Response to Low Cardiac Output: Developmental Differences in Metabolism during Oxygen Deficit and Recovery in Lambs

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ABSTRACT. When cardiac output is critically lowered, whole body O_2 consumption decreases and an O_2 deficit accumulates. With restoration of cardiac output, an excess O_2 consumption is expected in order to "repay" some or all of the O_2 deficit. We tested the hypothesis that young lambs, with higher resting O_2 consumption, cardiac output and growth rates than older lambs, would repay less of their O_2 deficit because they have a higher proportion of nonessential metabolism. We reduced cardiac output acutely by inflating a Foley catheter in the right atrium of spontaneously breathing, sedated lambs at ages 2 ($n = 5$) and 8 ($n = 5$) wk. Each lamb was studied with low cardiac output periods of 30 and 60 min on different days. Aortic and pulmonary artery blood pressures, gases, and O_2 saturations, venous Hb, and arterial lactate concentrations were measured every 10 min during baseline, low output, and 60 min of recovery. Oxygen consumption was monitored continuously. Oxygen deficit and excess O_2 of recovery were calculated from the time integral of the difference between O_2 consumption at baseline and during the respective study period. The average percent decreases in cardiac output (66.4 and 64.6%) and O_2 consumption (38.1 and 35.1%) were similar in the 2- and 8-wk groups, respectively. There was no consistent relation between O_2 deficit and O_2 repayment in either age group. However, on average the 2-wk group repaid a significantly lower percentage ($3 \pm 16\%$, mean $\pm$ SEM) than 8-wk-olds ($76 \pm 29\%$). Moreover, lactate increased linearly with time and O_2 deficit in both age groups, but lactate accumulated at a significantly lower rate in the 2-wk as compared to the 8-wk group for comparable deficits. We speculate that, during periods of very low cardiac output, 2-wk-old lambs not only decrease O_2 consumption, but also decrease metabolic demands, possibly by suppressing nonessential metabolism. This results in fewer energy stores that need to be replenished during recovery. This is a potential mechanism for the greater tolerance of young animals to hypoxic stresses. (*Pediatr Res* 26: 180–187, 1989)

transient excess in O_2 consumption above the initial baseline level and it has been suggested that this excess represents "repayment" of some or all of the O_2 deficit (4, 5) in a manner analogous to exercise (6). However, in studies of hypoxic hypoxia by Adams and Cain (5) in adult dogs, it was observed that there was neither "repayment" of all nor of a fixed proportion of the O_2 deficit. From this and other work they suggested that the fraction of the deficit not repaid was due to oxidative processes that were reduced or turned off during the period of hypoxia and thus represented nonessential, or "facultative," metabolism.

During studies in our laboratory in which O_2 delivery was reduced by selectively lowering cardiac output, we noted that young lambs had minimal, if any, transient excess O_2 consumption after restoration of O_2 supply, yet older lambs seemed to have a considerable excess in O_2 consumption for a period of time. It was our hypothesis that young lambs with a higher resting O_2 consumption, surface area to mass ratio, and growth rate than their older counterparts would repay less of an O_2 deficit because they have a higher proportion of metabolism devoted to nonessential processes. To test this, in our study we examined the relationship between O_2 deficit and excess O_2 of recovery under conditions of critically low cardiac output and determined whether this relationship varied as a function of age or with the degree of O_2 deficit. In addition, we compared the rate of lactate accumulation with respect to O_2 deficit to determine whether the deficit induced comparable degrees of tissue hypoxia at each age.

MATERIALS AND METHODS

Subjects. All animals studied were healthy lambs. We studied five lambs at 2 wk after birth (mean 18 d, range 13–21 d), a time of rapid growth when resting O_2 consumption and cardiac output are high, and five lambs at 8 wk (mean 57 d, range 54–66 d), when resting O_2 consumption and cardiac output have declined to near adult values (7). Four lambs were studied at both 2 and 8 wk of age. One lamb was studied only at 2 wk; another lamb was studied only at 8 wk of age.

Preparation. The lamb was sedated with intramuscular ketamine (10 mg/kg intramuscularly). Using local lidocaine analgesia and sterile technique, catheters were placed by means of an incision over the respective blood vessel. An arterial catheter was advanced from the hindleg to a distance estimated to reach the descending thoracic aorta. A balloon-tipped, end-hole venous catheter was advanced from the leg into the pulmonary artery, monitoring pressure to ensure proper placement. After this, a jugular vein was isolated through a small incision in the neck. A Foley catheter was inserted and advanced to the right atrium; again the pressure tracing was monitored to ensure proper placement. We have previously described a method to lower cardiac output in conscious lambs by placing a balloon-tipped (Foley)

