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BREATHING AND THE THERMAL ENVIRONMENT IN YOUNG RABBITS

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In new-born babies administration of low-oxygen mixtures caused a transient hyperpnoea, which was no longer present after a few minutes (Cross & Oppé, 1952). Later experiments showed that under similar circumstances the rate of oxygen consumption was reduced (Cross, Tizard & Trythall, 1958). The effect of changing the thermal environment was not observed. Both phenomena have been seen in new-born rabbits when the environmental temperature was low (Dawes & Mott, 1959), and it therefore seemed possible that there was a physiological relationship between them. However, oxygen consumption and breathing were not measured in the same animal. The present investigation was designed to make these measurements simultaneously, and hence to obtain a quantitative estimate of the changes in O_2 consumption and respiratory minute volume in the neutral environment (at a temperature such that O_2 consumption is minimal) and during cooling. A short account of this work has been given (Adamsons, 1959).

METHODS

Forty-six rabbits 0·5–60 days old were anaesthetized with either urethane (1–1·2 g/kg I.V.; 37) or chloralose (50 mg/kg I.V.; 5) or sodium pentobarbitone (20 mg/kg intraperitoneally; 4). Some new-born rabbits anaesthetized with 1·2 g/kg urethane required a supplementary dose of 0·2 g/kg after a few hours. The animal was placed on its side and the trachea was cannulated; as little restraint was used as possible. Rectal temperature was measured by a thermocouple or a mercury thermometer, inserted deeply into the rectum.

Respiratory rate, tidal air and O_2 consumption were measured by the apparatus described by Cross, Dawes & Mott (1959) for use in lambs or sheep, suitably reduced in size. The tracheal cannula was attached to a closed circuit, 1 l. in volume, through which gas was circulated by a rotary blower, and from which carbon dioxide was removed by soda-lime. The rate of gas flow through the circuit was measured by a rotameter and adjusted to be about five times the observed minute volume. The expiratory volume and O_2 content of the system were maintained constant by automatically replacing the oxygen used by the animal during each breath. The O_2 content of the inspired air was measured by passing a small fraction of it through a polarograph, whence it

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was returned to the closed circuit. The temperatures of the gas within the circuit and of the oxygen admitted to it were recorded at intervals. The O_2 content of the system was reduced either by flushing it with a gas mixture of low oxygen content or, more slowly, by replacing the oxygen used by the animal with air. After a period of time during which the animal breathed 10% O_2, the oxygen content of the circuit was rapidly restored to 21% or slightly more by diverting the flow of gas for 1–2 min through a reservoir filled with oxygen.

Tidal air was measured by a float recorder which was designed to give faithful records at high respiratory rates (Fig. 1). The float was made of 0·005 in. (0·127 mm) aluminium, pivoted on two needle points and counterbalanced by the writing lever made of the same material. The displacement was 72 ml./radian, which gave a deflexion of 4 mm/ml. at the writing point, with less than 1% departure from linearity over the working range. Its moment of inertia was less than

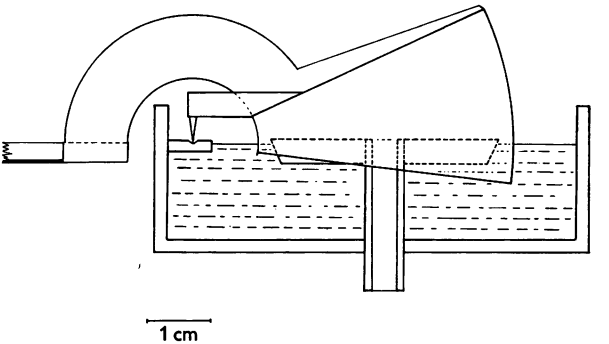

Fig. 1. Sectional view of float recorder for measuring tidal air in young rabbits.

150 g. cm², with a calculated natural frequency of 30 c/s when attached to an air reservoir of 1 l. When this float was placed in the conventional manner on water, the surface area of which was 96 cm² and depth 2·5 cm, and was displaced by a sinusoidal pump over 0·16 radian, it showed a resonating frequency at about 70 c/min (Fig. 2). This was attributed to the low natural frequency of the water. When the water surface area was reduced by 85% (by inserting a metal plate beneath the float), the performance was greatly improved. At a frequency of 240 c/min the harmonic increase in amplitude was only 12% (Fig. 2).

