OXYGEN CONSUMPTION OF HYPER- AND HYPOTHERMIC PREMATURE INFANTS

BY

GY. MESTYÁN, F. VARGA, E. FOHL and T. HEIM

From the Children's Clinic, University of Pécs, Hungary

(RECEIVED FOR PUBLICATION AUGUST 30, 1961, AND IN AMENDED FORM, MARCH 8, 1962)

Most newborn animals or human infants, when displaced from their thermal neutral environment by a sufficiently large fall or rise in environmental temperature, react by increasing their rate of O_2 consumption and heat production. In certain circumstances, however, the nervous mechanisms that control heat production may be impaired, so that when an animal is exposed to a cool environment it does not respond by increasing heat production. Under these conditions classical physiological teaching suggests that there should be a *direct linear* relation between body temperature and heat production or O_2 consumption (the van't Hoff law) such that a $10^\circ C.$ rise or fall in body temperature will cause a 2-3 times increase or decrease in heat production ($Q_{10} = 2-3$). The purpose of the present paper is to examine the extent to which this expectation is fulfilled in newborn human infants.

Although the changes in O_2 consumption in homeothermic animals with impaired thermo-regulation have usually been attributed to the consequential changes in body temperature, and although the Q_{10} so derived was 2-3 (Adolph, 1950; Bigelow, Lindsay, Harrison, Gordon and Greenwood, 1950; Horvath, Hutt, Spurr and Stevens, 1953; Spurr, Hutt and Horvath, 1954; Thauer, 1955; Behmann and Bontke, 1958), there are exceptions. Thus Balogh, Donhoffer, Mestyán, Pap and Tóth (1952), Donhoffer, Mestyán, Obrincák-Pap, Pap and Tóth (1953), and Donhoffer, Mestyán, Nagy and Szegvári (1957) found that the rise in O_2 consumption of hyperthermic rats was not directly related to the increase in body temperature. Similarly, in hypothermia caused by hypothalamic lesions, by local heating of the hypothalamus or by various drugs which interfered with the central nervous control of thermo-regulation, the change in O_2 consumption did not bear the anticipated relation to the fall in body temperature (Mestyán, Mess, Szegvári and Donhoffer, 1958; Mestyán, *et al.*, 1959a, b; Mestyán, Járαι, Szegvári and Farkas, 1960).

Under these particular conditions there was a considerable fall or rise in body temperature without any change in heat production.

A deliberate search has therefore been made for infants who spontaneously showed a low rectal temperature, and their reactions to changes of body temperature have been examined.

Methods

Premature infants, within one to 19 days of birth, who were admitted to hospital with profound hypothermia, were wrapped in swaddling clothes, placed in an environment of $30-32^\circ C.$ and gradually warmed with partly insulated hot water bottles. Behaviour and activity were carefully observed during this process. Rectal temperature was recorded from a thermocouple inserted 10 cm. into the rectum. Room air was drawn through a chamber over the infant's face at a flow rate which was accurately and continuously measured (from $1.0-1.5$ l./min.). The difference between the O_2 content of room air and of that which had flowed past the infant was measured (to nearer than 0.01%) by the Kipp-Noyons analyser, and the O_2 consumption was thus calculated. A fuller description of this method and tests of its validity are given elsewhere (Donhoffer, Szegvári, Varga-Nagy and Járαι, 1957; Donhoffer, Szegvári, Varga-Nagy, Járαι and Haug-László, 1957).

In other premature infants O_2 consumption and body temperatures were measured during spontaneous cooling at room temperature. The effect of hyperthermia was investigated in both premature and mature newborn infants, whose body temperature was raised by 1.5 to $2.0^\circ C.$ above $37^\circ C.$ by the cautious application of hot water bottles to the child at an environmental temperature of 30 to $32^\circ C.$

Results

Fig. 1 illustrates observations from one newborn mature human infant (3.0 kg. body weight) and five premature infants who, at the beginning of the period under review, had a rectal temperature of 35.8 to $36.8^\circ C.$ The room temperature was 30 to $32^\circ C.$ The infants were wrapped in thick swaddling clothes, so that only the face was exposed.

