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Oxygen Transport and Metabolism in the Conscious Lamb: The Effects of Hypoxemia

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ABSTRACT. We studied the response of O_2 consumption, systemic O_2 transport, arterial blood lactate concentration, base deficit, and respiratory exchange ratio (CO_2 production/O_2 consumption) to graded alveolar hypoxia (fractional concentration of inspired oxygen 0.21, 0.16, 0.12, and 0.08) in seven intact, conscious chronically catheterized lambs at <1 wk after birth, at 25–40 days and at >40 days. To test whether there was an age related difference in the metabolic response to a decline in O_2 transport due to hypoxemia, we related the changes in blood lactate and base deficit to the systemic O_2 transport and to the fractional change in O_2 consumption. Systemic O_2 transport and O_2 consumption decreased with severe hypoxemia, while lactate concentration and respiratory exchange ratio increased in all age groups. The changes in base deficit were not significant. When the hypoxemia-induced reduction in O_2 consumption was <15% of the baseline value (at fractional concentration of inspired oxygen 0.21) there was no elevation in lactate concentration; however, when O_2 consumption was reduced by more than 15%, lactate concentration consistently increased by more than 1 mmol/liter. There were no apparent differences amongst the age groups in this response. Therefore, the newborn lamb does show metabolic consequences of a fall in O_2 consumption with hypoxemia which is similar to the older sheep, however, there is a "buffer zone" in which O_2 consumption may decrease before evidence of tissue hypoxia can be found. The mechanism by which O_2 consumption can decrease without accumulation of lactate remains speculative. (*Pediatr Res* 22: 177–183, 1987)

Abbreviations

F_IO_2, fractional concentration of inspired oxygen
O_2, oxygen
CO_2, carbon dioxide
PCO_2, partial pressure of CO_2
PaO_2, arterial oxygen tension
$PaCO_2$, arterial carbon dioxide tension
pHa, arterial pH
PvO_2, mixed venous oxygen tension
VO_2, oxygen consumption
R, respiratory exchange ratio
CaO_2, arterial oxygen content
Hb, hemoglobin

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In anesthetized adult subjects, the systemic O_2 consumption has been found to be independent of the systemic O_2 transport (product of arterial O_2 content and cardiac output) when the transport is varied through a wide range (1–3). When systemic O_2 transport is reduced below a critical level, the O_2 consumption declines with further reductions in systemic O_2 transport. Tissue hypoxia then occurs resulting in a decrease in the ratio of aerobic to anaerobic metabolism. This metabolic alteration results in accumulation of lactate and the development of acidemia (3–6).

In contrast to the mature subject, the newborn animal does not necessarily have signs of tissue hypoxia in response to a fall in O_2 transport with hypoxemia (7–10). However, in most studies of hypoxemia (hypocapnic) in conscious newborn animals, pH or base buffering changes were used as markers of hypoxia and both of these variables are subject to confounding factors. Sidi *et al.* (7) compared the response of newborn and older lambs to severe hypoxemia induced by alveolar hypoxia (F_IO_2 = 0.09 and 0.06). Oxygen consumption consistently decreased in both groups as systemic O_2 transport declined. However, the newborns had a smaller increase in base deficit than the 2-month-old lambs when O_2 consumption was decreased by comparable proportion. Although lactate was not measured, the authors suggested from these data that age related metabolic differences may reflect a reduced nonessential metabolism as the initial response to hypoxemia in the newborn. This and similar observations prompted us to test whether there is a difference between the metabolic response of the newborn and the older lamb to a decline in systemic O_2 transport and O_2 consumption during hypoxemia.

We examined the changes in O_2 consumption and systemic O_2 transport during graded alveolar hypoxia (F_IO_2 0.21, 0.16, 0.12, and 0.08) in conscious healthy intact lambs studied at various postnatal ages. Because of the lack of a single marker for tissue hypoxia, we measured the blood lactate concentration, base deficit, CO_2 production, and O_2 consumption, and related these variables to hypoxemia-induced changes in systemic O_2 transport or O_2 consumption.

METHODS

Subjects. A total of seven lambs of mixed breed with documented dates of birth was studied. The lambs were surgically prepared and studied within 24 h after surgery. Two of these lambs, although in good health during the study, died after their initial study, one due to complications of an intracardiac catheter and another due to trauma. The lambs were studied multiple times over the next 2 to 3 months following surgery.

Under lidocaine local analgesia, a Tygon catheter was placed either in a hindlimb or carotid artery and advanced into the aorta. A Tygon catheter or balloon flow directed catheter was passed through a jugular vein into the pulmonary artery while pressure was monitored to ensure proper placement. All newborn lambs had a second venous catheter inserted through either the

same jugular vein or a hindlimb vein; this catheter was passed into the right ventricle and withdrawn slowly into the right atrium while monitoring pressure. The catheters were tunneled subcutaneously and exteriorized through a small flank incision. The lambs were then returned to their mothers and allowed to recover at least 12 h before being studied. They were each given antibiotics (200,000 U procaine penicillin and 0.25 g dihydrostreptomycin) by intramuscular injection for three days following surgery.

The catheters were flushed regularly with a heparin solution. If a catheter became dislodged or obstructed it was replaced using the technique described above.