During experiments in the neutral environment the surrounding air was maintained at 26–27° C; heat was simultaneously supplied by convection from below and by radiation from one 100 W lamp, the distance of which was adjusted according to the needs of the animal. The inspired gas had a temperature of 22–25° C and was saturated with water vapour. Cooling of the smaller rabbits was accomplished by removing the heat sources. In larger rabbits it was also necessary to apply small ice packs over the inguinal regions.

RESULTS

A number of preliminary experiments were undertaken to determine the response of young rabbits to low oxygen mixtures. One of these is illustrated in Fig. 3. When the rabbit (405 g weight, 20 days old) was placed in a warm environment (●), progressive reduction in the oxygen content of the inspired air had no significant effect on oxygen consumption until the oxygen content was less than 9%. When the rabbit was placed in a cool environment (○) and was given air to breathe, oxygen consumption was much increased. As the O_2 content of the inspired air was reduced below 12% oxygen consumption

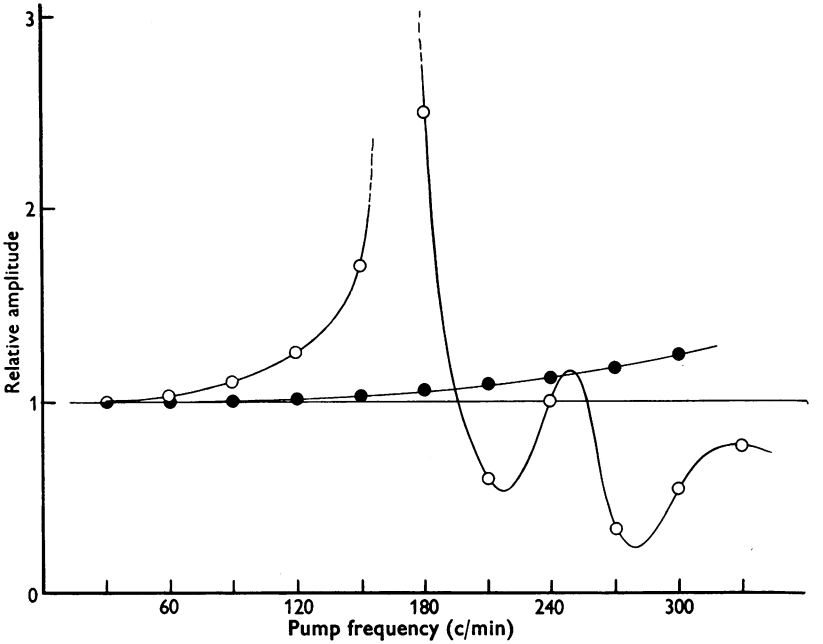

Fig. 2. Amplitude: frequency diagram of the float recorder illustrated in Fig. 1, without the metal plate used to reduce free water surface (○), and with this plate in position (●).

