0031-3998/90/2802-0101$02.00/0
PEDIATRIC RESEARCH

Vol. 28, No. 2, 1990
Printed in U.S.A.

Oxygen Extraction in Lamb Skeletal Muscle

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ABSTRACT. Past studies have found that total-body O_2 extraction during hypoxia was less in 1-wk-old lambs than in older animals. It was proposed that reduced O_2 extraction was secondary to suppression of growth-related oxygen consumption ($\dot{V}O_2$) in tissues such as skeletal muscle, bone, kidney, and skin, rather than a defect in peripheral O_2 use. To determine the capacity of immature skeletal muscle to extract O_2, we isolated the hind limb circulation of eight ketamine-anesthetized, 7- to 18-d-old lambs exposed to stagnant hypoxia by inflation of a right atrial balloon catheter. Femoral arterial and venous P_{O_2}, P_{CO_2}, pH, Hb concentration, O_2 saturation, and femoral arterial blood flow (Q) were measured and hind limb O_2 delivery (D_{O_2}), extraction ratio, and $\dot{V}O_2$ calculated. Individual critical levels of D_{O_2} below which $\dot{V}O_2$ was dependent on O_2 supply were determined by dual-line best-fit regression analysis. In six of eight animals, $\dot{V}O_2$ was clearly independent of supply until D_{O_2} reached critically low levels. However, O_2 extraction during extreme hypoxia appeared submaximal (baseline O_2 extraction ratio, 0.22 ± 0.06; at critical levels of D_{O_2}, 0.51 ± 0.11; at the lowest level of Q, 0.64 ± 0.15). When 2,4-dinitrophenol, an uncoupler of oxidative phosphorylation, was administered to four additional lambs exposed to stagnant hypoxia, O_2 extraction below critical levels of D_{O_2} increased from 0.48 ± 0.15 to 0.79 ± 0.10 ($p < 0.001$, unpaired t test). These data suggest that initial limitations in O_2 extraction were a result of the suspension of O_2-consuming processes, not an irreversible defect in peripheral O_2 use. (*Pediatr Res* 28: 101–105, 1990)

Abbreviations

DNP, 2,4-dinitrophenol
D_{O_2}, O_2 delivery
D_{O_2}crit, critical level of D_{O_2}
Q, blood flow
$\dot{V}O_2$, O_2 consumption
P_{50}, P_{O_2} at which Hb was 50% saturated
ANOVA, analysis of variance
[Hb], Hb concentration
pH_a, arterial pH

Sidi *et al.* (1) found that total-body O_2 extraction during extreme hypoxic hypoxia was significantly less in 1-wk-old lambs than in older (3–7 wk) animals. Because of the lack of acidosis with hypoxia and minimal increase in $\dot{V}O_2$ on recovery, they proposed that reduced O_2 extraction was secondary to a suppression of growth-related $\dot{V}O_2$ in tissues such as muscle, bone, kidney, and skin, rather than an impairment in peripheral tissue extraction. To test the hypothesis that immature skeletal muscle O_2 extraction is submaximal during extreme hypoxia, we isolated the hind limb circulation of eight anesthetized, 7- to 18-d-old lambs exposed to stagnant hypoxia.

If O_2 extraction in lamb skeletal muscle is reduced secondary to the suppression of growth-related $\dot{V}O_2$, increments in O_2 demand should increase O_2 extraction. We therefore exposed four additional animals to both stagnant hypoxia and DNP, an uncoupler of oxidative phosphorylation.

MATERIALS AND METHODS

Animal preparation. Our study was approved by The Children's Hospital Committee on Animal Investigation. Twelve lambs, 7–18 d of age, wt 3.6–8.2 kg, were studied. Animals were housed in air-conditioned rooms at the Children's Hospital Animal Facility. Lambs were anesthetized with ketamine (5–10 mg/kg i.v. bolus followed by a continuous infusion of 5–10 mg·kg^{-1}·h^{-1}). The exact dosage used was chosen to abolish motor, heart rate, and pressor responses to stimulation. After a satisfactory level of anesthesia was obtained, pancuronium (0.1 mg·kg^{-1}·h^{-1} i.v.) was given. Animals were endotracheally intubated and mechanically ventilated (Healthdyne, Marietta, GA) to keep arterial CO_2 pressure at approximately 4 kPa. Arterial O_2 pressure was maintained at or near 13 kPa. All animals were given 10 mL/kg of normal saline i.v. and maintained on 3 mL·kg^{-1}·h^{-1} of a solution of 5% dextrose and normal saline for the remainder of the experiment. Temperature was maintained at 38°C using a temperature probe, water-blanket, and temperature control unit.