Procedure. Each lamb was removed from its mother, weighed, and placed in a sling such that the lamb remained upright. A heating blanket was placed on the lamb to keep core temperature constant. A loose fitting mask was placed over the face to collect the mixed expired gas. A plastic reservoir bag connected to a gas source and mixer was placed around the mask and the lamb's head and was used to vary the concentration of inspired gases. The lamb was unsedated throughout the study.

Each lamb less than 2 wk old had 30 ml blood withdrawn into a heparinized syringe and 30 ml of saline infused 2 to 4 h before the study. It was then allowed to return to its mother until the study began. The blood remained refrigerated until the study and was given to the lamb in 5-ml aliquots to replace blood withdrawn for sampling. This was done to prevent large changes in blood volume during the study secondary to blood sampling in the smaller animals.

Oxygen consumption, CO_2 production, aortic pressure, pulmonary artery pressure, heart rate, and rectal temperature were monitored continuously during the study. The lambs were initially placed in an $F_IO_2 = 0.21$. When the above variables were stable, the lamb was quiet, and O_2 consumption remained constant for 10 min, baseline data were collected as described below. The F_IO_2 was then lowered to concentrations of 0.16, 0.12, and 0.08 sequentially by increasing the nitrogen concentration of the inhaled gas mixture. The lambs were maintained at each different F_IO_2 for at least 20 min or until the expired gas concentrations were constant before data were collected. Then, arterial and mixed venous blood samples were drawn. Three lambs in the initial study had evidence of a patent ductus arteriosus determined either by passage of the pulmonary arterial catheter into the descending aorta or by the marked elevation of pulmonary arterial Hb O_2 saturations in excess of 80%, at least 30% greater than values obtained from the right atrium. Right atrial blood was used for the mixed venous sample in these lambs; in other studies pulmonary arterial samples were used. Since pulmonary artery pressures remained below systemic levels during hypoxemia in the lambs with a patent ductus arteriosus, we assumed that there was no right-to-left ductus shunt and that ascending aortic blood would be appropriate for systemic blood flow calculation. At least three sets of simultaneous blood samples were drawn during a 20-min period. The initial two samples provided arterial and mixed venous Hb O_2 saturations. When these serial samples showed less than 10% variability, the following data were collected: arterial and mixed venous blood gases and Hb O_2 saturations, venous Hb concentration, and arterial lactate and pyruvate concentrations. This sequence of data collection was followed at each F_IO_2. The usual time period at each F_IO_2 was 50 min (20 to 30 min to stabilize and 15 to 20 min for three sets of blood samples). After the period with F_IO_2 of 0.08, the lamb was placed in room air and returned to its mother when blood gases, and O_2 consumption returned toward baseline.

Measurements and calculations. Oxygen consumption was measured by a flow through system (11). Expired gas was mixed with inspired gas drawn in around the facemask. Care was taken that the snout of the animal was secured so that all the mixed expired gas was collected. The O_2 consumption was calculated

Table 1. *Hemodynamic and oxygen transport data during progressive alveolar hypoxia (mean ± SE)**