When O_2 supply to the tissues is critically reduced by hypoxemia, anemia, or low cardiac output, whole body O_2 consumption decreases and an O_2 deficit accumulates throughout the hypoxic period (1–3). With restoration of O_2 supply, there is a

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catheter into the right atrium (8). Balloon inflation limits venous return and therefore lowers cardiac output. In previous observations, we found that balloon inflation causing very low levels of cardiac output raised inferior vena caval pressure only slightly, to the range of 6 to 8 mm Hg. In those studies, remarkably high levels of tissue O_2 extraction (0.90 to 0.95) were obtained suggesting that there was no tissue engorgement. Subsequent balloon deflation allows immediate restoration of venous return and cardiac output. Usually a catheter with 5 mL balloon volume was used for the younger lambs and 30 mL volume for the older subjects.

All catheters were sutured in place, and the lamb was placed upright in a sling. To test adequacy of placement of the Foley catheter, the Foley balloon was inflated with warmed saline to determine the volume necessary to lower arterial blood pressure by approximately 50%. The balloon was then deflated, and all catheters were flushed with heparinized saline, plugged, and fastened out of the reach of the animal. The lamb was then returned to the animal quarters and allowed to recover overnight. All lambs were given 400 000 U penicillin G procaine and 500 mg dehydrostreptomycin intramuscularly, for 3 d after the surgery. All lambs recovered from surgery for 24 to 96 h before study.

Experimental protocol. At 2 and 8 wk each lamb underwent two studies, one for 30 min of low cardiac output and another for 60 min of low cardiac output. The order was randomized and the studies were separated by at least 24 h.

At each study the lamb was removed from its pen, weighed, and then placed in a sling so that it was supported in an upright position. The lamb was blindfolded in an attempt to keep it calm. The lamb's snout was then secured in a mask to permit room air to be drawn in and expired gases to be collected for measurement of O_2 consumption and CO_2 production. All lambs were given ketamine 10 mg/kg intramuscularly followed immediately by continuous intravenous infusion at 10 mg $kg^{-1}h^{-1}$. Ketamine was used to sedate the lambs to maintain a stable baseline O_2 consumption. We have found in previous studies that this dose of ketamine does not change the mean resting O_2 consumption but prevents agitation and wide variations in O_2 consumption associated with external disturbances.

The aortic, pulmonary arterial and Foley catheters were connected via sampling stopcocks to pressure transducers (Statham P23Db, Gould Statham, Hato Rey, Puerto Rico) so that each pressure was monitored and recorded separately on a Beckman multichannel recorder (R611) (Beckman Instruments, Inc., Fullerton, CA).

During the study, O_2 consumption and CO_2 production were monitored continuously and recorded on a strip chart recorder. Additional data were collected every 10 min throughout the study (baseline, low cardiac output, and recovery periods). Systolic, diastolic and electronically derived mean pressures were recorded from the aorta and pulmonary artery at a rapid paper speed. Heart rate was measured from the aortic pressure trace. Blood samples (0.5 to 0.7 mL/sample) were slowly withdrawn from the aortic catheter (for blood gas tensions, pH, Hb O_2 saturation, and lactate and pyruvate determination) and from the pulmonary arterial catheter (for blood gas tensions, pH, Hb O_2 saturation, Hb concentration and hematocrit). The blood removed was replaced with an equal volume of normal saline. (In previous studies with prolonged right atrial balloon inflation, we found that the Hb concentration tended to increase slightly with time. As we were attempting to lower cardiac output without changing Hb concentration or arterial oxygen content, we elected to replace the blood drawn with normal saline and not blood.) Rectal and ambient temperatures were recorded every 10 min.

After the lamb had stabilized during the ketamine infusion and O_2 consumption was relatively constant, data (as above) were obtained during a 20 to 30-min baseline period. Then a period of low cardiac output was abruptly induced by inflation of the right atrial balloon to a level sufficient to reduce O_2

consumption by approximately 30% and blood pressure by approximately 50%. The period of low cardiac output was continued for 30 or 60 min and then the balloon was abruptly deflated allowing restoration of blood flow and recovery. Data were then obtained for 60 min of recovery. After this, the ketamine infusion was discontinued, the catheters were flushed and secured, and the lambs returned to the animal quarters for subsequent study. At the end of the studies at 2 wk, all catheters were removed and the lambs were returned with their ewes to the animal facilities. For the four lambs from this group restudied at 8 wk of age, catheters were placed (as described above) in vessels from the limbs or neck opposite to those used at 2 wk. No complications of recatheterization were encountered.