Hind limb arterial and venous Q were then isolated to the main femoral artery and vein. The left femoral artery, nerve, and vein were dissected free, and nylon ties (Akcess Medical Products, New Brunswick, NJ) passed under the femoral sheath to achieve arterial and venous occlusion. To prevent thrombosis, heparin (1000 U/kg i.v.) was given just before tightening. Another tie was secured at the ankle to exclude any contribution from the paw. Isolation of the hind limb was confirmed after each experiment by injecting india ink into the femoral artery; only muscle distal to the nylon ties stained black. In addition, femoral arterial and venous flows (see below) were the same in each experiment.

Hind limb Q was measured continuously by a nonocclusive ultrasonic flow probe (Transonic Systems, Ithaca, NY) placed around the femoral artery. Arterial placement was preferred due to the small cross-sectional area of the femoral vein (generally <2 mm^2). Periodic measurement of femoral venous flow revealed no difference between femoral venous and arterial flow. A vigorous reactive hyperemia in response to arterial occlusion was seen throughout each experiment, except just before cardiovascular collapse. The flow probe was calibrated before each experiment with saline pumped at a known rate through cellulose membrane tubing (Spectrum Medical Industries, Los Angeles, CA). Next, a ¾″ 24-gauge catheter (Critikon, Tampa, FL) was placed in a superficial branch of the femoral vein. The lumen of the catheter ended at the junction of the branch and main

Received August 29, 1989; accepted April 12, 1990.
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Supported by the CHMC Anesthesia Foundation and National Research Service Award 1-T32-HL07633-03.

Table 1. *Baseline group mean data (n = 8, mean ± SD)**

[Hb](g/dL)	10.0 ± 1.3
Pa_{O_2} (kPa)	13.7 ± 1.4
Pv_{O_2} (kPa)	5.7 ± 1.2
Pa_{CO_2} (kPa)	4.3 ± 0.9
P_{50} (kPa)	3.9 ± 0.5
Sa_{O_2} (%)	99 ± 1
Sv_{O_2} (%)	77 ± 7
pH_a	7.44 ± 0.07
pH_v	7.36 ± 0.07
Femoral artery Q ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	11.30 ± 3.80
Hind limb D_{O_2} ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	1.57 ± 0.60
Hind limb $\dot{V}_{O_2}$ ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	0.34 ± 0.04
O_2 ext	0.24 ± 0.06

* Values are mean ± SD. Pa_{O_2}, arterial O_2 pressure; Pv_{O_2}, venous O_2 pressure; Pa_{CO_2}, arterial CO_2 pressure; Sa_{O_2}, arterial saturation of Hb with O_2; Sv_{O_2}, venous saturation of Hb with O_2; pH_v, venous pH; O_2 ext, O_2 extraction ratio.

femoral vein. In this way, femoral venous blood samples could be obtained without inducing venous obstruction. Arterial samples were collected and arterial pressure monitored via a catheter placed in the contralateral femoral artery. Finally, an 8 French Foley catheter was placed in the right atrium via the right jugular vein for reducing cardiac output in a controlled, stepwise fashion (2).

Experimental protocol. In experiment 1, the capacity of immature skeletal muscle to extract O_2 was evaluated in eight lambs exposed to stagnant hypoxia. After a 1-h stabilization period, we made baseline measurements of femoral arterial and venous O_2 and CO_2 tensions, pH, [Hb], O_2 saturation, and femoral arterial Q. Blood gases were measured using a Corning (Medfield, MA) 168 pH/blood gas analyzer. [Hb] and O_2 saturation were measured using an Instrumentation Laboratories (Lexington, MA) 282 Co-Oximeter whose absorption wavelengths were adjusted to measure the [Hb] and O_2 saturation of bovine blood. Next, the atrial balloon was inflated to produce an approximately 1-kPa reduction in mean arterial pressure. Initially, small inflations of the balloon (0.5–1 mL) were sufficient to produce 1-kPa reductions in arterial pressure. Thereafter, compensatory increases in blood pressure often occurred, requiring larger inflations (approximately 2 mL). After 15 min, measurements of femoral arterial and venous [Hb], O_2 saturation, blood gases, and hind limb Q were again obtained. This process was repeated until cardiovascular collapse occurred. The hind limb was then injected with india ink, the animal killed, and the stained muscle dissected free and weighed.

