CO₂ Production, Body Temperature, and Ventilation in Hypoxic Newborn Cats and Dogs before and after Body Warming

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ABSTRACT. Many newborn mammals decrease metabolism and body temperature (Tb) during acute hypoxia. We asked what effects warming of the hypoxic newborn would have on these variables. In unanesthetized newborn cats and dogs, we measured the breathing pattern, CO₂ production, Tb, and ambient temperature during normoxia at an ambient temperature of 28°C, 30 min of hypoxia (10% O₂), and an additional 30 min of hypoxia plus warming. During hypoxia, Tb and CO₂ production decreased in both species, whereas the absolute value of ventilation did not change in kittens and increased in puppies. During hypoxia plus warming, Tb was gradually returned to the normoxic value by increasing ambient temperature by 3 to 4.5°C. This increase did not modify CO₂ production in either species, and it increased minute ventilation in kittens. We conclude that during hypoxia 1) warming the newborn can increase Tb, but not metabolism, to the normoxic value; 2) the decrease in Tb is not a causative prerequisite of the hypoxia-hypometabolism; and 3) an artificial increase in Tb to the normoxic value can stimulate minute ventilation, probably because it is perceived as an hyperthermic stimulus. (*Pediatr Res* 30: 165–169, 1991)

Abbreviations

Tb, rectal temperature (°C)
Ta, ambient temperature (°C)
 $\dot{V}\text{CO}_2$, CO₂ production (mL/min⁻¹)
V_T, tidal volume (mL)
f, breathing frequency (breaths/min)
V_E, minute ventilation (mL/min)
[CO₂], CO₂ concentration

newborn rats, metabolic rate decreases during hypoxia even at Ta values equivalent to the lower end of their normoxic thermoneutral range (3, 10). One hypothesis, therefore, could be that, in a newborn, even a small hypothermic stress favors the hypometabolic response during hypoxia. If this interpretation were correct, it would follow that in a hypoxic newborn both Tb and metabolism could be returned to the normoxic values by means of external body warming.

An alternative possibility could be that during hypoxia Tb decreases as the result of the hypometabolism and reduced heat production and adjusts to what would represent the normal value for that metabolic conditions, similarly to the mechanism of Tb resetting of hibernators (11). In such a case, external warming of the hypoxic newborn would act as an hyperthermic challenge, which could raise Tb but not necessarily increase metabolic rate.

In these experiments, we attempted to gain some insights into the relationship between body temperature and metabolic rate of the hypoxic newborn by simulating a condition of acute hypoxia in newborn cats and dogs at first maintained at the average Ta of their nest. As expected, we observed a drop in Tb and $\dot{V}\text{CO}_2$. With the animals under continuous hypoxia, we then gradually increased Ta, similar to the treatment of hypoxic infants in the incubator (12), until Tb was returned to the normoxic value and analyzed what effect this intervention had on $\dot{V}\text{CO}_2$. Because $\dot{V}\text{CO}_2$ is a key determinant of the ventilatory level, we also asked what effects gradual warming of the hypoxic newborn had on its ventilatory pattern.

MATERIALS AND METHODS

Experiments have been performed on 10 newborn cats and 10 newborn dogs of mixed breeds, all between 2 and 6 d old. Kittens were from two litters, at an average age and weight of, respectively, 4.5 d (± 1 SD) and 159 $\pm$ 19 g. Puppies were also from two litters and were studied at an average age and weight of, respectively, 3.5 $\pm$ 1 d and 309 $\pm$ 44 g.

The experiments consisted of individual measurements of breathing pattern and CO₂ production ($\dot{V}\text{CO}_2$) under three conditions: normoxia at Ta = 28°C, hypoxia (30 min of fractional inspired oxygen = 10%) at Ta = 28°C, and hypoxia with Ta sufficiently increased (+ 3 to 4.5°C; see Results) to maintain Tb as in normoxia (30 min). The three phases of the experiment will be referred to as, respectively, normoxia, hypoxia, and hypoxia plus warming.