Measurements. Oxygen consumption and CO_2 production were measured by a flow-through system in which ambient air was drawn at a constant rate through a face mask and was mixed with expired gas from the nose and mouth. The fractional concentrations of O_2 and CO_2 were monitored continuously for calculation of O_2 consumption and CO_2 production as described previously (3, 9). Blood gas tensions and pH were measured by standard electrodes at 37°C (Radiometer America Inc., Westlake, OH) and corrected to body temperature. Hb O_2 saturation was measured using a microoximeter (Radiometer OSM2). Hb concentration was measured by the cyanmethemoglobin method. Hematocrit was determined by use of a microhematocrit centrifuge. Lactate and pyruvate concentrations were determined using an enzymatic method (Sigma Chemical Co., St. Louis, MO) (10).

Calculations. Arterial and mixed venous blood O_2 contents (CaO_2 , $C\bar{v}O_2$, in mL O_2 /dL) were calculated from the PO_2 (mm Hg), fractional Hb O_2 saturation, and Hb (in g/dL) as:

$$CaO_2, C\bar{v}O_2 = (1.36 \times Hb \times Hb O_2) + (0.003 \times PO_2)$$

where 0.003 mL O_2 /dL plasma $^{-1}$ mm Hg $^{-1}$ is the Bunsen solubility coefficient for O_2 in plasma at 37°C.

Cardiac output (CO, in mL min $^{-1}$ kg $^{-1}$) indexed to animal wt was calculated using the Fick equation, from O_2 consumption ($\dot{V}O_2$, in mL min $^{-1}$ kg $^{-1}$), CaO_2 , and $C\bar{v}O_2$ as:

$$CO = [\dot{V}O_2 / (CaO_2 - C\bar{v}O_2)] \times 100$$

Fractional O_2 extraction was defined as:

$$O_2 \text{ extraction} = (CaO_2 - C\bar{v}O_2) / CaO_2$$

Total systemic resistance was calculated as the quotient of mean aortic pressure (MAP) and cardiac output:

$$\text{total systemic resistance} = MAP / CO$$

We did not monitor superior or inferior vena caval pressures. In fact, these pressures may be different from each other during right atrial balloon inflation. However, in earlier studies, we found that inferior vena caval pressures increased by only 3 to 5 mm Hg with comparable levels of balloon inflation. We therefore calculated total systemic vascular resistance (above) as our best estimate of changes in systemic vascular resistance during balloon inflation and recovery.

In order to determine the O_2 deficit of the tissues, the average baseline O_2 consumption was determined from the stable 20 to 30-min period proceeding the reduced cardiac output. The assumption was made that if the period of low cardiac output had not occurred, the tissue O_2 consumption would have remained constant from baseline to the end of the recovery period. The O_2 deficit was the integral with respect to time of the difference between the expected tissue O_2 consumption (*i.e.* the extrapolated baseline) and the tissue O_2 consumption measured during the period of low cardiac output. Similarly, the excess O_2 consumption of recovery was the time integral between the O_2 consumption during recovery and the extrapolation of the baseline value. For these calculations, we also accounted for changes in body stores of O_2 (in the lungs, tissue water, and blood) that take place during the transition from baseline to low cardiac

output, and then from low cardiac output to recovery (2). Changes in myoglobin stores were not accounted for as this compartment has been assessed to be quite small (4), amounting to less than 1 mL/kg of muscle (5). While the quantity of stored O₂ is changing and reaching a new level, the O₂ consumption measured at the mouth is transiently different than the actual tissue O₂ consumption. Because only O₂ extracted from the atmosphere is measured at the mouth (*i.e.* the difference between inspired and expired O₂), correction of the measured O₂ consumption by the change in stores should yield the actual tissue O₂ consumption.

O₂ stores in the lung were estimated as:

$$[(\text{PAO}_2 \text{ (@ B, E, or R)})/(\text{P}_\text{B} - \text{P}_{\text{H}_2\text{O}})] \times (30 \text{ mL/kg}) \times \text{wt} = \text{mL O}_2 \text{ STPD}$$

where PAO₂ (mm Hg) was determined by the alveolar gas equation; B represents the average value during the baseline period, E during the experimental period of low cardiac output, and R during the recovery period; P_B and P_{H₂O} were barometric pressure and water vapor pressure (mm Hg); and the value 30 mL/kg represents the estimated average functional residual capacity of lambs as measured in our laboratory in unrelated studies (Pérez-Fontán JJ, Personal communication) and wt is in kg.

O₂ dissolved in body water was estimated as:

$$[(\text{P}\bar{\text{v}}\text{O}_2 \text{ (@ B, E, or R)}) \times 0.003] \times [600 \text{ mL H}_2\text{O/kg}] \times \text{wt} = \text{ml O}_2 \text{ STPD}$$

where P $\bar{\text{v}}\text{O}_2$ was the average mixed venous PO₂ during the period designated; 0.003 is the Bunsen solubility coefficient for plasma as defined above. This formula assumes that there is 600 mL body water/kg body wt and that the change in mean tissue PO₂ is reflected as a comparable change in P $\bar{\text{v}}\text{O}_2$.