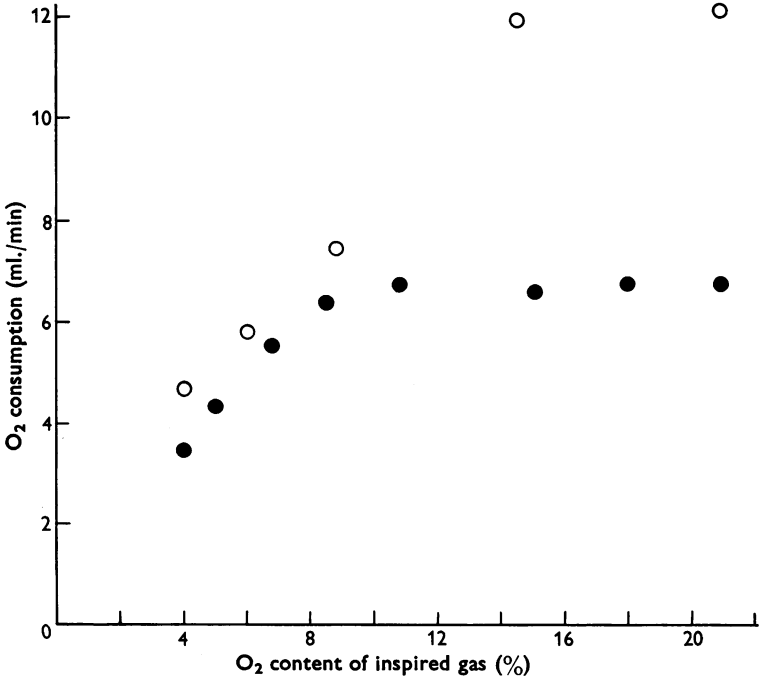

Fig. 3. Rabbit 405 g, 20 days old, urethane anaesthesia. The rate of O_2 consumption (ml./min s.t.p.) has been plotted against the O_2 content (%) of the inspired air in the neutral environment (●), and in a cool environment (○).

decreased, and approximated to that observed in the warm environment. Other similar experiments gave the same result, and it was also seen that the respiratory behaviour of the rabbits differed according to whether they were in a cool or a warm environment. It was decided to examine more closely the changes in response to administration of air or 10% O_2. The figure of 10% O_2 was chosen because at that level there was a considerable and well maintained increase of the minute volume of breathing, but no reduction of oxygen consumption in a warm environment.

Another unknown factor to be investigated was the response of the new-born rabbit to a cold environment. It was found that all new-born rabbits increased their O_2 consumption on exposure to cold. A rabbit weighing 50 g and less than 12 hr old more than doubled its rate of O_2 consumption, though its rectal temperature fell simultaneously from 38 to 37° C.

A further series of experiments concerned the method by which the oxygen content of the closed circuit was reduced from 20·9 to 10%. At first it was changed stepwise, over a period of up to an hour, as in the experiments from which Fig. 3 was derived. It was then difficult to be sure that any changes observed in breathing were only attributable to the changes in gas composition, because of the time interval and the possibility of an alteration in the depth of anaesthesia. Thereafter the gas content of the circuit was reduced rapidly, during 2–3 min, by washing it out with 10% O_2 the temperature of which had been adjusted to that of the circuit.

A number of initial experiments were done under pentobarbitone anaesthesia, but, unlike chloralose or urethane, this was found to reduce the respiratory rate very much below that observed in unanaesthetized rabbits. The effects of hypoxia and cooling under chloralose and pentobarbitone were qualitatively similar to those observed under urethane. But since urethane was easier than chloralose to administer, particularly in very young rabbits, all but two of the following experiments were done under urethane.

In the neutral environment

Breathing air. Usually, in each experiment, the first procedure after attaching a rabbit to the closed circuit was to determine the environmental conditions under which O_2 consumption was minimal, while it was breathing air. External heat was progressively applied until no further reduction in O_2 consumption was observed. At this point the mean rectal temperature was 38·2° C; environmental temperature was 26–27° C, but additional heat was also being supplied by convection and radiation. In a few instances still more heat was applied until the rabbit began to pant, and rectal temperature rose above 40° C. However, O_2 consumption did not increase significantly under these circumstances. The minimal O_2 consumption of seven rabbits less than 6 days old, breathing air, was $17{\cdot}2 \pm 1{\cdot}1$ (S.E.) ml./kg.min. That of eighteen

rabbits 6–28 days old was 15·3 ± 0·7 ml./kg.min. The difference between these two groups was not significant. On the other hand, respiratory minute volume per unit body weight was greater in the younger rabbits (720 ± 31 ml./kg.min) than in the older (480 ± 26 ml./kg.min), mainly because of their relatively

TABLE 1. Changes in O_2 consumption and in the minute volume of breathing in rabbits on exposure to 10% O_2 and to cold

		Change in O_2 consumption (%)			Change in minute volume (%)		
Age (days)	Breathing ... Environment ...	10% O_2 Neutral	Air Cool	10% O_2 Cool	10% O_2 Neutral	Air Cool	10% O_2 Cool
0–5		0·3 ±3·8	102±20	−12 ±7·1	66±10·7	33±7·1	16±3·7
6–28		0·55±0·96	40± 7·5	0·6±5·5	90± 6·9	22±4·1	46±5·6

All changes are related to standard conditions in the neutral environment and breathing air. The changes are calculated from mean observations over periods of 10–15 min steady conditions.