The ventilatory pattern was measured by the barometric method of Drorbaugh and Fenn (13), with the modifications previously described (14). Chamber temperature (Ta) and Tb were continuously monitored with probes connected to telethermometers (model YSI 400; Yellow Springs Instrument Co., Yellow Springs, OH). The chamber had a volume of 1.95 L, *i.e.* large enough to comfortably accommodate the animal. The Ta probe was positioned in the chamber at the middle length and height, because previous tests indicated that the Ta of this region corresponded to the average Ta of the chamber. Breathing-related

In many newborn mammals, including infants, metabolic rate and Tb decrease during acute hypoxia (1–7). The mechanisms responsible for these phenomena are not understood, nor is it clear whether the drop in Tb and the metabolic adaptation are linked by a cause-effect relationship. In newborn cats, hypoxia would not lower oxygen consumption if the animals were maintained at about 34°C, which is their normoxic thermoneutral value (8), whereas both Tb and metabolism decrease during hypoxia at 28 to 30°C (2, 5, 6), a range of Ta that is similar to or slightly higher than that experienced in the nest (9). In

Received January 3, 1991; accepted April 17, 1991.

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Supported by grants from the Canadian Foundation for the Study of Infant Deaths and the Medical Research Council of Canada. C.P. was supported by a Fellowship from the Fondo de Investigaciones Sanitarias de la Seguridad Social.

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pressure oscillations in the chamber were recorded on paper (pen-recorder; Gould Inc., Cleveland, OH) at a speed of 5 or 10 mm/s. Volume calibration was obtained by injecting a known volume into the chamber with a calibrated syringe and recording the corresponding change in chamber pressure. In between the records of breathing pattern, the chamber was continuously flushed by a humidified, steady flow (800–1000 mL/min) of air or hypoxic gas monitored by a flowmeter. $[CO_2]$ at inflow and outflow was measured by a CO_2 analyzer (Beckman Instruments Inc., Fullerton, CA) and recorded on paper at a speed of 5 mm/s.

After placing the animal in the chamber, T_a was set at $28^\circ C$ by adjusting an external heating lamp. Similarly to what was previously noted by others (5, 9), we have observed that $28^\circ C$ is the T_a value most frequently faced by the kitten when nursed by the mother. During the nonnursing period, newborn dogs and cats are often exposed to T_a values lower than $28^\circ C$. After 10 to 15 min, the experiment was begun by recording $[CO_2]$ for about 6 min. Breathing pattern was then recorded for the duration of 100 to 200 breaths. Hypoxia was introduced for 30 min, with $T_a = 28^\circ C$. During this time, values of T_b and T_a were recorded every 5 min. At the end of the 30 min, $[CO_2]$ and breathing pattern were again recorded. Because T_b decreased during hypoxia (see Results), during the 3rd phase of the experiment (hypoxia plus warming), T_a was gradually increased until T_b equalled the value during normoxia. Usually, this was achieved in about 20 min; during an additional 10 min, T_a was slightly decreased while T_b was kept at the normoxic value. Records of $[CO_2]$ and breathing pattern were then obtained.

The ventilatory records were analyzed with the help of a graphics tablet connected to a minicomputer. Analysis included computation of V_T , f , and $\dot{V}_E$. Values were stored for later statistical analysis and graphic representation. $\dot{V}CO_2$ was computed as the product of the average difference between inflow and outflow $[CO_2]$ and the gas flow. The average difference was measured by continuous digitizing of the $[CO_2]$ records over a 3 to 5 min period. Values were converted to stpd (dry), normalized by the animal's body weight.

All results are presented as means $\pm$ 1 SD. Statistically significant differences were evaluated by analysis of variance. When the F value was higher than the critical value at $p = 0.05$, comparisons were made with the Scheffe F test of paired or unpaired analysis, as appropriate. A significant difference was considered at 5%.

The study was approved by the local Animal Care Committee.

RESULTS

During the 30 min of hypoxia at $T_a = 28^\circ C$, T_b decreased in puppies and kittens by 1.4 and $0.4^\circ C$, respectively (Fig. 1, bottom). During hypoxia plus warming, T_b was returned to the normoxic values in 20 to 25 min by increasing T_a by 3 or $4.5^\circ C$ in puppies and kittens, respectively (Fig. 1, top).

During hypoxia, $\dot{V}CO_2$ decreased significantly, by 18% in puppies (from 19.9 ± 2.3 to 16.4 ± 3.7 mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$), and by 36% in kittens (from 37.7 ± 5.2 to 23.7 ± 5.4 mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$) (Fig. 2). During hypoxia plus warming, $\dot{V}CO_2$ averaged 16.8 ± 3.7 (puppies) and 23.5 ± 4.2 mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$ (kittens); in neither case did it differ significantly from the values in hypoxia (Fig. 2).

In puppies, during hypoxia, $\dot{V}_E/kg$ increased by 57% (from 953 ± 183 to 1495 ± 328 mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$), whereas in kittens it did not differ significantly from normoxia (from 1351 ± 360 to 1346 ± 478 mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$). Qualitatively similar changes occurred in mean inspiratory flow ($V_T/T_I/kg$). The observed ventilatory changes in puppies resulted from an increase in V_T with no changes in f ; in kittens, however, the similar absolute value of $\dot{V}_E$ between normoxia and hypoxia was accompanied by a drop in V_T and an increase in f .

