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Failure of hypothermia as treatment for asphyxiated newborn rabbits

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Oates, R. K., and Harvey, D. (1976). *Archives of Disease in Childhood*, **51**, 512. **Failure of hypothermia as treatment for asphyxiated newborn rabbits.** Cooling is known to prolong survival in newborn animals when used before the onset of asphyxia. It has therefore been advocated as a treatment for birth asphyxia in humans. Since it is not possible to cool a human baby before the onset of birth asphyxia, experiments were designed to test the effect of cooling after asphyxia had already started.

Newborn rabbits were asphyxiated in 100% nitrogen and were cooled either quickly (drop of 1 °C in 45 s) or slowly (drop of 1°C in 2 min) at varying intervals after asphyxia had started. When compared with controls, there was an increase in survival only when fast cooling was used early in asphyxia. This fast rate of cooling is impossible to obtain in a human baby weighing from 30 to 60 times more than a newborn rabbit.

Further litters of rabbits were asphyxiated *in utero*. After delivery they were placed in environmental temperatures of either 37 °C, 20 °C, or 0 °C and observed for spontaneous recovery. The animals who were cooled survived less often than those kept at 37 °C. The results of these experiments suggest that hypothermia has little to offer in the treatment of birth asphyxia in humans.

Hypothermia has been recommended several times in the past as a treatment for neonatal asphyxia (Miller, 1949; Cordey, 1964; Miller, 1971; Westin, 1971). The rationale for this approach is van't Hoff's rule which states that the rates of chemical reactions vary with temperature. The theoretical advantages of hypothermia are a decrease in oxygen demand (Bigelow *et al.*, 1950), a decrease in coronary and carotid resistance (Berne, 1959; Westin, Sehgal, and Assali, 1961), reduced glycogen loss from the heart and brain (Zakhary, Miller, and Miller, 1967), and an increase in oxygen transporting capacity of blood (Westin *et al.*, 1962). Experiments in animals show that cooling, induced immediately before experimental asphyxia, resulted in either longer survival or spontaneous recovery from a period of asphyxia which was lethal for warm litter mates (Miller, 1961; Miller, Miller, and Westin, 1964).

After demonstrating that hypothermia prolongs survival in asphyxiated newborn animals, deliberate cooling was recommended for the treatment of asphyxia in human newborn babies (Miller, 1971; Westin, 1971). The animal experiments on which this recommendation was based are not entirely applicable to humans. The rate of cooling in the small animals used was faster than could easily be achieved if deliberate cooling were used in the delivery room; the asphyxia was not induced immediately at birth (Miller *et al.*, 1964; Miller and Miller, 1965) and in most of the experiments the cooling preceded asphyxia (Miller, 1949; Miller *et al.*, 1964), whereas in the human situation asphyxia will precede cooling.

The following experiments were performed to investigate the effect of cooling started at varying intervals after the onset of asphyxia; to assess the relative effectiveness of different rates of cooling; and to assess the effects of cooling after varying periods of intrauterine anoxia.

Methods

Group A: Newborn rabbits asphyxiated at birth. Pregnant rabbits at term were killed by a blow on the head. The fetuses were delivered immediately by caesarean section and placed in a chamber containing

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air at 37 °C. All animals breathed spontaneously at delivery and were active; half of each litter served as controls for the remainder. The control group from each litter was transferred into a chamber, maintained at 37 °C, through which flowed 100% nitrogen. The animals were observed until all respiratory movements ceased. This interval, from the start of asphyxia to the end of all breathing movements, was recorded as the time to the last gasp (TLG). The mean TLG was calculated for the control group in each litter.

The experimental (hypothermic) group from each litter was kept in 100% nitrogen for one and a half times the mean TLG of their controls, so that any survivals could be attributed to hypothermia rather than to their being hardy animals. Previous experiments had shown that when hypothermia was induced before asphyxia, survivals occurred when the animals were anoxic up to three times the mean TLG of controls (Miller *et al.*, 1964). Asphyxia in the experimental group was carried out as described below. In each group five litters were used.