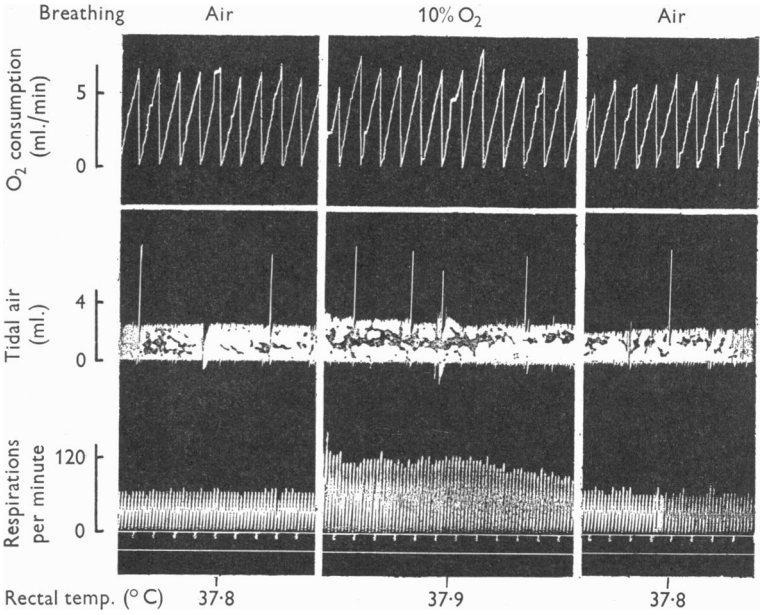

Fig. 4. Rabbit 307 g, 14 days old, urethane anaesthesia. Records from above downwards of O_2 consumption (ml./min s.t.p.), tidal air (ml. s.t.p., inspiration upwards) and respiratory rate in the neutral environment, while breathing air or 10% O_2. Time marker, 1 min.

larger tidal air. The respiratory rate showed no significant variation with body weight, and had a mean value of 63·0 ± 2·6/min for both groups combined.

Breathing 10% *O_2*. When the O_2 content of the inspired air was reduced to 10%, in the neutral environment, there was no significant change in O_2 consumption (Table 1). Figure 4 shows a representative experiment. There was always a large increase in respiratory rate (mean 69%) and a small increase in tidal air (mean 11%). It was not uncommon to see a small decline

in respiratory rate after the first 10–15 min. The minute volume was increased significantly more in rabbits 6–28 days old than in rabbits 0–5 days old (Table 1).

In a cool environment

Breathing air. After a period of time in the neutral environment the rabbits were cooled until the rate of O_2 consumption had increased to a plateau. This took 10–15 min for rabbits less than 6 days old (weighing 45–120 g), and as much as 45 min for older rabbits (up to 500 g). The increase in O_2 consumption averaged 102% in rabbits 0–5 days old, but shivering was not observed. In

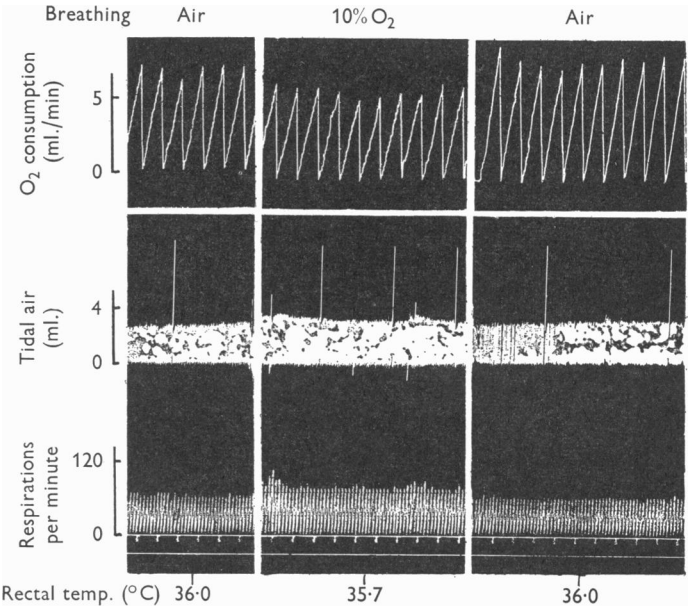

Fig. 5. As Fig. 4, while breathing air or 10% O_2 in a cool environment.

the older rabbits the increase in O_2 consumption was 40%, and shivering was visible. Body temperature fell to a greater extent in the younger rabbits (mean from 38·4 to 35·3° C) than in the older (mean from 38·1 to 36·0° C).

