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Hyperventilation in the Newborn Piglet Does Not Increase Whole Body Oxygen Consumption as Seen in Mature Animals

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ABSTRACT. Hyperventilation has been shown to cause increased whole body oxygen consumption ($\dot{V}O_2$) and lactic acid production in human and animal mature subjects, but limited data are available in neonates. We investigated the effect of hypocarbic and normocarbic hyperventilation during normoxia and hypoxia (fractional inspired oxygen concentration = 0.14) upon the $\dot{V}O_2$ in anesthetized and paralyzed piglets. Systemic arterial, pulmonary arterial, and left and right atrial pressures as well as cardiac output and body temperature were continuously recorded. Hypocarbic hyperventilation ($PaCO_2$ = 19 ± 1 mm Hg; pH = 7.58 ± 0.02) was associated with a significant decrease in systemic and pulmonary arterial pressures and cardiac output. These measurements returned to values similar to the initial normoventilation ones when $PaCO_2$ was increased by adding CO_2 to the inspired gas, whereas hyperventilation was continued. Neither hyperventilation alone nor in combination with hypoxia induced any significant change in $\dot{V}O_2$. We conclude that in the newborn pig, unlike what has been reported in mature subjects, cellular metabolic function is unaffected by hyperventilation as evidenced by the unchanged $\dot{V}O_2$. (*Pediatr Res* 23: 565–568, 1988)

Abbreviations

$\dot{V}O_2$, whole body oxygen consumption
PPHN, persistent pulmonary hypertension syndrome of the newborn
FiO_2, fractional inspired oxygen concentration
iv, intravenous

Hyperventilation is commonly used to treat infants with PPHN (1). Although respiratory alkalosis is a useful treatment modality in this syndrome, much concern has been raised regarding the effect of extreme pH changes and low $PaCO_2$ on cellular function and metabolism (2).

Active hyperpnea in humans and passive hyperventilation in adult dogs has been shown to cause a significant increase in $\dot{V}O_2$ and lactic acid concentration (3–5). This phenomenon appears to be pH related and secondary to an increase in muscle oxygen consumption (6, 7). Evidence for a similar phenomena in newborns is lacking.

Significant hypoxemia due to shunting across the fetal channels is commonly observed in infants with PPHN and may also influence the $\dot{V}O_2$ in affected newborns. Whereas a significant reduction in $\dot{V}O_2$ has been reported after only moderate hypoxia in ventilated newborn lambs (8), Cameron *et al.* (9), studying spontaneously breathing and paralyzed newborn lambs after moderate hypoxia, observed a decrease in $\dot{V}O_2$ only in the mechanically ventilated animals. This latter report suggests that the combination of paralysis and mechanical ventilation may alter the newborn's metabolic response to moderate hypoxia leading to a decrease in $\dot{V}O_2$.

Neither human nor animal data are available regarding the possible interactive effect of hyperventilation, hypoxia, and paralysis on the newborn's $\dot{V}O_2$. Inasmuch as hyperventilation is usually prescribed for hypoxemic neonates and often requires the concomitant use of muscle relaxants, it is important to evaluate the interactive effect of these factors on the $\dot{V}O_2$.

Thus, the purpose herein was to evaluate the effect of hyperventilation with and without hypoxia on the $\dot{V}O_2$ of the paralyzed newborn piglet.

MATERIALS AND METHODS

Surgical preparation. Camborough piglets kept with the sow until the day of the experiment were anesthetized with pentobarbital sodium (20 mg/kg intraperitoneal) and ketamine (10 mg/kg intramuscular), and prepared for study as follows. Initially the trachea was cannulated and the animals were connected to a Harvard animal volume ventilator. Pancuronium bromide (0.2 mg/kg intravenous) was administered and the ventilator settings were adjusted to deliver a fixed tidal volume (7 ml/kg). The tracheal pressures were measured with a P23 Db Statham pressure transducer from a needle tip positioned near the tracheal end of the endotracheal tube.