	Group I (1–6 days; $n = 6$) 4.5 ± 0.4 kg				Group II (25–40 days; $n = 5$) 12.1 ± 0.9 kg				Group III (>40 days; $n = 6$) 19.1 ± 1.7 kg			
F_IO_2 =	0.21	0.16	0.12	0.08	0.21	0.16	0.12	0.08	0.21	0.16	0.12	0.08
pHa	7.39 ±0.01	7.40 ±0.01	7.44 ±0.02	7.45 ±0.03	7.40 ±0.02	7.43 ±0.02	7.49 ±0.03	7.50 ±0.03	7.46† ±0.02	7.48 ±0.02	7.50 ±0.02	7.57‡ ±0.02
$PaCO_2$ (torr)	29.3 ±3.4	26.2 ±2.5	23.1 ±2.8	15.2‡ ±2.2	31.5 ±1.3	27.1‡ ±1.1	23.2‡ ±1.1	17.5‡ ±1.2	27.5 ±0.7	25.5 ±0.7	23.2‡ ±0.7	15.4 ‡ ±0.7
PaO_2 (torr)	79.0 ±3.6	54.4‡ ±2.2	35.3‡ ±2.4	25.5‡ ±1.8	92.0 ±4.0	61.6‡ ±3.1	42.0‡ ±2.0	31.1‡ ±0.8	81.5 ±6.0	60.3‡ ±3.6	37.3‡ ±2.6	26.9‡ ±2.3
CaO_2 (ml O_2/dl)	12.80 ±1.18	11.60 ±1.19	8.61‡ ±0.84	5.31‡ ±0.40	8.72§ ±0.47	7.62 ±0.41	5.63‡ ±0.44	3.88‡ ±0.24	11.85 ±0.66	10.18 ±0.68	7.12‡ ±0.43	4.66‡ ±0.30
PvO_2 (torr)	31.7 ±2.4	28.2 ±1.6	22.4‡ ±1.3	16.7‡ ±0.5	35.7 ±3.7	31.4 ±2.4	23.1 ±2.0	16.3‡ ±1.1	42.1 ±3.2	35.9 ±2.1	26.9‡ ±1.7	16.1‡ ±1.0
Hb (g/dl)	10.39 ±0.79	10.71 ±0.69	10.70 ±0.87	10.59 ±0.64	6.60§ ±0.36	6.68 ±0.32	6.62 ±0.46	7.38 ±0.81	9.24 ±0.34	9.00 ±0.40	9.65 ±0.24	10.83‡ ±0.37
Cardiac output (ml/min/kg)	252 ±30.5	251.2 ±30.4	289.8 ±35.6	268.2 ±46.6	195 ±14.5	193.8 ±20.7	221.8 ±16.7	163.6 ±18.9	150.2§ ±9.3	133.3 ±11.6	156.3 ±12.7	153.7 ±13.7
O_2 extraction	0.45 ±0.03	0.48 ±0.04	0.55 ±0.04	0.70‡ ±0.06	0.57 ±0.04	0.61 ±0.04	0.67 ±0.03	0.72‡ ±0.04	0.45 ±0.03	0.42 ±0.03	0.61 ±0.03	0.73‡ ±0.01
Lactate (mmol/liter)	1.11† ±0.18	1.10 ±0.27	1.52 ±0.28	2.66‡ ±1.08	0.55 ±0.05	0.67 ±0.04	1.03 ±0.05	1.26‡ ±0.50	0.79 ±0.09	0.74 ±0.05	1.32 ±0.21	4.08‡ ±0.56
R	0.82 ±0.02	0.85 ±0.02	0.80 ±0.02	1.01‡ ±0.09	0.80 ±0.02	0.84 ±0.04	0.91 ±0.03	1.32‡ ±0.17	0.78 ±0.02	0.87 ±0.06	0.91 ±0.06	1.15‡ ±0.03
Base deficit (mEq/liter)	6.58 ±1.77	7.78 ±1.51	8.07 ±2.30	12.05 ±2.71	4.40 ±1.89	5.36 ±1.55	5.78 ±1.71	8.94 ±1.43	3.28 ±1.19	3.87 ±1.01	4.20 ±1.33	6.35 ±1.34
Rectal temperature (°C)	39.3 ±0.2	38.9 ±0.2	38.7 ±0.5	37.6‡ ±0.4	39.7 ±0.2	39.1 ±0.4	39.1 ±0.4	39.3 ±0.3	39.3 ±0.2	39.3 ±0.3	39.5	38.8 ±0.3

* For temperature measurements the n was occasionally less than the total number in the group because the probe came out during some of the studies and was later replaced.

Comparison of baseline data: † greater than two other groups ($p < 0.05$). § Less than two other groups ($p < 0.05$). Comparison within each group at each F_IO_2: ‡ significant change from baseline ($p < 0.05$).

from the difference in inspired gas and mixed expired gas concentrations and the flow rate through the system, correcting for the difference between inspired volume and expired volume (using calculated nitrogen concentrations). The CO_2 production was calculated in a similar manner.

Blood gas tensions were measured at 37° C by standard electrodes (Radiometer 73/BMS 3 Mk 2 blood micro system). Hb O_2 saturations were measured with a micro-oximeter (Radiometer OSM 2). Blood O_2 content was calculated as the sum of dissolved O_2 and Hb bound oxygen. A Hb O_2 binding capacity of 1.36 ml O_2/g Hb was used to calculate the Hb bound O_2 (12). Cardiac output was calculated using the Fick method from O_2 consumption and the difference between arterial and mixed venous O_2 contents. Hb concentration was measured by the cyanomethemoglobin method. Lactate and pyruvate concentrations were determined by an enzymatic spectrophotometric method (Sigma Chemical Company). Base deficit was calculated with the Severinghaus blood gas calculator, using the pH and PCO_2 measured at 37° C, and the Hb concentration (13). Systemic O_2 transport was calculated as the product of cardiac output and arterial O_2 content. Fractional oxygen extraction was calculated as the O_2 consumption divided by systemic O_2 transport (which is equivalent to the arteriovenous O_2 content difference divided by arterial O_2 content). The R was determined as CO_2 production divided by O_2 consumption.

Data analysis. Studies were grouped into three categories: group I, defined as lambs less than 1 wk postnatal age; group II, defined as lambs between 25 and 40 days old; and group III, defined as lambs more than 40 days old (the oldest was 3 months). Baseline data in each group were compared using analysis of variance and contrasted according to the Newman-Keuls method. In each group, data from different F_IO_2 levels were tested against baseline using two-way analysis of variance and Dunnett's test. Regression analysis of data is described below. For all data comparisons, statistical significance was assumed if p was <0.05.