FIG. 1.—The rises in rectal temperatures (above) and changes in O₂ consumption (below) of six infants wrapped in swaddling clothes, have been plotted against time while they were progressively warmed in an environment of 32° C. The arrows indicate periods of restlessness. (1) Age 1 day, weight 1.84 kg.; (2) age 8 days, weight 1.38 kg.; (3) age 3 days, weight 1.75 kg.; (4) age 15 days, weight 3.00 kg.; (5) age 15 days, weight 2.24 kg.; (6) age 19 days, weight 1.63 kg.

They were then warmed by hot water bottles so that their rectal temperature rose by 2 to 2.5° C. over a period of one to two hours. Fig. 1 shows that there was no systematic increase in O₂ consumption, although there were fluctuations, sometimes regular but usually irregular. Two infants became restless (as indicated by arrows in Fig. 1), and a moderate increase in O₂ consumption was then recorded. In view of this restlessness and the dangers of hyperthermia, no infant was warmed above 39° C. rectal temperature.

Observations were also made upon four premature infants whose rectal temperatures had dropped to 33–35° C. They were warmed up over a period of

FIG. 2.—Shows the rise in rectal temperature (above) with little change in O₂ consumption (below) in four premature infants wrapped in swaddling clothes and placed in an environment of 30° C.; they were also warmed with hot water bottles. (1) Age 2 days, weight 1.4 kg.; (2) age 5 days, weight 1.55 kg.; (4) age 6 days, weight 1.64 kg.

two hours but, as Fig. 2 shows, during this period there was no change in O₂ consumption. In two other premature infants whose rectal temperatures had fallen to 30° C., warming also was not accompanied by a change in O₂ consumption (Fig. 3). Thus, combining the observations illustrated in Figs. 1 to 3, a rise of body temperature up to 38.5° C. or a fall to 30° C. was effected without any demonstrable change of O₂ consumption in this group of infants. Subsequent experience has shown that most infants, whether premature or mature, who are liable to such spontaneous hypothermia under the conditions in our department also show clinical signs of central nervous abnormality.

Occasionally, rewarming hypothermic infants (premature, and showing clinical signs of an intra-

FIG. 3.—Body temperature (above) and O₂ consumption (below) during rewarming of two very cold premature infants, wrapped in swaddling clothes in an environment of 32° C. (1) Age 2 days, weight 1.5 kg., with evidence of intracranial haemorrhage; (2) age 4 days, weight 1.75 kg.

FIG. 4.—Body temperature (above) and O₂ consumption (below) during rewarming of two very cold premature infants, wrapped in swaddling clothes in an environment of 32° C. (1) Age 4 days, weight 1.5 kg., with evidence of intracranial haemorrhage; (2) age 2 days, weight 1.10 kg., with evidence of intracranial haemorrhage.

FIG. 5.—(1) Age 8 days, weight 2.33 kg., with congenital hydrocephalus, cooled at 20° C. naked and then wrapped in swaddling clothes and rewarmed with hot water bottles in an environment of 32° C.

(2) Age 4 days, weight 1.75 kg., with evidence of intracranial haemorrhage. After the determination of O₂ consumption he was cooled naked at 20° C., followed by slower cooling in swaddling clothes interrupted by a longer pause during which cooling was continued (dotted line at 160 minutes). He was finally wrapped in swaddling clothes and rewarmed with hot water bottles in an environment of 32° C.

cranial haemorrhage) caused, at a certain temperature, an abrupt stepwise increase in O₂ consumption (Fig. 4). Deliberate search was then made for this phenomenon in premature infants who were liable to spontaneous hypothermia and who, when exposed to a cool environment, did not respond by increasing heat production. Two instances are shown in Fig. 5, from observations on a congenital hydrocephalic infant and one which had suffered an intracranial haemorrhage. On cooling, and on rewarming, there was an abrupt stepwise change in O₂ consumption at the same rectal temperature.

Discussion

The results show that in premature and damaged infants large changes in body temperature may be observed with no appreciable alteration in O₂ consumption. Such experiments are not possible in normal healthy mature children because they react so vigorously to cold exposure that rectal temperatures do not fall to the levels required within a reasonable period of time (one to two hours). Since these measurements were completed we have learnt that Brück and Brück (1960) have made similar observations in human premature infants. It should be emphasized that our observations have all been made in sleeping infants who, during the period of warming, showed no signs of distress or restlessness. It was also noticed that, when a conscious child was cooled by exposure without clothes to a room temperature of 22 to

23° C., it became at once restless and awake. When, after a period of exposure, the child was wrapped once more in swaddling clothes, it at once became quiet and fell asleep even though its rectal temperature was by then 32° C. or less; and yet its O₂ consumption was no different from that observed at a rectal temperature of 37° C.