Catheters were inserted in the femoral artery and vein and positioned in the abdominal aorta and right atrium, respectively. After a left lateral thoracostomy, the ductus arteriosus was exposed and ligated. A 5F polyvinyl catheter was advanced into the pulmonary artery with its tip located immediately proximal to the pulmonary artery bifurcation. A left atrial catheter was inserted via the appendage and a precalibrated electromagnetic flow probe (Carolina Medical Electronics, Inc. King, NC) was placed around the main pulmonary artery to allow for continuous measurement of cardiac output. Care was taken to choose a flow probe size that allowed for good contact with the vessel wall without constricting it. All flow measurements were read from the digital display, with a three digit resolution, when stable. The left chest was covered with a plastic sheet and care was taken to expand the left lung completely. Rectal temperature was monitored continuously (Yellow Springs telethermometer, Yellow Springs Instrument Co., Yellow Springs, OH) and maintained at 38.5 ± 0.5° C (normal piglet's temperature) by means of electric heating pads. End tidal CO_2 was measured continuously using a Beckman 0M-11 CO_2 analyzer sampling at the endotracheal level. Anesthesia was maintained by hourly pentobarbital sodium

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administration (3–5 mg/kg iv) and pancuronium bromide (0.05 mg/kg iv) was repeated when spontaneous breathing was noted. Ketamine was not used as part of the maintenance anesthesia.

After surgery, the animals were allowed a stabilization period of at least 1 h. A positive end expiratory pressure of 3 cm of water was added to the ventilator to maintain lung inflation and every 30 min it was increased to 10 cm of water for 5 s to prevent lung atelectasis. The catheters were connected to Statham pressure transducers (P23 Db) to allow for a continuous recording (Gould multi-channel recorder, Gould Inc., Oxnard, CA) of aortic, pulmonary, and atrial pressure as well as cardiac output, rectal temperature, and airway pressure. Mean pressures were obtained by electrical integration. Arterial blood gas measurements and pH were made by a microelectrode technique (0.2 ml of blood) on a model ABL3 Radiometer blood gas analyzer and corrected for the animal's body temperature. Blood oxygen saturation and Hb were measured in 0.1 ml of blood with a model OSM-2 hemoximeter (Radiometer, Copenhagen, Denmark). Oxygen content was calculated using a value of 1.36 ml of oxygen/g of Hb as the oxygen-carrying capacity. $\dot{V}O_2$ was calculated as the cardiac output multiplied by the arterial-mixed venous oxygen content difference.

Experimental procedure. Piglets were subjected to three distinct ventilatory patterns in random order as follows. 1) *Normoventilation* where the ventilator rate was adjusted to maintain normocarbia ($PaCO_2$ = 40 mm Hg); 2) *hyperventilation with hypocarbia* where the ventilator rate was increased to lower the $PaCO_2$ below 20 mm Hg, and 3) *hyperventilation with normocarbia* where the ventilator rate was maintained, increased, and CO_2 was added to the inspiratory port to raise the $PaCO_2$ to the normocarbic range. For each of the above three conditions, the animals were studied on room air and after ventilation with an FiO_2 of 0.14 for 10 min each, for a total of 20 min. In addition, the mean airway pressure was kept unchanged for all conditions by lowering the positive end expiratory pressure as the ventilator rate was increased.

Measurements obtained at each one of the conditions, for a total of six sets, included: systemic, pulmonary, and atrial pressures, cardiac output, heart rate (derived from the pressure tracing), and body temperature. Also, arterial and mixed venous simultaneous blood samples were drawn for pH, blood gases, oxygen saturation, and Hb determination at the end of each study period, and used to calculate the $\dot{V}O_2$.

Statistical analysis. Between-condition differences in the mean values for all study parameters were evaluated by analysis of variance for repeated measurements and tested for statistical significance using a multiple comparison test (Duncan's). Statistical significance was taken as $p < 0.05$ and all values are represented as mean ± SEM. We calculated the statistical power of our statistical analysis a posteriori, using the $\dot{V}O_2$ data obtained during normoventilation normoxia, according to Snedecor and Cochran (10).

RESULTS

Thirteen animals with a mean age of 5 ± 1 days and weight of 1.9 ± 0.1 kg were studied. All animals were successfully subjected to all three conditions on air and hypoxia ventilation.

The arterial blood gases, pH, and Hb concentration are shown in Table 1. Hyperventilation to a mean of $PaCO_2$ of 19 ± 2 mm Hg, led to an increase in pH to 7.58 ± 0.02. Hypoxia was associated with an approximately 50% decrease in PaO_2 for all conditions without any significant change in pH or $PaCO_2$. During normoxic and hypoxic hyperventilation, the PaO_2 was higher than normoventilation values, as would be expected with hyperventilation-induced increases in alveolar oxygen tension. In addition, the Hb concentration was not significantly different for the three study conditions.

Hypocapnic hyperventilation with and without hypoxia induced a significant decrease in systemic and pulmonary arterial pressures and in cardiac output (Table 2). Similar measurements during normocapnic hyperventilation did not reveal any differences as compared to normoventilation values, suggesting that the observed changes were related to pH and/or $PaCO_2$ alteration.