During hypoxia plus warming, f did not change in either species. Neither $\dot{V}_E$ nor V_T changed significantly in puppies,

Fig. 1. T_a (top) and T_b (bottom) in normoxia, during 30 min of hypoxia, and during an additional 30 min of hypoxia plus warming in newborn cats (circles) and dogs (triangles). Values are mean; bars represent 1 SD.

Fig. 2. CO_2 production ($\dot{V}CO_2$) in newborn cats (open columns) and dogs (filled columns) during normoxia, hypoxia, and hypoxia plus warming. During hypoxia and hypoxia plus warming, $\dot{V}CO_2$ was significantly less than in normoxia. Columns are mean values; bars represent 1 SD.

whereas both increased (by 51 and 42%, respectively) in kittens (Fig. 3). In summary, in both newborns $\dot{V}_E$ was significantly higher in hypoxia plus warming compared with normoxia; however, in the puppy this increase was already apparent in phase 2 of the experiment (hypoxia), whereas in the kitten it was manifest only in phase 3 (hypoxia plus warming).

Figure 4 summarizes the above results in kittens by presenting, on the left panels, the relationships between T_a , or T_b , and $\dot{V}CO_2$ in the three experimental conditions. From this plot, the mis-

Fig. 3. Breathing pattern in newborn cats and dogs during normoxia, hypoxia, and hypoxia plus warming. Columns are mean values; bars represent 1 SD.

Fig. 4. Results in newborn cats. Left, relationship between T_a (top panel) or T_b (bottom panel) and $\dot{V}_{\text{CO}_2}$ during normoxia, hypoxia, and hypoxia plus warming. Right, $\dot{V}_E$ - $\dot{V}_{\text{CO}_2}$ relationship during normoxia, hypoxia, and hypoxia plus warming. Oblique lines indicate the average $\dot{V}_E/\dot{V}_{\text{CO}_2}$ for each condition. The arrows indicate the sequence of the conditions during the experiment. Symbols are mean values and bars represent 1 SD.

match between $\dot{V}_{\text{CO}_2}$ and T_b during hypoxia plus warming becomes readily apparent. The panel on the right of Figure 4 summarizes the changes in $\dot{V}_E$ and the corresponding changes in $\dot{V}_{\text{CO}_2}$. In hypoxia, the $\dot{V}_E$ - $\dot{V}_{\text{CO}_2}$ ratio increased (on average from 36 to 57, i.e. 58%) because of the drop in metabolic rate. During hypoxia plus warming, the ratio increased further (to 87, i.e. an additional 53% above the hypoxic value) because of the rise in $\dot{V}_E$, with no metabolic changes.

DISCUSSION

Response to hypoxia. In both newborn species, hypoxia decreased $\dot{V}_{\text{CO}_2}$ and T_b , as we were expecting on the basis of previous observations of these and other newborns, including the human infant (1-7). The magnitude of these changes was also similar to that previously observed with analogous hypoxic challenges (5-7).

The larger T_b drop in the kitten probably resulted from the

greater metabolic adaptation of this species, although several other factors involved in the redistribution of blood flow and heat dispersion may have contributed to the quantitative difference. In addition, the considerations that heat dispersion depends on body surface and that the body surface-mass ratio is inversely proportional to body mass yield the expectation of a faster thermal loss in the smaller animals.

The kitten's ventilatory response to acute hypoxia, characterized by rapid and shallow breathing with minimal changes in $\dot{V}_E$, very closely resembled that previously observed in the same species (5, 6, 15) and conforms to the breathing pattern response of many other newborn mammals (7). The puppy, on the other hand, responded to 10% O_2 with an increase in $\dot{V}_T$ and no changes in f . This species difference could be attributed to the differences in sensitivity to hypoxia (7) as well as differences in the contribution of sleep state to the ventilatory response to hypoxia of newborn dogs and cats (15, 16). The $\dot{V}_E$ - $\dot{V}_{CO_2}$ ratio was increased in both species during hypoxia; this was previously shown in many newborn species (7), indicating the existence of a hyperventilatory response even in those cases, as in the kittens in our study, in which the absolute value of $\dot{V}_E$ was similar to the normoxic value (7). Previously, it was found that arterial PCO_2 decreased in the hypoxic kitten even when the ventilatory level was below the normoxic value (6), which emphasizes the importance of the metabolic adaptation in the acute ventilatory response of the newborn.