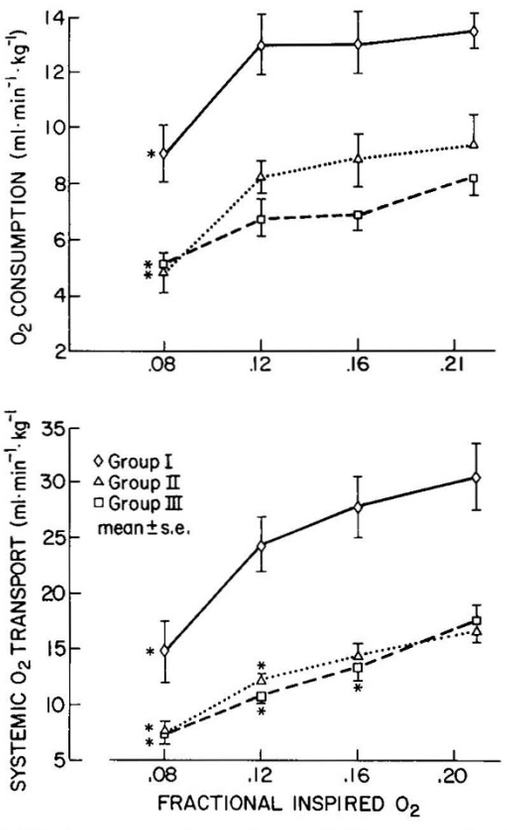

Fig. 1. The O_2 consumption and systemic O_2 transport in relation to the in F_IO_2 for all three age groups. Data are presented as mean ± SE; * represents a significant change from baseline, ($F_IO_2 = 0.21$), $p < 0.05$.

RESULTS

Data for hemodynamic and O_2 transport variables in relation to inspired O_2 concentration are shown in Table 1. Variables reflecting tissue metabolism, lactate, base deficit, and respiratory exchange ratio in room air and during hypoxemia are also shown in Table 1. The data collected at F_IO_2 0.21 in each group were considered baseline data with each lamb serving as its own control. The baseline values for blood gases and cardiac outputs were similar to prior reports (7–9, 12).

As the F_IO_2 was decreased, the PaO_2 fell similarly in all groups. In groups II and III as the PaO_2 fell, the lambs initially developed a respiratory alkalosis as evidenced by an increased pHa with a fall in $PaCO_2$ and no change in lactate concentration or base deficit. At the most severe hypoxemia all groups developed a respiratory alkalosis and a metabolic acidosis (note the increase in lactate concentration). In the oldest group there was a significant alkalemia with the lowest F_IO_2. As will be discussed, the alkalemia could have contributed to the elevated lactate concentration. The increases in lactate and R were significant at the severest hypoxemia in all three groups. These changes in lactate and in R are most consistent with the presence of anaerobic metabolism due to the hypoxemia, although there were no

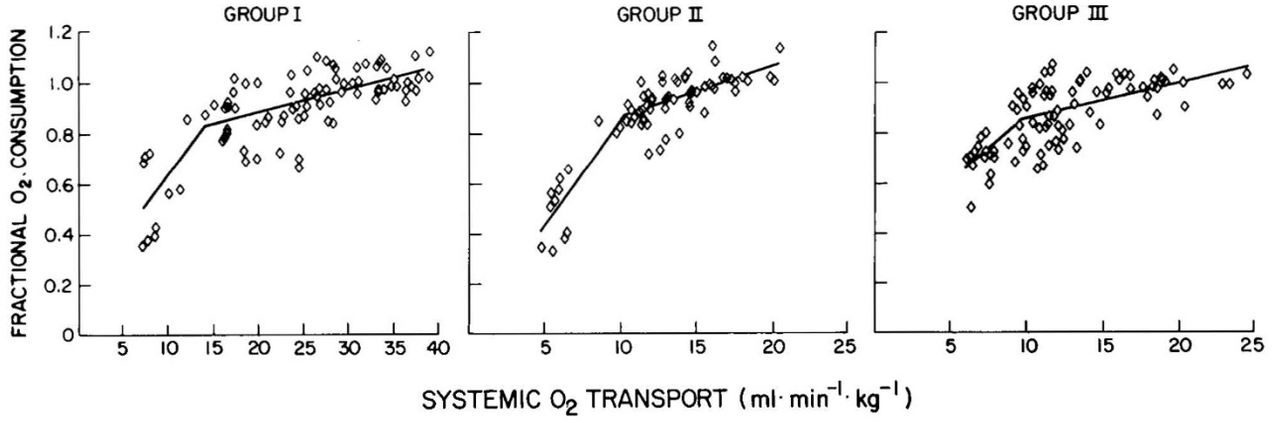

Fig. 2. The O_2 consumption in relation to systemic O_2 transport for three age groups. VO_2 is shown as fractional O_2 consumption (FVO_2: [VO_2 at $F_IO_2 = X$]/[VO_2 at $F_IO_2 = 0.21$]). *Lines* represent intersecting lines of regression (see text for description of construction). The two lines of regression are respectively, group I: $FVO_2 = 0.05$ SOT + 0.15 and $FVO_2 = 0.01$ SOT + 0.69; group II: $FVO_2 = 0.08$ SOT and $FVO_2 = 0.02$ SOT + 0.64; group III: $FVO_2 = 0.05$ SOT + 0.36 and $FVO_2 = 0.01$ SOT + 0.71.

significant changes in base deficit at any level of hypoxemia. In contrast to the other groups the youngest lambs had a significant decrease in rectal temperature while they were breathing the lowest inspired O_2 concentration as has been previously reported (7–9, 14).

As the F_IO_2 was decreased, there was some hemoconcentration in all groups of lambs. As expected the baseline Hb levels in group II were significantly less than the other two groups consistent with the physiologic postnatal decline in Hb concentration during the first months after birth (12). Because of the variation in Hb concentration the baseline arterial O_2 contents were different among the three groups.