In experiment 2, four additional animals were exposed to both stagnant hypoxia and DNP. DNP increases O_2 demand by uncoupling oxidative phosphorylation. As in experiment 1, measurements were obtained after stepwise inflation of the atrial balloon. When hind limb Q decreased to about 25% of baseline (just before cardiovascular collapse), lambs received 6 mg/kg of DNP dissolved in sodium bicarbonate. In each case, administration of DNP increased hind limb blood flow approximately 2-fold. Balloon inflation was then adjusted to produce a range of flows similar to that obtained before the administration of DNP. We were, however, unable to regain baseline flow in two lambs, most likely a result of myocardial injury from previous balloon inflation. The hind limb was then injected with ink and the animal killed, as described above.

Calculations and statistical analysis. Because the Co-Oximeter is unable to measure the O_2 saturation of sheep blood, and because the presence of fetal Hb may result in fictitious elevations in carboxyhemoglobin concentration (%HbCO) as determined by the Co-Oximeter (3), the Co-Oximeter was calibrated before the study with a Lex-O_2-Con-K O_2-sensitive cell (Hospex Fiberoptics, Waltham, MA). Assuming the Co-Oximeter-derived [Hb]

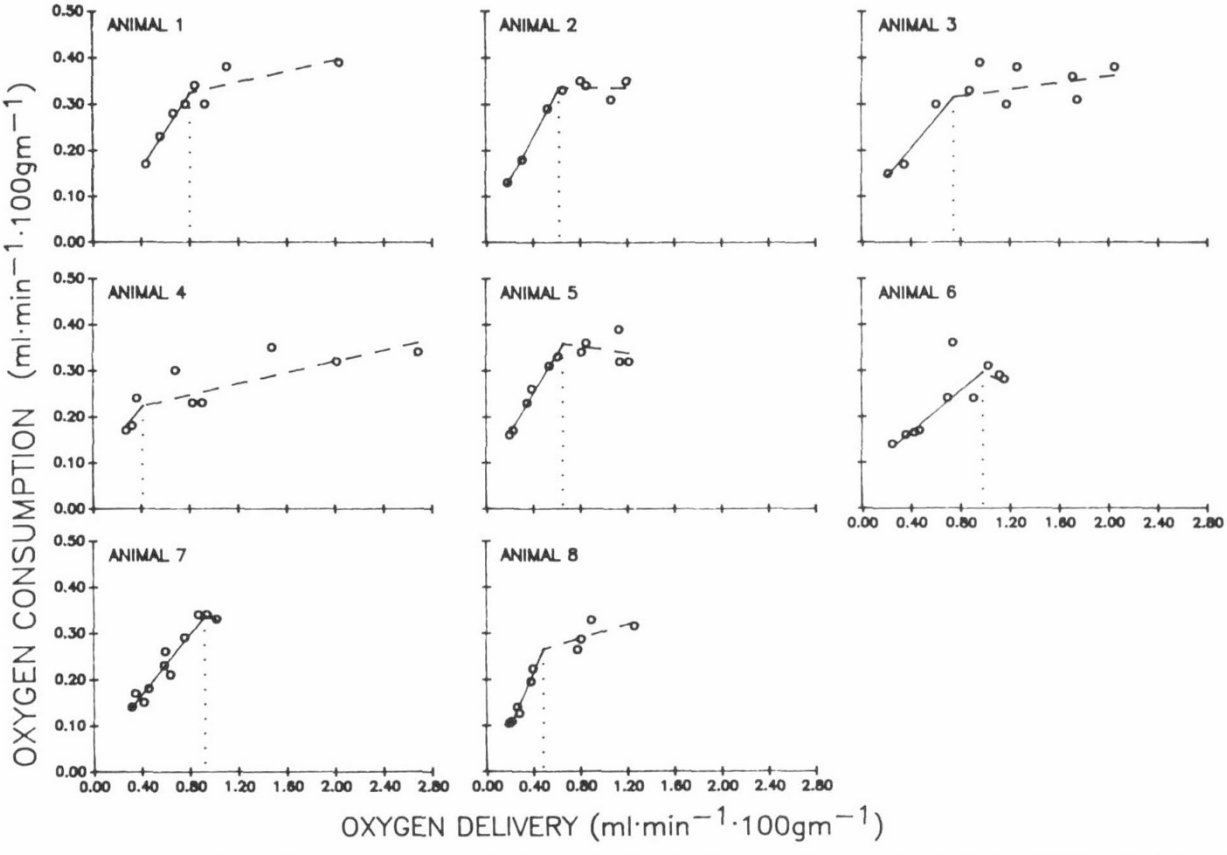