O₂ stores in blood were estimated as:

$$[\text{CaO}_2 \text{ (@ B, E, or R)}] \times 90 \text{ mL/kg} \times 0.25 \times \text{wt} + [\text{C}\bar{\text{v}}\text{O}_2 \text{ (@ B, E, or R)}] \times 90 \text{ mL/kg} \times 0.75 \times \text{wt} = \text{ml O}_2 \text{ STPD}$$

assuming that the total blood volume of lambs is 90 mL/kg and the total blood volume is distributed as if 25% were arterial and 75% were venous. We did not measure blood volume or its distribution and this is obviously an estimate. Further, this distribution probably changed during right atrial balloon inflation with more blood pooled in the venous circulation. However, with no better estimate, we assumed the 25% arterial – 75% venous distribution for all estimates of changes in blood O₂ stores. Changes in blood O₂ stores represented the largest change. The net change in O₂ stores was determined by summing the changes in stores calculated for lung, tissue water and blood.

Oxygen stores decreased during the change from baseline to low cardiac output because mixed venous PO₂ declined thereby decreasing O₂ stores in blood and body water even though arterial PO₂ increased slightly. We assumed that most of the change in O₂ stores occurred during the first 10 min of low cardiac output because the variables used to estimate stores usually did not change much after that. Oxygen consumption measured at the mouth thus underestimated the true tissue O₂ consumption over this time, and the net change in stores was added to the O₂ consumption measured at the mouth to determine the true tissue O₂ consumption during the first 10 min of low cardiac output. As O₂ stores increased during the change from low cardiac output to recovery, the recovery O₂ consumption overestimated tissue O₂ consumption. Accordingly, the net change in O₂ stores during this transition was subtracted from the O₂ consumption measured during the first 10 min of recovery.

Statistical analysis. Data are reported as mean $\pm$ 1 SD unless otherwise noted. To compare results from the two age groups, the respective data were compared by *t* test. Statistical significance was assumed if *p* was < 0.05 . Oxygen deficit and arterial lactate concentrations at each age were related by linear regres-

sion analysis (least squares model). The regression data were compared by analysis of covariance.

RESULTS

Every lamb had both a 30- and 60-min low cardiac output study at both ages. Selected measured and calculated data during baseline conditions are shown in Table 1. These data are comparable to those obtained in other studies from ours and other laboratories (3, 7, 11, 12). The lambs grew normally between studies. Hb concentration and resting O₂ extraction were similar at both ages. Resting cardiac output and O₂ consumption showed the expected decline with age (7). Baseline arterial blood lactate concentrations were within normal limits.

There were no significant differences between the 2-wk-old group and the 8-wk-old group in either baseline rectal temperature (2 wk: 40.0 $\pm$ 0.6 C; 8 wk: 40.1 $\pm$ 0.5 C), ambient temperature (2 wk: 24.7 $\pm$ 0.5 C; 8 wk: 24.2 $\pm$ 0.7 C), or the difference between rectal and ambient temperature in each study (2 wk: 15.3 $\pm$ 0.8 C; 8 wk: 15.9 $\pm$ 0.7 C). Ambient temperature did not change during the course of a study.

The time course of a single representative experiment for an 8-wk-old lamb with a 60-min period of low cardiac output and 60 min of recovery is shown in Figure 1. After a baseline period, the right atrial balloon was inflated at time zero. The cardiac output was acutely decreased to one-third of the resting level and increased after balloon deflation to a level above control. Mean aortic blood pressure was decreased by one-half and increased above baseline during recovery. Accordingly, total systemic vascular resistance increased during low cardiac output and declined after balloon deflation. Core temperature increased slightly during the period of low cardiac output, fell acutely with balloon deflation, and then more gradually decreased to baseline levels. Oxygen consumption was stable during the control period, decreased abruptly (by about 40%) during low cardiac output but remained relatively constant at this lower value throughout the period of low cardiac output. Oxygen consumption then increased transiently above the baseline and slowly returned to near baseline values over the 60-min recovery period. Carbon dioxide production showed a pattern similar to that of O₂ consumption, falling slightly less than O₂ consumption during low cardiac output (and respiratory exchange ratio increased above 1.0), and rising to slightly higher levels during recovery. Extraction increased and was maintained close to 70% throughout the period of low cardiac output. Arterial blood lactate increased in a linear fashion throughout the period of low cardiac output and more gradually declined during recovery. Arterial-venous differences in PO₂, pH, PCO₂, and Hb O₂ saturation widened greatly during the period of low output and recovered quickly when cardiac output was restored. There was no significant change in Hb concentration during the period of the study.

