Cardiovascular Effects of *d*-Tubocurarine and Pancuronium in Newborn Lambs during Normoxia and Hypoxia

CALVIN B. CAMERON,¹ GEORGE A. GREGORY,² ABRAHAM M. RUDOLPH,³ AND
MICHAEL A. HEYMANN⁴

*Departments of Anesthesia and Pediatrics and the Cardiovascular Research Institute, University of California,
San Francisco, California 94143*

ABSTRACT. Nondepolarizing muscle relaxants are administered to hypoxic neonates (including those with severe cyanotic congenital heart disease) to reduce oxygen consumption. However, it is unknown whether paralysis actually reduces oxygen consumption or whether the drugs used affect the cardiovascular system of neonates. Therefore, we studied the effects of *d*-tubocurarine and pancuronium induced muscle paralysis on oxygen consumption, cardiac output, and tissue oxygen delivery in healthy normoxic and hypoxic 1- to 3-day-old lambs. We measured intravascular pressures, cardiac output and its distribution (microspheres), and blood gases and pH during: 1) spontaneous respiration with room air (control); 2) spontaneous respiration with a PaO₂ of 27–33 mm Hg (hypoxia); 3) mechanical ventilation with room air; 4) mechanical ventilation with room air and paralysis with *d*-tubocurarine (0.3 mg/kg) or pancuronium (0.1 mg/kg); and 5) mechanical ventilation with hypoxia and paralysis. Mechanical ventilation, with or without muscle paralysis, had no effect on the oxygen delivery or oxygen consumption of normoxic animals. Hypoxia and spontaneous ventilation had no effect on oxygen consumption, but hypoxia, paralysis, and mechanical ventilation reduced it 35% ($p < 0.002$ *d*-tubocurarine) and 50% ($p < 0.001$ pancuronium). Cardiac output was unaffected by oxygenation, mechanical ventilation, or muscle paralysis. However, blood flow to the brain and heart increased during hypoxia, which maintained normal oxygen delivery to these organs. During hypoxia and spontaneous ventilation, mean pulmonary arterial pressures increased 34% (*d*-tubocurarine) and 54% (pancuronium) above control; during hypoxia, muscle paralysis, and mechanical ventilation, it increased 81%. Myocardial blood flows and right ventricular rate-pressure products increased during hypoxia and were greatest during hypoxia, paralysis, and mechanical ventilation. Serum lactate levels increased 30–50% during hypoxia and spontaneous ventilation and remained elevated for the rest of the study. These data indicate that muscle paralysis and mechanical ventilation reduce the total body oxygen consumption of

hypoxic lambs, but have no effect on the oxygen consumption of normoxic lambs. They also show that muscle paralysis increases the level of hypoxic pulmonary vasoconstriction, but that paralysis does not interfere with hypoxia induced redistribution of blood flow. We conclude that similar muscle relaxant induced changes may be beneficial to most hypoxic neonates, but that the pulmonary vascular effects, if similar to those found in our lambs, may be undesirable in neonates with pulmonary vascular or right-sided heart disease. (*Pediatr Res* 20: 246–252, 1986)

Abbreviations

d-TC, *d*-tubocurarine
Pan, pancuronium
V̇O₂, oxygen consumption

Despite aggressive therapy, neurologic damage or death may occur in hypoxic neonates. In an attempt to minimize the effects of hypoxia, clinicians commonly employ neuromuscular blockade with *d*-TC or Pan and mechanical ventilation on the assumption that muscle paralysis reduces total body V̇O₂. However, we know of no data that support this assumption. We, therefore, determined the effects of muscle paralysis on oxygen consumption, intravascular pressures, cardiac output, organ blood flow, and tissue oxygen delivery in 1- to 3-day-old normoxic and hypoxic lambs.

METHODS

Surgical preparation. After receiving approval from the UCSF committee on Animal Care to do these studies, we blindfolded and lightly restrained 12 term, 1- to 3-day-old lambs in the supine position. We then anesthetized the skin and tissues of their neck and one groin with 0.5% lidocaine and inserted catheters into a femoral artery and vein by cutdown. Next, we advanced a 5F Swan-Ganz catheter from a jugular vein into the pulmonary artery and inserted two catheters into a carotid artery. We positioned one of these catheters in the left ventricle for the injection of microspheres and the other in the arch of the aorta for blood sampling. We created a tracheostomy, inserted a 5.0 mm ID cuffed endotracheal tube, and inflated the cuff.

Study protocol. We maintained the rectal temperature at $39.0 \pm 0.5^\circ \text{C}$ (the normal temperature of lambs) with a warming blanket and a servocontrolled heating lamp, and maintained the environmental temperature at $25 \pm 0.5^\circ \text{C}$ with a heating lamp. Hydration was maintained with 4 ml/kg/h of normal saline. When the heart rate, systemic and pulmonary arterial blood

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Address reprint request to George A. Gregory, M.D., Department of Anesthesia, University of California, S436, 513 Parnassus Avenue, San Francisco, CA 94143.

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¹ Fellow in Anesthesia and the Cardiovascular Research Institute, Present address Department of Anaesthesiology, University of Manitoba, Winnipeg, Manitoba, Canada.