When the rabbits were cooled there was a maintained increase in the minute volume of respiration (Table 1). This was due to an increase in both tidal air and respiratory rate.

Breathing 10% O_2. After the rabbits had reached a steady state in a cool environment, they were given 10% O_2 to breathe. O_2 consumption invariably decreased (Fig. 5), in the 6–28-day-old rabbits to the level seen in the warm environment breathing air, in the 0–5-day-old rabbits to below this level (Table 1). Rectal temperature began to fall rapidly, particularly in the smaller rabbits. This was usually minimized by the application of a little extra

heat, in order that observations of the respiratory changes could be continued under approximately the same conditions.

Administration of 10% O_2 in a cool environment caused an immediate increase in the minute volume of breathing. But within a few minutes the hyperpnoea decreased to a lower value (Fig. 4). In the rabbits 0–5 days old the minute volume actually fell below that observed when breathing air in a cool environment. In the older rabbits the minute volume was, on the

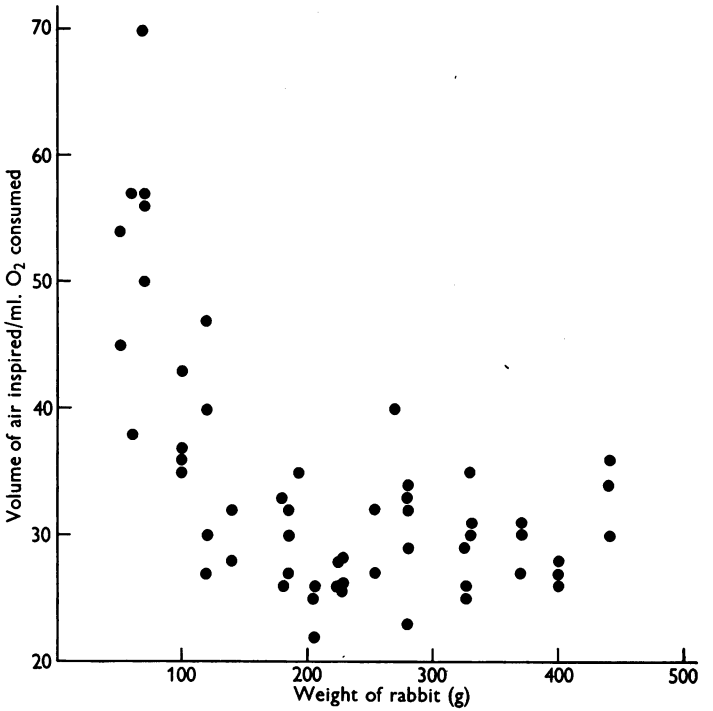

Fig. 6. Observations from twenty-four rabbits breathing air in the neutral environment to show the change in the ratio of minute volume of breathing to oxygen consumption with increasing weight.

average, greater than that observed when breathing air in a cool environment, but still much less than when breathing 10% O_2 in a warm environment (Table 1).

Qualitatively similar changes have been observed in rabbits several months old, weighing up to 1·2 kg, and also in three new-born puppies anaesthetized with chloralose. In the latter, however, both the increase in O_2 consumption and the ability to withstand hypoxia in the cold were less than in rabbits.

The ratio of minute volume to O_2 consumption

It will be apparent from the mean figures quoted above that, in the neutral environment and while breathing air, the ratio of minute volume to O_2 consump-

tion is greater in the younger rabbits. In Fig. 6 this ratio has been plotted against body weight. The volume of air moved through the respiratory passages for each millilitre of O_2 consumed is considerably greater in the smaller rabbits. Table 2 shows that under all the conditions studied, breathing air or 10% O_2, in the warm or in the cold, this was still true. (The discrepancy in the values of the ratio which can be derived from the mean figures given in Table 1, and those which are quoted in Table 2, is due to the different methods of calculation.) It is interesting that in new-born lambs no such difference was observed (Cross *et al.* 1959).

