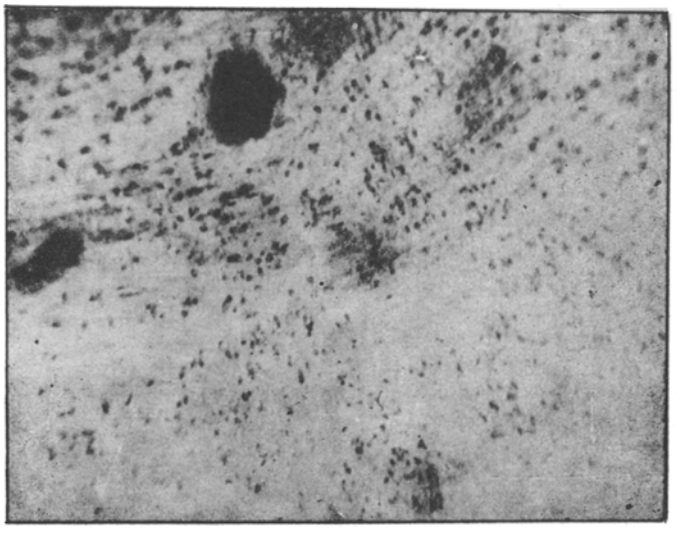

Fig. 1. Numerous small hemorrhages in the cortex of the brain of a dog which endured a state of hypoxia. Stained according to Nissl. Magnification 7 x 8.

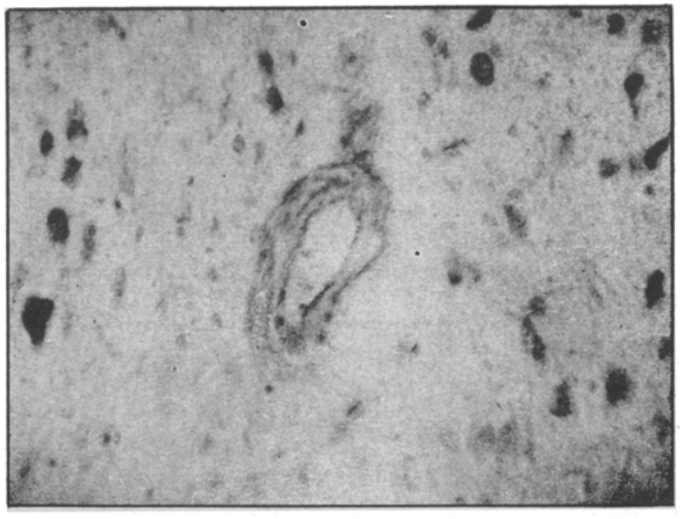

Fig. 2. Thickening and homogenicity of the vessel wall in the brain of a dog which endured a state of hyperoxia. Stained according to Nissl. Magnification 7 x 40.

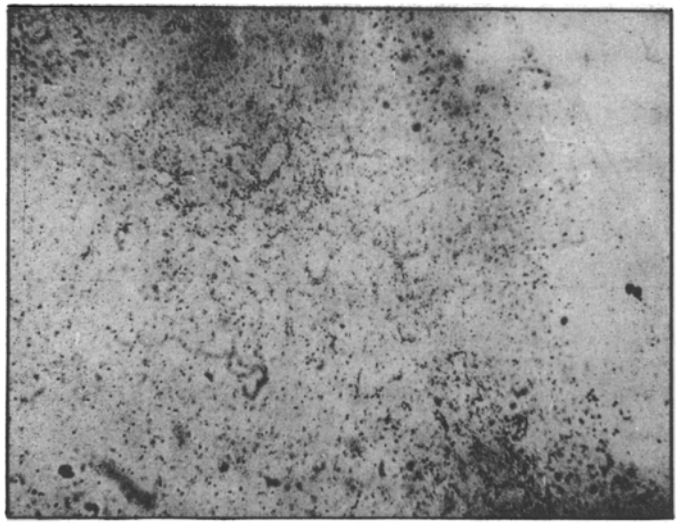

Fig. 3. Extensive focus of necrosis of nerve cells in the cortex of the brain of a dog with delayed re-establishment of respiration, sacrificed on the 67th day after the experiment. Stained according to Nissl. Magnification 7 x 8.