In general, the same patterns of changes in cardiac output,

Table 1. Comparison of baseline values (mean $\pm$ SD)*

	2-wk-old lambs	8-wk-old lambs	Statistical difference
Wt (kg)	9.0 $\pm$ 1.8	15.3 $\pm$ 2.7	<i>p</i> = 0.001
Hb concentration (mg/dL)	8.9 $\pm$ 1.2	9.5 $\pm$ 0.4	NS
Cardiac output (mL/min · kg)	216 $\pm$ 38	121 $\pm$ 31	<i>p</i> = 0.001
O ₂ consumption (mL O ₂ /min · kg)	10.3 $\pm$ 2.1	6.7 $\pm$ 1.4	<i>p</i> = 0.002
O ₂ extraction ratio	0.42 $\pm$ 0.09	0.46 $\pm$ 0.06	NS
Arterial lactate (mmol/L)	0.9 $\pm$ 0.1	1.1 $\pm$ 0.3	<i>p</i> = 0.019

* Groups compared by paired *t* test. NS, not statistically different (*p* > 0.05).

Fig. 1. Changes in hemodynamic (A), metabolic (A and B), and blood gas (C) variables as a function of time during baseline, 60 min of low cardiac output, and 60 min of recovery. Data are from a single experiment on an 8-wk-old lamb. After a 20-min baseline period, the right atrial balloon was abruptly inflated at time zero resulting in an acutely lowered cardiac output which was maintained nearly constant. After 60 min, the right atrial balloon was abruptly deflated, allowing recovery.

blood pressure, O₂ extraction, blood gases, and arterial lactate as shown in Figure 1 occurred in all studies (30 and 60 min) at both ages. The average percent decreases in cardiac output (2 wk $66.4 \pm 6.1\%$, 8 wk $64.6 \pm 4.8\%$) and O₂ consumption (2 wk $38.1 \pm 9.3\%$, 8 wk $35.1 \pm 10.9\%$) during the period of low cardiac output were also similar in the two age groups. However, the patterns of O₂ consumption during recovery varied considerably, especially between the two ages.

Figure 2 shows representative studies of a 2-wk-old lamb and an 8-wk-old lamb with changes in O₂ consumption during baseline, 30 min of low cardiac output, and 60 min of recovery. Oxygen consumption during low output decreased by approximately 33% in each case. After a rapid, but brief, overshoot above the baseline during recovery, the 2-wk-old lambs often maintained their O₂ consumption slightly below baseline during recovery despite having a cardiac output above baseline level. In contrast, the 8-wk-old lambs tended to overshoot the baseline during recovery and then maintain their O₂ consumption above the baseline. Thus, despite comparable disruptions in O₂ supply, these differences in the patterns of recovery of the two groups, as shown in Figure 2, were a consistent finding.

These age-related differences in O₂ consumption during recovery are shown in Figure 3, where excess O₂ consumption during recovery (O₂ recovery) is plotted as a function of the total O₂ deficit accumulated (O₂ deficit) for each experiment. It is apparent that during most studies there was little or no excess O₂ consumption during recovery of the 2-wk-old lambs. In fact, in four of the five 60-min studies, representing the largest O₂ deficits, the O₂ consumption was lower during recovery than during baseline and the net "payback" was negative. For the 2-wk-old

group, the excess O₂ consumption of recovery averaged $3 \pm 16\%$ (mean $\pm$ SEM) of the deficit. Although there is substantial scatter in the older group, there is considerably more excess O₂ consumption during recovery in these studies, an average of $76 \pm 29\%$ of the deficit. In neither age group was there any obvious relation between O₂ recovery and O₂ deficit.

Inasmuch as O₂ consumption remained relatively constant during low cardiac output, O₂ deficit increased linearly as a function of time in each study. Similarly arterial lactate concentration increased linearly as a function of time and these two variables were closely correlated for both individual lambs and also for grouped data. The relationship of arterial lactate concentration to accumulating O₂ deficit is shown in Figure 4. The 30- and 60-min data from all studies are shown, again grouped by age. A linear correlation can be seen for both groups. The slope of the relationship in the 8-wk-old lambs was the same as we have reported in 2-mo-old lambs under comparable conditions (3). However, this slope was significantly greater ($p < 0.01$, by ANOVA) than that found for the younger lambs.

In every study, lactate decreased progressively with time during recovery, usually in a linear fashion. This was true even in those 2-wk-old lambs whose O₂ consumption was below baseline during recovery and whose net O₂ payback was negative. There was no obvious correlation between lactate concentration and excess O₂ consumption of recovery in either age group.