² Professor of Anesthesia and Pediatrics.

³ Professor of Pediatrics, Physiology, and Obstetrics, Gynecology and Reproductive Sciences. Neider Professor of Pediatric Cardiology.

⁴ Professor of Pediatrics, Physiology and Obstetrics, Gynecology and Reproductive Sciences.

pressures (systolic, diastolic, mean), and the systemic arterial PO_2 , PCO_2 , and pH were stable for 2 h, we began the study. We recorded systemic and pulmonary arterial blood pressures with Statham P23 DB transducers and recorded these pressures on a Beckman Dynograph. The amplitude-frequency responses of the strain gauges, catheters, and connecting tubing were flat to 15 Hz. Heart rate was determined with a cardi tachometer.

We divided the animals into two groups: six were given *d*-TC and six Pan. Each lamb was studied during the following conditions: 1) spontaneous respiration with room air (control); 2) spontaneous respiration with an arterial PO_2 of 27–33 mm Hg (hypoxia); 3) mechanical ventilation with room air; 4) mechanical ventilation with room air and muscle paralysis with *d*-TC (0.3 mg/kg) or Pan (0.1 mg/kg) (paralysis); 5) mechanical ventilation with hypoxia and paralysis. The studies were always done in this sequence (1 through 5). In preliminary experiments, we attempted to study unparalyzed, hypoxic, mechanically ventilated animals, but were unable to do so because they breathed out of phase with the ventilator and developed severe acidosis. Every 30 min we tested for completeness of paralysis with a nerve stimulator. In all instances paralysis was complete.

Fifteen minutes after attaining each experimental condition, we withdrew 8 ml of blood from the femoral artery and determined PO_2 , PCO_2 , pH, O_2 saturation, and hemoglobin, glucose, and lactate concentrations. We achieved the desired level of hypoxia in 10 min in conditions 2 and 5 and waited an additional 15 min to make the next set of measurements. In condition 3 we returned the FiO_2 to 0.21 and made the measurements 15 min later. We also drew 2 ml of blood from the ascending aorta for blood gases and pH determinations. We measured $\dot{V}O_2$ by the flow through technique of Lister *et al.* (1, 2). Cardiac output and regional blood flow were measured by injecting radionuclide labeled microspheres (^{125}I , ^{51}Cr , ^{85}Sr , ^{113}Sn , and ^{65}Zn) into the left ventricle (3, 4) and collecting reference blood samples from the carotid and femoral arteries for 1.0 or 1.25 min. The withdrawal rate for the reference samples was either 4 or 7 ml/min. We replaced all blood losses with equal volumes of blood from lambs of the same age. During condition 3 through 5, we mechanically ventilated the lungs with a Harvard volume ventilator, set the tidal volume at 10 ml/kg, and adjusted the respiratory rate to maintain the $Paco_2$ at control levels. The Pao_2 was normal during mechanical ventilation except in condition 5 where it was intentionally decreased. To measure airway pressures, we inserted a 0.4-mm catheter into the endotracheal tube, connected the catheter to a P23 DB pressure transducer, and continuously recorded its output on the Beckman Dynograph.

At the end of the study, we killed the animals with intravenous phenobarbital and removed, weighed, and incinerated their organs. Later, we determined the level of radioactivity in each

organ with a 512-channel pulse height analyzer (Searle Analytic, Des Plaines, IL).

Measurements and calculation. We measured the systemic arterial blood gases with a Corning 175 blood gas analyzer and determined the hemoglobin concentration and O_2 saturation with a OSM-2 hemoximeter (Radiometer, Copenhagen, Denmark). Blood gas and pH values were corrected for body temperature.

We determined blood glucose concentrations by the glucose oxidase method and blood lactate concentrations by the lactic dehydrogenase method. The mean error for paired samples was 3% for glucose and 2% for lactate.

We used a modification of the flow through method of Lister *et al.* (1, 2) to continuously measure $\dot{V}O_2$ (Fig. 1). Inspired gas entered the Harvard ventilator from a reservoir bag. Gas leaving the ventilator was collected in a bag via a gas tight Sierra valve. We filled the gas collection bag with steel wool to improve gas mixing. In addition to the expired gas, a constant amount of inspired gas entered the gas collection bag from the inspired gas source to prevent the continuous suction of the oxygen analyzer from collapsing the gas collection bag. We continuously determined the oxygen concentration in the gas collection bag during 10 min periods. To calculate $\dot{V}O_2$, we used the formula: $\dot{V}O_2 = V_s(FiO_2 - F_eO_2) \times (STPD)$, where V_s is the flow rate through the oxygen analyzer; F_i is the concentration of the inspired gas; F_e is the concentration of mixed expired gas; STPD is the standard temperature and pressure of the gas when dry. Validation of this method has been reported elsewhere (2).

We calculated oxygen delivery to individual organs by multiplying organ blood flow (ml/100 g/min) by arterial oxygen content [(oxygen saturation $\times$ hemoglobin concentration $\times$ 1.36) + dissolved oxygen]. We calculated rate-pressure products for the right and left ventricles as an index of myocardial oxygen consumption (5).