Fig. 1. Individual plots of D_{O_2} *vs* $\dot{V}_{O_2}$, experiment 1. Individual critical levels of D_{O_2} are shown by (· · · ·). In six of eight animals (*numbers 1–5* and *8*), $\dot{V}_{O_2}$ was well maintained despite reductions in D_{O_2}.

Table 2. *Comparison of baseline group mean data with that obtained at critical $D\dot{O}_2$ and at lowest flow rate (n = 6, mean ± SD)**

	Baseline	Critical	Lowest Q
Femoral artery Q ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	12.30 ± 3.9†	4.80 ± 1.90	1.80 ± 0.10
Hind limb $D\dot{O}_2$ ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	1.73 ± 0.61†	0.61 ± 0.20	0.24 ± 0.10
Hind limb $V\dot{O}_2$ ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	0.35 ± 0.03‡	0.30 ± 0.05§	0.15 ± 0.03
O_2 ext	0.22 ± 0.06†	0.51 ± 0.11	0.64 ± 0.15
pH_a	7.46 ± 0.07†	7.34 ± 0.05§	7.18 ± 0.02

* Values are mean ± SD. O_2 ext, O_2 extraction ratio.
† Different from critical and lowest values, $p < 0.01$.
‡ Different from critical and lowest values, $p < 0.05$.
§ Different from baseline and lowest values, $p < 0.05$.

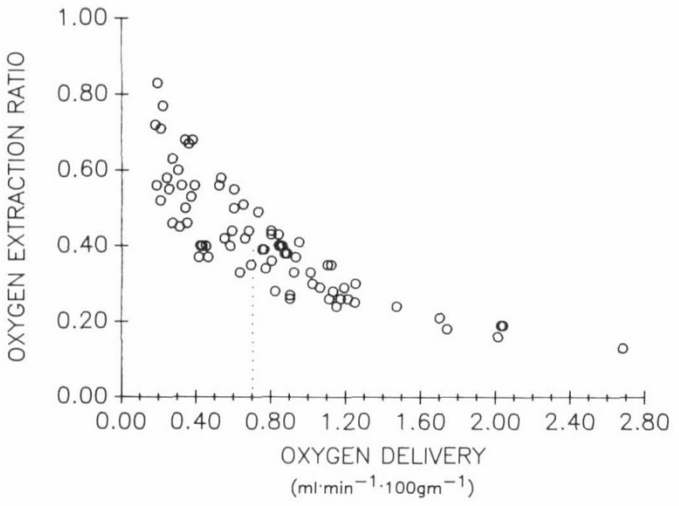

Fig. 2. Relationship between $D\dot{O}_2$ and O_2 extraction ratio, all animals, experiment 1. Below the mean critical level of $D\dot{O}_2$ (· · · ·), O_2 extraction continued to increase.

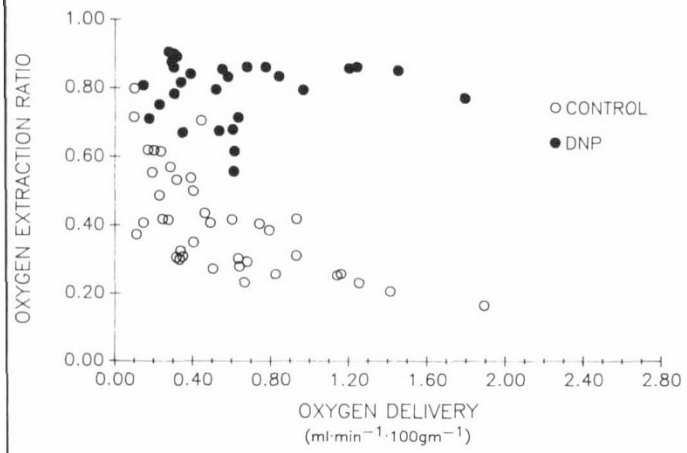

Fig. 3. Relationship between $D\dot{O}_2$ and O_2 extraction ratio, experiment 2. Administration of DNP increased O_2 extraction throughout the range of $D\dot{O}_2$ studied.