DISCUSSION

It was the aim of our study to make comparable disruptions in whole body O₂ metabolism in lambs at two different ages

Fig. 2. Representative studies of a 2-wk-old lamb (*top*) and an 8-wk-old lamb (*bottom*) showing changes in O_2 consumption (VO_2) during baseline, 30 min of low cardiac output, and 60 min of recovery. The extrapolated baseline is superimposed on the tracings. After an initial increase in O_2 consumption during recovery, the 2-wk-old lambs tended to maintain their O_2 consumption below baseline whereas the 8-wk-olds tended to maintain O_2 consumption above baseline.

which have very different basal O_2 requirements (Table 1). We used the calculated O_2 deficit as a common measure of O_2 lack during the low cardiac output period to compare the metabolic responses during the low cardiac output and recovery in the two age groups. We chose the level of reduction in cardiac output based on previous studies (3, 12) to be sure that: 1) it would be well below the critical level of O_2 delivery, 2) lactate would be produced, and 3) this state would be tolerated for periods up to 60 min. To ensure that the disruptions were comparable, in every study at both ages, we acutely decreased cardiac output so that the whole body O_2 consumption was reduced by one third (38.1% decrease at 2 wk and 35.1% decrease at 8 wk) with respect to baseline and was maintained at a nearly steady state. Fortunately, these reductions in O_2 consumption occurred with similar proportional decreases in cardiac output (66.4% decrease at 2 wk and 64.6% decrease at 8 wk). Inasmuch as Hb concentration and arterial O_2 saturation did not change significantly during the low cardiac output period, systemic O_2 delivery (= cardiac output $\times$ arterial O_2 content) varied directly with cardiac output. The decreases in O_2 consumption in the two groups therefore occurred with similar reductions in O_2 delivery as well. Thus, with these similar perturbations in O_2 consumption and supply at the two ages studied, we presume that differences that we detected in the metabolic responses during low cardiac output and recovery were primarily developmental differences.

We used ketamine at a constant infusion rate to sedate the lambs and minimize large variations in O_2 consumption associated with agitation or in response to disturbances during the study. In particular, we wanted to establish the most stable baseline O_2 consumption possible as this was crucial in determining the O_2 deficit and excess O_2 consumption of recovery (see Fig. 2). Ketamine stimulates the cardiovascular system through both central and peripheral mechanisms, resulting in increases in heart rate, cardiac output and arterial blood pressure,

Fig. 3. Excess O_2 of recovery (O_2 recovery) is plotted in relation to O_2 deficit (O_2 deficit) for the 2-wk-old (*top*) and 8-wk-old (*bottom*) lambs. The 30-min studies are shown by solid squares and the 60-min studies by open squares. The line of identity is shown for reference in each panel. Points in the shaded area represent studies in which mean O_2 consumption during recovery was less than that during baseline, *i.e.* there was no net excess O_2 of recovery.

with no change in systemic vascular resistance (13, 14). We could find no reports of any age-related differences in the cardiovascular stimulant properties of ketamine. Further, ketamine does not change resting whole body O_2 consumption in adult dogs (15). We routinely monitored O_2 consumption during the administration of ketamine and found decreases in the variations in O_2 consumption but no consistent changes in the mean level of O_2 consumption. Ketamine anesthesia resulted in slightly higher levels of arterial blood lactate concentration during acute blood loss (up to 30% of estimated blood volume) in adult dogs when compared to inhalational anesthetic agents (15). Unfortunately, no dogs were studied without any anesthesia, so it is impossible to determine if the lactate levels with ketamine were higher than expected, or whether the lactate levels were lower than expected with the inhalational agents during this degree of hemorrhage. Again, we could find no studies indicating a differential effect with age on lactate metabolism. Thus, although ketamine may have affected the level of lactate concentration during the low output period (16), we do not believe that it had any effect on the age-related differences we found.

We could not discern any relationship between O_2 deficit and excess O_2 of recovery in either age group (Fig. 3) nor have others in studies of adult dogs during either stagnant hypoxia (6) or hypoxic hypoxia (2, 4, 5). We found, as did these earlier studies, that O_2 "repayment" (excess O_2 of recovery) was usually less than the deficit. This observation has led to the thesis that the portion of the deficit not repaid during recovery (in the presence of adequate O_2 availability) represents facultative, or nonessential, O_2 metabolism (5). Facultative metabolism thus represents processes requiring O_2 that are a part of normal metabolism but are not essential for survival (16). These processes are thought to be

Fig. 4. Arterial blood lactate concentration shown as a function of accumulating O₂ deficit. Data from all studies are included, graphed by age. The linear regression line for the grouped data is superimposed.