We tested for significant differences between conditions with two way analysis of variance and the Neuman-Keuls test for multiple comparisons (6). We used the unpaired *t* test to test for differences between drugs. A *p* value of 0.05 or less was considered significant. Data are presented as means $\pm$ 1 SEM. *p* values of <0.05 are given in the text.

RESULTS

The data for *d*-TC are presented in Tables 1–4; those for Pan are presented in Tables 5–8. Both drugs had similar metabolic and cardiovascular effects.

Total body oxygen consumption decreased 35% ($p < 0.002$ *d*-TC) and 50% ($p < 0.001$ Pan) from control in hypoxic, paralyzed animals. During the other conditions, oxygen consumption was

Fig. 1. System for measuring oxygen consumption. Expired gas is collected in mixing bag via a one-way valve. In addition, a constant amount of inspired gas is added to the gas collection bag to prevent the oxygen analyzer's suction from collapsing the gas collection bag.

Table 1. *The effects of oxygenation, mechanical ventilation, and paralysis with d-TC on oxygen consumption, blood gases and pH, serum lactate and glucose concentrations, and body temperature in six newborn lambs (means $\pm$ SEM)*

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent paralysis	Hypoxia mech vent paralysis
Oxygen consumption (ml/kg/min)	12.3 $\pm$ 0.5	11.1 $\pm$ 1.0	12.5 $\pm$ 1.9	13.1 $\pm$ 1.2	8.0 $\pm$ 0.5†‡
Respiratory rate (breaths/min)	36 $\pm$ 1.6	65 $\pm$ 4.7†	17 $\pm$ 2†‡	17 $\pm$ 3†‡	17 $\pm$ 2†‡
Femoral artery					
PO ₂ (mm Hg)	80 $\pm$ 2.6	27 $\pm$ 1.8†	81 $\pm$ 4	82 $\pm$ 4	27 $\pm$ 0.5†
Pco ₂ (mm Hg)	34 $\pm$ 1.2	28 $\pm$ 1.7†	36 $\pm$ 1.7	35 $\pm$ 1.6	35 $\pm$ 1.1
pH	7.37 $\pm$ 0.01	7.29 $\pm$ 0.02†	7.35 $\pm$ 0.01	7.38 $\pm$ 0.01	7.34 $\pm$ 0.03
Lactate (mg/dl)	18.2 $\pm$ 2.4	37.6 $\pm$ 8.4†	34.9 $\pm$ 5.7†	26.6 $\pm$ 4.0†	33.3 $\pm$ 3.7†
Glucose (mg/dl)	93 $\pm$ 2.8	89 $\pm$ 3.0	88 $\pm$ 2.7	94 $\pm$ 4.0	91 $\pm$ 3.0
Temperature (°C)	38.7 $\pm$ 0.5	38.7 $\pm$ 0.7	38.9 $\pm$ 0.4	38.7 $\pm$ 0.4	38.0 $\pm$ 0.2

* Hypoxia = PaO₂ of 27–33 mm Hg.† Compared with normoxia and spontaneous ventilation, $p < 0.05$.‡ Compared with hypoxia and spontaneous ventilation, $p < 0.05$.Table 2. *The effects of oxygenation, mechanical ventilation, and paralysis with d-TC on cardiac output, heart rate, and systemic and pulmonary arterial pressures and resistances in six newborn lambs (means $\pm$ SEM)*

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent paralysis	Hypoxia mech vent paralysis
Cardiac output (ml/kg/min)	376 $\pm$ 53	482 $\pm$ 69	290 $\pm$ 26	288 $\pm$ 20	357 $\pm$ 38
Heart rate (beats/min)	243 $\pm$ 17	244 $\pm$ 25	250 $\pm$ 17	240 $\pm$ 13	262 $\pm$ 16
Mean systemic blood pressure (mm Hg)	90.8 $\pm$ 3	76 $\pm$ 2.5	82 $\pm$ 2.1	89 $\pm$ 3.7	89 $\pm$ 8.4
Mean pulmonary arterial blood pressure (mm Hg)	25.6 $\pm$ 3.1	34.3 $\pm$ 1.7†	29 $\pm$ 4.2	28 $\pm$ 3.4	46 $\pm$ 3.3†‡
Left ventricular rate-pressure product (beats/min/mm Hg)	31,283 $\pm$ 3,310	30,683 $\pm$ 4,461	30,008 $\pm$ 2,748	31,287 $\pm$ 1,307	36,500 $\pm$ 3,595
Right ventricular rate-pressure product (beats/min/mm Hg)	10,026 $\pm$ 1,493	13,720 $\pm$ 2,547	11,675 $\pm$ 1,739	12,106 $\pm$ 1,261	19,538 $\pm$ 2,293†
Pulmonary vascular resistance (mm Hg/ml/min/kg)	0.07 $\pm$ 0.01	0.08 $\pm$ 0.01	0.1 $\pm$ 0.02	0.1 $\pm$ 0.02	0.13 $\pm$ 0.02†‡
Systemic vascular resistance (mm Hg/ml/min/kg)	0.25 $\pm$ 0.03	0.17 $\pm$ 0.03	0.29 $\pm$ 0.04	0.32 $\pm$ 0.03	0.26 $\pm$ 0.04

