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The Effect of *Escherichia coli* Endotoxin Infusion on the Ventilatory Response to Hypoxia in Unanesthetized Newborn Piglets

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ABSTRACT

To determine the effects of endotoxemia on the neonatal ventilatory response to hypoxia, 17 chronically instrumented and unanesthetized newborn piglets (≤7 d) were studied before and 30 min after the administration of *Escherichia coli* O55:B5 endotoxin ($n = 8$) or normal saline ($n = 9$). Minute ventilation, oxygen consumption, heart rate, arterial blood pressure, and blood gases were measured during normoxia and 10 min of hypoxia (fraction of inspired oxygen, 0.10). Basal ventilation was not modified by *E. coli* endotoxin infusion (mean ± SE, 516 ± 49 *versus* 539 ± 56 mL/min/kg), but the ventilatory response to hypoxia was markedly attenuated at 1 min (955 ± 57 *versus* 718 ± 97 mL/min/kg, $p < 0.002$, saline *versus* endotoxin) and at 10 min (788 ± 51 *versus* 624 ± 66 mL/min/kg, $p < 0.002$). A larger decrease in oxygen consumption was observed during hypoxia and endotoxemia (6.3 ± 2.8 *versus* 18.3 ± 2.7%, $p < 0.03$, pre- *versus* post-endotoxin). A significant correlation was demonstrated between the changes in minute ventilation and oxygen consumption with hypoxia during endotoxemia ($r = 0.9$, $p < 0.002$). The ventilatory response to hypoxia was not modified by the saline infusion. These data show a significant attenuation in the ventilatory response to hypoxia during *E. coli* endotoxemia. This decrease in ventilation was associated with a significant decrease in the metabolic rate during hypoxia and endotoxemia. **(*Pediatr Res* 53: 950–955, 2003)**

Abbreviation

RA, room air
ABG, arterial blood gas
$\dot{V}_E$, minute ventilation
V_T, tidal volume
RR, respiratory rate
R_L, total lung resistance
C_{dyn}, dynamic lung compliance
$\dot{V}o_2$, oxygen consumption
HR, heart rate
ABP, arterial blood pressure
EOG, electrooculogram
Fio_2, fraction of inspired oxygen
NO, nitric oxide
BE, base excess

Changes in the breathing pattern and apnea episodes are frequently associated with neonatal sepsis, especially in the preterm infant (1). It has also been observed that the administration of *Escherichia coli* endotoxin to anesthetized adult cats produced an abrupt apnea followed by transient rapid and shallow breathing (2). However, the mechanisms explaining these changes in breathing pattern are not clearly understood. Respiratory muscle fatigue, a decrease in lung compliance, and an increase in pulmonary resistance have been cited as possible mechanisms for the ventilatory changes observed during Gram-positive and -negative septicemia (3–6).

It is well known that a variety of inflammatory mediators such as cytokines, prostaglandins, leukotrienes, and NO are released during sepsis or endotoxemia (3, 6, 7). Furthermore, the changes in the breathing pattern observed during *E. coli* infusion to adult cats were eliminated in the animals pretreated with indomethacin or thromboxane A_2 receptor antagonist (2). On the other hand, it has been demonstrated that prostaglandins and NO may mediate the ventilatory depression observed during hypoxia in newborn animals (8, 9). Therefore, the increased release of these inflammatory mediators may further depress the ventilatory response to hypoxia during *E. coli* endotoxemia.

The increased circulating cytokines during sepsis or endotoxemia can induce a systemic inflammatory response involving the microvascular system and trigger hemodynamic changes (7, 10, 11). These changes result in maldistribution of blood flow to different organs, which may be accompanied by

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an alteration in oxygen delivery (12). Sepsis also impairs oxygen utilization at the cellular level by affecting key enzymes involved in energy production (13, 14). Therefore, these changes in oxygen delivery and utilization can decrease $\dot{V}O_2$ during *E. coli* endotoxin infusion. This may also influence the ventilatory response to hypoxia during endotoxemia, because metabolic rate and alveolar ventilation are tightly linked (15). To the best of our knowledge, there are no published studies reporting the effect of endotoxemia on the ventilatory response to hypoxia in the newborn.