largely extramitochondrial, to occur in various intracellular compartments, and to regulate the degradation, detoxification, or biosynthesis of a number of molecular species (16–18). The extramitochondrial functions are assumed to have a lower affinity for O₂ than the cytochrome oxidase system and, as O₂ becomes limited, their activity would decrease before the more essential enzyme systems involved in oxidative phosphorylation. Energy used for growth, other anabolic processes, and thermoregulation are other potential examples of nonessential metabolism (11). During a period of limited O₂ transport, decreases of organ O₂ demand by reduction of nonessential metabolism might allow relatively normal organ function, at least over the short term, by maintaining mitochondrial O₂ supply, thereby sustaining cellular energy stores and decreasing the need for anaerobic metabolism. It is not known whether these facultative processes are altered before or simultaneous with the more essential metabolic processes during conditions of limited O₂ supply. Nor is it established what factors regulate such strategic metabolic choices (5, 11, 16).

In our studies, we would expect that at least part of the fall in tissue O₂ consumption during the low cardiac output period is

attributable to a decline in nonessential metabolism as a means of compensation for the decreased O₂ delivery. However, any decrease in the O₂ demands by loss of facultative metabolism means that extrapolation of the baseline O₂ consumption through the low output period overestimates the basal O₂ requirements, which would have shifted to a lower value. The O₂ deficit as we have calculated it would correspondingly overestimate the “true” debt for O₂ (as nonessential metabolism would not require “repayment”). Any difference between the calculated deficit and the actual excess O₂ of recovery would provide an estimate of decreased energy requirements (16). In other words, the larger the decline in O₂ demands, the more the calculated O₂ deficit will overestimate the “true” debt, and the smaller the fraction of the calculated deficit that will require “payback.” It would be expected that young, growing animals (and humans) would have higher proportions of nonessential metabolism and that this would be a more important mechanism for compensation of decreased O₂ delivery in these subjects. Our observation that the younger group of lambs “paid back” a significantly smaller fraction (0.03 ± 0.16) of their deficit as compared to the older group (0.76 ± 0.29) is in accord with this hypothesis. As estimated by Sidi *et al.* (12), 30–35% of O₂ consumption in the newborn lamb is used for growth, whereas this decreases to about 10% by 6 wk of age. Further evidence in support of this concept is the finding that the 2-wk-old lambs accumulated lactate at a significantly lower rate than the older lambs (slope of lines in Fig. 4) for comparable levels of accumulating deficit.

It is also important to note that in the young lambs O₂ consumption remained below baseline in the majority of the studies during recovery. This implies that there was a continued decrease in the O₂ demands during part of recovery in this age group even though core temperature was not decreased, cardiac output was restored and lactate was metabolized. This low O₂ consumption in the young lambs suggests that facultative and total metabolism remained depressed during at least part of recovery and this potentially represents an important mechanism in the recovery process for this age group. It also demonstrates that it may take a prolonged time for metabolism to be restored despite augmentation of perfusion.

Although we have presumed that a large part of the change in basal O₂ demands during low output was due to changes in nonessential metabolism, there are other factors that must be considered in this experimental model. Basal O₂ demands could also have been altered by changes in cardiopulmonary work, changes in core temperature, or changes in catecholamine concentrations (stimulating thermogenesis), any of which could make extrapolation of the baseline through the low output period inaccurate. We did not measure cardiorespiratory work directly, but can make some reasonable estimates. The metabolic expenditure for respiration in normal adult and young subjects at rest is generally estimated to be 5% or less of the whole body O₂ consumption (19, 20). Arterial PCO₂ decreased in all lambs during the low cardiac output period (Fig. 1), presumably as a controlled respiratory response to the lactic acidosis. We initially assumed that the lowered arterial PCO₂ (Paco₂) would be the result of increased alveolar ventilation and therefore increased work of breathing. However, it occurred to us that total CO₂ production decreased simultaneously and that alveolar ventilation may not have to increase much to achieve the lower arterial PCO₂ (because alveolar ventilation is proportional to CO₂ production/Paco₂) (21). In fact, CO₂ production decreased (to 70% of baseline) proportionally more than Paco₂ (to 83% of baseline) during the low output period and changes were similar in both age groups. Thus, alveolar ventilation actually decreased to 84% of baseline and respiratory work and O₂ consumption would presumably have decreased in proportion. Resting myocardial metabolism in lambs represents about 10% of whole body O₂ consumption (22). In both age groups, systolic (and mean) arterial blood pressure decreased relatively more (45% decrease) than heart rate increased (7% increase) during the low cardiac periods. We

estimated changes in myocardial O_2 consumption by calculating changes in the rate-pressure product (heart rate $\times$ peak systolic aortic pressure) and found that myocardial O_2 consumption would have decreased by approximately 41% in both age groups. Therefore, we estimate that cardiopulmonary O_2 consumption decreased during the low output period; this would cause extrapolation of baseline VO_2 to be an overestimate (by about 7%) of O_2 demands during low cardiac output.