* Hypoxia = PaO₂ of 27–33 mm Hg.† Compared with normoxia and spontaneous ventilation, $p < 0.05$.‡ Compared with hypoxia and spontaneous ventilation, $p < 0.05$.Table 3. *The effects of oxygenation, mechanical ventilation, and paralysis with d-TC on oxygen delivery in six newborn lambs (means $\pm$ SEM)*

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent paralysis	Hypoxia mech vent paralysis
Oxygen delivery (ml/100 g/min)					
Adrenal glands	25.70 $\pm$ 3.63	29.90 $\pm$ 5.32	31.02 $\pm$ 7.90	28.68 $\pm$ 3.17	22.68 $\pm$ 3.19
Brain	12.39 $\pm$ 1.89	12.91 $\pm$ 2.47	10.39 $\pm$ 0.82	9.11 $\pm$ 0.42	11.05 $\pm$ 1.78
Heart	40.73 $\pm$ 12.24	41.12 $\pm$ 8.37	29.34 $\pm$ 2.30	31.20 $\pm$ 3.35	44.10 $\pm$ 6.34
Liver	1.19 $\pm$ 0.31	1.5 $\pm$ 0.57	1.95 $\pm$ 0.33	2.19 $\pm$ 0.92	1.98 $\pm$ 0.74
Gut	23.03 $\pm$ 4.51	11.35 $\pm$ 2.72†	16.94 $\pm$ 3.56	17.52 $\pm$ 1.15	7.24 $\pm$ 1.02†
Kidney	32.49 $\pm$ 5.28	15.90 $\pm$ 5.12†	24.21 $\pm$ 4.97	25.32 $\pm$ 2.71	12.37 $\pm$ 2.35†
Spleen	52.69 $\pm$ 23.96	14.11 $\pm$ 7.34†	27.23 $\pm$ 6.10	28.26 $\pm$ 8.34	2.86 $\pm$ 0.84†
Carcass	2.51 $\pm$ 0.41	1.87 $\pm$ 0.57	2.07 $\pm$ 0.43	1.78 $\pm$ 0.28	0.83 $\pm$ 0.17†

* Hypoxia = PaO₂ of 27–33 mm Hg.† Compared with normoxia and spontaneous ventilation, $p < 0.05$.

not different from control (Tables 1 and 5). Blood lactate concentrations increased significantly ($p < 0.002$, Pan) during hypoxia and spontaneous ventilation, and remained elevated thereafter (Tables 1 and 5). Blood glucose levels were normal throughout the study.

Systemic arterial blood gases and pHs are also presented in Tables 1 and 5. The PaO_2 s were normal for animals of this age,

except when we intentionally induced hypoxia. The Paco_2 s and pHs were normal throughout the study, except during hypoxia and spontaneous ventilation when both decreased. There was no significant difference in the PO_2 s of ascending and descending aortic blood, indicating an absence of right-to-left shunting of blood through the ductus arteriosus. Less than 11% of the microspheres were found in the lungs, indicating that little right-

Table 4. *The effect of oxygenation, mechanical ventilation, and paralysis with d-TC on blood flow to various organs of six newborn lambs (means $\pm$ SEM)*

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent paralysis	Hypoxia mech vent paralysis
Blood flow (ml/100 g/ min)					
Adrenal glands	309 $\pm$ 68	481 $\pm$ 82	194 $\pm$ 51	329 $\pm$ 106	435 $\pm$ 57
Brain	97 $\pm$ 15	189 $\pm$ 22†	90 $\pm$ 9.8	78 $\pm$ 7.6	181 $\pm$ 24†‡
Heart	320 $\pm$ 15	635 $\pm$ 114†	236 $\pm$ 10†	239 $\pm$ 37†	798 $\pm$ 76†‡
Liver	9.1 $\pm$ 1.7	33 $\pm$ 12.5	19.8 $\pm$ 4.7	14.9 $\pm$ 6.0	22.4 $\pm$ 4.6
Gut	236 $\pm$ 26	227 $\pm$ 60	188 $\pm$ 40	216 $\pm$ 20	235 $\pm$ 32
Kidney	162 $\pm$ 23	165 $\pm$ 35	121 $\pm$ 22	131 $\pm$ 77	135 $\pm$ 13
Spleen	321 $\pm$ 122	202 $\pm$ 119	192 $\pm$ 44	216 $\pm$ 42	61 $\pm$ 19†‡
Carcass	20.3 $\pm$ 2.6	29.0 $\pm$ 6.0	17.8 $\pm$ 2.9	15.8 $\pm$ 2.7	16.7 $\pm$ 2.8

* Hypoxia = PaO_2 of 27–33 mm Hg.

† Compared with normoxia and spontaneous ventilation, $p < 0.05$.

‡ Compared with hypoxia and spontaneous ventilation, $p < 0.05$.