The baseline cardiac outputs indexed to the lamb's weight show a decrease with age as previously reported and discussed (7, 12, 15). The changes in cardiac output as the F_IO_2 was altered were variable. Each group had lambs that increased, decreased, or had no change in systemic blood flow during hypoxemia. Moreover, there was no consistency in a given lamb's response to hypoxemia as it matured.

Figure 1 shows the relationship between inspired O_2 concentration and O_2 consumption and systemic O_2 transport. The baseline levels of systemic O_2 transport were significantly higher in the group I (30.82 ± 7.24 ml/min/kg) than the two older groups (group II: 16.8 ± 2.09 ml/min/kg, group III: 17.71 ± 3.36 ml/min/kg). This was due to the newborn lambs' higher baseline cardiac outputs and arterial O_2 contents. Although group II had significantly lower arterial O_2 contents than group III because of physiologic anemia, group II also had a higher cardiac output resulting in similar levels of systemic O_2 transport in both groups. As the F_IO_2 was decreased in all age groups there was a fall in systemic O_2 transport. Despite the wide variability among animals of different ages the fractional change in systemic O_2 transport at each inspired O_2 concentration was similar in all groups. The baseline O_2 consumption was higher in group I (13.71 ± 1.33 ml/min/kg) than in the two older groups (group II: 9.30 ± 1.04 ml/min/kg and group III: 7.81 ± 0.61 ml/min/kg) as has been previously described (12). With progressive hypoxemia, O_2 consumption was unchanged except at the lowest inspired O_2 concentration.

The relationship between O_2 consumption and systemic O_2 transport was analyzed assuming it followed the previously described biphasic response (1, 2, 16). In Figure 2, O_2 consumption, normalized to control, is shown as a function of systemic O_2 transport for each age. In all groups there was a wide range over which O_2 consumption was minimally dependent on systemic O_2 transport (*i.e.* the slope of the line of O_2 consumption as a function of systemic O_2 transport was close to but significantly greater than 0). At lower levels of systemic O_2 transport the relationship of O_2 consumption to systemic O_2 transport had a steeper slope. In order to determine the breakpoint we used a technique to find the intersection of two lines of regression (17). Paired lines were chosen to include each point once and only once as part of a regression and to minimize the total residual sum of the squares for the two lines. In group I the breakpoint of 14.3 ml/min/kg was higher than groups II (10.2 ml/min/kg) and III (10 ml/min/kg).

Other alterations in metabolism during hypoxemia were also examined by plotting the changes in lactate concentration, base buffering, and the respiratory exchange ratio in relation to systemic O_2 transport. This is shown in Figure 3. Here the trends for lactate concentration and R to increase with decreasing systemic O_2 transport are clear.