TABLE 2. Volume of gas inspired for each millilitre O_2 consumed in rabbits

Environment	Breathing	0–5 days old (ml.)	6–28 days old (ml.)
Neutral	Air	45±2·8	29±0·7
Neutral	10% O_2	92±4·9	61±1·7
Cool	Air	38±2·8	29±0·6
Cool	10% O_2	66±5·6	47±1·0

The ratios are derived from simultaneous observations on each rabbit.

DISCUSSION

The rabbit is born in a relatively immature condition, and the numbers in each litter are large. It weighs about 50 g at birth, has little fur and can crawl only with difficulty. Its arterial blood pressure is only 30–40 mm Hg, and it is cared for in a nest, where the proximity of its litter mates and its mother must make temperature regulation easier. It was therefore surprising to find that within the first few hours after birth the rabbit can increase its oxygen consumption about twofold in response to cold. Nevertheless, because of its small size and relatively large surface area its thermal stability is poor. Shivering was not visible in the cold until several days from birth, but there is no reason to believe that the means by which O_2 consumption is increased is different from that in older rabbits.

The results demonstrate that, in the new-born or young rabbit, breathing 10% O_2 causes a well maintained hyperpnoea in the neutral environment. In a cool environment administration of 10% O_2 leads to a reduction in O_2 consumption, and the concomitant hyperpnoea is less, or even absent. How does this come about? There is one obvious explanation. When O_2 consumption is reduced, CO_2 production will be correspondingly less, and therefore the arterial partial pressure of CO_2 should be less. This stimulus to breathing will be correspondingly smaller, irrespective of the means whereby hypoxia reduces O_2 consumption. There are other possibilities which will need to be investigated. Thus, placing a rabbit in a cool environment may produce a change in the sensitivity of the respiratory centre to the arterial partial pressure of CO_2 or of O_2. It is interesting to note from Table 2 that reducing the O_2 content of the inspired air from 21 to 10% caused, in the neutral environment, an

increase in the volume of gas inspired for each ml. O_2 consumed by a factor of 2·04–2·10. But in a cool environment it increased only by a factor of 1·62–1·74.

The observations on the change in oxygen consumption during administration of 10% O_2 agree very well with those of Hill (1958) on unanaesthetized young kittens and adult guinea-pigs. In these, as well as in new-born and young rabbits, exposure to a cold environment caused a considerable increase in O_2 consumption, which increase was much reduced or abolished when the O_2 content of the inspired gas mixture was decreased from that of air to 10%. In rabbits the minute volume of breathing was less while breathing 10% O_2 in a cool than in a warm environment. Part of the reduction of O_2 consumption in these circumstances may therefore have been due to the decrease in the work of breathing. In young rabbits, as in new-born lambs (Cross *et al.* 1959), a further decrease in the O_2 content of the inspired air, below 10%, entails a fall in O_2 consumption below that observed while breathing air in the neutral environment (Fig. 3). The well established susceptibility of shivering (and of the accompanying increase in metabolic rate) to hypoxia in young and adult animals is not, therefore, the sole factor involved in the metabolic response to administration of low-oxygen mixtures. In a cool environment, the reduction of oxygen consumption caused by hypoxia is accompanied by a fall in body temperature, particularly in small animals, and this further complicates analysis of the physiological mechanisms which are involved.

Finally we may reconsider Cross & Oppé's (1952) conclusions in the light of the present observations. In 1952 it was not known that administration of 15% oxygen to new-born babies causes a fall in oxygen consumption. They therefore concluded that the failure to maintain hyperpnoea during hypoxia was due to depression of the respiratory centre. It is now clear that there is an alternative explanation for this phenomenon, since the observations may have been made in a thermal environment which, for the new-born baby, was below the neutral.

SUMMARY

1. Oxygen consumption and breathing were measured simultaneously in anaesthetized new-born and young rabbits, in either a neutral or a cool environment, breathing air or 10% oxygen.

2. In a neutral environment hypoxia caused a well maintained and considerable hyperpnoea, but no change in O_2 consumption.

3. Cooling caused an increase in O_2 consumption and a moderate hyperpnoea. In a cool environment, hypoxia caused a decrease in O_2 consumption and only a small change in breathing.

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