Table 5. *The effects of oxygenation, controlled ventilation, and paralysis with Pan on oxygen consumption, blood gases and pH, and serum lactate levels in six newborn lambs (means $\pm$ SEM)*

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent Pan	Hypoxia mech vent Pan
Oxygen consumption (ml/kg)	14 $\pm$ 1.1	12 $\pm$ 2.4	13 $\pm$ 2.4	14 $\pm$ 1.4c+h	7 $\pm$ 0.6†‡
Respiratory rate (breaths/ min)	42 $\pm$ 3.7	62 $\pm$ 2.2†	22 $\pm$ 1.1†‡	16 $\pm$ 0.8†‡	16 $\pm$ 0.8†‡
Femoral artery					
PO ₂ (mm Hg)	78 $\pm$ 4	30 $\pm$ 1†	80 $\pm$ 5	72 $\pm$ 4	29 $\pm$ 1†
PCO ₂ (mm Hg)	37 $\pm$ 1.9	30 $\pm$ 1.8†	39 $\pm$ 1	37 $\pm$ 2	36 $\pm$ 3
pH	7.33 $\pm$ 0.01	7.35 $\pm$ 0.02	7.32 $\pm$ 0.01	7.35 $\pm$ 0.01	7.33 $\pm$ 0.03
Temperature (°C)	38.6 $\pm$ 0.5	38.5 $\pm$ 0.3	38.7 $\pm$ 0.7	38.5 $\pm$ 0.5	38.5 $\pm$ 0.3

* Hypoxia = PaO_2 of 27–33 mm Hg.

† Compared with normoxia and spontaneous ventilation, $p < 0.05$.

‡ Compared with hypoxia and spontaneous ventilation, $p < 0.05$.

Table 6. *The effects of oxygenation, controlled ventilation, and paralysis with Pan on cardiac output, heart rate, systemic and pulmonary artery pressures, and resistances in six normal lambs (means $\pm$ SEM)*

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent Pan	Hypoxia mech vent Pan
Cardiac output (ml/kg/min)	354 $\pm$ 47	296 $\pm$ 10	292 $\pm$ 14	365 $\pm$ 24	334 $\pm$ 33
Heart rate (beats/min)	218 $\pm$ 23	235 $\pm$ 32	220 $\pm$ 29	236 $\pm$ 33	250 $\pm$ 32
Mean systemic blood pressure (mm Hg)	101 $\pm$ 9	90 $\pm$ 10	102 $\pm$ 8	102 $\pm$ 8	87 $\pm$ 5
Mean pulmonary arterial blood pressure (mm Hg)	26 $\pm$ 2	40 $\pm$ 4†	39 $\pm$ 1	32 $\pm$ 1	47 $\pm$ 3†‡
Left ventricular rate-pressure product (beats/min/mm Hg)	28,322 $\pm$ 5,415	27,694 $\pm$ 5,285	20,225 $\pm$ 6,390	32,030 $\pm$ 10,279	31,320 $\pm$ 8,465
Right ventricular rate-pressure product (beats/min/mm Hg)	9,316 $\pm$ 3,249	14,490 $\pm$ 6,091	11,808 $\pm$ 4,038	10,904 $\pm$ 6,133	19,556 $\pm$ 6,167†‡
Pulmonary vascular resistance (mm Hg/ml/min/kg)	0.08 $\pm$ 0.01	0.13 $\pm$ 0.02*	0.09 $\pm$ 0.03	0.09 $\pm$ 0.01	0.16 $\pm$ 0.02†‡
Systemic vascular resistance (mm Hg/ml/min/kg)	0.28 $\pm$ 0.03	0.30 $\pm$ 0.02	0.35 $\pm$ 0.03	0.30 $\pm$ 0.02	0.26 $\pm$ 0.04

* Hypoxia = PaO_2 of 27–33 mm Hg.

† Compared with normoxia and spontaneous ventilation, $p < 0.05$.

‡ Significant difference when compared with hypoxia and spontaneous ventilation $p < 0.05$.

Table 7. The effects of oxygenation, mechanical ventilation, and paralysis with Pan on tissue oxygen delivery in six newborn lambs (means $\pm$ SEM)

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent Pan	Hypoxia mech vent Pan
Oxygen Delivery (ml/ 100 g/min)					
Adrenal glands	37.79 $\pm$ 11.61	27.23 $\pm$ 9.92	28.60 $\pm$ 3.43	29.28 $\pm$ 3.98	20.64 $\pm$ 7.32
Brain	11.82 $\pm$ 0.61	9.05 $\pm$ 1.49	13.09 $\pm$ 2.11	12.43 $\pm$ 0.65	8.52 $\pm$ 2.02
Heart	39.78 $\pm$ 2.79	22.89 $\pm$ 4.14	24.43 $\pm$ 3.07	31.60 $\pm$ 6.81	32.55 $\pm$ 4.75
Liver	2.40 $\pm$ 1.19	2.41 $\pm$ 0.57	1.45 $\pm$ 0.07	2.32 $\pm$ 0.59	2.09 $\pm$ 0.35
Gut	18.02 $\pm$ 2.47	4.99 $\pm$ 0.74†	12.55 $\pm$ 1.89	16.77 $\pm$ 2.42	5.24 $\pm$ 0.48†‡
Kidney	31.42 $\pm$ 2.47	11.06 $\pm$ 2.30†	24.73 $\pm$ 2.55	29.57 $\pm$ 1.28	10.41 $\pm$ 2.32†‡
Spleen	70.53 $\pm$ 19.19	9.24 $\pm$ 2.17†	30.59 $\pm$ 12.20	40.31 $\pm$ 9.29	6.74 $\pm$ 2.18†
Carcass	2.19 $\pm$ 0.17	1.14 $\pm$ 0.30†	1.73 $\pm$ 0.18	2.30 $\pm$ 0.24	0.70 $\pm$ 0.08†‡
Diaphragm	3.86 $\pm$ 0.88	3.18 $\pm$ 1.19	3.99 $\pm$ 1.34	2.49 $\pm$ 0.30	1.10 $\pm$ 0.11†