We hypothesized that the administration of *E. coli* endotoxin to unanesthetized newborn piglets results in a depression of the ventilatory response to hypoxia and that this could be mediated by changes in the metabolic rate. Therefore, the objective of this study was to assess the ventilatory and metabolic responses to *E. coli* O55:B5 endotoxin infusion during normoxia and hypoxia in unanesthetized newborn piglets.

MATERIALS AND METHODS

Animals. Seventeen newborn Yorkshire piglets aged 3–7 d old were studied. The procedures used in the care and handling of the animals were in accordance with the guidelines of the National Institutes of Health and the study protocol was reviewed and approved by the Animal Care and Use Committee of the University of Miami School of Medicine.

Animal preparation. Anesthesia induction and maintenance was obtained with 2% isoflurane in O_2 at 2–3 L/min *via* a nonrebreathing anesthesia bag throughout the duration of surgery. HR, oxygen saturation by continuous pulse oximetry (Nellcor Inc., Hayward, CA, U.S.A.) and body temperature with a rectal thermistor (YSI Inc., Yellow Springs, OH, U.S.A.) were monitored throughout surgery. Body temperature was maintained by means of a heating pad. Femoral venous and arterial catheters were placed for antibiotic (cephoxitin, 100 mg/kg/d) injection and infusion of *E. coli* endotoxin solution, measurement of HR and ABP, and obtaining blood samples for determination of ABG. EEG electrodes were connected to bifrontal stainless steel screws placed approximately 10 mm anterior and lateral to the bregma. The outer canthus of one eyelid was sewn with paired fine-gauge stainless-steel wires, which were used to monitor the EOG.

A period of 48–72 h was allowed for postoperative recovery. After the effect of anesthesia wore off ,the piglets were able to ambulate and fed *ad libitum*. They had a weight gain between 20 and 30 g/d. Antibiotics were discontinued at least 12 h before the experiment. On the day of the study, in a thermoneutral environment, the piglets were placed in a sling and allowed to breathe through a customized airtight face mask. After 1 h of acclimatization, studies were performed only when they were in a quiet sleep (non–rapid eye movement) state. In addition, EEG and EOG were monitored to ensure that all measurements were obtained during non–rapid eye movement sleep, because sleep states can modify the ventilatory response to hypoxia in newborn animals (16, 17). Respiratory airflow was measured by a hot-wire anemometer (NVM-1, Bear Medical Systems Inc., Riverside, CA, U.S.A.) attached to the face mask. The flow signal was electronically integrated to obtain V_T using a Gould integrator (Gould Instruments, Cleveland, OH, U.S.A.). $\dot{V}_E$ was obtained by calculating the sum of inspiratory volumes measured over a 1-min period.

$\dot{V}O_2$ was measured by the open circuit technique as described previously (18). A constant bias flow of 3–4 L/min of heated, humidified RA or 10% O_2 was delivered through the breathing circuit and the difference between the inspiratory and the expiratory O_2 concentrations was measured continuously by an O_2 analyzer (model 570-A, Servomex, Crowborough, Sussex, UK). $\dot{V}O_2$ was calculated by the following formula: $\dot{V}O_2 = V_S \cdot (FiO_2 - FeO_2)$ at body temperature and ambient pressure and saturated with water vapor, where V_S is the flow rate through the system, FiO_2 is the fraction of inspired oxygen, and FeO_2 is the oxygen concentration in mixed expired gas. The flow rate through the system was measured before and after each run by a Matheson linear mass flowmeter (0–20.0 L/min, model 8100, Matheson Gas Products, Secaucus, NJ, U.S.A.).

To assess whether the changes in pulmonary mechanics observed after *E. coli* endotoxin administration have an effect on the ventilatory response to hypoxia, lung compliance and resistance were measured in four additional newborn piglets in RA and during hypoxia before and after endotoxin infusion. Esophageal pressure was measured using a water-filled 8F feeding tube with the tip placed in the lower esophagus and attached to pressure transducer (model P23XL, Gould Instruments). This measurement was obtained only after the piglet was adapted to the esophageal tube. Air flow, V_T, and esophageal pressure measurements were obtained and stored in the computer, and C_{dyn} and R_L were calculated using the method of Mead and Whittenberger (19).

