Invited Editorial on “Oxygen transport in conscious newborn dogs during hypoxic hypometabolism”

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The occurrence of hypometabolism during hypoxia was initially described many years ago, and a recent renewed interest in this phenomenon probably originates from the fact that the ventilatory response to hypoxia, which is now often studied in unanesthetized animals without external temperature control, may be affected by a decrease in metabolism (oxygen uptake ($V\dot{O}_2$)) and consequently in body temperature ($T_b$) (6). Since the original study of Hill (10), it has been recognized that several factors play an important role in the development of hypoxic hypometabolism. 1) The size and age of the animal: in contrast to newborn or small adult mammals or birds with a high $V\dot{O}_2$ per kilogram, the hypoxic drop in metabolism is smaller in larger species, with a lower $V\dot{O}_2$ per kilogram (5). 2) The ambient temperature ($T_a$): hypoxic hypometabolism is greater at low ambient temperature, when $V\dot{O}_2$ is increased by thermogenesis above values observed at thermoneutrality. 3) The level of hypoxia: a drop in $V\dot{O}_2$ may be observed with inspired oxygen fraction ($F\dot{IO}_2$) ranging from 0.15 to 0.17 at low $T_a$ values, whereas at normal $T_a$ values, a decrease in $V\dot{O}_2$ is observed only with $F\dot{IO}_2$ at or below 0.10. It should be noted that a drop in $V\dot{O}_2$ may also be observed with inhalation of low concentrations of CO (7).

Despite many recent studies, the mechanisms responsible for hypoxic hypometabolism remain unclear. The first possibility, proposed by Hemingway and Birzis (9), implies an effect of hypoxia on brain thermoregulatory mechanisms, resulting in a regulated decrease in $T_b$. As such, hypoxic hypothermia, sometimes aptly referred to as anaparexia (2), would be the opposite of fever. In this context, it should be noted that experimentally induced fever may be reduced by hypoxia (3). A downward resetting of the thermoregulatory set point is suggested by studies showing that the $T_b$ threshold of the thermoneutral zone, below which $V\dot{O}_2$ increases, is lowered in rats exposed to hypoxia (4). Similarly, it has been observed in cats exposed to heat that the $T_b$ threshold for panting is lower in hypoxia than in normoxia (1). The hypothesis of a hypoxic lowering in $T_b$ set point is supported by recent studies on behavioral thermoregulation, showing that many organisms, including mammals, studied in a thermocline, generally select a cooler $T_a$ when exposed to hypoxia (8). The increase in heat losses at lower $T_a$ in addition to the decrease in $V\dot{O}_2$ accentuates the hypoxic hypothermia. The way hypoxia can affect thermoregulatory centers is unknown, but several mediators (adenosine, opioids), which are released during hypoxia and which play also a role in $T_b$ regulation, are likely to be involved in the development of hypoxic hypothermia (13).

The second possibility that may account for hypoxic hypometabolism is a simple limitation in oxygen availability to the tissues. There is indirect evidence that this is unlikely because hypometabolism may occur with mild hypoxic levels, resulting in arterial $P_o_2\ (P_{aO_2})$ values much higher than necessary to induce a decrease in $V\dot{O}_2$ of exercising muscles (see Ref. 6). In addition, even during sustained hypoxia, $V\dot{O}_2$ can be raised by exposure to cold or by administration of mitochondrial uncouplers (12).

The above results have been obtained in adult mammals, but in the hypoxic newborn the possibility of $V\dot{O}_2$ being limited by the availability of oxygen has not been positively excluded. This possibility has been explored in the study of Rohlicek et al. (11) in this month’s issue of the Journal. Conscious instrumented newborn dogs aged 1–2 wk, studied at $T_a$ values of 30 or 20°C, were exposed to sequential decreases in $F\dot{IO}_2$ from 0.21 to 0.06. $V\dot{O}_2$, $CO_2$ production, and $T_b$ were measured, and arterial and mixed venous blood samples were withdrawn through indwelling catheters, allowing determination of several indexes of oxygen transport. The results show that during normoxia $V\dot{O}_2$ was 70% higher at 20 than at 30°C and that during hypoxia $V\dot{O}_2$ started to fall significantly with a $F\dot{IO}_2$ of 0.12 at 20°C and 0.10 at 30°C. Thus, with a $F\dot{IO}_2$ of 0.10, during both warm and cold conditions, the puppies were hypometabolic, but $V\dot{O}_2$ was significantly higher in the cold (14.1 ml·min$^{-1}$·kg$^{-1}$) compared with warm conditions (11.4 ml·min$^{-1}$·kg$^{-1}$), despite the fact that $P_{aO_2}$ was slightly lower at 20°C (25 Torr) than at 30°C (30 Torr). Similarly, at the same mixed venous $P_o_2\ (P_{vO_2})$, which may reflect the $P_o_2$ at the tissue level, $V\dot{O}_2$ was higher in the cold than in warm conditions. This indicates that neither $P_{aO_2}$ nor $P_{vO_2}$ was the limiting factor accounting for the hypoxic decrease in $V\dot{O}_2$. In addition, the linear regressions computed between $V\dot{O}_2$ and several indexes pertinent to blood oxygenation (e.g., $P_{aO_2}$, arterial oxygen content ($C_{aO_2}$), $P_{vO_2}$), have greater slopes in cold compared with warm conditions, confirming that for a given level of oxygenation, even during hypoxic hypometabolism $V\dot{O}_2$ is higher in a cold than in a thermoneutral environment.
From the data provided, the commonly used oxygen delivery index (cardiac output × \( \text{CaO}_2 \)) may be computed during hypoxia. It then appears that \( \text{VO}_2 \) decreases as a linear function of oxygen delivery. This supply-dependent oxygenation indicates, as emphasized by Rohlicek et al. (11), that these puppies do not behave like strict “regulators,” since they do not maintain body homeostasis during hypoxia and their \( T_b \) decreases by \(-4^\circ\text{C}\). However, the slope of the relationship between \( \text{VO}_2 \) and oxygen delivery is, like the regressions considered above, greater in cold compared with warm conditions.

Finally, the data provided by Rohlicek et al. (11) provoke speculation about changes in pulmonary ventilation and circulation, which are both markedly influenced by hypoxia but differently during warm and cold conditions.

In conclusion, this paper provides the first direct evidence that, in newborn puppies, \( \text{VO}_2 \) is dependent on, but not limited by, oxygen supply. Therefore, it confirms studies carried out in adult mammals, suggesting that hypometabolism is a regulated response to an hypoxic environment.

REFERENCES