* Hypoxia = PaO₂ of 27–33 mm Hg.† Compared with normoxia and spontaneous ventilation, $p < 0.05$.‡ Compared with hypoxia and spontaneous ventilation, $p < 0.05$.Table 8. The effects of oxygenation, mechanical ventilation, and paralysis with Pan on cardiac output distributed to various organs of six newborn lambs (means $\pm$ SEM)

	Normoxia spont vent	Hypoxia* spont vent	Normoxia mech vent	Normoxia mech vent Pan	Hypoxia mech vent Pan
Blood flow (ml/100 g/ min)					
Adrenal glands	296 $\pm$ 100	426 $\pm$ 168	216 $\pm$ 46	251 $\pm$ 32	413 $\pm$ 121
Brain	92 $\pm$ 7	146 $\pm$ 28†	115 $\pm$ 16	107 $\pm$ 8	174 $\pm$ 32†
Heart	311 $\pm$ 27	361 $\pm$ 66	215 $\pm$ 22	268 $\pm$ 53	773 $\pm$ 221†‡
Liver	20 $\pm$ 10	36 $\pm$ 9	13 $\pm$ 1	20 $\pm$ 5	47 $\pm$ 13
Gut	247 $\pm$ 28	172 $\pm$ 33	216 $\pm$ 11	255 $\pm$ 16	209 $\pm$ 33
Kidney	143 $\pm$ 24	78 $\pm$ 10†	111 $\pm$ 15	145 $\pm$ 22	109 $\pm$ 8
Spleen	572 $\pm$ 171	163 $\pm$ 50†	267 $\pm$ 96	354 $\pm$ 95	139 $\pm$ 62†
Carcass	19 $\pm$ 2	19 $\pm$ 3	18 $\pm$ 2	17 $\pm$ 2	16 $\pm$ 1
Muscle	9 $\pm$ 0	22 $\pm$ 6	8 $\pm$ 1	15 $\pm$ 7	18 $\pm$ 4
Diaphragm	35 $\pm$ 8	64 $\pm$ 16†	44 $\pm$ 1	23 $\pm$ 3†‡	27 $\pm$ 2†‡

* Hypoxia = PaO₂ of 27–33 mm Hg.† Compared with normoxia and spontaneous ventilation, $p < 0.05$.‡ Compared with hypoxia and spontaneous ventilation $p < 0.05$.

to-left shunting of blood occurred (3). The body temperature was normal throughout each study and the environmental temperature stable at 24.5 to 25.5° C.

Cardiac output, heart rates, and systemic arterial pressures remained relatively constant throughout the study (Tables 2 and 6). Mean pulmonary arterial pressures were unaffected by mechanical ventilation with room air. However, mean pulmonary arterial pressures increased during spontaneous breathing and hypoxia (34% d-TC $p < 0.01$, 54% Pan $p < 0.01$) and increased further during mechanical ventilation, hypoxia, and muscle paralysis, [80% ($p < 0.01$ d-TC) and 81% ($p < 0.01$ Pan) total increase from control]. Pulmonary vascular resistance increased 14% in the d-TC group and 63% in the Pan group ($p < 0.01$) during hypoxia and spontaneous ventilation. It increased 86% ($p < 0.001$ d-TC) and 100% ($p < 0.001$ Pan) with mechanical ventilation, hypoxia and muscle paralysis.

Oxygen delivery to the various organs was similar during spontaneous and mechanical ventilation with room air (Tables 3 and 7). During hypoxia and spontaneous ventilation, oxygen delivery to the adrenal glands, brain, heart, and liver (hepatic artery) remained at control levels. Oxygen delivery to the kidneys decreased 51% ($p < 0.05$ d-TC) and 65% ($p < 0.01$ Pan); delivery to the gut decreased 51% ($p < 0.05$ d-TC) and 72% ($p < 0.01$ Pan); delivery to the carcass decreased 48% ($p < 0.01$ Pan). Oxygen delivery to the diaphragm was unchanged (Pan).

During hypoxia, paralysis, and mechanical ventilation, oxygen delivery to the adrenal glands, brain, heart, and liver were also

not different from control levels. Oxygen delivery to the kidneys decreased 62% ($p < 0.001$ d-TC) and 67% ($p < 0.001$ Pan); that to the gut decreased 69% ($p < 0.01$ d-TC) and 71% ($p < 0.01$ Pan); that to the spleen decreased 95% ($p < 0.05$ d-TC) and 90% ($p < 0.01$ Pan); and that to the carcass decreased 67% ($p < 0.01$ d-TC) and 68% ($p < 0.01$ Pan). Oxygen delivery to the diaphragm was only determined in the Pan group; it decreased 71% ($p < 0.05$).