The effects of thermogenesis on O_2 demands during low cardiac output are much less predictable and cannot be quantified. We have no estimate of mean body temperature but increases in core temperature were always less than 1°C , were similar in both age groups, and should not have contributed significantly to changes in basal demands during low output. Furthermore, ambient temperature did not change during the studies and was similar for both age groups. Thus, a differential response to ambient temperature could not have accounted for the observed changes in O_2 consumption during the low output period. We did not measure serum catecholamine concentrations nor can we estimate how much calorogenesis was stimulated by changes in their concentrations. However, data from other studies in which β -adrenergic blockade was used to ablate the calorogenic effects of catecholamines during hypoxia suggest that this could increase O_2 consumption by about 10% (23, 24). We have no evidence that the influence of these thermogenic factors was different for the two age groups, although age-related differences in catecholamine stimulation or metabolic responsiveness during low cardiac output has not been studied to our knowledge. Therefore, although there were factors during low cardiac output that could have increased (temperature changes, catecholamines) or decreased (cardiopulmonary work) O_2 demands compared to baseline, the net effect was small and the extrapolation of baseline O_2 consumption was probably reasonable for both age groups.

We attempted to make steady state changes in O_2 consumption and cardiac output. This allowed us to correct for changes in body stores of O_2 and to consider time as a factor in O_2 deficit accumulation. As seen in the example in Figure 1, our model did establish a steady state in terms of blood pressure, cardiac output, and whole body O_2 consumption and CO_2 production, but not for arterial lactate concentration. Blood lactate concentration increased linearly with both time and O_2 deficit in all studies and never reached a plateau during low output. A linear relationship between arterial lactate concentration and time (as well as O_2 deficit) has been reported previously for both stagnant hypoxia (3) and hypoxia (3, 23, 25). The use of lactate concentration as a marker of "tissue hypoxia" is controversial (26–28). It has been traditional to attribute lactic acidemia to overproduction of lactic acid by hypoxic tissues; however, lactate accumulation is more accurately viewed as the balance between increased production rates and decreased removal rates (26–28). Although we measured neither lactate production nor lactate use in our studies, we would expect that the lactate accumulation we detected is caused by both increased production and decreased removal rates (3, 26–28). With the large decreases in whole body O_2 consumption and cardiac output we produced, it is likely that some tissues, *e.g.* the respiratory muscles and skeletal muscle (29, 30) increased their production of lactate. Concomitantly, hepatic lactate clearance (31, 32) and whole body net elimination of lactate (27, 33, 34) were probably diminished.

We also found that the increase in lactate concentration per increase in O_2 deficit (slope of the lines in Fig. 4) was significantly different between the two age groups, with the younger lambs having lower lactate levels at any given deficit. One explanation for this is that the lactate production rates were lower in this age group, reflecting better use of the available O_2 and less anaerobic metabolism (although there was no age-related difference in the fractional O_2 extraction during low cardiac output). This explanation would be in keeping with our hypothesis of a proportionally larger decline in nonessential metabolism in the younger age group. However, alternative explanations must be considered. It

may be that the lactate production rates were similar in the two age groups but the younger lambs were better able to metabolize the lactate load. The newborn liver and kidneys may have had higher fractional extractions of lactate or were able to maintain lactate metabolism in spite of decreases in blood flow and O_2 delivery. Alternatively, it may have been that there were differences in the distribution of blood flow during low output between the two age groups. For example, if the liver blood flow in the 2-wk-old lambs did not fall proportionately as much as in the older lambs, more lactate would have been delivered to the liver for removal in the younger age group. Higher removal rates in the younger group would have resulted in lower accumulation rates even if production rates were the same. We are currently undertaking further studies in our laboratory to determine lactate production and removal rates and sort out this interesting question.

To summarize, we found no obvious relationship between the excess O_2 of recovery and the O_2 deficit in either age group studied. However, our data show that, in contrast to older subjects, there was little or no "repayment" of an O_2 deficit in young lambs after a prolonged period of low cardiac output. Furthermore, lactate accumulated slower in the young lambs and was metabolized during recovery even in those lambs in which there was no excess O_2 consumption. We speculate that during a period of very low cardiac output, the young subject not only decreases its O_2 consumption but also decreases its metabolic demands by suppression of some or all of its nonessential O_2 metabolism. Cellular processes were diminished with minimal use of energy stores that needed to be replenished. This is in contrast to the older subject under comparable conditions. This may provide a mechanism for the greater tolerance in the newborn and young subject for such an hypoxic insult.

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