Group 1. Rabbits were asphyxiated either singly or in pairs in a small transparent chamber through which flowed 100% nitrogen. The chamber was immersed in a water bath at 37 °C. The animals were then asphyxiated at 37 °C for $\frac{3}{4}$ of $1\frac{1}{2}$ times the mean TLG of their litter mate controls. After that time had elapsed, and while asphyxia continued, the chamber was cooled in another water bath. In half the cases the water bath was at 20 °C, producing a fall in the rabbit's temperature of approximately 1° C every 2 minutes. In the remaining cases the water bath was at 10 °C and the nitrogen was cooled by passing it over ice to produce rapid fall in the animal's temperature. In each case, anoxia was continued until $1\frac{1}{2}$ times the mean TLG of the litter mate controls, then air was given and the rabbits were observed for spontaneous recovery. The temperature was recorded every 2 minutes by a thermistor inserted 1-2 cm into the rectum. The gasp pattern during asphyxia was observed and the TLG recorded.

Group 2. A similar procedure was used, but cooling in the experimental group was started at an earlier stage, after anoxia had been used for only half of $1\frac{1}{2}$ times the mean TLG of litter mate controls.

Group 3. In this group cooling was begun after anoxia had been in progress for $\frac{1}{4}$ of $1\frac{1}{2}$ times the mean TLG of litter mate controls.

Group B: Rabbits asphyxiated in utero. Pregnant rabbits were killed one day before term. The fetuses were quickly delivered by caesarean section between 17 and 18 minutes after the death of the mother. This period was chosen because it was the mean TLG of the first 25 control rabbits asphyxiated in group A (17 min 33 s). Immediately after delivery one-third of the litter was placed in air at 37 °C, one-third was placed in air at 20 °C, and one-third was placed in iced water, their heads being exposed to air. Allocation to these three groups was random and 4 litters were used. Apart from cooling, no attempts were made to resuscitate the animals and they were observed for signs of spontaneous recovery. Temperature in the cooled animals was recorded every 2 minutes by a rectal thermistor. After 30 minutes of cooling the animals were rewarmed by returning them to a chamber at 37 °C.

The same procedure was used for three more groups, each of 4 litters, with the exception that the time between the death of the mother and delivery of the fetuses was varied. In the 2nd, 3rd, and 4th groups delivery was after $\frac{7}{8}$, $\frac{3}{4}$, and $\frac{1}{2}$ of the time used in the first group (17 min 33 s).

Results

Group A. Table I shows the survival rates of those rabbits who were asphyxiated for $1\frac{1}{2}$ times the mean TLG of their litter mate controls, with hypothermia started after $\frac{3}{4}$, $\frac{1}{2}$, and $\frac{1}{4}$ of that time. Table I also compares the survival of rabbits which were cooled quickly and slowly. It can be seen that in the groups where cooling was started after $\frac{3}{4}$ and after $\frac{1}{2}$ of $1\frac{1}{2}$ times the mean TLG, few animals survived, suggesting that hypothermia has little to offer when there has already been a significant degree of asphyxia. When hypothermia was started earlier in asphyxia, after $\frac{1}{4}$ of $1\frac{1}{2}$ times the mean TLG of the controls, there was a marked improvement in survival, but only in those animals

TABLE 1

Survival of newborn rabbits asphyxiated for $1\frac{1}{2}$ times the mean time to the last gasp (TLG) of litter mate controls, when hypothermia was started after $\frac{3}{4}$, $\frac{1}{2}$, and $\frac{1}{4}$ way through asphyxia

Rate of cooling	Duration of asphyxia before cooling					
	$\frac{3}{4}$ of $1\frac{1}{2}$ TLG of controls		$\frac{1}{2}$ of $1\frac{1}{2}$ TLG of controls		$\frac{1}{4}$ of $1\frac{1}{2}$ TLG of controls	
	Died	Survived	Died	Survived	Died	Survived
Slow (20 °C)	10	0	12	1	10	0
Fast (10 °C)	9	0	12	0	5	5

which were cooled rapidly. Of the 10 rabbits cooled slowly, hypothermia did not produce any survivors, but 5 of 10 cooled rapidly did survive ($P > 0{\cdot}001$.)