It will also be noticed that the effect of body temperature upon O₂ consumption was studied in premature infants both during cooling and during rewarming. During cooling the environmental temperature was less, and during rewarming it was greater than the body temperature. In both circumstances the rate of O₂ consumption was much the same. This suggests that in these infants and under these particular environmental conditions, the direction of the skin temperature gradient had little effect upon metabolic rate. We had no infants whose body temperature fell below 30° C., and we are therefore unable to say whether there was a linear relation between body temperature and O₂ consumption in human babies below 30° C.

These observations on human infants, in spontaneous or induced hypothermia, do not accord with the general view expressed by van't Hoff's prediction, that there should be a direct linear relation between body temperature and O₂ consumption. Since it is unlikely that the effect of hypothermia on the O₂ consumption of a premature human infant (with impaired thermo-regulation) is entirely different from that of a homeothermic warm-blooded animal, and since previous observations on hypothermic adult rats (with hypothalamic lesions) agree well with the results reported in the present paper, it is necessary to reconsider the experimental application of van't Hoff's theory to living animals.

The most important difference between our experiments and those which have been cited in support of classical theory is the means used to abolish the metabolic response to cold. Adolph (1950), Bigelow *et al.* (1950), Horvath *et al.* (1953) and Spurr *et al.* (1954) used deep anaesthesia for this purpose. We have used either hypothalamic lesions in adult rats or local heating of the thermoregulatory region of the hypothalamus in adult cats (Mestyan *et al.*, 1959a; 1960), but the animals in question were then examined in the absence of anaesthesia. The hypothalamic operations abolished the *normal* metabolic response to cold, in that O₂ consumption did not then increase, and body temperature fell. Yet in these experiments O₂ consumption did not fall during cooling, while in deeply anaesthetized animals it did fall. This suggests that deep anaesthesia abolishes all the metabolic

responses to cold, while lesions or local heating of the hypothalamus abolish only the increase of O_2 consumption on exposure to cold, leaving intact some mechanism that maintains the basal metabolic rate. The present observations on premature human infants with impaired thermo-regulation agree with these earlier experiments on rats and cats and suggest that inefficiency or absence of chemical thermo-regulation does not necessarily render the newborn poikilothermic, in the sense that metabolic rate is then governed solely by body temperature. On the contrary, the facts are consistent with the view that metabolic rate is governed by two mechanisms, one which ensures that minimal O_2 consumption is maintained during cooling (at least down to $30^\circ C.$) and the other which causes the large increase of O_2 consumption that is well recognized as the chemical regulatory response to cold, provided that the animal is neither deeply anaesthetized nor damaged in other ways.

There is one further point that must be made. When the experiments under deep anaesthesia already quoted are re-examined, it is noteworthy that body temperature is often recorded as rising or falling by 3 to 5° C. without any change in O₂ consumption. This was especially obvious in the work of Behmann and Bontke (1958). Thus even the experiments thought to provide evidence of the applicability of van't Hoff's prediction to warm-blooded animals suggest the existence of some additional mechanism by which the rate of metabolism is maintained in spite of changes in body temperature.

Leaving aside the theoretical aspects of this interesting problem, the fact that changes in body temperature over a surprisingly wide range may not affect metabolic rate is of possible practical importance in the care of newborn premature infants.

Summary

The metabolic effect of hyper- and hypothermia was investigated in premature human infants aged 1 to 18 days. An elevation of body temperature

by 1.5 to 2.0° C. above 37° C. did not affect basal metabolism. In hypothermic premature infants during rewarming, a rise of 2 to 7° C. in body temperature usually had no effect on minimal heat production. In a few premature infants, however, the low basal metabolic rate increased rapidly as body temperature rose over a narrow range and remained thereafter unchanged at this higher level. These results contrast with the general view, that under conditions of severely impaired thermoregulation the rate of O₂ consumption is directly related to body temperature.

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