All the cardiorespiratory measurements were digitized by AT-CODAS (Dataq Instruments, Akron, OH, U.S.A.) at a frequency of 100 Hz and recorded into a microprocessor for later analysis. While in non-REM sleep, $\dot{V}_E$, V_T, RR, $\dot{V}O_2$, HR, and ABP were measured during a 10-min period of stable breathing in RA, and ABG were measured at the end of this period. These measurements were considered as RA baseline values. To induce hypoxia, the FiO_2 was decreased to 0.10 using an O_2-N_2 gas mixture. All cardiorespiratory measurements were repeated after 10 min of hypoxia. The piglets were then returned to RA and allowed to recover for 30 min, after which time all measurements were repeated in RA to ensure that ventilation had returned to baseline status. Following this, the animals who had been randomly assigned to receive endotoxin were given *E. coli* O55:B5 endotoxin (Sigma Chemical, St. Louis, MO, U.S.A.) at a dose of 0.125 mg/kg in 10 mL saline infused intravenously over 15 min. The dose of endotoxin and the time frame for the study were selected based on pilot studies, which demonstrated no significant change in basal $\dot{V}_E$ and ABP before and 30 min after endotoxin infusion. The control animals received 10 mL saline intravenously. The investigators were blinded to which solutions were infused. Thirty minutes after the completion of the infusion of endotoxin or saline, all cardiorespiratory, $\dot{V}O_2$, and ABG measurements were again obtained in RA and during hypoxia. An unanesthethized animal model was chosen for this study to avoid the effect of anesthesia on the changes in metabolic rate

and cardiorespiratory function during hypoxia and endotoxemia (17, 20).

Data analysis. Repeated measures ANOVA was used to compare the cardiorespiratory and metabolic responses to hypoxia before and after saline or *E. coli* endotoxin infusion. The relationship between the changes in $\dot{V}_E$ and $\dot{V}O_2$ with hypoxia after endotoxin infusion was determined by linear regression analysis. Data were expressed as mean ± SE and a value of $p < 0.05$ was considered significant.

RESULTS

Eight piglets (age, 5.5 ± 0.4 d; weight, 2.0 ± 0.2 kg) received *E. coli* endotoxin and nine piglets (age, 5.2 ± 0.2 d; weight, 1.8 ± 0.1 kg) received saline. There was no significant difference in age and weight between the groups.

Figure 1 shows the ventilatory response to hypoxia before and after saline or endotoxin infusion. Before saline infusion, there was a marked increase (80 ± 8%) in $\dot{V}_E$ during the first minute of hypoxia, followed by a decline to values that were sustained above baseline values (40 ± 10%) at 10 min of hypoxia. This biphasic ventilatory response to hypoxia was unchanged after saline infusion. Before endotoxin infusion, the biphasic hypoxic ventilatory response was similar to that displayed by the saline group. Although the basal ventilation remained unchanged after endotoxin infusion, a significant attenuation in the ventilatory response to hypoxia (32 ± 7% at 1 min and 16 ± 5% at 10 min, $p < 0.02$) was observed when compared with the saline group. The decline in ventilation with hypoxia after endotoxin administration was primarily the result of a blunting of the increase in respiratory frequency (Table 1).