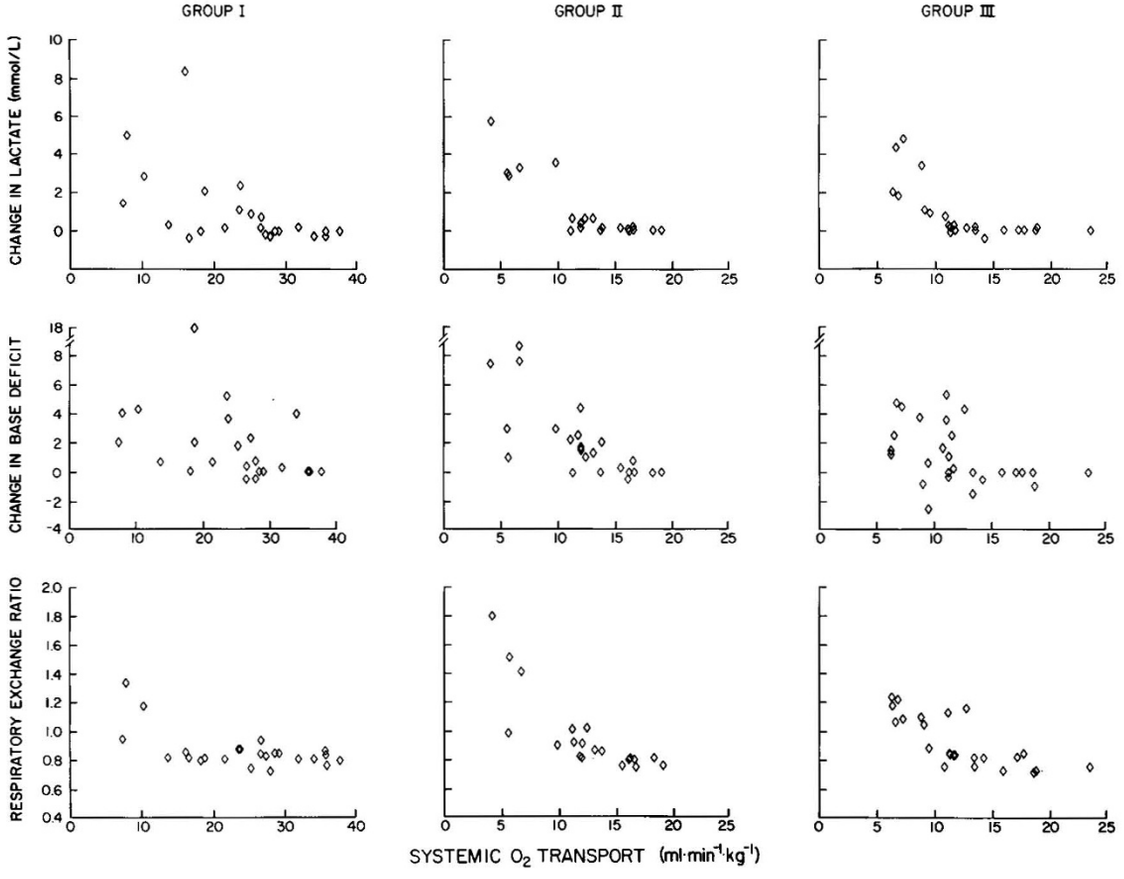

Fig. 3. Change in arterial blood lactate concentration, base deficit, and respiratory exchange ratio with a fall in systemic O_2 transport for three age groups. The change in lactate is (lactate at low F_IO_2 − lactate at F_IO_2 0.021]. The change in base deficit is (base deficit at low F_IO_2 − base deficit at F_IO_2 0.21). For example, if base deficit were 3 at F_IO_2: 21 and 15 during hypoxia, the change would be (+)12. Respiratory exchange ratio = (CO_2 production/O_2 consumption), measured at steady state.

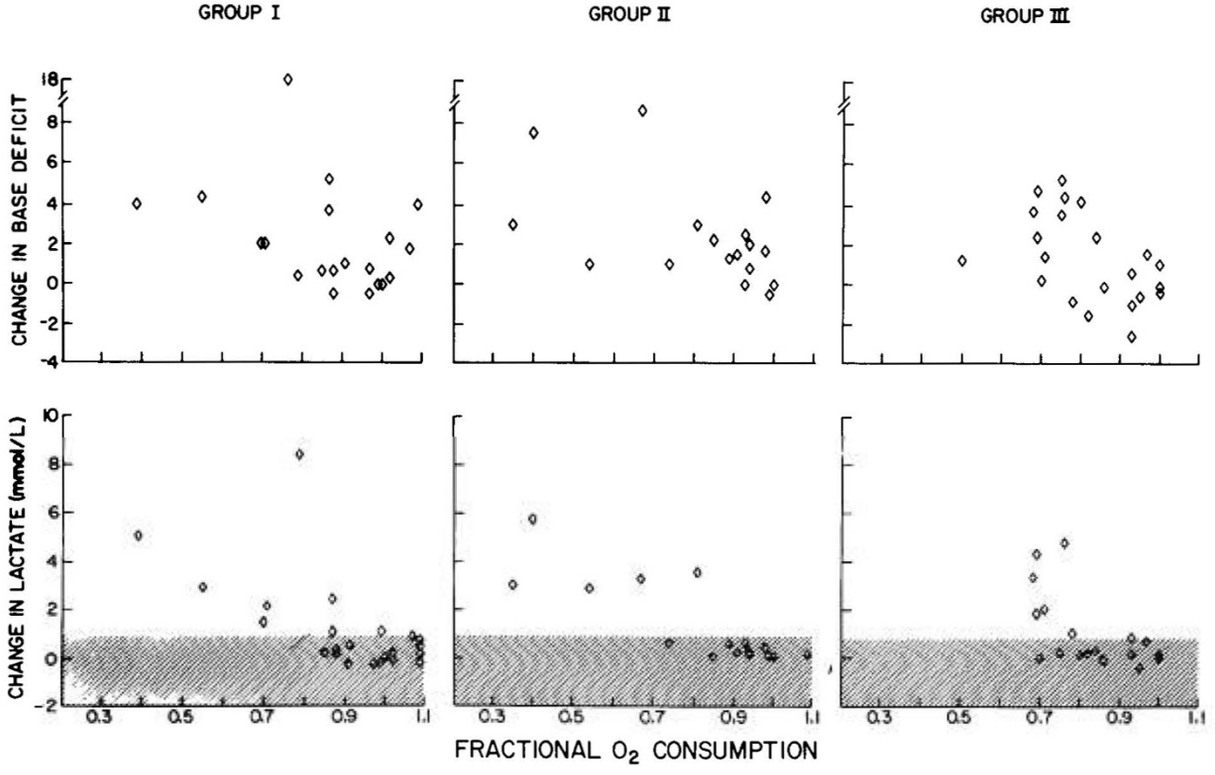

Fig. 4. Change in arterial blood lactate concentration and in base deficit in relation to the fractional O_2 consumption for three age groups. *Shaded area* represents a change in lactate <1 mmol/liter; this is within 2 × SD of the baseline variability.

Finally we examined the relationship between the change in arterial lactate concentration or base deficit and the hypoxemia-induced reduction in O_2 consumption as shown in Figure 4. Again, O_2 consumption was normalized to control values. We considered an increase in lactate of more than 1 mmol/liter as physiologically significant (this represents a change of more than 2 × SD of the grouped baseline data). Lactate concentration remained low until O_2 consumption decreased by at least 15% in all age groups. With few exceptions lactate concentration was elevated whenever O_2 consumption was less than 0.85 of control.