to be correct, we determined the relationship between O_2 content as measured by the Lex-O_2-Con-K and O_2 content as calculated from blood gas and Co-Oximeter measurements to be best described by the equation:

$$O_2\ content_{Lex\text{-}O2\text{-}Con\text{-}K}\ (mL/dL) = 1.36\ [Hb]_{Co\text{-}Oximeter} \times (\%HbO_{2\,Co\text{-}Oximeter} + 0.85 \times \%HbCO_{Co\text{-}Oximeter}) + 0.003\ Po_2$$

where $\%HbO_2$ is oxyhemoglobin concentration. $D\dot{O}_2$ was calculated by multiplying hind limb Q by CaO_2. $V\dot{O}_2$ was calculated with the Fick equation. O_2 extraction ratio was calculated by dividing $C_{a\text{-}v}O_2$ by CaO_2. P_{50} was calculated for individual animals by fitting venous O_2 tension and saturation (sat) to the coordinates suggested by Hill (4), *i.e.* log Po_2 *versus* log (sat/1 − sat). By use of the linear regression equations thus obtained, P_{50} was calculated by setting log (sat/1-sat) equal to 0.

All Q, $D\dot{O}_2$, and $V\dot{O}_2$ data were reported per 100 g of muscle. Group mean data were described as the mean ± SD. Individual $D\dot{O}_2$crit, defined as the level of $D\dot{O}_2$ below which $V\dot{O}_2$ became dependent on O_2 supply, were identified at the intersection of the two regression lines maximizing the ratio of the regression sum of squares to the residual sum of squares (least sum of squares technique). Regression analysis was modified to minimize the perpendicular distance between each point and the regression line. The lines selected were chosen from all possible combinations of points grouped to construct two independent regression lines (5, 6). ANOVA was used to compare baseline Q, $D\dot{O}_2$, $V\dot{O}_2$, O_2 extraction, and pH_a values with those obtained at $D\dot{O}_2$crit and at the lowest level of Q. Newman-Keuls' multiple range test was used to pinpoint differences identified by ANOVA (7). Single sample, paired, and unpaired *t* tests were used where appropriate.

RESULTS

Experiment 1. Baseline measurements (Table 1). Mean baseline Q was 11.3 ± 3.8 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, slightly greater than that found in the canine hind limb (8–10). The mean P_{50} of 3.9 ± 0.5 kPa was typical of lambs of this age, and substantially less than the adult value of 5.6 kPa (11). Although pH_a was slightly elevated, these data suggest a preponderance of fetal Hb.

Effects of stagnant hypoxia. Individual plots of hind limb $D\dot{O}_2$ *versus* $V\dot{O}_2$ are shown in Figure 1. Mean $D\dot{O}_2$crit, below which $V\dot{O}_2$ was supply-dependent, was 0.70 ± 0.20 $mL \cdot min^{-1} \cdot 100\ g^{-1}$. The mean slope and $V\dot{O}_2$-intercept representing those data below $D\dot{O}_2$crit were 0.38 ± 0.11 and 0.05 ± 0.04 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, respectively. This y-intercept is significantly greater than 0 ($p < 0.01$, single sample *t* test), demonstrating that O_2 extraction continued to increase below $D\dot{O}_2$crit.

In six of eight lambs, hind limb $V\dot{O}_2$ was clearly independent of $D\dot{O}_2$ until a critically low level was reached (Fig. 1). Group mean data for these animals demonstrate that $V\dot{O}_2$ was not flow-limited (Table 2). As $D\dot{O}_2$ decreased from baseline to critical levels (1.73 ± 0.61 to 0.61 ± 0.20 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, $p < 0.01$, ANOVA), hind limb $V\dot{O}_2$ decreased only slightly (0.35 ± 0.03 to 0.30 ± 0.05 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, $p < 0.05$) and O_2 extraction ratio increased (0.22 ± 0.06 to 0.51 ± 0.11, $p < 0.01$). Although O_2 extraction ratio continued to increase below $D\dot{O}_2$crit (Fig. 2), it appeared submaximal, reaching only 0.64 ± 0.15 at the lowest level of Q. There was a modest reduction in pH_a (baseline, 7.46 ± 0.07; at $D\dot{O}_2$crit, 7.34 ± 0.05, $p < 0.01$).