No significant change in $\dot{V}O_2$ was observed during hyperventilation with or without hypoxia (Table 3). The significant increase in arterial and venous oxygen content during hyperventilation was likely due to the alveolar oxygen tension increase. The body temperature, according to the protocol, was similar for all conditions.

DISCUSSION

Hyperventilation in the newborn anesthetized and paralyzed pig did not change the $\dot{V}O_2$, a result that is unlike what has been reported in mature humans (4) and dogs (3, 5–7), but similar to what others have observed in the newborn dog (11).

It is unlikely that the discordance between results in newborns and those in mature animals results from methodological differences alone. The reported adult animal data involved acute preparations under pentobarbital anesthesia (3, 5–7) similar to the present protocol. The duration of hypocarbia in the present experiment was somewhat shorter than that used by other investigators; however, in four of our experiments in which measurements were delayed for as much as 20–25 min we also saw no difference in $\dot{V}O_2$. In addition, our results are in accordance with the ones in puppies (11) where the duration of hypocarbia exceeded 2 h. Another methodological consideration is the accuracy of the cardiac output measurements, especially because in newborns there is a potential for flow across the fetal channels leading to inaccurate calculated $\dot{V}O_2$ values. We believe that in the present experiment the measurement of cardiac output by the electromagnetic flow probe around the pulmonary artery was probably identical to the left ventricular output. This assumption

Table 1. *Arterial blood gases, pH, and Hb (mean ± SEM)*

	FiO_2	pH	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)	Hb (g/100 ml)
Normoventilation					
	0.21	7.34 ± 0.02	39 ± 1	82 ± 1	8.8 ± 0.7
	0.14	7.33 ± 0.02	39 ± 1	37 ± 2	8.9 ± 0.8
Hyperventilation hypocarbia					
	0.21	7.58 ± 0.02*	19 ± 2*	108 ± 6*	9.1 ± 0.8
	0.14	7.60 ± 0.02*	19 ± 2*	63 ± 4*	9.1 ± 0.8
Hyperventilation normocarbia					
	0.21	7.34 ± 0.02	39 ± 2	113 ± 19*	8.9 ± 0.7
	0.14	7.33 ± 0.02	42 ± 2	57 ± 3*	8.8 ± 0.7

* $p < 0.01$ as compared to normoventilation values.

Table 2. *Hemodynamic data (mean ± SEM)*

		Pressures					
	FiO_2	Systemic arterial (mm Hg)	Pulmonary arterial (mm Hg)	Left atrial (mm Hg)	Right atrial (mm Hg)	Cardiac output (ml/kg/min)	Heart rate (beats/min)
Normoventilation							
	0.21	61 ± 3	22 ± 1	4.7 ± 0.4	2.5 ± 0.2	173 ± 9	222 ± 14
	0.14	63 ± 3	34 ± 1	4.9 ± 0.4	2.9 ± 0.2	178 ± 8	249 ± 11
Hyperventilation hypocarbia							
	0.21	53 ± 3*	18 ± 1*	4.5 ± 0.3	2.5 ± 0.2	162 ± 9*	238 ± 11
	0.14	53 ± 3*	20 ± 1*	4.4 ± 0.3	2.4 ± 0.2	163 ± 8*	243 ± 10
Hyperventilation normocarbia							
	0.21	63 ± 3	20 ± 1	4.3 ± 0.3	2.4 ± 0.2	167 ± 9	227 ± 11
	0.14	64 ± 3	27 ± 1	4.7 ± 0.3	2.6 ± 0.2	172 ± 7	240 ± 12

* $p < 0.01$ as compared to normoventilation values.

Table 3. *Arterial (CaO_2) and mixed venous (CvO_2) oxygen content and oxygen consumption ($\dot{V}O_2$) (mean ± SEM)*

	FiO_2	Ventilator rate (breaths/min)	Temperature (°C)	CaO_2 (ml/100 ml)	CvO_2 (ml/100 ml)	$\dot{V}O_2$ (ml/kg/min)
Normoventilation						
	0.21	24 ± 2	38.7 ± 0.1	11.5 ± 0.9	6.3 ± 0.8	9.0 ± 0.7
	0.14	24 ± 2	38.7 ± 0.1	7.0 ± 0.6	1.8 ± 0.3	9.3 ± 0.9
Hyperventilation hypocarbia						
	0.21	53 ± 2*	38.5 ± 0.1	12.5 ± 1.0*	6.9 ± 0.8*	9.0 ± 0.9
	0.14	53 ± 2*	38.4 ± 0.1	11.7 ± 1.1*	5.6 ± 0.8*	10.0 ± 1.0
Hyperventilation normocarbia						
	0.21	53 ± 2*	38.6 ± 0.1	12.0 ± 1.0	6.6 ± 0.8	9.1 ± 0.8
	0.14	53 ± 2*	38.6 ± 0.1	10.2 ± 0.9*	4.9 ± 0.7*	9.2 ± 0.9