The mean time for rectal temperature to fall by 1 °C in each group is shown in Table II. The rate

TABLE II

Average time in seconds for rectal temperature to fall by 1 °C

Time of starting cooling	Cooled slowly	Cooled quickly
After ¾ of 1½ mean TLG of controls	117	41
After ½ of 1½ mean TLG of controls	103	47
After ¼ of 1½ mean TLG of controls	124	50
Mean	115	46

of temperature fall in the group cooled at 20 °C is approximately 1 °C every 2 minutes, while the temperature in the group cooled quickly fell at an average of 1 °C every 45 seconds.

Group B. *Rabbits delivered after mean TLG of controls (17 min 33 s of intrauterine anoxia).* None of these animals gasped at delivery and there was no recovery at either 37 °C, 20 °C, or in iced waer.

Rabbits delivered after ⅞ mean TLG of controls (15 min 20 s of intrauterine anoxia). Fig. 1 shows the number of animals gasping at delivery and the number which survived when placed in air at 37 °C, 20 °C, and in iced water. No animals which were not gasping at delivery subsequently recovered. There is no difference in survival in the three groups.

Rabbits delivered after ¾ of mean TLG controls (13 min 9 s of intrauterine anoxia). Fig. 2 shows the results for this experiment. Survival rates in

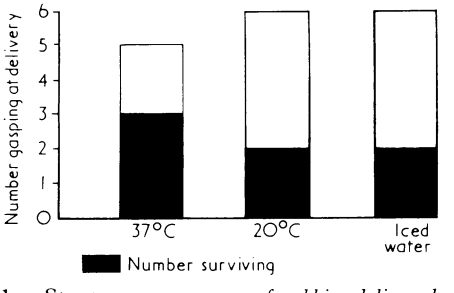

FIG. 1.—*Spontaneous recovery of rabbits delivered after 15 min 20 s of intrauterine anoxia.*

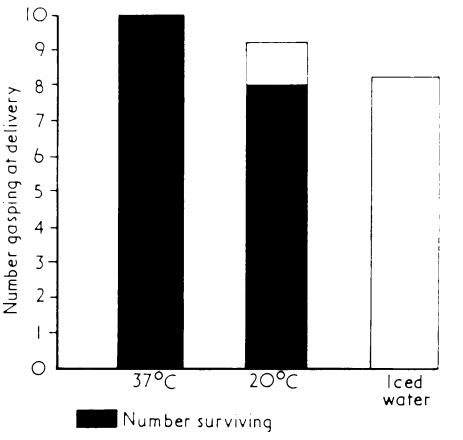

FIG. 2.—*Spontaneous recovery of rabbits delivered after 13 min 9 s of intrauterine anoxia.*

rabbits left in air at 37 °C and at 20 °C were very similar, but there were no survivors in the group placed in iced water, even though 8 of this group gasped at birth ($P > 0{\cdot}01$). The gasps stopped within 4–6 minutes of placing the rabbits in iced water and did not begin again during the cooling period or during the rewarming which was begun after 30 minutes of cooling. No animals which were not gasping at delivery subsequently recovered.

Rabbits delivered after ½ of mean TLG of controls (8 min 46 s of intrauterine anoxia). Fig. 3 shows that the incidence of recovery at 37 °C and 20 °C was similar, but fewer animals survived when they were placed in iced water, even though they were