In two lambs (animals 6 and 7), there was only a small plateau during which $V\dot{O}_2$ was independent of supply. $V\dot{O}_2$ may therefore have been supply-dependent in these animals.

Experiment 2. Despite balloon inflation, hind limb Q and $D\dot{O}_2$ increased immediately after DNP administration (Q before DNP, 1.8 ± 1.3 $mL \cdot min^{-1} \cdot 100\ g^{-1}$; after DNP, 3.3 ± 1.8 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, $p < 0.05$, paired *t* test; $D\dot{O}_2$ before DNP, 0.22 ± 0.13 $mL \cdot min^{-1} \cdot 100\ g^{-1}$; after DNP, 0.40 ± 0.02 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, $p < 0.05$).

DNP increased O_2 extraction and $V\dot{O}_2$ throughout the range

Table 3. *Effects of DNP on O_2 extraction, pH_a, and P_{50}**

	Control	DNP
O_2 ext below hind limb Do_2crit	0.48 ± 0.15 (n = 24)	0.79 ± 0.10 (n = 18)†
O_2 ext at lowest femoral artery Q	0.64 ± 0.18 (n = 4)	0.80 ± 0.08 (n = 4)
pH_a below hind limb Do_2crit	7.24 ± 0.11 (n = 24)	7.10 ± 0.16 (n = 18)†
pH_a at lowest level of femoral artery Q	7.21 ± 0.06 (n = 4)	7.04 ± 0.23 (n = 4)
P_{50} (kPa)	4.4 ± 0.50 (n = 4)	4.5 ± 0.50 (n = 4)

* Values are mean ± SD. O_2 ext, O_2 extraction ratio.
† Different from control, $p < 0.01$.

of Do_2 studied (Fig. 3, Table 3). Below 0.61 mL·min^{-1}·100 g^{-1} (mean Do_2crit from experiment 1), DNP increased O_2 extraction during stagnant hypoxia by 65% [control, 0.48 ± 0.15 (n = 24); DNP, 0.79 ± 0.10 (n = 18); $p < 0.001$, unpaired t test]. DNP increased O_2 extraction at the lowest level of Q by 25% (control, 0.64 ± 0.18; DNP, 0.80 ± 0.08, an increase exceeding that found in the canine hind limb during hypoxic hypoxia (10).

Addition of DNP significantly reduced mean pH_a below Do_2crit (7.24 ± 0.11 to 7.10 ± 0.16, $p < 0.001$). Mean P_{50} was unchanged, however, suggesting that improved O_2 extraction was not related to a rightward shift in the oxyhemoglobin dissociation curve.

DISCUSSION

In experiment 1, hind limb $\dot{V}o_2$ was clearly independent of Do_2 in six of eight animals. In these lambs, reductions in hind limb Q failed to substantially decrease hind limb $\dot{V}o_2$, suggesting that $\dot{V}o_2$ was not flow-limited. Qualitatively similar results have been found in the canine hind limb; however, the level of O_2 extraction in 7- to 18-d-old lambs was less than that previously observed in the mature dog (5, 9, 12, 13): The mean critical O_2 extraction ratio of 0.51 in the lamb hind limb compares unfavorably with that obtained in the canine hind limb by Samsel *et al.* (5) (critical O_2 extraction ratio, 0.67). In addition, the mean O_2 extraction ratio at the lowest level of blood flow (0.64) was considerably less than that found in the canine hind limb by Stainsby and Otis (13) (0.75), Duran and Renkin (12) (0.80), and Cain and Chapler (9) (0.80). Although we have not repeated these experiments in mature sheep, the comparisons presented above and the high level of O_2 extraction in experiment 2 strongly suggest that O_2 extraction during extreme hypoxia was submaximal in the skeletal muscle of young lambs.