* $p < 0.01$ as compared to normoventilation values.

is based on the low likelihood of a significant right to left shunt, given that the ductus arteriosus was ligated in all animals and the left atrial pressure was consistently higher than the right one preventing any shunt at the foramen ovale level. Further, the $\dot{V}O_2$ calculated from the arterial-venous oxygen content difference and the cardiac output has been shown in the chronically prepared awake newborn pig (12) to yield values similar to the ones obtained by the closed circuit $\dot{V}O_2$ method (13).

Inasmuch as we failed to observe a significant change in $\dot{V}O_2$ in the newborn pig during hyperventilation, the possibility of a type-2 error or false-negative results deserve some considerations. Accepting a β of 0.20 (power of 0.8) and a two tail α of 0.05 the sample size in the present experiment allows for the detection of a $\dot{V}O_2$ difference of 16% during normoxic hyperventilation hypocarbia. The sample size of the present experiment was large enough to detect the 20% average increase in $\dot{V}O_2$ reported in mature subjects after hyperventilation (3–7).

For all these reasons we believe that our results and those of others (11) are not explicable by methodological differences but represent a real difference between newborns and adults in the $\dot{V}O_2$ response to hyperventilation.

The reason for this difference is not entirely clear. One possibility is related to the major difference in basal $\dot{V}O_2$ between adult and newborn animals. $\dot{V}O_2$ in newborns is much higher than in adults when indexed to body weight (14). It is conceivable that this higher basal $\dot{V}O_2$ renders any stimulatory effect of increased pH less important. However, it is also clear that basal $\dot{V}O_2$ in newborns is still far from maximal $\dot{V}O_2$, as has been demonstrated in studies of cold stress in newborn lambs (15).

Alternatively, differences in activation and maturation of the phosphofructokinase system in newborns could account for the discrepant results. In dogs, the increase in $\dot{V}O_2$ with hyperventilation has been linked to an observed increase in skeletal muscle metabolism. The proposed mechanism is an increase in glycolysis secondary to activation of phosphofructokinase by the higher intracellular pH (6), and not the decrease in $PaCO_2$, because alkaline infusion in the adult dogs also increase $\dot{V}O_2$ (16).

Earlier studies have indicated that total 6-phosphofructo-1-kinase activity increases during rat heart and muscle maturation (17, 18). Similarly, heart and skeletal muscle in humans have also shown changes in the isoenzyme pool and activity during neonatal development (19). Although data regarding the effect of pH on the kinetics of muscle phosphofructokinase in newborn animals are not available, we speculate that the activity of this enzyme may not be significantly increased during alkalosis as demonstrated in mature subjects (20). It is also possible that the lesser baseline activity of this enzyme in newborns makes pH-induced changes in activity less important physiologically.

In our study, neither hypoxia ($FiO_2 = 0.14$) nor the combination of hypoxia and hyperventilation induced any significant change in $\dot{V}O_2$ in the paralyzed piglets. In previous studies, it has been shown that the changes in $\dot{V}O_2$ with hypoxia are greatly affected by the environmental temperature and the degree of oxygen deprivation to which the newborn animals are subjected

(15). In human newborns (21–25) and in lambs (26) a significant reduction in $\dot{V}O_2$ in the absence of a cold stress was only observed when the FiO_2 was decreased below 0.12; a result not unlike that of Cameron *et al.* (9) who saw a substantial reduction in the $\dot{V}O_2$ of the awake and paralyzed lamb after a decrease in PaO_2 to 29 ± 1 mm Hg. In the present protocol we used anesthetized and normothermic piglets subjected to a lesser degree of hypoxia, as judged by the PaO_2 during hypoxia (37 ± 2 mm Hg), than the studies mentioned above. Therefore, differences in protocol design probably accounted for the discrepancy between our results and the ones reported by other investigators on the effect of hypoxia on the $\dot{V}O_2$ in newborn animals.

In summary, we have observed that unlike adult animals, newborn pigs fail to demonstrate hyperventilation-induced increases in $\dot{V}O_2$. Differences in the maturation pattern and activity of the glycolytic pathway enzymes during the neonatal period may account for the discrepant results. Further investigation is necessary before the results of our study are extrapolated to infants. Nevertheless, these data suggest that hyperventilation-induced hypocarbia may have less impact on metabolic rate in newborns than has been reported to occur in mature humans and animals.

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