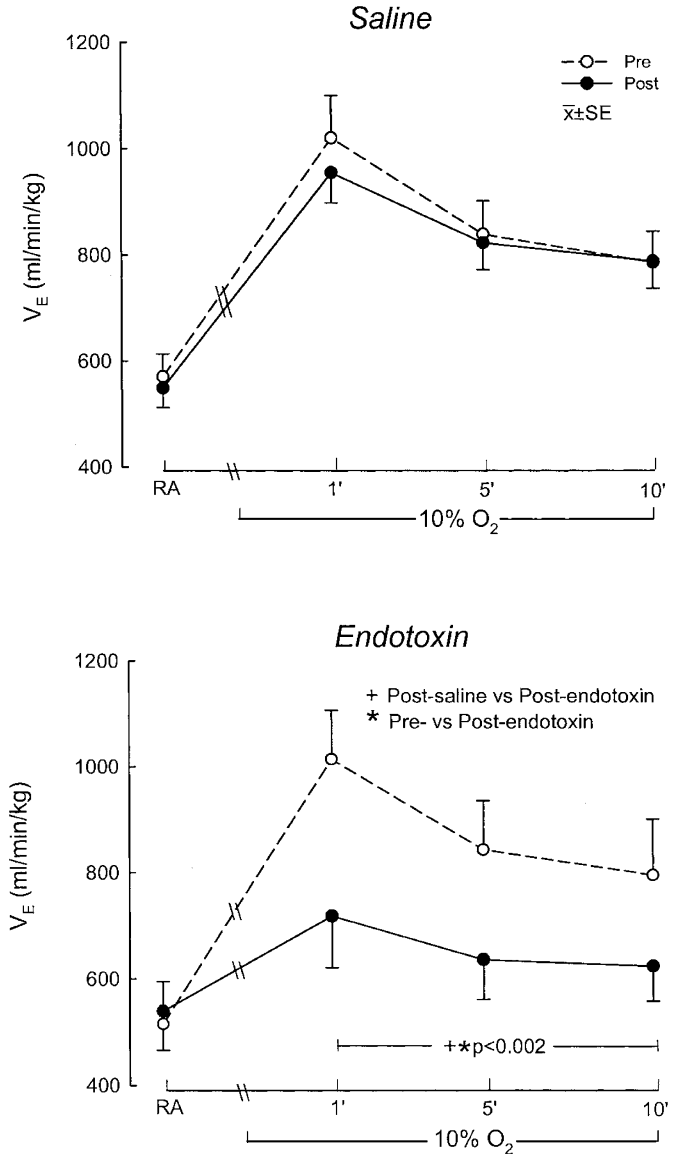

Figure 1. Change in $\dot{V}_E$ with hypoxia before and after saline or endotoxin infusion. The ventilatory response to hypoxia was markedly attenuated in piglets receiving *E. coli* endotoxin.

ABG and acid base values before and after saline or endotoxin infusions in RA and 10 min hypoxia are shown in Table 1. The fall in mean arterial pressure of O_2 (Pao_2) and CO_2 ($Paco_2$) with hypoxia from baseline was not modified by saline or endotoxin infusion. Changes in BE with hypoxia were similar before and after saline or endotoxin infusion. However, a significant decrease in the baseline BE was observed after endotoxin infusion (4.8 ± 0.9 *versus* 1.1 ± 1.2 mM, $p < 0.03$). The basal BE was not modified by saline infusion (5.6 ± 0.5 *versus* 5.8 ± 0.8 mM).

Figure 2 illustrates the $\dot{V}O_2$ response to hypoxia before and after endotoxin infusion. Although there was a decrease in $\dot{V}O_2$ with hypoxia before endotoxin infusion (6.3 ± 2.8%), a more pronounced decrease in $\dot{V}O_2$ with hypoxia was observed following endotoxin infusion (18.3 ± 2.7%, $p < 0.03$). The decrease in $\dot{V}O_2$ observed during hypoxia before and after saline infusion was not significantly different. Although there was no correlation between the changes in $\dot{V}O_2$ and $\dot{V}_E$ at 10 min of hypoxia before endotoxin infusion ($r = 0.16$, $p < 0.98$), a significant linear correlation was observed after endotoxin infusion ($r = 0.9$, $p < 0.002$) (Fig. 3). There was no correlation between the changes in $\dot{V}O_2$ and $\dot{V}_E$ at 10 min of hypoxia before or after saline infusion.

In the four animals in which pulmonary mechanics was measured, a similar decrease in C_{dyn} with hypoxia before (1.9 to 1.7 mL/cm H_2O/kg; 13.8 ± 4.7%) and after (1.7 to 1.5 mL/cm H_2O/kg; 13.5 ± 4.7%) endotoxin infusion was demonstrated. Although baseline R_L increased after endotoxin infusion, the decrease in R_L with hypoxia before (71 to 51 cm H_2O/L/s; 29 ± 3%) and after (100 to 69 cm H_2O/L/s; 31 ± 4%) endotoxin infusion was similar.

The basal ABP was not significantly modified by endotoxin infusion, but the fall in ABP by 13 ± 7% with hypoxia was statistically significant ($p < 0.009$) only after endotoxin infusion (Table 1). The increase in HR with hypoxia was similar before and after endotoxin infusion. Changes in ABP and HR with hypoxia did not differ before and after saline infusion.

Basal body temperature and the change in temperature with hypoxia were not modified by endotoxin infusion.