Body warming. By increasing T_a by about 2 to 4 or 4 to 6°C in puppies and kittens, respectively, it was possible to raise T_b to the prehypoxic values. The need for a larger increase in T_a in the kitten is not surprising in view of the fact that, during hypoxia in this species, T_b dropped much more than in the puppy.

The important result of this study was that in neither species did the externally induced warming significantly alter $\dot{V}_{CO_2}$, which remained at the same low level for the whole hypoxic exposure (Fig. 4). This indicates that hypoxia-induced hypometabolism is not a phenomenon strictly dependent upon T_b or T_a . Of course, these results do not dispute the well-known fact that large changes in T_a can affect metabolic rate. What these results do show, however, is that, within the T_b range of the hypoxic adaptation, metabolic changes are independent of T_b . This also supports the view that the T_b decrease during hypoxia is the consequence of, and not a contributor to, the metabolic drop. The same conclusion can be reached by considering that the Q_{10} (i.e. the change in metabolic rate for a 10°C temperature range) is several orders of magnitude larger than the Q_{10} value of the passive effect of temperature on biologic reactions (7). For example, in the kittens in our study, during hypoxia the 40% drop of $\dot{V}_{CO_2}$ was paralleled by a 1.5°C drop in T_b , which would yield a Q_{10} of almost 30.

If hypoxia decreases the set point of thermoregulation, as is postulated to occur in adult hypoxic cats (17), it is conceivable that in hypoxia the range of thermoneutrality may be lower than in normoxia; in such a case, the T_a that represented the thermoneutral condition in normoxia may become an hyperthermic situation in hypoxia, which is expected to increase $\dot{V}_E$, presumably via hypothalamic stimulation. The fact that breathing rate did not contribute to the ventilatory increase during warming may indicate that this component of the response is reduced under hypoxia, possibly in line with the concept that a ventilatory stimulus added on a tachypneic condition does not further stimulate frequency (18). The finding that, after 30 min of hypoxia, the kitten's $\dot{V}_E$ was stimulated by warming also implies that hypoxia-induced depression of central neuronal activity was not a major contributor to the lack of sustained $\dot{V}_E$. A similar conclusion was reached by observing that the decrease in $\dot{V}_E$ in hypoxic kittens could be readily reversed by adding CO_2 to the inspired gas (6, 19).

Clinical implications. A question of practical importance is whether or not, in a hypoxic infant, an effort should be made to

maintain the same T_b of the normoxic condition. Because the drop in T_b during hypoxia appears to be the expression of the resetting of the thermoregulatory mechanisms at a lower value, presumably metabolically mediated, the low T_b value in hypoxia could be interpreted as the new normothermic level, and artificial attempts to raise T_b to the normoxic value would, therefore, represent a hyperthermic stimulus. Therefore, the question should be rephrased as to whether or not a hyperthermic situation may be beneficial to the hypoxic newborn by improving O_2 delivery (defined as the product of organ blood flow and O_2 content) to the vital organs. From the viewpoint of the ventilation-metabolism ratio, this study may suggest a positive answer, because the ratio is either the same or improved. However, hyperthermic conditions are known to decrease systemic vascular resistance; whether or not the perfusion of peripheral districts, which would normally be underperfused in hypoxic conditions (20), may reduce the blood flow to vital organs depends on the cardiac output response to warming. In severe hypoxia, the cardiac output response may be impaired (21) and, therefore, during warming, cardiac output may not increase enough to maintain adequate regional perfusion. For example, in lambs during hypoxia in a warm environment, cardiac output not only did not exceed, but actually tended to be less than, that in a cool environment (21). Therefore, one can envision the possibility that the artificial attempt to restore T_b in a hypoxic newborn may actually result in a decrease below the prewarming levels in oxygen delivery to some body districts, because the possible improvement in O_2 content of a higher ventilation-metabolism ratio can be more than offset by the deterioration in regional blood flow.

Conclusions. In kittens and puppies, acute hypoxia determines a decrease in $\dot{V}_{CO_2}$ and T_b , the latter possibly representing the resetting of the thermoregulatory mechanisms at a lower level. An artificial increase in T_b to the normoxic value, via a rise in T_a , does not alter $\dot{V}_{CO_2}$, but can increase $\dot{V}_E$. This may improve alveolar PO_2 , but does not necessarily imply an increase in oxygen delivery to the vital organs.

Acknowledgment. The authors thank Lina Naso for technical assistance.

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