To test whether a decrease in O_2 consumption of 15% was predictive of an increase in arterial blood lactate concentration, we derived 2 × 2 contingency tables for each group; a change in lactate concentration of ≥1 mmol/liter and of <1 mmol/liter constituted two columns and a decrease in O_2 consumption to ≤0.85 and to >0.85 of baseline were used for the rows. For group I a reduction in O_2 consumption to ≤0.85 of the control value was 71% sensitive and 100% specific for an elevation in lactate concentration of ≥1 mmol/liter, and the positive predictive accuracy of a decrease in O_2 consumption to ≤0.85 for an increase in lactate concentration of ≥1 mmol/liter was 100%. For group II the sensitivity was 100%, the specificity was 87%, and positive predictive accuracy was 71%. For group III, the sensitivity was 100%, with a specificity of 76% and positive predictive accuracy of 60%. In other words in the group I lambs, a decrease in O_2 consumption of ≥15% was always associated with an increase in arterial lactate concentration (the 100% predictive accuracy) and a lesser decrease in O_2 consumption was occasionally associated with such an increase in lactate concentration (the 71% sensitivity). In the older animal, a decrease in O_2 consumption of ≥15% was not necessarily associated with an elevated arterial lactate concentration (combined predictive accuracy of groups II and III was 65%) and lactate concentration consistently remained low when O_2 consumption was reduced by 15% or less (combined sensitivity for groups II and III was 100%). Furthermore (as shown in Fig. 4), O_2 consumption could decrease somewhat in all groups without an associated increase in lactate concentration. The changes in base deficit were not as predictable from the fractional O_2 consumption.

DISCUSSION

We found, as have others, that when systemic O_2 transport is sufficiently diminished by alveolar hypoxia in lambs there is a fall in O_2 consumption (7–9, 14). We also found that newborn lambs have a much higher resting systemic O_2 transport than older sheep; it has been suggested that this is due to their higher resting tissue O_2 demands (7, 12, 15). In accord with this, our data show that in newborn lambs a rapid fall in O_2 consumption occurred when systemic O_2 transport was decreased to approximately 14 ml/min/kg whereas both the 1-month-old and older lambs could tolerate a decrease in systemic O_2 transport to approximately 10 ml/min/kg before there was a rapid fall in O_2 consumption. However, in all three groups this represented a similar limitation of systemic O_2 transport to approximately 60% of baseline.

In prior studies of perturbations in O_2 transport a critical systemic O_2 transport has been identified by the intersection of regression lines from the flat and steep portions of the relationship showing O_2 consumption as a function of systemic O_2 transport (1, 2, 16). A flat or independent portion (slope = 0) generally occurs because O_2 consumption is maintained despite the decrease in systemic O_2 transport by virtue of an increase in the fractional O_2 extraction. The steeper portion begins at a point where O_2 consumption becomes limited and dependent on the systemic O_2 transport (1, 2). Although such a clear demarcation has been seen in studies of healthy anesthetized subjects during physiologic manipulation of O_2 supply while O_2 demands were kept constant (18), other studies using subjects with diseases such as the adult respiratory distress syndrome or chronic obstructive pulmonary disease have not always exhibited a distinct dependent and independent O_2 transport-consumption relationship (16, 19–22), rather, O_2 consumption has been found to be dependent on systemic O_2 transport regardless of the level of transport. In

addition to a fall in O_2 consumption as systemic O_2 transport decreases, evidence of tissue hypoxia also appears as a hallmark of the critical level (3–6). Therefore, either the abrupt decline in O_2 consumption or a rise in arterial lactate concentration might be used to define a critical systemic O_2 transport.

When we examined the systemic O_2 transport/O_2 consumption relationship in the present study, we did not find O_2 consumption to be independent of systemic O_2 transport (slope = 0) even in the high ranges of systemic O_2 transport. A number of phenomena may have accounted for or contributed to this: 1) with the grouped data there may have been biologic variability between animals obscuring any point of demarcation; 2) a conscious intact animal may decrease metabolism during hypoxemia by gradually reducing "nonessential" activity; and 3) in the present study it was difficult to be absolutely certain that metabolic demands remained constant. Despite our efforts to ensure that the lambs were quiet when data were obtained, this factor is clearly more difficult to control than in anesthetized subjects. Individual changes in the work of breathing and cardiac work could not be controlled and may have also added to the variability of the data. Finally, as discussed later, changes in body temperature with hypoxemia may have altered metabolic demands.

Although a change in the slope of the O_2 transport/O_2 consumption relationship was found for all age groups, it is not clear whether this is the same as a "critical value" that has been identified in studies of anesthetized subjects; therefore, we not only examined the change in O_2 consumption with a fall in systemic O_2 transport, but also sought to determine whether there were changes in other markers of tissue hypoxia. In fact, we found that there was an increase in lactate concentration in all groups when systemic O_2 transport and O_2 consumption decreased substantially. However, we found that O_2 consumption declined prior to the onset of a blood lactate elevation as borne out in Figure 4. Thus, the initial fall in O_2 consumption with systemic O_2 transport usually caused no clear evidence of tissue hypoxia in these conscious hypoxemic lambs.