Mechanical ventilation, with or without muscle paralysis, had no effect on the organ blood flow of normoxic animals (Tables 4 and 8). Hypoxia and spontaneous ventilation, increased brain blood flow 95% ($p < 0.002$ d-TC) and 59% ($p < 0.05$ Pan) from control. Hypoxia, paralysis, and mechanical ventilation increased brain blood flow 87% ($p < 0.002$ d-TC) and 89% ($p < 0.05$ Pan) from control. Blood flow to the heart increased 98% ($p < 0.001$ d-TC) and 16% ($p < 0.05$ Pan) during hypoxia and spontaneous ventilation. Heart blood flow increased 149% ($p < 0.01$ d-TC) and 149% ($p < 0.001$ Pan) during hypoxia, paralysis, and mechanical ventilation. Blood flow to the diaphragm increased 83% from control ($p < 0.05$ Pan) during hypoxia and spontaneous ventilation; it decreased 33% from control levels ($p < 0.05$) during hypoxia, paralysis, and mechanical ventilation (Table 8). During normoxia, paralysis, and mechanical ventilation diaphragmatic blood flow was similar to flow during the control period.

Left ventricular rate-pressure products were unchanged throughout the study (Tables 2 and 6). Right ventricular rate-

pressure products increased 95% ($p < 0.001$ d-TC) and 110% ($p < 0.001$ Pan) from control levels in mechanically ventilated, hypoxic, paralyzed animals. The respiratory rate increased from 36 ± 2 (control) to 65 ± 5 breaths/min ($p < 0.004$) during hypoxia and spontaneous ventilation (Tables 1 and 5) in the d-TC group, and it increased from 42 ± 4 to 52 ± 2 breaths/min ($p < 0.001$) in the Pan group. The mean airway pressure of both groups was 6 ± 3 mm Hg and the end-expiratory pressure 0 mm Hg during mechanical ventilation.

DISCUSSION

We used the method of Lister *et al* (1, 2) rather than the Fick method, to determine $\dot{V}O_2$ because the former directly measures oxygen uptake by the lungs. Consequently, Lister's method is less likely to give erroneous results because multiple measurements (hemoglobin, blood gases, pH, and cardiac output) and calculations are not required, as they are with Fick's method.

The $\dot{V}O_2$ (7) (ml/kg/min) and cardiac output (ml/kg/min) (8) of resting neonates are twice those of adults. Both of these variables increase with fever (9), surgery (10), and with respiratory and cardiovascular distress (11). Physicians often administer nondepolarizing muscle relaxants to reduce the $\dot{V}O_2$ of hypoxic neonates. Until now, there has been no evidence that these drugs do this. The present study shows that the $\dot{V}O_2$ of mechanically ventilated lambs is reduced during muscle paralysis and hypoxia but not during muscle paralysis and normoxia. Since paralysis only affects muscle movement and breathing, one might not expect it to have much effect on the $\dot{V}O_2$ of lambs who were breathing quietly. Breathing accounts for <5% of basal oxygen consumption under normal conditions in adults; in the presence of conditions which increase airways resistance or decrease lung compliance, as occurs with numerous forms of cardiorespiratory disease causing hypoxia, the work of breathing may approach nearly half of the metabolic rate (12). Despite the fact that our spontaneously breathing, hypoxic lambs doubled their respiratory rate, their $\dot{V}O_2$ was similar to that of normoxic animals, probably because breathing induced increases in $\dot{V}O_2$ were offset by decreases in $\dot{V}O_2$ in other organs. This hypothesis is substantiated in part by the fact that diaphragmatic blood flow nearly doubled in spontaneously breathing, hypoxic animals; but fell below control levels in hypoxic, paralyzed, mechanically ventilated animals. Others have reported no change or a decrease in $\dot{V}O_2$ during hypoxia and spontaneous ventilation (13). These differences were probably caused by variations in environmental temperature and inspired oxygen concentration (14, 15). We maintained the environmental temperature constant throughout each study, and found no change in $\dot{V}O_2$ during hypoxia and spontaneous ventilation. Since the environmental temperature was constant and the inspired oxygen concentration was 10.5–11.5% in all instances, we do not believe that the decrease in $\dot{V}O_2$ was caused by changes in environmental temperature or by low inspired oxygen concentrations (16).

Muscle paralysis or mechanical ventilation per se had no effect on organ blood flow or oxygen delivery to the various organs of normoxic animals. Hypoxia, paralysis, and mechanical ventilation, decreased oxygen delivery to the gut, kidneys, carcass, and spleen, allowing normal oxygen delivery to the heart, brain, liver, and adrenal glands. Despite the decreases in oxygen delivery to some organs, there was no significant increase in base deficit. There was, however, a small increase in the serum lactate concentration. Thus, we cannot say for certain that tissue oxygen requirements were met, but the fact that O_2 delivery was similar during hypoxia and mechanical ventilation, and during hypoxia and spontaneous ventilation, suggests that the changes in oxygen delivery were due to hypoxia and not to mechanical ventilation.