DISCUSSION

The present study demonstrates a marked attenuation in the ventilatory response to hypoxia after *E. coli* endotoxin infusion

Table 1. *ABG, acid base values, respiratory frequency (RR), V_T, ABP, and HR before and after saline or endotoxin infusion*

	Control				*E. coli* endotoxin			
	Pre-saline		Post-saline		Pre-endotoxin		Post-endotoxin	
	RA	10% O_2	RA	10% O_2	RA	10% O_2	RA	10% O_2
pH	7.46 ± 0.01	7.52 ± 0.01*	7.46 ± 0.01	7.52 ± 0.01*	7.46 ± 0.01*	7.52 ± 0.01*	7.40 ± 0.01	7.45 ± 0.02*†‡
$Paco_2$ kPa	5.5 ± 0.1	4.3 ± 0.1*	5.3 ± 0.1	4.3 ± 0.1*	5.2 ± 0.1	4.1 ± 0.1*	5.5 ± 0.3	4.4 ± 0.3*
Pao_2 kPa	12.9 ± 0.3	4.4 ± 0.1*	13 ± 0.4	4.5 ± 0.3*	13.4 ± 0.3	4.1 ± 0.1*	12 ± 0.5	4.5 ± 0.3*
BE, mM	5.6 ± 0.5	4.7 ± 0.6	5.8 ± 0.8	4.6 ± 0.9	4.8 ± 0.9	3.6 ± 0.9	1.1 ± 1.2	0.1 ± 1.3*†
RR, breaths/min	44 ± 5	70 ± 7*	40 ± 3	67 ± 7*	40 ± 6	66 ± 10*	39 ± 7	44 ± 7†‡
V_T mL/kg	13.5 ± 0.9	11.6 ± 0.7*	14.0 ± 0.8	12.4 ± 1.0*	13.7 ± 1.0	12.9 ± 1.3*	15.3 ± 1.8	15.1 ± 1.8
ABP, mm Hg	72 ± 3	73 ± 2	71 ± 2	70 ± 3	68 ± 3	69 ± 3	63 ± 2	53 ± 3†‡
HR, beats/min	196 ± 5	252 ± 12*	193 ± 1610	247 ± 15*	179 ± 16	221 ± 14*	212 ± 23	241 ± 23*

Values are mean ± SEM.
* $p < 0.05$, RA *vs* 10% O_2.
† $p < 0.01$, pre- *vs* post-endotoxin.
‡ $p < 0.01$, post-saline *vs* post-endotoxin.

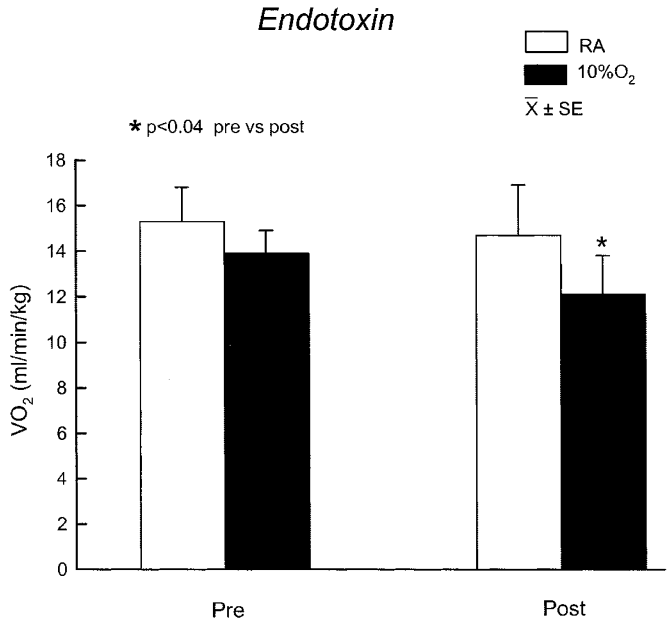

Figure 2. Changes in $\dot{V}O_2$ during normoxia (RA) and hypoxia before and after endotoxin infusion. A greater decrease in $\dot{V}O_2$ with hypoxia was observed after *E. coli* endotoxin infusion compared with before *E. coli* endotoxin infusion.

in unanesthetized newborn piglets. This response correlated with a greater decrease in $\dot{V}O_2$ with hypoxia during endotoxemia, suggesting that the lower ventilation during hypoxia and endotoxemia was associated with a fall in metabolic rate.