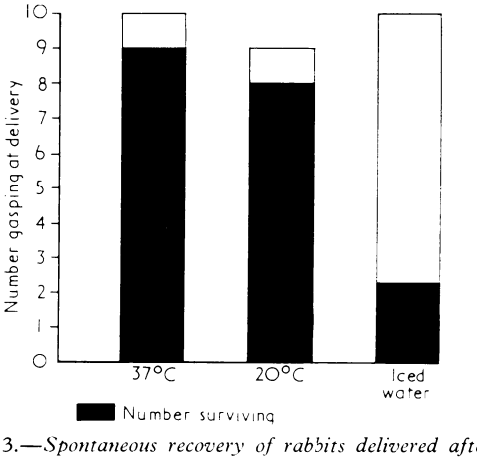

FIG. 3.—*Spontaneous recovery of rabbits delivered after 8 min 46 s of intrauterine anoxia.*

gasping at birth. The 2 surviving animals from the group placed in iced water did not start breathing until they had had 25 and 30 minutes rewarming, even then there was only a short period of unsustained gasping. Again, the survival rate of the rabbits in iced water was significantly less than the other groups ($P > 0 \cdot 01$).

Discussion

These experiments differ from those of Miller *et al.* (1964) in which it was shown that newborn animals continued to gasp for longer periods when they had been cooled. They showed, for example, that neonatal rabbits at 15 °C–20 °C will gasp in nitrogen for three times longer than at 37 °C. The deduction from these results that cooling an asphyxiated human newborn will enhance his survival is open to question and conflicts with standard teaching (Klaus and Fanaroff, 1973; Schaffer and Avery, 1971).

The present experiments were designed to simulate the human situation more closely and differed from previous experiments (Miller *et al.*, 1964; Miller and Miller, 1965) in that the animals were delivered by caesarean section and asphyxia was started as soon after birth as possible or *in utero*; the asphyxia *preceded* the cooling and some of the animals were cooled at a rate closer to that possible for a human newborn baby.

The results show that if the cooling is rapid and begins early in asphyxia survival is prolonged. This has been shown before (Westin *et al.*, 1962; Westin, Miller, and Boles, 1963). However, the present studies show that when cooling does not occur rapidly, hypothermia does not improve survival. This confirms the conclusions of Daniel *et al.* (1966) from experiments on rhesus monkeys, that while rapid cooling early in asphyxia does prolong gasping, it becomes progressively less effective when applied nearer to the time of the last gasp.

Human infants, because of their smaller surface area : volume ratio, cannot be cooled as rapidly as small newborn animals. The temperature of a 3 kg infant placed in water at 10 °C falls at about 1 °C every 3 minutes (Westin *et al.*, 1959). Baby rabbits cooled at 20 °C have a temperature fall of about 1 °C every 2 minutes (Table II). This rate of cooling has no beneficial effect (Table I). Only those rabbits cooled rapidly, at 1 °C every 45 seconds (Table II), benefitted from hypothermia and only then if cooled soon after the onset of asphyxia (Table I). It is clear that it would take a considerable time to produce a large enough fall in the human baby's temperature for the theoretical advantages of hypothermia to be seen. Rather than wait a long time in the presence of continuing apnoea, active methods of resuscitation such as endotracheal intubation with intermittent positive pressure ventilation, maintenance of temperature, and correction of acidaemia should be instituted early. If these accepted measures are not effective, there seems to be little advantage in cooling.

Several authors have described improved survival in asphyxiated newborn babies using hypothermia (Westin *et al.*, 1959; Cordey, 1964; Miller *et al.*, 1964; Ehrström *et al.*, 1969). These were all small, uncontrolled series and it was not always clear whether the babies were in primary or secondary apnoea. If they were in primary apnoea, any stimulus could provoke breathing even though it had not materially contributed to recovery. Some of the infants had been exposed to general anaesthetics given to their mother which may have prolonged the duration of primary apnoea (Westin *et al.*, 1962; Cordey, 1964). In other cases hypothermia was started after only 5 minutes of intermittent positive pressure ventilation (Westin *et al.*, 1962; Cordey, 1964). It cannot be said with certainty that the babies would not have recovered if ventilation alone had been continued.

The results presented in this paper show that cooling has no beneficial effect after intrauterine asphyxia or when used late in asphyxia. Survival may be prolonged if cooling is very rapid and begins quite soon after the onset of asphyxia, but this would not be possible in a human baby. Lack of convincing evidence from human trials leads to the conclusion that hypothermia has little to offer in the treatment of neonatal asphyxia.

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