A factor other than tissue hypoxia should be considered as a potential cause for the elevation in lactate. It has been shown that hypocapnia and alkalosis without a decrease in PaO_2 may cause lactate to increase (23–27). However, the increase in lactate with a reduction in $PCO_2 \leq 20$ mm Hg alone is usually less than 1 mmol/liter (23–27), whereas the increase in lactate is greater when both hypocapnia and hypoxemia (27, 28). Furthermore, Cain (25) has shown that lactate increases as a function of O_2 debt during hypoxic hypoxia with or without hypocapnia, the differences being the initial lactate concentration rather than the rate of rise of lactate. Therefore, for the present study we believe the increase in lactate concentration of more than 1 mmol/liter was evidence of tissue hypoxia. The addition of CO_2 to the hypoxic gas mixture could have prevented the fall in PCO_2 and eliminated the confounding effect on lactate. However, this also markedly interferes with the study of O_2 transport in spontaneously breathing subjects; by increasing the inspired CO_2 concentration during hypoxic hypoxia, the minute ventilation is increased, raising the work of breathing, and the pulmonary vascular resistance is increased, altering right ventricular work. Therefore, we chose not to alter the inspired CO_2 concentration in this study.

In contrast to the data of Sidi *et al.* (7) we could find no difference in the metabolic response to hypoxemia of the newborn and older subject. This may be because we used lactate in addition to base deficit as a marker for tissue hypoxia. We recognize that arterial lactate concentration represents the balance between production and utilization rates and we cannot determine the degree to which either or both of these were altered; nor can we discern whether there were age related differences in lactate utilization which influence the response to hypoxemia. Regardless, in all groups of lambs we found an increase in arterial lactate concentration with acute hypoxemia as has been noted previously by Weismann (29). Our data for base deficit alterations vary widely and show no consistent response to hypoxemia. This could be due to the fact that base deficit is a calculated variable dependent on accurate measurement of Hb, pH, and PCO_2, the latter of which is subject to some variability under the best of circumstances. Moreover base deficit calculation has been based on Hb buffering (13) of adult human red blood cells. The assumptions under which this construct was derived may not hold for sheep blood with fetal Hb and different Bohr and Haldane effects (30–32), and caution needs to be used in interpreting base deficit data for sheep blood.

Although arterial lactate concentration increased and O_2 consumption decreased in all groups with the most severe hypoxemia, only in the youngest lambs (group I) did rectal temperature decrease significantly. We can only speculate on the cause for this difference in response. A decline in temperature (rectal or blood) has been observed in young lambs under comparable conditions, yet the degree to which the temperature decreases has been variable and unpredictable (7–9, 14). Many factors including environmental temperature, inspired O_2 concentration, and age and size of the subject have been shown to influence the response (8, 14). Even though the young lambs have brown fat (33, 34) while older lambs do not, and may thereby have proportionally more nonshivering thermogenesis, with the reduction in O_2 consumption heat production decreased substantially in all groups (14, 33), minimizing any age related differences in fuel utilization. The rise in respiratory gas exchange ratio in all groups is consistent with this interpretation. We therefore assume that the major difference in thermoregulation was that the young lambs have a large surface area to mass ratio and limited insulation, both of which compromise their capacity to conserve heat in the presence of reduced thermogenesis.

The decrease in rectal temperature with hypoxemia also has implications for the interpreting the relationship between O_2 consumption and O_2 transport. If thermogenesis is stimulated, metabolic demands may be increased. Alternatively, because of a "q_{10}" effect a fall in core temperature could reduce metabolic demands and lower O_2 consumption (14, 35). Therefore, in the youngest lambs, the decrease in body temperature could be a cause as well as an effect of the diminished O_2 consumption with hypoxemia. The net result is that some of the reduction in O_2 consumption may not have been due primarily to O_2 transport limitation. However, as discussed previously, the lactic acidemia in the young lambs strongly suggests that tissue hypoxia was also present during severe hypoxemia.

In summary, from our data we conclude that the conscious newborn lamb does show metabolic consequences of a fall in O_2 consumption with an hypoxemic reduction in systemic O_2 transport and this response is similar to the older subject. However, as Sidi *et al.* (7) suggested, there is a "buffer zone" in which O_2 consumption may decrease before evidence of tissue hypoxia can be found. Furthermore, we found that base deficit may not be a sensitive method of detecting tissue hypoxia.

Why O_2 consumption could decrease somewhat without lactate accumulation in these conscious lambs is not clear. We believe the decrement in O_2 consumption was out of the range of the variability at rest and therefore a true biologic change. We can only speculate that during mild hypoxemia either lactate production was increased but the clearance of lactate was more than adequate, preventing any rise in serum concentration, or that the conscious subject does have the ability to decrease its "nonessential" metabolism as an initial response to hypoxemia. This issue may be approached more directly by quantifying the decrement in O_2 consumption as a function of time in relation to the increased O_2 consumption after reoxygenation. This strategy has been used successfully by Cain (25) to distinguish "essential" from "nonessential" metabolism in the anesthetized subject, but is clearly more difficult to do in the conscious subject for many reasons noted previously. Alternatives such as the use of nuclear magnetic resonance or the study of lactate production in

individual organs may provide other useful approaches to this important issue.

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