Reports on the effect of infection on basal ventilation have been inconsistent (21–23). It has been reported that a 1-min infusion of *E. coli* endotoxin to adult cats resulted in an abrupt apnea followed by rapid shallow breathing, and this change in the breathing pattern was mediated by the release of thromboxane A_2 (2). Furthermore, a significant decrease in RR was observed after the administration of lipopolysaccharide to conscious adult rabbits (22). In contrast, a significant increase in RR has been reported after endotoxin infusion to adult rats, and this response was augmented by the denervation of the peripheral chemoreceptors, suggesting that the carotid bodies may have a modulating effect on the endotoxin-induced hyperventilation (23). In the present study, no significant change in basal ventilation was observed after 30 min of *E. coli* endotoxin infusion. These conflicting findings of the changes in the breathing pattern during endotoxemia may be related to the differences in animal species, age, and dose of endotoxin infused.

The attenuation in the ventilatory response to hypoxia after *E. coli* endotoxin infusion in the newborn piglets was observed throughout the hypoxia exposure, suggesting that *E. coli* endotoxin has both peripheral and central effects on the respiratory control mechanisms. The attenuation in ventilation during the first minute of hypoxia suggests an inhibitory effect of endotoxemia on the peripheral chemoreceptors. Because NO inhibits the peripheral chemoreceptor discharge and its release is increased during endotoxemia and hypoxia, NO may mediate this attenuation in ventilation during the first minute of hypoxia (24). The further decrease in ventilation to values close to baseline level after 10 min of hypoxia in the endotoxemic piglets may be explained by hypometabolism, metabolic acidosis, arterial hypotension, and changes in pulmonary mechanics.

Cross *et al.* (25) described that preterm infants exposed to acute hypoxia had a decrease in metabolic rate and ventilation. This finding was supported by studies that showed an association between the decline in ventilation and metabolism in newborn kittens exposed to hypoxia (15). In contrast, Suguihara *et al.* (18) demonstrated in sedated newborn piglets that the decrease in $\dot{V}O_2$ at 10 min of hypoxia was independent of whether the ventilatory response to hypoxia was sustained or depressed concluding that the decrease in metabolic rate was not the major cause for the late decline in ventilation. In the present study, the decrease in $\dot{V}O_2$ (6.3%) during hypoxia before endotoxin infusion in unanesthetized newborn piglets was slightly less than that reported previously (18), and this may be explained by the lack of sedation in this study.

An apparent discrepancy was observed between the magnitude of the decrease in $Paco_2$ and the ventilatory response to hypoxia before and after endotoxin infusion. Although there was a relative decline in ventilation during hypoxia and endotoxemia, $\dot{V}E$ values remained above baseline levels. The increase in $\dot{V}E$ with hypoxia was significantly less (16%) during endotoxemia compared with the increase (40%) observed before endotoxin infusion. This was accompanied by a similar