The animals lay quietly in the tent, the pulse rate fell (from 70-150 to 50-90), moderate slowing down of blood flow ($1\frac{1}{2}$-2 times) and of pulmonary ventilation were noted. Respiration and body temperature showed no uniform changes. Changes in oxygen saturation of the blood were slight – 2-4% and only while in the tent. The normal difference between oxygen and carbon dioxide levels in arterial and venous blood was observed to increase and a rise in the carbon dioxide level in both arterial and venous blood and in the oxygen content of arterial blood was observed. These changes in the gas content of blood were analogous to the findings obtained by us in experiments without administration of oxygen therapy [15].

Histological examination of the brain disclosed diffuse and focal changes; their character varied depending upon the dosage of oxygen and the length of survival after the experiment. Diffuse changes in the nerve cells, glia and argyrophilic granules did not differ from those observed by us in animals which were not given oxygen therapy as a resuscitation measure after a 5 minute clinical death, i. e. controls [12].

Characteristic of the animals which exhibited the clinical phenomenon of hyperoxia and which perished in the days immediately following the experiment, was the large number of hemorrhages (Fig. 1), perivascular edema and changes in vessel walls (Fig. 2) in all parts of the brain.

The animals with delayed restoration of respiration (5-$9\frac{1}{2}$ minutes) which we succeeded in keeping alive 8-97 days were regarded by us from the clinical standpoint as having benefited somewhat from the effect of oxygen. Histological examination revealed considerable changes in these animals. In the cortex, cerebellum and the horn of Ammon were found numerous areas with small foci of necrotic nerve cells; in the cerebellum, besides the death of the cells of Purkinje, there were extensive areas of rarefaction in the granular layer. Such large numbers of widely scattered areas of nerve cell necrosis were never seen in controls. Besides, in some of these animals we discovered focal changes in the cortex with destruction of tissue architecture (Fig. 3). Depending on the length of survival of the animal after the experiment, various stages of scar organization were observed at the site of focal tissue destruction.

In the dog with neurosis, which died after a one hour stay in the oxygen tent, numerous hemorrhages and acute congestion of the viscera were observed at autopsy. Microscopic examination disclosed numerous hemorrhages in the brain and viscera as well as acute swelling of many nerve cells in various parts of the brain.

In the internal organs, besides changes also seen in controls (hyperemia, edema) and depending on the severity of hypoxia suffered during clinical death, were seen numerous hemorrhages and changes in vessel walls similar to those in the brain. Pneumonia with large numbers of epithelial cells within the alveoli was found in almost all the animals.

Investigation indicated that in animals undergoing clinical death there was an alteration is response and consequently administration of oxygen resulted in death of 13 out of 40 during the first day; in 15 animals oxygen therapy had no effect and the outcome of the experiment depended, as in controls, upon the period of re-establishment of respiration; in 8 nonviable dogs oxygen therapy permitted prolongation of life to 5-97 days, but all animals died and in their brains marked changes, including focal ones, were found; only in 4 animals was there evidence of favorable effect of oxygen therapy and in these complete restoration of vital functions was observed in association with longer periods of re-establishment of respiration ($4\frac{1}{2}$-7 minutes). Therefore animals undergoing clinical death possess an increased sensitivity to oxygen. Its administration easily produces hyperoxia and leads to death.

Artificial inhalation of 100% oxygen in resuscitation from clinical death appears to be inexpedient. The dosage of oxygen must be strictly supervised when oxygen therapy is given during the recovery period. A limited favorable effect of oxygen therapy is produced when oxygen therapy is administered in a tent containing 40-50% oxygen for not less than 4 hours and starting 80-112 minutes after beginning of resuscitation.

The elimination of hypoxia during the recovery period is not a basic therapeutic measure. Strictly controlled oxygen therapy, it seems, is more effective when combined with other therapeutic measures.

SUMMARY

Forty experiments were carried out on dogs with the employment of oxygen therapy during the period of recovery from clinical death caused by acute hemorrhage. Oxygen therapy was carried out by 3 methods commonly used in the clinic: by an apparatus for artificial circulation, by inhalation of oxygen from a pillow or

in an oxygen tent after rehabilitation of spontaneous respiration. The efficacy of oxygen therapy was judged by the general condition of animals, the span of life after the clinical death and by the morphological changes in the brain and internal organs.

The animals which are in condition of hypoxia after clinical death possess an increased sensitivity to oxygen and hyperoxia may easily occur, causing their death. Artificial respiration with 100% oxygen in resuscitation during clinical death is not expedient. During the recovery period after clinical death strict dosimetry of oxygen therapy should be observed. Certain favorable effects are obtained only when resuscitation is carried out for 4 hours in a tent with oxygen content of 40-50% in 80-112 minutes after commencing the resuscitation.

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