If submaximal O_2 extraction was related to a defect in peripheral O_2 use, increments in O_2 demand might not increase O_2 extraction. Such defects might include a smaller number of recruitable capillaries or an immaturity of mechanisms acting to match local O_2 supply and demand. (We know of no data describing such developmental differences.) Tissue O_2 extraction might also be limited by the increased affinity of fetal Hb for O_2 (14). If, alternatively, O_2 extraction in lamb skeletal muscle was reduced secondary to suppression of $\dot{V}o_2$, increments in O_2 demand should increase O_2 extraction. In experiment 2, DNP significantly increased O_2 extraction during extreme hypoxia, suggesting that reduced O_2 extraction was related to the suppression of O_2-consuming processes, not defective peripheral O_2 use. DNP increased mean hind limb O_2 extraction at the lowest level of Q to 0.80, a value comparable to that obtained in mature dogs exposed to DNP (10). We therefore speculate that when O_2 demand is accelerated (as with DNP or exercise), the capacity of immature lamb skeletal muscle to extract O_2 during hypoxia is similar to that of mature animals.

Our data are consistent with those of Sidi *et al.* (1), who found that total-body O_2 extraction during extreme hypoxia was significantly less in 1-wk-old lambs than older (3–7 wk) animals. Because of the lack of acidosis with hypoxia and minimal increase in $\dot{V}o_2$ on recovery, Sidi *et al.* hypothesized that reduced O_2 extraction was secondary to suppression of growth-related $\dot{V}o_2$. Arguing that blood flow at the tissue level is directly related to O_2 demand, Sidi *et al.* further hypothesized that reductions in growth-related $\dot{V}o_2$ occurred in muscle, bone, kidney, and skin, tissues to which Do_2 had decreased during hypoxia. Similarly, Fahey and Lister (15) found that 2-wk-old lambs had smaller increases in $\dot{V}o_2$ after stagnant hypoxia than 8-wk-old lambs, suggesting a reduction in nonessential metabolism during hypoxia. Because as much as 30–35% of basal metabolic rate in the newborn lamb may be devoted to growth (1), reduction of growth-related $\dot{V}o_2$ seems a most adaptive and likely response to hypoxemia. Transient cessation of more fundamental O_2-consuming processes (such as ion transport) may also be possible, however (10).

In two lambs, hind limb $\dot{V}o_2$ appeared to be dependent on Do_2. It is possible that autoregulatory response of the skeletal muscle capillary bed to reduced Do_2 may have been limited in these animals. Alternatively, a plateau in which $\dot{V}o_2$ was independent of Do_2 might have been obtained had initial flow rates been higher. Femoral artery flow in these animals may have been limited by such factors as anesthetic depression of O_2 demand, or partial arterial or venous obstruction.

To avoid the myocardial depression and reduced venous return associated with barbiturates, we chose ketamine to anesthetize our experimental animals. The cardiovascular effects of ketamine are primarily related to CNS stimulation, and consist of peripheral vasoconstriction and increased heart rate (16). Vasoconstrictor tone has been shown to promote O_2 extraction (17), suggesting that the relatively low level of O_2 extraction observed in experiment 1 was not an artifact of ketamine anesthesia.

Determination of a critical level of Do_2 assumes that O_2 extraction below Do_2crit is maximal; further reductions in Do_2 must then result in proportional reductions on $\dot{V}o_2$. This model, although useful in assessing tissue O_2 extraction, may be an oversimplification, however. In our study, O_2 extraction increased even after Do_2crit was reached (Fig. 2). Because reductions in cardiac output were induced in a sequential manner, increments in O_2 extraction below Do_2crit may have resulted from more prolonged exposure to hypoxia or increasing acidosis, both of which have been shown to increase O_2 extraction (8, 17). Alternatively, O_2 extraction might have increased below Do_2crit because the time for O_2 diffusion is lengthened at low flow rates. Red cell transit time in muscle capillaries is on the order of 1000 ms, however, too slow to limit O_2 extraction at rest (18).

We have shown that although the $\dot{V}o_2$ of immature lamb skeletal muscle is not flow-limited, O_2 extraction during stagnant hypoxia is submaximal. The increase in O_2 extraction after administration of DNP suggests that limitations in O_2 extraction result from a reduction in O_2-consuming metabolism during hypoxia, rather than a defect in peripheral O_2 use.

Acknowledgments. The authors thank Lindy King and Juli Koleske for their assistance in preparing the manuscript.

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