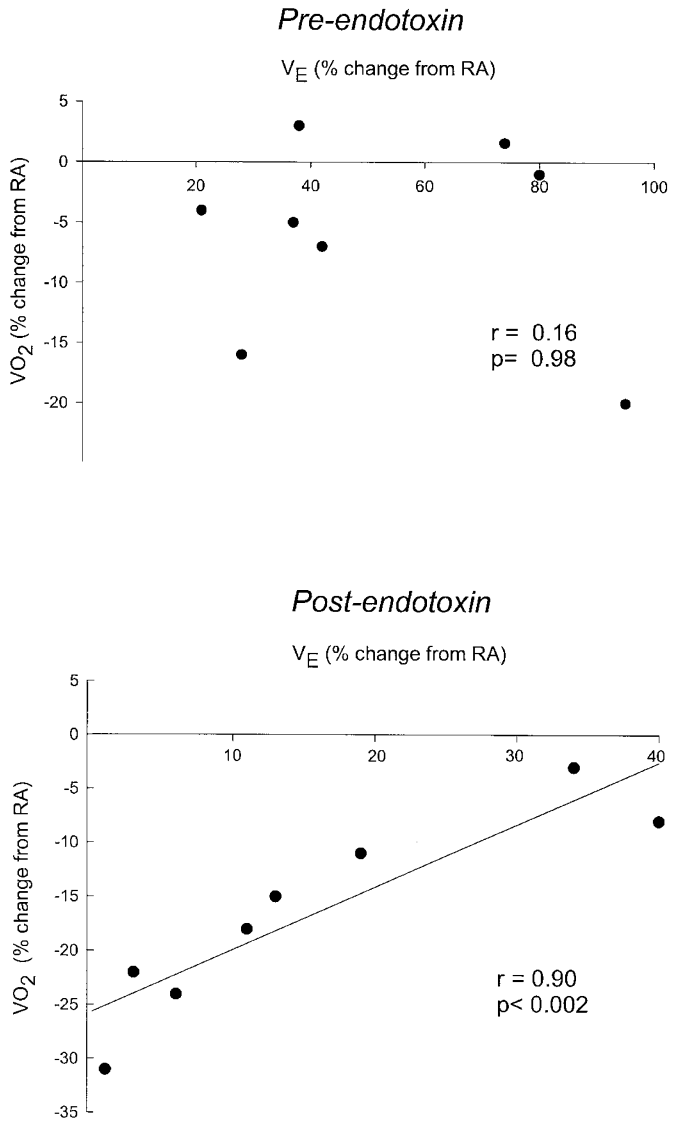

Figure 3. Relationship between the percentage change in $\dot{V}_E$ and $\dot{V}_{O_2}$ during hypoxia before and after endotoxin infusion. A significant linear correlation between the changes in $\dot{V}_{O_2}$ and $\dot{V}_E$ with hypoxia was observed only after *E. coli* endotoxin infusion.

decrease in Pa_{CO_2} before and after *E. coli* infusion. This can be explained by the marked decrease in metabolism (18%) observed during hypoxia and endotoxemia compared with the 6.3% fall in $\dot{V}_{O_2}$ observed before endotoxin infusion.

In addition to the hypoxia-induced hypometabolism, endotoxemia can also affect metabolic rate. Several of the inflammatory mediators released during sepsis can have deleterious hemodynamic effects resulting in severe vasoconstriction of some vascular beds and vasodilatation of other areas (11, 26), and this can lead to a redistribution of blood flow resulting in perfusion that may not be appropriate for the metabolic demands of certain organs or tissues (7, 11, 27, 28). Sepsis can also impair oxygen utilization at the cellular level, resulting in an inhibition of key mitochondrial enzymes in the electron transport chain, thereby uncoupling oxidative phosphorylation (13, 14, 29–31). Therefore, altered O_2 delivery and utilization may result in reduced $\dot{V}_{O_2}$. The attenuation of the hypoxic ventilatory response after endotoxin infusion may be explained by the decreased metabolic demands during hypoxia, which was exacerbated by endotoxin.

The decrease in ABP with hypoxia after endotoxin infusion was more marked than after saline infusion. However, this arterial hypotension does not explain the decrease in ventilation during hypoxia in endotoxemic piglets, because an intact ventilatory response to hypoxia has been observed in newborn piglets with mean ABP as low as 30 mm Hg (32).

Other mechanisms possibly contributing to the attenuation in the ventilatory response to hypoxia during endotoxemia include lung injury and ventilatory pump failure. Endotoxemia-induced lung injury is manifested by impaired gas exchange together with changes in lung mechanics (6, 33). In the present study, a similar decrease in C_{dyn} and R_L with hypoxia and endotoxemia was observed in the two groups, ruling out this possibility as a mechanism for the attenuated ventilatory response to hypoxia.

Endotoxin can elicit a significant decline in contractile function of the respiratory muscles (4, 5, 34–37), which can be the result of an imbalance between energy supply and demand caused by arterial hypotension and blood flow redistribution, impaired energy production or utilization with abnormal neuromuscular transmission, and failure of excitation-contraction coupling (5, 34, 38). Respiratory muscle function was not evaluated in the present study, but the attenuation of the ventilatory response to hypoxia was probably not the result of respiratory pump failure because endotoxic shock with significant arterial hypotension did not develop after *E. coli* endotoxin infusion.

Different degrees of metabolic acidosis can attenuate or augment the ventilatory response to hypoxia (39). A depression in the ventilatory response to hypoxia was noted in awake newborn piglets with induced lactic acidosis when the BE was > -12 mM (40). In the present study, the basal BE decreased after *E. coli* endotoxin administration, but remained within the normal range. Furthermore, the decrease in BE with hypoxia was similar before and after endotoxin infusion, making this change unlikely to be the explanation for the attenuated hypoxic ventilatory response during *E. coli* endotoxemia.

In conclusion, the hypoxic ventilatory response was markedly attenuated during *E. coli* endotoxemia and this was associated with a greater decrease in $\dot{V}_{O_2}$. The mechanisms by which endotoxin-induced inflammatory mediators modify the metabolic rate and both peripheral and central respiratory control mechanisms need to be further elucidated.

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