Hypoxia, with or without muscle paralysis, did not cause tachycardia, hypertension, or increase cardiac output as it does in adults (16). This agrees with the findings of Cross *et al.* (17) in sheep. The reason(s) for this lack of change are unknown, but

may be related to several features of the neonate's cardiovascular system. First, stressed neonatal rabbits are less able to increase myocardial contractility than adults because the myocardial cells have fewer contractile elements than those of adults (18). Second, the resting heart rates are high. Consequently, further increases in heart rate may decrease, rather than increase, cardiac output. Third, sympathetic innervation of the neonate's (rabbits) heart is incomplete (18). As a result, sympathetic stimulation increases cardiac output to a lesser degree in neonates than it does in adults. Furthermore, neonates [humans (19), sheep (20)] have high endorphin levels during the first few weeks of life, and these levels increase during hypoxia (20). It is possible that endorphins reduce $\dot{V}O_2$. If so, the need to increase cardiac output during hypoxia should decrease. Hypoxia may not increase the mean arterial pressure of neonatal sheep because their peripheral vessels are less responsive to catecholamines than those of adults (21). Pan did not increase the heart rate of our lambs, as it occasionally does in children (22, 23) probably because the heart rates of lambs are normally higher than those of human neonates.

Arterial hypoxia increases the cardiac output of adult sheep (17) and maintains normal cerebral and myocardial oxygen delivery. Neonatal sheep, on the other hand, maintain cerebral and myocardial oxygen delivery by increasing the blood flow of these organs while decreasing the flow to other organs (3). Cardiac output is not increased. In our animals, myocardial blood flow was greatest during hypoxia, paralysis, and mechanical ventilation, probably because right ventricular $\dot{V}O_2$ increased. We did not measure myocardial $\dot{V}O_2$, but we did calculate right ventricular rate-pressure products as an index of myocardial $\dot{V}O_2$ (5). Right ventricular rate-pressure product increased in parallel with increases in pulmonary vascular resistance and pressures. The right ventricular function of neonatal lambs is similar to left ventricular function for several days after birth (24). Right ventricular blood flow and work equal or exceed those of the left ventricle. It is possible that myocardial work increased during mechanical ventilation and hypoxia. If so, the decrease in $\dot{V}O_2$ with mechanical ventilation caused by decreasing respiratory work may have been underestimated. We are unable to calculate myocardial work because we did not measure central venous pressure.

We do not know why pulmonary arterial pressures increased more during hypoxia, paralysis, and mechanical ventilation than they did during hypoxia, and spontaneous ventilation. We doubt that it was caused by mechanical ventilation per se because the mean airway pressure was low (6 ± 3 mm Hg) and the end-expiratory pressure was 0 mm Hg. Furthermore, pulmonary arterial pressures did not increase when normoxic animals were mechanically ventilated. We also do not believe that the rise was due to CO_2 because the $Paco_2$ in condition 4 (normoxia) was not different from condition 5 (hypoxia).

A possible explanation for the additional increase in pulmonary arterial pressure during hypoxia, paralysis, and mechanical ventilation might be an interaction between muscle relaxants, vasoactive hormones, and the pulmonary vasculature. It is unlikely that histamine is responsible for these changes because histamine decreases the pulmonary arterial pressure of neonates (25), and because Pan, which does not cause histamine release, produced similar changes in pulmonary arterial pressure and resistance to those caused by d-TC, which does release histamine. Angiotensin might also be responsible for these changes. Hypoxia increases the blood level of angiotensin in neonates (26) and angiotensin constricts pulmonary vessels and potentiates central and peripheral sympathetic activity (27, 26). This possibility requires further investigation. The rise in pulmonary arterial pressure might also result from repeated episodes of hypoxia (28). However, there must be five or six closely spaced episodes of hypoxia for this to occur. We used only two short hypoxic challenges, and they were separated from each other by an hour of normoxia.

Lactate levels increased during hypoxia and spontaneous ven-

tilation and remained elevated for the rest of the study, probably because we allowed insufficient time between conditions for lactate metabolism to occur. It is likely that the lactate concentration increased because of the hypoxia, but a small portion of the rise may have been due to the fall in PaCO_2 during condition 2. The second bout of hypoxia (condition 5) only raised the serum lactate concentration 25% above the value during condition 4, while the initial bout of hypoxia (spontaneous ventilation) raised the serum lactate concentration 106%. These differences occurred despite similar levels of hypoxia in both hypoxic conditions. This suggests that paralysis and mechanical ventilation reduces anaerobic metabolism during hypoxia, possibly because $\dot{V}\text{O}_2$ decreases.

In summary, muscle paralysis had no effect on the $\dot{V}\text{O}_2$ of normoxic animals, but significantly reduced that of hypoxic animals. Furthermore, muscle relaxants did not interfere with the redistribution of blood flow during hypoxia. However, muscle paralysis significantly increased right ventricular rate-pressure products and pulmonary arterial pressures of hypoxic lambs. If similar changes in pulmonary vascular resistance and pressure occur in hypoxic infants who have pulmonary vascular or right-sided heart disease, paralysis may adversely affect their right ventricular function.

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